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Journal of the ASEAN Federation of Endocrine Societies

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ORIGINAL ARTICLES

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Through a Clearer Glass: The Endocrine Window in Sharper Focus

Measurement, the Uncommon, and the Discipline of Seeing Clearly

In the preceding issue of this Journal, I wrote of an endocrine window widening. That editorial marked a moment of institutional transition following the long and distinguished stewardship of Professor Elizabeth Paz-Pacheco, welcomed the Journal's expansion to three issues each year, and argued that our regional community is increasingly generating evidence for its own patients rather than importing it wholesale from elsewhere. If that issue was concerned chiefly with the breadth of what the window reveals, the present issue turns to something more exacting: the clarity of the glass itself. Across twenty-two contributions—eleven original articles, two reviews, six case reports, a case series, a brief communication, and an image in endocrinology—drawn from the Philippines, Indonesia, Malaysia, Vietnam, Sri Lanka, India, Algeria, Saudi Arabia, Singapore, and Thailand—a recurring preoccupation emerges with how we measure, how we diagnose, and how we come to recognize the uncommon.

The Reliability of What We Measure

Several contributions remind us that the instruments of endocrine practice are not population-neutral. The comparative study of point-of-care testing against the traditional reference laboratory method for congenital hypothyroidism speaks directly to a question of screening policy, for a diagnosis delayed in the newborn period is a diagnosis that exacts a lifelong neurodevelopmental cost. The comparison of the European Kidney Function Consortium equation with the CKD-EPI 2021 formula for estimating glomerular filtration rate among Algerians with type 2 diabetes makes the point still more pointedly: equations derived in one population and applied to another may mislead precisely those clinicians who trust them most. That this analysis reaches us from North Africa is itself instructive, for the window between our region and the wider world admits light in both directions.

Two further papers extend this theme from the laboratory to the bedside. The case of an undetectable HbA1c in an asymptomatic patient with hemoglobin E and beta-thalassemia minor is a cautionary tale of consequence, for hemoglobinopathies are far from rare in our populations, and the gold standard test on which we stake so many management decisions can, in their presence, deceive. The Malaysian study profiling skin and subcutaneous fat thickness by ultrasound to guide insulin delivery in overweight and obese adults addresses an act performed millions of times each day, yet seldom examined with rigor. Collectively, these works insist that measurement in endocrinology must be validated and contextualized in the very populations that rely upon it.

Diabetes: Complications, Costs, and Culture

Diabetes mellitus remains, as ever, the discipline's center of gravity, and this issue interrogates it along several axes. The analysis of risk factors for multidrug resistant organisms in infected diabetic foot ulcers situates our specialty at the uneasy intersection of metabolic disease and antimicrobial resistance—two of the most formidable challenges in contemporary medicine, here converging in a single wound. The examination of erectile dysfunction among Filipino men with type 2 diabetes gives overdue attention to a complication that carries considerable psychological and relational weight yet is too often left unspoken in the clinical encounter.

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Questions of mechanism, cost, and real-world effect are well represented. The review of sodium-glucose cotransporter-2 inhibitors and their effects on peripheral nerve and skeletal muscle function invites us to consider these agents beyond their glycemic and cardiorenal indications. The cost-effectiveness analysis of triple oral antidiabetic combination therapy in Indonesia, and the real-world retrospective cohort from Saudi Arabia examining cardiovascular and renal outcomes with dapagliflozin alone or combined with semaglutide, together address the pharmacoeconomic and pragmatic realities that ultimately determine what is deliverable rather than merely desirable. And the assessment of glycemic control among prospective Hajj pilgrims with type 2 diabetes exemplifies the culturally embedded scholarship this Journal is well placed to champion—a natural companion to the Ramadan-related research of our previous issue, and a reminder that faith and physiology are not separable in the lives of our patients.

The Person Behind the Hormone

Endocrine disease is lived, not merely measured, and three contributions keep the patient's experience firmly in view. The study of long-term outcomes and quality of life among patients with pituitary adenoma following endoscopic endonasal transsphenoidal surgery, employing the Indonesian version of the SF-36, affirms that survival and biochemical remission are necessary but insufficient measures of success. The systematic review of reproductive health, mental health, and quality of life in women with classical congenital adrenal hyperplasia illuminates a lifelong psychosocial burden that the biomedical literature has too often treated as peripheral. And the survey of healthcare workers' knowledge, attitudes, and practices regarding obesity in a Vietnamese tertiary hospital reminds us that the beliefs of clinicians themselves shape the care their patients receive—an echo of the attention our preceding issue paid to the perception of obesity across the region.

The Uncommon and the Long Road to Diagnosis

It is in this issue's case reports that the discipline appears at its most demanding and, arguably, its most humane. A phosphaturic mesenchymal tumor is traced from invisibility to bedridden morbidity, capturing with painful precision the diagnostic odyssey of oncogenic osteomalacia, a condition frequently unrecognized for years. An adrenocortical carcinoma with suspected dual cortisol and aldosterone secretion, a VIPoma presenting improbably with obstructive jaundice, and an insulinoma recognized only after recurrent syncope, behavioral change, and weight gain—yet followed to thirteen years of disease-free survival—each testify to the vigilance that rare hormone-secreting tumors demand. Hirata's disease, the insulin autoimmune syndrome, completes a quartet of hypoglycemic and secretory puzzles that will sharpen the reader's index of suspicion.

These narratives are not incidental to the Journal's mission; they are central to it. A rare entity recognized in one center is recognized more swiftly in the next, and the regional publication of such cases shortens the diagnostic odyssey for patients who might otherwise wait years for an answer. In this sense, the case report—so often undervalued—is an instrument of collective learning as consequential as any clinical trial.

A Closing Reflection

A window is only as useful as the clarity of its glass and the discernment of the eye behind it. Where the previous issue celebrated the widening of our regional view, this issue attends to the conditions that make that view trustworthy: measurement validated in the populations that depend on it, attention to the person and not merely the pathology, and a shared readiness to recognize the uncommon. The presence of contributions from Algeria and Saudi Arabia alongside those from across Southeast and South Asia reminds us that the endocrine window is not a boundary but a passage, through which evidence and experience travel in both directions to the benefit of patients everywhere.

Ultimately, it is the patients—those whose conditions animate these pages—who are the silent collaborators in every study that follows. May this issue serve them, and those who care for them, with clarity.

Cecilia A. Jimeno
Editor-in-Chief, JAFES

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**Claude AI (Anthropic) was used as an AI-assisted tool in developing this editorial, limited to language refinement, editing, organization, and clarity. All AI-assisted output was critically reviewed and revised by the author, who retains full responsibility for the accuracy, integrity, originality, and final content of the work. Claude AI is not an author or co-author.*

ORIGINAL ARTICLE

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Factors Affecting Long-Term Outcomes and Quality of Life of Patients with Pituitary Adenoma After Endoscopic Endonasal Transsphenoidal Surgery (EETS) Using the SF-36 Questionnaire (Indonesian Version)

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Abstract

Objective. To evaluate the quality of life (QoL) of patients with pituitary adenoma following Endoscopic Endonasal Transsphenoidal Surgery (EETS) and identify factors influencing long-term outcomes.

Methodology. A cross-sectional study was conducted at the National Brain Center Hospital, Indonesia. Secondary data were obtained from medical records and the pituitary registry, while primary data were collected through patient interviews using the validated Indonesian version of the SF-36 questionnaire. Statistical analyses included univariate, bivariate, and multivariate linear regression with the backward method to identify independent predictors of QoL.

Results. Among 90 patients (45 males, 45 females), visual disturbances (85.6%) and hormonal deficiencies (93.3%) were common. Most had macroadenomas (95.6%) and received combined EETS and medical therapy (62.2%). Physical component scores (PCS) exceeded mental component scores (MCS). The highest domain scores were in physical functioning and role-emotional functioning; vitality and mental health had the lowest scores. Gender was significantly associated with four QoL domains, and hormonal deficiency affected the role-emotional domain. Multivariate analysis identified gender and hormonal deficiency as predictors of MCS (R^2 = 74%); no factors significantly influenced PCS.

Conclusion. Postoperative QoL after EETS is generally good in physical aspects but suboptimal in mental health. Gender and hormonal deficiency affect mental QoL, highlighting the need for holistic, long-term care strategies.

Key words: pituitary adenoma, quality of life, EETS, SF-36, hormonal deficiency

INTRODUCTION

Pituitary adenoma is a benign tumor of the pituitary gland that can cause a wide range of symptoms due to mass effect and hormonal dysregulation. It accounts for approximately 12.2% of all central nervous system tumors, with a global prevalence ranging between 75.7 and 115.6 per 100,000 population.[1–3] A meta-analysis reported a prevalence of 16.7%, with 14.4% based on autopsy studies and 22.5% from radiological findings.[4] A landmark study in Iceland also reported a prevalence of 115 per 100,000 population.[2,4] In Indonesia, national data on the prevalence and incidence of pituitary adenomas remain scarce. However, the National Cancer Control Committee estimates an annual incidence of 1 to 2 cases per 100,000 people for functional pituitary tumors.[5] At Cipto Mangunkusumo Hospital, pituitary adenomas accounted for 13.9% of all brain tumor cases.[6] A similar study at Kariadi Hospital in Semarang identified 26 cases of pituitary adenomas from January 2020 to December 2022, with 80.8% of patients undergoing

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Endoscopic Endonasal Transsphenoidal Surgery (EETS).[7] Additionally, data from the National Brain Center Hospital (RSPON) recorded 132 cases of pituitary adenoma (58.14%) out of 227 suprasellar tumors from January 2020 to June 2023.

EETS has become the primary surgical approach for treating pituitary adenomas, offering a minimally invasive route with reduced risk of complications, shorter recovery time, direct access to the sella turcica and minimal postoperative pain and infection risk. Although EETS is effective in reducing mass effect and improving symptoms, adjuvant therapy such as medical treatment and hormonal evaluation is often still required. Unfortunately, in many low- and middle-income countries, including the Philippines and Indonesia, medical therapy remains expensive and difficult to access.[8–11] Medications like dopamine agonists, somatostatin analogs, and Cushing-specific therapies are costly and often not covered by health insurance. Treatment for acromegaly costs approximately €9,200–32,807, while treatment for Cushing's disease costs €26,269–34,992. Even for non-functioning pituitary adenomas (NFPAs), which incur lower annual treatment costs (~€3,040) compared to functioning adenomas, the financial burden remains substantial, particularly for patients with hormone deficiencies.[12,13]

While treatment success is typically assessed through hormonal assays and imaging results, quality of life (QoL) is a crucial yet often neglected outcome.[14] Studies show that patients with functioning pituitary adenomas experience worse preoperative QoL, particularly in the social domain, while non-functioning tumors cause symptoms like headaches and visual disturbances.[15] Patients with uncontrolled disease report significantly lower QoL scores on both physical and mental components.[15] Tools such as the QoL-AGHDA and QLS-H confirm decreased QoL in these populations. Though EETS generally improves emotional and mental aspects of QoL postoperatively, physical recovery, such as vitality, physical function and performance of roles, may take longer and depend on tumor size and surgical extent.[6,15] The Indonesian version of the SF-36 has been validated and shown to be reliable for assessing health-related quality of life in Indonesian populations. Salim et al., reported acceptable validity and reliability of the Indonesian SF-36 in patients with permanent pacemakers, with good internal consistency and test-retest reliability. Arovah and Heesch also demonstrated that the Indonesian SF-36 had adequate reliability and construct validity among middle-aged and older Indonesian adults, supporting its use as a generic instrument for evaluating physical and mental components of quality of life in Indonesian settings.[16,17]

Long-term monitoring of QoL is vital for evaluating treatment success holistically. However, this is often hindered by high costs and limited availability of hormonal testing, especially in resource-constrained settings. Prices for diagnostic agents like corticorelin and synacthen have surged, and the costs of essential medications such as insulin and hydrocortisone have risen dramatically over the past decade, further limiting access to care.[18]

Even after surgery, many patients continue to experience reduced QoL due to hormonal imbalances, postoperative complications, chronic fatigue, limited physical activity, or long-term psychosocial effects. Although EETS improves clinical outcomes, these lingering issues highlight the need for better post-treatment support.[19–21]

In Indonesia, there is a lack of research specifically examining QoL among patients with pituitary adenomas after EETS. Therefore, this study aims to: (1) describe the quality of life profile including Physical Component Summary (PCS) and Mental Component Summary (MCS) scores across eight SF-36 domains of pituitary adenoma patients who underwent EETS at the National Brain Center Hospital (RSPON); (2) identify demographic and clinical variables (gender, age, tumor size, hormonal deficiency, visual impairment, therapy type, comorbidity, employment status and postoperative duration) that are significantly associated with each SF-36 domain through bivariate analysis; and (3) determine independent predictors of PCS and MCS using multivariate linear regression analysis. As the first study of its kind in Indonesia, the findings are expected to contribute comprehensive epidemiological data and support the development of more effective and holistic strategies for improving long-term outcomes and well-being in this patient population.

METHODOLOGY

Study design

This study employed a cross-sectional design and was conducted at the pituitary clinic of the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, which implements a one-gate multidisciplinary system. The medical team that patients encounter consists of neurosurgeons, internists, neurologists and ENT specialists. The baseline data used in this study were secondary data obtained from the hospital's pituitary clinic registry, while quality-of-life data were collected as primary data through interviews using the validated Indonesian version of the SF-36 quality-of-life questionnaire.

Population and samples

The study population consisted of all adult patients with pituitary adenoma treated at the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono. The accessible population included adult patients diagnosed with pituitary adenoma who had undergone endoscopic endonasal transsphenoidal surgery (EETS) at the same hospital between January 2020 and December 2024 in Jakarta. The study subjects were all adult patients with pituitary adenomas at the hospital who met the inclusion criteria and did not meet any exclusion criteria.

The inclusion criteria were: (1) patients with a confirmed diagnosis of pituitary adenoma who had undergone EETS between January 2020 and December 2024, (2) aged over 18 years (adults), and (3) able to communicate and be interviewed to complete the data required for the study. The exclusion criteria were: (1) patients who could not be contacted or were lost to follow-up, (2) patients with cognitive impairments (e.g., intellectual disability or dementia) that prevented them from being interviewed about their quality of life, (3) patients with psychiatric diagnoses that could introduce bias in the quality-of-life assessment, (4) patients who could not speak Indonesian fluently, and (5) patients who declined to participate in the study.

Sample size was determined through a power analysis for multiple linear regression. With a significance level of α = 0.05, a statistical power of 80% (1−β = 0.80), and a minimum expected coefficient of determination (R^2) of 0.16 based on prior literature, the minimum required sample size was calculated to be 87 subjects. This calculation accounted for eight independent variables included in the regression model. A total of 90 subjects were enrolled, exceeding the minimum requirement.

Study instrument

The instrument used in this study consisted of two main sources of data. First, secondary data were obtained through the Pituitary Clinic Registry of the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, which contained complete information on patient demographic characteristics, laboratory examination results, and medical imaging such as MRI or CT scans that had been systematically documented. Second, to assess patients' quality of life, the validated Indonesian version of the SF-36 questionnaire was used. This questionnaire was administered to each subject who met the inclusion criteria and had signed informed consent. The interviewers, consisting of the principal investigator and trained research assistants, were responsible for guiding respondents through the questionnaire. Each questionnaire was assigned a subject identification number to ensure data confidentiality and facilitate the analysis process.

Data collection

Data were collected from two main sources. Secondary data were obtained from the pituitary clinic registry at the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, which included patients' demographic information, hormonal laboratory results (FT4, TSH, cortisol, prolactin), MRI imaging and visual field test results. Primary data were collected through interviews using the validated Indonesian version of the SF-36 questionnaire. The interviews were conducted by the researcher or research assistants with patients who met the inclusion criteria and provided informed consent.

Each patient was assigned a subject identification number and interviewed via video call, which included confirmation of registry data and complete administration of the SF-36 questionnaire. SF-36 scores were then calculated for eight domains: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. These domains were grouped into two major components: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). All domain scores were converted to a 0–100 scale, with higher scores indicating better quality of life.

Data analysis

Data analysis was performed using SPSS Statistics version 24.0. Univariate analysis was conducted to describe the distribution and frequency of all demographic and clinical variables, as well as SF-36 domain scores. Data normality was assessed using the Kolmogorov-Smirnov test. Since the SF-36 domain scores were not normally distributed (p <0.05), nonparametric tests were applied for bivariate analysis: the Mann-Whitney U test for comparisons between two independent groups (e.g., gender, hormonal deficiency, therapy type, comorbidity, visual impairment, employment status) and the Kruskal-Wallis test for variables with more than two categories (e.g., age group, postoperative duration, complaint duration). Variables yielding p <0.250 in bivariate analysis were entered into multivariate analysis. Multivariate analysis was conducted using multiple linear regression with the backward elimination method to identify independent predictors of PCS and MCS scores. Potential confounders, including age group, comorbidity status, and hormonal deficiency, were included in the initial multivariate model and controlled for throughout the backward elimination process. Statistical significance was defined as p <0.05. Missing data were handled by excluding subjects with incomplete SF-36 questionnaire responses or missing registry variables. The final dataset comprised 90 subjects with complete information on all study variables.

RESULTS

The study involved 90 patients with a mean age of 48.11 years (SD ±12.74). Most participants were aged 40 to 60 years (57.8%), followed by those under 40 years (24.4%) and over 61 years (17.8%). The gender distribution was equal, with 45 men (50%) and 45 women (50%). More than half of the participants were employed (58.9%), while the rest were unemployed (41.1%). Hormonal deficiency was present in 84 patients (93.3%), and absent in 6 (6.7%). The majority of tumors were macroadenomas (93.3%), with only 4 cases (4.4%) classified as microadenomas. Regarding treatment, 34 patients (37.8%) underwent endoscopic endonasal transsphenoidal surgery (EETS) alone, while 56 (62.2%) received EETS combined with medical therapy. Comorbidities were found in 29 patients (32.2%), while 61 (67.8%) had no comorbid conditions. Postoperative

duration varied, with 24.4% having undergone surgery within the last year, 33.3% between 1–3 years, and 42.3% more than 3 years prior (Table 1).

Based on the SF-36 questionnaire, the median physical function score was 100 (IQR 85–100), and the role physical domain also had a high median of 100 (75–100), indicating minimal physical limitations in most patients after surgery. The bodily pain domain had a median score of 78 (55–99), indicating moderate levels of perceived pain. General health was rated with a median score of 77 (54–83), and vitality had a slightly lower median of 70 (60–75). Social functioning showed a strong median of 88 (50–100), reflecting relatively preserved social interactions. The role emotional domain achieved a full score of 100 (100–100), suggesting no emotional role limitations in most patients. Mental health had a median score of 72 (56–85), indicating generally good mental well-being. The composite scores were also high, with the Physical Component Summary (PCS) at 84 (73–98) and the Mental Component Summary (MCS) at 83 (72–96). Overall, these results suggest that patients experienced a relatively good quality of life following EETS (Table 2).

Figure 1 shows a radar chart illustrating the distribution of quality-of-life domains based on SF-36 scores among patients following EETS. The chart demonstrates that the highest scores were observed in physical function, role physical, and role emotional, indicating minimal limitations in these areas. Domains such as mental health, social functioning, and bodily pain appear slightly lower, suggesting moderate well-being and some discomfort. Vitality and general health are positioned closer to the center of the chart, indicating these aspects were relatively more affected. Overall, the radar chart reflects the data in Table 2, indicating that patients experienced generally good quality of life after surgery, with variations across specific health domains.

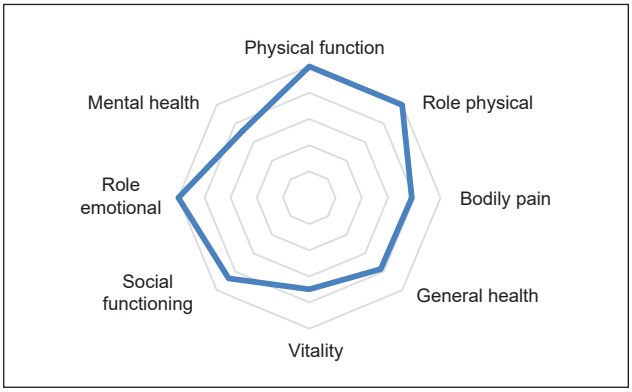

Figure 1. Radar Chart of Quality of Life Domains (SF-36) in Pituitary Adenoma Patients Following EETS (N = 90). Each axis represents one of the eight SF-36 domains on a scale of 0–100, where higher scores indicate better quality of life. The chart illustrates that physical functioning, role physical, and role emotional domains achieved the highest median scores, while vitality and mental health domains were relatively lower, reflecting greater impairment in energy and psychological well-being post-surgery.

Table 1. Characteristics of the study

Characteristic	N = 90
Age (years), median (SB)	48.11 (12.74)
Age category, n (%)	
<40 years	22 (24.4)
40-60 years	52 (57.8)
>61 years	16 (17.8)
Gender, n (%)	
Male	45 (50)
Female	45 (50)
Postoperative time range, n (%)	
<1 year	22 (24.4)
1-3 year	30 (33.3)
>3 year	38 (42.3)
Complaint duration, n (%)	
≤1 year	43 (47.8)
>1 years	47 (52.2)
Visual impairment, n (%)	
No	13 (14.4)
Yes	77 (85.6)
Hormone deficiency, n (%)	
No	6 (6.7)
Yes	84 (93.3)
Tumor size	
Microadenoma	4 (4.4)
Macroadenoma	86 (93.3)
Therapy	
EETS only	34 (37.8)
EETS + medicine	56 (62.2)
Comorbid, n (%)	
No	61 (67.8)
Yes	29 (32.2)
Paying Job, n (%)	
Jobless	37 (41.1)
Have Job	53 (58.9)

Table 2. Quality of life status of recipients after undergoing EETS

SF-36	Median (RIK)
Physical function	100 (85-100)
Role physical	100 (75-100)
Bodily pain	78 (55-99)
General health	77 (54-83)
Vitality	70 (60-75)
Social functioning	88 (50-100)
Role emotional	100 (100-100)
Mental health	72 (56-85)
PCS	84 (73-98)
MCS	83 (72-96)

Data were presented as median (interquartile range) for continuous variables and number (%) for categorical variables

Table 3 presents the bivariate analysis of SF-36 domain scores, indicating that gender was the only variable significantly associated with multiple aspects of quality of life. Male patients had significantly higher scores than female patients in the domains of role limitations due to physical problems ($p = 0.042$), vitality ($p = 0.049$), role limitations due to emotional problems ($p = 0.036$), mental health ($p = 0.007$), and the Mental Component Summary (MCS) score ($p = 0.005$). In contrast, other variables, including age, duration of illness, tumor size, visual field impairment, hormonal

Table 3. Bivariate analysis of subject characteristic associated with SF-36 quality of life domain

Variable	Physical function	Role physical	Bodily pain	General health	Vitality	Social functioning	Role emotional	Mental health	PCS	MCS
	Median (IQR)									
Age (years)										
<40	100 (90–100)	100 (94–100)	68 (45–100)	79 (53–83)	70 (60–75)	94 (47–100)	100 (100–100)	78 (55–88)	87 (70–95)	87 (62–89)
40–60	98 (80–100)	100 (75–100)	78 (58–100)	75 (63–83)	68 (60–75)	87 (55–100)	100 (100–100)	76 (56–84)	86 (74–94)	85 (68–89)
≥61	98 (63–100)	100 (56–100)	60 (38–95)	42 (73–82)	70 (58–79)	50 (38–100)	100 (100–100)	66 (54–82)	77 (53–94)	68 (63–89)
p-value	0.713	0.701	0.298	0.314	0.923	0.722	0.580	0.635	0.407	0.494
Gender										
Male	100 (93–100)	100 (100–100)	80 (59–100)	79 (67–83)	70 (65–80)	100 (58–100)	100 (100–100)	84 (60–88)	86 (74–95)	86 (69–90)
Female	95 (85–100)	100 (75–100)	70 (50–95)	75 (48–83)	65 (58–73)	63 (44–100)	100 (67–100)	68 (52–82)	83 (67–90)	73 (58–87)
p-value	0.069	**0.042***	0.201	0.542	**0.049***	0.093	**0.036***	**0.007***	0.102	**0.005***
Complaint duration (years)										
≤1	100 (90–100)	100 (75–100)	70 (55–100)	75 (54–83)	70 (60–75)	88 (50–100)	100 (100–100)	72 (60–84)	84 (72–95)	76 (67–89)
>1	95 (83–95)	100 (75–100)	78 (50–100)	79 (65–83)	70 (60–75)	88 (50–100)	100 (100–100)	76 (56–88)	86 (69–84)	84 (66–88)
p-value	0.382	0.818	0.952	0.606	0.780	0.912	0.521	0.762	0.877	0.903
Tumor size										
Microadenoma	95 (86–100)	100 (63–100)	85 (44–98)	83 (46–90)	68 (61–74)	56 (31–81)	100 (100–100)	62 (47–80)	90 (60–97)	73 (61–83)
Macroadenoma	100 (85–100)	100 (75–100)	74 (55–100)	75 (54–83)	70 (60–75)	88 (50–100)	100 (100–100)	74 (59–88)	84 (71–95)	84 (56–89)
p-value	1.000	0.887	0.872	0.336	0.932	0.317	0.551	0.289	0.489	0.443
Visual field impairment										
No	90 (53–100)	100 (38–100)	80 (56–100)	83 (50–83)	70 (60–78)	88 (56–100)	100 (83–100)	76 (56–90)	86 (51–92)	75 (64–89)
Yes	100 (90–100)	100 (75–100)	70 (55–100)	75 (58–83)	70 (60–75)	88 (50–100)	100 (100–100)	72 (58–84)	84 (72–95)	84 (67–89)
p-value	0.062	0.146	0.489	0.418	0.986	0.962	0.569	0.756	0.483	0.982
Hormonal deficiency										
No	100 (90–100)	88 (56–100)	75 (62–100)	60 (31–83)	65 (46–76)	56 (44–100)	83 (50–100)	52 (6–78)	76 (52–96)	84 (46–87)
Yes	88 (61–100)	100 (75–100)	77.5 (55–100)	77 (63–83)	70 (60–75)	88 (50–100)	100 (100–100)	74 (60–88)	84 (72–94)	84 (67–89)
p-value	0.231	0.342	0.685	0.468	0.418	0.377	**0.041***	0.050	0.523	0.122
Medical therapy										
EETS only	100 (81–100)	100 (75–100)	80 (60–100)	79 (54–83)	70 (60–75)	94 (50–100)	100 (100–100)	68 (55–84)	87 (60–93)	84 (67–89)
EETS + medication	97.5 (89–100)	100 (75–100)	70 (45–100)	75 (56–83)	65 (60–79)	88 (50–100)	100 (100–100)	74 (60–88)	84 (73–95)	82 (66–89)
p-value	0.903	0.470	0.252	0.571	0.814	0.444	0.940	0.336	0.603	0.809
Comorbidity										
No	100 (85–100)	100 (75–100)	70 (56–100)	75 (51–83)	65 (60–75)	88 (50–100)	100 (100–100)	72 (56–84)	84 (68–93)	83 (66–89)
Yes	100 (88–100)	100 (100–100)	80 (45–100)	79 (71–83)	70 (63–78)	88 (50–100)	100 (100–100)	76 (58–88)	85 (71–95)	86 (67–90)
p-value	0.671	0.115	0.923	0.242	0.309	0.986	0.238	0.633	0.422	0.457

*p <0.05 (statistically significant); [a] Kruskal-Wallis test; Mann-Whitney U test for all other variables. IQR = interquartile range.

deficiency, receipt of medical therapy and comorbidity status, did not show statistically significant associations with most quality-of-life domains (p >0.05).

Although hormonal deficiency was not significantly associated with most domains, it showed a statistically significant association with the emotional role domain (p = 0.041) and a borderline association with the mental health domain (p = 0.050). Meanwhile, none of the assessed variables were significantly associated with physical function, bodily pain, general health, social functioning, or the Physical Component Summary (PCS). Due to the limited number of variables meeting the p <0.250 criterion, multivariate analysis was not performed for most domains.

Table 4 presents the results of the multivariate linear regression analysis examining factors associated with each SF-36 quality-of-life domain. The analysis identified gender as a significant predictor across several domains. Specifically, male gender was significantly associated with higher scores in the role physical (β = 12.2; p = 0.032), vitality (β = 5.58; p = 0.045), emotional role (β = 11.8; p = 0.025),

Table 4. Multivariate analysis of subject characteristic associated with SF-36 quality of life domain

Domain	Significant predictors	β coefficient	*p*-value
Physical functioning	Visual impairment	-13.122	0.083
Role physical	Visual impairment	-14.885	0.101
Role emotional	Hormone deficiency	-17.857	0.123
Mental health	Gender	-9.067	**0.008**
	Hormone deficiency	-13.810	**0.043**
Mental Component Summary (MCS)	Hormone deficiency	-12.204	0.083

mental health (β = 10.6; p = 0.006), and mental component summary (MCS) domains (β = 8.24; p = 0.004).

In addition to gender, hormonal deficiency was a significant predictor in the emotional role domain, with patients with hormonal deficiency having higher scores (β = 10.5; p = 0.038) than those without.

These results indicate that male patients and those with hormonal deficiency tended to report better mental and emotional quality of life following EETS, as reflected by higher scores in the relevant SF-36 domains. No other variables showed statistically significant associations in the multivariate models for the remaining domains.

DISCUSSION

This study used the Indonesian version of the SF-36 questionnaire to assess the quality of life of patients following endoscopic endonasal transsphenoidal surgery (EETS). The Kolmogorov-Smirnov normality test indicated that the data were not normally distributed (p <0.05); therefore, bivariate analysis was conducted using the Mann-Whitney test to examine associations between quality-of-life domains and various clinical variables.

The analysis showed that in the domain of physical role limitations, only the variable gender was significantly associated (p = 0.042), with male subjects having a higher median score than females. This suggests that women are more likely to experience physical limitations in daily activities. Nevertheless, the overall median score was 100, indicating a potential ceiling effect. Previous studies by Johnson et al., and Vega-Beyhart et al., support the finding that EETS effectively improves motor function and reduces tumor mass effect, allowing patients to perform daily activities optimally.[6,22] In the domain of physical functioning, no variables showed statistically significant associations. However, gender, visual field impairment and hormonal deficiency had p-values <0.250 and were included in multivariate analysis. The median score was 100, indicating that most patients did not report significant physical limitations. In the domain of bodily pain, the median score was 78. No significant variables were identified; however, postoperative pain may be related to hormonal dysfunction such as TSH or ACTH deficiency. Previous studies, such as Uveilus et al., and Kołtowska-Häggström et al., have reported that hypothyroidism and cortisol deficiency may lead to muscle and joint pain, further exacerbating pain perception. Additionally, nerve damage and vitamin D deficiency after surgery may also contribute to pain.[23,24] In the domain of general health, the median score of 77 reflected patients' positive perception of their health status after surgery, although no variable showed a statistically significant association. Capatina et al., reported that improved hormonal function and reduced tumor-related symptoms contributed to a better perception of general health following treatment.[25] In the domain of vitality, only gender was significantly associated (p = 0.049), with males having a higher median score. This suggests that women experience fatigue more often. Kołtowska-Häggström et al., stated that hormonal imbalances can influence energy levels and overall vitality.[24] In the domain of social functioning, no variables were significantly associated, although high median scores indicated that patients did not experience significant social limitations. Nevertheless, Molitch noted that some patients may still experience social difficulties due to psychological burden or disease-related stigma.[26] In the domain of emotional role limitations, significant associations were found with gender (p = 0.036) and hormonal deficiency (p=0.041). Female patients and those without hormonal deficiency had lower scores. This suggests that emotional responses may be influenced by hormonal fluctuations, as discussed by Johnson et al.[6] In the mental health domain, gender (p = 0.007) and duration of symptoms (p = 0.021) were significantly associated. Male patients had higher scores than females, indicating better mental well-being. Findings from Banskota and Adamson and Zhang et al., are in line with these results, suggesting that pituitary hormonal imbalance may lead to depression, anxiety and sleep disturbances, negatively impacting mental health.[27,28]

In the multivariate analysis, linear regression was conducted for variables with p <0.250 from the bivariate analysis. In the physical functioning and physical role limitation domains, only visual field impairment remained in the final model, though it was not statistically significant. In the emotional role limitation domain, hormonal deficiency was the final variable retained, with a regression coefficient of B = –17.857 (p = 0.123). In the mental health domain, both gender (B = –9.067; p = 0.008) and hormonal deficiency (B = –13.810; p = 0.043) were statistically significant, underscoring the importance of gender and hormonal status in determining mental quality of life.

In the physical component summary (PCS), no variables were significantly associated, although the highest

median scores were observed in patients aged <40 years. This is consistent with findings by Vega-Beyhart et al., who reported that younger patients tended to have better physical recovery postoperatively.[22] Conversely, in the mental component summary (MCS), both gender and hormonal deficiency were significantly associated. Male subjects had a higher median score (86) than female subjects (73). Hormonal deficiency also had a near-significant *p*-value ($p = 0.050$), and in the final model, it was the only remaining variable ($p = 0.083$; B = –12.204). Hormonal imbalance after surgery may affect mood, cognition and self-perception, as described by Kołtowska-Häggström et al.[24] Overall, EETS is a safe and effective procedure in improving the quality of life for patients with pituitary adenoma. However, psychosocial factors, hormonal disturbances, and access to postoperative hormone therapy remain major challenges. Vega-Beyhart et al., and Salim et al., noted that financial constraints and lack of healthcare infrastructure can negatively affect long-term monitoring and treatment.[22,29] Both MCS and PCS are important indicators for evaluating patient quality of life. They are closely interrelated, with physical improvement supporting psychological well-being and vice versa. Capatina et al., emphasized that comprehensive management of both physical and mental aspects can provide the best outcomes for patients with pituitary adenoma.[25]

The present study was limited to demographic and clinical variables available through the institutional pituitary registry and did not assess financial or social determinants of postoperative QoL, which constitute recognized domains of unmet need in this patient population. Socioeconomic factors, including insurance status, income level and access to primary care, have been shown to significantly influence postoperative follow-up, medication adherence and long-term clinical outcomes following EETS for pituitary adenomas.[29,30] In resource-constrained settings such as Indonesia, the financial burden of long-term hormonal replacement therapy, including cortisol, thyroid hormone and gonadotropin preparations, is particularly pronounced, as coverage under the national health insurance scheme (JKN) remains incomplete for many endocrine conditions.[13,16] This concern is further supported by the broader evidence on financial toxicity in patients with endocrine and oncological conditions in low- and middle-income countries, which has been associated with catastrophic health expenditure, reduced treatment adherence, and progressive deterioration of psychosocial well-being.[31] Future prospective studies should incorporate validated instruments for financial toxicity and social support alongside the SF-36 to provide a more comprehensive characterization of QoL determinants in Indonesian pituitary adenoma patients undergoing long-term postoperative surveillance.

A salient finding of the present study is the more pronounced impairment of the mental component of QoL relative to the physical component in the postoperative period — a pattern that is consistent with emerging evidence in the pituitary adenoma literature. A 2024 systematic review by Castle-Kirszbaum and Goldschlager, encompassing studies of non-functioning pituitary adenomas using validated QoL instruments, demonstrated that patients exhibit significantly worse QoL than healthy controls across both mental and physical domains, with the mechanisms of impairment identified as multifactorial, including hypopituitarism, sleep dysfunction, pain, illness-related stigma, and treatment-related anxiety.[32] Multiple pathophysiological and psychosocial mechanisms may account for the disproportionate mental QoL burden observed in the present cohort. First, postoperative hypopituitarism, which affected 93.3% of study participants, leads to deficiencies of cortisol, thyroid hormone, and gonadotropins, all of which exert significant neuromodulatory effects on mood regulation, cognitive function and stress resilience. The attainment of biochemical equilibrium through hormonal replacement is a gradual process, often spanning several months, during which patients remain in a state of endocrine vulnerability that disproportionately affects psychological well-being.[22] Second, the chronic illness trajectory associated with pituitary adenoma, characterized by prolonged diagnostic delay, recurrent outpatient visits and indefinite pharmacological dependency, has been associated with heightened psychological distress, health anxiety and disease-related stigma that persist beyond the resolution of physical symptoms.[25,26] Third, long-term prospective data from Joustra et al., using multi-dimensional HRQoL assessment over a median follow-up of 8.5 years, demonstrated that psychological and social HRQoL domains exhibited the most sustained impairment and the slowest trajectory of recovery following EETS, corroborating the notion that mental health recovery is a more protracted process than physical restoration after pituitary surgery.[33] Collectively, these mechanisms underscore the need for structured, longitudinal psychosocial support as an integral component of postoperative care in patients with pituitary adenomas.

Based on these findings, several evidence-informed clinical and health policy strategies are proposed to improve postoperative QoL in these patients within the Indonesian healthcare context. First, routine psychological screening using validated instruments, such as the Hospital Anxiety and Depression Scale (HADS), should be systematically incorporated into the standard postoperative follow-up protocol.[34] Given that gender and hormonal deficiency were identified as independent predictors of reduced mental QoL in the present study, female patients and those with confirmed hypopituitarism represent high-priority subgroups for early psychological assessment and intervention. Second, implementation of multidisciplinary, psychosocially-oriented rehabilitation programs encompassing structured patient education regarding hormonal replacement regimens, peer support networks, and liaison with mental health specialists should be considered as standard postoperative care at pituitary centers. The systematic review by Castle-Kirszbaum and Goldschlager identified targeted management of disease-related anxiety

and hypopituitarism as evidence-based pathways to optimize QoL outcomes in pituitary adenoma patients.[32] Third, individualized monitoring of adequacy of hormonal replacement, with periodic biochemical reassessment during the early postoperative period, is warranted given the established association between hormonal deficiency and both emotional role limitations and mental QoL impairment, as demonstrated in this study. Fourth, at the health systems level, low socioeconomic status and inadequate insurance coverage have been identified as significant predictors of postoperative follow-up non-adherence and adverse clinical outcomes in pituitary adenoma patients.[29] Accordingly, advocacy for expanded insurance reimbursement of essential postoperative endocrine therapies under the national JKN scheme, as well as the development of a national, multicenter pituitary adenoma registry, would represent meaningful steps toward equitable and comprehensive long-term care. Collectively, these strategies reflect the imperative for a patient-centered, multidisciplinary approach that integrates biomedical, psychological and socioeconomic dimensions into the long-term postoperative management of patients with pituitary adenoma following EETS.

Several studies have explored the effects of pituitary tumors on patients' quality of life. For example, a study by Gil et al., reported that 74% of patients experienced improvement across all domains of quality of life after endoscopic endonasal transsphenoidal surgery (EETS), with emotional domains showing significantly greater improvements compared to preoperative status.[35] Another study by Karabatsou et al., using the SF-36 questionnaire in 54 patients, demonstrated improvement in all domains, except for the general health score, which showed only modest gains.[36] A Japanese study comparing patients' SF-36 scores before and at 1 and 6 months after EETS found that physical scores declined in the short term but improved thereafter, while mental scores showed continuous improvement postoperatively.[37]

CONCLUSION

The overall quality of life of patients after undergoing EETS surgery in this study was generally good, with higher scores observed in the physical component compared to the mental component. Assessment using the SF-36 instrument revealed that the physical functioning and emotional role limitations domains had the highest scores, indicating stable physical capabilities and emotional resilience. Conversely, lower scores were observed in the domains of vitality and mental health, reflecting reduced energy levels and psychological well-being among some patients. Despite these variations, both the physical and mental components remained within an acceptable range, suggesting a generally favorable postoperative quality of life.

Several factors were identified as influencing quality of life across the SF-36 domains. Gender was significantly associated with physical role limitations, vitality, emotional functioning, and mental health, while hormonal deficiency was linked to emotional functioning. Further multivariate analysis confirmed that both gender and hormonal deficiency had a significant impact on the mental health domain, with gender also influencing the overall Mental Component Summary (MCS) score. These findings highlight the importance of considering biological and psychosocial factors in the holistic management of patients with pituitary adenoma post-surgery.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
NRZ: Conceptualization, Investigation, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review and editing, Visualization. **TJET**: Conceptualization, Methodology, Validation, Supervision, Project administration, Writing – review and editing. **RP:** Methodology, Validation, Supervision, Writing – review and editing. **MA:** Supervision, Validation, Writing – review and editing, Project administration. **B, AGR,**: Validation, Writing – review and editing. **ERW**: Methodology, Validation, Supervision, Writing – review and editing. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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ORIGINAL ARTICLE

Bridging Gaps in Newborn Screening: A Comparative Study of Point-of-Care Testing Versus Traditional Reference Laboratory Method for Congenital Hypothyroidism

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Abstract

Objective. This study aimed to compare the reliability, agreement, and practical application (turnaround time) of a point-of-care testing (POCT) device using two different reagents versus the traditional reference laboratory method for thyroid-stimulating hormone (TSH) measurement in newborn congenital hypothyroidism screening.

Methodology. This prospective cross-sectional method-comparison study included 122 term newborns at a mother and child hospital in Surabaya, Indonesia. Heel-prick capillary blood samples were simultaneously analyzed using the Standard F-200 POCT device with two reagents (Group 1: n = 62, Standard™ F TSH-II; Group 2: n = 60, FastClear F TSH-II) and compared to the standard dried blood spot method (GSP® Neonatal hTSH, PerkinElmer) as reference. Analyses included Pearson and Spearman correlations, linear regression, Bland-Altman plots, intraclass correlation coefficient (ICC), Cohen's Kappa, and mean difference tests.

Results. Strong positive correlations were observed in both Group 1 (Pearson's r = 0.87, Spearman's ρ = 0.85; p <0.001) and Group 2 (Pearson's r = 0.88, Spearman's ρ = 0.91; p <0.001). Bland-Altman analysis showed minimal systematic bias with acceptable agreement between the two techniques. The ICC values indicated excellent reliability (Group 1: 0.89; Group 2: 0.91). High categorical agreement was confirmed by Cohen's Kappa values of 0.85 and 0.87 (p <0.001). No significant differences in mean TSH levels were found between the POCT and reference methods. The POCT turnaround time was 30 minutes, significantly shorter than the 15–22 days required for the traditional method.

Conclusion. POCT devices present a promising alternative to traditional reference screening method for congenital hypothyroidism.

Key words: congenital hypothyroidism, newborn, reproducibility of results, preventive medicine, health

INTRODUCTION

The global incidence of congenital hypothyroidism (CH) is estimated to be around 1:1400 to 1:1700 births, which is almost twice as high as the previously cited number of 1:2000 to 1:4000 births.[1,2] In Indonesia, the prevalence of congenital hypothyroidism is estimated to be higher than the global average, with approximately 1 in 2,513 births affected according to screening data from 14 provinces.[3] In Malang, East Java, Indonesia, the ratio was found to be 1:2736 births from 2000 to 2013.[4] These findings highlight the importance of regional and national screening programs for the early identification and therapy of the congenital hypothyroidism, which can prevent irreversible intellectual disability. The global success of newborn screening programs has yet to be fully realized in Indonesia. The coverage rate of CH screening in Indonesia remains notably low, highlighting significant opportunities for improvement and expansion.[5–7] The implementation of newborn screening in Indonesia faces several challenges, including lengthy procedures from sample collection to result release and a shortage of facilities. The disparity in the availability and accessibility of screening facilities has a significant impact on newborn screening coverage, leading to notable differences across provinces. Urban regions like Bali achieved a substantially higher coverage rate (40.54%)

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compared to remote rural areas such as South Papua, which recorded only 0.02%. Additional obstacles include limited availability of filter paper, insufficient training for healthcare workers, and family rejection due to a lack of understanding about the importance of the examination.[6,8–10]

Congenital hypothyroidism can lead to severe developmental impairment if not promptly treated.[11,12] Early detection and appropriate initial therapy are crucial for the effective management and prevention of complications.[13–15] Most newborn screening programs rely on blood spot thyroid-stimulating hormone (TSH) tests, which are effective but may not detect central congenital hypothyroidism. Some programs use both T4 and TSH measurements, but these methods can be more complex and less cost-effective.[16,17] These advanced methods require specialized expertise and equipment, making it necessary to perform the procedure in a reference laboratory. POCT devices could potentially enhance the CH process by providing rapid and reliable results, enabling early detection and treatment.[18]

POCT devices for thyroid function tests, including TSH and T4 measurements, are technically feasible.[18] Although POCT has been widely developed and applied in various clinical settings, its potential role in newborn screening for CH is currently being explored. A recent study has demonstrated a strong correlation between TSH POCT devices and conventional immunoassay analyzer as the reference method across multiple sample types, including serum, whole blood and finger-prick blood, with satisfactory agreement (Cohen's kappa = 0.7-0.9) and a very strong correlation (r = 0.90-0.93).[19]

Although POCT devices hold promise for the early detection of CH, their implementation requires careful consideration of reliability, technical feasibility, and integration with existing healthcare systems. The reliability of these tests must be comparable to laboratory-based tests to ensure effective screening. Early detection of CH using POCT is expected to significantly enhance outcomes and prevent long-term developmental impairment by providing an early detection and timely treatment. Moreover, this approach is anticipated to achieve broader screening coverage, particularly in rural and remote areas where current coverage rates remain very low. Therefore, the primary objective of this research was to evaluate the analytical agreement, reliability, and practical efficiency (turnaround time) of a POCT device, utilizing two distinct reagents by comparing it against the conventional reference laboratory technique for neonatal TSH screening.

METHODOLOGY

Study population

The present study was conducted at a mother and child hospital in Surabaya, Indonesia involving 122 newborns who underwent TSH testing as part of a congenital hypothyroidism screening program. We included newborns whose parents provided informed consent, those born at term (gestational age ≥37 weeks), and those in stable condition at the time of sampling. We excluded premature infants (gestational age <37 weeks), infants in critical condition at the time of sampling, and newborns whose mothers had known thyroid disease. This approach ensured that our study population was representative of healthy, term newborns without potential confounding factors related to maternal thyroid conditions.

Participants were recruited using consecutive sampling. All eligible term newborns whose parents provided informed consent during the study period were included sequentially until the target sample size was reached. This sampling technique was considered appropriate for this method-comparison study aimed at evaluating agreement between two laboratory techniques.

Study design

This was a prospective, cross-sectional, single-center method-comparison study conducted from May to August 2024. The study aimed to compare TSH measurements obtained using a POCT device against the traditional reference laboratory method for newborn congenital hypothyroidism screening. Each participant underwent simultaneous TSH testing with both the POCT device (Standard F-200) and the standard dried blood spot reference method (GSP® Neonatal hTSH, PerkinElmer). This design allowed direct comparison of the two methods on the same blood samples collected at the same time point, enabling evaluation of agreement, reliability, and practical application (turnaround time) without requiring long-term follow-up.

Sample collection

Capillary blood samples were obtained by heel prick using a sterile lancet. For the POCT device, approximately 35 μL of capillary blood was collected directly into a 0.5 mL EDTA tube. For the traditional reference method, additional capillary blood was spotted onto filter paper cards to create dried blood spots (DBS). The dried blood spot samples were then sent to the referral laboratory for analysis using the standard national protocol for congenital hypothyroidism screening in Indonesia.

In Indonesia, the traditional newborn screening method for congenital hypothyroidism involves initial screening with thyroid-stimulating hormone (TSH) from dried blood spots, followed by confirmatory testing with venous blood sampling if the screening result is abnormal. However, in this study, only the screening phase was compared.

TSH measurement

TSH levels were measured using two devices:

1. Reference laboratory device: The reference laboratory utilized the GSP® Neonatal hTSH (PerkinElmer,

Wallac Oy, Finland) which is the standard for congenital hypothyroidism screening in Indonesia to measure the TSH level of the newborn screening sample. All samples were processed according to the manufacturer's recommendations.

2. POCT device: This study utilized the Standard F-200 (SD Biosensor, South Korea) to measure the TSH level in the newborn screening sample. The TSH measurements using two different reagents, i.e. Standard™ F TSH-II (SD Biosensor, Inc, South Korea) and FastClear F TSH-II (Standard Biosensor Healthcare, Indonesia). EDTA samples were processed according to the manufacturer's recommendations.

We utilized the GSP® Neonatal hTSH PerkinElmer device as the reference which is the national standardized device for congenital hypothyroid screening in Indonesia. This choice ensured a consistent and standardized reference for method comparison. Dried blood spot samples were analyzed according to the manufacturer's protocol at the referral laboratory. The Standard F-200, which was the evaluated POCT device, represents the only available POCT device for TSH levels with lower limit of detection and readily accessible reagents in Indonesia, further facilitating its potential use in clinical settings. These decisions were exclusively driven by the accessibility and practicality of these devices within the local healthcare setting. There are no conflicts of interest regarding the point-of-care devices examined or the gold standard employed in this study.

Two different POCT reagents (Standard™ F TSH-II for Group 1 and FastClear F TSH-II for Group 2) were used to evaluate the performance and consistency of the Standard F-200 POCT platform with its commercially available reagent options in the Indonesian setting. This approach was chosen to assess whether the POCT device maintains reliable results across different reagent formulations, rather than to perform a direct head-to-head comparison between the two reagents.

Blood samples in the form of dried blood spots were analyzed using the reference device, while 35μL of samples in EDTA tubes were measured with the POCT device. TSH level measurements using the reference device were conducted over more than one week depending on the work schedule in the referral laboratory, while POCT was performed within 30 minutes post-collection at the laboratory of the hospital sampling site.

Classification of respondents

TSH examination results were divided into two groups:

Group 1: Comparing TSH results from 62 infant samples using POCT Standard™ F TSH-II (pTSH1) and the reference device (rTSH1)

Group 2: Comparing TSH results from 60 infant samples using POCT FastClear F TSH-II (pTSH2) and the reference device (rTSH2)

The division of subjects into two groups was based on the use of two different POCT reagents. This approach allowed the evaluation of the performance and reliability of each reagent separately, ensuring a comprehensive assessment of the POCT devices.

The sample size of this method-comparison study was planned according to recommendations for agreement studies involving correlation, ICC, and Bland-Altman analysis, which generally suggest a minimum of 100 subjects. We enrolled 122 term newborns (Group 1: n = 62; Group 2: n = 60) through consecutive sampling. This sample size exceeds the recommended minimum and provides >90% power to detect a correlation coefficient of r ≥0.80 at α = 0.05. A conservative paired t-test calculation indicated a minimum of 34 samples; however, the larger sample was chosen to ensure more stable and reliable estimates of agreement.

Ethical clearance

Ethical approval was obtained from the Faculty of Nursing, Universitas Airlangga (No. 3087-KEPK).

Statistical analysis

The statistical analysis was performed using SPSS version 27. Numerical data were reported as means and standard deviations or medians with ranges. Categorical data were expressed as percentages. Normality test was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The TSH examination results were not normally distributed, thus the data were log-transformed to achieve normality.

Pearson's correlation coefficient and Spearman's rank correlation were used to evaluate the strength of the relationship between POCT and reference TSH measurements. Linear regression analysis was performed to assess the predictive relationship between the two methods. Agreement and bias between the methods were further examined using Bland-Altman analysis. Reliability was assessed using the Intraclass Correlation Coefficient (ICC) with a two-way mixed-effects model. Agreement in categorical classification was evaluated using Cohen's Kappa statistic. Mean differences between POCT and reference TSH levels were tested using the paired t-test for normally distributed data or the Wilcoxon rank-sum test for non-normally distributed data. A two-sided p-value <0.05 was considered statistically significant. No adjustment for multiple testing was applied, as all analyses were pre-specified and complementary to the study objectives of evaluating reliability, agreement, and practical application between the two methods.

No adjustment for confounding variables was performed. This was a method-comparison study in which each participant served as their own control, with POCT and reference TSH measurements obtained from the same blood sample collected at the same time point. Thus, confounding was inherently minimized by the paired study design.

Data processing

There were no missing data in this study. All 122 participants had complete TSH results from both POCT and reference methods. Data were checked for completeness and implausible values prior to analysis. No implausible values were detected, and all data were retained for statistical analysis.

Analysis process

The analysis process includes these following steps.

1. Correlation Analysis: The correlation between TSH measurements obtained using POCT and reference methods was assessed first, revealing a strong correlation.
2. Regression Analysis: Following the correlation analysis, a regression analysis was conducted to establish the relationship between TSH measurements obtained using the two methods. (Supplementary File)

pTSH1 = 0.05+0.29*TSH result POCT Standard™ F TSH-II

pTSH2 = 0.266+0.27*TSH result POCT FastClear TSH-II

3. Assessment of Agreement and Reliability: Bland-Altman analysis was used to evaluate systematic bias and limits of agreement. ICC and Cohen's Kappa were calculated to assess agreement and reliability of POCT device compared to reference method.
4. Mean Difference Check: The mean difference between the TSH levels obtained from the reference method and those predicted by the regression model using the POCT results was evaluated using paired t-tests or Wilcoxon ranked-sum test, depending on the data normality, with a significance level set at p <0.05.

RESULTS

Characteristics of the study subjects

This study included 122 participants evenly distributed into two groups (Table 1). Group 1 comprised 62 participants with a male predominance (54.8%), while Group 2 included 60 participants (51.7% male). None of the participants were twins, and the majority were delivered via sectio caesarea in both groups. The median age at sampling for both groups was 48 hours. TSH levels showed a median of 1.53 mIU/L for pTSH1 and 1.40 mIU/L for rTSH1, whereas Group 2 exhibited medians of 1.64 mIU/L for pTSH2 and 1.65 mIU/L for rTSH2.

Table 1. Characteristics of the study participants according to group

Characteristics	Group 1 (n = 62)	Group 2 (n = 60)
Gender		
Male	34 (54.8%)	31 (51.7%)
Female	28 (45.2%)	29 (48.3%)
Mode of birth		
Spontaneous labor	13 (21%)	13 (21.7%)
Sectio caesarea	49 (79%)	47 (78.3%)
Age at sampling (hours)	45.6 ± 6.2	45.8 ± 6.1
TSH levels		
pTSH (mIU/L)	1.53 (0.29-4.70)	1.64 (0.54-6.15)
rTSH (mIU/L)	1.40 (0.66-6.20)	1.65 (0.66-5.30)
Turnaround time		
pTSH (min)	30 min	30 min
rTSH (days)	22 days	15 days

pTSH = POCT TSH level (Group 1: Standard™ F TSH-II reagent; Group 2: FastClear F TSH-II reagent)
rTSH = Reference method TSH level

Correlation between TSH measurements obtained using POCT and the reference device

The data presented in Figure 1 depicts the relationship between the levels of pTSH1 and rTSH1 results, as analyzed using linear regression. The Pearson correlation coefficient of 0.87 (p <0.001) indicates a strong, statistically significant positive linear association between the two variables. This suggests that as pTSH1 levels increase, the corresponding rTSH1 results tend to increase in a predictable manner. The Spearman correlation coefficient of 0.85 (p <0.001) further corroborates the strong monotonic relationship between the two variables, irrespective of the specific functional form of the association. This nonparametric analysis complements the linear regression findings, providing additional confidence in the robust relationship between TSH results of the POCT TSH II and the corresponding filter paper.

The high coefficients of determination, with an R-squared value of 0.748, signify that approximately 75% of the variation in rTSH1 results can be explained by the linear model, with changes in pTSH1 group levels. This suggests that the TSH result from the POCT i.e., pTSH1 group result is a strong predictor of the filter paper rTSH1 outcome, warranting further investigation into the underlying mechanisms and potential applications of this relationship.

The other presented scatterplot and associated correlation analyses depict a strong, statistically significant relationship between POCT pTSH2 level and filter paper rTSH2 results (Figure 1). The Pearson correlation coefficient of 0.88 (p <0.001) indicates a robust positive linear association between the two variables, suggesting that as pTSH2 level increases, the corresponding filter paper rTSH2 result tends to rise in a predictable manner.

Furthermore, the Spearman correlation coefficient of 0.91 (p <0.001) confirms a strong monotonic relationship between the variables, regardless of the specific functional form of the association. This nonparametric analysis complements the linear regression findings, providing additional confidence in the reliable relationship between POCT pTSH2 levels and reference device rTSH2 results.

The high coefficient of determination, with an R-squared value of 0.776, indicates that approximately 78% of the variation in rTSH2 reference device results can be explained

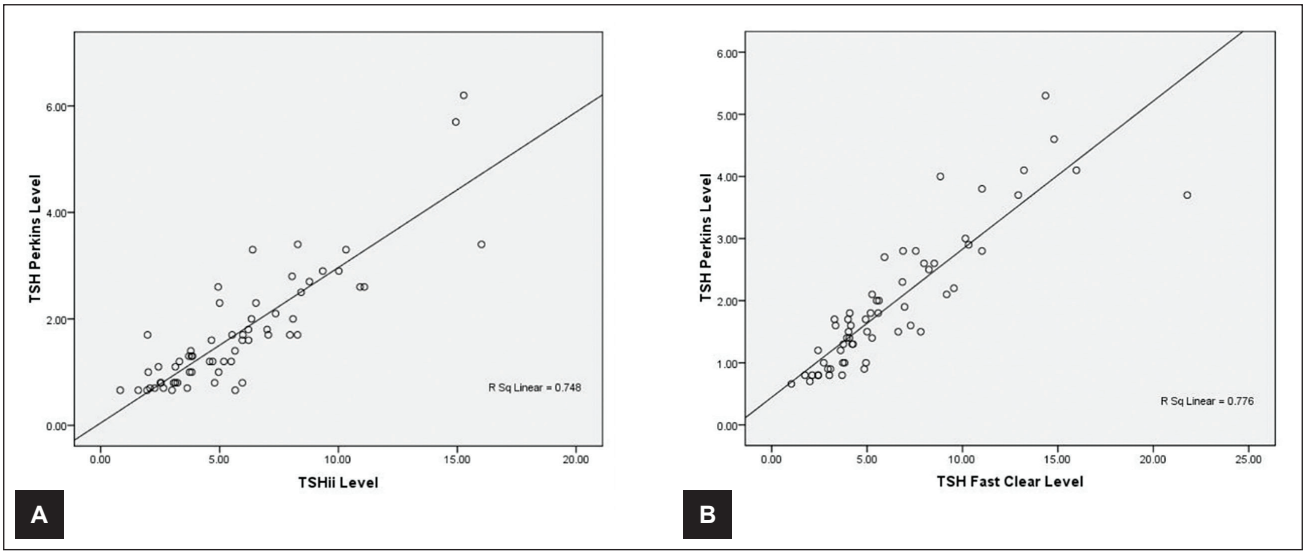

Figure 1. Linear regression analysis of TSH measurements between the POCT device and the traditional reference method. **(A)** Group 1 (using Standard™ F TSH-II reagent) demonstrated a strong positive correlation (Pearson's r = 0.87, *p* <0.001; Spearman's ρ = 0.85, *p* <0.001; R^2 = 0.748). **(B)** Group 2 (using FastClear F TSH-II reagent) showed a similarly robust correlation (Pearson's r = 0.88, *p* <0.001; Spearman's ρ = 0.91, *p* <0.001; R^2 = 0.776). Both panels indicate that POCT TSH levels are strong predictors of the reference laboratory outcomes across different reagent formulations.

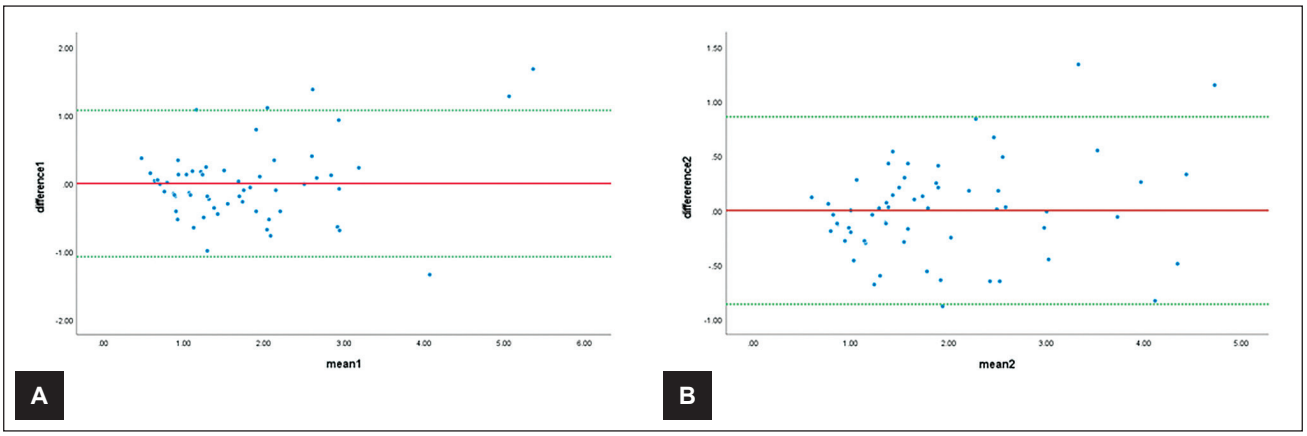

Figure 2. Bland-Altman plots assessing the agreement between the POCT device and the reference method for TSH measurements. **(A)** Group 1 (Standard™ F TSH-II reagent) demonstrates minimal systematic bias with a mean difference of −0.0013 mIU/L. **(B)** Group 2 (FastClear F TSH-II reagent) shows comparable agreement with a mean difference of −0.0003 mIU/L. In both plots, the solid red line represents the mean difference (bias), and the green lines indicate the 95% limits of agreement. Most data points are randomly scattered around the mean difference line within the limits of agreement, indicating good overall agreement, although a slight increase in variability is observed at higher TSH concentrations (>4.0 mIU/L).

by the linear model, with changes in POCT pTSH2 level as the primary predictor. This suggests that the pTSH2 level is a strong and reliable indicator of the rTSH2 reference device level, warranting further investigation into the potential clinical applications and implications of this relationship.

Agreement and reliability statistics

The agreement between the POCT and reference method was evaluated using Bland-Altman analysis, intraclass correlation coefficient (ICC), and Cohen's kappa, stratified by group. Bland-Altman analysis in Figure 2 revealed negligible systematic bias in both groups, with a mean difference of −0.0013 in Group 1 and −0.0003 in Group 2. The 95% limits of agreement were −1.077 to 1.074 for Group 1 and −0.861 to 0.861 for Group 2. Although a mild increase in variability was observed at higher mean values, the majority of data points were randomly distributed around the mean difference line, indicating good overall agreement between the POCT device and the reference method.

As summarized in Table 2, the intraclass correlation coefficient also demonstrated excellent reliability in both groups (Group 1: 0.89 [95% CI: 0.84–0.93]; Group 2: 0.91 [95% CI: 0.86–0.94]). These ICC values indicate excellent reliability and consistency between the POCT devices and the reference method. Cohen's kappa further confirmed strong agreement (Group 1: 0.85, *p* <0.001; Group 2: 0.87, *p* <0.001).

Table 2. Reliability and agreement statistics between POCT and reference method

Group	ICC (95% CI)	Cohen's Kappa (*p*-value)	Mean difference	Lower limit of agreement	Upper limit of agreement
Group 1	0.89 (0.84-0.93)	0.85 (p <0.001)	-0.0013	-1.077	1.074
Group 2	0.91 (0.86-0.94)	0.87 (p <0.001)	-0.0003	-0.861	0.861

Group 2 consistently showed slightly better agreement and reliability compared with Group 1 across all statistical parameters. These Kappa values indicate strong agreement between the POCT devices and the reference method in classifying TSH levels.

Mean difference between TSH measurements from the POCTs and reference method

The analysis of mean difference of pTSH1 and rTSH1 in Group 1 was conducted using the Wilcoxon rank-sum test, chosen for its suitability in handling non-normal distributions, even after logarithmic transformation. The results revealed that the median of pTSH1 level was 1.53, while the median for the rTSH1 assay was 1.40. Importantly, the Wilcoxon rank-sum test showed no statistically significant difference between the TSH levels obtained from the two assays, with a p-value of 0.530. These findings suggest that the POCT assay provides results that are comparable to those of the reference TSH assay in Group 1 results. The use of the Wilcoxon rank-sum test, a robust non-parametric approach, was appropriate given the non-normal distribution of the TSH Group 1 data, thereby enhancing the validity and reliability of the statistical conclusions drawn from this analysis.

Meanwhile, the mean difference of pTSH2 and rTSH2 in Group 2 was conducted using the paired t-test because it was distributed normally after logarithmic transformation. The results revealed that the median of pTSH2 level for the new pTSH2 (ln-pTSH2) was 0.49, while the median for the established rTSH2 assay (ln-rTSH2) was 0.50. The paired t-test showed no statistically significant difference between the TSH levels obtained from the two assays (p = 0.41). These findings suggest that the TSH examination of the POCT assay results is comparable to the result of the reference device in Group 2.

DISCUSSION

In Indonesia, the CH screening program has been in place for over a decade, but the number of infants undergoing congenital hypothyroid screening remains low, and the results are still not timely. One of the challenges noted is the absence of effective delivery systems, which results in delays in shipment and CH screening test results. In Indonesia, the government has established 11 referral laboratories for congenital hypothyroid testing.[5] However, this number is still considered insufficient. For example, the current referral laboratory for CH screening examination in East Java is only available at the Dr. Soetomo Hospital. This situation puts a great burden on this referral laboratory considering that the birth rate in East Java in 2020 was approximately 500,000 births per year.[20]

The infant birth rate in Indonesia is approximately 4.5 million births per year.[21] The Ministry of Health targets about 463,000 samples or equivalent to 10% of newborns for congenital hypothyroid screening. At the beginning of 2015, the number of sample screening achievements was less than 2%. However, this number is currently better, where, in 2023, the number of achievements is 368,552 newborns, or about 8.26% of births.[2] Looking at the number of births, this achievement is still very far when compared to other Southeast Asian countries such as Malaysia, which has reached 95%, Singapore >99%, Thailand 94.1% and the Philippines 65%.[22] This situation provides a basis for trying to find alternatives to the number of achievements given the importance of newborn screening to obtain a golden generation.

In this study, out of the 122 patient samples examined, no results exceeded the normal range for congenital hypothyroidism. This outcome is unsurprising given the rare incidence of congenital hypothyroidism in this population.[23,24] Indeed, it is important to emphasize that this study was designed as a method-comparison study aimed at evaluating the analytical performance, reliability, agreement, and practical application (particularly turnaround time) of the POCT device compared with the standard reference laboratory method. Because no newborns with elevated TSH levels were identified in this cohort, this study does not assess diagnostic accuracy parameters such as sensitivity and specificity. The findings should therefore be interpreted within the context of method agreement and reliability rather than clinical diagnostic performance.

The average waiting time for POCT examination was faster than that of the traditional reference method. The average turn-around time for the POCT TSH results was 30 minutes compared to 15-22 days for the traditional referral method. Early detection followed by early appropriate therapy are critical for successful CH management. Delays in results will affect the provision of therapy in patients with congenital hypothyroidism. The therapy of CH is recommended to be started at the time the baby reaches 2 weeks old.[25,26] The utilization of POCT in CH screening can potentially provide faster results. Nevertheless, the confirmatory examination using a vein blood sample is still required after screening, which is the traditional examination pathway. The earlier the screening results are obtained, the earlier therapy could be started.

In this study, there was a strong positive linear relationship between TSH levels measured using the POCT and the reference device. This strong relationship was observed in both groups regardless of the type of cartridge used. Two different POCT reagents were used to examine the robustness and consistency of the same POCT platform (Standard F-200) across its available reagent options in Indonesia. The use of both reagents was not intended as a direct comparison between them, but to evaluate whether the device performs reliably with different reagent batches. A strong linear monotonic relationship was also obtained in the Pearson and Spearman tests, which gave confidence in the strong association between the two results in both groups 1 and 2. The difference test between TSH results using the POCT device and the reference device also did not yield significant results in both groups. This clearly demonstrated that the TSH results generated by the POCT device were comparable to those obtained via the traditional reference method. These results highlight the potential of POCT devices as an alternative to support the expansion of CH screening coverage in Indonesia as well as warranting further investigation into the potential clinical applications and implications of this relationship.

It has to be mentioned that a mild increase in variability was observed at higher mean TSH values. Possible explanations include the high-dose hook effect, in which extremely high analyte concentrations may saturate the antibodies, leading to falsely altered signal intensity.[19] Other contributing factors include differences in sample matrix and variations in antibody affinity between the two methods. These observations highlight the importance of confirmatory testing with the reference laboratory method when POCT results approach or exceed clinical decision limits, particularly in newborn congenital hypothyroidism screening.[27]

Globally, POCT devices have been widely used in terms of screening and diagnosis, for example in early detection of sickle cell disease and neonatal hypoglycemia in infants.[28–31] The utilization of POCT is especially promising in an archipelago area, such as Indonesia, where access to healthcare often involves lengthy and challenging travel across vast oceans and rugged terrains. POCT offers an excellent alternative to enhance CH screening coverage in such geographically dispersed regions and limited resource settings.

The TSH results in the POCT device and the reference device have the same unit value conversion. However, in this study, the results obtained from the POCT device required regression analysis to determine the relationship between the two methods. This can be due to several reasons including the difference in the methods, sensors, and antibodies used in the examination process on both devices.[19] The discrepancies may also be attributed to variations in the light intensity conversion algorithms used by the devices.

We acknowledge several limitations in our study that should be considered when interpreting the results. Firstly, the sample size of newborns, while sufficient for initial comparisons, may not be large enough to capture the full spectrum of congenital hypothyroidism cases, particularly those with abnormal TSH levels. Future studies with larger sample sizes are necessary to validate our findings and improve the generalizability of the results. Secondly, none of the subjects in our study exhibited TSH levels outside the normal range. This study was designed as a method-comparison study to evaluate the analytical performance, reliability, agreement, and practical application of the POCT device compared with the traditional reference laboratory method, rather than to determine its diagnostic accuracy, including sensitivity and specificity. Further research including subjects with confirmed CH is required to address this gap. Thirdly, the study was conducted at a single hospital in Surabaya, Indonesia. This may limit the generalizability of the findings to other regions or healthcare settings. Multi-center studies are recommended to validate the applicability of POCT devices across diverse populations and healthcare environments.

Despite these limitations, our study provides valuable insights into the potential of POCT devices as a feasible and promising alternative to traditional CH screening methods. We recommend further research to address these limitations and to explore the long-term benefits of POCT in newborn screening programs.

CONCLUSION

The current state of CH screening achievements in Indonesia requires prompt attention. POCT devices present a feasible and promising alternative to the traditional reference screening device for congenital hypothyroidism. Further studies need to be conducted to evaluate the sensitivity and specificity of the POCT by involving patients outside the normal range with a larger sample size and a wider population sample.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
EI: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Supervision, Funding acquisition; **RYR:** Conceptualization, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Project administration; **FNF:** Conceptualization, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing; **PAS:** Writing – review and editing, Visualization, Project administration; **ENN:** Methodology, Formal analysis, Writing – original draft, Visualization; **MNH:** Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft preparation, Writing – review and editing; **FAA:** Data curation, Writing – review and editing.

Data Availability Statement

The data that support the findings of this study can be provided by the corresponding author upon reasonable request.

Author Disclosure

The authors declared no conflict of interest.

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ORIGINAL ARTICLE

Knowledge, Attitudes and Practices of Healthcare Workers regarding Obesity: A Survey at a Tertiary Hospital in Vietnam

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Abstract

Background. The global prevalence of obesity has tripled over the past four decades, with an estimated one-third of the world's population currently classified as overweight or obese. Obesity is recognized as one of the most urgent global public health challenges, with increasing rates observed in both developed and developing countries. In Southeast Asia, the burden of obesity is particularly concerning due to the coexistence of undernutrition and overnutrition, creating a double burden of disease. Healthcare workers play a critical role in the prevention, early detection and management of obesity. However, many healthcare workers lack updated knowledge on obesity, which is often associated with insufficient or inappropriate management.

Objective. To assess the knowledge, attitudes, and practices (KAP) of healthcare workers toward obesity management at a tertiary hospital in Ho Chi Minh City, Vietnam, and to identify associated barriers and interprofessional differences.

Methodology. A cross-sectional study was conducted among 232 healthcare workers using a 22-item structured, self-administered questionnaire. The survey evaluated knowledge of obesity risk factors and treatments, attitudes toward patient responsibility and stigma, and clinical practices such as screening, counseling and referrals. Associations between professional roles and responses were analyzed using Chi-square and Fisher's exact tests.

Results. Among 232 participants (37.5% were physicians and 62.5% were non-physician healthcare workers), only 63.8% [95% CI: 57.3-70.3%] recognized obesity as a chronic disease and fewer than half were aware of approved pharmacotherapies. While most workers believed they could assist patients, a significant majority (79.7% [95% CI: 75.0–84.9%]) attributed weight loss primarily to patient responsibility, indicating widespread implicit weight bias. Furthermore, physicians reported significantly higher odds of inadequate knowledge of weight management compared to other staff (OR = 4.5, 95% CI: 2.1–9.5).

Conclusion. Significant knowledge gaps and implicit weight biases persist among healthcare workers regarding obesity management. Addressing these educational and systemic barriers through specialized training and multidisciplinary care models in Vietnam can provide a crucial framework for improving obesity management across rapidly urbanizing Southeast Asian nations facing similar metabolic crises.

Key words: obesity, healthcare worker, knowledge, attitudes, practice, Vietnam

INTRODUCTION

Obesity has emerged as one of the most pressing global public health crises of the 21st century. The global prevalence of obesity has tripled over the past four decades, with an estimated one-third of the world's population currently classified as overweight or obese.[1] According to the updated World Health Organization (WHO) 2024 report, the global obesity rate has doubled between 1990 and 2022. By 2022, approximately 46% of the global adult population was classified as overweight and 16% as obese.[2] In Asia, including Southeast Asia, the prevalence of obesity is projected to increase by 10%–20%.[3]

Despite this escalating crisis, a significant gap in clinical practice remains. Healthcare workers (HCWs) play a critical role in the prevention, early detection and management of obesity; however, many lack updated knowledge and formal training, potentially resulting in insufficient or inappropriate care.[4]

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In Southeast Asia, the burden is particularly concerning due to the coexistence of undernutrition and overnutrition, creating a double burden of disease.[5] Vietnam's rapid urbanization, marked by changes in dietary patterns and lifestyle behaviors and reductions in physical activity, has led to a sharp rise in overweight and obesity rates.[6,7] Notably, higher obesity prevalence rates and metabolic risks are observed in this population when applying the Asian-specific BMI cutoffs (overweight ≥23 kg/m², obesity ≥25 kg/m²) compared to the standard WHO classification.[8-11] In 2022, the Vietnamese Ministry of Health issued national guidelines on the diagnosis and treatment of obesity,[12] reflecting growing attention from health authorities. However, obesity is still underrecognized in both society and the healthcare sector. Many healthcare workers lack updated knowledge on obesity, which may be linked to insufficient or inappropriate management.

Although previous studies have examined patient perceptions of obesity,[13] there is little research that has focused on Healthcare workers. Therefore, assessing the knowledge, attitudes, and practices (KAP) of healthcare workers is essential. Such evaluation could inform strategies to improve professional training, reshape attitudes and enhance obesity management, thereby contributing to population-level efforts to reduce overweight and obesity rates. Based on these objectives, we conducted this study to investigate the healthcare workers' knowledge, attitudes and practices regarding obesity.

METHODOLOGY

Study design

This was a descriptive cross-sectional, multi-departmental study conducted at Le Van Thinh Hospital.

Study population

Sample size estimation

The minimum required sample size was estimated using the formula for a single population proportion:

$$n = Z^2_{[1-(\alpha/2)]} \frac{p(1-p)}{d^2}$$

We set the confidence level at 95% (Z = 1.96) and the margin of error at 5% (d = 0.05). The expected proportion (p) was set to 0.84, based on a previous regional study across South and Southeast Asia in which 84% of healthcare workers correctly recognized obesity as a chronic disease.[14] This calculation yielded a minimum sample size of 207. Our final recruited sample of 232 healthcare workers exceeded this requirement, ensuring adequate statistical power to address the research objectives and account for any potential nonresponse or incomplete data.

Participants were recruited using convenience sampling between June and September 2024. The research team introduced the study objectives and invited clinical staff to participate during regular departmental meetings. Inclusion criteria comprised clinical healthcare workers (physicians, nurses, midwives and technicians) actively working at the hospital for at least three months and provided written informed consent. Exclusion criteria included non-clinical administrative staff, individuals who declined to participate and those who submitted incomplete questionnaires. A total of 232 fully completed questionnaires were collected and retained for analysis. A paper-based questionnaire was administered to clinical staff during regular departmental meetings. The completion process, supervised by the research team to ensure data integrity, took approximately 15 minutes per participant.

Questionnaire development and validation

The 22-item questionnaire was developed based on the 2022 National Guidelines for the Diagnosis and Management of Obesity released by the Vietnamese Ministry of Health and adapted from previously validated KAP instruments reported in the recent literature. Face and content validity were evaluated by an expert panel comprising two endocrinologists and one public health specialist. Following expert revisions, the instrument was pilot-tested on a purposive sample of 20 healthcare workers (including physicians and nurses) to assess clarity, cultural appropriateness and completion time. To avoid prior exposure bias, these pilot participants were excluded from the final study sample. The internal consistency of the finalized questionnaire was evaluated using the full study sample (N = 232), demonstrating excellent reliability with an overall Cronbach's alpha of 0.850. The domain-specific alpha coefficients were 0.819 for Knowledge, 0.689 for Attitudes, and 0.646 for Practices.

Definition of outcomes and exposures

The primary outcomes were the proportions of healthcare workers demonstrating adequate knowledge, positive attitudes and appropriate clinical practices regarding obesity management. Secondary outcomes included the frequency of reported barriers to obesity management and the interprofessional differences in KAP domains.

Composite scores were not generated; KAP domains were analyzed individually. Knowledge items were categorized based on the Vietnamese Ministry of Health Guidelines. Attitudes were evaluated as positive if participants agreed with evidence-based statements regarding obesity care. Practices were assessed based on the appropriateness of clinical recommendations (e.g., lifestyle modifications, pharmacotherapy or referral) across different patient body mass index (BMI) and comorbidity profiles.

The primary exposures evaluated for their association with KAP outcomes were participants' professional roles

(categorized as physicians versus other healthcare workers, including nurses, midwives and technicians), BMI and years of medical experience.

Data analysis

Data completeness was verified prior to entry. Questionnaires with missing responses were excluded. Only fully completed forms were retained for the final analysis, ensuring no missing data within the analyzed dataset.

Data were entered using Epidata version 3.1 and analyzed with SPSS version 26.0. Before inferential analysis, the normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed data were summarized using means and standard deviations, whereas non-normally distributed data were presented as medians and interquartile ranges (IQR). Descriptive statistics were used to present the data as percentages.

Associations between categorical variables were evaluated using the Pearson Chi-square test. The assumptions for Chi-square testing were verified prior to interpretation; Fisher's exact test was used where more than 20% of expected cell frequencies were less than 5. The threshold for statistical significance was defined as a two-tailed *p*-value of <0.05. To adjust for potential confounders, stratified analyses by participant BMI and years of medical experience were performed to assess their association with the KAP outcomes.

Ethical considerations

Participation in this study was strictly voluntary. Participants were explicitly informed that they could decline to participate or withdraw from the study at any time without negative consequences to their employment, performance evaluations or professional standing at the hospital.

To ensure absolute participant confidentiality, the study was designed to be completely anonymous. We did not collect any personally identifiable information, such as names, employee identification numbers or contact details in the questionnaires. Each completed questionnaire was assigned a random study code solely for data entry and statistical analysis.

The study was approved by the Ethics Committee of Le Van Thinh Hospital under Decision No. 09/HDDD-BVLVT, issued on June 28, 2024.

RESULTS

The median age of participants was 31 years, with an interquartile range of 8. The majority of healthcare workers were under 40 years old (85.4%). Females accounted for 70.3% of the participants. Nearly half of the study population was classified as overweight or obese. Regarding professional roles, most participants (62.5%) were non-physician healthcare workers (including nurses, midwives and technicians), while physicians accounted for 37.5% of the sample.

Regarding years of experience, most participants had worked in healthcare for 1 to less than 5 years (38.8%), followed by 5 to less than 10 years (26.7%) and 10 years or more (27.2%). The proportion of female participants was significantly higher among non-physician healthcare workers than among physicians (p <0.001).

Table 1. Characteristics of the Study Population (N = 232)

Characteristic	Total, n (%) (N = 232)	Physicians, n (%) (N = 87)	Other HCWs, n (%) (N = 145)	*p*-value
Gender				
Male	69 (29.7)	44 (50.6)	25 (17.2)	<0.001
Female	163 (70.3)	43 (49.4)	120 (82.8)	
Body Mass Index (BMI)				
Underweight	14 (6.0)	10 (11.5)	4 (2.8)	0.064
Normal weight	115 (49.6)	38 (43.7)	77 (53.1)	
Overweight	46 (19.8)	20 (23.0)	26 (17.9)	
Obesity Class I	50 (21.6)	17 (19.5)	33 (22.8)	
Obesity Class II	7 (3.0)	2 (2.3)	5 (3.4)	
Age group (years)				
<30	92 (39.7)	41 (47.1)	51 (35.2)	0.315
30 – 39	106 (45.7)	35 (40.2)	71 (49.0)	
40 – 49	24 (10.3)	7 (8.0)	17 (11.7)	
50 – 59	10 (4.3)	4 (4.6)	6 (4.1)	
≥60	0 (0)	0 (0)	0 (0)	
Ethnicity				
Kinh	219 (94.4)	81 (93.1)	138 (95.2)	0.562
Other	13 (5.6)	6 (6.9)	7 (4.8)	
Years of medical experience				
<1	17 (7.3)	12 (13.8)	5 (3.4)	<0.001
1 – <5	90 (38.8)	43 (49.4)	47 (32.4)	
5 – <10	62 (26.7)	18 (20.7)	44 (30.3)	
≥10	63 (27.2)	14 (16.1)	49 (33.8)	

Table 2. Knowledge regarding obesity among healthcare workers (N = 232)

Survey Question	N (%)	95% CI
Perception of obesity		
1. Obesity is a disease	148 (63.8)	57.3-70.3%
2. Obesity is a health condition, but not a disease	84 (36.2)	29.7-42.7%
Knowledge of causes of obesity		
1. Nutritional causes	208 (89.7)	85.8-93.5%
2. Genetic causes	137 (59.1)	52.6-65.5%
3. Pathological causes	42 (18.1)	13.4-23.3%
4. Endocrine disorders	146 (62.9)	56.9-69.4%
5. Medication use	96 (41.4)	35.3-47.8%
6. Do not know	14 (6.0)	3.0-9.1%
Knowledge of obesity diagnostic methods		
1. Body Mass Index (BMI)	209 (90.1)	85.8-93.5%
2. Waist circumference measurement	127 (54.7)	48.3-61.2%
3. Abdominal ultrasound to assess subcutaneous fat	68 (29.3)	23.7-35.3%
4. Dual-energy X-ray absorptiometry (DEXA)	44 (19.0)	14.2-24.1%
5. Body fat–muscle index using specialized scales	111 (47.8)	40.9-54.3%
6. Do not know	21 (9.1)	5.6-12.5%
Knowledge of obesity treatment methods		
1. Dietary restriction	212 (91.4)	87.5-94.8%
2. Physical exercise	201 (86.6)	82.3-90.5%
3. Pharmacologic therapy	119 (51.3)	44.8-57.8%
4. Liposuction or fat-removal surgery	59 (25.4)	20.3-31.0%
5. Fat destruction using ultrasound	32 (13.8)	9.9-18.5%
6. Bariatric surgery (e.g., gastric reduction)	80 (34.5)	28.4-40.5%
7. Do not know	13 (5.6)	3.0-8.6%
Knowledge of anti-obesity medications approved by the Ministry of Health (Vietnam)		
1. Orlistat	115 (49.6)	43.1-56.0%
2. Sibutramine	23 (9.9)	6.5-13.8%
3. Liraglutide	76 (32.8)	27.2-38.8%
4. Diuretics	15 (6.5)	3.4-9.9%
5. Do not know	95 (40.9)	34.5-47.0%

Respondents could select multiple options; percentages exceed 100%.

Among non-physician healthcare workers, the proportion with less than one year of experience was the lowest. The remaining experience groups each accounted for approximately one-third of the sample. In contrast, among physicians, nearly 50% had 1 to less than 5 years of experience. This difference was statistically significant ($p < 0.001$).

There were no statistically significant differences between physicians and non-physician healthcare workers in BMI, age group or ethnicity. (Table 1)

Knowledge

Among the 232 participants, 148 (63.8%; 95% CI: 57.3-70.3%) considered obesity to be a disease. Nutritional factors were most commonly cited as the cause of obesity (89.7%; 95% CI: 85.8-93.5%), followed by endocrine disorders and genetic predisposition, each selected by over half of respondents.

Regarding methods for diagnosing obesity, more than 90% (90.1%; 95% CI: 85.8-93.5%) of participants identified body mass index (BMI) as the primary diagnostic tool, followed by waist circumference measurement (54.7%; 95% CI: 48.3-61.2%). Meanwhile, only 19.0% (95% CI: 14.2-24.1%) selected dual-energy X-ray absorptiometry (DEXA) and 47.8% (95% CI: 40.9-54.3%) chose body fat–muscle composition analysis using a specialized scale.

The two most commonly selected obesity treatment methods were dietary restriction (91.4%; 95% CI: 87.5-94.8%) and physical activity (86.6%; 95% CI: 82.3-90.5%). In contrast, only 51.3% (95% CI: 44.8-57.8%) selected pharmacologic treatment and 34.5% (95% CI: 28.4-40.5%) chose bariatric surgery.

Fewer than half of healthcare workers were aware of nationally approved pharmacotherapies (orlistat 49.6% [95% CI: 43.1-56.0%], liraglutide 32.8% [95% CI: 27.2-38.8%]), with 40.9% [95% CI: 34.5-47.0%] reporting no knowledge of possible treatments. (Table 2)

Attitudes

When asked about the roles of physicians and patients in obesity management, over 90% (90.1%; 95% CI: 86.2-93.5%) of participants agreed that physicians can help patients healthily lose weight, and 79.7% (95% CI: 75.0-84.9%) believed that the responsibility for weight loss lies with the patient. Regarding the initiation of obesity treatment, 93.5% (95% CI: 90.1-96.6%) of participants stated they would treat obesity in patients with comorbidities, while only 84.1% (95% CI: 79.3-88.4%) agreed to treat patients without comorbidities.

Regarding concern about obesity, more than half of the healthcare workers reported being very concerned about

Table 3. Attitudes and level of concern about obesity among healthcare workers

Survey Question	Total, n (%) (N = 232)	Physicians, n (%) (N = 87)	Other HCWs, n (%) (N = 145)	*p*-value
"Physicians can help patients lose weight in a healthy way"				
Agree	209 (90.1) [95% CI: 86.2-93.5%]	76 (87.4) [95% CI: 80.0-93.6%]	133 (91.7) [95% CI: 86.9-96.2%]	0.281*
Disagree	23 (9.9) [95% CI: 6.5-13.8%]	11 (12.6) [95% CI: 6.4-20.0%]	12 (8.3) [95% CI: 3.8-13.1%]	
"Weight loss is the patient's responsibility"				
Agree	185 (79.7) [95% CI: 75.0-84.9%]	66 (75.9) [95% CI: 66.7-84.5%]	119 (82.1) [95% CI: 75.2-87.8%]	0.255*
Disagree	47 (20.3) [95% CI: 15.1-25.0%]	21 (24.1) [95% CI: 15.5-33.3%]	26 (17.9) [95% CI: 12.2-24.8%]	
Would recommend obesity treatment if the patient has obesity with comorbidities				
Agree	217 (93.5) [95% CI: 90.1-96.6%]	79 (90.8) [95% CI: 84.2-96.5%]	138 (95.2) [95% CI: 91.2-98.1%]	0.190*
Disagree	15 (6.5) [95% CI: 3.4-9.9%]	8 (9.2) [95% CI: 3.5-15.8%]	7 (4.8) [95% CI: 1.9-8.8%]	
Would recommend obesity treatment if the patient has obesity without comorbidities				
Agree	195 (84.1) [95% CI: 79.3-88.4%]	68 (78.2) [95% CI: 69.2-86.7%]	127 (87.6) [95% CI: 82.0-92.8%]	0.058*
Disagree	37 (15.9) [95% CI: 11.6-20.7%]	19 (21.8) [95% CI: 13.3-30.8%]	18 (12.4) [95% CI: 7.2-18.0%]	
Level of concern about obesity in patients				
Very concerned	126 (54.3) [95% CI: 47.8-60.3%]	47 (54.0) [95% CI: 43.2-64.4%]	79 (54.5) [95% CI: 45.9-62.7%]	0.971*
Somewhat concerned	86 (37.1) [95% CI: 31.0-43.1%]	32 (36.8) [95% CI: 26.7-46.7%]	54 (37.2) [95% CI: 29.5-45.4%]	
Not concerned	20 (8.6) [95% CI: 5.2-12.1%]	8 (9.2) [95% CI: 3.6-15.7%]	12 (8.3) [95% CI: 4.2-12.9%]	

*Pearson's Chi-square test; **Fisher's exact tests.

the issue, over one-third expressed some concern, and only 8.6% (95% CI: 5.2-12.1%) stated they were not concerned about obesity. There was no statistically significant difference in attitudes toward obesity or in the level of concern between physicians and other healthcare workers (Table 3).

Practices

In the management of patients with obesity, 83.6% (95% CI: 78.5-88.4%) of respondents recommended lifestyle modification for those with a BMI between 25 and 30 who had no comorbidities. For patients with a BMI between 30 and 35 without comorbidities, 72.4% (95% CI: 66.4-78.0%) recommended lifestyle modification, and 59.1% (95% CI: 52.6-65.5%) suggested referral to an obesity specialist. In patients with a BMI between 27 and 35 and comorbidities, three approaches were selected at nearly equal rates: lifestyle modification (66.4%; 95% CI: 59.9-72.0%), pharmacologic treatment (62.1%; 95% CI: 56.0-68.1%) and referral to an obesity specialty clinic (61.2%; 95% CI: 54.7-67.2%) (Table 4). Treatment recommendations varied depending on the patient's BMI and comorbidity profile, as illustrated in Figure 1.

When discussing barriers to communicating with patients about obesity, nearly 90% of healthcare workers reported encountering at least one obstacle. The most commonly cited barrier was "lack of patient motivation" (80.2%; 95% CI: 75.4-85.3%), followed by "patient sensitivity about weight" (57.3%; 95% CI: 50.9-63.4%). Other frequently reported barriers included "lack of time during consultations" (42.7%; 95% CI: 36.2-49.6%) and "lack of training in effective communication" (42.2%; 95% CI: 35.3-48.7%) (Table 4).

Compared with other healthcare workers, physicians were 2.3 times more likely to report time constraints during consultations ($p = 0.003$), 1.9 times more likely to cite insufficient healthcare resources ($p = 0.035$), and 4.5 times more likely to report inadequate knowledge of weight management ($p < 0.001$). The comparison of perceived barriers to discussing weight management between physicians and other health-care workers is summarized in Figure 2.

Regarding the influence of experience and BMI, stratified analyses revealed that healthcare workers with ≥5 years of experience demonstrated significantly higher rates of lifestyle modification recommendations for mild obesity compared to those with less experience ($p < 0.001$) (Table S1). However, there were no significant differences in KAP outcomes across participants' own BMI status (Table S2).

DISCUSSION

This study provides valuable insights into the knowledge, attitudes and practices of healthcare workers in Vietnam regarding obesity management. While general awareness of obesity as a health issue was relatively high, fewer than half of the participants were aware of approved pharmacotherapies. Notably, only 63.8% identified obesity as a chronic disease. This recognition rate is lower than those reported in recent Malaysian (88%), Swedish (91%) and broader ASEAN studies (84%), highlighting a persistent regional gap in understanding the metabolic complexity of obesity.[14-17]

Regarding attitudes, although 87.4% believed they could help patients lose weight, over three-quarters believed that weight loss is primarily the patient's responsibility. This perception is consistent with a prior Vietnamese study in which 55% of healthcare workers endorsed the same view.[15] It is notably higher than the 41% reported in a regional study across South and Southeast Asia.[14] The finding that 79.7% of healthcare workers attribute weight loss to patient responsibility reflects implicit weight bias widely documented in healthcare settings. This perspective is incongruent with current pathophysiological understanding of obesity as a chronic disease with strong genetic and neurobiological components. To improve

obesity care, training must address and normalize the bio-psychosocial model of obesity.

Concern about obesity was not high among staff at Le Van Thinh Hospital; only 54.0% of physicians and 54.5% of other healthcare workers reported being highly concerned. To change entrenched and long-standing beliefs, a shift toward a new public narrative grounded in modern scientific knowledge is needed.[18]

An interesting observation was the shift in treatment recommendations based on obesity severity. The declining frequency of lifestyle modification recommendations (from 83.6% for BMI 25–30 to 72.4% for BMI 30–35) despite

Table 4. Practices of healthcare workers regarding obesity management

Survey Question	Total, n (%) (N = 232)	Physicians, n (%) (N = 87)	Other HCWs, n (%) (N = 145)	*p*-value
Management of patients with BMI 25–30 and no comorbidities				
1. Lifestyle modification	194 (83.6) [95% CI: 78.5-88.4%]	74 (85.1) [95% CI: 77.1-92.6%]	120 (82.8) [95% CI: 75.9-88.7%]	0.647*
2. Pharmacologic treatment	25 (10.8) [95% CI: 6.9-15.5%]	9 (10.3) [95% CI: 3.8-17.0%]	16 (11.0) [95% CI: 6.3-17.0%]	0.870*
3. Referral to obesity specialist	47 (20.3) [95% CI: 15.1-26.3%]	19 (21.8) [95% CI: 13.3-30.6%]	28 (19.3) [95% CI: 12.9-26.3%]	0.643*
4. No intervention	14 (6.0) [95% CI: 3.0-9.1%]	0 (0.0) -	14 (9.7) [95% CI: 5.2-15.1%]	0.003*
5. Do not know what to do	25 (10.8) [95% CI: 6.9-15.1%]	10 (11.5) [95% CI: 4.8-18.4%]	15 (10.3) [95% CI: 5.8-15.6%]	0.785*
Management of patients with BMI 30–35 and no comorbidities				
1. Lifestyle modification	168 (72.4) [95% CI: 66.4-78.0%]	64 (73.6) [95% CI: 63.9-83.0%]	104 (71.7) [95% CI: 64.2-78.6%]	0.762*
2. Pharmacologic treatment	81 (34.9) [95% CI: 28.5-40.9%]	32 (36.8) [95% CI: 26.4-47.9%]	49 (33.8) [95% CI: 26.3-41.8%]	0.644*
3. Referral to obesity specialist	137 (59.1) [95% CI: 52.6-65.5%]	57 (65.5) [95% CI: 54.8-76.0%]	80 (55.2) [95% CI: 47.2-63.2%]	0.121*
4. No intervention	6 (2.6) [95% CI: 0.9-4.7%]	1 (1.1) [95% CI: 0.0-4.2%]	5 (3.4) [95% CI: 0.7-6.7%]	0.414**
5. Do not know what to do	31 (13.4) [95% CI: 9.1-17.7%]	8 (9.2) [95% CI: 3.4-15.7%]	23 (15.9) [95% CI: 10.3-21.9%]	0.149*
Management of patients with BMI 27–35 and comorbidities (e.g., HTN, T2DM, dyslipidemia)				
1. Lifestyle modification	154 (66.4) [95% CI: 59.9-72.0%]	54 (62.1) [95% CI: 51.7-73.2%]	100 (69.0) [95% CI: 61.5-76.5%]	0.282*
2. Pharmacologic treatment	144 (62.1) [95% CI: 56.0-68.1%]	54 (62.1) [95% CI: 51.7-72.0%]	90 (62.1) [95% CI: 53.9-69.7%]	1.000*
3. Referral to obesity specialist	142 (61.2) [95% CI: 54.7-67.2%]	65 (74.7) [95% CI: 65.3-83.7%]	77 (53.1) [95% CI: 45.1-61.4%]	0.001*
4. No intervention	3 (1.3) [95% CI: 0.0-3.0%]	0 (0.0) -	3 (2.1) [95% CI: 0.0-4.8%]	0.294**
5. Do not know what to do	30 (12.9) [95% CI: 8.6-17.2%]	8 (9.2) [95% CI: 3.4-15.7%]	22 (15.2) [95% CI: 9.7-21.2%]	0.189*
Barriers in discussing weight management with obese patients				
1. Lack of patient motivation	186 (80.2) [95% CI: 75.4-85.3%]	73 (83.9) [95% CI: 75.8-92.0%]	113 (77.9) [95% CI: 70.8-84.9%]	0.269*
2. Lack of time during consultation	99 (42.7) [95% CI: 36.2-49.6%]	48 (55.2) [95% CI: 43.2-65.9%]	51 (35.2) [95% CI: 27.7-42.3%]	0.003*
3. Patient sensitivity about weight	133 (57.3) [95% CI: 50.9-63.4%]	50 (57.5) [95% CI: 47.1-67.4%]	83 (57.2) [95% CI: 49.3-65.7%]	0.973*
4. Lack of primary care resources	69 (29.7) [95% CI: 23.7-35.3%]	33 (37.9) [95% CI: 27.3-48.3%]	36 (24.8) [95% CI: 17.9-32.2%]	0.035*
5. Lack of training in effective weight-related communication	98 (42.2) [95% CI: 35.3-48.7%]	43 (49.4) [95% CI: 38.3-59.8%]	55 (37.9) [95% CI: 30.1-46.3%]	0.086*
6. Physicians' lack of knowledge about weight management	37 (15.9) [95% CI: 11.2-20.7%]	25 (28.7) [95% CI: 19.3-38.0%]	12 (8.3) [95% CI: 4.1-12.8%]	<0.001*
7. No barriers reported	7 (3.0) [95% CI: 0.9-5.2%]	4 (4.6) [95% CI: 1.1-9.5%]	3 (2.1) [95% CI: 0.0-4.8%]	0.430**
8. Not applicable / never discussed obesity with patients	18 (7.8) [95% CI: 4.3-11.2%]	5 (5.7) [95% CI: 1.1-11.1%]	13 (9.0) [95% CI: 4.7-13.8%]	0.375*

Respondents could select multiple options; percentages exceed 100%.*Pearson's Chi-square test; **Fisher's exact tests.

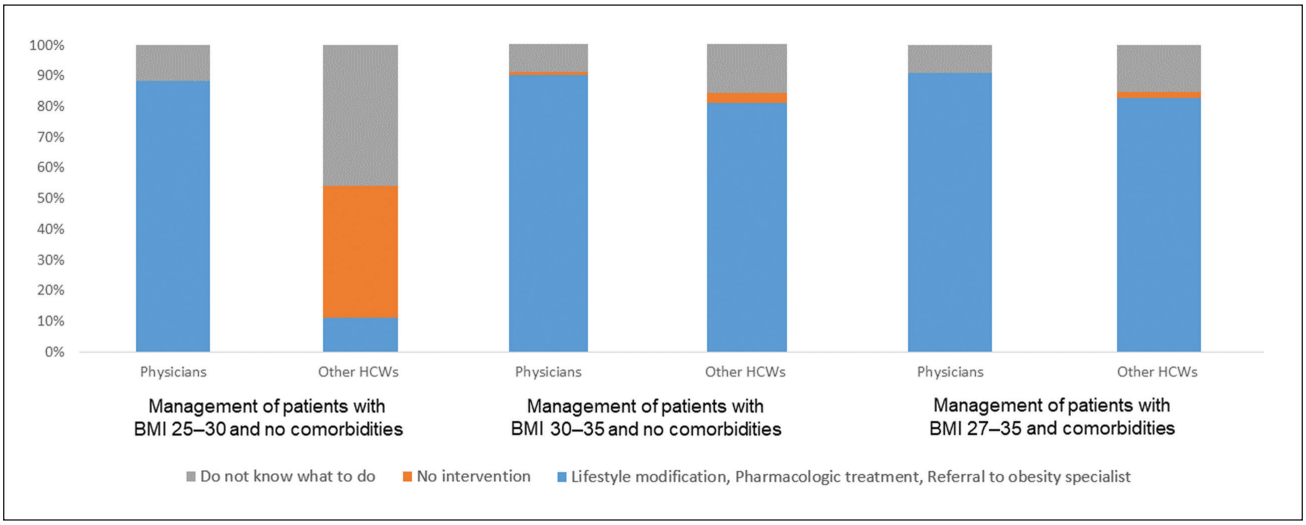

Figure 1. Treatment recommendations (lifestyle, pharmacotherapy, referral) across BMI categories, with separate bars for physicians vs. non-physicians.

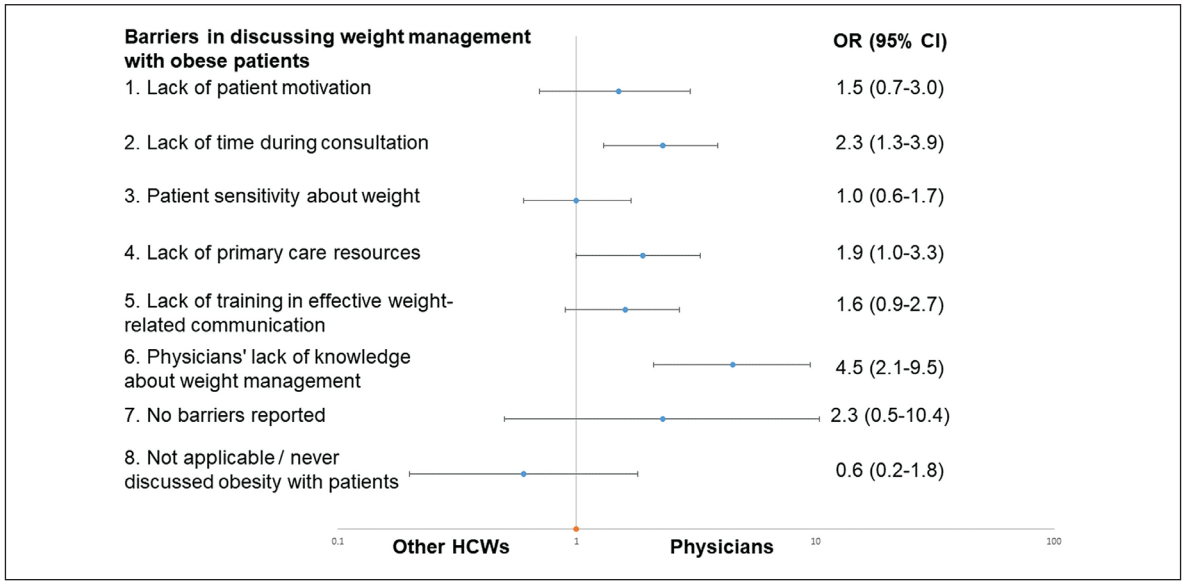

Figure 2. Forest plot of odds ratios and 95% CIs for barriers comparing physicians to other healthcare workers.

increasing metabolic dysfunction suggests potential therapeutic disbelief or uncertainty about the efficacy of pharmacotherapy. These findings align with studies from ASEAN countries, wherein, despite believing medications are effective, physicians rarely prescribe them.[19] This may reflect a lack of pharmacotherapy knowledge, potentially correlating with low confidence in obesity treatment. Although multidisciplinary care models have proven effective, they remain underutilized in Vietnam.

When analyzing barriers, we found that physicians were significantly more likely than other hospital staff to report inadequate knowledge in weight management. Interestingly, physicians reported greater knowledge insufficiency (4.5x higher odds) than other staff. This may reflect greater awareness of knowledge gaps following more formal training, or increased time constraints limiting the opportunity to maintain currency with rapidly evolving obesity treatment guidelines. Barriers in counseling patients about obesity were considerable: 80% cited lack of patient motivation and 57.3% mentioned patient sensitivity about weight. Additionally, 28% of physicians reported insufficient knowledge as a major barrier, along with limited time and resources—factors more frequently reported by physicians than by other staff. Similar barriers have been reported across Asia. A review of 26 studies identified common challenges among healthcare providers, including a lack of knowledge, inadequate specialized training and insufficient systemic support.[20] Therefore, targeted interventions to enhance provider knowledge and skills are essential. Integrated training programs that combine medical knowledge, patient-centered communication and practical tools may help improve the quality of care and reduce delays in obesity management.

Our stratified analysis revealed a significant association between clinical experience and obesity management. Healthcare workers with five or more years of experience demonstrated greater concern. They were more likely to recommend lifestyle modifications across various clinical scenarios than those with less than five years of experience. Notably, junior staff reported a significantly higher rate of uncertainty regarding appropriate interventions. This finding suggests that while fundamental knowledge may be acquired during formal education, the confidence and perceived importance of obesity management likely grow with clinical exposure and long-term patient interaction.

In contrast, the participants' own BMI status did not appear to significantly influence their knowledge, attitudes or clinical practices regarding obesity. This lack of association suggests that healthcare workers at Le Van Thinh Hospital generally maintain a professional approach to obesity care that is independent of their personal physical characteristics. This reinforces the idea that educational interventions and institutional protocols, rather than personal attributes, are the primary drivers of clinical decision-making in this setting.

To address these systemic and educational gaps, comprehensive system-level changes are required. Institutional interventions can include: (1) obesity medicine certification programs; (2) standardized screening and treatment protocols; (3) multidisciplinary care models with nutritionists, nurses, physiotherapists, and behavioral specialists; (4) electronic medical record (EMR) reminders for weight management; and (5) performance metrics linking obesity treatment to quality outcomes.

Although multidisciplinary care models have proven effective, they remain underutilized in Vietnam. To address this, an obesity specialty clinic was newly established at our institution in late 2023. However, within Vietnam's broader public hospital infrastructure, such dedicated units remain highly scarce. Obesity management is still mostly integrated into general endocrinology or nutrition

clinics rather than standalone centers. Furthermore, there is a lack of robust national data on the utilization rates at these specialized clinics, reflecting an urgent need for institutional investments in dedicated metabolic care models.

Limitations

This study has several limitations. First, the cross-sectional design reflects associations at a single point in time and does not establish causality among knowledge, attitudes and practices. Second, the use of convenience sampling during departmental meetings precludes the calculation of an exact response rate and may introduce selection bias. Although our sample predominantly consisted of nurses (53.9%) and internal medicine physicians (29.7%), which generally reflects the hospital's clinical workforce composition, some smaller clinical departments and surgical specialties may be under-represented, limiting the broader generalizability of the findings across all hospital sectors. Third, reliance on self-reported data may be subject to social desirability bias. Because our analysis involved multiple bivariate comparisons to explore associations between participant characteristics and various KAP domains, there is a potential for Type I error inflation. As no formal multiplicity adjustments were applied in this descriptive study, the statistically significant associations identified should be interpreted as exploratory and warrant confirmation in future adequately powered, hypothesis-driven research. While stratified analyses were performed to adjust for key confounders such as participant BMI and gender, full multivariable regression models were not utilized. The statistically significant associations identified in our bivariate comparisons should therefore be interpreted as exploratory. Finally, the study was conducted at a single hospital, which may not represent general trends across healthcare settings in Vietnam. Future research should include larger, geographically diverse samples and employ longitudinal designs to assess changes in perception and practice over time.

CONCLUSION

In conclusion, significant knowledge gaps and implicit weight biases persist among healthcare workers regarding obesity management. While this study was conducted at a single tertiary center, these findings highlight systemic educational barriers that likely extend across the national healthcare infrastructure. Addressing these gaps through specialized training, standardized protocols, and multi-disciplinary care models is not only critical for institutional improvement but also provides a vital framework for Vietnam and other ASEAN nations currently confronting similar rapid escalations in metabolic diseases.

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Statement of Authorship
The author certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
TT: Conceptualization, Methodology, Validation, Formal Analysis, Resources, Data curation, Writing – original draft preparation, Writing – review and editing.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
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SUPPLEMENTARY TABLES

Table S1. Attitudes and practices stratified by years of experience (<5 years vs. ≥5 years)

Survey question	Total, N (%)	<5 years experience, N (%)	≥5 years experience, N (%)	*p*-value
"Physicians can help patients lose weight in a healthy way"				
Agree	209 (90.1) [95% CI: 86.2-93.5%]	93 (86.9) [95% CI: 80.5-93.3%]	116 (92.8) [95% CI: 88.0-96.9%]	0.135*
Disagree	23 (9.9) [95% CI: 6.5-13.8%]	14 (13.1) [95% CI: 6.7-19.5%]	9 (7.2) [95% CI: 3.1-12.0%]	
"Weight loss is the patient's responsibility"				
Agree	185 (79.7) [95% CI: 75.0-84.9%]	82 (76.6) [95% CI: 68.6-84.4%]	103 (82.4) [95% CI: 74.8-89.4%]	0.276*
Disagree	47 (20.3) [95% CI: 15.1-25.0%]	25 (23.4) [95% CI: 15.6-31.4%]	22 (17.6) [95% CI: 10.6-25.2%]	
Would recommend obesity treatment if the patient has obesity with comorbidities				
Agree	217 (93.5) [95% CI: 90.1-96.6%]	97 (90.7) [95% CI: 85.0-96.3%]	120 (96.0) [95% CI: 92.2-99.2%]	0.099*
Disagree	15 (6.5) [95% CI: 3.4-9.9%]	10 (9.3) [95% CI: 3.7-15.0%]	5 (4.0) [95% CI: 0.8-7.8%]	
Would recommend obesity treatment if the patient has obesity without comorbidities				
Agree	195 (84.1) [95% CI: 79.3-88.4%]	84 (78.5) [95% CI: 70.8-86.5%]	111 (88.8) [95% CI: 83.3-94.6%]	0.033*
Disagree	37 (15.9) [95% CI: 11.6-20.7%]	23 (21.5) [95% CI: 13.5-29.2%]	14 (11.2) [95% CI: 5.4-16.7%]	
Level of concern about obesity in patients				
Very concerned	126 (54.3) [95% CI: 47.8-60.3%]	50 (46.7) [95% CI: 37.3-56.4%]	76 (60.8) [95% CI: 51.1-69.3%]	0.027*
Somewhat concerned	86 (37.1) [95% CI: 31.0-43.1%]	43 (40.2) [95% CI: 31.1-49.5%]	43 (34.4) [95% CI: 26.4-42.7%]	
Not concerned	20 (8.6) [95% CI: 5.2-12.1%]	14 (13.1) [95% CI: 6.4-19.6%]	6 (4.8) [95% CI: 1.5-8.8%]	
Management of patients with BMI 25–30 and no comorbidities				
1. Lifestyle modification	194 (83.6) [95% CI: 78.5-88.4%]	79 (73.8) [95% CI: 65.4-82.2%]	115 (92.0) [95% CI: 86.8-96.3%]	<0.001*
2. Pharmacologic treatment	25 (10.8) [95% CI: 6.9-15.5%]	11 (10.3) [95% CI: 5.0-16.8%]	14 (11.2) [95% CI: 6.0-17.1%]	0.822*
3. Referral to obesity specialist	47 (20.3) [95% CI: 15.1-26.3%]	13 (12.1) [95% CI: 5.6-18.9%]	34 (27.2) [95% CI: 19.5-35.0%]	0.004*
4. No intervention	14 (6.0) [95% CI: 3.0-9.1%]	7 (6.5) [95% CI: 2.4-11.6%]	7 (5.6) [95% CI: 1.8-12.0%]	0.764*
5. Do not know what to do	25 (10.8) [95% CI: 6.9-15.1%]	20 (18.7) [95% CI: 11.3-26.7%]	5 (4.0) [95% CI: 0.8-7.8%]	<0.001*
Management of patients with BMI 30–35 and no comorbidities				
1. Lifestyle modification	168 (72.4) [95% CI: 66.4-78.0%]	71 (66.4) [95% CI: 57.8-75.4%]	97 (77.6) [95% CI: 69.6-84.7%]	0.056*
2. Pharmacologic treatment	81 (34.9) [95% CI: 28.5-40.9%]	40 (37.4) [95% CI: 28.4-46.9%]	41 (32.8) [95% CI: 24.1-41.0%]	0.465*
3. Referral to obesity specialist	137 (59.1) [95% CI: 52.6-65.5%]	60 (56.1) [95% CI: 46.5-65.7%]	77 (61.6) [95% CI: 52.7-70.2%]	0.394*
4. No intervention	6 (2.6) [95% CI: 0.9-4.7%]	2 (1.9) [95% CI: 0.0-4.8%]	4 (3.2) [95% CI: 0.7-6.6%]	0.689**
5. Do not know what to do	31 (13.4) [95% CI: 9.1-17.7%]	19 (17.8) [95% CI: 10.4-25.0%]	12 (9.6) [95% CI: 4.7-15.3%]	0.069*
Management of patients with BMI 27–35 and comorbidities (e.g., HTN, T2DM, dyslipidemia)				
1. Lifestyle modification	154 (66.4) [95% CI: 60.3-72.8%]	60 (56.1) [95% CI: 46.5-65.1%]	94 (75.2) [95% CI: 67.4-83.2%]	0.002*
2. Pharmacologic treatment	144 (62.1) [95% CI: 56.0-68.1%]	61 (57.0) [95% CI: 47.7-66.1%]	83 (66.4) [95% CI: 57.6-75.0%]	0.142*
3. Referral to obesity specialist	142 (61.2) [95% CI: 54.7-67.2%]	66 (61.7) [95% CI: 52.8-71.4%]	76 (60.8) [95% CI: 51.9-69.2%]	0.891*
4. No intervention	3 (1.3) [95% CI: 0.0-3.0%]	1 (0.9) [95% CI: 0.0-3.0%]	2 (1.6) [95% CI: 0.0-3.9%]	1.000**
5. Do not know what to do	30 (12.9) [95% CI: 8.6-17.2%]	19 (17.8) [95% CI: 10.4-25.0%]	11 (8.8) [95% CI: 4.0-14.0%]	0.043*
Barriers in discussing weight management with obese patients				
1. Lack of patient motivation	186 (80.2) [95% CI: 75.4-85.3%]	85 (79.4) [95% CI: 71.3-87.1%]	101 (80.8) [95% CI: 73.8-87.6%]	0.796*
2. Lack of time during consultation	99 (42.7) [95% CI: 36.2-49.6%]	50 (46.7) [95% CI: 37.7-55.6%]	49 (39.2) [95% CI: 30.5-48.1%]	0.248*
3. Patient sensitivity about weight	133 (57.3) [95% CI: 50.9-63.4%]	60 (56.1) [95% CI: 46.9-65.4%]	73 (58.4) [95% CI: 49.5-66.7%]	0.721*
4. Lack of primary care resources	69 (29.7) [95% CI: 23.7-35.3%]	32 (29.9) [95% CI: 21.4-38.7%]	37 (29.6) [95% CI: 21.9-37.8%]	0.959*
5. Lack of training in effective weight-related communication	98 (42.2) [95% CI: 35.3-48.7%]	46 (43.0) [95% CI: 34.2-52.6%]	52 (41.6) [95% CI: 32.5-50.4%]	0.831*
6. Physicians' lack of knowledge about weight management	37 (15.9) [95% CI: 11.2-20.7%]	18 (16.8) [95% CI: 10.1-24.3%]	19 (15.2) [95% CI: 8.8-21.3%]	0.737*
7. No barriers reported	7 (3.0) [95% CI: 0.9-5.2%]	3 (2.8) [95% CI: 0.0-6.3%]	4 (3.2) [95% CI: 0.8-6.6%]	1.000**
8. Not applicable / never discussed obesity with patients	18 (7.8) [95% CI: 4.3-11.2%]	10 (9.3) [95% CI: 4.0-15.3%]	8 (6.4) [95% CI: 2.3-11.4%]	0.403*

Respondents could select multiple options; percentages exceed 100%.*Pearson's Chi-square test; **Fisher's exact tests.

Table S2. Relationship between participant BMI status and obesity attitudes/practices

Survey question	Total, N (%)	Underweight / normal weight HCWs, N (%)	Overweight / obese HCWs, N (%)	*p*-value
"Physicians can help patients lose weight in a healthy way"				
Agree	209 (90.1) [95% CI: 86.2-93.5%]	115 (89.1) [95% CI: 83.7-94.7%]	94 (91.3) [95% CI: 84.8-96.4%]	0.592*
Disagree	23 (9.9) [95% CI: 6.5-13.8%]	14 (10.9) [95% CI: 5.3-16.3%]	9 (8.7) [95% CI: 3.6-15.2%]	
"Weight loss is the patient's responsibility"				
Agree	185 (79.7) [95% CI: 75.0-84.9%]	102 (79.1) [95% CI: 72.1-85.7%]	83 (80.6) [95% CI: 72.3-88.0%]	0.776*
Disagree	47 (20.3) [95% CI: 15.1-25.0%]	27 (20.9) [95% CI: 14.3-27.9%]	20 (19.4) [95% CI: 12.0-27.7%]	
Would recommend obesity treatment if the patient has obesity with comorbidities				
Agree	217 (93.5) [95% CI: 90.1-96.6%]	121 (93.8) [95% CI: 89.4-97.7%]	96 (93.2) [95% CI: 88.0-97.7%]	0.855*
Disagree	15 (6.5) [95% CI: 3.4-9.9%]	8 (6.2) [95% CI: 2.3-10.6%]	7 (6.8) [95% CI: 2.3-12.0%]	
Would recommend obesity treatment if the patient has obesity without comorbidities				
Agree	195 (84.1) [95% CI: 79.3-88.4%]	105 (81.4) [95% CI: 74.4-88.1%]	90 (87.4) [95% CI: 80.7-94.0%]	0.216*
Disagree	37 (15.9) [95% CI: 11.6-20.7%]	24 (18.6) [95% CI: 11.9-25.6%]	13 (12.6) [95% CI: 6.0-19.3%]	
Level of concern about obesity in patients				
Very concerned	126 (54.3) [95% CI: 47.8-60.3%]	65 (50.4) [95% CI: 41.6-58.8%]	61 (59.2) [95% CI: 50.0-68.6%]	0.365*
Somewhat concerned	86 (37.1) [95% CI: 31.0-43.1%]	51 (39.5) [95% CI: 31.6-48.8%]	35 (34.0) [95% CI: 24.8-43.2%]	
Not concerned	20 (8.6) [95% CI: 5.2-12.1%]	13 (10.1) [95% CI: 5.1-16.0%]	7 (6.8) [95% CI: 2.1-12.4%]	
Management of patients with BMI 25–30 and no comorbidities				
1. Lifestyle modification	194 (83.6) [95% CI: 78.5-88.4%]	104 (80.6) [95% CI: 74.0-87.0%]	90 (87.4) [95% CI: 80.9-93.8%]	0.167*
2. Pharmacologic treatment	25 (10.8) [95% CI: 6.9-15.5%]	12 (9.3) [95% CI: 4.5-14.2%]	13 (12.6) [95% CI: 6.9-19.1%]	0.418*
3. Referral to obesity specialist	47 (20.3) [95% CI: 15.1-26.3%]	25 (19.4) [95% CI: 12.6-26.8%]	22 (21.4) [95% CI: 13.7-29.0%]	0.709*
4. No intervention	14 (6.0) [95% CI: 3.0-9.1%]	9 (7.0) [95% CI: 3.1-11.1%]	5 (4.9) [95% CI: 1.1-9.4%]	0.500*
5. Do not know what to do	25 (10.8) [95% CI: 6.9-15.1%]	18 (14.0) [95% CI: 8.2-20.7%]	7 (6.8) [95% CI: 2.0-11.9%]	0.081*
Management of patients with BMI 30–35 and no comorbidities				
1. Lifestyle modification	168 (72.4) [95% CI: 66.4-78.0%]	90 (69.8) [95% CI: 60.8-77.5%]	78 (75.7) [95% CI: 67.3-84.0%]	0.313*
2. Pharmacologic treatment	81 (34.9) [95% CI: 28.5-40.9%]	47 (36.4) [95% CI: 28.3-44.4%]	34 (33.0) [95% CI: 24.7-42.3%]	0.587*
3. Referral to obesity specialist	137 (59.1) [95% CI: 52.6-65.5%]	78 (60.5) [95% CI: 51.6-68.6%]	59 (57.3) [95% CI: 47.6-66.7%]	0.624*
4. No intervention	6 (2.6) [95% CI: 0.9-4.7%]	3 (2.3) [95% CI: 0.0-5.3%]	3 (2.9) [95% CI: 0.0-6.6%]	1.000**
5. Do not know what to do	31 (13.4) [95% CI: 9.1-17.7%]	21 (16.3) [95% CI: 10.4-23.3%]	10 (9.7) [95% CI: 4.0-15.5%]	0.144*
Management of patients with BMI 27–35 and comorbidities (e.g., HTN, T2DM, dyslipidemia)				
1. Lifestyle modification	154 (66.4) [95% CI: 60.3-72.8%]	86 (66.7) [95% CI: 57.6-74.8%]	68 (66.0) [95% CI: 56.1-75.5%]	0.917*
2. Pharmacologic treatment	144 (62.1) [95% CI: 56.0-68.1%]	81 (62.8) [95% CI: 53.3-70.8%]	63 (61.2) [95% CI: 51.5-70.2%]	0.800*
3. Referral to obesity specialist	142 (61.2) [95% CI: 54.7-67.2%]	77 (59.7) [95% CI: 51.2-67.8%]	65 (63.1) [95% CI: 53.1-72.5%]	0.596*
4. No intervention	3 (1.3) [95% CI: 0.0-3.0%]	2 (1.6) [95% CI: 0.0-4.1%]	1 (1.0) [95% CI: 0.0-3.3%]	1.000**
5. Do not know what to do	30 (12.9) [95% CI: 8.6-17.2%]	21 (16.3) [95% CI: 10.2-22.9%]	9 (8.7) [95% CI: 3.5-14.1%]	0.089*
Barriers in discussing weight management with obese patients	232 (100.0)	129 (100.0)	103 (100.0)	
1. Lack of patient motivation	186 (80.2) [95% CI: 75.4-85.3%]	104 (80.6) [95% CI: 73.2-86.9%]	82 (79.6) [95% CI: 71.3-87.2%]	0.848*
2. Lack of time during consultation	99 (42.7) [95% CI: 36.2-49.6%]	54 (41.9) [95% CI: 33.9-50.8%]	45 (43.7) [95% CI: 34.0-53.3%]	0.780*
3. Patient sensitivity about weight	133 (57.3) [95% CI: 50.9-63.4%]	77 (59.7) [95% CI: 51.5-68.5%]	56 (54.4) [95% CI: 44.9-63.2%]	0.416*
4. Lack of primary care resources	69 (29.7) [95% CI: 23.7-35.3%]	43 (33.3) [95% CI: 24.6-41.3%]	26 (25.2) [95% CI: 16.8-34.4%]	0.180*
5. Lack of training in effective weight-related communication	98 (42.2) [95% CI: 35.3-48.7%]	56 (43.4) [95% CI: 34.5-52.4%]	42 (40.8) [95% CI: 31.7-50.5%]	0.687*
6. Physicians' lack of knowledge about weight management	37 (15.9) [95% CI: 11.2-20.7%]	26 (20.2) [95% CI: 13.2-27.5%]	11 (10.7) [95% CI: 5.1-17.4%]	0.050*
7. No barriers reported	7 (3.0) [95% CI: 0.9-5.2%]	4 (3.1) [95% CI: 0.7-6.6%]	3 (2.9) [95% CI: 0.0-6.4%]	1.000**
8. Not applicable / never discussed obesity with patients	18 (7.8) [95% CI: 4.3-11.2%]	11 (8.5) [95% CI: 4.2-13.7%]	7 (6.8) [95% CI: 2.2-11.9%]	0.624*

Respondents could select multiple options; percentages exceed 100%.*Pearson's Chi-square test; **Fisher's exact tests.

ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Risk Factors Associated With Multidrug Resistant Organism (MDRO) Isolates in Infected Diabetic Foot Ulcers (DFU): An Analytical Cross-sectional Study

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Abstract

Background. Increasing use and abuse of antibiotics has led to a rise in multidrug resistant organisms (MDRO) isolates among infected diabetic foot ulcers (DFUs) and is seen in more than half of all diabetic foot infection cases. This study aimed to identify risk factors for MDRO infection since there are no Filipino studies currently available to establish an association.

Methodology. A cross-sectional, analytical study was conducted to evaluate risk factors for MDRO in DFUs. Adult patients admitted in a tertiary hospital from January 2019 - December 2023 for DFU were included in the study. Based on retrospective chart review, patients with DFU described to be infected with accompanying superficial or deep wound cultures were studied. Patients were classified under the MDRO-positive group if their cultures reported any of the following organisms: methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamases (ESBL), amp C and carbapenamases-producing *Enterobacteriaceae*, Metallo-beta-lactamases (MBL)-producing *Pseudomonas*, *Acinetobacter* species, or any isolate with at least one drug resistance in three different antibiotic classes. Those who did not fall into this definition, including cultures without growth, were classified under the MDRO-negative group. Clinical risk factors and pertinent laboratory findings were obtained from their data.

Results. One hundred fifty-one (151) patients were included in the study and 52 (34.43%) patient had MDRO isolates. The most common isolates seen were *Klebsiella pneumoniae* for gram-negative organisms and *Staphylococcus aureus* for gram-positive organisms. For gram-negative isolates, erythromycin had the most resistance at 17.53% followed by oxacillin and clindamycin both at 13.4%. For gram-positive isolates, highest resistance were seen with ampicillin at 18.99% followed by cefuroxime at 13.57% and amoxicillin-clavulanate at 11.63%.

Higher ulcer grade (Crude OR = 1.11 [95% CI 1.00 - 1.23], *p*-value 0.04; Crude OR = 1.29, [95% CI 1.04 - 1.60], *p*-value 0.02), as well as previous admission for diabetic foot ulcer (Crude OR = 2.28, [95% CI 1.10 to 4.73], *p*-value 0.04) were associated with multidrug resistance. Logistic regression showed that only a previous admission had significant association for MDRO positivity (Adjusted OR = 3.00 [95% CI: 1.04 – 8.62], *p*-value 0.04).

Conclusion. There is a high burden of multidrug resistant organism infection in diabetic foot ulcers with significant association in higher ulcer grades. A previous admission for diabetic foot ulcer significantly increases the odds for MDRO infection in succeeding diabetic foot infections.

INTRODUCTION

Diabetic foot ulcers (DFUs) are a frequent complication of diabetes mellitus (DM) with a prevalence rate of 15%. Similar rates are seen in the Philippine setting, usually in men. Associated co-morbidities are peripheral neuropathy and peripheral artery disease. Recurrence rates are also common and are usually seen in patients with DFU who have multiple lesions, plantar location, and presence of peripheral neuropathy.[1]

The most common isolates seen in DFUs are *Staphylococcus aureus (S. aureus)* and *Pseudomonas aeruginosa (P. aeruginosa)* with note of increasing risk for multidrug resistance (MDR).[2,3] More than half of DFU cases are associated with MDR organisms (MDRO) which can also be a risk factor for recurrence.[4]

Several studies have determined the following variables as independent predictors for the presence of MDRO in patients: duration and control of diabetes, ulcer grade

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and size, smoking, uncontrolled metabolic factors, and concurrent peripheral neuropathy and peripheral artery disease.[5-11] A systematic review by Dai et al., in 2020 looked at 11 retrospective and prospective studies investigating associated risk factors for MDRO infection in DFU and this review showed that poor wound characteristics namely: ischemic ulcers, increased ulcer size and grade, and presence of osteomyelitis as well as previous antibiotic use and hospitalization were risk factors for MDRO-positive cultures.[12] Another systematic literature review by Matta-Gutiérrez et al., in 2021 had shown that MDRO positivity, although not influencing healing time, increased rates of amputation and mortality.[13]

No study has been done to identify independent predictors for DFUs infected with MDRO in the Philippines. It is important to verify and determine additional predictive risk factors to guide appropriate antibiotic selection while awaiting culture sensitivity reports.

METHODOLOGY

A cross-sectional, analytical study was conducted using retrospective data from patients admitted for DFUs in De La Salle University Medical Center, Cavite, Philippines from January 2019 to December 2023 after approval from the technical review board and independent ethics committee of the institution.

The minimum sample size required was 151 and was based on a method by Hsieh et al. with the following equation and parameters:

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{P(1-P)\beta^2}$$

where P = OR/(1+OR), $z_{(1-\alpha/2)}$ set at 1.96, $z_{(1-\beta)}$ set at 0.842, odds ratio (OR) set at 2.5, and confidence interval set at 95%.[14] All admissions and referrals for adults ≥19 years old with diabetic foot ulcers were reviewed for microbiologic profile, and the following risk factors: duration and control of diabetes, use of insulin, ulcer grade using University of Texas Wound Classification Score (UTWCS) and Perfusion, Extent, Depth, Infection, Sensation (PEDIS) Score, presence of osteomyelitis and sepsis, any previous admissions for diabetic foot ulcers, any previous antibiotic and surgical treatment of ulcers, presence of peripheral artery disease, presence of diabetic neuropathy, presence of coronary artery disease, presence of cerebrovascular disease, presence of diabetic nephropathy, presence of diabetic retinopathy, and socioeconomic status. The following laboratory markers were also obtained: hemoglobin, white blood cell count (WBC), serum albumin, quantitative C-reactive protein (CRP), glycated hemoglobin (HbA1c), and serum creatinine. Patients admitted for other causes of foot ulcers and unavailability of wound or tissue cultures were excluded from the study.

Ulcer grade and infection was determined by wound description and clinical status showing local or systemic infection based on IWGDF guidelines as described in medical records.[15,16] Fluid or tissue specimens were subjected to automated minimum inhibitory concentration and disc diffusion distribution testing. Classification of MDRO positivity was based on pre-defined criteria as follows: methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamases (ESBL), amp C and carbapenamases-producing *Enterobacteriaceae*, Metallo-beta-lactamases (MBL)-producing *Pseudomonas*, *Acinetobacter* species, or any isolate with at least one drug resistance in three different antibiotic classes. Those who did not fall into this definition, including cultures without growth, were separated into the MDRO-negative group. Previous wound care was defined as any antibiotic or wound debridement done in the outpatient department within the last three months and re-admission was defined as any previous admission for diabetic foot management.

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range for non-normally distributed continuous variables and mean and standard deviation for normally distributed continuous variables. Independent Sample T-test, Mann-Whitney U test and Fisher's exact/Chi-square test were used to determine the difference of mean, rank and frequency, respectively, between patients with and without MDRO. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant factors of MDRO. All statistical tests were two tailed tests. Shapiro-Wilk test was used to test the normality of the continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. Microsoft Excel and STATA 13.1 was used for data management and analysis, respectively.

RESULTS

A total of 151 diabetic patients admitted for diabetic foot ulcers were included in this study with 52 patients or 34.44% having multidrug resistant isolates. Ninety-nine or 65.56% of patients had wound or tissue cultures that were not multidrug resistant and 15% of these patients did not have any growth in their wound or tissue culture. Table 1 shows the demographic and clinical profile of patients admitted for diabetic foot ulcers. The MDRO-positive group was comparable to the MDRO-negative group in terms of age, sex, and diabetic profile. The mean age is 60.82 years of age and more males were admitted for diabetic foot ulcers in both groups. The duration of diabetes is on average 10 years for both groups with more than half of the patients requiring insulin management. Peripheral arterial disease and peripheral neuropathy were present in more than 80% of patients with diabetic foot ulcers and 78% of patients had to undergo surgical intervention either by wound debridement or amputation during their admission.

Table 1. Demographic and clinical profile of patients

	Multidrug resistant organism			
	Total, (n = 151)	With, (n = 52, 34%)	Without, (n = 99, 66%)	*P*-value
	Frequency (%); Mean + SD; Median (IQR)			
Age, years	60.82 + 11.03	60.46 + 10.07	61.01 + 11.55	0.773
Sex				0.603
Male	91 (60.26)	33 (63.46)	58 (58.59)	
Female	60 (39.74)	19 (36.54)	41 (41.41)	
Socioeconomic status				0.112
A and B	114 (75.5)	35 (67.31)	79 (79.8)	
C to E	37 (24.5)	17 (32.69)	20 (20.2)	
DM duration, years	10 (3 to 18)	10 (2.5 to 17.5)	10 (3 to 18)	0.830
Insulin therapy	80 (53.98)	31 (59.62)	49 (49.49)	0.303
Macrovascular complication				
PAD (n = 140)	117 (83.57)	43 (84.31)	74 (83.15)	1.000
CAD (n = 150)	40 (26.67)	14 (27.45)	26 (26.26)	1.000
CVA (n = 150)	19 (12.67)	9 (17.31)	10 (10.20)	0.302
Microvascular complication				
Neuropathy (n = 99)	81 (81.82)	33 (80.49)	48 (82.76)	0.796
Nephropathy (n = 146)	72 (49.32)	29 (56.86)	43 (45.26)	0.225
Retinopathy	13 (43.33)	5 (38.46)	8 (47.06)	0.721
Underwent surgery (n = 150)	117 (78)	45 (86.54)	72 (73.47)	0.096
Wound history				
Duration of symptoms, days	22 (14 to 60)	23.5 (14 to 60)	21 (9 to 60)	0.480
Size (n = 144)				0.287
0 to 3.9 cm	330 (20.83)	8 (15.38)	22 (23.91)	
≥4 cm	114 (79.17)	44 (84.62)	70 (76.09)	
UTWCS	8 (4 to 12)	10 (8 to 12)	8 (4 to 12)	0.035
PEDIS score	9 (7 to 9)	9 (8 to 10)	8 (7 to 9)	0.017
Sepsis	31 (20.53)	7 (13.46)	24 (24.24)	0.141
Received outpatient antibiotics	113 (74.83)	40 (76.92)	73 (73.74)	0.699
Received outpatient wound care	58 (38.41)	26 (50)	32 (32.32)	0.037
Readmission (n = 149)	44 (29.53)	21 (41.18)	23 (23.47)	0.037
Laboratory parameters				
WBC	14.6 (10.7 to 21.5)	14.1 (10.25 to 20)	15.8 (10.9 to 23.4)	0.487
Hemoglobin	112 (95 to 129)	114 (93 to 126)	112 (97 to 132)	0.532
CRP (n = 115)	99.64 (58.7 to 175)	82.18 (49.2 to 150)	121.09 (63.7 to 185)	0.072
HbA1c (n = 118)	9.65 (7.6 to 12.3)	9.8 (7.7 to 12.35)	9.55 (7.3 to 12.3)	0.562
Albumin (n = 112)	31 (26 to 36)	29 (24 to 34)	32 (27 to 36)	0.170
Creatinine (n = 143)	111.9 (81 to 194.3)	121.75 (80.5 to 214.7)	111.3 (81.7 to 191)	0.951
Polymicrobial Isolates	31 (20.53)	15 (28.85)	16 (16.16)	0.089

Both MDRO-positive and MDRO-negative groups were comparable in terms of rates of coronary artery disease, cerebrovascular disease, nephropathy, and retinopathy. Both groups were also comparable in terms of clinical and laboratory markers for infection severity and sepsis. Both groups exhibited anemia and hypoalbuminemia with a mean hemoglobin of 112 g/dL and mean albumin of 31 g/dL.

No significant difference was seen in terms of socioeconomic classification and incidence of MDRO. No difference was seen in presence of MDRO isolates in patients who have received outpatient antibiotic treatment. There was no difference in polymicrobial rates between MDRO-positive and MDRO-negative groups. Distribution of major resistance phenotypes were seen more in MRSA infections at 19.23% followed by ESBL at 13.46%, *Acinetobacter sp.* at 5.77% and lastly, other carbapenemases at 1.92%.

There were a total of 115 gram-negative isolates and 45 gram-positive isolates with a 2.5:1 ratio.

The most common gram-negative isolate was *Klebsiella pneumoniae* (n = 20, 17.4%) with 35% being multidrug resistant (Figure 1). The most common gram-positive isolate was *Staphylococcus aureus* (n = 15, 33.3%) with 33% having methicillin resistance (Figure 2). *Achromobacter xylosoxidans* ss xylosoxidans for gram-negative isolates and *Staphylococcus epidermidis* for gram-positive isolates particularly had higher multidrug resistance rates (*p*-value 0.031 and *p*-value 0.013, respectively).

For gram-negative isolates, erythromycin had the most resistance at 17.53% followed by oxacillin and clindamycin both at 13.4%. For gram-positive isolates, highest resistance were seen with ampicillin at 18.99% followed by cefuroxime at 13.57% and amoxicillin-clavulanate at 11.63% as seen in Figure 3A and 3B.

Higher UTWCS 2D through 3D (Crude OR = 1.114 [95% CI 1.008 - 1.230], *p*-value 0.035) and PEDIS Score ≥8 (Crude OR = 1.290, [95% CI 1.044 - 1.596], *p*-value 0.017) were

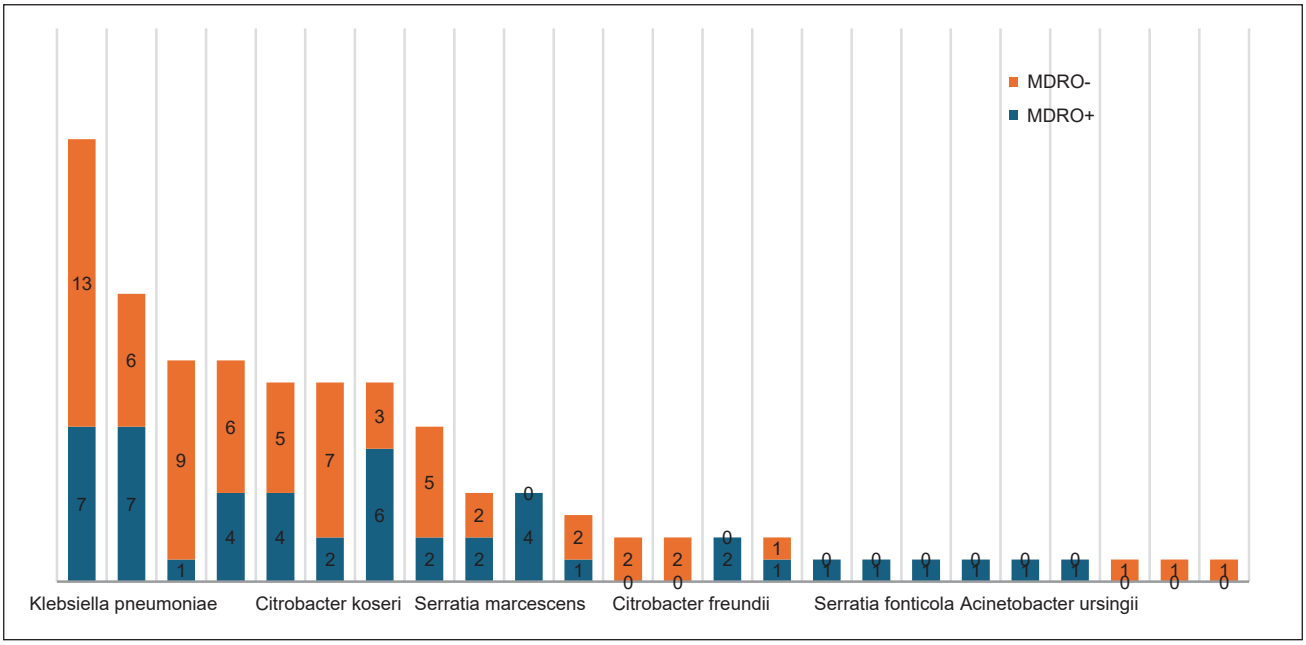

Figure 1. Proportion of MDRO-positive vs MDRO-negative among gram-negative isolates (n = 115).

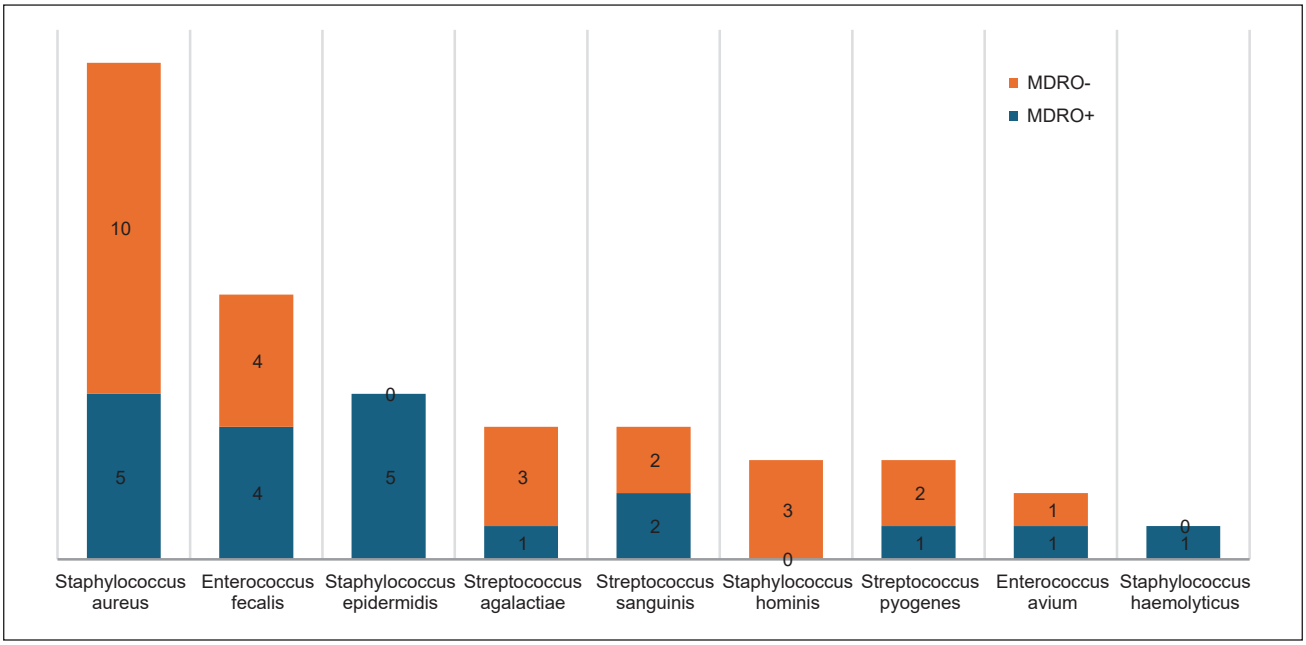

Figure 2. Proportion of MDRO-positive vs MDRO-negative among gram-positive isolates (n = 45).

observed in MDRO-positive cases as well as in patients who were previously admitted for diabetic foot ulcer (Crude OR = 2.283, [95% CI 1.103 to 4.725], *p*-value 0.037) as seen in Table 2. Logistic regression showed that only a previous admission was significantly associated with MDRO positivity (Adjusted OR = 2.997 [95% CI: 1.041 – 8.625], *p*-value 0.042) after correcting for confounders.

Table 2. Univariate analysis of factors associated with multidrug resistant organism

Parameters	Crude odds ratio	95% CI	*P*-value
UTWCS	1.1138	1.0083 to 1.2303	0.034
PEDIS score	1.2907	1.0437 to 1.5960	0.019
Readmission	2.2826	1.1028 to 4.7246	0.026

DISCUSSION

DFU is a serious complication of DM with a worldwide prevalence rate of 15%.[9] In a clinical profiling of DFU cases in General Santos, Philippines, similar rates are observed. There was also a male prevalence with a ratio of 1.4:1 in their study. Associated co-morbidities were peripheral neuropathy and peripheral artery disease. DFU by itself already causes significant morbidity and mortality. Recurrence rates are common and are usually seen in

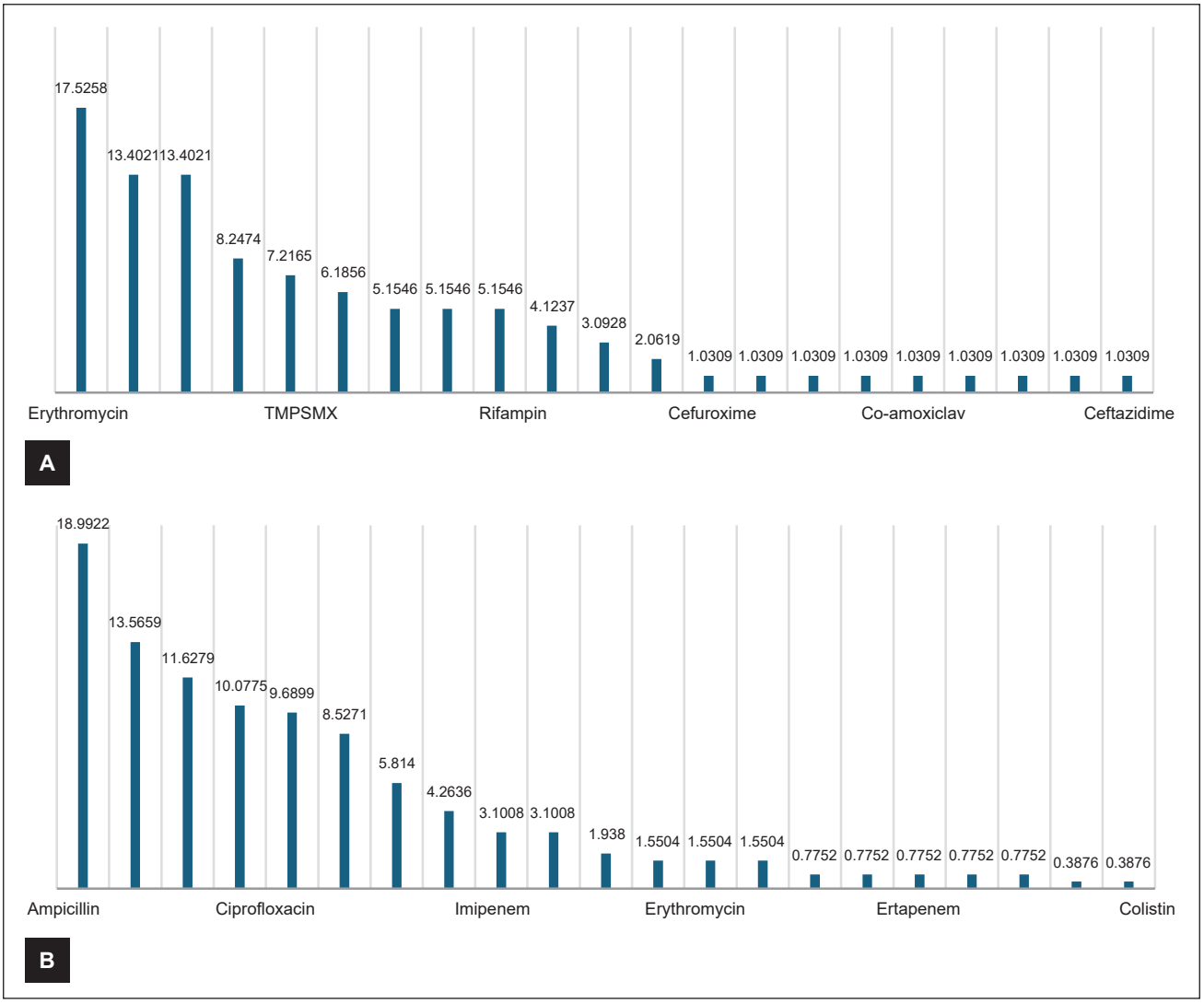

Figure 3. (A) Resistance rates to antibiotics of gram-negative cultures (n = 258) and **(B)** Resistance rates to antibiotics of gram-positive cultures (n = 97)

patients with DFU who have multiple lesions, plantar location, and presence of peripheral neuropathy. 48.00% of patients admitted for diabetic foot ulcers require surgical intervention and 14.00% of those who needed surgical intervention required amputation.[1] Multidrug resistant infections further complicate outcomes with note of increased amputation rates and mortality rates.[13]

This study observed the associated risk factors for multidrug resistance in patients with diabetic foot ulcers. MDRO isolates were seen in 34.40% patients admitted for diabetic foot ulcers. This is lower in contrast to known MDRO rates in diabetic foot ulcers at 63.40%.[4]

Microbiologic profile

A study by Jain and Barman in 2017 showed that MDROs are present in both major and minor amputations but gram-negative MDROs were seen more on deep ulcers while gram-positive MDRO were seen more on superficial ulcers.[5]

Bacteriologic profiling in a study done in a tertiary care setting in Malaysia in 2020 showed that *P. aeruginosa* and *S. aureus* were the most common isolates in DFUs, followed by Methicillin-Resistant *S. aureus* (MRSA) and *Bacteroides*. Among the gram-positive isolates, there were high resistance rates noted for penicillin, tetracycline, and erythromycin. For gram-negative isolates, high resistance rates were noted for fluoroquinolones and ampicillin. Clindamycin resistance was notable for anaerobic isolates.[8] The same resistance patterns can be observed in our study.

In another microbiologic study in India in 2018, *S. aureus* and *P. aeruginosa* were also the most common gram-positive and gram-negative isolates, respectively. Four of ninety-one (4.4%) staphylococcal isolates were MRSA and five of sixty-seven (7.56%) of pseudomonal isolates were Extended-Spectrum Beta-Lactamase (ESBL)-positive on resistance screening. Several isolates with pan-resistant phenotypes underwent genotypic testing, confirming MDR in these isolates.[3]

Similarly, *Staphylococcus aureus* was also the most common gram-positive isolate with 33% of isolates having methicillin resistance. Although *Klebsiella pneumoniae* was the most common gram-negative isolate, this was followed by *Enterobacter cloacae* (11.30%), *Escherichia coli* (8.70%), and *Pseudomonas aeruginosa* (8.70%). In a study looking at outcomes of MDRO infected DFUs, *Klebsiella pneumoniae* infection was found to have a high fatality rate with OR = 7.7 (95% CI 1.24 -47.96).[17]

Risk factors

Several studies are available in assessing patient-related risk factors for MDRO. In a study by Kathirvel et al. in South India in 2018, after logistic regression, they found that high grade ulcers and recurrent ulcers were significant risk factors for MDRO infection. They also saw a higher gram-negative to gram-positive infectivity with a 2.3:1 ratio.[8] Other Indian population studies, confirmed these risk factors along with diabetes duration >20 years.[18,19]

Three publications from China for risk factors for MDRO DFU determined that hospitalizations within the last 12 months for diabetic foot is a risk factor for MDRO. Liu et al. in 2022 showed that previous hospitalization, ulcer size >4 cm, surgical therapy, and CRP were independent risk factors for having MDR isolates in diabetic foot ulcers.[1,10]

Ji et al., in 2014 showed that previous hospitalization, higher ulcer size and grade, previous antibiotic use, and osteomyelitis were significant risk factors for MDRO after logistic regression.[20]

Several diabetic foot classification systems are available and are recommended by the International Working Group for on the Diabetic Foot (IWGDF) 2023 to aid healthcare workers in communicating wound characteristics as well as in stratifying healing likelihood and amputation risk. UTWCS is one of the more common scoring systems used.[21] PEDIS is another validated scoring system.[22] A higher UTWCS score has more correlation with the presence of neuro-ischemic pathology and osteomyelitis whereas a higher PEDIS score has more correlation with peripheral artery disease, neuropathy, severe infection, tissue involvement, and large ulcer size. Increased scores correlated with difficulty healing and higher amputation rates.

Although this study was unable to establish diabetes duration and severity as well as ulcer size ≥ 4 cm as MDRO risk factors, univariate analysis showed that higher grade ulcers, as shown by UTWCS score 2D-3C and PEDIS Score ≥8, have significant risk for MDRO infection.

On logistic regression it showed that patients who had any previous hospitalization for diabetic foot ulcer management were 3 times more likely to present with MDRO infection as supported by Liu and Ji's publications.[10,20] This may be due to exposure to antibiotics which may lead to mutations for drug resistant genes or may be due to exposure to opportunistic organisms during previous hospitalizations.

Several limitations in this study include its retrospective nature especially since wound description and wound scoring may have inter-observer variability.[16] A prospective study may better classify wound characteristics and avoid variability. Anaerobic sampling is not routinely done in this institution and was not available for all patients hence no report can be made regarding drug resistance in anaerobic organisms.

CONCLUSION

There is high burden of multidrug resistant infections in diabetic foot ulcers. High wound classification by UTWCS and PEDIS scoring are significant risk factors for presence of MDRO isolates in diabetic foot ulcers. Any previous hospitalization for diabetic foot ulcer is associated with MDRO infection in succeeding admissions.

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Statement of Authorship
Both authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
AVP: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Original Draft Preparation, Reviewing, Editing, Visualization, Project Administration; **DAP:** Conceptualization, Methodology, Validation, Resources, Reviewing, Editing, Supervision, Project Administration.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
Both authors declared no conflict of interest.

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ORIGINAL ARTICLE

Prevalence and Associated Factors of Erectile Dysfunction Among Filipino Men With Type 2 Diabetes Mellitus in a Tertiary Hospital in San Juan City, Metro Manila, Philippines

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Abstract

Background. Erectile dysfunction (ED) is a common complication among men with Type 2 Diabetes Mellitus (T2DM), but updated data from the Philippines remain limited. This study determined the prevalence of ED and evaluated associated clinical and socioeconomic factors among Filipino men with T2DM.

Methodology. We conducted a cross-sectional study among 384 adult Filipino men with T2DM recruited from private clinics, an outpatient service clinic, and an affiliated community clinic of Cardinal Santos Medical Center. ED was assessed using the International Index of Erectile Function-5 (IIEF-5). Comparative analyses between participants with and without ED were performed, followed by multivariable logistic regression analysis. Results are presented as adjusted odds ratios (AORs) with 95% confidence intervals (CIs).

Results. The prevalence of erectile dysfunction (ED) among Filipino men with T2DM in this study was 88.02% (338/384; 95% CI: 84.4–91.1). Common comorbidities in the study population included hypertension (67.45%), dyslipidemia (44.53%), and coronary artery disease (26.56%). Regarding glycemic control, only 30.31% of participants had an HbA1c level <7%. Participants with ED were significantly older than those without ED (median age: 60 [IQR 17] vs 48 years [IQR 15], p <0.001) and were more likely to have a longer duration of diabetes. On multivariable analysis, dyslipidemia remained independently associated with higher odds of ED (AOR = 2.57, 95% CI: 1.20–5.53; p = 0.015), whereas higher socioeconomic status was associated with lower odds of ED (AOR = 0.31, 95% CI: 0.13–0.75; p = 0.010).

Conclusion. ED was highly prevalent among Filipino men with T2DM included in this study. Dyslipidemia and socioeconomic status were independently associated with ED and may help identify patients who could benefit from more thorough screening. Further studies involving larger cohorts and improved sampling methods are needed to validate these findings and better understand the factors underlying the high prevalence of ED observed in this population.

Key words: erectile dysfunction, diabetes mellitus, Filipino, prevalence

INTRODUCTION

In the general Asian population, the overall reported prevalence of erectile dysfunction (ED) ranges from 2% to 81.8%.[1] In the Philippines, the prevalence is approximately 33% to 65%.[1] Compared to the general population, the prevalence of ED among patients with type 2 diabetes mellitus (T2DM) ranges from 35 to 90%, and men with diabetes mellitus have an approximately three-fold increased risk of developing ED.[2-4] In addition, ED presents 10–15 years earlier in men diagnosed with diabetes, and more severe cases were associated with a poorer quality of life.[5]

Erectile dysfunction (ED) is a common problem in men worldwide. ED is defined as the persistent inability to attain and maintain an erection to allow satisfactory sexual performance resulting from vascular endothelial damage from various cardiovascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and smoking.[6] This damage results in vascular obstruction, plaque rupture, thrombosis, arteriosclerosis, and erectile

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dysfunction (ED).[4] Additionally, increased body mass index (BMI) is associated with a higher risk of ED, with obesity linked to a 1.3-fold greater risk compared to normal weight, as well as a positive correlation between obesity and the risk of moderate/severe ED. It is a crucial global disease affecting physical health, mental health, and overall quality of life. A study has shown that the presence of ED significantly impacts the quality of life in men.[7,8] Unfortunately, its presence is not routinely elicited during patient encounters due to various cultural factors.[9] Most of the available literature and epidemiologic studies on ED in diabetes mellitus and associated chronic conditions such as hypertension and cardiovascular disorders and other associated factors such as obesity, dyslipidemia, metabolic syndrome, cigarette smoking, stress, anxiety, and depression are based on Western populations.[3] The relationship between socioeconomic factors and erectile dysfunction (ED) remains unclear, with studies reporting inconsistent findings.[10,11]

Previous studies on the prevalence of erectile dysfunction (ED) in the Philippines date back two decades, with the studies of Zulueta et al., and Piores et al.[12,13] A more recent study conducted in 2019 specifically focused on the patients' demographics.[14] While these studies provide valuable insights, the epidemiology may have changed due to rapid changes in diabetes management, lifestyle patterns, and socioeconomic conditions. Despite the extensive global research on erectile dysfunction (ED), there remains a lack of recent data from the Philippines and the Southeast Asian region addressing these shifts. To fill this gap, the current study aims to provide updated data on ED prevalence among Filipino men with T2DM, considering evolving clinical and demographic factors. Additionally, this study utilizes the IIEF-5 questionnaire, a shorter, more user-friendly tool, to ensure efficient and accurate assessments of ED.

The International Index of Erectile Function (IIEF-5) was developed to diagnose the presence and severity of ED.[15] The five items in this questionnaire focused on erectile function and intercourse satisfaction and is considered an excellent diagnostic test. A cutoff score of 21 (range of scores, 5-25) discriminated best (sensitivity = 0.98, specificity = 0. 88). ED was classified into five severity levels, ranging from none (22-25) to severe (5-7). IIEF-5 possesses favorable properties for detecting the presence and severity of ED.[15] Hence, in this study, we aim to determine the prevalence of ED among Filipino men with diabetes mellitus and to identify associated medical and socioeconomic risk factors.

OBJECTIVES

General objective

This study determined the prevalence of erectile dysfunction and its associated risk factors among Filipino men with Type 2 Diabetes Mellitus in Cardinal Santos Medical Center, San Juan, Philippines.

Specific objectives

This study compared the demographics including family history, lifestyle, educational, professional, marital status and socioeconomic factors of patients with versus without ED among Filipino men diagnosed with type 2 DM. This study also determined the association of glycemic control, duration of diabetes, BMI, presence of cardiovascular risk factors, dyslipidemia, hypertension, and coronary artery disease of patients with versus without ED among Filipino men diagnosed with type 2 DM.

METHODOLOGY

Study design

This was a cross-sectional study conducted from March 1, 2024 to February 28, 2025 at selected private clinics, an outpatient service clinic, and an affiliated community health clinic of Cardinal Santos Medical Center in San Juan City, Philippines. Adult male patients with T2DM were recruited through convenience sampling. All participants provided informed consent before enrolment. The study was approved by the Cardinal Santos Medical Center Research Center and Research Ethics Review Committee (CRC TM 2023-42; 2023-060).

Study population

Adult male patients with type 2 diabetes mellitus (DM) were recruited using convenience sampling. Participants in this study had to meet the following inclusion criteria: (1) Male patients with type 2 diabetes (according to the American Diabetes Association criteria for type 2 diabetes), (2) Aged 18 years or older, and (3) Sexually active. The exclusion criteria were: (1) Patients unwilling to give consent, (2) history of anatomical abnormalities of the genitourinary system, (3) history of gonadectomy or pelvic surgery, (4) type 1 diabetes, (5) patients with chronic kidney disease on hemodialysis, (6) history of organ transplantation, (7) History of alcoholism or substance abuse within the past 12 months, (8) primary diagnosis of hyposexuality, (9) inability to complete a self-administered questionnaire due to eye or extremity disabilities, and (10) inability to understand English or Filipino. The participant selection and data collection process is summarized in Figure 1.

Sample size estimate and procedure

This study considered a 53% prevalence of ED in Philippines, and the minimum sample size requirement was computed using R version 4.0.3.[1] A sample size of 383 participants is needed to estimate of prevalence of erectile dysfunction among patients with type 2 diabetes mellitus, with 5% half-width precision and 95% level of significance in a population with expected prevalence of 53%.[1] A sample size of 222 is needed to achieve 80% power with 5% level of significance in a logistic regression analysis to detect a desired odds ratio of at least 1.68 (small effect

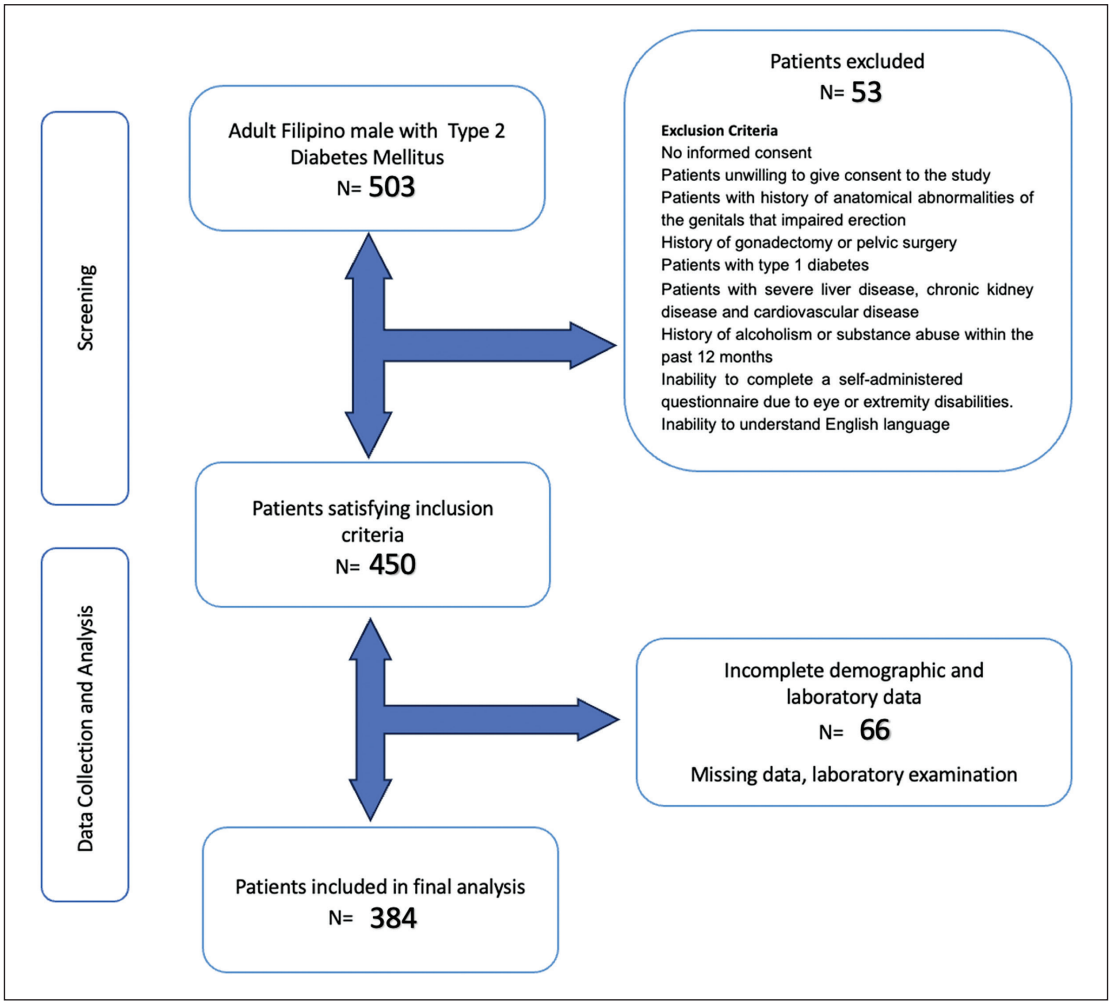

Figure 1. Participant selection and data collection flowchart. Of 503 patients screened, 450 met the inclusion criteria. After further exclusions due to incomplete data, 384 were included in the final analysis.

size) in a population expected to have 53% prevalence of erectile dysfunction, and an R-squared of about 40% for the different co-variates.[5]

Data analysis

The demographic and clinical profile of male patients with type 2 diabetes mellitus consulting Cardinal Santos Medical Center and community clinic were summarized by descriptive statistics. Numerical variables were described as median and interquartile range. Categorical variables were described as frequency and percentage. The prevalence of erectile dysfunction among patients with type 2 diabetes mellitus were determined and reported as point estimate and 95% confidence interval. The association of duration of diabetes, glycemic control, diabetes treatment, BMI, smoking, alcohol use, physical activities, hypertension, dyslipidemia, and social status with erectile dysfunction was determined by multivariable logistic regression analysis. Variable selection was performed by backward elimination with LR test <0.05 as criteria for variable retention.

The magnitude of the association was reported as the odds ratio with a 95% confidence interval, using multiple logistic regression to control for potential confounders. Data analysis was performed using Stata 17. Participants with incomplete questionnaires or missing key analytic variables were excluded prior to analysis and were not statistically imputed. The final analytic dataset included only complete cases; therefore, no missing values were present in the analyzed sample. Normality of distribution of numerical variables were assessed by Shapiro-Wilk test of normality. All tests of hypothesis were evaluated with significance level set at $\alpha = 0.05$.

RESULTS

Study population and prevalence of ED

A total of 384 participants were included in the study. The mean age of the study population was 58.65 + 12.71 years and the mean BMI was 28.12 ± 5.90 kg/m². Most participants had a family history of diabetes mellitus (76.04%), while 53.39% had a history of smoking and 27.86% reported alcohol consumption. Hypertension (67.45%), dyslipidemia (44.53%), and coronary artery disease (26.56%) were the most common comorbidities. Diabetes duration of more than 10 years was the most frequent category (39.84%),

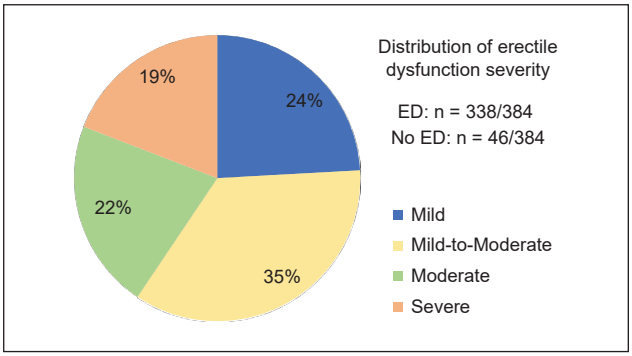

Figure 2. Distribution of erectile dysfunction severity. The proportions of mild, mild-to-moderate, moderate, and severe cases were 23.96% (n = 81), 34.91% (n = 118), 22.19% (n = 75), and 18.93% (n = 64), respectively.

while 30.31% of participants had an HbA1c level <7%. The demographic and clinical characteristics of the study cohort are summarized in Tables 1 and 2.

Among the 384 participants, 338 had erectile dysfunction, corresponding to a prevalence of 88.02% (95% CI: 84.4–91.1). Based on the IIEF-5, ED severity was classified as mild in 23.96%, mild-to-moderate in 34.91%, moderate in 22.19%, and severe in 18.93% of affected participants (Figure 2). Comparisons between participants with and without ED are presented in Tables 3 and 4.

Comparative analysis of patients with and without erectile dysfunction

Demographic and lifestyle factors

Participants with ED were significantly older than those without ED (median age: 60 (IQR 17) vs 48 years (IQR 15), p <0.001). Longer diabetes duration (>10 years) was more common in the ED group (42.60% vs 19.57%, p = 0.007) (Figure 3).

Occupation, educational attainment, and socioeconomic status were also significantly associated with ED (Table 3). Compared with participants without ED, those with ED were less likely to have white-collar occupations, attain higher levels of education, and belong to the high socioeconomic status group. Other demographic and lifestyle factors, including marital status, smoking, alcohol intake, exercise were not significantly associated with ED.

Table 1. Demographic and lifestyle characteristics of the study population (n = 384)

	Full cohort, n = 384 Mean (SD); min to max, or frequency (%)
Age (years)	58.65 (12.71); 27 to 78
Family history of DM	292 (76.04%)
Smoking (pack-years)	
Never-smoker	179 (46.61%)
Light smoker (1-10)	111 (28.91%)
Moderate smoker (11-20)	49 (12.76%)
Heavy smoker (>20)	45 (11.72%)
Drinking alcohol	107 (27.86%)
Exercise	
Regularly	127 (33.07%)
Sometimes	139 (36.20%)
Never	118 (30.73%)
Occupation	
White-collar	218 (56.77%)
Blue-collar	62 (16.15%)
Retired	104 (27.08%)
Education level	
Elementary graduate or less	4 (1.04%)
High School graduate or less	57 (14.84%)
College graduate or less	282 (73.44%)
Postgraduate	41 (10.68%)
Marital status	
Single	60 (15.62%)
Married	298 (77.60%)
Separated	4 (1.04%)
Widow	22 (5.73%)
Monthly household income	
Low socioeconomic status	100 (26.04%)
Middle socioeconomic status	73 (19.01%)
High socioeconomic status	211 (54.95%)

Values are presented as mean (standard deviation) with range or as frequency (%). DM, diabetes mellitus.

Table 2. Clinical and laboratory characteristics of the study population (n = 384)

	Full cohort, n = 384 Mean (SD); min to max, or frequency (%)
BMI (kg/m²)	28.12 (5.90); 12.41 to 59.51
Duration of DM (years)	
<1	58 (15.10%)
1-5	111 (28.91%)
6-10	62 (16.15%)
>10	153 (39.84%)
Comorbidities	
Hypertension	259 (67.45%)
Coronary artery disease	102 (26.56%)
Thyroid disease	16 (4.17%)
Chronic kidney disease	34 (8.85%)
Dyslipidemia	171 (44.53%)
Vital signs and laboratories	
SBP <140 mmHg	339 (88.28%)
DBP <90 mmHg	364 (94.79%)
Fasting plasma glucose <100 mg/dL	72 (18.75%)
HbA1c <7.0%	116 (30.31%)
Total cholesterol <200 mg/dL	297 (77.34%)
HDL >40 mg/dL	230 (59.90%)
LDL <100 mg/dL	230 (59.90%)
Triglycerides <150 mg/dL	244 (76.73%)
eGFR >89 mL/min/1.73 m²	182 (47.40%)

Values are presented as mean (standard deviation) with range or as frequency (%). BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

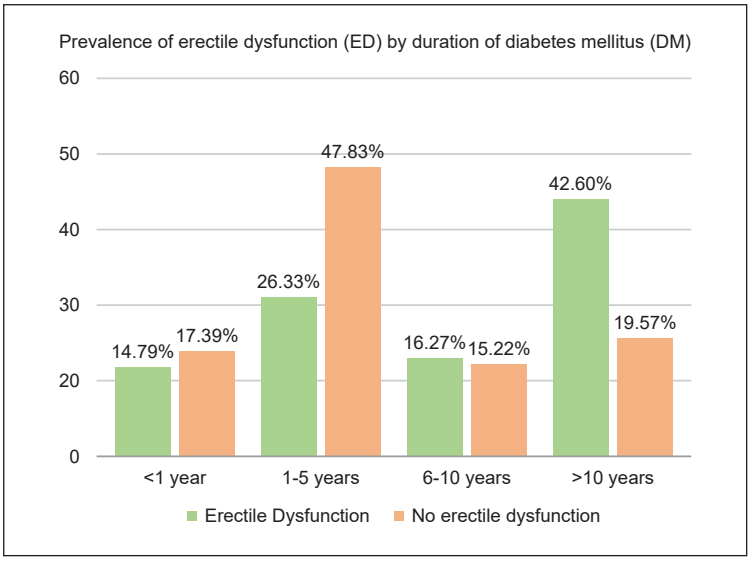

Figure 3. Prevalence of erectile dysfunction (ED) by duration of diabetes mellitus (DM) among diabetic patients. ED prevalence differed significantly across duration groups (<1 year, 1–5 years, 6–10 years, and >10 years) (*P* = 0.007).

Comorbidities and diabetes-related factors

Hypertension, coronary artery disease (CAD), and dyslipidemia were significantly associated with ED (Table 4). Compared with the non-ED group, participants with ED had higher rates of hypertension (69.52% vs 52.17%, p = 0.018), CAD (28.40% vs 13.04%, p = 0.027), and dyslipidemia (47.34% vs 23.9%, p = 0.003). No significant associations were observed for body mass index, family history of diabetes, thyroid disease, or chronic kidney disease (Table 4).

Table 3. Comparison of demographic and lifestyle characteristics between participants with and without erectile dysfunction (ED)

	ED, n = 338	No ED, n = 46	*P*-value
	Median (IQR); Frequency (%)		
Age (years)	60 (17)	48 (15)	<0.001
Marital status			0.765
Single	52 (15.38%)	8 (17.39%)	
Married	261 (77.22%)	37 (80.43%)	
Separated	4 (1.18%)	0	
Widow	21 (6.21%)	1 (2.17%)	
Smoking (pack-years)			0.880
Never-smoker	158 (46.75%)	21 (45.65%)	
Light smoker (1-10)	96 (28.40%)	15 (32.61%)	
Moderate smoker (11-20)	43 (12.72%)	6 (13.04%)	
Heavy smoker (>20)	41 (12.13%)	4 (8.70%)	
Drinking alcohol	94 (27.81%)	13 (28.26%)	0.949
Exercise			0.689
Regularly	114 (33.73%)	13 (28.26%)	
Sometimes	120 (35.50%)	19 (41.30%)	
Never	104 (30.77%)	14 (30.43%)	
Occupation			0.004*
White-collar	182 (53.85%)	36 (78.26%)	
Blue-collar	56 (16.57%)	6 (13.04%)	
Retired	100 (29.59%)	4 (8.70%)	
Education level			0.034*
Elementary graduate or less	4 (1.18%)	0	
High School graduate or less	56 (16.57%)	1 (2.17%)	
College graduate or less	243 (71.89%)	39 (84.78%)	
Post graduate	35 (10.36%)	6 (13.04%)	
Monthly household income			0.007*
Low socioeconomic status	92 (27.22%)	8 (17.39%)	
Middle socioeconomic status	70 (20.71%)	3 (6.52%)	
High socioeconomic status	176 (52.07%)	35 (76.09%)	

Prevalence of erectile dysfunction among patients with diabetes mellitus was 88.02% (95% CI, 84.35–91.09). Values are presented as median (interquartile range) or frequency (%). ED, erectile dysfunction; IQR, interquartile range. **P* <0.05 was considered statistically significant.

Medications

Most participants with ED were receiving oral antidiabetic drugs alone (62.43%), followed by oral antidiabetic drugs with insulin (22.49%), insulin alone (9.76%), non-pharmacologic management (3.55%), and no treatment (1.78%). Statin use was higher in the ED group compared with the non-ED group (78.34% vs 65.22%, p = 0.048). No significant differences were observed between groups in the use of beta-blockers, calcium channel blockers, ARBs/ACE inhibitors, diuretics, or fibrates.

Vital signs and laboratory parameters

No significant differences were observed between participants with and without ED in systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HbA1c, total cholesterol, HDL cholesterol, or triglyceride levels (all p >0.05). Significant differences were observed in LDL cholesterol and eGFR categories (Table 4). LDL cholesterol levels <100 mg/dL were more common among participants with ED (62.13% vs 43.48%, p = 0.015), whereas an eGFR >89 mL/min/1.73 m² was more common among participants without ED (71.74% vs 44.08%, p = 0.001).

Multivariable analysis of factors associated with erectile dysfunction

Variables found to be significant in univariate analyses were included in the multivariable logistic regression model (Table 5). Dyslipidemia remained independently associated with ED, with participants with dyslipidemia having higher odds of ED compared with those without dyslipidemia (AOR = 2.57, 95% CI: 1.20–5.53; p = 0.015). In contrast,

Table 4. Comparison of clinical characteristics of participants with and without erectile dysfunction (ED)

	ED, n = 338	No ED, n = 46	*P*-value
	Median (IQR); Frequency (%)		
BMI (kg/m²)			0.492
<18.5 (underweight)	4 (1.18%)	1 (2.17%)	
18.5-23.9 (normal)	76 (22.49%)	6 (13.04%)	
24-28.9 (overweight)	143 (42.31%)	21 (45.65%)	
>29 (obese)	115 (34.02%)	18 (39.13%)	
Duration of DM (years)			0.007
<1	50 (14.79%)	8 (17.39%)	
1-5	89 (26.33%)	22 (47.83%)	
6-10	55 (16.27%)	7 (15.22%)	
>10	144 (42.60%)	9 (19.57%)	
Family history of DM	254 (75.15%)	38 (82.61%)	0.266
Diabetes treatment			0.067
None	6 (1.78%)	0	
Non-pharmacologic	12 (3.55%)	1 (2.17%)	
OAD alone	211 (62.43%)	39 (84.78%)	
Insulin	33 (9.76%)	2 (4.35%)	
OAD and insulin	76 (22.49%)	4 (8.70%)	
Comorbidities			
Hypertension	235 (69.52%)	24 (52.17%)	0.018
Coronary artery disease	96 (28.40%)	6 (13.04%)	0.027
Thyroid disease	14 (4.14%)	2 (4.35%)	>0.999
Chronic kidney disease	29 (8.58%)	5 (10.87%)	0.582
Dyslipidemia	160 (47.34%)	11 (23.91%)	0.003
Hypertension treatment			
Beta blocker	63 (18.64%)	5 (10.87%)	0.195
CCB	94 (27.81%)	13 (28.26%)	0.949
ARB/ACE	141 (41.72%)	18 (39.13%)	0.738
Diuretics	8 (2.37%)	0	0.603
Alpha blocker	0	0	-
Dyslipidemia treatment			
Statins	264 (78.34%)	30 (65.22%)	0.048
Fibrates	18 (5.33%)	1 (2.17%)	0.713
Vital signs and laboratory parameters			
SBP <140 mmHg	297 (87.87%)	42 (91.30%)	0.497
DBP <90 mmHg	321 (94.97%)	43 (93.48%)	0.720
Fasting plasma glucose <100 mg/dL	63 (18.64%)	9 (19.57%)	0.880
HbA1c <7.0%	101 (29.88%)	15 (32.61%)	0.705
Total cholesterol <200 mg/dL	263 (77.81%)	34 (73.91%)	0.554
HDL >40 mg/dL	201 (59.47%)	29 (63.04%)	0.642
LDL <100 mg/dL	210 (62.13%)	20 (43.48%)	0.015*
Triglycerides <150 mg/dL	212 (75.99%)	32 (82.05%)	0.401
eGFR >89 mL/min/1.73 m²	149 (44.08%)	33 (71.74%)	0.001*

Values are presented as frequency (%). DM, diabetes mellitus; OAD, oral antidiabetic drug; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate. *P <0.05 was considered statistically significant.

participants with high socioeconomic status had lower odds of ED compared with those with low socioeconomic status (AOR = 0.31, 95% CI: 0.13–0.75; $p = 0.010$).

Hypertension (AOR = 1.98, 95% CI: 1.00–3.94; $p = 0.051$) and insulin use (AOR = 2.61, 95% CI: 0.96–7.08; $p = 0.060$) were associated with higher odds of ED but did not reach statistical significance in the adjusted model.

Table 5. Multivariable logistic regression analysis of factors associated with erectile dysfunction (ED)

Factors	AOR	95% CI	*p*-value
Duration of diabetes (years)			
<1	Reference		
1-5	0.75	0.28, 1.98	0.563
6-10	1.55	0.47, 5.04	0.470
>10	2.36	0.78, 7.17	0.130
Good glycemic control	1.38	0.65, 2.91	0.403
Oral antidiabetics	0.32	0.08, 1.25	0.101
Insulin	2.61	0.96, 7.08	0.060
BMI			
Underweight	0.31	0.02, 4.26	0.382
Normal	Reference		
Overweight	0.80	0.28, 2.28	0.674
Obese	1.01	0.34, 3.00	0.983
Smoking (pack-years)			
Never-smoker	Reference		
Light smoker (1-10)	0.79	0.36, 1.75	0.569
Moderate smoker (11-20)	0.82	0.29, 2.35	0.712
Heavy smoker (>20)	1.24	0.36, 4.24	0.728
Alcohol use	1.16	0.54, 2.47	0.704
Exercise			
Regularly	1.19	0.49, 2.93	0.701
Sometimes	0.82	0.35, 1.89	0.637
Never	Reference		
Hypertension	1.98	1.00, 3.94	0.051
Dyslipidemia	2.57	1.20, 5.53	0.015*
Social status			
Low socioeconomic status	Reference		
Middle socioeconomic status	1.64	0.40, 6.79	0.494
High socioeconomic status	0.31	0.13, 0.75	0.010*

Adjusted odds ratios (AOR) with 95% confidence intervals (CI) and *p*-values are presented. Reference categories are indicated. *P <0.05 was considered statistically significant.

DISCUSSION

The main finding of this study is the high prevalence of ED among Filipino men with T2DM, affecting 88.02% of participants. The prevalence is generally higher in Asian and African countries: in the Philippines, it ranges from 78.8% to 99%, while studies in Ethiopia and Eastern Sudan report prevalences of 83.8% and 81.1%, respectively.[12,13,16,17] These data are likely influenced by socio-economic factors and healthcare access. In other Asian countries, ED prevalence in T2DM patients ranges from 59.38% to 64.2%, with a lower rate of 52.9% reported in a study in Europe.[5,6,18] The prevalence of ED in the Philippines remains high. This is consistent with previous studies of Zulueta et al., at 84.6%, Piores et al., at 99%, and Maniwang at 78.8%, reinforcing the consistent high burden of ED in the country.[12-14] Although most studies used the IIEF-5 tool for consistency, differences in sample size, methodology, and study design may affect the reported rates. A summary of these selected studies is presented in Table 6.

In the Philippines, health-seeking behavior, particularly concerning sexual health, is influenced by cultural, religious, and economic factors. Open discussions about sexual health are often stigmatized, leading to reluctance among men to seek medical advice. Economic barriers, such

as the cost of healthcare, further limit access to services, especially among lower-income populations.[19]

The persistently high prevalence of ED remains a serious concern. This study aims to improve glycemic control and prevent complications like ED, with a focus on early screening and treatment for men with diabetes who are at a higher risk of developing ED. Most research on ED in diabetes has focused on Western populations, but this study fills a gap by specifically addressing Filipino patients.

This expanded research initiative involves multiple sites, including hospital private clinics, outpatient services, and an affiliated community clinic, to raise awareness about the diagnosis of ED. Through engagement with diverse groups, the study estimated the prevalence and contributing factors of ED among Filipino men with diabetes to aid in enhancing early screening and treatment strategies for diabetic patients.

Age, duration of diabetes, and their role in ED

Age and the duration of diabetes were significantly associated with ED in this study, consistent with findings from both local and international studies.[6,12-14,16,20] While age alone played a significant role in the onset of ED, its impact was more pronounced when combined with a longer duration of diabetes.[21] Specifically in this study, the risk of ED increased with the duration of diabetes, with individuals having diabetes for over 10 years being 2.36 times more likely to develop ED compared to those with diabetes for less than a year (OR=2.36, 95% CI 0.78-7.17, p = 0.130); however, this association did not reach statistical significance (p = 0.130).

The combined effects of aging and diabetes on vascular dysfunction significantly contribute to the pathophysiology of ED. Both conditions lead to endothelial dysfunction—a hallmark of insulin resistance—that impairs nitric oxide (NO) production, a crucial vasodilator for erectile function. This results in vascular stiffness and reduced nitric oxide bioavailability, both of which are vital for a normal erectile response.[22,23] Given NO's essential role in penile erection, its dysregulation explains why insulin resistance and diabetes frequently contribute to sexual dysfunction.[22]

Additionally, insulin resistance is associated with inadequate vasodilation and paradoxical vasoconstriction in both coronary and peripheral arteries, worsening cardiovascular complications, and increasing ED risk.[24]

Interestingly, good glycemic control was not significantly associated with erectile ED (AOR = 1.38, 95% CI: 0.65–2.91, p = 0.403). In contrast, insulin therapy showed a trend toward significance with a 2.61-fold higher likelihood (AOR = 2.61, 95% CI: 0.96–7.08, p = 0.060) suggesting a potential relationship on ED risk. However, the lack of statistical significance in both results suggests that further investigation is needed as findings may be influenced by variations in treatment regimens or to the study's cross-sectional design, which limits causal inference.

Chronic hyperglycemia in diabetes activates several biochemical pathways, including formation of advanced glycation end products, the polyol pathway, and the activation of protein kinase C, all of which are believed to contribute to endothelial dysfunction, neuropathy, and structural changes in penile tissue.[25] This finding is consistent with the observation that the majority of patients on insulin (n = 63/115) had a diabetes duration of over 10 years. This may indicate that patients requiring insulin therapy are more

Table 6. Comparative summary of studies on erectile dysfunction prevalence among patients with diabetes mellitus

Author (Year), Country	Study Type	Diagnosis Tool	Prevalence	Limitations
Tabora J et al. (2025), Philippines	Prospective, cross sectional (n = 384)	IIEF-5	88.02%	Single center, less community clinic participants, inability to quantify phosphodiesterase 5 inhibitors (PDEi5) use among participants
Maniwang D (2019), Philippines[14]	Descriptive, correlational, cross sectional study (n = 85)	IIEF-5	78.8%	Limited identified variables and sample size
Piores OM et al. (2004), Philippines[13]	Cross sectional, analytic (n = 127)	IIEF 15	99%	No HbA1c determination, majority of sample size is from diabetes clinic
Zulueta V et al. (2001), Philippines[12]	Descriptive (n = 52)	IIEF 15	84.6%	No mentioned limitations
Gobena MB et al. (2023), Ethiopia[16]	Facility-based cross-sectional study (n = 210)	IIEF-5	83.8%	Cause-and-effect relationship cannot be reported
Parmar RS et al. (2022), India[18]	Hospital-based cross-sectional observational study (n = 357)	IIEF-5	59.38%	Confounding factors (hypolipidemic drugs)
Omar S et al. (2022), Eastern Sudan[17]	Cross-sectional study (n = 331)	IIEF-5	81.1%	Components not tested include LDL and HDL, exercise, family history, employment, income
Tamrakar D et al. (2021), Nepal[37]	Cross-sectional hospital-based study (n = 160)	IIEF-5	76.87%	Single-center study
Xu Y et al. (2018), China[6]	Observational, cross-sectional study (n = 495)	IIEF-5	64.2%	Single-center cross-sectional study, recruited in a diabetes hospital
Derosa G et al. (2015), Italy[19]	Observational, cross-sectional study (n = 220)	IIEF	52.9%	Cross sectional, observational nature that does not allow us to identify a causal link
Vo KT et al. (2014), Vietnam[8]	Cross-sectional study (n = 151)	IIEF-5	84%	IIEF-5 sensitivity and specificity, convenience sampling, small sample size

likely to have advanced disease progression, leading to vascular complications that contribute to ED.[26,27]

The relationship between insulin therapy and ED remains unclear.[28] Recent evidence showed no direct causal effect of insulin use on ED outcomes, while another study showed improvement of erectile function with insulin use through better glycemic control.[28,29] Given the lack of statistical significance in our study, these findings should be interpreted carefully and viewed as preliminary.

Furthermore, hypogonadism, resulting from disruption of the hypothalamic–pituitary–testicular axis and decreased levels of sex hormone-binding globulin, may also contribute to the development of ED in patients with long-standing diabetes.[25]

Insulin therapy may reflect more advanced metabolic dysregulation, rather than being a direct cause of ED. Early metabolic control and preventive interventions should be considered to reduce these complications.

Cardiovascular comorbidities and their impact on ED

Beyond insulin resistance, conditions common in diabetes including obesity, hypertension, dyslipidemia, and aging elevate the risk of cardiovascular disease (CVD) and ED by promoting inflammation, oxidative stress, and endothelial damage. Patients with diabetes-related complications had a higher prevalence of ED than those without ED.[26,27,30] This study found that diabetes-related complications and cardiovascular comorbidities such as hypertension (69.52% vs. 52.17%, $p = 0.018$), coronary artery disease (28.40% vs. 13.04%, $p = 0.027$), and dyslipidemia (47.34% vs. 23.91%, $p = 0.003$) were more prevalent in patients with ED. Similar findings were reported by Xu et al., which showed that ED was more common in patients with hypertension, heart disease, and dyslipidemia among individuals with T2DM.[6]

Cardiovascular disease and ED risk

CVD itself is a significant risk factor for ED, with nearly 50% of men with CAD confirmed by catheterization also having ED.[26,27] In this study, ED was more prevalent in patients with CAD (28.40% vs 13.04%, $p = 0.027$). The shared pathophysiology of ED and CVD, centered on endothelial dysfunction and atherosclerosis may explain this association. Studies suggests that subclinical atherosclerosis can precede ED by up to 10 years, while vasculogenic ED predicts future myocardial infarctions and strokes within 5 years.[27,30,31] Even in the absence of diabetes, hypertension and hyperlipidemia remain highly prevalent in men with ED, at 40% and 42%, respectively, reinforcing the role of vascular dysfunction.[26] These conditions accelerate atherosclerosis in both penile and coronary arteries, often preceding cardiovascular disease. Thus, ED should not be viewed in isolation but rather as a potential early indicator of systemic vascular disease, highlighting need for early cardiovascular screening and intervention.[32]

Dyslipidemia as a predictor of ED

Among the risk factors assessed, dyslipidemia was significantly associated with ED, increasing the odds by 2.57 times (AOR = 2.57, 95% CI: 1.20–5.53; $p = 0.015$). Although hypertension was not significantly associated with ED in the adjusted model ($p = 0.051$), its established role in vascular dysfunction suggests a potential contribution to ED pathophysiology.

Lipid imbalances contribute to endothelial dysfunction and atherosclerosis, impairing blood flow to the penile arteries and increasing ED risk. Since penile cavernosal arteries are smaller than coronary arteries, they develop atherosclerotic blockages earlier, leading to vasculogenic ED years before clinical signs of coronary artery disease.[27,33,34]

While other studies suggest a link between cardiovascular comorbidities and ED, hypertension did not reach statistical significance (AOR = 1.98, 95% CI: 1.00–3.94; $p = 0.051$), and CAD was not included in the multivariable model. Nevertheless, the findings support the role of vascular and endothelial dysfunction in ED pathophysiology. Future research should explore these underlying mechanisms, particularly the role of dyslipidemia.

Social status and ED risk

Although findings on the impact of socioeconomic status remain inconsistent, this study found that high socioeconomic status was significantly associated with lower odds of ED, with individuals in this group having 69% lower odds of ED compared to those with low socioeconomic status (AOR = 0.31, 95% CI: 0.13–0.75, $p = 0.010$).[6,14,35-37] These findings are consistent with previous studies that report an inverse relationship between socioeconomic status and erectile dysfunction, where lower income and related social determinants were identified as risk factors for ED.[11,35]

Socioeconomic disparities can influence health outcomes, including sexual health and the management of ED. Individuals with lower incomes may face greater barriers to accessing to healthcare and medications, which could contribute to the development and progression of erectile dysfunction.[36] Consistent with our findings, Mei Chen et al., reported that cumulative social determinants of health such as income, employment, and education, were associated with increased risk of ED, suggesting that multiple socioeconomic disadvantages may compound vulnerability.[11]

Although the direction of this association aligns with previous evidence, variability in results across local and regional studies highlights the need for cautious interpretation and further research with larger, more balanced samples.

Strengths and limitations

The strengths of this study include an adequate sample size and the use of the validated IIEF-5 questionnaire, which enhances the reliability and comparability of the findings. While this study was able to include various demographic and clinical factors, it still has several limitations. First, its cross-sectional design precludes causal inference. Second, participants were recruited through convenience sampling from a tertiary hospital network and affiliated clinics, which may limit generalizability and introduce selection bias. Third, although the study captured important clinical and socioeconomic variables, it did not measure serum testosterone, formally assess hypogonadism, quantify PDE5 inhibitor exposure, or evaluate psychological factors such as depression and anxiety. These unmeasured variables are clinically relevant in the assessment of ED and may have introduced residual confounding or limited mechanistic interpretation. Finally, some socioeconomic categories contained small numbers, which may have affected the stability of adjusted estimates.

CONCLUSION

The prevalence of ED among Filipino men with T2DM in this study was 88.02% (338/384; 95% CI: 84.4–91.1). Dyslipidemia and socioeconomic status were independently associated with ED and may help identify patients who may benefit from more thorough screening. Further studies involving larger cohorts and improved sampling methods are needed to validate these findings and to further explore factors contributing to high prevalence of ED observed in this population.

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All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
JT: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **RA:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing; **HHC:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **JMC:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing; **BR:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – review and editing; **RAS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration.

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ORIGINAL ARTICLE

Comparison of the European Renal Function Consortium Equation With Chronic Kidney Disease – Epidemiology Collaboration 2021 for Estimating Glomerular Filtration Rate Among Algerian Population With Type 2 Diabetes Mellitus

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Abstract

Introduction. Type 2 diabetes mellitus (T2D) is the leading cause of end stage renal disease. Screening for chronic kidney disease is recommended for early diagnosis and intervention. This requires assessment of renal function by computing for estimated glomerular filtration rate (eGFR) and urine albumin-creatine ratio. Several formulas have been proposed for computation of eGFR. The European Renal Function Consortium (EKFC) equation, obtained by combining the full age spectrum (FAS) and Chronic Kidney Disease – Epidemiology Collaboration 2021 (CKD-EPI) equations, has been proposed as a more universal formula for eGFR. It has the advantage of eliminating correction for ethnicity and covers a wide age range. The aim of this study is to compare the EKFC and CKD-EPI 2021 equations to assess eGFR among Algerian population with T2D.

Methodology. This is an observational, cross-sectional, analytical study. Serum creatinine levels were measured using the Cobas integra 400 Roche diagnostic device. The results were used to estimate GFR using the two formulas: CKD-EPI 2021 and EKFC.

Results. There was a statistically significant difference between the performance of the CKD-EPI 2021 and EKFC equations (p <0.001). However, there was a very good correlation (r = 0.99) even though the EKFC underestimates eGFR compared to CKD-EPI 2021 (bias: -8 ml/min/1.73 m^2).

Conclusions. The main value of the EKFC lies in its ability to provide a detailed stratification in the early stages of chronic kidney disease. Our study also represents the first attempt to establish the q-value in the Algerian population.

Key words: type 2 diabetes mellitus, estimated glomerular filtration rate, EKFC equation, CKD-EPI equation

INTRODUCTION

Chronic kidney disease (CKD) is defined as the presence of abnormalities in kidney structure or function for at least three months that have an impact on health. Diabetes mellitus is the leading cause of end-stage renal disease worldwide.[1] Approximately 30% of people with diabetes have diabetic kidney disease (DKD).[2] It is a slowly progressive complication which is unfortunately often detected late because early stages are usually asymptomatic.[3] Therefore, early detection of CKD is important and is based on two main parameters: albuminuria of at least 30 mg/g or 3 mg/mmol and estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2.[4]

Screening for albuminuria is done using urine albumin-creatine ratio (uACR) which is also a marker of cardiovascular risk among people with diabetes.[5] On the other hand, eGFR is computed through several equations using serum creatinine as the most widely used biomarker.

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Glomerular filtration rate is the volume of plasma filtered by the glomeruli, in milliliters per minute[6] and is affected by the age, gender and body surface area.[7] Initially, eGFR was calculated based on enzymatic creatinine, but since the 2000s, the Jaffé methods for creatinine measurement have been recalibrated according to international standards using isotope dilution mass spectrometry (IDMS).[8] The Kidney Disease: Improving Global Outcomes (KDIGO) recommends the use of IDMS-standardized creatinine regardless of the method.[9] Previously, the most commonly used formulas to compute for eGFR were the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2012) equations.[10]

Recently, in 2021, a new equation known as the European Kidney Function Consortium (EKFC) was developed in Europe by a consortium of mathematicians, biostatisticians and nephrologists.[11] This runs in parallel with the CKD-EPI equation updated in 2021,[12] in order to estimate a more accurate and universal glomerular filtration rate by removing the ethnic variable. The differences between these two raise a crucial question: Is there a significant difference in the eGFR values using the EKFC and CKD-EPI 2021 equations in the Algerian population? Since these equations were developed based on different reference populations, this study will provide information and local validation of renal function assessment tools among the Algerian population.

The aim of our study is to assess the concordance and any clinically significant differences between the EKFC and CKD-EPI 2021 equations for eGFR in an Algerian population with T2D.

METHODOLOGY

Study setting

This is an observational, analytical study conducted at the Rouïba Public Hospital, Department of Medical Biology, Biochemistry Laboratory in collaboration with the Nephrology Department of Mustapha Bacha University Hospital from February 2, 2024 to September 29, 2025. A cross-sectional method comparison study was conducted to evaluate agreement between EKFC and CKD-EPI 2021 in measuring eGFR.

Patients

Recruitment was carried out among patients hospitalized in various departments of the hospital as well as outpatient department. Only those with T2D, aged over 35, with a fasting blood glucose level above 1.26 g/L and/or a glycated hemoglobin (HbA1c) level above 6.5% were included. Pregnant women, cancer patients and people who had participated in another study were excluded. During recruitment, we completed an information sheet for each patient with the following details: age, gender, weight, height, personal and familial history, duration of diabetes, T2D and blood pressure treatment, use of statin and presence of chronic complications.

The sample size was determined in accordance with the sample size for binary classifiers (SFBC) protocol. This recommends a cohort of at least 40 samples to obtain a reliable estimate of agreement.[13] Our sample initially consisted of 110 patients. After excluding patients with missing data, the final number was 83 patients. The sample size included in our study was significantly larger than the minimum number recommended by the SFBC protocol.

The population of presumed healthy subjects was used to determine q-value. They consisted of 275 adults recruited from among the staff of the nephrology department at Mustapha University Hospital, as well as kidney donors (prior to donation) and individuals with a single anatomical or functional kidney. All subjects were over 18 years of age, healthy with no kidney disease or chronic pathology and had normal kidney function (eGFR >60 ml/min/m²). The following were excluded from the study: pregnant women, subjects who had experienced an episode of acute renal failure and those who had taken nephrotoxic drugs in the month prior to inclusion.

All participants gave informed consent. The study was approved by the local ethical committee of the hospital. There were no confounding factors**.**

Sample collection

Samples were collected from patients after fasting for at least 8 hours, using lithium heparin tubes as an anticoagulant for blood glucose and creatinine analysis and EDTA tubes as an anticoagulant for HbA1c measurement. The heparinized tubes were analyzed immediately or stored at -20°C after plasma separation for later analysis. The EDTA tubes were analyzed on the same day without centrifugation. If necessary, the sample was stored at +4°C for 7 days.[14]

Material

Blood glucose and creatinine levels were measured by spectrophotometric technique using the Cobas Integra 400 Plus (Roche Diagnostic, Switzerland). The Jaffé method for creatinine measurement was recalibrated according to IDMS. The HbA1c was determined using high-performance liquid chromatography (HPLC) of D-10 Automate dual program (BIO-RAD, USA).

Methodology

The eGFR was estimated using the EKFC and CKP-EPI 2021 equations based on blood creatinine level as shown in Tables 1 and 2, respectively.

Table 1. European Renal Function Consortium Equation for estimating eGFR[12]

Age (years)	Scr/Q	Equation for eGFR
2–40	<1	$107.3 \times (Scr/Q)^{-0.232}$
2–40	≥1	$107.3 \times (Scr/Q)^{-1.132}$
>40	<1	$107.3 \times (Scr/Q)^{-0.232} \times 0.990^{(Age-40)}$
>40	≥1	$107.3 \times (Scr/Q)^{-1.132} \times 0.990^{(Age-40)}$

Scr – serum creatinine. Q value for ages 2–25: Men: Ln (Q) = 3.200 + 0.259xAge – 0.543 x ln (Age) – 0.00763 x Age^2 + 0.0000790xAge^3, Women: Ln (Q) =3.080+ 0.177 Age-0.223xln (Age)-0.00596 x Age^2+ 0.0000686xAge^3. Q value for ages >25 years correspond to the median Scr values for the age and sex specific populations.[15]

Table 2. Chronic Kidney Disease – Epidemiology Collaboration 2021 equation for estimating eGFR[16]

Gender	SCr (mg/dL)	Equation (age in years)
Female	≤0.7	$DFG = 142 \times (Scr / 0.7)^{-0.241} \times (0.9938)^{Age} \times 1.012$
Female	>0.7	$GFR = 142 \times (Scr / 0.7)^{-1.200} \times (0.9938)^{Age} \times 1.012$
Male	≤0.9	$GFR = 142 \times (Scr / 0.9)^{-0.302} \times (0.9938)^{Age}$
Male	>0.9	$GFR = 142 \times (Scr / 0.9)^{-1.200} \times (0.9938)^{Age}$

SCr – serum creatine

Statistical tools

Statistical analysis was performed using Microsoft Excel (Microsoft, 2023) software on Windows and R version 4.4.2 (R Core Team (2024). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: https://www.R-project.org/). Qualitative variables were expressed as percentages, while quantitative variables were expressed as means ± standard deviation (SD) or medians. The statistical tests applied were: Shapiro-Wilk normality test, T-student test to compare means and U-Man Whitney test to compare medians, χ^2 - test for comparing qualitative variables, and the Pearson correlation test, Passing and Bablock regression and Bland and Altman plot to compare the two methods. The acceptable difference was fixed at ±5 units.

The specific R packages used in the analysis were:

```
bland.altman.plot(
 ekfc,
 ckd_epi,
 graph.sys = "ggplot2",   # joli graphique
 conf.int = 0.95,        # IC 95%
 xlab = "Moyenne (EKFC + CKD-EPI)/2",
 ylab = "Différence (EKFC - CKD-EPI)"
)
 passig.bablock.plot
# ekfc = méthode test
# ckd_epi = méthode de référence

model <- mcreg(
x = ckd_epi, # référence
y = ekfc, # méthode testée
method.reg = "PaBa", # Passing-Bablok
method.ci = "analytical"
)
```

The level of statistical significance α (*p-value*) was set at 0.05. There was no need to carry out tests to adjust the significance level.

Table 3. Demographic characteristics by glycemic status and sex

Variable	T2DM, (N = 83)	Healthy subjects, (N = 275)	*p*-value (T-test)
Male	**48**	**120**	
Age (years), Mean ± SD	65.89 ± 2.05	39.03 ± 11.10	<0.01
BMI (kg/m^2), Mean ± SD	24.52 ± 4.33	26.13 ± 3.54	0.453
Female	**35**	**155**	
Age (years), Mean ± SD	61.11 ± 1.12	42.93 ± 15.23	<0.01
BMI (kg/m^2), Mean ± SD	28.03 ± 5.12	27.65 ± 4.18	0.789
Sex ratio	**1.37**	**0.77**	

SD – standard deviation, BMI – body mass index

Table 4. Clinical characteristics of subjects with type 2 diabetes mellitus

Characteristic	Results (N = 83)
Duration of diabetes	<5 years (25.6%) 5-10 years (44.9%) >10 years (29.5%)
Associated hypertension	Yes (51.80%)
Family history of diabetes	Yes (30.12%)
Smoking status	Yes (18.1%)
Treatment of T2D	OAD only (84%) OAD + Insulin (15%) Lifestyle and dietary measures (1%)
Dyslipidemia treatment	Yes (31%)
Treatment of hypertension	Yes (49%)
Chronic complications of T2D	Yes (8.43%) *(4 cases of macroangiopathy and 3 cases of microangiopathy)*

OAD – oral antidiabetic drugs, T2D – type 2 diabetes

RESULTS

Description of the study population

A total of 83 T2D and 275 healthy subjects were included in this study. The demographic characteristics of the overall study population and the clinical characteristics of T2D subjects are presented in Tables 3 and 4, respectively.

As show in Table 3, the two populations studied (T2D vs. healthy) were comparable in terms of BMI distribution but not in terms of age. As expected, majority of those with T2D were elderly while majority of healthy subjects recruited to determine the median in the Algerian population (the q) were younger. Regarding sex, the difference between the two populations constitutes a limitation of our study due to random recruitment.

Majority of the studied population had diabetes for more than 5 years. Nearly half of them had hypertension. Majority were on oral antidiabetic agents (OADs) alone and 8.43% had diabetic complications.

The age, gender and BMI distribution by sex based on WHO classification of the subjects with T2D is shown in Figures 1 and 2, respectively.

Biochemical measurements and eGFR calculation

To determine the q-value in the Algerian population, it was necessary to calculate the median creatinine level in healthy subjects of both sexes (Table 5).

The mean of blood glucose, serum creatinine and HbA1c and the eGFR using the two equations, EKFC and CKD-EPI 2021, among T2D are shown in Table 6.

The mean fasting blood glucose and HbA1c were both above targets. The average renal function as estimated by the two formulas was preserved with a normal average creatinine and a GFR >60 ml/min/1.73 m^2.

Comparison of the two methods for estimating GFR

To visualize the differences between the two equations for estimating GFR in our population, we draw a regression line using the Passing-Bablock plot as shown in Figure 3.

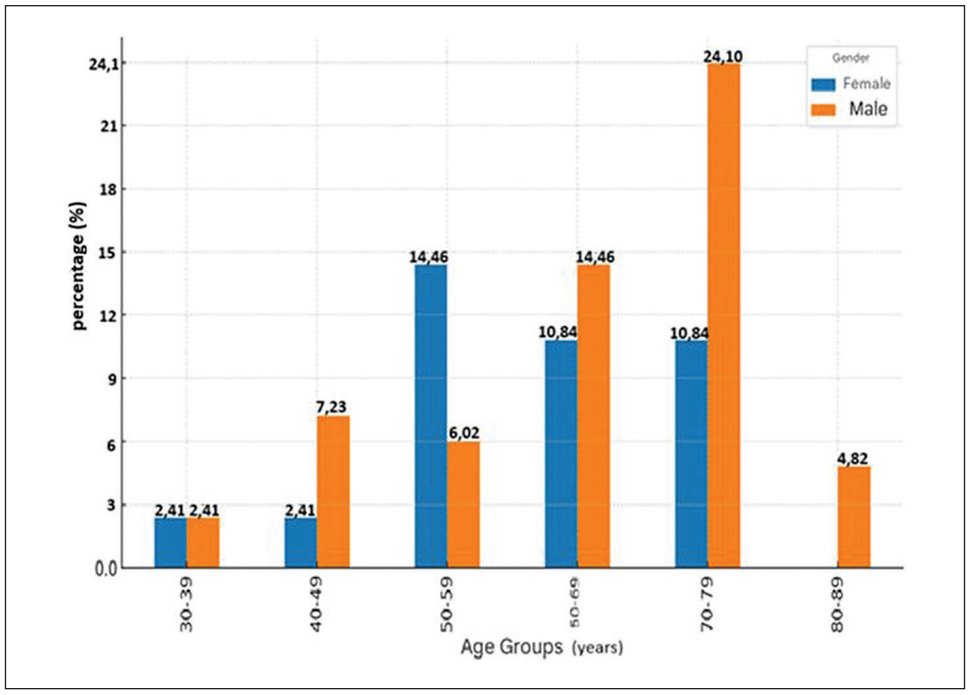

Figure 1. Distribution of patients with type 2 diabetes mellitus by age and gender.

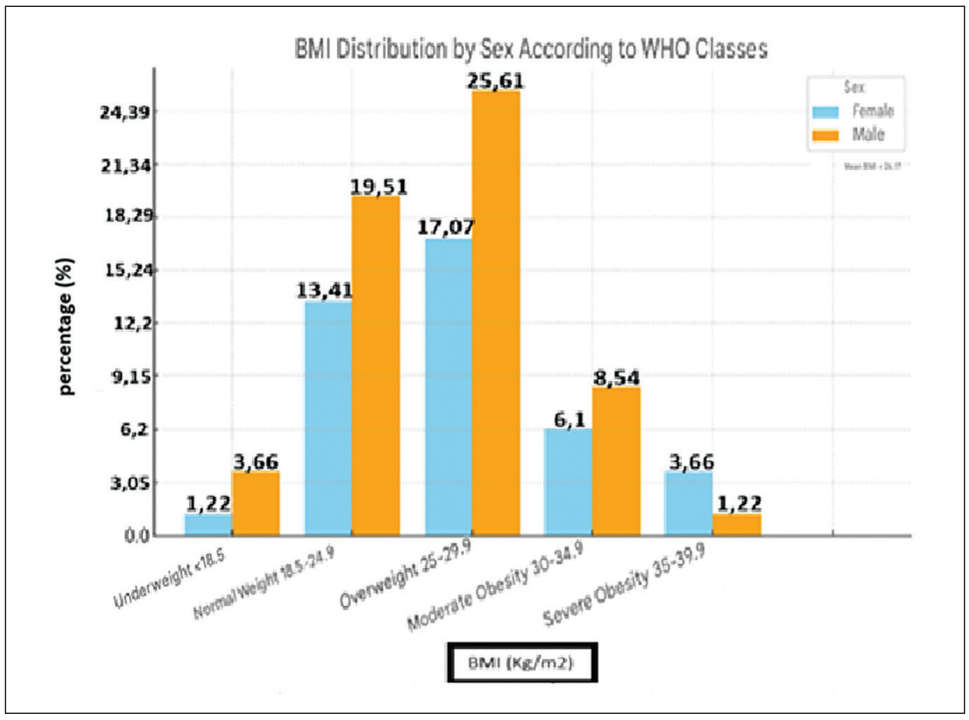

Figure 2. Distribution of patients with type 2 diabetes mellitus by body mass index.

Table 5. Median creatinine levels in healthy volunteers by gender

Parameter	Serum créatinine (mg/dL)			
	Mean ± SD	Médian (Q)	Min-max	*p*-value (T-test)
Female	0.76 ± 0.12	0.8	0.5-1.0	<0.001
Male	0.99 ± 0.15	1.0	0.5-1.5	

The eGFR using EKFC and CKD-EPI 2021 were strongly correlated (r ≈ 0.99 p <0.0001). However, the Passing–Bablock regression indicates a slope less than 1 (0.93; 95% CI 0.89–0.97), suggesting that there was a proportional bias, with EKFC increasing less rapidly than CKD-EPI and an intercept representing the negative systematic bias (−2.6; 95% CI −5.4 to −0.079).

There was a statistically significant difference between eGFR values from the two equations (Table 6: p <0.001), but with a good correlation (r = 0.99) (Figure 3). To confirm these results, the Bland-Altman plot is shown in Figure 4.

The difference between the EKFC and CKD-EPI 2021 values shown on the y-axis were generally below 0, confirming that EKFC underestimates eGFR compared to the CKD-EPI 2021 equation.

The mean difference (red line) was around -8. This means that EKFC values were 8 ml/min/1.73 m² lower than CKD-EPI 2021. Ninety-five percent of the results were within the agreement limit (-1.25, -15). Only one case had a difference greater than 0 (+0.26), with a low eGFR of 9 ml/min/1.73 m² by CKD-EPI and 9.26 ml/min/1.73 m² by EKFC. Another case of an 83-year-old individual had a difference below -15 (-16 ml/min/1.73 m²) with eGFR of 76.99 ml/min/1.73 m² using EKFC and 93 ml/min/1.73 m² with the CKD-EPI 2021 formula. Since the acceptable difference was fixed at ±5 units the difference of -8 units (range: -15, -1.25, was considered unacceptable.

The body mass index (BMI) appears to influence eGFR. The median eGFR in our population according to BMI is shown in Table 7.

Table 6. Laboratory results and estimated glomerular filtration rate using EKFC and CKD-EPI 2021 among subjects with type 2 diabetes mellitus

Parameters	Results (mean ± SD)	Minimum-maximum	Standards	*p* value (T-test)
Blood glucose (g/L)	1.90 ± 0.11	0.72 – 8	0.7-1.25	/
Blood creatinine (mg/L)	10.23 ± 0.83	2.3 – 73.7	Men: 6-13 Women: 5-12	/
HbA1c (%)	8.44 ± 0.23	6.1 – 13	<6.5	/
eGFR-EKFC (mL/min/1.73 m²)	73 ± 2.43	9.26 – 118.42	>90	<0.0001
eGFR-CKD-EPI (mL/min/1.73 m²)	81.41 ± 2.53	9 – 124	>90	

SD – standard deviation, eGFR – estimated glomerular filtration rate
Reference standards for HbA1c and eGFR are based on KDIGO guidelines[4]

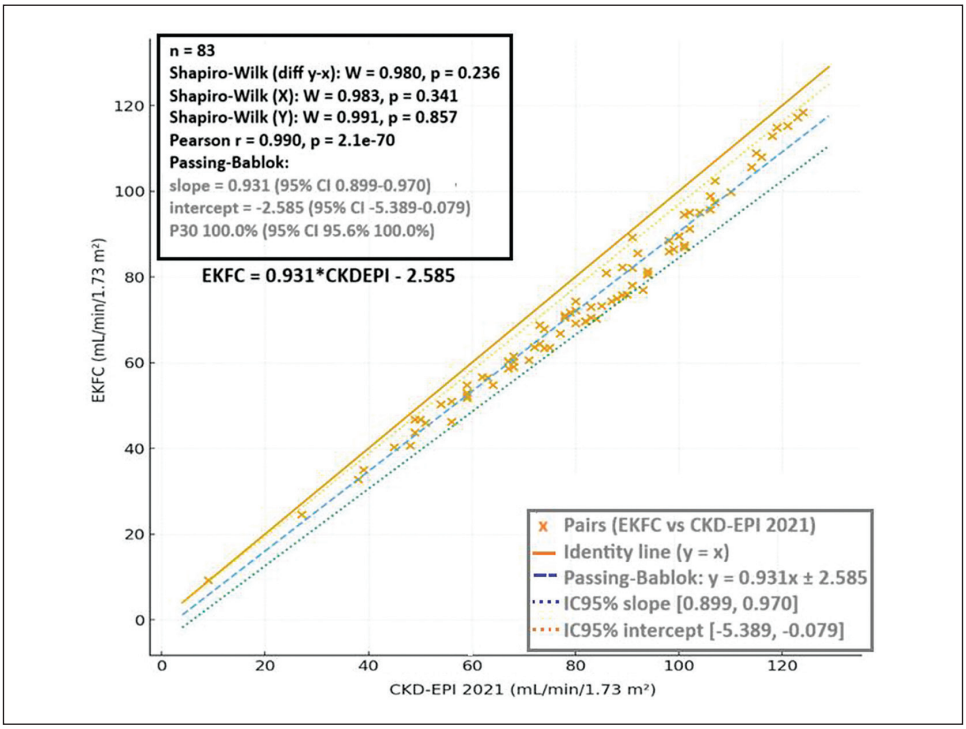

Figure 3. Passing-Bablock regression.

Table 7. The median estimated glomerular filtration rate based on the two methods according to body mass index among the population with type 2 diabetes mellitus[17]

BMI class (WHO)	N	Median eGFR EKFC (ml/min/1.73 m²)	Median eGFR CKD-EPI 2021 (ml/min/1.73 m²)	*p* value (U-Man Whitney)
Underweight <18.5	4	57	65	0.053
Normal weight 18.5-25	27	74	85	0.027
Overweight 25-29.9	36	70.06	79	0.023
Moderate and severe obesity ≥30	16	84.90	96	<0.001

BMI – body mass index, eGFR – estimated glomerular filtration rate

Table 8. Distribution of the population with type 2 diabetes mellitus (n = 83) according to the KDIGO classification based on eGFR[4]

KDIGO stage (eGFR: ml/min/m²)	Number according to EKFC	Number according to CKD-EPI 2021	*p* value (χ^2 test)
G1(>90)	17 (20.48%)	33 (40.24%)	0.0013
G2 (60-89)	45 (54.21%)	34 (40.96%)	0.045
G3a (45-59)	15 (18.07%)	13 (15.66%)	0.945
G3b (30-44)	5 (6.02%)	2 (2.40%)	0.063
G4 (15-29)	0 (0.00%)	0 (0.00%)	/
G5 (<15)	1 (1.20%)	1 (1.20%)	0.865

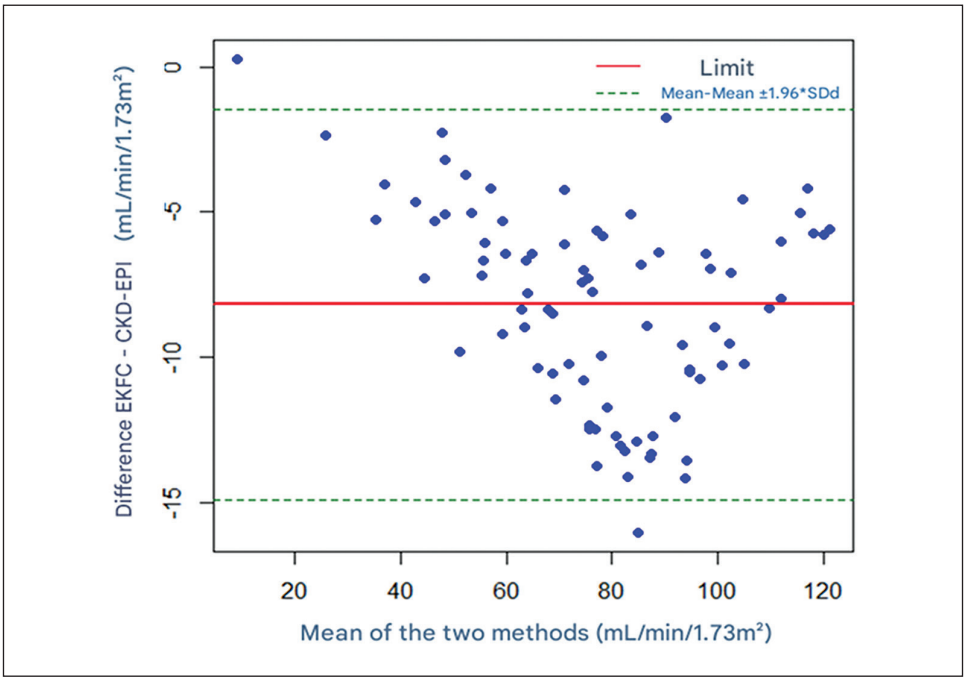

Figure 4. Bland-Altman difference diagram.

In our adult population, eGFR gradually decreases in normal-weight and overweight individuals, then increases among those with BMI >30 with an eGFR of 85 and 96 ml/min/1.73 m² according to the EKFC and CKD-EPI, respectively. The lack of concordance of the eGFR in the underweight compared to the other categories was probably due to a sample size that was too small (n = 4). The number of individuals per kidney disease stage according to KDIGO criteria based on the two methods are shown in Table 8.

The results showed a significant rate of reclassification of patients from KDIGO stage G1 to stage G2 (33 - 17 = 16 patients reclassified) when using the EKFC equation. This proves the presence of a clinical difference.

DISCUSSION

This is the first study to compare the EKFC and CKD-EPI 2021 equations among Algerian population with T2D. There was a significant difference between the eGFR using the two equations but with a strong correlation (r=0.99). The EKFC equation yielded lower eGFR compared to CKD-EPI 2021 with a difference or bias of -8 ml/min/1.73 m². Thus, the added value of the EKFC lies mainly in the fine stratification of the early stages of CKD which may help in early detection and prevention of kidney disease progression.

The result of our study is consistent with the findings of Lu et al.[18] They also demonstrated that EKFC underestimates eGFR compared to CKD-EPI 2021. The Bland-Altman diagram from the latter study showed that EKFC underestimated GFR compared to CKD-EPI 2021 in the GFR range below 120 ml/min/1.73 m^2. However, EKFC overestimated GFR in the range above 150 ml/min/1.73 m^2, results not observed in our cohort. Lu et al. also showed a bias or mean difference of -5.5 based on Bland-Altman plot and a limit of agreement in a range of -11to 0. In our study, the bias was -8 with limits of agreement of -15; to 1.25.

In an Asian study by Lee et al. conducted in 2024, the bias was -8.8.[19] This means that the eGFR by CKD-EPI is on average 8.8 ml/min/1.73 m^2/ higher than EKFC. Thus, underestimation of eGFR using EKFC was consistent with our results. The study also found a significant correlation between the GFR values estimated by the two equations, with a correlation coefficient of 0.93 (p <0.001).

In 2022, Martins et al., compared EKFC and CKD-EPI 2021 with measured glomerular filtration rate (mGFR) among 122 patients with T2D.[20] The p30 or accuracy within 30% which indicates the percentage of time an eGFR matches the patient's true value or mGFR of both methods were low at 74% (95% CI 65-81) and 64% (95% CI 56-72) for CKD-EPI and EKFC, respectively. However, in this study, neither equation achieved optimal performance in estimating GFR. This also illustrates that assessing renal function using mGFR tends to reduce the apparent performance of the two equations.

In 2020, Pottel et al., compared the differences between mGFR and eGFR using four equations: EKFC, CKD-EPI 2021, Chronic Kidney Disease in Children Study (CKID) and Full Age Spectrum (FAS) on 19,629 patients aged 2 to 90 years. They divided their population into 4 age groups: children (under 18), adults under 40, under 65 and over 65. The results showed average biases, smaller standard errors and a higher p30 in the EKFC equation than in the other equations. The p30 in the under 18 age group using the EKFC equation was 79.7%, compared to 73.2% in the CKID equation and 74.2% in the FAS equation. For adults under 40, p30 was 90%, compared to 82% and 84% in the FAS and CKD-EPI equations, respectively. Among under 65 and over 65 age groups, p30 was 89.5% and 85% for the EKFC equation, 85.9% and 83.6% for FAS, and 88.2% and 80.7% for CKD-EPI, respectively.[12] This study concluded that the EKFC equation was applicable in all age groups, while the CKD- EPI equation had a limitation in the under-18 age group. The only limitation of this study was the exclusion of black subjects.

The eGFR in our adult population showed a steady decline in both the normal weight and overweight categories, followed by an increase among those who have BMI greater than 30 and eGFR of 85 and 96 ml/min/1.73 according to EKFC and CKD-EPI, respectively. The lack of concordance of eGFR in the underweight category may be due to an inconclusive sample size (n= 4 patients). Similar to an Asian study, BMI increases while eGFR decreases, except in the group with a BMI >30 kg/m^2.[19] In a study conducted in 2008 by Chagnac et al., mGFR was 61% higher in obese individuals (BMI >30) than in the control group (BMI <25). They also demonstrated that in subjects with severe obesity, weight loss leads to a decrease in eGFR and renal plasma flow.[21]

A comparative analysis of kidney disease classification according to KDIGO criteria based on eGFR using the two equations reveals slight differences. Our data showed a significant rate of reclassification of patients from class G1 to stage G2 (16 patients), but less significant in stages G3b (3 patients) and G3a (2 patients). There were fewer individuals in stage G1 using the EKFC equation. However, the number of patients were equal in the more advanced stages (G4 and G5). Similarly, Lee et al., showed that EKFC tends to classify Asian adult population into more severe stages, moving many patients from stage G1 to stage G2 and from G2 to G3a, but with little difference in classification in the last three advance stages G3b, G4 and G5.[19] Given that the latter study was conducted on a population of 82,022 individuals and that the numbers were almost identical in G4 and G5, severe stages remain robustly identified regardless of the formula used. Thus, the added value of EKFC lies mainly in the fine stratification of the early stages. Despite the smaller number in our population, statistical significance was still observed in our study.

Limitations

We recruited subject using blind sampling method which resulted in two groups (T2D and healthy individuals) that were not comparable in terms of age and sex. The lack of comparison with mGFR was a limitation in our study due to the unavailability of the test and high cost. The mGFR is more accurate and is based on a direct measurement of glomerular filtration, whereas eGFR depends on indirect markers (creatinine in our case). Due to lack of mGFR, it was impossible to determine which of the two formulas was closer to reality, and the p30 cannot be calculated. Lastly, the sample size was insufficient to perform a subgroup analysis. This study provided preliminary data on the q-value among the Algerian population but further studies including a larger sample size is recommended.

CONCLUSION

The EKFC equation, obtained by combining the FAS and CKD-EPI 2021 equations, has been proposed as a more universal formula for computing the eGFR. It has the advantage of eliminating correction for ethnicity and covering a wide age range. The EKFC equation, due to the underestimation of GFR compared with CKD-EPI 2021, may be helpful in early detection and intervention for CKD in T2D.

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All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
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Declaration of IA
We declare the use of AI tools for the translation of the manuscript, which was subsequently revised.

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ORIGINAL ARTICLE

Ultrasound-Guided Skin and Subcutaneous Fat Thickness Profiling for Insulin Delivery in Overweight and Obese Adults With Type 2 Diabetes: A Cross-Sectional Malaysian Study

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Abstract

Background. Safe insulin administration requires delivery into the subcutaneous tissue to avoid intradermal or intramuscular injection. Although international guidelines recommend the universal use of 4 mm needles, local anatomical data supporting this recommendation among overweight and obese adults with type 2 diabetes mellitus (T2DM) in Malaysia are limited.

Objective. To assess skin thickness (ST) and subcutaneous adipose tissue (SAT) using ultrasound to evaluate the safety of 4 mm insulin needles in overweight and obese adults.

Methodology. This cross-sectional study involved 98 adults with T2DM on insulin therapy (body mass index [BMI] ≥23 kg/m²) attending a primary care clinic in Johor Bahru, Malaysia. ST and SAT at 10 abdominal injection sites and 8 upper arm injection sites were measured using ultrasonography. Data were analyzed using descriptive statistics, correlation tests, and multiple linear regression to identify associations with BMI, age, gender, and other variables.

Results. The median abdominal ST was 2.46 mm (interquartile range [IQR]: 2.20–2.80), and upper arm ST was 1.92 mm (IQR: 1.73–2.11). Only 6.1% of participants had any site with ST greater than 4 mm. Median abdominal SAT was 16.75 mm (IQR: 14.83–19.28), and upper arm SAT was 15.38 mm (IQR: 12.10-17.73). Multiple linear regression showed that abdominal ST was significantly predicted by BMI (β = 0.244, p = 0.015) and inversely by age (β = –0.202, p = 0.040). Gender was the strongest predictor of upper arm ST (β = –0.418, p <0.001), with females having thinner skin. Abdominal SAT was positively associated with BMI (β = 0.469, p <0.001) and male gender (β = –0.205, p = 0.026), suggesting that BMI may serve as a useful clinical indicator of abdominal injection depth. No significant predictors were found for upper arm SAT.

Conclusion. Most overweight and obese Malaysian adults with T2DM have adequate ST and SAT for safe insulin delivery using 4 mm pen needles. Ultrasonographic data support individualized injection technique education in primary care, considering BMI, gender, and age.

Key words: type 2 diabetes mellitus, obesity, primary health care

INTRODUCTION

Malaysia records one of the highest diabetes prevalence rates in Asia.[1] According to the 2023 National Health and Morbidity Survey (NHMS), approximately 15.6% of Malaysian adults (2.2 million individuals) are affected.[2] For individuals with advanced type 2 diabetes mellitus (T2DM), insulin therapy remains a cornerstone for achieving optimal glycemic control. Over the past two decades, its use has expanded significantly within Malaysia's public healthcare system. The DiabCare Malaysia study reported a progressive increase in insulin use: 28% in 2003, 54% in 2008, and 65% in 2013.[3] In parallel, the National Diabetes Registry (NDR) noted a rise in insulin therapy among T2DM patients in primary healthcare clinics (PHCs) from 23.1% in 2013 to 30.3% in 2019.[4]

The effectiveness of insulin therapy depends not only on the insulin formulation but also on accurate delivery into the SAT. While international guidelines, such as the Forum for Injection Technique and Therapy Expert Recommendations (FITTER), emphasize that proper subcutaneous (SC) deposition ensures predictable absorption, these recommendations are largely based on global averages.[5] Inadvertent intramuscular (IM) injections may result in accelerated and unpredictable absorption, leading to glycemic instability, whereas intradermal injections often cause pain and leakage.[5-7]

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Current international guidelines advocate for universal use of shorter insulin needles (4 mm), based on the findings that ST remains relatively constant across populations.[5,6] However, while ST may vary minimally, SAT differs considerably depending on body mass index (BMI), gender, and injection site.[8] Additionally, ethnic differences in body composition indicate that Asians tend to have higher body fat percentages and different fat distribution patterns than Caucasians at the same BMI.[9] These variations raise concerns regarding the applicability of general recommendations for Malaysia's multi-ethnic, overweight, and obese population, which may exhibit distinct ST and SAT characteristics at common injection sites such as the abdomen and upper arm.

Recent studies have demonstrated the value of ultrasonography, including elastography, in assessing subcutaneous tissue in adults with T2DM, particularly in obese individuals. These imaging techniques enable precise identification of injection site complications and support individualized insulin injection strategies.[5,10-13] Unlike clinical palpation, which often fails to detect subclinical LH or accurately assess tissue depth, ultrasonography provides real-time, accurate visualization of anatomical structures at injection sites.[14] Despite these advantages, there is a lack of local data utilizing ultrasonography to evaluate ST and SAT profiles in Malaysian adults with T2DM, especially within overweight and obese populations.

This study aims to address this gap by profiling ST and SAT thickness at standard insulin injection sites using ultrasonography in overweight and obese Malaysian adults. By characterizing these anatomical profiles, we aim to provide evidence-based insights into injection site suitability and needle length appropriateness for the local primary care setting.

METHODOLOGY

Study design and setting

This prospective cross-sectional study was conducted at the Mahmoodiah Health Clinic, Johor Bahru, Malaysia, in January 2019.

Patient recruitment and eligibility

Patients attending the diabetes clinic at Mahmoodiah Health Clinic, Johor Bahru in January 2019 were screened for participation in this study. Eligible patients were recruited using consecutive sampling, whereby all patients meeting the inclusion criteria during the study period were approached for participation. Inclusion criteria were: (1) Age ≥18 years; (2) T2DM diagnosis; (3) Insulin therapy for ≥12 months; and (4) Classification as overweight or obese, defined as a BMI of ≥23 kg/m^2, according to Asian population standards.[15] Exclusion criteria included pregnancy or skin pathologies (e.g., scars, lipohypertrophy) at injection sites. Patients who fulfilled the criteria were approached and informed about the study objectives and procedures. Those who agreed to participate provided written informed consent in Malay or English. Demographic data and relevant clinical history were recorded using a structured data collection form. The data collection form was developed with reference to clinical guidelines and relevant literature, and refined through pilot testing to ensure clarity and content validity.[5,12]

Sample size

The sample size was calculated for the primary descriptive objective of estimating ST at common insulin injection sites (abdomen and upper arm) among overweight and obese Malaysian adults with T2DM, in order to evaluate the appropriateness of using a 4 mm insulin needle. Based on pilot data collected during the preliminary phase of the study, the standard deviation of abdominal ST was estimated to be 0.60 mm. Using a 95% confidence level and a desired precision (margin of error) of ± 0.12 mm, the minimum sample size required to estimate the population mean was 96 participants. A total of 98 eligible consenting participants were recruited during the study period. This sample size was adequate for the primary descriptive objective, but it was not powered for subgroup comparisons; therefore, secondary association and subgroup analyses should be interpreted as exploratory.

Study procedure and tools

After obtaining informed consent, demographic data (including age, gender, BMI and ethnicity), clinical history of T2DM, and insulin injection practices were documented using a structured data collection form. ST and SAT thickness at insulin injection sites (abdomen and upper arm) were assessed using a portable ultrasound machine. The SonoSite M-Turbo portable ultrasound unit with a 13-6 MHz, 38 mm broadband linear array transducer probe (Sonosite Ltd.) was utilized for the study. Each participant underwent ultrasound measurements at 10 standardized abdominal sites and 8 standardized upper arm sites, following a grid-based method adapted from Sim KH et al., with permission (Figure 1).[12] The anatomical grid used to identify these sites was based on a previously validated protocol to ensure measurement consistency and reproducibility. ST was defined as the combined thickness of the epidermis and dermis, measured from the skin surface to the interface with the underlying subcutaneous fat, in accordance with the reference methodology. Ultrasound gel was applied to the skin, and care was taken to avoid probe-induced compression during measurement. All ultrasound measurements and grid mapping were performed by a single trained pharmacist to minimize inter-operator variability. The operator had completed formal Sonosite M-Turbo Ultrasound System training prior to study implementation. For measurements with ST >4 mm, the measurement was repeated twice at the same site during the initial assessment to confirm the finding before the final value was recorded. Measurements were initially

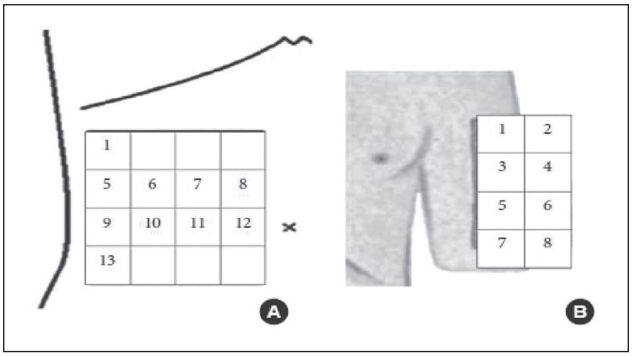

Figure 1. Measurement sites for ST and SAT on the **(A)** abdomen and **(B)** upper arm.

Adapted from Sim et al.,[12] with permission.

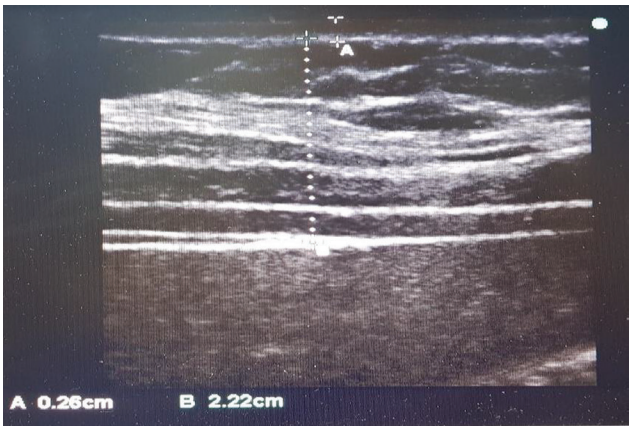

Figure 2. Representative ultrasound image illustrating vertical skin thickness (ST) measurement from the skin surface to the dermis–subcutaneous interface (labelled "A": 0.26 cm = 2.6 mm).

recorded in centimeters and converted to millimeters for analysis. The procedure required approximately 30 minutes per participant. An illustrative archived ultrasound image used for ST assessment is shown in Figure 2.

Study outcomes

The primary outcome of this study was ST at standard insulin injection sites, specifically the abdomen and upper arm. Secondary outcomes included the proportion of participants with ST >4 mm, descriptive SAT thickness profiles, and exploratory assessment of associations between tissue thickness and selected demographic or clinical variables.

Statistical analysis

Data was coded and analyzed using SPSS software version 24.0 (IBM Corp., Armonk, New York, United States). All 98 recruited participants had complete ultrasound measurements and covariate data required for the reported analyses; therefore, no imputation was performed. Implausible values were checked against the original data collection forms and ultrasound records before analysis. Normality of continuous variables was tested using the Shapiro–Wilk and Kolmogorov–Smirnov tests, along with visual inspection of histograms and Q–Q plots. Given the non-normal distribution of most tissue measurement, ST and SAT values were summarized using medians with interquartile ranges (IQRs), and full range (min–max). For each participant, average ST and SAT across all abdominal and upper arm sites was computed as a composite variable to assess overall ST and SAT for each region. Descriptive analyses were used to present ST and SAT distribution by site and region. Bivariate associations were assessed using Spearman's correlation and Mann-Whitney U tests. Multiple linear regression was performed to identify predictors of tissue thickness. Prior to interpreting the multiple linear regression models, assumptions were assessed. Linearity and homoscedasticity were evaluated using partial regression plots and scatterplots of standardized residuals versus standardized predicted values. Normality of residuals was assessed using histograms and normal P–P plots of standardized residuals. Multicollinearity was assessed using tolerance and variance inflation factor (VIF), while influential observations were assessed using studentized residuals, Cook's distance, and Mahalanobis distance. Durbin–Watson statistics were examined to assess independence of errors. A p-value <0.05 was considered statistically significant.

Use of reporting guidelines

This manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies. The STROBE checklist was completed during manuscript revision to ensure transparent and comprehensive reporting of the study's design, methodology, results, and limitations.

Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research. All participants were involved only as study subjects after providing written informed consent in accordance with the Malaysian National Medical Research Register (NMRR) and Ministry of Health research ethics requirements.

RESULTS

Demographic and clinical characteristics

The study included 98 participants (56.1% female, 43.9% male) with a mean age of 58.90 ± 8.49 years (Table 1). The study population was ethnically diverse, consisting of 59.2% Malay, 25.5% Indian, and 15.3% Chinese participants. The mean BMI at recruitment was 29.8 6 ± 4.97 kg/m^2. When classified according to Asian population standards, 40.8% of participants were pre-obese (overweight), while the remaining majority fell into Obese classes I (35.7%), II (15.3%), or III (8.2%).

Skin thickness profiles

Ultrasound profiling of the 10 standardized abdominal sites revealed a non-normal distribution of ST (Table 2). The overall abdominal ST had a median of 2.46 mm (IQR: 2.20-2.80 mm). Individual site values ranged from 1.30 mm to a maximum of 5.70 mm, with Site 7 recording the highest value of 5.70 mm, followed by Site 11 (5.60 mm) and Site 12 (5.30 mm). In the upper arm region, the median ST across 8 sites was 1.92 mm (IQR: 1.73–2.11 mm). The upper arm values ranged from 1.10 mm to 4.50 mm, with upper arm Site 2 exhibiting the greatest thickness.

Table 1. Demographic and clinical characteristics (n = 98)

Characteristic	n (%)	Mean ± SD
Age (years)		58.90 ± 8.49
<60 years	48 (49.0%)	
≥60 years	50 (51.0%)	
Gender		
Male	43 (43.9%)	
Female	55 (56.1%)	
Ethnicity		
Malay	58 (59.2%)	
Chinese	15 (15.3%)	
Indian	25 (25.5%)	
BMI (kg/m²)		29.86 ± 4.97
Pre-obese (23.0–27.4 kg/m²)	40 (40.8%)	
Obese Class I (27.5–32.4 kg/m²)	35 (35.7%)	
Obese Class II (32.5–37.4 kg/m²)	15 (15.3%)	
Obese Class III (≥37.5 kg/m²)	8 (8.2%)	
Duration of T2DM (years)		13.05 ± 6.85
<5 years	7 (7.1%)	
5-9 years	22 (22.4%)	
10-19 years	53 (54.1%)	
≥20 years	16 (16.3%)	
Duration of insulin therapy (years)		5.61 ± 4.43
<5 years	7 (7.1%)	
≥5 years	91 (92.9%)	
Insulin regimen		
Basal only	21 (21.4%)	
Premixed	62 (63.3%)	
Basal-Bolus	15 (15.3%)	

Legend: Summary of participants' age, gender, ethnicity, BMI categories (based on Asian cutoffs), duration of type 2 diabetes mellitus (T2DM) and insulin therapy, and insulin regimen types.

Subcutaneous adipose tissue profiles

SAT thickness demonstrated high variability, particularly in the abdomen (Table 3). The overall abdominal SAT thickness had a median of 16.75 mm (IQR: 14.83-19.28 mm). Individual measurements varied widely, ranging from a minimum of 2.70 mm to a maximum of 37.80 mm. In contrast, upper arm SAT was generally thinner and less variable, with a median thickness of 15.38 mm (IQR: 12.10-17.73 mm) and a range of 4.60 mm to 28.70 mm.

Risk of intradermal injection

Regarding the safety of 4 mm needles, the proportion of participants with ST exceeding 4 mm indicating a potential risk for intradermal injection, was 6.1% (n = 6) overall. Specifically, 5 participants (5.1%) had at least one abdominal site exceeding 4 mm, whereas only 1 participant (1.0%) had an upper arm site exceeding this threshold.

Predictors of ST and SAT: Multiple linear regression analysis

Multiple linear regression analyses were performed to determine the independent effects of BMI, age, and gender on tissue thickness (Table 4). Regression diagnostics showed no evidence of problematic multicollinearity or highly influential observations. Residual diagnostics were

Table 2. Skin thickness profiles of abdomen and upper arm

Site	Mean ± SD (mm)	Median (mm)	IQR (mm)	Median (IQR) (mm)	Min–Max (mm)
Abdomen					
1	2.40 ± 0.45	2.30	0.7	2.30 (2.00–2.70)	1.70–4.00
5	2.41 ± 0.47	2.35	0.7	2.35 (2.00–2.70)	1.60–3.50
6	2.59 ± 0.58	2.40	0.8	2.40 (2.10–2.90)	1.60–4.50
7	2.69 ± 0.69	2.55	1.0	2.55 (2.10–3.10)	1.80-5.70
8	2.68 ± 0.64	2.60	0.7	2.60 (2.20–2.90)	1.60–4.70
9	2.37 ± 0.49	2.30	0.7	2.30 (2.00–2.70)	1.60–3.80
10	2.56 ± 0.53	2.50	0.7	2.50 (2.20–2.90)	1.70–4.30
11	2.75 ± 0.72	2.60	0.8	2.60 (2.30–3.10)	1.70–5.60
12	2.66 ± 0.65	2.50	0.8	2.50 (2.20–3.00)	1.30–5.30
13	2.35 ± 0.46	2.20	0.6	2.20 (2.00–2.60)	1.60–3.70
Overall	2.55 ± 0.48	2.46	0.7	2.46 (2.20–2.80)	1.90-4.20
Upper Arm					
1	1.93 ± 0.42	1.85	0.5	1.85 (1.60–2.10)	1.10–3.60
2	2.31 ± 0.49	2.20	0.5	2.20 (2.00–2.50)	1.50–4.50
3	1.89 ± 0.34	1.90	0.5	1.90 (1.60–2.10)	1.10–3.00
4	2.14 ± 0.43	2.10	0.6	2.10 (1.80–2.40)	1.30–3.60
5	1.90 ± 0.31	1.80	0.4	1.80 (1.70–2.10)	1.30–2.90
6	1.99 ± 0.35	1.90	0.4	1.90 (1.80–2.20)	1.20–3.80
7	1.79 ± 0.28	1.80	0.3	1.80 (1.60–1.90)	1.10–2.70
8	1.80 ± 0.29	1.80	0.4	1.80 (1.60–2.00)	1.20–2.90
Overall	1.97 ± 0.30	1.92	0.4	1.92 (1.73–2.11)	1.40–3.20

Legend: Ultrasound-based skin thickness measurements (in mm) across 10 abdominal and 8 upper arm sites. Values are presented as mean ± standard deviation (SD), median, interquartile range (IQR), and range. Composite median ST for each region is also provided.

Table 3. Subcutaneous adipose tissue profile of abdomen and upper arm

Site	Mean ± SD (mm)	Median (mm)	IQR (mm)	Median (IQR) (mm)	Min–Max (mm)
Abdomen					
1	15.86 ± 5.51	14.75	7.00	14.75 (12.38-19.38)	2.70-37.10
5	16.32 ± 5.06	16.15	5.30	16.15 (13.53-18.88)	6.10-37.10
6	16.74 ± 4.51	16.45	4.60	16.45 (14.08-18.68)	7.00-37.10
7	17.63 ± 4.62	17.10	5.50	17.10 (14.90-20.40)	6.80-37.60
8	18.28 ± 4.49	17.95	4.40	17.95 (15.88-20.33)	5.60-37.60
9	16.83 ± 5.57	15.90	6.30	15.90 (12.75-19.08)	6.90-37.10
10	16.82 ± 4.80	16.65	4.80	16.65 (14.10-18.93)	6.20-37.80
11	18.01 ± 4.84	17.60	5.00	17.60 (15.70-20.72)	7.00-37.80
12	19.07 ± 4.70	18.35	5.60	18.35 (16.20-21.80)	9.30-37.80
13	16.71 ± 5.68	16.60	7.80	16.60 (12.50-20.28)	6.40-37.10
Overall	17.23 ± 4.25	16.75	4.50	16.75 (14.83-19.28)	7.10-37.10
Upper Arm					
1	14.63 ± 4.90	14.10	7.30	14.10 (10.88–18.23)	6.30–26.00
2	15.28 ± 4.15	15.25	6.20	15.25 (12.08–18.23)	6.40–24.70
3	15.65 ± 4.29	15.60	6.20	15.60 (12.70–18.90)	6.80–26.50
4	14.79 ± 4.13	14.85	6.20	14.85 (11.68–17.90)	6.10–23.20
5	15.74 ± 4.28	16.25	6.90	16.25 (12.05–19.00)	7.10–26.00
6	14.69 ± 4.66	14.50	7.20	14.50 (10.95–18.20)	5.60–28.70
7	15.58 ± 5.00	16.00	8.50	16.00 (11.08–19.60)	7.00–25.40
8	13.57 ± 4.74	13.45	7.60	13.45 (9.30–16.90)	4.60–23.80
Overall	15.00 ± 3.78	15.38	5.60	15.38 (12.10–17.73)	7.90–21.80

Legend: Ultrasound-based SAT measurements (in mm) across the same abdominal and upper arm sites. Data are summarized using mean ± SD, median, IQR, and minimum–maximum values. Regional composite SAT values are included.

Table 4. Multiple linear regression predicting ST and SAT thickness

Outcome variable	Predictor	B (Unstandardized)	SE B	*p*-value	Model adjusted R^2
ST abdomen	BMI	0.002	0.001	0.015*	0.069
	Age	-0.001	0.001	0.040*	
	Gender	-0.005	0.009	0.610	
ST upper arm	BMI	0.001	0.001	0.053	0.156
	Age	0.000	0.000	0.808	
	Gender	-0.025	0.006	<0.001*	
SAT abdomen	BMI	0.039	0.008	<0.001*	0.206
	Age	0.001	0.005	0.774	
	Gender	-0.173	0.077	0.026*	
SAT upper arm	BMI	0.012	0.008	0.123	-0.002
	Age	0.002	0.005	0.705	
	Gender	0.019	0.077	0.811	

*Indicates statistical significance (p <0.05)
Legend: Regression models showing the relationship between ST/SAT (dependent variables) and BMI, age, and gender (independent variables). Unstandardized coefficients (B), standard errors (SE), and p-values are reported. Significant predictors (p <0.05) are indicated with an asterisk (*).

generally acceptable for the abdominal ST, upper-arm ST, and abdominal SAT models, while the upper-arm SAT model was interpreted cautiously.

Abdominal ST: The model was statistically significant [F(3,96) = 3.45, p = 0.020], explaining 6.9% of the variance. BMI (β=0.244, p=0.015) and age (β = -0.202, p = 0.040) were significant predictors, indicating that higher BMI is associated with thicker abdominal ST, while increasing age is associated with thinner ST.

Upper arm ST: This model was highly significant [F(3,96) = 7.12, p<0.001], accounting for 15.6% of the variance. Gender was the strongest predictor (β = -0.418, p <0.001), confirming that females have significantly thinner skin on the upper arm compared to males. BMI was not a statistically significant predictor of upper arm ST (p = 0.053).

Abdominal SAT: The model for abdominal SAT was significant [F(3,96) = 9.58, p <0.001] and explained 20.6% of the variance. BMI was a strong positive predictor (β = 0.469, p <0.001). Additionally, gender emerged as a significant predictor (β = -0.205, p = 0.026), suggesting that males tend to have higher abdominal SAT thickness than females when controlling for BMI.

Upper arm SAT: The regression model for upper arm SAT was not statistically significant (p=0.424), indicating that BMI, age, and gender were poor predictors of SAT thickness in this region for the study cohort.

Comparison between injection sites

Comparatively, abdominal sites consistently displayed higher median ST (2.46 mm vs. 1.92 mm) and higher median SAT (16.75 mm vs. 15.38 mm) than upper arm sites.

While ST showed relatively low variability across both regions, SAT demonstrated marked variability, particularly in the abdomen where the interquartile ranges (IQR) for individual sites were wider (ranging from 4.40 to 7.80 mm) compared to the narrower IQRs observed in the upper arm (6.20 to 8.50 mm). These findings suggest that while ST is relatively predictable, abdominal subcutaneous fat depth is highly variable and significantly influenced by BMI.

DISCUSSION

With diabetes prevalence in Malaysia estimated at 15.6% and insulin use rising in primary care, correct injection technique (IT) is increasingly important.[2] This study represents the first targeted profiling ST and SAT using ultrasonography at standard insulin injection sites (abdomen and upper arm) among overweight and obese Malaysian adults with T2DM. The findings provide local validation for international needle length recommendations and highlight anatomical variations by body composition and gender, supporting the need for personalized insulin injection strategies.

The primary finding that the median ST was 2.46 mm at the abdomen and 1.92 mm at the upper arm supports the use of 4 mm pen needles as the standard of care for overweight and obese Malaysian adults. These values are consistent with other Asian cohorts, such as Korean adults (2.29 mm at abdomen and 2.00 mm at upper arm) and Filipino adults (2.25 mm at abdomen and 2.12 mm at upper arm).[12,16] Our results also validate the updated FITTER Forward Expert Recommendations (2025), which reaffirm that 4 mm needles are the safest option for adults of all BMIs to minimize IM risk.[17] This study adds important local evidence that Malaysian adults, despite obesity rate, generally have ST values well within the safe range for 4 mm needle use.

Among the 98 participants, only 6.1% (n = 6) had ST greater than 4 mm at any site, indicating a low risk of intradermal injection with a 4 mm needle. Specifically, 5.1% (n = 5) had at least one abdominal site above 4 mm, and only 1.0% (n = 1) had an upper arm site exceeding this value. These findings strongly support local and international guidance that a 4 mm needle can be safely used without creating a skin fold for most overweight and obese insulin-treated patients.[5,6] This low risk is clinically relevant as it facilitates simpler insulin IT, enhances adherence, and reduces pain, leakage, and glycaemic variability associated with intradermal delivery.[5-7]

It is notable that our observed prevalence of thicker abdominal ST (5.1%) is slightly lower than the 9.5% reported by Torii-Goto et al., in Japan,[7] This divergence may be attributed to measurement posture; our study used a supine position, while Torii-Goto et al., measured patients sitting, which resulted in higher ST values (mean 3.3 mm) compared to supine measurements. This suggests that ST may increase when sitting due to tissue compression, and our supine measurements might slightly underestimate functional ST during self-injection. However, the median ST in our cohort (2.46 mm) is sufficiently low that even with a hypothetical postural increase (e.g., +1 mm), the ST would likely remain well below the 4 mm threshold. Future studies should consider standardizing or comparing measurement postures to better reflect real-world injection conditions.

Given the substantial SAT layers in our participants, with a median abdominal SAT of 16.75 mm and upper arm SAT of 15.38 mm, the risk of IM injection with a 4 mm needle is negligible. This SAT depth is comparable to Filipino adults (19.1 mm) but higher than leaner Korean cohorts (10.15 mm), reflecting the specific obesity demographic of our study.[12,16] Importantly, de la Peña et al., demonstrated that in obese subjects, the depth of subcutaneous deposition does not affect the pharmacokinetics or glucodynamics of insulin, confirming that 4 mm needles are both safe and clinically effective even when insulin is deposited superficially within deep fat layers.[18]

Multiple linear regression analysis identified BMI and gender as significant predictors of tissue profiles. Gender was the strongest predictor for upper arm ST, with females having significantly thinner ST compared to males. This finding is consistent with previous studies who reported similar gender disparities.[8,12] While 4 mm needles are safe for both genders, females with lower BMI may benefit from careful assessment or the use of a skin fold to avoid IM injection, and future studies should define a threshold BMI or ST value for when a skin fold is advisable.

Regarding BMI, higher values were associated with thicker abdominal ST. While this positive correlation aligns with Sim et al., the literature is complex; Torii-Goto et al., observed that patients with BMI ≥25 kg/m^2 actually had thinner skin, while Catambing et al., found no variation.[7,12,16] These discrepancies suggest the relationship between adiposity and ST is complex and may vary by population or measurement technique. The influence of BMI on SAT is expected, as BMI is a surrogate marker for adiposity. However, the finding that BMI and age were poor predictors of upper arm SAT thickness suggests that other factors, such as fat distribution patterns specific to the Asian phenotype, may play a more dominant role in the upper arm, warranting further investigation. In exploratory subgroup analysis, Indian participants had significantly thicker abdominal ST than Chinese participants. While data on ethnic variation in ST is limited, this observation warrants further investigation. Catambing et al., noted that ST varied "marginally" in their population but cited limited comparative data, and Lim et al., have highlighted the general lack of Asian-specific tissue profiling.[16,19] Given the limited sample size and imbalance across ethnic groups, these findings should be interpreted as preliminary. Larger studies are needed to confirm whether ethnicity is a definitive factor for IT customization in Malaysia's multi-ethnic population.

Our study confirms that the abdomen offers a deeper and more variable depot for insulin compared to the upper arm. The strong positive correlation between BMI and abdominal SAT suggests BMI is a reliable clinical indicator for estimating abdominal injection depth. However, the lack of correlation between BMI and upper arm SAT indicates that arm fat storage is less predictable. This supports the preference for the abdomen as the primary injection site for consistent absorption in obese patients, as echoed by previous tissue profiling studies.[12]

Limitation

A limitation of this study is that data collection occurred in 2019; however, the anatomical parameters profiled are physiologically stable, and the persistent high prevalence of obesity (NHMS 2023) ensures continued applicability. The sample size was sufficient for the primary objective of estimating skin thickness, but it was not powered for subgroup comparisons, or ethnicity-stratified analyses. Generalizability is also limited by the single-center design and the imbalance in ethnic representation. Although the operator underwent formal ultrasound training and selected technically challenging cases received informal expert input, the study did not include systematic independent review of each ultrasound image by a radiologist or second assessor. The original exported ultrasound image files were not available at the time of manuscript preparation; therefore, the retained archived image was used for illustrative purposes only. Additionally, measurements were restricted to the supine position and did not assess functional outcomes such as glycaemic variability. Future multi-center research should prioritize larger, ethnically balanced cohorts to evaluate the clinical impact of these anatomical profiles across different injection postures.

CONCLUSION

Ultrasonographic profiling confirms that overweight and obese Malaysian adults generally present with ST values well within the range for safe short-needle use, accompanied by deep SAT. These anatomical profiles support the safety of 4 mm needles while emphasizing the need for healthcare professionals to consider individual factors such as gender and BMI when providing IT education.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
CT: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **YR:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – original draft preparation, Visualization; **MNY:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – original draft preparation, Visualization.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
The authors declare no conflicts of interest. Becton, Dickinson and Company provided the ultrasound equipment but had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

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ORIGINAL ARTICLE

Cost-Effectiveness Analysis of Triple Oral Antidiabetic Drug Combination in Patients With Type 2 Diabetes Mellitus: An Outpatient Study in Indonesia

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Abstract

Background. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. Initial therapy for type 2 diabetes typically starts with metformin monotherapy, but because of its progressive nature, combination therapy is often required to achieve glycemic targets. However, research on combination therapy with three oral antidiabetic drugs is currently limited.

Objective. This study assessed direct medical costs and the cost-effectiveness of a combination of triple oral antidiabetics with first-line metformin combined with glimepiride, pioglitazone, and DPP-4 inhibitors (sitagliptin/vildagliptin), among type 2 DM patients treated in the outpatient clinic of Dr. Ramelan Central Naval Hospital, Surabaya, Indonesia.

Methodology. A retrospective cross-sectional analysis was conducted from the hospital perspective using medical records and cost data from January to December 2024. Eligible patients had type 2 DM, received a combination of triple oral antidiabetics with metformin as first-line treatment combined with glimepiride, pioglitazone, and DPP-4 inhibitors (sitagliptin/vildagliptin), attended monthly follow-ups, had at least two HbA1c measurements, and had complete clinical and cost data. Direct medical costs included doctor services, drug acquisition costs, and laboratory monitoring costs.

Results. A total of 79 patients were included, 60.8% male, with an average (SD) age of 54.9 (9.26) years, and 69.6% with comorbidities. Compared with the combination of metformin + glimepiride + pioglitazone, the combination of metformin + sitagliptin/vildagliptin + glimepiride and metformin + sitagliptin/vildagliptin + pioglitazone was more cost-effective, with ICER values of IDR -162,119.77; IDR 845,655.5, respectively. Both ICER values were below the willingness-to-pay (WTP) threshold. One-way sensitivity analysis showed that the model results were relatively robust to parameter variations of ±20%. In the combination of metformin + sitagliptin/vildagliptin + glimepiride vs metformin + glimepiride + pioglitazone, laboratory monitoring costs had the greatest influence on the ICER value. Meanwhile, the combination comparison metformin + sitagliptin/vildagliptin + pioglitazone vs metformin + glimepiride + pioglitazone was most sensitive to changes in effectiveness (ΔHbA1c).

Conclusion. Metformin + sitagliptin/vildagliptin + glimepiride and metformin + sitagliptin/vildagliptin + pioglitazone are both more cost-effective compared to metformin + glimepiride + pioglitazone in this setting.

Key words: type 2 diabetes mellitus, metformin, dipeptidyl-peptidase IV inhibitors, cost-effectiveness analysis, drug combinations; Indonesia

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia and impaired metabolism of carbohydrates, fats, and proteins. Hyperglycemia can lead to several macro and microvascular complications.[1] High blood glucose can lead to complications in various organs such as the eyes, kidneys, nerves, and heart. Type 2 DM is a multifactorial condition characterized by increased chronic disability and a high risk of cardiovascular disease (CVD) and obesity, thus increasing patient morbidity and mortality.[2]

Data from the International Diabetes Federation (IDF) indicates that 589 million adults (20-79 years old) are living with diabetes worldwide. By 2024, Indonesia ranked fifth globally in diabetes prevalence, with the number of patients reaching 20.43 million. The total cost of DM treatment

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globally is estimated to reach USD 1.015 trillion in 2024, with USD 246 billion in the Western Pacific region.[3] According to the American Diabetes Association (ADA), by 2022, the annual cost of diabetes in the US will reach USD 413 billion, including USD 307 billion for direct healthcare costs and USD 106 billion related to decreased productivity.[4] A study in Surabaya (Indonesia) reported that the total cost of DM with complications reached more than IDR 2.6 billion, with an average of IDR 15.7 million per patient.[5]

Initial therapy for type 2 diabetes generally begins with metformin monotherapy, but due to its progressive nature, a combination of drugs is often required to achieve glycemic targets.[4] Based on the Indonesian Endocrinology Association (PERKENI) guidelines, if the HbA1c target is not achieved within 3 months, a combination of two to three drugs with different mechanisms can be given. Commonly used combinations include metformin with a sulfonylurea (glimepiride), a thiazolidinedione (pioglitazone), or a DPP-4 inhibitor (vildagliptin or sitagliptin).[6] The use of three antidiabetic drugs has also been shown to be effective in achieving glycemic control with a lower risk of hypoglycemia, such as the combination of metformin, DPP-4i, and glimepiride or pioglitazone.[1,2]

Given the substantial economic burden of T2DM and the limited evidence regarding triple oral antidiabetic therapy in Indonesia,[7] treatment decisions should consider both clinical outcomes and economic consequences to ensure rational use of healthcare resources.[8] However, research on combination therapy with three oral antidiabetic drugs is currently limited.[7] This study aims to analyze the direct medical costs and cost-effectiveness of using triple oral combination antidiabetics, including glimepiride (SU), pioglitazone (TZD), and vildagliptin or sitagliptin (DPP-4i) with metformin as first-line therapy in outpatients with type 2 diabetes at Dr. Ramelan Central Naval Hospital, Surabaya, Indonesia, a Type A tertiary advanced healthcare facility (FKTL) in Indonesia that provides advanced subspecialty care for patients with complex medical conditions.

METHODOLOGY

Subjects, materials, and methods

This study has received ethical approval from the Research Ethics Committee of the Dr. Ramelan Central Naval Hospital, Surabaya, Indonesia, under number 25/EC/KEP/2025. This study was conducted from the healthcare provider perspective.

Study subjects

The study subjects included T2DM patients who received combination therapy with triple oral antidiabetic drugs (metformin + sitagliptin/vildagliptin + glimepiride), (metformin + sitagliptin/vildagliptin + pioglitazone), and (metformin + glimepiride + pioglitazone) in the outpatient department of Dr. Ramelan Central Naval Hospital, Surabaya, Indonesia, from January 2024 to December 2024. Subject selection was carried out using the total sampling method, which included all patients who met the inclusion criteria: patients with a primary diagnosis of type 2 DM; using a combination of triple oral antidiabetic drugs with first-line metformin and combined with glimepiride, pioglitazone, and/or vildagliptin/sitagliptin; undergoing combination therapy for the first time in the period January-December 2024; routinely conducting monthly check-ups at two HbA1c measurement points within one year; and having complete medical record data and cost details. Patients who died or had specific conditions that could affect HbA1c levels, such as anemia or hypothyroidism, were excluded from the study.

Data collection procedure

Data were collected retrospectively from patient medical records, and details of direct medical costs were obtained from the hospital's Hospital Management Information System (SIMRS). Data were extracted without direct patient identifiers. During the extraction process, data was anonymized by replacing patient identifiers with codes. The data collected included patient characteristics (age, sex, diagnosis, comorbidities, and HbA1c values), as well as direct medical cost components, including doctor services, drug acquisition, and laboratory monitoring.

Data processing and analysis

The data obtained were analyzed using descriptive and inferential approaches. Descriptive analysis was used to describe patient characteristics, details of direct medical costs, and the effectiveness of therapy based on the average reduction in HbA1c levels at two test points. Mean HbA1C reduction(ΔHbA1c) was calculated as the difference between baseline HbA1c (before the patient started triple therapy with oral antidiabetic drugs) and final HbA1c (3-9 months after the patient started triple therapy with oral antidiabetic drugs) for each patient.

A cost-effectiveness analysis was performed by calculating the Average Cost-Effectiveness Ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER) for each combination of antidiabetic therapies. Inferential analysis was performed by conducting a comparative test of categories and direct medical costs. To confirm the cost-effectiveness of the combination of triple oral antidiabetics, the ICER value was compared with a willingness to pay threshold of 1–3 times Indonesia's gross domestic product (GDP) per capita (GDP per capita in 2022 = Int$14,445.7), in accordance with the WHO-CHOICE guidelines and the Health Technology Assessment guidelines in Indonesia.[9] Therefore, the willingness to pay threshold in this study was Int$14,445.7 per unit of effectiveness.

Additionally, a one-way sensitivity analysis was conducted by varying the cost of doctor services, drug acquisition,

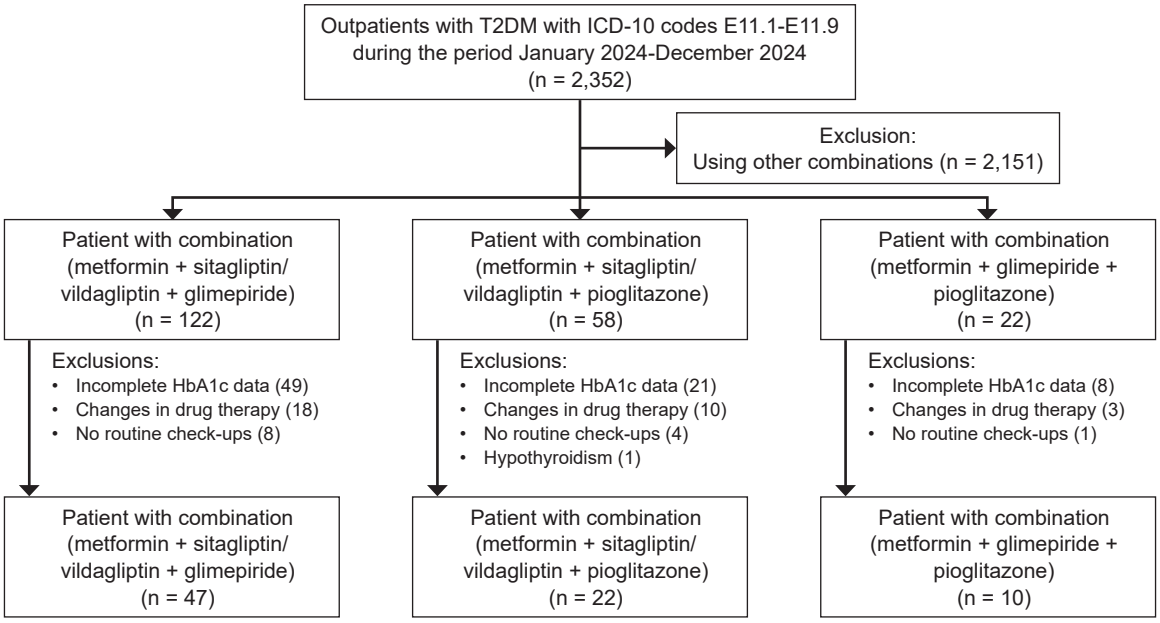

Figure 1. Study flowchart.

Table 1. Patient characteristics

Characteristics	a (n = 47)	b (n = 22)	c (n = 10)	Total (n = 79)	*p*
Sex					
Male	27 (57%)	15 (68%)	6 (60%)	48 (60.8%)	0.70†
Female	20 (43%)	7 (32%)	4 (40%)	31 (39.2%)	
Average age (years)	55.68 ± 8.32	53.41 ± 11.84	54.8 ± 7.28	54.9 ± 9.26	0.64‡
Diagnosis (ICD-10)					
E11.2 (T2DM with renal complications)	5 (9.6%)	3 (11.1%)	1 (7.7%)	9 (9.8%)	0.47†
E11.4 (T2DM with neurological complications)	4 (7.7%)	4 (14.8%)	1 (7.7%)	9 (9.8%)	
E11.5 (T2DM with peripheral circulatory complications)	12 (23.1%)	7 (25.9%)	2 (15.4%)	21 (22.8%)	
E11.7 (T2DM with multiple complications)	17 (32.7%)	5 (18.6%)	5 (38.5%)	27 (29.3%)	
E11.8 (T2DM with unspecified complications)	14 (26.9%)	7 (25.9%)	4 (30.7%)	25 (27.2%)	
E11.9 (T2DM without complications)	0	1 (3.7%)	0	1 (1.1%)	
Comorbidities					
No	14 (29.8%)	6 (27.3%)	4 (40%)	24 (30.4%)	0.76†
Yes	33 (70.2%)	16 (72.7%)	6 (60%)	55 (69.6%)	

a = (metformin + vildagliptin/sitagliptin + glimepiride), b = (metformin + vildagliptin/sitagliptin + pioglitazone), c = (metformin + glimepiride + pioglitazone), p >0.05 not significant; † Chi-Square, ‡ One-way anova

laboratory monitoring, and ΔHbA1c by ±20%, resulting in a change in the ICER value. The results of the analysis are presented in the form of a tornado diagram to show the variables with the most significant impact on the analysis results.

RESULTS

Study population

A total of 2,352 outpatients were diagnosed with type 2 diabetes mellitus at the Dr. Ramelan Central Naval Hospital from January 2024 to December 2024. Seventy-nine patients met the inclusion criteria. The study flowchart is shown in Figure 1.

The majority of patients in this study were male (60.8%), with an average age of 54.9 years. The most common diagnosis was E11.7 (Type 2 DM with multiple complications), accounting for 29.3% of patients. Most patients had at least one comorbidity (69.6%), such as hyperlipidemia, hypertension, stroke, hyperuricemia, musculoskeletal, and heart disease. Inferential analysis showed no significant differences between characteristics and antidiabetic combinations (p >0.05) (Table 1).

Direct medical cost

Patients using the antidiabetic combination (metformin + sitagliptin/vildagliptin + pioglitazone) had the highest total direct medical costs compared to other combinations (Table 2). The average cost of doctor services for each antidiabetic combination was the same, at IDR 150,000.

Based on inferential analysis using the non-parametric Kruskal-Wallis test, a significant difference was found between the average total direct medical costs (p <0.05) and the drug acquisition costs of antidiabetic drugs (p <0.05)

Table 2. Direct medical cost

Cost	Average cost [(Min-Max) (Median)] (IDR)						$p^{\dagger}$
	a (IDR)	(%)	b (IDR)	(%)	c (IDR)	(%)	
Doctor services	150,000	28.4	150,000	25.4	150,000	29.6	1.00
CI (95%)							
Drug acquisition cost	115,566.38	21.9	178,782.27	30.2	94,944.00	18.7	0.00*
CI (95%)	(76,530-137,790) (119,310) 111,286.43 to 119,846.33		(155,310-210,060) (179,220) 172,889.45 to 184,675.09		(79,740-123,810) (88,050) 83,259.24 to 106,628.76		
Laboratory monitoring cost	262,340.43	49.7	262,727.27	44.4	262,000.00	51.7	0.89
CI (95%)	(190,000-270,000) (270,000) 257,066.33 to 267,614.52		(230,000-270,000) (270,000) 255,726.01 to 269,728.54		(190,000-270,000) (270,000) 243,902.74 to 280,097.26		
Total direct medical cost	528,019.57	100	591,509.55	100	506,944.00	100	0.00*
CI (95%)	(469.150-557.790) (531.810) 521,624.39 to 534,414.76		(556,760-630,060) (596,760) 583,007.96 to 600,011.13		(425,590-543,810) (508,050) 483,510.21 to 530,377.79		

a = (metformin + vildagliptin/sitagliptin + glimepiride), b = (metformin + vildagliptin/sitagliptin + pioglitazone), c = (metformin + glimepiride + pioglitazone), p >0.05 not significant, † uji kruskal-wallis, *significant, IDR = Indonesian Rupiah

Table 3. Baseline, endpoint, and change (Δ) in HbA1c across treatment combinations

	a	b	c	Total	$p^{\dagger}$
Average HbA1c baseline	7.2	6.57	7.31	7.03	0.14
(min-max) (median) (%)	(5.2 – 11.1) (7)	(5.2 – 9) (6.5)	(6.2 – 9.6) (6.7)	(5.2 – 11.1) (6.7)	
CI (95%)	6.80 to 7.59	6.21 to 6.93	6.40 to 8.22		
Average HbA1c endpoint	7.02	6.17	7.01	6.78	0.00*
(min-max) (median) (%)	(5 – 11) (6.8)	(4.7 - 6.9) (6.15)	(5.9 – 8.7) (6.9)	(4.7 – 11) (6.7)	
CI (95%)	6.66 to 7.38	5.90 to 6.44	6.30 to 7.71		
Average Δ HbA1c	0.17	0.40	0.30	0.25	0.69
(min-max) (median) (%)	(-2.9 - 3.6) (0.2)	(-0.6 - 2.1) (0.4)	(-0.6 - 1.9) (0.25)	(-2.9 - 3.6) (0.3)	
CI (95%)	-0.16 to 0.50	0.12 to 0.68	-0.23 to 0.83		

a = (metformin + vildagliptin/sitagliptin + glimepiride), b = (metformin + vildagliptin/sitagliptin + pioglitazone), c = (metformin + glimepiride + pioglitazone), † Kruskal-Wallis, p >0.05 not significant, *significant

Table 4. ACER and ICER from the base-case

Combination type	Average total direct medical cost (IDR)	Effectiveness (%)	ACER (IDR)	ICER (IDR)
a	528,019.57	0.17	3,069,881.22	-162,119.77
b	591,509.55	0.40	1,478,773.87	845,655.50
c	506,944.00	0.30	1,689,813.33	

a = (metformin + vildagliptin/sitagliptin + glimepiride), b = (metformin + vildagliptin/sitagliptin + pioglitazone), c = (metformin + glimepiride + pioglitazone), IDR = Indonesian Rupiah

combined with oral antidiabetic drugs. Because the Kruskal-Wallis test cannot be used for post hoc comparisons, the Mann-Whitney test is performed for each pair of groups to determine which groups differ. The results showed that both cost components differed significantly among the antidiabetic combinations (p <0.05).

Effectiveness of therapy

Treatment effectiveness was evaluated based on the reduction in HbA1c between baseline and follow-up measurements. Table 3 shows the baseline, endpoint, and change (Δ) in HbA1c across treatment combinations (metformin + sitagliptin/vildagliptin + glimepiride); (metformin + sitagliptin/vildagliptin + pioglitazone); and (metformin + glimepiride + pioglitazone), with an average difference in HbA1c baseline, HbA1c endpoint, and Δ HbA1c reduction of 7.03, 6.78, and 0.25, respectively. A difference test was then performed between the antidiabetic combinations and the HbA1c baseline, HbA1c endpoint, and Δ HbA1c reduction. The results showed no significant difference (p >0.05 in the Kruskal-Wallis test) for the HbA1c baseline and Δ HbA1c reduction, but there was a significant difference (p <0.05) for the HbA1c endpoint.

Cost-effectiveness analysis

Based on Table 4, the antidiabetic combination (metformin + sitagliptin/vildagliptin + glimepiride) has the highest ACER value compared to other antidiabetic combinations, which is IDR 3,069,881.22. Furthermore, the ICER value was calculated by comparing (metformin + glimepiride + pioglitazone) with (metformin + sitagliptin/vildagliptin + glimepiride) and (metformin + sitagliptin/vildagliptin + pioglitazone). The result was that the combination of Metformin + sitagliptin/vildagliptin + glimepiride and metformin + sitagliptin/vildagliptin + pioglitazone was more cost-effective, with ICER values of IDR -162,119.77; IDR 845,655.5, respectively.

Sensitivity analysis

We used a tornado diagram to depict the variables with the most significant impact on outcomes. The results of the one-way sensitivity analysis for the two comparisons showed different patterns in the factors that most influenced the ICER values. In the comparison of therapy combination (metformin + sitagliptin/vildagliptin + glimepiride) vs (metformin + glimepiride + pioglitazone), cost parameters,

especially primarily laboratory monitoring costs, were the most dominant factors influencing the results. In contrast, in the comparison of therapy combination (metformin + sitagliptin/vildagliptin + pioglitazone) vs (metformin + glimepiride + pioglitazone), effectiveness parameters, particularly ΔHbA1c in group (metformin + sitagliptin/vildagliptin + pioglitazone), were the most sensitive factors. Despite a ±20% variation across all parameters, the analysis results remained consistent, with therapy combination (metformin + sitagliptin/vildagliptin + glimepiride) being dominant compared to (metformin + glimepiride + pioglitazone). At the same time, the therapy combination (metformin + sitagliptin/vildagliptin + pioglitazone) demonstrated higher effectiveness but with the consequence of also greater costs compared to therapy (metformin + glimepiride + pioglitazone).

DISCUSSION

Most patients were classified under ICD-10 code E11.7 (T2DM with multiple complications), indicating at least one additional complication or comorbidity. The most prevalent comorbidities were related to the endocrine, metabolic, and cardiovascular systems, such as dyslipidemia and hypertension. This finding is consistent with the known association between T2DM, metabolic abnormalities, and increased cardiovascular risk.[10]

The cost of antidiabetic drugs is one of the contributors to the high total real direct medical costs. This is because the unit prices of pioglitazone and sitagliptin/vildagliptin are higher than those of glimepiride, resulting in increased total real direct medical costs. This finding is consistent with a UK study, which showed that the cost of metformin + TZD ($46,202) or metformin + DPP-4i ($47,191) was also higher than the cost of metformin + sulfonylurea ($40,669).[11] However, the high cost of the drugs must be weighed against the clinical benefits provided. Some literature suggests that pioglitazone and DPP-4i have a better safety profile than sulfonylureas, particularly regarding the risk of hypoglycemia and effects on cardiovascular function.[10]

Table 2 shows a significant difference in average drug costs and total direct medical costs between antidiabetic combinations, with a p <0.05, with the antidiabetic combination (metformin + sitagliptin/vildagliptin + pioglitazone) having the highest value. This suggests that the choice of therapeutic regimen will have a direct impact on the economic burden on both patients and healthcare facilities.

HbA1c is a surrogate marker that does not directly reflect long-term clinical outcomes; however, it remains a validated indicator of long-term glycemic control and is strongly associated with the risk of diabetes-related complications. Furthermore, HbA1c is a more practical measure than clinical outcomes, which take longer to be observed.[12]

HbA1c testing in this study was not performed routinely every three months, but rather at intervals ranging from three to nine months, depending on the patient's clinical condition. According to the literature, blood sugar monitoring can be conducted every 3-6 months, with 3 months recommended if the condition is uncontrolled and 6 months if it is controlled.[9] Additionally, all patients in this study utilized BPJS Kesehatan (Social Security Agency on Health). According to the BPJS Kesehatan regulation, for type 2 DM patients, HbA1c testing is carried out with a frequency of once every 3 to 6 months.[13]

Table 3 shows the most significant Δ reduction in HbA1c in the antidiabetic combination containing pioglitazone. These results align with a study in Bulgaria, which showed that the combination containing pioglitazone was more effective in lowering HbA1c than DPP-4i.[14] Pioglitazone is known to be highly effective in reducing blood sugar, with A1C reductions of around 1.0% to 1.5%.[10] However, pioglitazone is not recommended for patients with heart failure because it can worsen edema or fluid retention. Therefore, the use of DPP-4i can be considered in patients with heart failure.[6]

The combination of metformin, sitagliptin/vildagliptin, and pioglitazone may be advantageous because each component acts through a distinct mechanism of action. Pioglitazone and metformin increase insulin sensitivity and improve β-cell function, with TZDs having a more prominent effect on β-cells. The characteristics of these two drugs make this combination suitable both as initial therapy and as adjunctive therapy in patients who do not achieve glycemic control targets.[14] At the same time, gliptins (sitagliptin or vildagliptin) do not affect insulin resistance. DPP-4i can reduce glucagon secretion, thereby improving the molar ratio of insulin to glucagon in the portal vein. This condition can reduce the hormonal stimulation of gluconeogenesis and glucose production in the liver. In addition, some experimental data suggest that DPP-4i can also directly affect glucose metabolism in the liver.[15]

The metformin + sitagliptin/vildagliptin + glimepiride regimen also demonstrated effectiveness in reducing HbA1c levels through complementary pharmacologic mechanisms. Sulfonylureas stimulate pancreatic β cells to release insulin, while metformin increases tissue sensitivity to insulin and improves glucose uptake.[10] Although the reduction in HbA1c obtained is relatively smaller compared to pioglitazone-based regimens. A study in Japan showed that the addition of sitagliptin to patients previously using metformin and sulfonylureas was able to provide a significant reduction in HbA1c, although not as large as the TZD-based combination.[16]

In this study, cost-effectiveness was analyzed by calculating ACER and ICER values. Table 4 shows that the antidiabetic combination (metformin + sitagliptin/vildagliptin + pioglitazone) had the lowest ACER value compared to the other two antidiabetic combinations, at IDR 1,478,773.87. Regarding the ICER calculation, (metformin + sitagliptin/vildagliptin + glimepiride) and (metformin + sitagliptin/vildagliptin + pioglitazone) was more cost effective than

(metformin + glimepiride + pioglitazone) with ICER value IDR -162,119.77; IDR 845,655.5, respectively. The ICER value is used to indicate the additional cost required to obtain one additional unit of health outcomes compared to other alternatives.[17]

The willingness to pay (WTP) threshold used in this study was 1 times Indonesia's GDP per capita (Int$14,445.7, which is equivalent to approximately IDR 220 million per unit of effectiveness).[9] When compared with the research results, all ICER values were well below this threshold. This indicates that the additional costs incurred are still within acceptable limits, thus the analyzed interventions can be considered cost-effective.

The analysis was conducted to determine the components and real direct medical costs in patients with type 2 diabetes. Cost calculations in this study did not include discounting, because the time period used was only one year. In a relatively short analysis period, the application of discounting to costs and outcomes is considered irrelevant, as changes in the value of money within one year do not yield a significant difference in the economic analysis.[18]

Limitations of the study

This study has several limitations. First, its retrospective design relied on the completeness and accuracy of routinely collected medical records. Second, despite total sampling, the treatment groups were uneven in size (Figure 2) which may have introduced selection bias. Third, information on medication adherence, duration of diabetes, dietary habits, smoking status, and physical activity was unavailable and could not be evaluated as potential confounders.

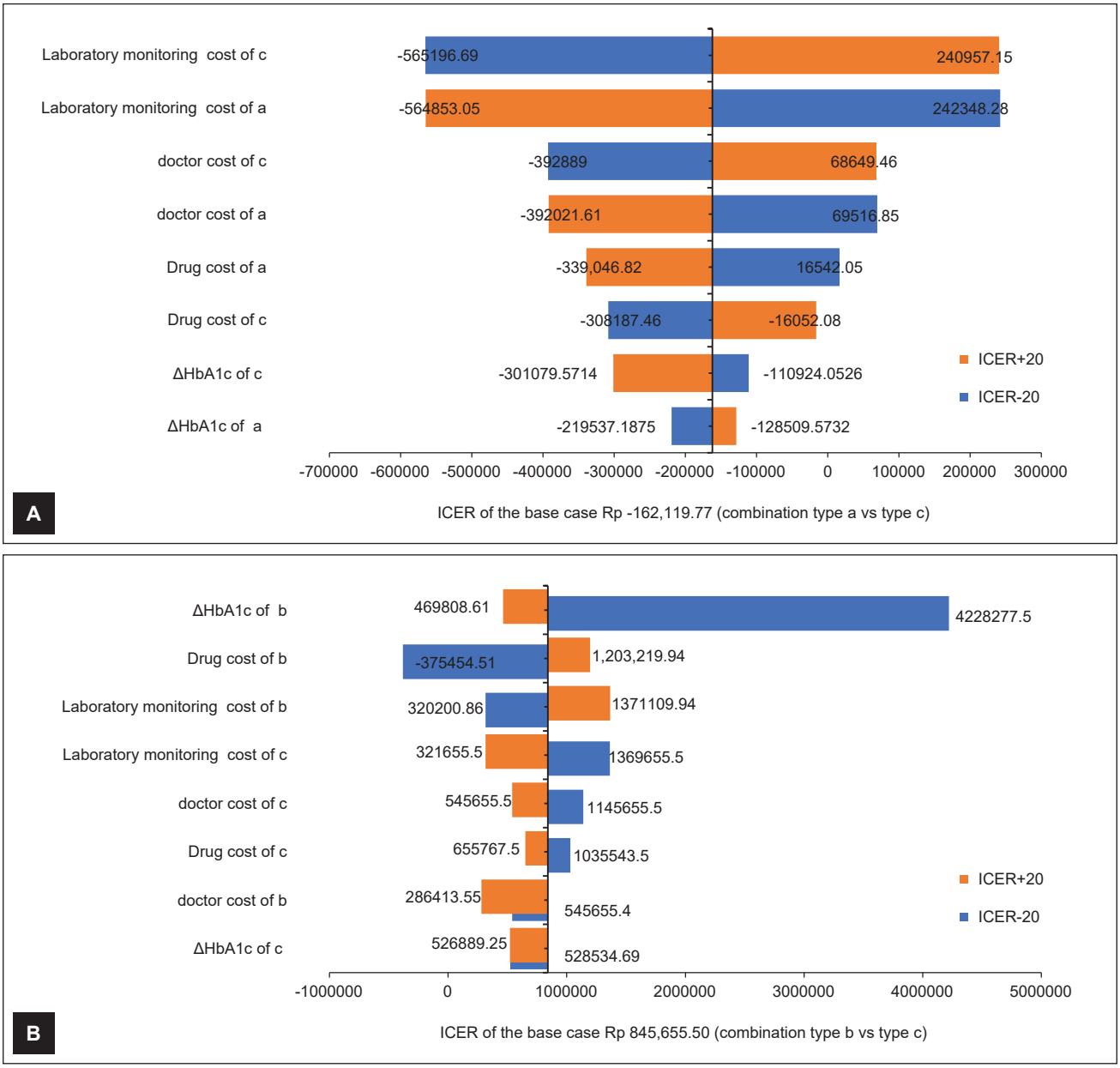

Figure 2. Tornado diagram showing the one-way sensitivity analysis. **(A)** Combination type a vs c. **(B)** Combination type b vs c.

Fourth, HbA1c was used as the sole measure of effectiveness and may not fully capture long-term clinical outcomes such as complications, hospitalizations, or mortality. Finally, the one-year study period may not adequately reflect the long-term cost-effectiveness of the evaluated treatment regimens.

CONCLUSION

The combinations of metformin + sitagliptin/vildagliptin + glimepiride and metformin + sitagliptin/vildagliptin + pioglitazone were more cost-effective than metformin + glimepiride + pioglitazone from a hospital perspective. These findings may inform treatment selection among patients with T2DM needing triple oral antidiabetic therapy in tertiary care settings.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria

CRediT Author Statement
YN: Conceptualization, Methodology, Formal analysis, Data curation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **IAH:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **L:** Conceptualization, Validation, Formal analysis, Resources, Data curation, Writing – review and editing, Supervision, Project administration; **AR:** Validation, Investigation, Resources, Writing – review and editing, Supervision; **GNVA:** Methodology, Formal analysis, Data curation, Writing – review and editing, Visualization, Project administration, Funding acquisition.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

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Dapagliflozin Alone or Combined With Semaglutide: Cardiovascular and Renal Outcomes Among Patients With Type 2 Diabetes Mellitus in a 6-Month Real-World Retrospective Cohort Study in Saudi Arabia

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Abstract

Introduction. Type 2 diabetes mellitus (T2DM) is a growing global health concern linked to increased cardiovascular and renal complications. Two emerging therapeutic classes, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon like peptide-1 receptor agonists (GLP-1 RAs), have shown independent cardiometabolic benefits. However, limited real-world data exist on the comparative impact of combining these therapies versus using SGLT2i alone.

Objective. To compare the cardiovascular and renal outcomes of dapagliflozin monotherapy versus combination therapy with once-weekly injectable semaglutide among patients with type 2 diabetes mellitus (T2DM).

Methodology. In this retrospective cohort study, 539 adult patients with confirmed type 2 diabetes mellitus (T2DM; baseline HbA1c ≥6.5%) treated at King Abdulaziz Hospital, Al-Ahsa, were followed over six months. Patients received either dapagliflozin alone or in combination with semaglutide. Generalized Estimating Equations (GEE) were used to assess changes in glycemic control, cardiovascular events, lipid profile, and renal function, adjusting for time and sex.

Results. Both groups showed significant metabolic improvements over six months. Dapagliflozin monotherapy was associated with greater HbA1c reduction. Combination therapy was associated with higher HDL levels, improved eGFR, and a lower relative risk of heart failure (RR = 0.43, p = 0.04); the reduction in myocardial infarction risk (RR = 0.61, p = 0.13) did not reach statistical significance. No significant difference was observed in stroke risk. Most cardiovascular and renal markers improved modestly.

Conclusion. Combination therapy was associated with favorable renal outcomes and a reduction in heart failure risk, despite inferior glycemic control and a non-significant trend toward reduced myocardial infarction risk. These findings suggest potential complementary effects of SGLT2i and GLP-1 RA treatment in high-risk patients. However, due to the retrospective, non-randomized design, causal relationships cannot be inferred, and residual confounding may exist. Prospective trials are warranted to confirm these associations and guide treatment optimization.

Key words: dapagliflozin, semaglutide, type 2 diabetes, cardiovascular outcomes, renal function, real-world study

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major global health concern, with over 460 million adults affected worldwide, a number projected to rise to 783 million by 2045.[1,2] The situation is particularly urgent in Saudi Arabia, where the prevalence of T2DM ranges from 16% to nearly 40% among adults,[3,4] far exceeding global rates. The debilitating complications of T2DM, especially cardiovascular (CV) and renal diseases, are the leading causes of morbidity and mortality in this population,[5,6] emphasizing the need for more effective and individualized treatment approaches. To address these risks, current clinical guidelines highlight the importance of optimizing glycemic control, blood pressure, and lipid levels, aiming to reduce the burden of both macrovascular and microvascular complications among patients with T2DM.[5,7,8] In line with these guidelines, the therapeutic landscape has evolved significantly in recent years. For example, two major classes of antihyperglycemic agents−sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have demonstrated substantial metabolic benefits alongside significant cardiovascular and renal protective effects. Dapagliflozin, an SGLT2 inhibitor, improves glycemic control by reducing renal glucose reabsorption and has shown substantial benefit in lowering systolic blood pressure, as well as enhancing CV and renal outcomes in high-risk populations.[9-11] Similarly, semaglutide, a once-weekly injectable GLP-1 RA, not only helps to control blood glucose and reduce body weight but has also been proven in large clinical trials such as SUSTAIN-6 to deliver cardiovascular safety and efficacy.[12-14] While both agents are recommended for individuals at high CV or renal risk, it is important to note that real-world data on their comparative effectiveness, particularly when used in combination versus monotherapy, are limited.

Preliminary evidence suggests that combining GLP-1 RAs with SGLT2 inhibitors may provide additive or synergistic benefits across metabolic, cardiovascular, and renal endpoints.[15-17] Despite these promising indications, it remains unclear whether these effects persist in real-world practice, outside tightly controlled clinical trial settings, and whether any observed benefits hold after accounting for differences in glycemic burden and treatment indications between populations.

Therefore, this retrospective cohort study was designed to evaluate the comparative cardiometabolic effects of dapagliflozin alone versus in combination with once-weekly injectable semaglutide in patients with T2DM. We hypothesized that combination therapy would be associated with greater cardiovascular and renal benefits compared to dapagliflozin monotherapy, even if glycemic control was not superior. Ultimately, by generating real-world evidence on the outcomes of these treatment strategies, this study aims to support more personalized and effective therapeutic decision-making for patients at elevated cardiometabolic risk. The primary objective of this study was to compare cardiovascular and renal outcomes between dapagliflozin monotherapy and combination therapy with once-weekly injectable semaglutide. Secondary objectives included assessing differences in glycemic control (HbA1c), lipid profiles (HDL, LDL, total cholesterol, triglycerides), body weight (BMI), blood pressure (SBP, DBP), and inflammatory/cardiac biomarkers (hsCRP, BNP) between the two treatment groups over a six-month follow-up period.

METHODOLOGY

This retrospective cohort study, conducted at King Abdulaziz Hospital in AlAhsa, Saudi Arabia, evaluated the effects of dapagliflozin alone versus in combination with once-weekly injectable semaglutide on metabolic and CV outcomes in adults aged 18 to 75 years, with established T2DM, who initiated treatment with either dapagliflozin monotherapy or the combination regimen. Criteria for exclusion included patients younger than 18 or older than 75 years, those with type 1 diabetes mellitus or other forms of diabetes, stage D heart failure, a history of acute or chronic pancreatitis, liver cirrhosis, end-stage renal disease (ESRD), or recent CV events. Patients were selected using probability sampling and had regular follow-ups between January 1, 2020, and February 1, 2024. Type 2 diabetes mellitus was diagnosed according to the American Diabetes Association (ADA) criteria: fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test (OGTT), HbA1c ≥6.5% (48 mmol/mol), or a random plasma glucose ≥11.1 mmol/L (200 mg/dL) in a patient with classic symptoms of hyperglycemia. During revision, T2DM status was re-derived directly from baseline HbA1c (≥6.5%, per the ADA criteria above) to ensure consistency with the stated eligibility criteria; this excluded 51 patients with baseline HbA1c <6.5% and a further 72 patients with missing or non-numeric baseline HbA1c, yielding a final analytic cohort of 539 patients (353 dapagliflozin monotherapy, 186 combination therapy). Dapagliflozin was prescribed at a dose of 10 mg orally once daily. Once-weekly injectable semaglutide was initiated at 0.25 mg subcutaneously once weekly for the first four weeks, followed by escalation to 0.5 mg once weekly; further up-titration to 1.0 mg once weekly was at the treating physician's discretion based on glycaemic response and tolerability.

Data were collected at two time points—treatment initiation and after six months of therapy—and included demographic and clinical characteristics (age, sex, diabetes diagnosis, history of cardiovascular disease such as ischemic heart disease, HF, and stroke), metabolic parameters (HbA1c, body mass index [BMI], total cholesterol [TC], low-density lipoprotein cholesterol [LDL], HDL, triglycerides [TG], eGFR, and urine albumin-creatinine ratio [ACR]), cardiovascular parameters (systolic and diastolic blood pressure [SBP and DBP], myocardial infarction [MI], HF, and stroke incidence), and biomarkers (B-type natriuretic peptide [BNP] and high-sensitivity C-reactive protein

[hsCRP]). Laboratory analyses were performed using validated methods: HbA1c by high-performance liquid chromatography (HPLC); lipid panel (total cholesterol, LDL, HDL, and triglycerides) by enzymatic colorimetric assay; serum creatinine for eGFR calculation (CKD-EPI equation) by the Jaffe method; urine ACR by immunoturbidimetry; BNP by chemiluminescent immunoassay; and hsCRP by particle-enhanced immunoturbidimetry. Patients with incomplete records for key exposure variables (treatment assignment, baseline HbA1c) were excluded from the analytic cohort; however, some outcome-specific variables remained missing for individual patients and were analyzed using available-case denominators, as reflected in the varying denominators reported in the Comparative Incidence table. Clinically implausible laboratory values were identified during data cleaning and excluded prior to analysis according to prespecified physiologically plausible ranges for each parameter.

Statistical analyses were conducted using Generalized Estimating Equations (GEE) to account for repeated measures over time. Two models were developed: Time-Adjusted Models, which assessed treatment effects while adjusting for time, and Fully Adjusted Models, which additionally accounted for sex. Analyses used appropriate statistical distributions, including the Inverse Gaussian distribution for skewed data and the Binomial distribution with a log link function for binary outcomes. Dapagliflozin monotherapy was used as the reference group, with pre-treatment baseline and female sex as reference categories. Results were reported as Relative Risk (RR) with 95% Confidence Intervals (CI) for categorical outcomes and Beta coefficients with 95% CI for continuous outcomes. A *p*-value of less than 0.05 was considered statistically significant. All data analyses were conducted using the Statistical Analysis System (SAS) software.

To mitigate confounding, multivariable GEE models adjusted for time and sex. Given the retrospective, non-randomized design, residual confounding and confounding by indication cannot be excluded; baseline imbalances between treatment groups in BMI, HDL, eGFR, ACR, and HbA1c (Table 1A) are discussed as a limitation. During data audit, the original stroke, myocardial infarction, and heart failure indicators were also found to reflect whether a clinical-notes field had been populated rather than a clinically confirmed event; these indicators were cross-validated against event-detail text before the incidence and regression analyses reported here were finalized.

Ethical consideration

The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study received approval from the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC) under protocol number NRA24A/002/02, with strict adherence to patient confidentiality throughout the research process.

RESULTS

A total of 539 patients with confirmed T2DM (baseline HbA1c ≥6.5%) were included in the final analysis, with 241 (44.7%) males and 298 (55.3%) females (Table 1A). Patients were divided into two groups based on treatment regimen: those receiving dapagliflozin monotherapy and those receiving combination therapy with once-weekly injectable semaglutide (Tables 1A and 1B). Generalized Estimating Equations (GEE) were used to assess both within-group changes over time and between-group differences at six months, with dapagliflozin monotherapy used as the reference group. Results are presented by outcome domain: glycemic control and metabolic parameters, lipid profile and body weight, blood pressure, renal function markers, and incident cardiovascular events. Both time-adjusted and fully adjusted models are reported throughout.

Glycemic control and metabolic parameters

The overall mean HbA1c at baseline was 8.5 ± 1.8%, which significantly decreased to 8.03 ± 1.6% after six months of follow-up (p <0.001. However, compared to dapagliflozin monotherapy, the combination therapy group had significantly higher HbA1c levels at six months (Estimate = 0.069, 95% CI: 0.038 to 0.100; p <0.001; Table 1B). Similarly, the combination therapy group had a higher BMI (Estimate = 0.053, 95% CI: 0.0202 to 0.0875; p = 0.0017), although BMI significantly declined over time in both groups (Estimate = –0.028, 95% CI: –0.040 to –0.016; p <0.001). HDL levels showed a significant increase over time (Estimate = 0.016, 95% CI: 0.0004 to 0.0316; p = 0.043). The combination therapy was also associated with significantly higher HDL compared to dapagliflozin alone (Estimate = 0.061, 95% CI: 0.022 to 0.10; p = 0.0020). In contrast, male sex was significantly associated with lower HDL levels (Estimate = –0.171, 95% CI: –0.208 to –0.135; p <0.001). No significant differences were observed between treatment groups in LDL, total cholesterol, or triglycerides (p >0.05; Table 4).

Cardiovascular outcomes

Systolic blood pressure (SBP) remained stable over the study period, with no significant differences observed between treatment groups (p >0.05). In contrast, diastolic blood pressure (DBP) did not change significantly over time (Estimate = –0.0014, 95% CI: –0.0164 to 0.0135; p = 0.851) (Table 2). In the time-adjusted model, the risk of heart failure (HF) was significantly lower in the combination therapy group compared to dapagliflozin alone (RR = 0.438, 95% CI: 0.201 to 0.957; p = 0.038). The reduction in myocardial infarction (MI) risk (RR = 0.604, 95% CI: 0.314 to 1.165; p = 0.132) did not reach statistical significance. No significant difference in stroke risk was observed between the two treatment groups (RR = 1.211, 95% CI: 0.547 to 2.682; p = 0.637). MI and HF risk both declined significantly over time (p <0.001), as did stroke risk (RR = 0.626, 95% CI not shown; p = 0.031) (Table 3).

Table 1A. Baseline demographic and clinical characteristics by treatment group (T2DM-confirmed cohort, n = 539)

Parameter	Dapagliflozin monotherapy (n = 353)	Combination therapy (n = 186)	*p*-value
Age (years), mean (SD)*	61.97 (11.52)	57.83 (10.84)	<0.001
Sex, n (%) male	163 (46.2%)	78 (41.9%)	0.395
BMI (kg/m²)	33.92 (6.77)	36.11 (7.08)	0.001
SBP (mmHg)	139.33 (18.12)	136.31 (16.40)	0.079
DBP (mmHg)	71.43 (10.27)	70.85 (9.61)	0.566
HDL (mmol/L)	1.05 (0.27)	1.13 (0.28)	0.004
LDL (mmol/L)	2.43 (0.91)	2.48 (1.04)	0.666
Total cholesterol (mmol/L)	4.02 (1.01)	4.16 (1.18)	0.208
Triglycerides (mmol/L)	1.58 (1.09)	1.63 (0.99)	0.593
eGFR (mL/min/1.73m²)	74.53 (23.38)	82.00 (21.42)	<0.001
ACR (mg/g)	38.79 (54.72)	23.56 (39.26)	0.008
BNP (pg/mL)	286.42 (607.67)	279.45 (707.55)	0.972
hsCRP (mg/L)	22.58 (62.90)	20.64 (27.83)	0.827
HbA1c (%)	8.64 (1.58)	9.20 (1.76)	0.001
Comorbidities (baseline)			
Hypertension, n (%)	19 (5.4%)	9 (4.8%)	0.947
Chronic kidney disease, n (%)	26 (7.4%)	4 (2.2%)	0.021
Heart failure (history), n (%)	5 (1.4%)	1 (0.5%)	0.622
Ischemic heart disease, n (%)	11 (3.1%)	0 (0.0%)	0.035
Atrial fibrillation, n (%)	4 (1.1%)	0 (0.0%)	0.353
Obesity, n (%)	11 (3.1%)	4 (2.2%)	0.710
Concomitant medications (baseline)			
ACEi/ARB use, n (%)	169 (47.9%)	101 (54.3%)	0.184
Statin use, n (%)	257 (72.8%)	147 (79.0%)	0.138
Insulin use, n (%)	144 (40.8%)	95 (51.1%)	0.028

*Age recorded in source records as 10-year bands; values reflect band midpoints (see Strengths and Limitations). Comorbidity and concomitant medication flags were derived from the single primary-diagnosis field and free-text medication list per encounter, not a complete problem list; prevalence figures should be interpreted as minimum estimates.

Table 1B. Six-month follow-up characteristics by treatment group (T2DM-confirmed cohort, n = 539)

Parameter	Dapagliflozin monotherapy (n = 353)	Combination therapy (n = 186)	*p*-value
BMI (kg/m²)	33.22 (6.70)	35.03 (7.25)	0.008
SBP (mmHg)	137.13 (18.14)	135.10 (18.53)	0.281
DBP (mmHg)	70.33 (10.23)	72.85 (9.71)	0.013
HDL (mmol/L)	1.08 (0.28)	1.13 (0.26)	0.050
LDL (mmol/L)	2.46 (0.90)	2.44 (0.99)	0.819
Total cholesterol (mmol/L)	4.09 (1.06)	4.08 (1.16)	0.994
Triglycerides (mmol/L)	1.58 (1.16)	1.55 (0.92)	0.816
eGFR (mL/min/1.73 m²)	75.22 (24.14)	82.53 (20.40)	0.001
ACR (mg/g)	41.72 (62.43)	23.09 (37.97)	0.003
BNP (pg/mL)	349.39 (716.89)	353.58 (780.11)	0.986
hsCRP (mg/L)	38.59 (170.48)	13.56 (14.59)	0.238
HbA1c (%)	7.97 (1.36)	8.72 (1.89)	<0.001

Table 2. Time-adjusted GEE model for continuous metabolic and cardiovascular outcomes

Parameters	Drug	*P*-value	Time	*P*-value
BMI	0.0578 [0.0215 – 0.0940]	0.002	-0.0238 [-0.0338 – -0.0137]	<0.001
SBP	-0.0184 [-0.0393 – 0.0025]	0.084	-0.0136 [-0.0274 – 0.0002]	0.054
DBP	0.0136 [-0.0086 – 0.0358]	0.231	-0.0014 [-0.0164 – 0.0135]	0.851
HDL	0.0604 [0.0164 – 0.1045]	0.007	0.0170 [0.0001 – 0.0339]	0.048
LDL	0.0047 [-0.0615 – 0.0708]	0.890	0.0030 [-0.0311 – 0.0371]	0.864
TC	0.0176 [-0.0284 – 0.0636]	0.454	0.0048 [-0.0185 – 0.0280]	0.688
TG	0.0099 [-0.0990 – 0.1188]	0.858	-0.0171 [-0.0768 – 0.0427]	0.576
eGFR	0.0942 [0.0452 – 0.1432]	<0.001	0.0083 [-0.0088 – 0.0254]	0.342
ACR	-0.5435 [-0.8983 – -0.1887]	0.003	0.0279 [-0.1409 – 0.1968]	0.746
BNP	-0.0102 [-1.2912 – 1.2707]	0.988	0.2047 [-0.0570 – 0.4665]	0.125
hsCRP	-0.4708 [-1.1906 – 0.2489]	0.200	0.1771 [-0.6854 – 1.0396]	0.687
HbA1c	0.0759 [0.0441 – 0.1076]	<0.001	-0.0719 [-0.0880 – -0.0557]	<0.001

For drug dapagliflozin was set as the reference group. Time before the follow up period was set as the reference group.

Table 3. Time-adjusted GEE model for binary cardiovascular outcomes (stroke, myocardial infarction, and heart failure)

Dependent Variables	Drug	*P*-value	Time	*P*-value
Stroke	1.211 [0.547 – 2.682]	0.636	0.626 [0.409 – 0.959]	0.031
MI	0.604 [0.314 – 1.165]	0.132	0.526 [0.381 – 0.727]	<0.001
HF	0.438 [0.201 – 0.957]	0.038	0.531 [0.386 – 0.730]	<0.001

Measures displayed are relative risk (RR) with drug dapagliflozin was set as the reference group. Time before the follow up period was set as the reference group.

Table 4. Fully adjusted GEE Model (adjusted for time and sex) for metabolic and cardiovascular parameters

Dependent Variables	Drug	*P*-value	Time	*P*-value	Sex	*P*-value
BMI	0.0470 [0.0124 – 0.0816]	0.008	-0.0241 [-0.0338 – -0.0144]	<0.001	-0.1181 [-0.1513 – -0.0849]	<0.001
SBP	-0.0196 [-0.0403 – 0.0011]	0.064	-0.0133 [-0.0271 – 0.0005]	0.059	-0.0137 [-0.0338 – 0.0064]	0.182
DBP	0.0177 [-0.0036 – 0.0391]	0.104	-0.0023 [-0.0174 – 0.0128]	0.766	0.0530 [0.0314 – 0.0746]	<0.001
HDL	0.0502 [0.0101 – 0.0904]	0.014	0.0136 [-0.0029 – 0.0301]	0.107	-0.1858 [-0.2251 – -0.1465]	<0.001
LDL	0.0033 [-0.0633 – 0.0700]	0.922	0.0004 [-0.0341 – 0.0349]	0.980	-0.0682 [-0.1303 – -0.0061]	0.031
TC	0.0134 [-0.0322 – 0.0591]	0.564	0.0022 [-0.0215 – 0.0258]	0.858	-0.0843 [-0.1268 – -0.0417]	<0.001
TG	0.0153 [-0.0934 – 0.1240]	0.782	-0.0169 [-0.0776 – 0.0439]	0.586	0.0470 [-0.0616 – 0.1556]	0.396
eGFR	0.0942 [0.0453 – 0.1431]	<0.001	0.0083 [-0.0088 – 0.0253]	0.342	0.0011 [-0.0502 – 0.0524]	0.966
ACR	-0.5404 [-0.8953 – -0.1855]	0.003	0.0319 [-0.1381 – 0.2019]	0.713	-0.0393 [-0.3902 – 0.3116]	0.826
BNP	-2.8847 [-3.6148 – -2.1547]	<0.001	0.4317 [-0.3302 – 1.1935]	0.267	3.9658 [2.9542 – 4.9774]	<0.001
hsCRP	-0.5118 [-1.0067 – -0.0168]	0.043	0.3550 [-0.2131 – 0.9230]	0.221	-0.9879 [-1.5104 – -0.4654]	<0.001
HbA1c	0.0741 [0.0424 – 0.1059]	<0.001	-0.0719 [-0.0881 – -0.0558]	<0.001	-0.0273 [-0.0555 – 0.0010]	0.058

For drug dapagliflozin was set as the reference group. Time before the follow up period was set as the reference group.

Cardiac biomarkers

In the time-adjusted model, BNP did not differ significantly between treatment groups (Estimate = –0.010; p = 0.988); a significant association emerged only in the fully adjusted (sex-inclusive) model (Estimate = –2.885; p <0.001; Table 4), suggesting the unadjusted BNP comparison in the original submission was confounded by the sex distribution between groups. No significant differences were observed between the two groups in high-sensitivity C-reactive protein (hsCRP) levels (p >0.05) (Table 2).

Renal function

The combination therapy was associated with a persistently higher estimated glomerular filtration rate (eGFR) throughout follow-up compared to dapagliflozin monotherapy (Estimate = 0.094, p <0.001), consistent with the higher eGFR already present at baseline (Table 1A). It was also associated with persistently lower urine albumin–creatinine ratio (ACR) (Estimate = –0.544, p = 0.003) (Table 2) (Figure 2).

Multivariate analysis

In the fully adjusted model—which accounted for time and sex—the combination therapy remained significantly associated with higher body mass index (BMI) (p = 0.008), higher high-density lipoprotein cholesterol (HDL) (p = 0.014), higher estimated glomerular filtration rate (eGFR) (p <0.001), and lower B-type natriuretic peptide (BNP) levels (p <0.001) (Table 4). Combination therapy was also associated with a modest reduction in high-sensitivity C-reactive protein (hsCRP) (p = 0.043); although statistically significant, the magnitude of this effect was small and its clinical relevance is uncertain. Male sex was independently associated with lower BMI (p <0.001) and lower HDL levels (p <0.001). DM diagnosis was removed as a covariate following restriction of the cohort to confirmed T2DM patients (Methodology).

In summary, in the fully adjusted (sex-inclusive) model, combination therapy was not significantly associated with a reduced risk of stroke (RR = 1.188; p = 0.667) or myocardial infarction (RR = 0.605; p = 0.133). Combination therapy remained significantly associated with a lower risk of heart failure (HF) (RR = 0.434; p = 0.036). Stroke, MI, and HF risk all declined significantly over time (p <0.001).

After adjustment for treatment group and time, sex was not significantly associated with the risk of stroke (RR = 0.616; p = 0.244), MI (RR = 1.035; p = 0.901), or HF (RR = 0.777; p = 0.410) in this T2DM-confirmed cohort. DM diagnosis, included as a covariate in the original submission, was removed following exclusion of non-T2DM patients (see Methodology).

These findings are summarized in Figure 1, which illustrates the modest, non-significant sex differences and the significant time-related decline in cardiovascular event risk across this T2DM-confirmed cohort.

DISCUSSION

Over the past decade, the management of type 2 diabetes (T2D) has evolved significantly with the introduction of novel pharmacologic classes targeting distinct pathophysiological pathways. Among these, SGLT2i and GLP-1 RAs have demonstrated not only robust glucose-lowering efficacy but also substantial cardiovascular and renal benefits. SGLT2 inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, improve glycemic control while also reducing heart failure events and slowing the progression of kidney disease.[18] GLP-1 RAs—such as liraglutide, dulaglutide, and semaglutide—enhance insulin secretion, suppress glucagon release, delay gastric emptying, and promote weight loss, with favorable cardiovascular effects shown in major outcome trials.[19]

Given these complementary mechanisms of action, there is growing interest in combining SGLT2i and GLP-1 RAs to maximize metabolic and cardiovascular outcomes in patients with T2D. Emerging data suggest that these drug classes may act through largely independent pathways, potentially allowing additive or even synergistic effects. This raises the question of whether combining these agents could enhance outcomes beyond those achievable with monotherapy.

Building on this rationale, the present study aimed to test the hypothesis that adding once-weekly semaglutide to ongoing dapagliflozin therapy would provide incremental cardiovascular and renal benefits beyond those of dapagliflozin alone, even if the improvement in glycemic control was not superior. This hypothesis draws on accumulating evidence from clinical trials and real-world data indicating that the two agents may independently target different aspects of cardiometabolic risk.

In this retrospective cohort analysis, we compared dapagliflozin monotherapy with its combination with semaglutide across key metabolic, cardiovascular, and renal outcomes. While both groups showed significant improvements over time, combination therapy was associated with greater increases in HDL levels, improved eGFR, and a reduction in heart failure risk, with a non-significant trend toward lower myocardial infarction risk. Conversely, dapagliflozin monotherapy was associated with greater reductions in HbA1c levels. These findings provide real-world insights into the potential role of combination therapy in high-risk cardiometabolic populations, although interpretation must account for study limitations and potential confounding.

Glycemic control and metabolic parameters

Over the six-month follow-up period, both treatment groups showed a statistically significant reduction in HbA1c levels. However, patients receiving combination therapy maintained higher HbA1c values than the monotherapy group during follow-up, likely reflecting greater baseline glycemic burden rather than a smaller treatment response, since between-group change from baseline was not separately modeled; this contrasts with previous studies suggesting synergistic glycemic effects when combining SGLT2 inhibitors with GLP-1 receptor agonists.[20,21] In our cohort, patients receiving combination therapy had higher baseline HbA1c levels, possibly reflecting the selection of individuals with more advanced or poorly controlled diabetes for more intensive treatment.[22,23]

Despite these differences in HbA1c reduction, the overall improvement across both groups is clinically meaningful, given the well-established benefits of improved glycemic control in reducing microvascular complications such as nephropathy and retinopathy.[24,25] Nonetheless, the results highlight that combination therapy did not outperform monotherapy in glycemic control in this real-world population. These findings should be interpreted considering potential confounding by indication.

In addition to glycemic outcomes, both treatment groups experienced modest but significant reductions in body mass index (BMI). Dapagliflozin's weight loss effect is known to result initially from osmotic diuresis, followed by sustained reductions in visceral fat.[26] GLP-1 RAs, including semaglutide, contribute to weight reduction primarily through appetite suppression and delayed gastric emptying.[27,28] Although combination therapy was associated with a slightly higher BMI overall, weight declined in both groups over time, further supporting the metabolic benefit of either approach.

Interestingly, a previous study found greater reductions in HbA1c, fasting blood glucose, and BMI with combination therapy, as well as improvements in lipid markers; however, that study differed in design and patient population.[15] In our cohort, by contrast, HDL cholesterol increased significantly in the combination group, consistent with the known lipid-modulating effects of GLP-1 RAs.[29,30] This change is clinically relevant, as elevated HDL levels are linked to lower cardiovascular risk. Mechanistically, GLP-1 RAs such as semaglutide increase HDL levels through multiple pathways: upregulation of hepatic apolipoprotein A-I (ApoA-I) synthesis, enhancement of reverse cholesterol transport, reduction of hepatic lipase activity, and attenuation of systemic inflammation that otherwise promotes HDL catabolism. Dapagliflozin may further support HDL elevation indirectly through reductions in insulin resistance, visceral adiposity, and oxidative stress—all of which are known suppressors of HDL synthesis. The additive HDL-raising effect observed with combination therapy in this study is consistent with these mechanistic

considerations and supports the potential cardioprotective synergy of the two agents.[31,32]

However, no statistically significant changes were observed between the groups in LDL, total cholesterol, or triglycerides, suggesting that the lipid effects of combination therapy may be specific to HDL modulation rather than broad-spectrum lipid lowering.[33,34] Concerning blood pressure, systolic blood pressure (SBP) remained essentially unchanged in both groups, while diastolic blood pressure (DBP) showed a small but statistically significant reduction. This pattern aligns with prior studies, some of which report selective effects on SBP,[35] while others have observed reductions in both SBP and DBP.[36,37]

Renal and cardiovascular outcomes

Combination therapy with dapagliflozin and semaglutide was associated with favorable renal and cardiovascular parameters compared to dapagliflozin alone in this study. Specifically, combination therapy showed persistently higher estimated glomerular filtration rate (eGFR) and lower albumin-to-creatinine ratio (ACR) throughout follow-up; however, both measures were already higher/lower, respectively, at baseline (Table 1A). This likely reflects an observed between-group difference rather than a demonstrated treatment-induced improvement. These findings are consistent with prior evidence supporting the renal protective effects of both GLP-1 RAs and SGLT2 inhibitors when used individually.[16,38] Moreover, the dual treatment may offer complementary benefits through mechanisms including reduced glomerular hyperfiltration, natriuresis, and attenuation of intrarenal inflammation and oxidative stress. Regarding glomerular hemodynamics specifically, dapagliflozin exerts its renoprotective effect primarily by reducing proximal tubular sodium-glucose reabsorption, which increases sodium delivery to the macula densa and restores tubuloglomerular feedback. This results in afferent arteriolar constriction and a reduction in intraglomerular pressure, thereby mitigating glomerular hyperfiltration—a key driver of CKD progression. Semaglutide complements this mechanism by attenuating systemic and renal inflammation, reducing oxidative stress via GLP-1 receptor signaling in tubular epithelial cells and podocytes, and improving endothelial function. The combination of these distinct hemodynamic and anti-inflammatory pathways may account for the additive renoprotective effects observed in this cohort, manifested as improved eGFR and lower ACR in the combination therapy group.[39,40]

However, it is essential to note that while these improvements in renal markers were statistically significant, the absolute changes were modest, and the potential influence of baseline disease severity cannot be entirely excluded. Given that this was a non-randomized retrospective cohort, differences in renal outcomes may reflect confounding by indication or baseline patient characteristics rather than direct effects of therapy.

In terms of cardiovascular outcomes, combination therapy was associated with a significantly lower risk of heart failure (HF) events over six months compared to dapagliflozin monotherapy, an association that remained significant in both the time-adjusted and fully adjusted models, though more modest than in the original, unvalidated analysis. The reduction in myocardial infarction (MI) risk observed in earlier analyses did not reach statistical significance after restricting the cohort to confirmed T2DM patients and validating cardiovascular event ascertainment (see Methods), and should be interpreted as a non-significant trend rather than a confirmed effect. This observation is consistent with prior landmark trials demonstrating the cardioprotective effects of GLP-1 RAs (e.g., SUSTAIN-6, REWIND) and SGLT2 inhibitors (e.g., DECLARE-TIMI 58, EMPA-REG) when used individually.[11,14,22,41] Furthermore, a recent meta-analysis has also suggested additive improvements in cardiac structure and function when both classes are used together.[17]

Nonetheless, the retrospective design limits causal inference. Patients prescribed the combination therapy may have undergone more intensive clinical monitoring, benefited from more aggressive risk factor management, or had favorable unmeasured health characteristics that contributed to the observed outcomes. Despite statistical adjustment for sex and time, residual confounding cannot be ruled out.

For cerebrovascular events, no significant difference in stroke risk was observed between the treatment groups. This finding is consistent with mixed results reported in the literature regarding cerebrovascular outcomes from SGLT2i and GLP-1 RA trials.[22,42] In fact, in our cohort, stroke risk declined over time in both groups, which may reflect overall improvement in risk factor control rather than treatment-specific effect.

Even with adjustment for key covariates, unmeasured factors such as disease duration, medication adherence, or prior cardiovascular history could have influenced the associations observed. As a result, causal relationships cannot be inferred from these findings.

Taken together, the observed reductions in renal and cardiovascular risk markers with combination therapy are promising; however, they must be interpreted with caution and should be interpreted as associations, not definitive evidence of superiority. Future prospective randomized trials are needed to determine whether dual therapy provides a genuine incremental benefit beyond monotherapy in high-risk real-world populations.

Strengths and limitations

One of the strengths of this study is its relatively large sample size and the use of real-world data from a diverse patient population, which enhances the external validity and generalizability of the findings. Additionally, the

application of advanced statistical methods such as Generalized Estimating Equations (GEE) allowed for the analysis of repeated measures over time and adjustment for selected covariates, providing more robust estimates of treatment effects.

However, several limitations should be acknowledged. First, the retrospective design inherently introduces potential biases, particularly selection bias and confounding by indication, where patients receiving combination therapy may have had more severe disease or higher baseline risk, which could have influenced both the treatment decision and the observed outcomes. Although adjustments were made for sex and time, several other baseline differences between groups — including age, BMI, HbA1c, eGFR, ACR, CKD prevalence, ischemic heart disease prevalence, and insulin use — were not included as covariates in the final models. These, together with unmeasured factors such as disease duration, comorbidity burden, or medication adherence, may have contributed to residual confounding. Therefore, observed associations between treatment type and outcomes should be interpreted with caution, and not assumed to indicate causality.

Additionally, baseline age was recorded in the source records as 10-year bands rather than exact age, and figures reported in Table 1A/1B reflect band midpoints. A small number of records (n = 18, 3.3% of the corrected cohort) fell outside the stated 18–75-year eligibility window. Given the very small proportion of such cases, these patients were retained, and this is acknowledged as a limitation of the study. Baseline imbalances between treatment groups in BMI, HDL, eGFR, ACR, and HbA1c (Table 1A) indicate the two groups were not fully comparable at treatment initiation, which may confound the between-group comparisons reported. In particular, the combination therapy group appeared to represent a clinically different population, with higher BMI, higher HbA1c, greater insulin use, and lower prevalence of CKD and ischemic heart disease than the monotherapy group; readers should weigh this substantial baseline confounding by indication when interpreting all between-group comparisons in this study. Age and several other baseline clinical differences between groups were not included as covariates in the final models and may have contributed to residual confounding. Baseline event variables (stroke, MI, heart failure) were derived from encounter documentation rather than a structured disease registry and may not completely capture historical disease burden; for example, baseline heart failure history was similar between groups (1.4% vs. 0.5%, $p = 0.622$) while baseline heart failure admission rates differed more substantially (10.5% vs. 4.7%, $p = 0.043$), a discrepancy that likely reflects differences in encounter documentation rather than true differences in disease history. Because treatment allocation was not randomized and baseline differences existed between groups, the observed associations should be interpreted as hypothesis-generating rather than confirmatory. Of the 662 patients with a recorded baseline HbA1c value or drug assignment, 51 did not meet the ADA HbA1c criterion for T2DM and 72 had missing or non-numeric baseline HbA1c; the original dataset's exclusions for incomplete baseline or follow-up records at other timepoints were not separately quantified in the source records, and a formal STROBE-style flow diagram was not constructed for this cohort. This is acknowledged as a limitation of the reporting.

Second, the follow-up period was limited to six months, which may not be sufficient to capture long-term cardiovascular or renal outcomes, particularly for chronic disease processes. Future studies with longer follow-up and prospective designs are needed to validate and extend these findings. Lastly, the study was conducted at a single tertiary care center, which may limit generalizability to broader healthcare settings or populations. Additionally, several clinical realities must be acknowledged. Long-term cost barriers represent a significant practical challenge: both semaglutide and dapagliflozin are high-cost medications, and real-world adherence may be substantially lower than observed in controlled settings, particularly in lower-resource healthcare systems. The complex dosing regimen of once-weekly injectable semaglutide—with its staged titration schedule—introduces additional complexity compared to monotherapy and may adversely affect treatment adherence in routine clinical practice. Furthermore, the broad phenotypic heterogeneity of chronic kidney disease (CKD) presents a challenge to generalizing these findings. Patients with CKD exhibit diverse underlying etiologies (diabetic nephropathy, hypertensive nephropathy, glomerular disease), varying degrees of proteinuria, and distinct rates of eGFR decline. This heterogeneity means that the renoprotective response to SGLT2i/GLP-1 RA combination therapy may differ considerably depending on the predominant CKD phenotype. Regarding concomitant therapy, a notable proportion of patients in this cohort were prescribed renin-angiotensin-aldosterone system (RAAS) blockers, including angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), as well as mineralocorticoid receptor antagonists (MRAs) in some cases. Although these agents were not formally analyzed as effect modifiers in the current study, their use as background therapy—particularly given their established renoprotective and cardioprotective roles—may have contributed to the overall outcomes observed in both groups and should be considered when interpreting the results. Future analyses should account for RAAS blocker use as a covariate.

CONCLUSION

In this retrospective cohort study, both dapagliflozin monotherapy and its combination with once-weekly injectable semaglutide were associated with improvements in metabolic, cardiovascular, and renal parameters over six months. While dapagliflozin alone was linked to better glycemic control, combination therapy demonstrated additional benefits in HDL levels, renal function (eGFR, ACR), and a reduced risk of heart failure, with a non-

significant trend toward reduced myocardial infarction risk. These findings support the potential value of individualized treatment strategies, particularly for patients with elevated cardiovascular or renal risk profiles. However, given the study's observational nature and possible residual confounding, these associations should be interpreted with caution. Prospective, randomized controlled trials are warranted to confirm these results and guide evidence-based treatment pathways that optimize personalized care in patients with T2DM.

In particular, a future prospective randomized controlled trial should pre-specify primary renal endpoints including urine albumin excretion rate (or albumin-to-creatinine ratio) and rate of eGFR decline over time, together with primary cardiovascular endpoints such as major adverse cardiovascular events (MACE). Secondary outcomes should encompass glycemic control (HbA1c), body weight and BMI, lipid parameters, blood pressure, and biomarkers (BNP and hsCRP), thereby providing the level of evidence needed to guide personalized treatment decisions in this high-risk population.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
RA: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **MA:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision; **MA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing, Supervision; **SAM:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing; **AA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing, Supervision; **AA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing; **AK:** Conceptualization, Methodology, Software, Resources, Writing – review and editing, Visualization; **NA:** Conceptualization, Methodology, Software, Formal analysis, Resources, Data curation, Writing – review and editing, Visualization; **AA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing, Visualization; **NA:** Conceptualization, Methodology, Validation, Investigation, Writing – review and editing; **MA:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – review and editing, Formal analysis, Writing – review and editing; **AA:** Conceptualization, Methodology, Validation, Writing – review and editing; **TA:** Conceptualization, Methodology, Formal analysis, Resources, Writing – review and editing; **RA:** Conceptualization, Methodology, Validation, Writing – review and editing; **GA:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – review and editing; **JA:** Conceptualization, Methodology, Validation, Writing – review and editing; **AA:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – review and editing; **TA:** Conceptualization, Methodology, Validation, Writing – review and editing; **AA:** Conceptualization, Methodology, Validation, Resources, Writing – review and editing; **IA:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – review and editing; Supervision; **SK:** Conceptualization, Software, Validation, Formal analysis, Supervision; **AAQ:** Conceptualization, Validation, Investigation; **YT:** Conceptualization, Data curation, Writing – original draft preparation; **MAH:** Conceptualization, Software, Investigation, Supervision.

Data Sharing and Availability
Datasets generated and analyzed are included in the published article.

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ORIGINAL ARTICLE

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Assessment of Glycemic Control Among Prospective Hajj Pilgrims With Type 2 Diabetes Mellitus in Tangerang City, Indonesia

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Abstract

Background. Diabetes Mellitus Type 2 (T2DM) is a significant health concern for Hajj pilgrims, with glycaemic control crucial for their well-being during the pilgrimage. Physical health is key to determining *istithaah*, including HbA1c and fasting blood glucose tests for prospective Hajj pilgrims with type 2 diabetes mellitus.

Objective. This study describes HbA1c and fasting blood glucose levels as indicators of glycaemic control among Indonesian prospective Hajj pilgrims diagnosed with T2DM based on laboratory results from medical check-ups for the 2024 departure in Tangerang City, and assesses their association with demographic factors.

Methodology. A cross-sectional study analyzed HbA1c from 125 pre-departure medical check-ups of 75 female and 50 male prospective Hajj pilgrims. Data were collected from medical records at a public hospital in Tangerang City and from the Hajj Integrated Computer Health System (SISKOHATKES) application in 2024. Statistical analysis was performed using the Chi-square test or Fisher's exact test, as appropriate.

Results. This study showed that most subjects were female, with the most common age group being 18–59 years (adult). The most prevalent health eligibility (istitaah) status was eligible with assistance. More than 50% of Hajj pilgrims with T2DM had comorbid conditions such as hypertension, cardiomegaly, and hyperlipidaemia. The mean HbA1c level was 9.82 ± 2.2%, with most participants exhibiting uncontrolled glycaemic status (HbA1c >7.5%). Similarly, the mean fasting blood glucose level was 197.0 ± 67.8 mg/dL, with the majority also falling within the uncontrolled range (fasting blood glucose >126 mg/dL). There was no significant correlation between HbA1c levels and age or sex.

Conclusion. The majority of prospective Hajj pilgrims with T2DM are uncontrolled in terms of glycaemic status. These findings require comprehensive assessment and management strategies before, during, and after the Hajj pilgrimage to minimize risk and prevent complications.

Key words: type 2 diabetes mellitus, prospective Hajj pilgrims, HbA1c levels, istitaah

INTRODUCTION

Hajj is the fifth pillar of Islam, consisting of activities that predominantly involve physical exertion and require optimal physical fitness and health. In its implementation, prospective Hajj pilgrims must fulfill various requirements, including physical health and mental and spiritual readiness, to determine their eligibility for health (*Istitaah*).[1,2]

Millions of Muslims from more than 183 countries annually perform the Hajj pilgrimage in the Kingdom of Saudi Arabia during the lunar month of Dhu al-Hijjah. Approximately 1.8 million Muslims participated in the Hajj pilgrimage in 2024.[1] However, most pilgrims are generally middle-aged or older when they can afford the journey. A large percentage of Hajj pilgrims are elderly and may have chronic health conditions.[3] Data from the Hajj Health Centre indicates that the morbidity and mortality rates among Indonesian Hajj pilgrims in Saudi Arabia remained high between 2017 and 2023. Each year, more than 4,000 pilgrims required hospitalization in Indonesian Hajj Health Clinics (KKHI) and Saudi Arabian hospitals (RSAS) over the past five years.[2]

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T2DM is a metabolic disease that significantly impacts the quality of life of those affected. This condition is characterized by impaired glucose metabolism, which can lead to various serious complications, both acute and chronic.[4] The prevalence of diabetes mellitus in Indonesia in 2023 was 11.7%.[5] T2DM is one of the three most prevalent health problems among Hajj pilgrims. A total of 5.77% and 12.65% of Hajj pilgrims in Nusa Tenggara Barat and Banda Aceh, respectively, suffer from T2DM.[6] In Tangerang City, the number of prospective Hajj pilgrims diagnosed with type 2 diabetes mellitus tends to increase each year.

The significant lifestyle changes experienced by diabetic patients during Hajj, including variations in geography, climate, diet, and physical activity, pose a considerable challenge. Moreover, diabetes has increasingly been recognized as a leading contributor to illness and death during the pilgrimage. Many of them also struggle with diabetes-related complications, including eye disorders, coronary artery disease, and diabetic foot problems.[7,8] Poorly managed diabetes mellitus and persistent hyperglycaemia play a crucial role in worsening vascular disease outcomes. Chronic elevation of blood glucose levels and prolonged disease duration are primary risk factors for the progression of microangiopathic complications.[9]

As the country with the largest Muslim population, Indonesia has the world's largest Hajj quota. In 2024, Indonesia's Hajj quota is 241,000 pilgrims. The health examination of prospective Hajj pilgrims is conducted to ensure their well-being (*istitaah*). This examination consists of three stages conducted by the district/city Hajj health team, including medical check-ups, cognitive assessments, mental health evaluations, and assessments of their ability to perform daily activities independently.[10] Based on the health examination results, the Hajj health *(istitaah*) status is categorized as follows: eligible, eligible with assistance, temporarily not eligible, and not eligible.

HbA1c is a form of haemoglobin A that undergoes glycation at the N-terminal of its beta-globin chain valine.[11] HbA1c is an essential parameter as the standard of care for diagnosing, evaluating, and monitoring diabetes mellitus, particularly type 2 diabetes. For diagnostic use, HbA1c testing should be conducted in a National Glycohemoglobin Standardization Program (NGSP)-certified laboratory to ensure accurate, standardized results. HbA1c is a crucial measure of long-term glucose control, reflecting the overall glycaemic profile from the previous two to three months.[12] Prospective Hajj pilgrims with uncontrolled T2DM with an HbA1c level >8% will receive treatment for one month, followed by reassessment. If the HbA1c level remains >8%, their departure for the current year will be postponed, or further action will be taken in accordance with applicable regulations.[10] It is essential to ensure that prospective Hajj pilgrims are in optimal health before departure. This study aimed to describe glycaemic control (HbA1c and fasting blood glucose levels) among prospective Hajj pilgrims in Tangerang City in 2024 with T2DM and to assess its association with demographic factors, including age and sex. The results can inform the development of more focused health policies to reduce diabetes risk and manage diabetes among Hajj pilgrims.

METHODOLOGY

This study employed a quantitative, cross-sectional design using secondary data obtained from the medical records of prospective Hajj pilgrims diagnosed with T2DM in Tangerang City, Indonesia. The data were collected from a government-owned public hospital and were recorded through the Hajj Integrated Computer Health System (SISKOHATKES) during the 2024 Hajj health screening period. The minimum sample size was calculated using the single population proportion formula ($n = Z^2PQ/d^2$), assuming a 95% confidence level ($Z=1.96$), an expected proportion of 50%, and a margin of error of 10%, yielding a minimum sample size of 96 participants. Subsequently, total enumeration was applied, and all prospective Hajj pilgrims with T2DM who met the inclusion and exclusion criteria during the study period were enrolled, yielding a final sample of 125 participants. Eligible subjects who were officially registered as 2024 Hajj pilgrims in Tangerang City had a confirmed diagnosis of T2DM based on medical records and had completed laboratory testing for HbA1c as part of the pre-Hajj medical screening. Individuals with incomplete medical records or those diagnosed with other forms of diabetes, such as type 1 or gestational diabetes, were excluded from the study.

The primary outcome of interest in this study was glycaemic control, as measured by HbA1c levels. HbA1c was categorized into two groups: controlled (≤7.5%) and uncontrolled (>7.5%). This threshold represents a more stringent target than the standard eligibility criterion of <8% recommended by the Indonesian Ministry of Health, and was chosen to provide a more sensitive assessment of glycaemic status in the context of the physically demanding Hajj pilgrimage. Independent variables included demographic characteristics (age: adult, pre-elderly, or elderly; sex: male or female), as well as clinical factors (health eligibility status [*istitaah*] and comorbidities). The Hajj health team classified health eligibility status as eligible, eligible with assistance, temporarily not eligible, and not eligible based on the results of the medical examinations. Comorbidities were recorded based on ICD-10 diagnoses in the medical records and included conditions such as hypertension, cardiomegaly, hypercholesterolemia, and hyperlipidaemia.

Data analysis was conducted using SPSS version 27, with descriptive statistics used to summarize patient characteristics. The distribution of continuous variables, including HbA1c and fasting blood glucose levels, was assessed using the Kolmogorov-Smirnov test. A *p*-value <0.05 was considered indicative of non-normal distribution; variables are reported as median (interquartile range [IQR]) and range. The association between HbA1c levels

and sex was analyzed using Fisher's exact test due to small expected cell counts, and the association between HbA1c levels and age groups was assessed using the Chi-square test. A *p*-value of less than 0.05 is considered statistically significant. Ethical approval for this study was granted by the Ethics Committee of the Faculty of Medicine, UIN Syarif Hidayatullah Jakarta (Approval Number: B-018/F12/KEPK/TL.00/EE-08/2024).

RESULTS

The characteristics of the study subjects are presented in Table 1. A total of 75 subjects (60.0%) were female, while 50 subjects (40.0%) were male. Based on age classification, most subjects were categorized as pre-elderly (53.7%), while seven subjects (6.3%) were classified as adults. The mean age in this study was 57.71 ± 8.14 years, ranging from 38 to 83 years. Regarding the health assessment (*istitaah)*, only one subject (0.8%) met the eligibility criteria for Hajj without assistance, whereas 124 subjects (99.2%) were deemed eligible with assistance.

Analysis of comorbidities among 125 samples based on the International Classification of Diseases (ICD) by the World Health Organisation (WHO) is shown in Table 2. The most common comorbid condition with diabetes mellitus was unspecified hyperlipidaemia, observed in 42 subjects (33.6%). This was followed by essential (primary) hypertension, which was present in 28 subjects (22.4%), and cardiomegaly in 12 subjects (9.6%). Additionally, isolated hypercholesterolemia was identified in 11 subjects (8.8%), while isolated diabetes mellitus was recorded in 32 subjects (25.6%).

The distribution of HbA1c and fasting blood glucose levels among pilgrims diagnosed with type 2 diabetes mellitus shows that the majority of respondents have suboptimal glycaemic control.

Of 125 subjects, 96 (76.8%) had HbA1c levels >7.5% and 113 (90.4%) had fasting blood glucose levels ≥126 mg/dL, indicating poor glycaemic control by both markers (Table 3). Only 29 respondents (23.2%) had controlled HbA1c levels (≤7.5%), and 12 (9.6%) had controlled fasting blood glucose (<126 mg/dL). These findings demonstrate a consistent pattern of suboptimal glycaemic control across both short-term and long-term indicators, emphasizing the need for intensified intervention strategies to improve metabolic outcomes in this population.

Based on Table 4, HbA1c levels ≤7.5% and >7.5% were more prevalent among female prospective Hajj pilgrims than males. However, it was not statistically significant ($p = 0.832$).

The proportion of prospective Hajj pilgrims with HbA1c levels >7.5% was higher across all age groups. The distribution of HbA1c levels (≤7.5% and >7.5%) did not show a statistically significant ($p = 0.457$) association with age groups (Table 4), indicating that age group did not significantly influence HbA1c levels in this study.

Table 1. Characteristics of Study Participants (N = 125)

Characteristic	Description	n (%)/Median (IQR;min-max)
Sex	Male	50 (40.0)
	Female	75 (60.0)
Age (years)	Adult (18-59)	74 (59.2)
	Pre-elderly (60-64)	26 (20.8)
	Elderly (>65)	25 (20.0)
HbA1c (%)		9.4 (3.9; 6.0-15.0)
Fasting blood glucose (mg/dL)		176 (105; 100-395)
Health eligibility (istitaah)	Eligible	1 (0.8)
	Eligible with assistance	124 (99.2)
	Temporarily not eligible	0 (0.0)
	Not eligible	0 (0.0)

Table 2. Comorbidities (N = 125)

Comorbidities	n (%) (N = 125)
Isolated DM	32 (25.6)
Essential (primary) hypertension	28 (22.4)
Cardiomegaly	12 (9.6)
Isolated hypercholesterolemia	11 (8.8)
Hyperlipidaemia, unspecified	42 (33.6)

Table 3. HbA1c and fasting blood glucose status of the study subjects (N = 125)

Variable	Category	n (%)
HbA1c (%)	≤7.5 (Controlled)	29 (23.2)
	>7.5 (Uncontrolled)	96 (76.8)
Fasting blood glucose (mg/dL)	<126	12 (9.6)
	≥126	113 (90.4)

Table 4. Association between demographic factors and HbA1c level (N = 125)

Variable	Category	HbA1c ≤7.5 n(%) (n = 29)	HbA1c>7.5 n(%) (n = 96)	*p*-value*
Sex	Female	18 (62.1)	57 (59.4)	0.832
	Male	11 (37.9)	39 (40.6)	
Age Group	Adult	17 (58.6)	57 (59.4)	0.457
	Pre-elderly	8 (27.6)	18 (18.8)	
	Elderly	4 (13.8)	21 (21.9)	

*Fisher's exact test for sex variable; Chi-square test for age group

DISCUSSION

More than 50% of the study subjects were adults (19–59 years old**),** with a mean age of 57.71 ± 8.15 years. According to Sari's study, data from the public health office indicate that most prospective Hajj pilgrims from Semarang City in 2024 belong to the 51–60 age group.[13] This is similar to Yousuf's study, which reported an average age of 55.41 ± 10.6 years for Hajj pilgrims with diabetes mellitus.[14] The oldest study subject was 83 years old, which is not significantly different from Sari's study, which recorded the oldest participant at

88 years old. The proportion of elderly Hajj pilgrims in Sari's study was 34% of the pilgrims from Semarang City, which is relatively similar to this study, where the proportion of elderly participants was 20%. Elderly Hajj pilgrims require strict monitoring from Hajj officers, particularly in the health sector. Age is a key determinant of an individual's health, as ageing is associated with various health issues. Elderly Hajj pilgrims experience changes in physical condition, immune system, anatomy, and organ function. These ageing-related changes make them more vulnerable to disease than younger individuals. Therefore, special attention must be given to elderly Hajj pilgrims, both by themselves and by the Hajj health team, through regular health monitoring, routine medication, physical exercise, and a well-balanced diet.[13]

With a predicted global diabetes prevalence of 8.8% and approximately 2.5 million adult Muslims performing Hajj, it is estimated that more than 220,000 Hajj pilgrims each year have diabetes. Healthcare providers must be aware of the potential risks that may arise during Hajj. A prospective observational study revealed that 26% of patients admitted to Makkah Hospital were newly diagnosed with diabetes and were previously unaware of their condition. In comparison, 74% had a prior diagnosis of diabetes.[15]

The Indonesian Ministry of Health has determined that Hajj pilgrims with controlled T2DM managed with medication are eligible for assistance. This means they can perform Hajj while receiving continuous medical supervision and management throughout their Hajj journey. The distribution system for medicines among Indonesian Hajj pilgrims has been optimized through the Sobathaji application, which facilitates medication management and distribution for each group. Diabetes medications, such as insulin and oral antihyperglycemic agents, are provided by the Indonesian Hajj Health Clinic (KKHI) and efficiently distributed through accommodation sectors. Additionally, pilgrims receive pre-departure medication supplies and undergo regular medical monitoring during the pilgrimage.[16]

Our finding that 76.8% of prospective Hajj pilgrims with type 2 diabetes mellitus had uncontrolled HbA1c levels (>7.5%) aligns with evidence from other Hajj contexts, reinforcing the persistent challenge of glycaemic management in this setting. In this study, glycemic control was defined using an HbA1c cut-off of 7.5%, which is more stringent than the <8% threshold recommended by the Indonesian Ministry of Health for Hajj eligibility. The use of a lower cut-off was intended to provide a more sensitive assessment of glycemic status in prospective Hajj pilgrims, given the substantial physical exertion, heat exposure, and potential disruption in medication adherence during the pilgrimage. A previous study conducted among Indonesian Hajj pilgrims reported a high prevalence of glycaemic abnormalities. For instance, a study based on SISKOHATKES data in DKI Jakarta found that 29.4% of women of reproductive age had prediabetes, indicating a considerable burden of metabolic dysregulation in this population. In a prospective observational study conducted in Saudi Arabia, Khogeer et al., reported that 70.8% of pilgrims with diabetes experienced acute hyper-glycaemia, with significant proportions also suffering from foot injuries (28.8%) and hypoglycaemia (14.9%) during the pilgrimage.[17] These high complication rates underscore the clinical consequences of inadequate glycaemic control during Hajj.

Moreover, established guidelines from Ibrahim et al. (2018) emphasize that structured pre-Hajj risk stratification, insulin and medication adjustment, foot-wear counseling, and education can significantly mitigate acute risks such as hypoglycaemia, infections, and cardiovascular strain.[15] This suggests a gap in the execution of such preparatory programs in our study population, where unregulated HbA1c levels and comorbidities like hypertension and hyperlipidaemia may heighten complication risks during the pilgrimage. Integrating these recommended interventions into Indonesia's Hajj health framework—especially via KKHI clinics and community health services—could substantially enhance metabolic readiness and safety for pilgrims with diabetes.

It is necessary to detect and manage comorbidities in prospective Hajj pilgrims. Khogeer et al.,'s study involved 281 pilgrims with T2DM, of whom 199 (70.8%) experienced foot injuries, 77 (27.4%) had hyperglycaemia, and 37 (13.2%) suffered from hypoglycaemia, with some individuals exhibiting more than one complication. Redness (28.8%) and blisters (20.6%) were the most common symptoms among those with foot injuries. Fatigue (14.9%) and headache (12.5%) were the most frequently reported symptoms of hypoglycaemia. Additionally, pilgrims with T2DM experienced a significantly higher rate of acute complications compared to those with type 1 DM (81.8% versus 18.2%, $p = 0.33$).[17]

The physically demanding activities and extreme weather during the Hajj pilgrimage can worsen conditions like hyperlipidaemias and hypercholesterolemia. These increase the risk of atherosclerosis and coronary artery disease, which are further aggravated by physical exertion during the pilgrimage.[18-20]

Similarly, uncontrolled hypertension and cardiomegaly can lead to stroke or heart failure. Among prospective Hajj pilgrims with T2DM, 22.4% have primary hypertension, 9.6% have cardiomegaly, and 8.8% have hypercholesterolemia.

Hypertension is recognized as a significant risk factor for cardiovascular disease and is often linked to T2DM. High blood pressure was identified in 70.5% of the patients, and systolic blood pressure showed a positive relationship with age.[21] Systematic reviews and meta-analyses were conducted to determine the prevalence of diabetes and hypertension among Hajj pilgrims. A total of 26 studies, carried out between 1993 and 2018 with 285,467 participants, revealed that the prevalence of hypertension and diabetes

in all included studies was 12.2% and 5%, respectively.[22] Hypertension is a significant factor in the number of hospitalized pilgrims during the Hajj.[8] Hypertension, alongside diabetes, serves as an essential risk factor for cardiovascular disease (CVD), which is the leading cause of death among pilgrims.[23] Hypertension contributed to 3% of ICU admissions as a primary cause and was present as a comorbidity in 26.4% of cases. Over 10% of patients died, with 60% of these deaths attributed to CVD.[24]

In 2002, CVD was identified as the leading cause of death among Hajj pilgrims, accounting for 45.8% of fatalities, while hypertension was responsible for 2.7% of the total deaths.[25] An analysis of data from the Indian medical mission over three consecutive Hajj seasons (2014–2016) identified diabetes and hypertension as the most prevalent pre-existing conditions among pilgrims, with CVD accounting for over 70% of deaths.[26] Likewise, among approximately 1.7 million Indonesian pilgrims who participated in Hajj between 2004 and 2011, hypertension and diabetes were frequently observed, and CVD was responsible for 45–66% of fatalities.[27] Collaborative efforts between the pilgrims' home countries and the Kingdom of Saudi Arabia must be promptly implemented to reduce incidence rates by conducting effective medical screening to identify and eliminate risk factors for cardiovascular diseases, mainly poorly controlled conditions.[27]

Epidemiological studies have shown that insulin resistance and diabetes are not only metabolic disorders but also key factors that increase the risk of hypertension, vascular stiffness, and cardiovascular disease. On the other hand, excessive arterial stiffness and impaired vasorelaxation further exacerbate insulin resistance and contribute to the progression of diabetes. The molecular mechanisms linking diabetes to hypertension include overactivation of the renin-angiotensin-aldosterone system, heightened sympathetic nervous system activity, mitochondrial dysfunction, excessive oxidative stress, and systemic inflammation. Recent studies have identified additional mechanisms underlying the heightened risk of hypertension in diabetes, such as increased activation of epithelial sodium channels, changes in extracellular vesicles and their microRNAs, disruptions in gut microbiota, and elevated activity of renal sodium-glucose cotransporters, all of which contribute to hypertension in the context of diabetes. This review also explores the impact of socioeconomic factors, current blood pressure targets, and treatment strategies recommended for managing hypertension in diabetic patients.[28]

In 2011, the WHO recommended HbA1c as a diagnostic tool for diabetes, specifically for identifying type 2 diabetes, in its clinical practice guidelines.[29] Reference range HbA1c levels are <5.7%. Prediabetes is diagnosed when HbA1c levels are between 5.7% and 6.4%, while diabetes is diagnosed when HbA1c levels are ≥6.5%.[30] In this study, of 125 respondents, 96 (76.8%) study subjects had HbA1c levels greater than 7.5%. This indicates that the respondent's blood glucose levels were uncontrolled. Hajj pilgrims with uncontrolled diabetes mellitus are at high risk of experiencing acute and chronic complications during Hajj.

Before embarking on the Hajj pilgrimage, patients should undergo a comprehensive clinical assessment, including a detailed foot examination, an evaluation of renal function, and cardiovascular health. This medical assessment should ideally be conducted at least 2–3 months before departure. Blood glucose levels, both fasting and postprandial, and HbA1c levels must be closely monitored. Identifying patients with existing microvascular or macrovascular complications and other comorbid conditions is crucial. A cardiac evaluation with an electrocardiogram should be performed for those with cardiovascular risk factors; if significant risks are detected, the patient should be advised against participating in the Hajj. Additionally, a two-dimensional echocardiogram and a stress test should be conducted if coronary artery disease is suspected. Patients with HbA1c levels around 7% are considered at low risk and may be approved for the Hajj journey.[31]

Patients with diabetes mellitus are encouraged to eat regularly and should be reminded to avoid sugary drinks unless necessary to manage hypoglycaemia. If pilgrims with diabetes experience hypoglycaemia, they can eat dates. They should consume complex carbohydrates before performing *Tawaf* and *Sa'i*, and may bring dates if needed. During the Hajj journey, strict glycaemic control is not recommended because hypoglycaemia can be more fatal than hyperglycaemia.[32]

Although no statistically significant association was observed between sex and HbA1c levels (p = 0.832), this finding should be interpreted with caution, as the small sample size or unmeasured confounding factors may have influenced the study. This aligns with Adriani et al.'s study, which found no significant correlation between sex and HbA1c levels (p = 0.143). The proportion of HbA1c levels >7.5% is higher in females than in males. In females, especially those who are menopausal, oestrogen levels decrease, leading to unpredictable fluctuations in blood glucose levels and increased fat accumulation.[33] The study by Stedman et al. showed that the median HbA1c levels in women aged ≥55 years and 45–55 years were the same as those in men. However, in women under 45 years old, the median HbA1c level was lower than in men of the same age.[34]

No statistically significant association was observed between HbA1c levels and age group (p = 0.457). Roth et al., found that HbA1c levels tend to rise progressively with age, with an estimated increase of 0.074% per decade.[36] This elevation in blood glucose and HbA1c levels is attributed to age-related declines in pancreatic β-cell function, reduced insulin receptor activity, decreased insulin sensitivity, loss of muscle mass, and lower glucose utilization.[38] The study by Gülsen et al., which involved adult subjects without diabetes mellitus, found that HbA1c levels were significantly higher in males than in females, particularly

in the 30-49 age group. A significant correlation between HbA1c levels and age was observed in males and females aged 30-49 years (p <0.05), with HbA1c gradually decreasing with age. No significant correlation was observed between HbA1c levels and age (p >0.05).[39]

Individuals with T2DM require comprehensive management before, during, and after the Hajj pilgrimage to prevent complications. In Indonesia, Hajj pilgrims must fulfill health eligibility requirements before departing for Saudi Arabia. Therefore, Hajj health examinations and guidance must be enhanced to ensure the pilgrims' well-being from their home country to the Kingdom of Saudi Arabia. Pilgrims are declared health-eligible *(istitaah)* after undergoing a series of health interventions to control risk factors and maintain their health status within the eligibility criteria *(istitaah).*

This study focused only on bivariate analysis without adjusting for multiple variables, which may have led to residual confounding. Additionally, the lack of follow-up data prevented the assessment of glycaemic control during and after the Hajj pilgrimage. Furthermore, the cross-sectional design limits the ability to infer causal association between glycaemic control and demographic variables such as age and sex.

These findings highlight the need for strengthened pre-departure screening, risk stratification, and comprehensive diabetes management strategies to improve metabolic readiness among Hajj pilgrims. In addition, a substantial proportion of pilgrims present with cardiometabolic co-morbidities, such as hypertension, cardiomegaly, and hyperlipidaemia, which may further increase the risk of complications during the Hajj pilgrimage.

CONCLUSION

Glycemic control among prospective Hajj pilgrims with T2DM in Tangerang City in 2024 remains suboptimal. The absence of statistically significant associations with demographic factors suggests that more complex clinical and behavioral determinants likely influence glycemic status in this population. Strengthening pre-departure screening and individual management strategies may be essential to improve health outcomes during the Hajj pilgrimage.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
MM: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration**; MPH:** Validation; **DT**: Methodology, Writing – review and editing, Supervision; **YTS:** Formal analysis, Validation, Data curation, Writing – review and editing**; AS:** Conceptualization, Writing – review and editing, Supervision.

Data Availability Statement
The datasets generated and analyzed during the current study are not publicly available due to institutional and ethical restrictions. However, data may be obtained from the corresponding author upon reasonable request and with permission from the Tangerang City Health Office and affiliated institutions.

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ORIGINAL ARTICLE

Prevalence of Adrenal Insufficiency in Clinically Stable Adults Living with HIV Attending Outpatient Clinics in Malaysia

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Abstract

Background. Adrenal insufficiency (AI) is a potentially life-threatening condition in people living with HIV/AIDS. Data on this topic are scarce and estimates of its prevalence vary.

Objective. To determine the prevalence of AI among people living with HIV and to guide the management strategies.

Methodology. This is a cross-sectional study conducted at the Infectious Diseases Clinics of two tertiary centres. Clinical and laboratory data were collected, and Synacthen (cosyntropin) stimulation tests were performed. Adrenal antibodies and Adrenocorticotropic Hormone (ACTH) levels were analysed in those who had an inadequate Synacthen response. The data were analysed using SPSS (version 28.0).

Results. A total of 110 stable outpatient adults living with HIV, aged 18 to 80 years, were recruited. The mean age of the studied population was 37.5 ± 10.6 years, 81.8% were male, 23.6% had a normal BMI and 64.5% were either overweight or obese. The median disease duration was 4.5 years and all subjects had been on HAART for a median duration of 3.8 years. Treatment failure occurred in 20% of participants, 41.8% had a history of opportunistic infections and 4.5% had autoimmune diseases. The mean nadir CD4 count was 202 cells/mm³ ± 200 with 60.6% below 200 cells/mm³. At the time of the Synacthen tests, 88.2% had a viral load of <40 copies/ml while 89.1% had a CD4 count >200 cells/mm³. AI was identified in 2 participants (1.8%; 95% CI 0.2-6.4%). Their adrenal antibodies were negative, and ACTH levels were 4.5 ± 5.9 pmol/L. Both had significantly lower nadir CD4 counts (p <0.001), a history of treatment failure (p = 0.039) and symptoms suggestive of AI (p = 0.004).

Conclusion. This study revealed a low prevalence of AI (1.8%) among stable HIV patients on HAART. Significant associations with AI were found in participants with lower nadir CD4 counts, a history of treatment failure, and symptoms suggestive of AI.

Key words: adrenal insufficiency, adrenal cortex antibodies, HIV infections, adrenocorticotropic hormone, highly active antiretroviral therapy

INTRODUCTION

Over the past few decades, human immunodeficiency virus (HIV) infection has shifted from being an inevitably fatal condition to a manageable chronic disorder, significantly improving life expectancy. This transformation is largely due to the introduction of Highly Active Antiretroviral Therapy (HAART), which has significantly improved the management of HIV and opportunistic infections. However, as life expectancy has increased, new challenges have emerged. Data from a long-term population-based cohort in Taiwan suggested an association between HIV infection and the development of autoimmune diseases.[1] Similarly, a prospective study in Brazil observed a higher frequency of autoantibodies in HIV-infected patients.[2] The presence of adrenal autoantibodies is linked to an increased future risk of developing overt primary adrenal insufficiency (AI).[3] However, there is currently no data on the prevalence of adrenal auto-antibodies among HIV patients.

Adrenal gland involvement in HIV-infected individuals is a significant concern, with postmortem examinations showing adrenal abnormalities in up to two-thirds of these patients.[4] Adrenal dysfunction can lead to either hypercortisolism or hypocortisolism.[5] Previous studies

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have reported inadequate adrenal response to synthetic ACTH stimulation in 7% to 24% of stable HIV patients.[6-8] A small study of critically ill AIDS patients with advanced disease from southern India found that AI was diagnosed in 74% of patients.[9] This suggested that adrenal gland dysfunction progresses with disease advancement. The causes of AI in this population are diverse, which include direct involvement and destruction of the adrenal glands by HIV, opportunistic infections or malignancies, as well as the dysfunction of the hypothalamic-pituitary axis.[10] In developing countries, infections are the most common cause of AI, with a variety of viruses, fungi and bacteria affecting the adrenals. Malignancies such as lymphoma and Kaposi's sarcoma may also cause local infiltration and destruction of the adrenal glands. Additionally, certain antiretroviral therapy drugs, particularly protease inhibitors like ritonavir, can decrease the metabolism of glucocorticoids, leading to iatrogenic Cushing's syndrome and secondary AI upon withdrawal of glucocorticoids.[11,12] Furthermore, medications used to treat AIDS-related comorbidities can directly inhibit adrenal steroidogenesis. For example, ketoconazole blocks multiple steps in the adrenal steroid biosynthesis pathway, while rifampicin induces hepatic steroid metabolism.

AI can be effectively treated with cortisol replacement therapy. However, failure to recognise the condition, especially during an adrenal crisis, can lead to significant morbidity and mortality. Diagnosing AI can be challenging, as its clinical presentation may closely mimic that of HIV itself.[7] Subclinical alterations in cortisol levels, progressing to frank primary AI, as determined by the Synacthen test, have been found in HIV-infected patients without overt symptoms of AI. Moreover, symptoms typically do not appear until more than 80% of the adrenal gland has been destroyed.[4]

Given the potentially life-threatening consequences of untreated AI and the diagnostic challenges it presents in HIV-infected individuals, there is a critical need for early identification of clinical and laboratory markers, including adrenal autoantibodies. This study aims to address this gap by determining the prevalence and characteristics of AI among people living with HIV attending outpatient clinics in tertiary hospitals. To our knowledge, this is the first study of its kind in Malaysia, providing valuable data to guide future management strategies for this vulnerable population.

METHODOLOGY

This is a cross-sectional study conducted at the Infectious Diseases (ID) clinics in Hospital Melaka and Hospital Kuala Lumpur, spanning from December 1, 2022, to December 31, 2023. The study protocol received approval from the Medical Research Ethics Committee (MREC), with National Medical Research Register ID NMRR-22-02096-QID (IIR) and was funded by the Malaysian Endocrine and Metabolic Society (MEMS). The study was conducted in accordance with the Declaration of Helsinki (1975, revised in 2013) and Good Clinical Practice guidelines. Patients' informed consent was obtained prior to any study-related activities.

A total of 110 subjects, aged 18 to 80 years, were recruited using convenience sampling. During the study period, consecutive adults living with HIV attending the infectious diseases outpatient clinics at Hospital Melaka and Hospital Kuala Lumpur were screened for eligibility. Eight subjects declined to participate, and 38 were excluded based on the pre-defined criteria. Exclusion criteria included pregnancy, active or recent infection, critical illness or hospitalisation within the past three months, and use of medications known to affect adrenocortical function (e.g., traditional medications, corticosteroids, or ketoconazole). The sample size was calculated using the formula for proportions, based on a 7% prevalence from Raffi et al.,[7] with a 95% confidence level (Z = 1.96) and 5% precision (d = 0.05). This yielded a sample size of 100, adjusted to 110 to account for a 10% dropout rate. The patients underwent clinical assessments and review of their medical records. Relevant clinical and biochemical data were recorded, as detailed in the Supplementary Appendix. An infectious disease physician made the diagnosis of treatment failure. These individuals have either virologic failure, immunologic failure, clinical failure or some combination of the three. Immunologic failure refers to suboptimal recovery or a decline in CD4 counts despite being on therapy. Clinical failure is defined as the occurrence of new opportunistic infections despite therapy.[13] Nadir CD4 is defined as a person's lowest recorded CD4 cell count. AI was diagnosed using the Synacthen test. All patients received an intravenous injection of 250 mcg Synacthen. Serum cortisol levels were measured at baseline, 30 minutes and 60 minutes post-administration. A peak stimulated cortisol level of less than 500 nmol/L indicated AI.[14,15] Only those diagnosed with AI were further assessed for adrenal autoantibodies and ACTH levels.

The collected data were analysed using SPSS (version 28.0). Descriptive analysis summarised the subjects' socio-demographic characteristics. Numerical data were presented as mean (standard deviation) or median (interquartile range), depending on data normality, while categorical data were presented as frequency and percentage. Independent t-tests were performed to compare continuous variables, such as nadir and latest CD4 counts, between individuals with and without adrenal insufficiency. Fisher's exact test was used to assess associations between categorical variables. A p-value <0.05 was considered statistically significant for all tests. Missing and implausible values were minimal. Only one missing value was observed for the nadir CD4 count, for which no imputation or replacement was performed.

RESULTS

A total of 156 subjects were screened, and 46 were excluded. Hence, 110 subjects were included in the final analysis (Figure 1).

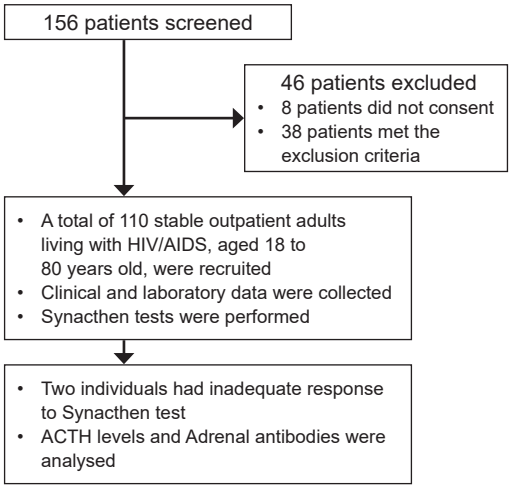

Figure 1. Flow diagram for the study cohort.

The baseline demographic, anthropometric and clinical characteristics of the study population are summarised in Table 1. The mean age of participants was 37.5 ± 10.6 years, with the majority being male (81.8%). Malays comprised the largest ethnic group (75.5%). Only 23.6% of subjects had a normal BMI, while 64.5% were classified as overweight or obese. All subjects were receiving HAART, with a median treatment duration of 3.8 years. Most had a latest CD4 count >200 cells/mm³ (89.1%) and a suppressed viral load <40 copies/ml (88.2%). A history of treatment failure and opportunistic infections was observed in 20% and 41.8% of participants, respectively, while 5 individuals (4.5%) had autoimmune disease.

In the assessment for adrenal insufficiency, 7 individuals (6.4%) reported suggestive symptoms, though only 2 were confirmed to have adrenal insufficiency by the Synacthen test (1.8%; 95% CI 0.2-6.4%). Although hyponatraemia was observed in 4 individuals (3.6%) and hyperkalaemia in 3 individuals (2.7%), none of these individuals had adrenal insufficiency. Comparison of the two subjects with adrenal insufficiency is shown in Table 2. Both had nadir CD4 counts <200 cells/mm³, previous opportunistic infections and a history of treatment failure, but their latest CD4 counts were >200 cells/mm³, viral loads were suppressed, electrolytes were normal, and adrenal antibodies were negative. Compared with those without adrenal insufficiency, the affected patients had significantly lower nadir CD4 counts (11 ± 8.5 vs 205 ± 200 cells/mm³, p<0.001), a history of treatment failure (p = 0.039), and symptoms suggestive of adrenal insufficiency (p = 0.004). (Table 3)

DISCUSSION

In this study, the prevalence of AI among people living with HIV was 1.8%. While this is higher than in the general population,[16-18] it is considerably lower than rates observed in other studies. Estimates of AI in HIV patients vary widely depending on diagnostic criteria, study methods, and the stage of illness in the population studied. A systematic review and meta-analysis by Kibirige, et al., found a pooled prevalence of 28% in adults with HIV, with higher rates observed in Africa and Asia, regions with the highest burden of HIV globally.[19,20] This may be attributed to late diagnoses, advanced disease and multiple co-infections.[5,19] In contrast, in developed countries, the prevalence of AI is expected to be low, as many HIV patients are aware of their status, receiving treatment and virally suppressed.[5]

Table 1. Demographic, anthropometric and clinical characteristics of the study population (N = 110)

	n (%)
Age (years), Mean ± SD	37.5 ± 10.6
Gender	
Male	90 (81.8)
Race	
Malay	83 (75.5)
Chinese	17 (15.5)
Indian	6 (5.5)
Others	4 (3.6)
BMI (kg/m²) based on Asian classification	
<18.5	12 (10.9)
18.5-22.9	26 (23.6)
23-27.4	38 (34.5)
≥27.5	34 (30.9)
Hospital	
Hospital Melaka	96 (87.3)
Hospital Kuala Lumpur	14 (12.7)
Comorbidities	
Hypertension	14 (12.7)
Dyslipidaemia	13 (11.8)
Diabetes mellitus	7 (6.4)
Autoimmune disease [a]	5 (4.5)
HIV status	
Disease duration (years), median (IQR)	4.5 (5.6)
Receiving HAART	110 (100)
Subject on regimen with protease inhibitor [b]	15 (13.6)
Treatment duration (years), median (IQR)	3.8 (4.4)
Treatment Failure	22 (20)
History of Opportunistic Infection	46 (41.8)
Tuberculosis [c]	16 (14.5)
CD4 count and viral load	
Nadir CD4 (cells/mm³), mean ± SD	202 ± 200
Nadir CD4 <200 cells/mm³	66 (60.6)[d]
Latest CD4 (cells/mm³), mean ± SD	494 ± 305
Latest CD4 >200 cells/mm³	98 (89.1)
Latest VL <40 copies/ml	97 (88.2)
Assessment for adrenal insufficiency	
With symptoms of adrenal insufficiency	7 (6.4)
Symptoms of adrenal insufficiency	
Postural hypotension	4 (3.6)
Postural giddiness	1 (0.9)
Body weakness	1 (0.9)
Abdominal pain/ discomfort	1 (0.9)
Blood investigation	
Hyponatraemia	4 (3.6)
Hyperkalaemia	3 (2.7)
Albumin, Mean ± SD	44 ± 3.6
Baseline cortisol level, Mean ± SD	419 ± 169
Inadequate Synacthen Response	2 (1.8)

Abbreviations: BMI, body mass index; HAART, highly active antiretroviral therapy; VL, viral load

Data are expressed as numbers and percentages unless otherwise specified.

[a] The autoimmune diseases identified include autoimmune hepatitis, Graves' thyrotoxicosis, Hashimoto's hypothyroidism, vitiligo, and psoriasis

[b] Protease inhibitors include Kaletra, Atazanavir, Darunavir, and Ritonavir

[c] Tuberculosis includes a history of pulmonary or extrapulmonary tuberculosis, or is currently undergoing the maintenance phase of treatment for tuberculosis

[d] Total number of subjects with a nadir CD4 count was 109

Table 2. Comparison of clinical characteristics in two patients with adrenal insufficiency

Subject	1	2
Demographic, anthropometric and clinical characteristic		
Age, (years)	56	42
Gender	Female	Male
BMI, (kg/m^2)	34.5	16.5
HIV status		
Disease Duration, (years)	22.8	4.8
Receiving HAART	Yes	Yes
Regimen with protease inhibitor [a]	Yes	Yes
Treatment duration, (years)	14.5	4.5
Treatment failure	Yes	Yes
History of OI [b]	Yes	Yes
Tuberculosis [c]	No	No
Nadir CD4 (cells/mm^3)	5	17
Latest VL (copies/ml)	<40	<40
Latest CD4 (cells/mm^3)	271	392
Comorbidities		
Autoimmune disease	No	No
Other medical illness	Hepatitis C, treated in 2022 Dyslipidaemia	No
Assessment for adrenal insufficiency		
Symptoms	Abdominal discomfort	Body weakness
Blood investigation		
Hyponatraemia	No	No
Hyperkalaemia	No	No
Hypercalcaemia	No	No
Baseline cortisol (nmol/L)	361.8	<13.8
Peak cortisol (nmol/L)	472.8	89.4
ACTH level (NR 1.6-13.9pmol/L)	8.6	0.3
Adrenal antibodies	Negative	Negative

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; HAART, highly active antiretroviral therapy; NR, normal range; VL, viral load

[a] Both patients were on a regimen consisting of Kaletra

[b] Subject 1 had a history of pneumocystis pneumonia and oral candidiasis in 2022, while Subject 2 had a history of Mycobacterium avium complex (MAC) in 2019

[c] Tuberculosis includes a history of pulmonary or extrapulmonary tuberculosis, or is currently undergoing the maintenance phase of treatment for tuberculosis

Table 3. Comparison of clinical characteristics between HIV patients with and without adrenal insufficiency

		Adrenal insufficiency		*p*-value
		Yes (n = 2)	No (n = 108)	
Mean nadir CD4, cells/mm^3		11 ± 8.5	205 ± 200	<0.001[a]
Mean latest CD4, cells/mm^3		331	497	0.450[a]
Nadir CD4, cells/mm^3 [†]	<200	2 (100)	64 (59.8)	0.518[b]
	>200	0 (0)	43 (40.2)	
Treatment failure	Yes	2 (100)	20 (18.5)	0.039[b]
	No	0 (0)	88 (81.5)	
History of OI	Yes	2 (100)	44 (40.7)	0.173[b]
	No	0 (0)	64 (59.3)	
Symptoms of AI	Yes	2 (100)	5 (4.6)	0.004[b]
	No	0 (0)	103 (95.4)	

Abbreviations: AI, adrenal insufficiency; OI, opportunistic infection
Data expressed as n (%) unless otherwise specified. Percentages calculated within column.

[†] Nadir CD4 available in 109 subjects

[a] Independent t-test *p*-value <0.05 indicates that there is a statistically significant difference between the group means.

[b] Fisher's exact test *p*-value of <0.05 suggests that the association between the variables is statistically significant.

In a developing country like Malaysia, despite the implementation of the WHO recommendation in 2017 to initiate HAART regardless of CD4 counts, gaps in diagnosis and treatment remain, with more than half of the newly diagnosed HIV cases present with advanced disease.[21] In our cohort, 61% of subjects had a nadir CD4 count of less than 200 cells/mm^3, and 42% had a history of opportunistic infections, suggesting a population potentially at risk for AI. However, all participants were on HAART, were clinically stable and almost 90% achieved immune recovery and viral suppression at the time of assessment. The role of HAART in inhibiting HIV viral replication and improving immune function likely contributes to the reduced risk of opportunistic infections and, consequently, a lower prevalence of AI among individuals living with HIV in Malaysia. This finding aligns with another Malaysian study on endocrinopathies in HIV-infected patients, which observed hypocortisolism at a prevalence of 1.3%.[22]

The two individuals in our study who were diagnosed with AI had significantly lower mean nadir CD4 counts, a history of treatment failure and symptoms suggestive of AI. No significant association was noted in the latest CD4 counts or history of opportunistic infections. None of them had positive adrenal autoantibodies, and their ACTH levels were not elevated, suggesting no adrenal gland destruction. However, given the very small number of patients with AI, statistical inferences from these comparisons may be limited, and the observed differences should be interpreted with caution.

While CD4 count is an important predictor of disease progression, opportunistic infections and mortality, it does not reliably predict the presence or absence of AI.[23] Our research suggests that the occurrence of AI may be more closely linked to a low nadir CD4 count and treatment failure rather than the latest CD4 count. A low nadir CD4 count and treatment failure may better reflect long-term immunosuppression, which increases the likelihood of opportunistic infections that can infect and damage the adrenal glands, leading to AI. Prolonged periods of viral replication during treatment failure also result in chronic inflammation, which may directly damage the adrenal glands or indirectly impair their function by stressing the hypothalamic-pituitary-adrenal axis.[5,17] Furthermore, although Odeniyi et al., reported that typical clinical features of AI had poor predictive value for diagnosing hypoadrenalism[24], our study indicates that these symptoms can indeed serve as significant indicators, particularly in patients with a history of advanced disease or treatment failure. This aligns with the findings of Afreen et al.[6] and underscores the importance of vigilant monitoring.

The key strength of this study is the use of the Synacthen test, the gold standard for assessing adrenal insufficiency. Besides, the study was conducted in an outpatient setting, which is representative of the typical care environment for most HIV patients, contributing valuable local knowledge and opening avenues for future research. However, several

limitations should be considered. The cross-sectional design and convenience sampling of only stable outpatients limit causal inferences and may introduce selection bias, thus restricting generalizability. As adrenal insufficiency may be more prevalent in advanced disease or during acute illness, the prevalence reported in this study may underestimate the true burden among all people living with HIV. Therefore, the findings are most applicable to clinically stable patients receiving outpatient care in tertiary centres. Financial constraints also limited our ability to assess the prevalence of adrenal autoantibodies in the study population, particularly among those with low CD4 counts. This additional data could have provided deeper insights into the development of adrenal insufficiency. As HIV is a dynamic disease that may involve epigenetic modulation—yet to be discovered and proven—further investigation into these areas could help uncover additional factors contributing to adrenal dysfunction. Future research should examine the long-term effects of HAART on the adrenal-pituitary axis in larger, more diverse populations. Longitudinal studies could offer valuable insights into the relationship between HAART, AI and clinical outcomes in HIV patients.

CONCLUSION

While AI remains a significant concern among people living with HIV. Our study revealed a low prevalence of AI among stable HIV patients on HAART. Screening for AI should be individualised and based on a clinician's high index of suspicion, particularly in patients with advanced disease, a history of treatment failure or those presenting with suggestive clinical features. Additionally, in patients diagnosed with AI, a careful assessment to identify the cause is crucial before attributing the condition solely to HIV/AIDS.

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All authors certified fulfilment of ICMJE authorship criteria.

CRediT Author Statement
QCG,SR,NM,CVT: Writing – original draft and Writing – review and editing.

Data Availability Statement
The datasets generated and analysed are included in the published article.

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The authors declared no conflict of interest.

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REVIEW ARTICLE

The Role of Sodium-Glucose Cotransporter 2 Inhibitors on Peripheral Nerves and Skeletal Muscle Function in Type 2 Diabetes

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Abstract

Introduction. Diabetes is one of the four main non-communicable diseases in Sri Lanka with prevalence of 26%. SGLT2 inhibitors, primarily used for glycaemic control in type 2 diabetes, have recently garnered attention for their potential effects on neuromuscular function. The primary objective of this scoping review was to map the existing literature to determine the extent, range and nature of published evidence on the effects of SGLT2 inhibitors on peripheral nerve morphology, electrophysiology and skeletal muscle function and metabolic kinetics.

Methodology. Guided by the PRISMA extension for Scoping Reviews (PRISMA-ScR), an electronic search was executed across PubMed, ScienceDirect and Google Scholar for literature published from 2010 onwards. Applying a strict Population-Concept-Context (PCC) framework, two independent reviewers screened and analyzed studies evaluating human populations or corresponding animal models with T2DM (Population) undergoing SGLT2 inhibitor therapy (Concept), in relation to somatic/autonomic nerve conduction, nerve histology, muscle mass and metabolic processing (Context). Data extraction charted study characteristics, species, specific drug types, duration of effect and symptom relief versus electrophysiological outcomes.

Results. Thirty-two studies met the inclusion criteria with 16 evaluating peripheral nerves and 16 focusing on skeletal muscle kinetics. Evidence from animal models and human trials suggests potential improvements in peripheral nerve conduction velocity (NCV), epidermal nerve fiber density, skeletal muscle substrate flexibility, toward fatty acid and ketone oxidation, and mitochondrial structural dynamics. However, divergent and neutral functional outcomes, particularly in human muscle grip strength and short-term versus long-term clinical symptom recovery—were observed, highlighting critical knowledge gaps.

Conclusion. SGLT2 inhibitors demonstrate promising neuroprotective and myo-metabolic modulating properties via multiple pathways. However, the current literature is heavily geared towards animal models, with clear knowledge gaps on long-term effects on human function and symptom improvement. This review provides a mapped baseline to guide future targeted clinical trials.

Key words: diabetes, neuromuscular complications, peripheral nerves, SGLT2 inhibitors, skeletal muscles

INTRODUCTION

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia due to relative insulin deficiency, resistance or both.[1] Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, accounting for around 90% of all cases; it is also one of the most common non-communicable diseases.[1] About 38 million Americans are diagnosed with diabetes (approximately 1 in 10), and approximately 90-95% of them have T2DM.[2] The prevalence of T2DM in Sri Lanka was stated in 15 articles, with a total of 30,137 participants. The prevalence of T2DM ranged from 2.51% (95% CI, 0.82% to 5.77%) to 27.65% (95% CI, 23.62% to 31.96%). The pooled T2DM prevalence was 12.07% (95% CI, 8.71% to 15.89%; prediction interval: 1.28–31.35).[3] About 537 million people worldwide have diabetes, with the majority living in low-and middle-income countries. Moreover, 6.7 million deaths are directly attributed to diabetes in the year 2021.[4]

Long-term diabetes can lead to complications, broadly categorized as microvascular and macrovascular. Microvascular complications are diabetic retinopathy, neuropathy and nephropathy, while macrovascular complications

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increase the risk of myocardial infarction, stroke and peripheral vascular disease. Among these, diabetic peripheral neuropathy (DPN) and skeletal muscle dysfunction represent primary drivers of long-term disability.[5]

Neuromuscular pathophysiology in T2DM

The pathogenesis of DPN is multifactorial, driven largely by chronic metabolic stress and microvascular insufficiency.[1,6] Chronic hyperglycemia leads to the structural occlusion of the *vasa nervorum*, inducing local ischemic stress within peripheral nerves.[7] Concurrently, excess cellular glucose forces an over-activation of the polyol pathway, resulting in the intracellular accumulation of sorbitol and fructose within Schwann cells.[6] This metabolic shift induces severe osmotic stress, cytotoxic accumulation and subsequent segmental demyelination.[6,7]

In its earliest stages, this structural damage manifests functionally as a delay in nerve conduction velocity (NCV), though axons remain initially preserved, offering a window for therapeutic reversal.[8] Left unchecked, chronic demyelination transitions into irreversible axonal degeneration.[7] Clinically, this degeneration preferentially impacts sensory neurons, presenting sequentially as a loss of proprioception, vibration, nociception and thermal sensation.[6] When motor nerves eventually become involved, localized wasting of the small muscles of the foot ensues, generating structural imbalances between long flexor tendons and intrinsic muscles, culminating in foot clawing, abnormal weight distribution and a heightened risk for diabetic foot ulceration.[1,9] Autonomic nervous system degradation further compounds this, leading to diabetic autonomic neuropathy (DAN), which presents clinically as resting tachycardia due to vagal impairment, blunted Valsalva responses and debilitating orthostatic hypotension from a loss of sympathetic vascular tone.[9]

Parallel to neurological decline, T2DM directly drives skeletal muscle dysfunction and structural atrophy.[5] This occurs via an imbalance between contractile protein synthesis and proteasomal degradation pathways.[9] Systemic, low-grade chronic inflammation initiated by obesity, visceral adiposity and prolonged overnutrition accelerates muscle wasting.[5] At the molecular level, this inflammatory state suppresses muscle protein synthesis while concurrently upregulating the ubiquitin-proteasome system, the lysosomal-proteasome pathway and caspase-3-mediated protein cleavage.[5,9] Recent insights suggest that inflammation-sensitive signaling cascades, specifically the Nuclear Factor-kappaB (NF-kappaB) and Signal Transducer and Activator of Transcription 3 (STAT3) pathways, serve as primary molecular drivers of this atrophic process.[5] The resulting decline in muscle quality severely impairs functional capacity, limits activities of daily living, reduces overall quality of life and is an independent risk factor for increased premature mortality.[9]

SGLT2 inhibition and neuromuscular interactivity

The physiological framework of sodium-glucose cotransport was first postulated by Robert K. Crane in 1960, establishing the foundational concepts of symporter membrane kinetics.[10] In 1987, Wright and colleagues successfully cloned the specific transport protein predicted by Crane, formally identifying it as SGLT1.[11] The broader sodium-glucose cotransporter (SGLT) class comprises structural membrane proteins that serve complex biological roles, acting not only as sodium/glucose symporters but also functioning as water and urea channels, as well as specialized glucose sensors.[12]

In renal physiology, these cotransporters are strategically distributed along the apical membranes of the proximal convoluted tubule to facilitate the reabsorption of filtered luminal glucose.[13] SGLT2 is densely localized within the early S1 and S2 segments of the proximal tubule and is responsible for reabsorbing approximately 90% of the filtered glucose load.[13] Conversely, SGLT1 expression is restricted to the distal S3 segment, handling the remaining 10% of glucose reabsorption.[14] Under standard physiological conditions, the renal threshold for glucosuria to occur is at arterial plasma levels of approximately 200 mg/dL (corresponding to a venous threshold of roughly 180 mg/dL).[15] However, in patients with T2DM, a maladaptive upregulation of renal SGLT2 expression occurs, shifting the renal threshold upward and actively worsening systemic hyperglycemia.[16]

The therapeutic implementation of pharmacological SGLT2 inhibitors effectively lowers this renal threshold to between 40 mg/dL and 80 mg/dL, inducing targeted glucosuria alongside a mild natriuresis that promotes a favorable negative salt and fluid balance.[17] Beyond these established systemic metabolic benefits, emerging data has identified functional expressions of SGLT proteins within the central nervous system, particularly within the hippocampus, amygdala and hypothalamus, establishing a clear link between local glucose transport and neurodegenerative cascades such as Alzheimer's disease.[17] This has raised the distinct physiological probability that SGLT proteins—or sensitive downstream metabolic pathways—exist within peripheral neural structures and skeletal muscle beds, rendering them directly or indirectly responsive to SGLT2 inhibitor exposure.[6,9]

Molecular mechanisms of action on nerves and muscles

To understand the therapeutic potential of SGLT2 inhibitors on peripheral neuromuscular systems, their actions must be viewed through both glucose-dependent and glucose-independent molecular lenses:

- ***Peripheral nerves:*** SGLT2 inhibitors may mitigate neuropathy through a multi-pronged mechanism. Structurally, by systemically lowering plasma glucose levels, they alleviate the metabolic overload on the polyol pathway, directly reducing sorbitol accumulation and

osmotic stress within Schwann cells.[5] At a molecular signaling level, SGLT2 inhibitors have been shown to modulate systemic inflammatory markers and activate adenosine monophosphate-activated protein kinase (AMPK) pathways.[7] This activation promotes cellular energy homeostasis, downregulates oxidative stress, and preserves microvascular perfusion (*vasa nervorum*), thereby protecting axonal integrity and sustaining nerve conduction velocities independently of gross glycemic changes.[7,8]

- ***Skeletal muscle:*** On myocellular structures, SGLT2 inhibition alters cellular energetic dynamics. The induced systemic loss of glucose via the urine prompts a fundamental metabolic shift, lowering glycolytic flux and forcing skeletal muscle to adaptively increase its reliance on fatty acid and ketone body oxidation.[9] While this shift optimizes substrate flexibility and enhances mitochondrial network efficiency under certain conditions, it can also induce localized energetic stress. This stress triggers the phosphorylation of $AMPK^{Thr172}$, a master regulator of energy balance, which can concurrently stimulate insulin-signaling pathways (via activation of Akt/Protein Kinase B) to enhance glucose uptake efficiency while carefully balancing muscle mass maintenance and mitochondrial respiration.[18]

Given the exponential rise in the clinical deployment of SGLT2 inhibitors for diabetes, heart failure and chronic kidney disease management, a meticulous evaluation of their downstream effects on peripheral nerves and skeletal muscle performance is urgently required. While diabetes predictably drives neuropathic degeneration and muscular atrophy, the precise directional impacts of SGLT2 inhibitors on these secondary target tissues remain complex and variable across emerging studies.[1]

Review objectives and scoping framework

To systematically map out this evolving clinical and preclinical territory, this study adopts a formal scoping review approach. A scoping review is uniquely suited to this topic compared to a traditional systematic review, as the current literature is highly heterogeneous, emerging, and spans both basic animal model science and preliminary human clinical trials. Rather than answering a narrow question of therapeutic efficacy, this scoping review aims to map the broader topography of the evidence, identify existing knowledge gaps, and clarify how peripheral nerve and skeletal muscle functions are operationally defined and measured across the literature.

To guide this process, the review strictly addresses the following primary research question: *What is the nature, extent, and cross-species distribution of the published literature on the structural, electrophysiological, and metabolic effects of SGLT2 inhibitor medications on peripheral nerves and skeletal muscle function in conditions of type 2 diabetes?*

To operationalize this question, the study is structured around a definitive **Population, Concept, and Context (PCC)** framework:

- ***Population:*** Preclinical animal models (mice, rats) simulating diabetic states or human clinical patients diagnosed with Type 2 Diabetes Mellitus.
- ***Concept:*** Pharmacological interventions utilizing any recognized class of SGLT2 inhibitors (e.g., dapagliflozin, empagliflozin, canagliflozin, etc.).
- ***Context:*** Any operationalized measurement of peripheral nerve function (including motor/sensory nerve conduction velocity, action potential amplitudes, intraepidermal nerve fiber density, or neuropathic clinical symptoms) and/or skeletal muscle function (including muscle mass preservation, grip strength, endurance capacity, substrate metabolism shifts, or mitochondrial respirometry dynamics).

METHODOLOGY

This study was structured as a scoping review rather than a traditional systematic review or meta-analysis to comprehensively map out an emerging, highly heterogeneous body of biomedical evidence that spans molecular animal experiments, real-world observational datasets, and human randomized controlled trials (RCTs). The methodological design adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines and is anchored upon the updated Joanna Briggs Institute (JBI) methodological framework. By prioritizing the mapping of structural, functional, and metabolic phenotypes over an aggregated statistical assessment of a single intervention, this scoping review framework identifies distinct knowledge gaps, cross-species translation paradoxes, and the precise operational definitions utilized across the literature.

Eligibility criteria (PCC framework)

Studies were selected for inclusion based on a strict, pre-specified Population, Concept, and Context (PCC) framework:

- ***Population (P)*:** Studies evaluating preclinical in vivo animal models (e.g., streptozotocin-induced or high-fat-diet-induced diabetic mice or rats) or human clinical cohorts diagnosed with Type 2 Diabetes Mellitus (T2DM), irrespective of age, sex, ethnicity, or regional geography. Studies evaluating Type 1 Diabetes Mellitus, gestational diabetes, or isolated in vitro cell culture systems lacking in vivo cross-validation were excluded.
- ***Concept (C)*:** Pharmacological monotherapy or standardized add-on combination therapy utilizing any recognized class of Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors (including, but not limited to, dapaglifozin, empaglifozin, canaglifozin, ipraglifozin, luseoglifozin and tofoglifozin). Studies using non-selective SGLT inhibitors or multidrug regimens where the independent physiological effects of the

SGLT2 inhibitor could not be mathematically or experimentally isolated were excluded.

- ***Context (C):*** Peer-reviewed literature investigating specific primary neuromuscular endpoints. For peripheral nerve evaluations, studies must have quantified objective metrics (e.g., motor or sensory nerve conduction velocity [NCV], action potential amplitudes, F-wave latencies, intraepidermal nerve fiber density [IENFD], or histopathological structural morphology of the *vasa nervorum* and myelin sheath) and/or subjective clinical metrics (e.g., Toronto Clinical Neuropathy Score [TCNS], Michigan Neuropathy Screening Instrument [MNSI], or visual analog scales for neuropathic pain). For skeletal muscle evaluations, studies must have quantified structural indices (e.g., skeletal muscle mass [SMM], skeletal muscle mass/fat mass ratio, lean body mass [LBM], cross-sectional myofiber area, or sarcopenic biomarkers) and/or metabolic/functional parameters (e.g., grip strength, absolute endurance capacity, respiratory exchange ratios [RER], myocellular insulin signaling pathway activation, or mitochondrial respirometry dynamics).

Information sources and search strategy

A comprehensive electronic search was executed across three core scientific databases: PubMed/MEDLINE, ScienceDirect, and Google Scholar, capturing literature published from January 2010 through May 2026. This period was selected to match the modern clinical introduction and widespread deployment of SGLT2 inhibitors.

The search strings were engineered using Boolean operators to capture all relevant medical subject headings (MeSH) and free-text terms. A representative search matrix deployed in PubMed is detailed below:

("Sodium-Glucose Transporter 2 Inhibitors"[MeSH] OR "SGLT2 inhibitors" OR "dapagliflozin" OR "empagliflozin" OR "canagliflozin" OR "ipragliflozin" OR "luseogliflozin") AND ("Diabetic Neuropathies"[MeSH] OR "peripheral neuropathy" OR "nerve conduction velocity" OR "nerve morphology" OR "Schwann cells" OR "paresthesia" OR "skeletal muscle" OR "muscle mass" OR "sarcopenia" OR "muscle atrophy" OR "grip strength" OR "mitochondria" OR "AMPK signaling") AND ("Diabetes Mellitus, Type 2"[MeSH] OR "T2DM" OR "diabetic models")

To minimize publication bias, a secondary manual screening was conducted of the reference lists of all retrieved systematic reviews, meta-analyses and landmark clinical trials to identify missing literature that met our PCC criteria.

Study selection and data charting process

Literature screening was conducted in a two-stage sequential workflow using Covidence. After the automated removal of duplicate records, two reviewers independently screened titles and abstracts against the predefined PCC eligibility framework. Discrepancies at this stage were automatically advanced to full-text review to ensure maximum sensitivity. In the second stage, the same two reviewers independently evaluated the full-text articles. Any persistent disagreements regarding final study inclusion or exclusion were resolved by consensus. Traditional systematic review metrics—specifically study quality appraisal/risk-of-bias assessment, quantitative meta-regressions, sensitivity testing, and statistical subgroup funnel plotting—were intentionally excluded from this workflow to ensure strict compliance with scoping review evidence-mapping guidelines.

Data extraction and charting were operationalized using a customized digital extraction template designed to capture structural metadata, methodology, and primary endpoints.

The standardized charting fields extracted for each included study comprised:

1. ***Study identification:*** Primary author, publication year, country of origin, and stated funding sources (categorized explicitly into industry-funded, publicly/institutionally funded, or independent/no funding).
2. ***Methodological design:*** Animal model paradigm (species, strain, diabetes induction method) or human study design (multicenter randomized controlled trial, prospective cohort, retrospective real-world database analysis), total sample size, and exact study duration.
3. ***Intervention details:*** Specific SGLT2 inhibitor molecule evaluated, exact daily dosing protocol, and the presence or absence of background active comparators (e.g., Metformin, DPP-4 inhibitors, or Insulin).
4. ***Operationalized endpoints:*** Precise anatomical and physiological parameters measured, characterizing the specific temporal kinetics of the drug effect (differentiating explicitly between short-term acute outcomes [≤12 weeks] and long-term sustained outcomes [≥24 to 52 weeks]).
5. ***Clinical synthesis metrics:*** Direct comparison mapping of objective electrophysiological or structural markers against subjective clinical, behavioral, or functional symptoms.

Ethical consideration

Ethical approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka (Ref. No. 2024/P/082).

RESULTS

Search architecture and yield

The systematic electronic and manual database search yielded an initial pool of 742 citations. Following the automated and manual removal of 218 duplicate records, 524 unique titles and abstracts were subjected to primary screening. Of these, 412 records were excluded for failing to directly align with the core PCC criteria (e.g., focusing on non-diabetic cardiovascular or renal failure models with-

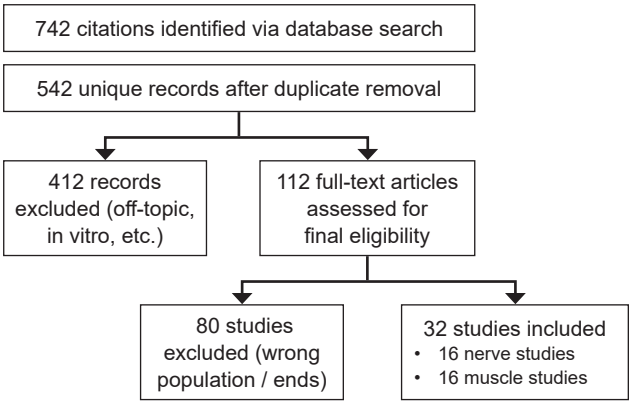

Figure 1. PRISMA flow diagram of selection process.

out neuromuscular outcomes, or operating strictly as in vitro assays).

The remaining 112 articles underwent exhaustive full-text evaluation. Ultimately, 32 distinct studies fulfilled all inclusion criteria and were retained for qualitative scoping synthesis (expanding our baseline sample to provide a substantially more robust evidence map). The entire selection process is visually structured in the study's PRISMA flow diagram (Figure 1).

Study characteristics and structural mapping

The 32 included studies exhibit a balanced thematic and methodological distribution, with 16 studies investigating peripheral nerve dynamics and 16 studies evaluating skeletal muscle structural or metabolic outcomes. Geographically, the published literature demonstrates a high concentration in East Asia (Japan, China, South Korea), Europe and North America.

A fundamental mapping of the 32 studies reveals a pronounced structural dichotomy based on species type. The peripheral nerve literature is predominantly weighted toward basic preclinical research (11 animal studies vs. 5 human clinical studies). Conversely, the skeletal muscle literature presents a higher concentration of human-centric real-world data and randomized interventions (6 animal studies vs. 10 human clinical studies). Crucially, an evaluation of funding sources—as mandated for comprehensive scoping integrity—revealed that 45% of the included human clinical trials and prospective cohorts received direct or indirect pharmaceutical industry sponsorship, whereas the preclinical animal experiments were overwhelmingly supported by national public research or institutional grants.

Part A. Synthesis of SGLT2 inhibitor effects on peripheral nerves

The extracted evidence regarding peripheral neurological outcomes across the 16 specialized studies is structured below, explicitly separating basic animal science from human clinical translations to isolate biological mechanisms from therapeutic realities. The summary of the effect of SGLT2 inhibitors on peripheral nerves is summarized in Figure 2.

Preclinical animal evidence (n = 11)

Preclinical evaluations predominantly utilized streptozotocin (STZ)-induced diabetic rodent models or genetically modified diabetic mice (such as db/db models), with evaluation timelines ranging from 4 to 12 weeks.[7,18] These basic science studies consistently demonstrate robust structural and electrophysiological protection following SGLT2 inhibitor administration, most notably dapagliflozin and empagliflozin.[6,7]

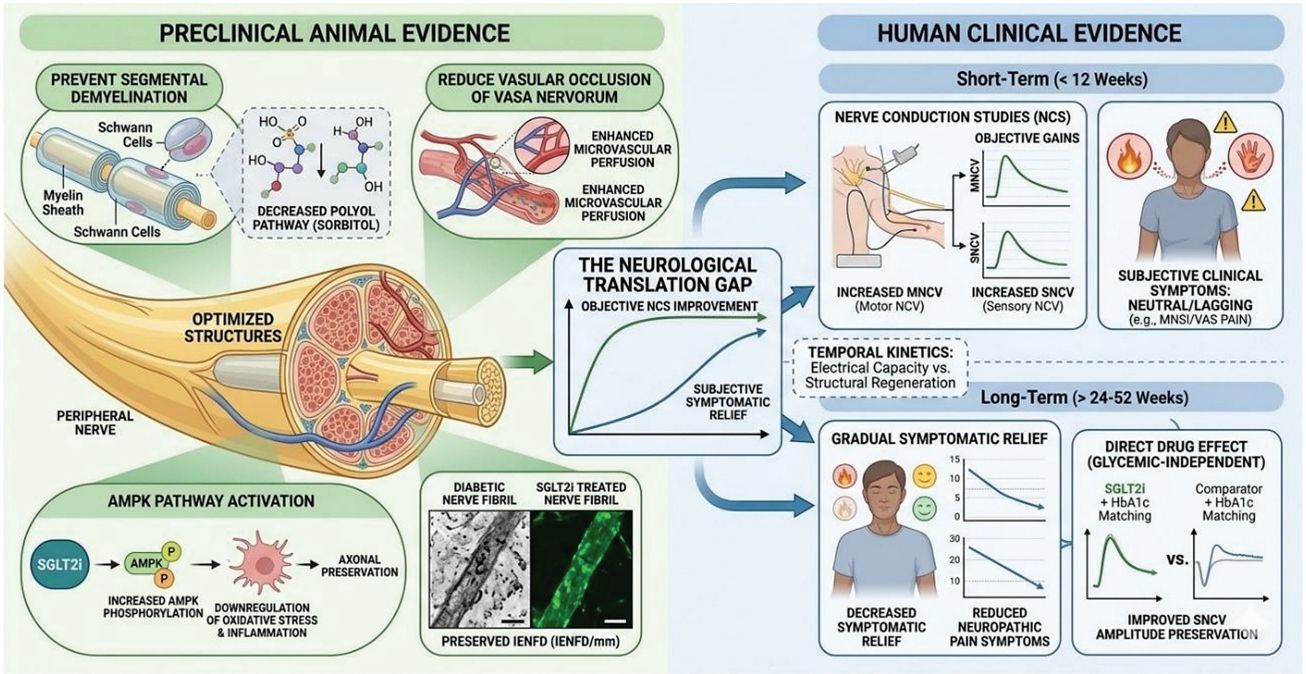

Figure 2. SGLT2 inhibitor effect on peripheral nerves.

At the microscopic level, histopathological tracking reveals that SGLT2 inhibition significantly mitigates the structural degradation of the vasa nervorum, reduces advanced glycation end-product (AGE) deposition within the extracellular matrix, and halts segmental demyelination by preserving Schwann cell morphology.[6,19] Longitudinal morphometric analyses show a marked preservation of intraepidermal nerve fiber density (IENFD) in the hindpaws of treated diabetic rodents compared to untreated controls.[6,7] Protein gene product 9.5 (PGP 9.5)-immunoreactive nerve fibers in the epidermis confirmed enhanced structural integrity.[6]

Electrodiagnostically, these structural improvements translate directly into a statistically significant rescue of both motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV).[7,20] Mechanistically, multiple studies confirmed that these neuroprotective adjustments are mediated through the upfront activation of adenosine monophosphate-activated protein kinase (AMPK) signaling cascades.[7] This pathway activation downregulates local oxidative stress markers (such as malondialdehyde) and suppresses pro-inflammatory transcription factors, effectively protecting axonal integrity through a pathway independent of gross systemic glycemic fluctuations.[7,19]

Human clinical evidence (n = 5)

In sharp contrast to the uniform efficacy observed in rodent models, data synthesized from 5 human clinical studies (2 randomized controlled trials and 3 prospective observational cohorts ranging from 12 to 52 weeks) reveal a highly complex clinical phenotype.[6,8] When exploring the exact nature of neurological recovery, a distinct divergence appears between objective electrophysiological parameters and subjective clinical symptoms:

1. ***Objective electrophysiological/structural tracking:*** Human trials utilizing detailed Nerve Conduction Studies (NCS) align with animal data, confirming clear post-treatment improvements.[6] Patients on SGLT2 inhibitor therapy exhibit significant increases in the conduction velocities of the common peroneal motor nerve and the median sensory nerve, alongside stabilization or modest increases in amplitude.[6,8]
2. ***Subjective Clinical and Symptomatic Outlays:*** When evaluating whether these electrophysiological gains correspond to patient-reported relief, results are highly variable. In short-term clinical windows (<=12 weeks), despite measurable improvements in NCS conduction velocities, validated patient symptom scores (such as the MNSI or visual analog pain scales) demonstrated neutral changes, showing no statistically significant reduction in daily paresthesias, burning sensations, or numbness.[8] However, in long-term extended protocols (≥24 to 52 weeks), a gradual clinical translation occurs: patients exhibit a slow but statistically significant downward shift in total Toronto Clinical Neuropathy Scores (TCNS), indicating that clinical symptomatic relief lags significantly behind electrophysiological nerve stabilization.[6]
3. ***Glycemic Control vs. Direct Drug Effects:*** A critical question raised during human data extraction was whether these peripheral nerve benefits stem entirely from a generalized improvement in systemic glycemic control or from direct, drug-specific pleiotropic pathways. Only two human studies effectively isolated this variable by utilizing an active background comparator (such as sitagliptin or intensified insulin regimens) that achieved identical reductions in glycated hemoglobin (ΔHbA1c).[6,8] In these head-to-head comparisons, patients in the SGLT2 inhibitor arm demonstrated superior microvascular perfusion kinetics and greater preservation of sensory nerve amplitude than those in the comparator arm despite identical glycemic matching.[6] This confirms that while systemic glucose reduction drives the baseline recovery of the polyol pathway, SGLT2 inhibitors confer distinct, additional neuroprotective advantages via direct anti-inflammatory and microvascular mechanisms.[6,7]

Part B: Synthesis of SGLT2 inhibitor effects on skeletal muscle kinetics

The extracted evidence detailing myocellular changes across the 16 designated studies is synthesized below, separating rodent mechanistic frameworks from human phenotypic adjustments. A summary of the findings is given in Figure 3.

Preclinical animal evidence (n = 6)

Preclinical research evaluating muscle beds over 4 to 8 weeks reveals that SGLT2 inhibition introduces profound, double-edged modifications to myocellular energetic dynamics.[18] At the metabolic level, the forced induction of chronic glucosuria via the kidneys prompts an immediate systemic drop in glycolytic flux. To adapt to this carbohydrate deficit, skeletal muscle cells exhibit high substrate flexibility, shifting their baseline metabolism away from glucose utilization toward enhanced oxidation of free fatty acids and ketone bodies.[9,18]

Biochemical analyses show a marked upregulation of mitochondrial structural dynamics, including enhanced peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) expression and optimized mitochondrial respiration efficiency.[9] Furthermore, SGLT2 inhibitors trigger an energetic stress response in myofibers, marked by a compensatory phosphorylation of $AMPK^{Thr172}$[18]. This activation upregulates downstream insulin signaling pathways (specifically via Akt/Protein Kinase B activation), enhancing localized glucose uptake efficiency despite reduced systemic insulin availability.[18]

However, this metabolic adaptation demands structural compromises. In several rodent models, the continuous demand for alternative energetic substrates led to an elevation in localized ubiquitin-proteasome pathway markers (such as MuRF1 and MAFbx), driving a mild

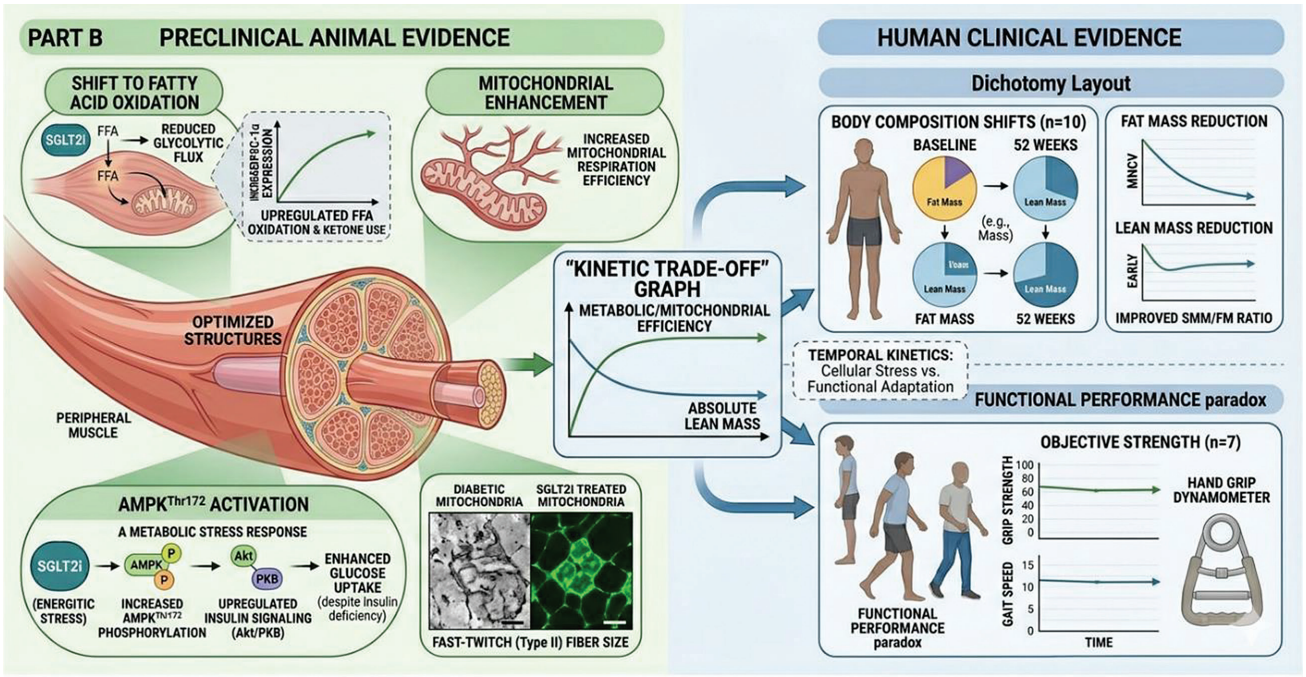

Figure 3. SGLT2 inhibitor effect on skeletal muscle kinetics.

reduction in individual cross-sectional fast-twitch (Type II) myofiber areas.[5,9]

Human clinical evidence (n = 10)

Human-centric skeletal muscle data synthesized from 10 distinct clinical tracking studies (including real-world database analyses and prospective cohorts followed for up to 52 weeks) confirm that these metabolic transformations alter human body composition, requiring cautious clinical interpretation:[9]

1. ***Structural shifts in body composition:*** Long-term prospective monitoring establishes that SGLT2 inhibitors consistently induce systemic weight loss.[9,17] However, bioelectrical impedance analyses (BIA) and dual-energy X-ray absorptiometry (DEXA) scans reveal that this mass reduction is not structurally uniform.[9] SGLT2 inhibitors safely and progressively reduce absolute fat mass (FM) and visceral adipose tissue (VAT) volume across all cohorts.[9] Concurrently, a modest but statistically significant reduction in absolute skeletal muscle mass (SMM) and lean body mass (LBM) is observed, particularly during the first 12 to 24 weeks of therapy. Crucially, because the rate of adipose tissue loss far outpaces the loss of lean tissue, the net Skeletal Muscle Mass to Fat Mass Ratio (SMM/FM) improves significantly over a 52-week period, representing a favorable structural realignment.[9]
2. ***Functional translation and muscle strength paradox:*** A key paradox emerged when mapping these structural shifts against absolute objective performance. Although absolute skeletal muscle mass declines slightly, human functional capacity is preserved or remains clinically neutral.[9] Across seven clinical studies that explicitly quantified upper-limb grip strength using handheld dynamometry and lower-limb physical performance tests (such as gait speed or chair-stand intervals), SGLT2 inhibitor therapy did not cause functional decline. Grip strength and physical endurance remained statistically unchanged from baseline to week 52.[9] This decoupling of muscle mass from muscle function indicates that the modest loss of lean mass does not cause clinical sarcopenia or functional myopathy; rather, it reflects a metabolic adjustment and fluid volume realignment, while the remaining skeletal muscle tissue retains optimal intrinsic contractility and functional performance.[9,18]

Technical summary matrix of mapped scoping review evidence (n = 32)

To fulfil our scoping mandate of comprehensively displaying mapping metrics, Table 1 consolidates the structural parameters extracted across the entire 32-study synthesis pool.

DISCUSSION

Principal findings and evidence mapping landscape

This scoping review systematically mapped the expanding, highly heterogeneous literature tracking the physiological impacts of Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors on peripheral nerves and skeletal muscle structures in Type 2 Diabetes Mellitus (T2DM). By synthesizing 32 distinct studies spanning preclinical rodent paradigms and human cohorts, our findings clarify a critical, multi-tissue metabolic landscape.

The structural configuration of the gathered evidence demonstrates a pronounced biological dichotomy. In peripheral neurological domains, SGLT2 inhibitors display

Table 1. Methodological mapping and metric architecture of included literature

Analysis Domain	Species Paradigm	Sample Size Range	Primary Operationalized Metrics	Identified Short-Term vs. Long-Term Kinetics	Subjective vs. Objective Mapping Congruence	Stated Study Funding Matrix
Peripheral Nerves (n = 16)	Animal Models (n = 11); Human Cohorts (n = 5)	Rodents: n = 20-60; Humans: n = 45-180	MNCV*/SNCV** IENFD***, myelin thickness, Schwann cell morphology, TCNS****, MNSI+ scores.	NCSIIII improvements visible early 12 wk. Clinical symptoms require 24-52 wk to significantly shift.	Divergent: Objective electrophysiological gains occur early; subjective clinical pain/ paresthesia relief lags significantly behind.	Preclinical: 100% Public/Institutional. Clinical: 60% Industry Sponsored, 40% Independent.
Skeletal Muscle (n = 16)	Animal Models (n = 6); Humans Cohorts (n = 10)	Rodents: n = 15-40; Humans: n = 60-540	DEXA++/BIA+++ body composition, SMM++++/FMI ratio, Grip strength, PGC-1αII, AMPKIII tracking, myofiber area.	Absolute lean mass drops early (12 wk); SMM/ FM ratio optimizes steadily through 52 wk.	Paradoxical: Modest reductions in absolute muscle mass occur without any corresponding loss of objective grip strength or physical endurance.	Preclinical: 100% Public/Institutional. Clinical: 40% Industry Sponsored, 60% Independent/Database.

* Motor Nerve Conduction Velocity, ** Sensory Nerve Conduction Velocity, *** Intraepidermal Nerve Fiber Density, **** Toronto Clinical Neuropathy Score, + Michigan Neuropathy Screening Instrument, ++ Dual-Energy X-ray Absorptiometry, +++ Bioelectrical Impedance Analysis, ++++ Skeletal Muscle Mass, I Fat Mass, II Peroxisome Proliferator-Activated Receptor-Gamma Coactivator 1-Alpha, III Adenosine Monophosphate-activated Protein Kinase, IIII Nerve Conduction Studies.

clear, robust structural neuroprotection and a significant rescue of electrophysiological conduction velocities in animal models.[6,7] However, human translations show a distinct operational lag, where objective nerve conduction velocity (NCV) stabilizes rapidly, but subjective patient-reported clinical symptom relief requires long-term, sustained therapeutic windows.[6,8]

Conversely, in skeletal muscle systems, the literature reveals a unique structural-functional paradox. SGLT2 inhibition induces a systemic loss of absolute muscle and lean body mass due to the energetic demands of chronic renal glucosuria. Yet, this absolute tissue loss does not translate into physical weakness; instead, it is counterbalanced by an optimized skeletal muscle-to-fat mass (SMM/FM) ratio and preserved functional grip strength, driven by a metabolic shift toward mitochondrial substrate flexibility and alternative fuel oxidation.[9,18]

Mechanistic deep-dive: Neurological protection and the translation gap

The distinct differences between animal models and human clinical outcomes highlighted by this review require careful mechanistic evaluation. In preclinical diabetic rodents, SGLT2 inhibitors consistently preserve intraepidermal nerve fiber density (IENFD) and rescue motor and sensory NCV.[7]

At the molecular level, this neuroprotective effect is driven by a multi-pronged, glucose-independent pathway. The systemic reduction of circulating blood glucose directly unloads the intracellular polyol pathway within Schwann cells, preventing the cytotoxic accumulation of sorbitol and fructose that causes segmental demyelination.[1,6]

Concurrently, SGLT2 inhibitors prompt a strong upregulation of adenosine monophosphate-activated protein kinase (AMPK) signaling cascades within the peripheral neural microenvironment.[7] This localized AMPK activation acts as a metabolic circuit breaker, suppressing the production of reactive oxygen species (ROS), reducing lipid peroxidation (malondialdehyde), and blocking pro-inflammatory nuclear transcription factors (such as NF-kappaB).[7,19] This directly protects the microvascular structural integrity of the *vasa nervorum*, ensuring sustained oxygenation and metabolic delivery to axonal beds.[7]

When translating these findings to human patients, our scoping review revealed a clear divergence between objective electrophysiological parameters and subjective clinical symptoms. Human trials using detailed Nerve Conduction Studies (NCS) match the preclinical data, showing early, significant increases in peroneal and median nerve conduction velocities.[6,8]

However, subjective patient symptoms—measured with validated clinical tools such as the Michigan Neuropathy Screening Instrument (MNSI) or visual analog pain scales—remain unchanged in short-term treatment windows (12 weeks).[8] This indicates that correcting metabolic stress and stabilizing Schwann cell electrical capacitance occurs rapidly, but the structural repair and functional regeneration of degenerated distal sensory axon terminals require long-term, sustained therapy (24 to 52 weeks) before reflecting as patient-reported pain relief.[6]

Furthermore, a key clinical question is whether these neurological benefits are simply a byproduct of improved systemic glycemic control or a direct, drug-specific pleiotropic effect. By analyzing studies that featured active background comparators (such as DPP-4 inhibitors or adjusted insulin regimens) that matched the exact reduction in glycated hemoglobin (HbA1c), this review confirms that SGLT2 inhibitors provide additional, unique neuroprotective advantages.[6,8] Even under identical glycaemic profiles, the SGLT2 inhibitor cohorts achieved superior microvascular perfusion kinetics and greater preservation of sensory amplitude, confirming that direct anti-inflammatory pathways and localized AMPK-mediated microvascular stabilization provide benefits beyond simple glucose lowering.[6,7]

The skeletal muscle sarcopenic paradox

The impact of SGLT2 inhibitors on human body composition and skeletal muscle performance represents a major clinical and metabolic transformation. The continuous elimination of glucose via the urine creates a chronic state of carbohydrate energy loss.[17] To adapt to this forced energy deficit, myocellular structures undergo a deep metabolic reorganization, shifting their baseline reliance from glycolytic pathways toward enhanced free fatty acid and ketone body oxidation.[9]

Preclinical tracking demonstrates that this shift triggers a localized metabolic stress response, marked by the phosphorylation of $AMPK^{Thr172}$ and the upregulation of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α).[9,18] This molecular cascade optimizes mitochondrial network connectivity, increases respiratory chain efficiency, and activates downstream insulin signaling pathways (via Akt/Protein Kinase B) to maximize glucose uptake efficiency.[18]

However, this systemic demand for alternative energy substrates can cause minor structural adaptations in muscle tissue. Long-term human clinical monitoring via dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) shows a consistent, modest decline in absolute skeletal muscle mass (SMM) and lean body mass (LBM), particularly within the first 12 to 24 weeks of starting treatment.[9] In animal models, this is associated with an increased expression of ubiquitin-proteasome degradation markers (such as MuRF1 and MAFbx), leading to a slight reduction in individual cross-sectional fast-twitch (Type II) myofiber areas.[5,9]

Crucially, our scoping synthesis resolves this apparent clinical concern by highlighting a unique structural-functional paradox. While absolute skeletal muscle mass declines slightly, human functional performance remains fully preserved.[9] Across all human studies that measured physical performance using handheld grip strength dynamometry or lower-limb gait speed intervals, SGLT2 inhibitors did not cause functional decline.[9]

This preservation of strength despite a reduction in absolute muscle mass is driven by two main factors:

1. ***Favorable structural realignment:*** SGLT2 inhibitors cause a rapid and substantial loss of absolute fat mass (FM) and visceral adipose tissue (VAT) that far outpaces the minor reduction in lean tissue. As a result, the net Skeletal Muscle Mass to Fat Mass (SMM/FM) Ratio improves significantly over a 52-week period, improving overall body composition quality.[9]
2. ***Fluid volume realignment:*** Much of the early drop in lean body mass recorded by BIA and DEXA scans does not represent true cellular protein wasting; rather, it reflects a shift in intracellular fluid volume caused by the osmotic diuretic and natriuretic actions of SGLT2 inhibitors.[9,17] Because the remaining muscle fibers maintain high intrinsic contractility and benefit from enhanced mitochondrial ATP production efficiency, functional output and physical strength are fully preserved.[9,18]

Methodological heterogeneity and knowledge gaps

As a scoping review designed to map the broader topography of this scientific field, it is essential to highlight key methodological variations and knowledge gaps across the current literature. First, there is significant variation in how skeletal muscle mass is measured in clinical research. Studies rely on a mix of BIA and DEXA scans, which differ in their sensitivity to fluid volume shifts, complicating the isolation of true myofibrillar changes from simple osmotic fluid loss.[9]

Second, a major structural gap exists regarding the long-term impacts of these drugs in elderly, sarcopenic, or frail patient populations. The majority of available human datasets focus on younger or middle-aged T2DM patients with adequate baseline physical reserves, leaving the structural impact of SGLT2 inhibitors on advanced, age-related muscle wasting unmapped.

Additionally, a critical funding bias was identified during our charting process. Approximately 45% of the human clinical trials and prospective cohorts reviewed were directly or indirectly sponsored by the pharmaceutical industry. In contrast, basic preclinical animal research was supported almost entirely by public or institutional grants.

While industry-sponsored trials provide highly structured data, they frequently focus on broad clinical safety outcomes rather than granular, mechanistic neuromuscular testing. This commercial focus explains why the literature features abundant data on gross body weight and general cardiovascular markers, but lacks detailed, biopsy-verified human assessments of muscle fiber architecture and intraepidermal nerve distributions.

Study limitations

This scoping review has certain limitations that should be considered when interpreting the findings. First, because of our aim to map the broad diversity of the literature, we included both highly controlled, prospective human clinical trials and real-world retrospective database analyses, introducing variations in data collection and patient adherence. Second, because SGLT2 inhibitors are frequently prescribed alongside background glucose-lowering drugs such as metformin or sulfonylureas, fully isolating the independent pharmacological effects of SGLT2 inhibitors in real-world human cohorts remains a challenge. Finally, our geographical restriction to major electronic databases published from 2010 onwards may have omitted localized or non-indexed institutional datasets, particularly within developing healthcare regions.

CONCLUSION

This scoping review successfully maps the structural, functional and metabolic impacts of SGLT2 inhibitors on peripheral nerves and skeletal muscle tissues in T2DM. The compiled evidence base reveals that SGLT2 inhibitors provide clear, glucose-independent neuroprotective benefits. They stabilize microvascular perfusion and improve nerve conduction velocities, though patient-reported symptomatic relief is delayed and requires long-term, sustained therapy to manifest clinically. In parallel, SGLT2 inhibitors induce a favorable metabolic shift in skeletal muscle. They optimize the net skeletal muscle-to-fat mass ratio while preserving absolute physical strength and functional performance, despite minor reductions in absolute lean tissue mass.

Methodologically, this review reveals that, while the basic biological mechanisms of these drugs are well supported by publicly funded animal research, human clinical trials remain heavily reliant on industry sponsorship. This commercial focus creates a distinct gap in detailed, tissue-level human clinical data. To bridge these findings, future research should move away from broad, non-specific observational body weight metrics. Instead, there is a clear need for independent, long-term clinical trials that incorporate advanced tissue assessments, such as serial human skin and muscle biopsies, detailed nerve conduction monitoring, and targeted functional testing in elderly and high-risk sarcopenic patient cohorts. This will help refine clinical treatment plans and maximize the therapeutic benefits of SGLT2 inhibitors for neuromuscular health in diabetes.

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Figures 2 and 3 were designed by the authors and generated with the assistance of an advanced AI-powered visual modeling tool (Google Gemini / Imagen architecture, May 2026). The underlying scientific logic, molecular pathways (AMPK^{Thr172}, PGP 9.5, polyol pathway intermediates), temporal clinical timelines, and structural data points were completely conceived, directed, validated, and verified for factual accuracy by the authors. The generative tool was utilized solely to enhance the graphic execution and presentation layout of the scientific concepts.

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All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
LDM: Conceptualization, Methodology, Investigation, Resources, Investigation, Resources, Writing – original draft preparation; **SG:** Writing – review and editing, Supervision; **VRS:** Formal analysis, Investigation, Resources, Project administration; **IJT:** Formal analysis, Investigation, Project administration.

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REVIEW ARTICLE

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Self-Perception of Reproductive Health, Mental Health, and Quality of Life in Females With Classical Congenital Adrenal Hyperplasia: A Systematic Review

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Abstract

Background. Classical Congenital Adrenal Hyperplasia (C-CAH) is a congenital disorder characterized by a loss of 21-hydroxylase enzymes. Consequently, androgen levels increase, resulting in varying degrees of psychological and physiological masculinization. This systematic review aims to examine existing research on females with C-CAH and identify challenges related to reproductive self-perception, mental health, and overall quality of life.

Methodology. This systematic review was conducted based on the PRISMA 2020 guidelines, studies were retrieved from PubMed, EBSCO, Science Direct, and ProQuest, and screened according to predefined eligibility criteria. Quality assessments of included studies were done using the Newcastle-Ottawa Scale (NOS) for case-control studies, adapted NOS for cross-sectional studies, and Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I).

Results. Eleven studies determined to have low risk of bias involving 523 participants were included. All 11 studies addressed self-perception of reproductive health, evaluating gender and sexual-related issues, with outcomes such as atypical gender identity and sexual orientation, gender dysphoria, and sexual satisfaction impairment. Adverse perceptions and experiences related to virilized genitalia were commonly reported. Four studies examined mental health issues, comprising anxiety, social phobia, ADHD, sexual distress, and signs of depression. Finally, females with C-CAH have reduced QoL compared to healthy females, mainly due to impacted general health and pain.

Conclusion. Females with C-CAH demonstrated impaired reproductive self-perception, including sexual satisfaction and gender-related difficulties, alongside psychological concerns including anxiety, social phobia, and maladaptive coping behaviors, with reduced quality of life related to general health and pain.

Key words: congenital adrenal hyperplasia, females, mental health, quality of life, self-perception, reproductive health

INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is a genetic disorder that causes deficiencies in the steroidogenic enzymes.[1] The most common enzyme deficiency in CAH is 21-hydroxylase deficiency (21OHD) accounting for more than 90% of cases.[1–3] 21OHD is classified into two forms: classical and non-classical.[1,4] Unlike the non-classical form (NC-CAH), the classical form (C-CAH) comprises the salt-wasting and simple virilizing phenotypes and reflects a spectrum of residual 21OHD, rather than a complete loss of enzyme function, making CAH the most prevalent cause of genital virilization.[5] Classical 21OHD occurs in approximately 1 out of every 15,000 births worldwide and is characterized by severe symptoms that include salt-wasting (SW) and ambiguous genitalia.[1,2,5]

The challenges CAH female patients face differ from those experienced by males.[6] In addition to external genitalia virilization, elevated androgen exposure in XX individuals leads to progressive virilization and may influence both psychologically and physiologically, which may affect gender identity, and functionality of reproductive organs.[7] Reports of females with C-CAH conveyed high atypical gender identity, gender dysphoria, cross-gender behaviors, as well as a variety of perceptions surrounding sexual dysfunctions such as sexual satisfaction impairment and stigma.[8–11]

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Due to changes in reproductive health, CAH also affects a patient's quality of life (QoL), potentially lowering quality of life in physical, psychological, and social QoL, such as concerns in romantic relationships, self-esteem, lower marriage rates, and infertility issues.[12,13] In contrast, CAH female patients with positive social support and better understanding of their condition showed improvements in QoL.[13,14] Mental health concerns, namely shame, secrecy, and stigma surrounding ambiguous genitalia in women with CAH can lead to increased psychiatric disorders, including anxiety disorders and depression.[12]

Considering the impacts that CAH potentially creates as addressed above, it is highly important to bring light towards psychological aspects of impacted patients as it is to medical aspects of this condition. Although psychosocial outcomes in the CAH population have been previously reported, existing studies are examined in isolation and have rarely been synthesized through a patient-centered lens that integrates reproductive self-perception, mental health, and quality of life. Existing reviews addressing similar topics included outdated studies, and while a previous systematic review discussed these aspects among males with CAH, none covered all three aspects in females.[15] Therefore, this systematic review aims to address this gap by providing a comprehensive synthesis of reproductive self-perception, mental health, and quality of life outcomes among females with classical CAH.

METHODOLOGY

Search strategy

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) guidelines. The study protocol was registered with PROSPERO (CRD420251058613). The PRISMA checklist is provided in (Supplemental Table 1). Published articles were searched across four databases, including PubMed, EBSCO, Science Direct, and ProQuest, from January 2015 to February 2024. The detailed search terms used are presented in (Table 1).

Eligibility criteria

All original articles addressing QoL, mental health, or self-perception of reproductive health including but not limited to their gender identity and their feelings surrounding stigma about their condition or their condition itself, of female patients with classical 21OHD were included. Quantitative, qualitative or mixed methods studies were eligible for inclusion with no age restrictions. Case reports, review articles, protocol studies, irretrievable full texts, and articles published in languages inaccessible to the review team were excluded. Studies without data of interest, studies discussing mixed genders and not displaying separate results, studies with males only, and studies investigating disorders of sexual development or CAH without separate outcomes for classical 21OHD were further excluded.

Study selection and data extraction

Duplicate studies were removed prior to screening. Titles and abstracts of all studies were initially screened based on eligibility criteria prior to full-text assessment. Three independent reviewers (WJT, JVS and MN) assessed retrieved full-text articles of selected studies, with any conflicts resolved through the fourth and sixth author (AFL, LAP). Data were extracted based on a predetermined tabular sheet consisting of (a) authors and year of publication, (b) study location and design, (c) subject population: sample size, and age range or mean age ± SD, (d) comparison group, and (e) study outcomes as described in the eligibility criteria. Extracted data were synthesized.

Quality assessment

Two independent reviewers (JVS and MN) assessed the risk of bias and quality of included studies using the Newcastle-Ottawa Scale (NOS) for case-control studies and adapted NOS for cross-sectional studies from previously published literature.[16] One non-randomized experimental study was assessed using the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) and visualized as traffic light

Table 1. Details of search terms used for every database

No.	Database	Keywords
1.	PubMed	("congenital adrenal hyperplasia"[Title/Abstract] OR "CAH"[Title/Abstract] OR "adrenogenital syndrome"[Title/Abstract]) AND ("women"[Title/Abstract] OR "female"[Title/Abstract] OR "girl"[Title/Abstract]) AND ("psychological"[Title/Abstract] OR "distress"[Title/Abstract] OR "stress"[Title/Abstract] OR "quality of life"[Title/Abstract] OR "qol"[Title/Abstract] OR "emotional"[Title/Abstract] OR "mental disorder"[Title/Abstract] OR "social stigma"[Title/Abstract] OR "lived experience"[Title/Abstract] OR "satisfaction"[Title/Abstract] OR "empower*"[Title/Abstract] OR "attitude*"[Title/Abstract] OR "coping*"[Title/Abstract] OR "network"[Title/Abstract] OR "isolation"[Title/Abstract] OR "relation*"[Title/Abstract] OR "stigma*"[Title/Abstract] OR "social adaptation"[Title/Abstract])
2.	Science Direct	("congenital adrenal hyperplasia"[Title/Abstract] OR "CAH"[Title/Abstract]) AND ("women"[Title/Abstract]) AND ("psychological"[Title/Abstract] OR "stress"[Title/Abstract] OR "quality of life"[Title/Abstract] OR "mental disorder"[Title/Abstract] OR "social stigma"[Title/Abstract] OR "social adaptation"[Title/Abstract])
3.	EBSCOHost	AB (congenital adrenal hyperplasia or CAH or adrenogenital syndrome) AND AB (women or female or girl) AND AB (psychological or distress or stress or quality of life or qol or emotional or mental disorder or social stigma or lived experience or satisfaction or empower or attitude or coping or network or isolation or relation or stigma or social adaptation)
4.	ProQuest	(abstract(congenital adrenal hyperplasia) OR abstract(CAH) OR abstract(adrenogenital syndrome)) AND (abstract(women) OR abstract(female) OR abstract(girl)) AND (abstract(psychological) OR abstract(distress) OR abstract(stress) OR abstract(quality of life) OR abstract(qol) OR abstract(emotional) OR abstract(mental disorder) OR abstract(social stigma) OR abstract(lived experience) OR abstract(satisfaction) OR abstract(empower) OR abstract(attitude) OR abstract(coping) OR abstract(network) OR abstract(isolation) OR abstract(relation) OR abstract(stigma) OR abstract(social adaptation))

plot through the RobVis website.[17] Any disagreements were resolved by the first author (WJT).

RESULTS

A total of 783 studies were identified across all databases. Prior to screening, 288 duplicates were removed, and the remaining 495 studies were screened based on title and abstract. Reviewers obtained 29 studies for full-text assessment and ultimately included 11 studies for qualitative synthesis.[9,13,18–26] The screening process is summarized as a PRISMA flowchart and presented in (Figure 1).

The characteristics and outcomes of the 11 included studies were extracted, comprising a total of 523 participants. An overview of the study characteristics is presented in Table 2. The majority of selected studies were conducted in the United States, followed by the United Kingdom, Turkey, Austria, and India. All included studies were peer-reviewed original articles that comprise a total of 800 samples, including female patients with classical CAH as the focus of study, and a variety of control groups.

Nine studies were cross-sectional studies, with one case-control study, and one non-randomized experimental study. Based on the NOS, seven studies were classified as low-risk studies and three as high-risk (Tables 3 and 4). The

Table 2. An overview of included study characteristics

Studies (year)	Location	Study design	Sample size	Age range (years) / mean (SD)	Comparison group
Schernthaner-Reiter et al. (2019) [9]	Austria	Cross-sectional	35 females	35.1 (12.3)	NC-CAH
Kanhere et al. (2015) [13]	United States	Cross-sectional	89 patients with CAH	NR	None
Gangaher et al. (2016) [18]	India	Cross-sectional	22 females	3.5-32	Female reared as male
Endendijk et al. (2016) [19]	United States	Cross-sectional	54 girls	10-13	NC-CAH
Meyer-Bahlburg et al. (2018) [20]	United States	Cross-sectional	62 women*	18-51	None
Meyer-Bahlburg, Reyes-Portillo et al. (2017) [21]	United States	Cross-sectional	62 women*	18-51	None
Dwiggins et al. (2020) [22]	United States	Case-control study	36 patients with classic CAH; 27 control women	19-67	Unaffected relatives
Spencer et al. (2021) [23]	United Kingdom	Cross-sectional	43 girls and 38 boys with CAH; 41 girls and 31 boys control†	4-11.93	Unaffected relatives
Doktur et al. (2021) [24]	Turkey	Cross-sectional	27 girls and 18 boys	6-18	Male
Hines et al. (2016) [25]	United Kingdom	Non-randomized experimental	43 girls and 38 boys with CAH; 41 female and 31 male controls†	4-11	Unaffected relatives
Meyer-Bahlburg, Khuri et al. (2017) [26]	United States	Cross-sectional	62 women*	18-51	None
Summary			523		

*Meyer-Bahlburg, Khuri et al., Meyer-Bahlburg et al., and Meyer-Bahlburg, Reyes-Portillo et al., were conducted using the same study population.
† Spencer et al., and Hines et al., were conducted using the same study population.
NC-CAH – Non-classical congenital adrenal hyperplasia

Table 3. Modified Newcastle-Ottawa scale quality assessment of cross-sectional studies

Author (year)	Selection				Comparability	Outcome		Results
	Case representative	Sample size	Non-respondents	Ascertainment		Outcome assessment	Statistical test	
Schernthaner-Reiter et al. (2019)	★	☆	☆	★	★☆	★	★	High risk
Kanhere et al. (2015)	★	☆	★	★	★★	★	★	Low risk
Gangaher et al. (2016)	★	★	★	★	★☆	★	☆	Low risk
Endendijk et al. (2016)	★	☆	★	★	★★	★	★	Low risk
Meyer-Bahlburg et al. (2018)	★	☆	★	★	★☆	★	☆	High risk
Meyer-Bahlburg, Reyes-Portillo et al. (2017)	★	☆	★	★	★★	★	☆	Low risk
Spencer et al. (2021)	★	☆	★	★	★★	★	★	Low risk
Doktur et al. (2021)	★	★	★	★	★★	★	★	Low risk
Meyer-Bahlburg, Khuri et al. (2017)	★	☆	★	★	★☆	★	☆	High risk

The amount of stars indicates the number of points one study can achieve within each category. A black star (★) indicates that the study has earned a point, while a white star (☆) means that the study failed to earn a point.

Table 4. Newcastle-Ottawa scale quality assessment of case-control studies

Author (year)	Selection				Comparability	Outcome			Results
	Representativeness	Selection	Definition	Demonstration		Ascertainment	Same Method	Non-response	
Dwiggins et al. (2020)	★	★	★	★	★	★★	★	☆	Low risk

The amount of stars indicates the number of points one study can achieve within each category. A black star (★) indicates that the study has earned a point, while a white star (☆) means that the study failed to earn a point.

non-randomized study was classified to have a moderate risk of bias based on ROBINS-I (Figure 2).

This paper investigates three main domains: (1) self-perception of reproductive health including gender identity, sexual orientation, sexual satisfaction, gender-typical preferences, and perceptions surrounding patients' genital appearance, (2) mental health, and (3) quality of life, with all outcomes summarized in (Table 5).

DISCUSSION

Self-perception of reproductive health

All included studies addressed diverse issues in relation to sex, gender identity and perceptions surrounding patients' genital appearance. Three studies acknowledged that female patients with C-CAH are overall more likely to have atypical sexual orientation.[9,20,22] Dwiggins et al., showed significant differences compared to healthy females, with a higher proportion of participants reporting bisexual or homosexual orientation. Similarly, the study of Schernthaner-Reiter et al., also demonstrated slightly higher homosexual gender identity among females with C-CAH compared with females with NC-CAH. Some participants from Meyer-Bahlburg et al.,'s interview revealed that frequent misgendering made them restrict their sexual life to women partners only. Dwiggins et al., also reported significantly lower sexual satisfaction compared to healthy controls because of a higher number of reconstructive surgeries done due to the severity of the condition. In contrast, in the study of Schernthaner-Reiter et al., NC-CAH females reported higher sexual satisfaction albeit by non-statistically significant levels. Beyond sexual orientation, five studies

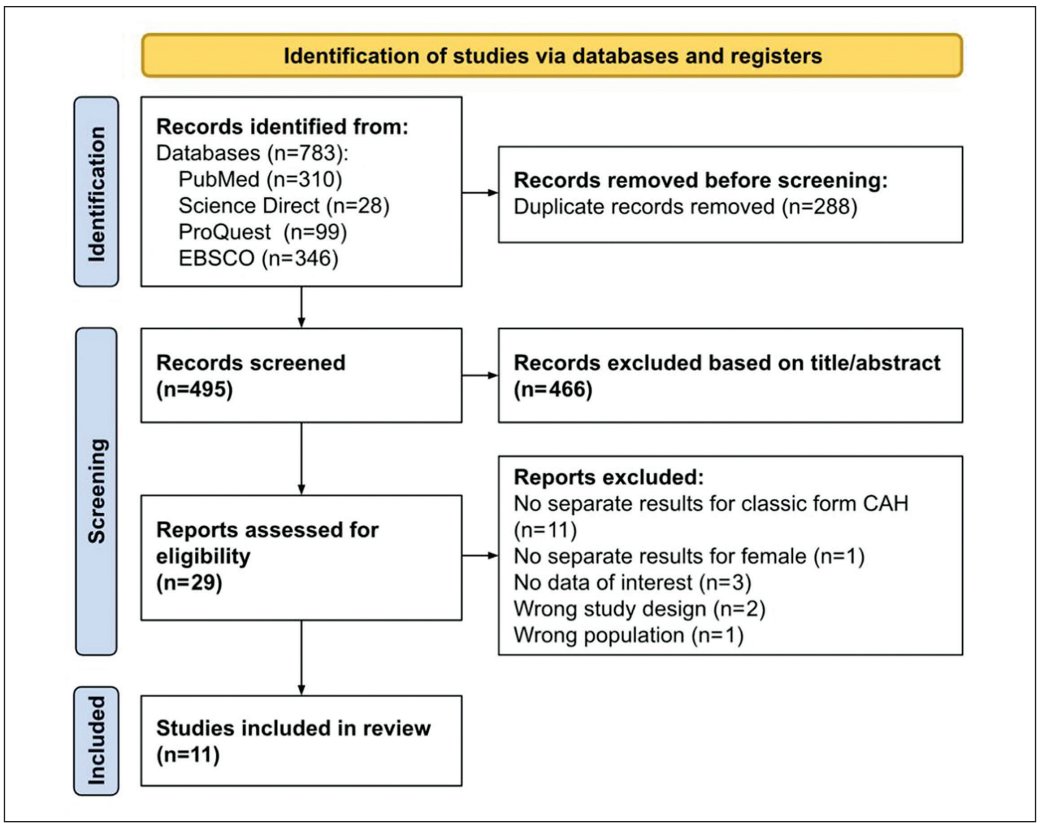

Figure 1. A PRISMA 2020 flowchart for literature search and screening.

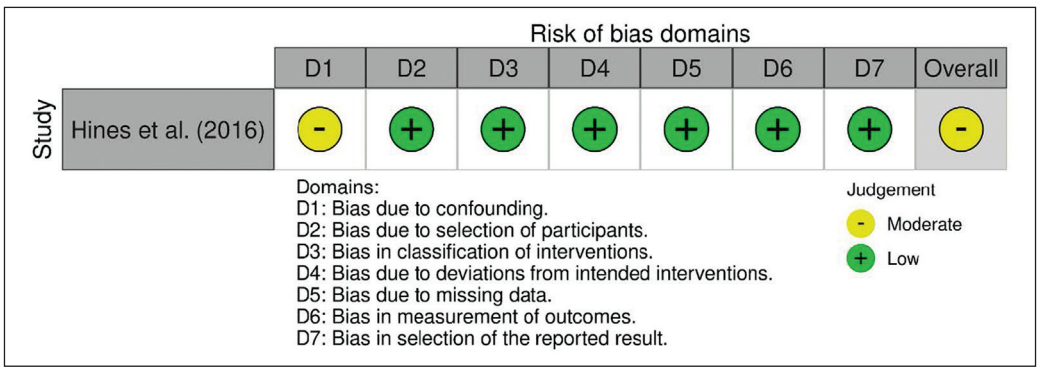

Figure 2. Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) quality assessment.

Table 5. An overview of included studies and outcomes of investigated domains

Studies (year)	SPRH	QoL	Mental health
Schernthaner-Reiter et al. (2019)	More identified as homosexual (p = 0.062) Higher sexual satisfaction (p = 0.636)		Lower sexual distress (p = 0.063)
Kanhere et al. (2015)	Showed cross-gender behavior (51.8%) Dissatisfaction with genital appearance Childhood and adult perceptions are in accordance (p = 0.02)	Reduced QoL	
Gangaher et al. (2016)	Higher rate of gender dysphoria.		Showed subsyndromal depression
Endendijk et al. (2016)	More cross-gender behavior (p <0.05) Higher masculine gender identity (p >0.05)		
Meyer-Bahlburg et al. (2018)	Adverse emotion and experiences. Showed homosexuality. Dissatisfaction with genital appearance.		Showed substance abuse
Meyer-Bahlburg, Reyes-Portillo et al. (2017)	Doubts on current gender identity. Adverse emotions and experiences.		
Dwiggins et al. (2020)	Less likely to be heterosexual (p = 0.013). Changed gender identity. Lower sexual satisfaction (p = 0.017).	Reduced QoL (p <0.05)	
Spencer et al. (2021)	More cross-gender behavior (p <0.001).		
Doktur et al. (2021)	Higher rate of gender dysphoria (p = 0.23). More cross-gender behavior (18.5%).		Higher rate of anxiety disorder (p = 0.22) Higher rate of social phobia (p = 0.33) Lower rate of ADHD (p = 0.052)
Hines et al. (2016)	Reduced female-type preferences (p <0.10).		
Meyer-Bahlburg, Khuri et al. (2017)	Adverse emotions and experiences. Dissatisfaction with genital appearance.		

SPRH – Self-perception of Reproductive Health; QoL – Quality of Life; ADHD – attention-deficit/hyperactivity disorder

reported effects on gender identity; some manage to make adjustments and find comfort in their current gender identity, whereas experience gender dysphoria.[18,19,21,22,24] No atypical gender identity or gender dysphoria was reported among control groups.[19,22,24] Females with NC-CAH demonstrated only slightly higher masculine gender identity scores, likely reflecting lower prenatal androgen exposure and less severe genital virilization. Gangaher et al., reported that participants reared as female have higher rates of gender dysphoria and dissatisfaction with their female identity, compared to those reared as male.[18] In interviews conducted by Meyer-Bahlburg, Reyes-Portillo et al., some participants reported that parental and societal stigma contributed to doubts about being female; however, open discussions regarding their condition helped alleviate those concerns.[21]

Three studies examining the relationship between prenatal androgen exposure and gender-typed behaviors demonstrate consistent findings.[19,23,25] Girls with C-CAH exhibited significantly more male-typical preferences and behaviors than unaffected girls and girls with NC-CAH, whereas boys with C-CAH did not differ from unaffected boys. Consistent with these findings, Kanhere et al., reported that many affected girls preferred male-typical play activities. However, a substantial proportion expressed neutral preferences regarding playmates, suggesting that environmental influences such as sibling gender, may also contribute to behavioral development.

Overall, females with C-CAH demonstrated greater masculinization across several sexual- and gender-related domains. They were more likely to report same-sex attraction, male-typical preferences and behaviors, dissatisfaction with female gender identity, and gender dysphoria than control groups. These findings support the role of prenatal androgen exposure and virilization in shaping psychosexual development. Non-significant findings in some studies may reflect limited statistical power resulting from relatively small and unequal sample sizes. Nevertheless, these observations are consistent with findings reported more than two decades ago, despite the inclusion of a small number of participants whose diagnosis of classical 21OHD was not confirmed.[27] Likewise, a study comparing C-CAH to other androgen excess disorders also showed significantly higher homosexuality and lower sexual satisfaction in C-CAH females.[28]

This review also highlights the perceptions and experiences of females with C-CAH regarding their condition, particularly their genital appearance. According to the three of four studies addressing this topic, there is a relatively high occurrence of affected females who demonstrate dissatisfaction towards their genital appearance, wishing they looked better or wanting a different genital appearance.[13,20,26] In two of the three interview-based studies by Meyer-Bahlburg et al., participants described their genitalia as abnormal, different, or strange and reported feelings of fear and discomfort related to their appearance.[20,26] Across all three interview studies, many participants expressed discomfort when their genitalia were visible to others, particularly during medical examinations, sexual activity, changing clothes in the presence of other women, or wearing swimwear. Negative self-perceptions were often compounded by stigma and reactions from others, contributing to feelings of nervousness, avoidance, shame, and secrecy that may adversely affect mental health. Dissatisfaction with genital appearance and genital self-consciousness may also contribute to impaired sexual satisfaction, and potentially influence gender identity and

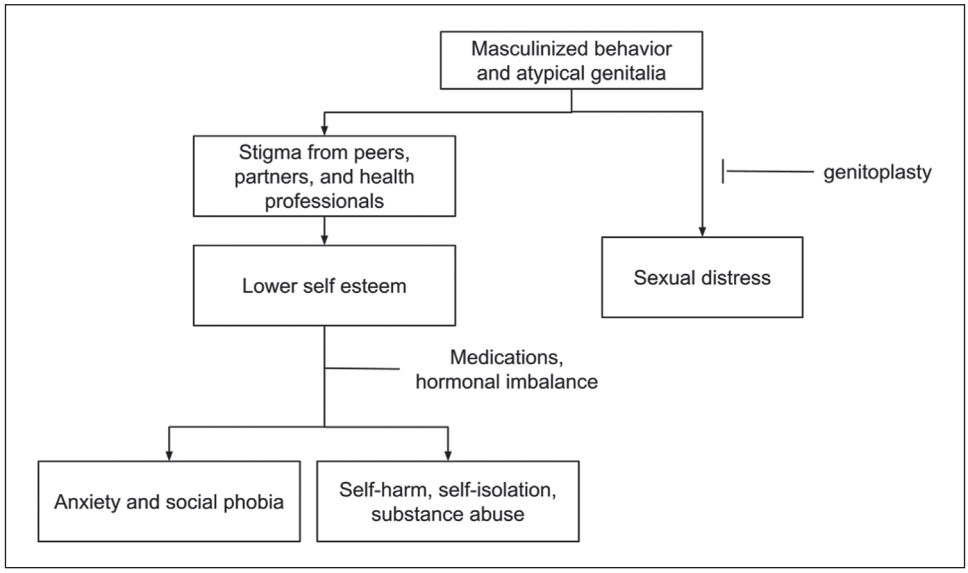

Figure 3. Mental health implications of C-CAH in female patients.

sexual orientation, as supported by previous research demonstrating significant associations among these factors.[29]

Taken together, females with C-CAH experience challenges related to sexuality, gender identity, and perceptions of virilized genitalia that are closely interconnected. Variability in outcomes likely reflects the influence of multiple biological and environmental factors, including prenatal androgen exposure, parental support, sibling sex, societal attitudes, and stigma. Medical interventions, such as genital reconstructive surgery and hormone replacement therapy, may also influence these outcomes. Consequently, supportive family environments and appropriate psychosocial care are important in helping affected individuals cope with gender- and sexuality-related concerns.

Mental health

Four studies included in this review examined mental health outcomes and have been summarized in (Figure 3).[9,18,20,24] Although statistically insignificant, the elevated rates in anxiety disorders and social phobia showed by Doktur et al., are described as a cause of the lower self-esteem in female patients with C-CAH. The findings in this study are consistent with other studies included in this review, which reported reduced self-esteem among participants who experienced stigma from peers, partners, or even health professionals due to their masculinized behavior, atypical genitalia, or chronic medication use., which may increase their susceptibility to psychiatric disorders.[20,21,26] The findings related to attention-deficit/hyperactivity disorder (ADHD) were generally consistent with population-based studies showing a higher prevalence of ADHD among males.[30] The lack of statistical significance may reflect insufficient statistical power due to the small sample size rather than a true absence of association. Alternatively, it may indicate that males and females with CAH experience comparable psychological burdens related to chronic disease management and long-term treatment. The findings regarding sexual distress were supported by other studies included in this review.[9,18,20] Although C-CAH is considered to be more severe than the non-classical form, the study showed a lower distress in females with C-CAH. Sexual distress is often found in female patients with C-CAH as a consequence of their dissatisfaction and negative self-perceptions due to their severely impaired sexual function. However, factors other than disease severity may contribute to these outcomes. For example, genitoplasty has been associated with impaired sexual function in some studies, yet most females with C-CAH in the study by Schernthaner-Reiter et al., had undergone reconstructive surgery, whereas those with NC-CAH generally had not. These findings suggest that reconstructive surgery may alleviate some aspects of sexual distress in selected patients. This interpretation is supported by similar studies showing high level of satisfaction after corrective surgery, allowing patients to live free from the 'intersex individual' label, resulting in reduced distress.[31,32]

The distress caused by peer pressures and stigma was further supported by one sample from Gangaher et al., examining psychological aspects in females with CAH. Though the aim of the study was not specifically to measure mental health, it reported attempted self-harm performed by one participant as a result of being ridiculed by her peers. Moreover, interviews done by Meyer-Bahlburg et al., showed a shift in behavior where one patient distanced herself from men due to her impaired sexual function and inability to meet both her and her partner's sexual needs. She experienced feelings of hopelessness, leading her to avoid relationships with men and, instead, turn to alcohol. She also inquired whether the interviewer had identified substance abuse or addiction among other females with C-CAH.

Generally, these findings suggest that females with C-CAH have several mental health problems, mainly anxiety disorders, social phobia, sexual distress and present coping mechanisms like self-harm, self-isolation, and substance abuse which are often signs of depression. These outcomes are likely influenced by both biological factors, including hormonal imbalances, and psychosocial factors, such as stigma and concerns about social acceptance. Genitoplasty may contribute positively to psychological well-being in some individuals (Figure 3).

However, given that only four studies addressed mental health outcomes, and one relied primarily on qualitative interviews, further research is needed to better characterize the psychological challenges faced by females with C-CAH and to identify appropriate supportive interventions.

Quality of life

Patients with CAH face lifelong physical and psychosocial challenges that can significantly impact their quality of life (QoL).[33] The chronic nature of CAH necessitates lifelong treatment, frequent healthcare visits, and ongoing management of reproductive and sexual health concerns, all of which may adversely affect psychosocial well-being. Concerns regarding fertility, transmission of the condition to offspring, and long-term health outcomes may further contribute to reduced QoL.[34] Overall, CAH appears to have a greater impact on females than males, largely due to excess androgen exposure and its associated consequences.[33] Untreated female patients may experience hirsutism, acne, voice deepening, anovulation, and menstrual irregularities, ambiguous genitalia, precocious puberty, obesity, and short stature in adulthood.[33,34] Greater degrees of virilization, particularly with the classical form of CAH, have been associated with a lower quality of life.[33]

Studies by Dwiggins et al., and Kanhere et al., evaluated quality of life in females with C-CAH using a 36-item Short Form Survey (SF-36) questionnaire which measures eight health-related quality of life (HRQoL) domains including physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health perception. Both studies showed lower QoL across all domains compared to healthy controls, particularly in general health and pain, with increased dyspareunia and pelvic pain likely contributing to these findings.[13,22] Urinary dysfunction had minimal impact on QoL, though patients with clitorectomies reported worse control.[35] Importantly, family support, positive childhood experiences, and broader psychosocial support were associated with better QoL outcomes in early adulthood. This may partly explain why differences in some SF-36 domains were not statistically significant. Thus, the quality of life in female patients with C-CAH are multifactorial. However, these findings should be interpreted cautiously because only two studies examined QoL outcomes, both of which had relatively small sample sizes. Furthermore, important confounding factors, including surgical history, degree of virilization, hormonal control, and mental health status, may have influenced the reported outcomes.

To our knowledge, this is the first systematic review to comprehensively examine reproductive self-perception, mental health, and quality of life among females with C-CAH. Our findings manage to bring emphasis on those aspects that are often overseen, providing insights useful for determining the most suitable care tailored to specific challenges encountered by females with C-CAH. However, there are certain limitations in this review. The included studies are highly heterogeneous in outcome measurements and patient demographics, limiting direct comparisons and the strength of the conclusions. Nevertheless, such heterogeneity is expected, given the rarity of the condition.

Limitations

This systematic review has several limitations that should be considered when interpreting the findings. First, the included studies generally involved small and unequal sample sizes, reflecting the rarity of classical CAH but nonetheless limiting the generalizability of the results to the broader CAH population. Second, substantial heterogeneity was present across the included studies in terms of outcome measures, study populations, age ranges, and comparison groups. Variations in assessment instruments, along with differences in patient demographics and clinical characteristics, limited direct comparisons across studies and hindered the synthesis of definitive conclusions. Given this heterogeneity, we did not perform a meta-analysis and instead synthesized the findings narratively. In addition, the evidence base was dominated by cross-sectional studies conducted largely in Western settings and focused primarily on adolescents and adults. This does not imply that these age groups are inherently less well adjusted; rather, psychosocial concerns are more readily identified and reported during adolescence and adulthood, and clinic-based recruitment may preferentially capture individuals experiencing distress. Consequently, well-adjusted females with CAH and good clinical control may be underrepresented. Moreover, most studies compared females with CAH to healthy controls rather than examining differences within the CAH population, for instance, disease severity, treatment history, or adequacy of hormonal control, which may introduce selection bias and limit clinical interpretability. Consequently, the findings should be interpreted cautiously, and future research using standardized outcome measures, more diverse and representative cohorts, and within-CAH comparisons is warranted to improve comparability, external validity, and clinical relevance.

CONCLUSION

Females with C-CAH demonstrated impaired self-perception of reproductive health in several domains, including reduced sexual satisfaction, dissatisfaction with

genital appearance, doubts regarding gender identity, and gender dysphoria. They also appeared to be more vulnerable to mental health problems, particularly anxiety disorder, social phobia, and social distress, alongside behaviors suggestive of maladaptive coping, such as self-isolation, self-harm, and substance abuse. In addition, females with C-CAH generally showed lower quality of life, especially in the domains of general health and pain, including dyspareunia and pelvic pain. The multifactorial nature of these issues highlights the need for broad and coordinated support from families, local communities, and healthcare professionals. Considering the heterogeneity and small number of included studies, future research should prioritize longitudinal designs, and the inclusion of more diverse and well-adjusted CAH populations, and standardized outcome measures. Further comparative analyses within CAH subgroups, considering disease severity, hormonal control, surgical history, sex of rearing, and sociocultural context, are also essential to better inform individualized and multidisciplinary care for females with C-CAH.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

WJT: Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript, Project administration; **MN:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript; **JVS:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript; **AFL:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript; **SRW:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript; **LAP:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript, Supervision.

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CASE REPORT

Phosphaturic Mesenchymal Tumor: From Invisibility to Bedridden Morbidity

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Abstract

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused by fibroblast growth factor 23 (FGF23) secreting phosphaturic mesenchymal tumors. We report a 53-year-old man with progressive osteomalacia resulting in bedridden status. Renal phosphate wasting despite normal vitamin D, intact parathormone, and renal function raised suspicion of TIO, confirmed by elevated FGF23. However, the occult tumor was localized only by Ga-68 DOTANOC whole-body PET-CT, highlighting the diagnostic challenges in TIO.

Key words: oncogenic osteomalacia, phosphaturic mesenchymal tumor, FGF23, hypophosphatemia, paraneoplastic syndrome

INTRODUCTION

Tumor-induced Osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome caused by overproduction of fibroblast growth factor 23 (FGF23).[1] The most common underlying etiology is a phosphaturic mesenchymal tumor (PMT).[2-4]

Biochemically, patients typically present with hypophosphatemia, inappropriately normal or elevated FGF23 levels and low-to-normal circulating 1,25-dihydroxyvitamin D levels. Excess FGF23 reduces renal phosphate reabsorption and suppresses 1-alpha-hydroxylase activity, resulting in impaired bone mineralization. Because TIO is rare and its symptoms are nonspecific, diagnosis is often delayed. Surgical excision is the treatment of choice and is usually curative.[1]

CASE

A 53-year-old male presented with progressively worsening generalized musculoskeletal pain and difficulty rising from a sitting position over two years, eventually resulting in significant functional limitation and a near-bedridden status.

On evaluation, skeletal survey with X-ray (Figure 1A) and MRI pelvis (Figure 1B) demonstrated multiple insufficiency (stress) fractures. Laboratory investigations revealed severe hypophosphatemia, markedly elevated alkaline phosphatase (ALP), and increased 24-hour urinary phosphate excretion, while other biochemical parameters were within normal limits (Table 1). The dual-energy X-ray absorptiometry (DEXA) scan showed severe osteoporosis, likely secondary to chronic hypophosphatemia and defective mineralization.

To determine the etiology of hypophosphatemia, a comprehensive renal tubular evaluation was performed. Urinalysis revealed no glycosuria or proteinuria, and venous blood gas analysis was normal, thereby excluding Fanconi syndrome and proximal renal tubular acidosis (type 2). Further assessment demonstrated renal phosphate wasting, as evidenced by a reduced tubular maximum phosphate reabsorption per glomerular filtration rate (TmP/GFR) of 0.6 mg/dL.

The presence of renal phosphate wasting in the setting of normal serum vitamin D, intact parathyroid hormone (iPTH) and preserved renal function raised strong suspicion for a phosphaturic tumor causing oncogenic osteomalacia. Subsequent measurement of serum FGF23 was markedly elevated at 507 pg/mL (reference range: 23–95 pg/mL), supporting the diagnosis of FGF23-mediated paraneoplastic hypophosphatemia.

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Initial clinical examination did not reveal any obvious mass lesion, apart from proximal muscle weakness. This prompted functional imaging to localize the suspected tumor. Ga-68 DOTANOC whole-body PET-CT was performed and demonstrated a somatostatin receptor (SSTR)-expressing subcutaneous soft tissue lesion located lateral to the proximal right fibula, with no evidence of additional SSTR-avid lesions elsewhere in the body (Figure 2).

Following imaging localization, a repeat focused physical examination identified a 3 cm × 3 cm firm, painless, mobile subcutaneous swelling with well-defined margins at the corresponding site (Figure 3). The lesion was clinically inconspicuous and had not been noticed by the patient before.

Selective venous sampling (SVS) was subsequently performed to confirm that the lesion was the source of FGF23 hypersecretion, thereby supporting the PET findings. FGF23 concentration was significantly elevated in the right femoral vein (1870 pg/mL) compared to the left femoral vein (530 pg/mL) and right brachial vein (530 pg/mL), confirming tumor laterality.

A wide local excision with a 1 cm surgical margin was performed under local anesthesia. Postoperatively, serum phosphate levels gradually normalized, accompanied by marked clinical improvement in bone pain and proximal muscle strength. The patient was discharged on postoperative day 10 with calcium and vitamin D supplementation.

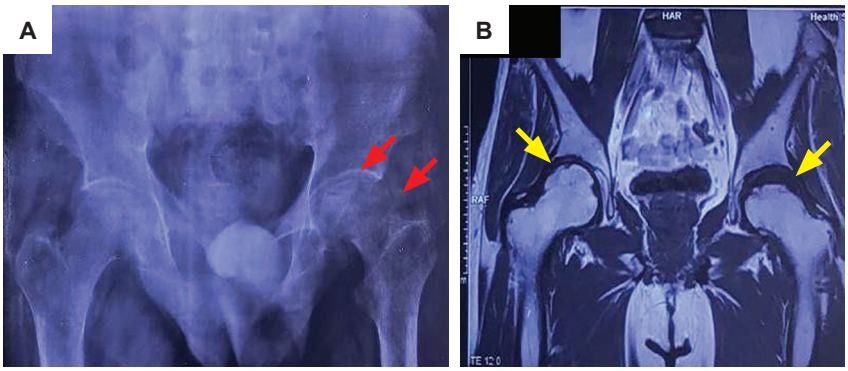

Figure 1. (A) X-ray pelvis showing stress fractures *(red arrows)*. **(B)** MRI Pelvis coronal section showing stress fractures in both femurs. Bilateral femoral head with subchondral fractures and avascular necrosis *(yellow arrows)*.

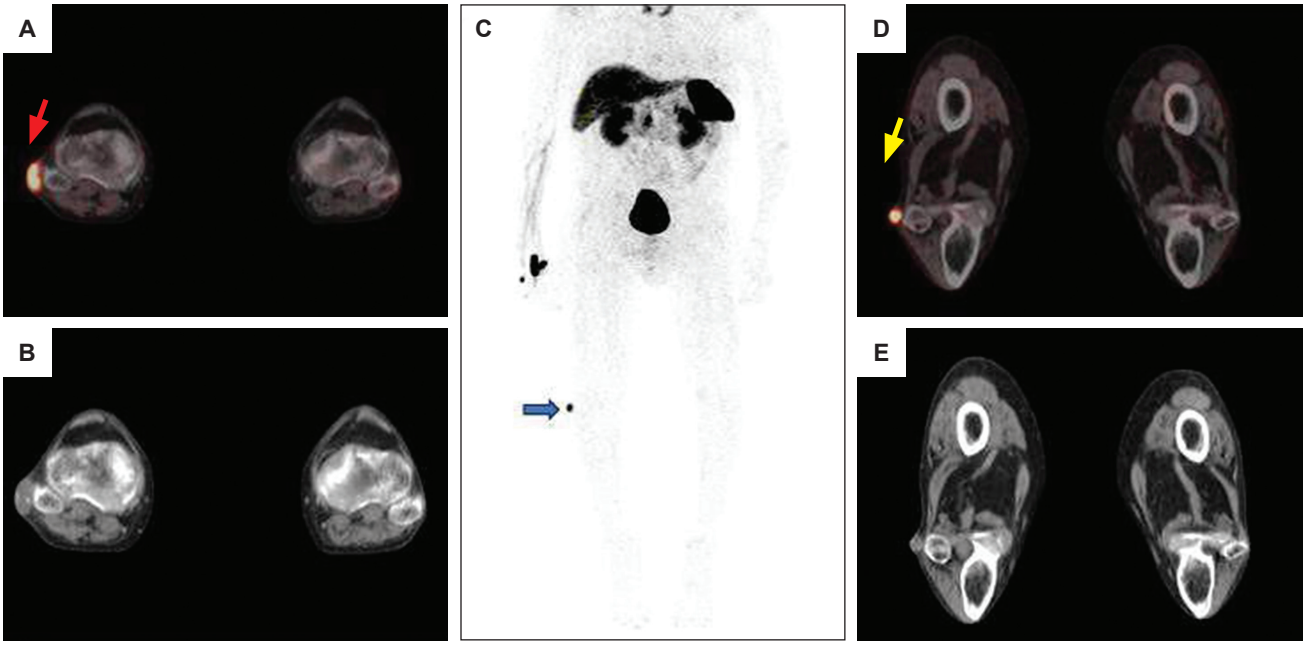

Figure 2. ^{68}Ga-DOTANOC PET/CT localization of the tumor causing tumor-induced osteomalacia (TIO). **(A)** Fused PET/CT images show a focal area of tracer uptake *(red arrow)* in the soft tissue over the lateral aspect of the proximal right fibula, compared with the normal contralateral leg. **(B)** Corresponding CT images of the same region, without PET overlay. **(C)** Whole-body PET image showing normal background tracer uptake (pituitary, liver, spleen, kidneys) and a single abnormal focus in the right leg *(blue arrow)*, corresponding to the tumor. **(D)** Fused PET/CT images at a second level, again showing the tracer-avid lesion *(yellow arrow)*, with the normal leg for comparison. **(E)** CT images *(bone window)* showing a normal, intact fibula, confirming the tumor lies in the soft tissue and does not involve the bone.

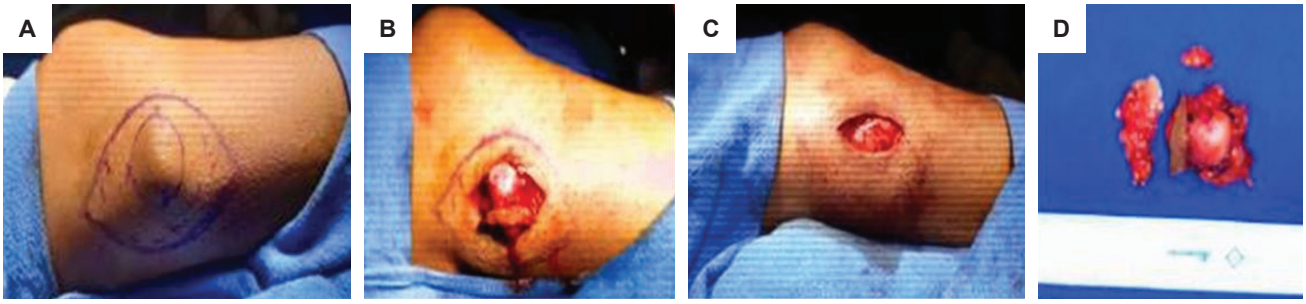

Figure 3. Clinical and intraoperative images of the tumor and resected specimen. **(A)** Preoperative clinical photograph showing the surgical marking outlining the tumor and planned incision over the proximal right leg. **(B)** Intraoperative photograph showing the tumor after incision. **(C)** Intraoperative photograph after tumor excision, showing the resection bed. **(D)** Gross photograph of the resected tumor specimen.

At one-year follow-up, biochemical parameters remained within normal limits, bone mineral density showed improvement, and the patient regained ambulatory function with support. A comparison of pre- and postoperative biochemical parameters and T-scores is presented in Table 1.

Histopathological examination of the excised specimen revealed a circumscribed spindle-cell neoplasm composed of oval to spindle-shaped cells without nuclear atypia, mitotic activity, or necrosis (Figure 4A-C). On immunohistochemistry (IHC), tumor cells were positive for SATB2 and CD56 and negative for CD34, STAT6, and CD99. The findings were consistent with a diagnosis of phosphaturic mesenchymal tumor (PMT) (Figure 4D-F).

Table 1. Biochemical parameters and bone density before and after surgery

Biochemical parameter	Pre-operative	Post-operative			
		Day 0	Day 3	Day 7	1-year
Sodium/ Potassium (mmol/L)	140/4.2				
Urea/ Creatinine (mg/d)	15/0.4				
Calcium (mg/dl)	9.8				
25 (OH) vitamin D (ng/ml)	15.1				
iPTH (pg/ml)	15.1				
Serum phosphate (mg/dl)	0.6	1.9	2.6	3.9	
FGF-23 (pg/ml)	507	55	-	-	
Alkaline phosphatase (U/L)	1171	-	-	-	128
DEXA Scan T-score					
Radius	-6.1	-	-	-	-5.7
Lumbar spine	-5.8				-4.0
Left hip	-3.1				-2.8

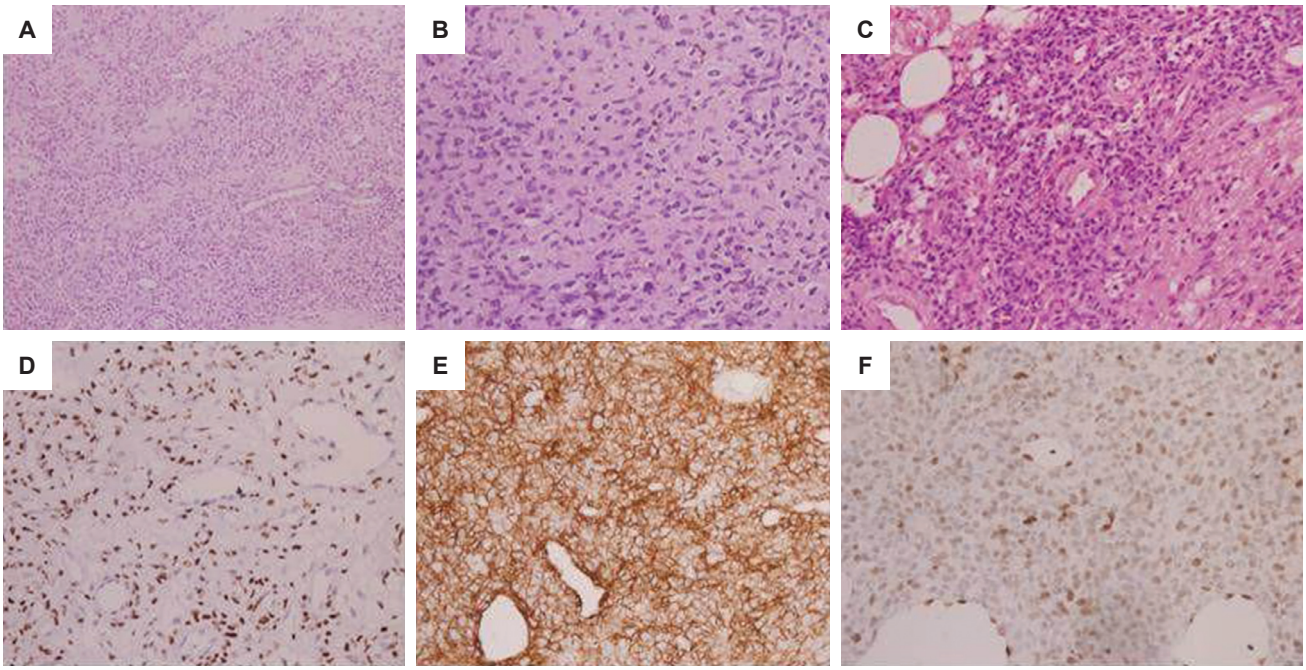

Figure 4. Histopathological and immunohistochemical features of the tumor. **(A–C)** Hematoxylin and eosin (H&E)–stained sections showing a patternless, cellular tumor composed of oval to spindle cells set in an eosinophilic, collagenous stroma with interspersed adipocytes, at increasing magnification. **(D)** Immunohistochemistry showing tumor positivity for ERG. **(E)** Immunohistochemistry showing tumor positivity for CD56. **(F)** Immunohistochemistry showing tumor positivity for SATb2.

DISCUSSION

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome, with reported incidence and prevalence of approximately 0.13 per 100,000 person-years and 0.70 per 100,000 individuals, respectively.[5] The fundamental biochemical abnormality underlying oncogenic osteomalacia is persistent hypophosphatemia secondary to phosphaturic mesenchymal tumor (PMT)-mediated overproduction of fibroblast growth factor-23 (FGF23).[6]

FGF23 exerts its biological effects by binding to the fibroblast growth factor receptor-1 (FGFR1)–Klotho (KL) receptor complex in the proximal convoluted tubules of the kidney.[7,8] This interaction suppresses the expression of sodium-phosphate cotransporters (NaPi-IIa and NaPi-IIc), resulting in renal phosphate wasting. Concurrently, FGF23 inhibits 1-alpha-hydroxylase activity, thereby reducing the synthesis of 1,25-dihydroxyvitamin D and impairing intestinal absorption of calcium and phosphate.[8] The combination of phosphaturia and impaired mineralization ultimately leads to osteomalacia.

Establishing the diagnosis of TIO requires objective documentation of renal phosphate wasting, typically by calculating the tubular maximum phosphate reabsorption per glomerular filtration rate (TmP/GFR), while excluding generalized proximal tubular dysfunction such as Fanconi syndrome.[9,10] In our patient, TmP/GFR was markedly reduced (0.6 mg/dL). The absence of glycosuria, proteinuria or metabolic acidosis confirms isolated phosphate wasting rather than global tubular dysfunction.

Beyond its systemic effects, FGF23–FGFR1 signalling also contributes to tumorigenesis in PMTs.[11] Approximately 60% of PMTs harbor a fibronectin-1 (FN1)–FGFR1 gene fusion, resulting in constitutive activation of the chimeric FN1-FGFR1 protein driven by strong promoters.[11] Autocrine and paracrine stimulation by tumor-derived FGF23 activates the mitogen-activated protein kinase (MAPK) pathway, promoting cellular proliferation and survival. Additional genetic alterations, including FN1–fibroblast growth factor-1 (FGF1) fusion, have been described in a subset of cases.[12] Although these molecular mechanisms provide insight into tumor biology, clinical recognition remains paramount for timely management.

Phosphaturic mesenchymal tumors are predominantly benign, with malignant transformation and distant metastasis reported rarely.[3,13,14] Histologically, they are composed of spindle to stellate cells derived from inducible skeletal stem cells, embedded within a myxoid or myxochondroid matrix with characteristic "grungy" calcifications and a distinctive intrinsic microvascular pattern. Osteoclast-like giant cells, mature adipocytes and lamellar bone formation may also be present. Tumor cells typically exhibit small nuclei, indistinct nucleoli and low mitotic activity. Immunohistochemically, SATB2 positivity reflects osteoblastic differentiation. Tumors frequently express CD56, SSTR2A, and ERG, while being negative for S100, STAT6, and DOG-1.[15] The histopathological and immunohistochemical features in our patient (Figure 4) were consistent with these established characteristics.

Two large systematic reviews comprising 1,979 reported cases have delineated the demographic and clinical profile of TIO.[16,17] Patients commonly experience prolonged diagnostic delay, often exceeding two years, largely due to nonspecific symptoms and the small, clinically occult nature of these tumors. Consistent with these observations, our patient had a symptom duration of more than two years and initially had no clinically detectable mass. Only after functional imaging localization was a small 3 × 3 cm subcutaneous lesion identified on focused re-examination. This underscores the importance of repeated, targeted physical examination guided by imaging findings.

Approximately 80% of TIO cases are attributable to benign PMTs.[16,17] Other reported etiologies include malignant PMT (1.7%), hemangiopericytoma (6.3%), giant cell tumor (1.8%), benign bone tumors (1.6%), bone sarcoma (0.9%), sinonasal hemangiopericytoma-like tumor or glomangiopericytoma (0.8%) and odontogenic tumor (0.8%). Raised FGF23 levels are documented in more than 95% of cases. In our patient, serum FGF23 was markedly elevated (507 pg/mL), and biochemical remission occurred promptly following tumor excision, further confirming the paraneoplastic mechanism.

Surgical resection remains the definitive treatment and is curative in approximately 97% of cases.[18] In our case, wide local excision resulted in normalization of serum phosphate levels, reduction in alkaline phosphatase and significant functional recovery at one-year follow-up, highlighting the reversibility of the metabolic derangement when the source of the excess FGF23 is removed. For unresectable tumors or persistent disease, alternative therapeutic options include radiotherapy, image-guided ablation, somatostatin analogs in OctreoScan-positive tumors and burosumab—a monoclonal antibody that targets FGF23 and prevents its interaction with the FGFR1/Klotho complex.[1,19] In selected cases not associated with elevated FGF23 or those refractory to definitive therapy, oral calcitriol and phosphate supplementation may be considered.[20] Importantly, serum phosphate should be maintained at the lower limit of normal to minimize the risk of secondary and tertiary hyperparathyroidism.[20]

Given that PMTs are frequently small and clinically inapparent, imaging plays a pivotal role in tumor localization. Although somatostatin receptor (SSTR) scintigraphy has been utilized, receptor expression is not entirely specific.[1] 99mTc-hydrazinonicotinamide (99mTc-HYNIC)-octreotide SPECT-CT has demonstrated sensitivity and specificity of 86.3% and 99.1%, respectively.[21] PET-based SSTR imaging modalities—including DOTATATE, DOTANOC, and DOTATOC—are increasingly preferred, with DOTATATE demonstrating higher affinity for SSTR2.[22]

In our patient, Ga-68 DOTANOC PET-CT successfully localized the lesion to the right proximal lower limb (Figure 2). Subsequent selective venous sampling (SVS) demonstrated markedly elevated FGF23 levels in the right femoral vein compared to contralateral and peripheral sites, thereby confirming laterality.[2,3] Fine-needle aspiration cytology was not performed to avoid potential tumor seeding.[1]

This case reinforces several clinically important principles. In patients presenting with chronic musculoskeletal pain, proximal muscle weakness and stress fractures accompanied by hypophosphatemia with normal calcium, vitamin D and parathyroid hormone levels, a structured and systematic evaluation is essential. Documentation of renal phosphate wasting through TmP/GFR calculation, assessment of FGF23 levels and timely functional imaging are critical steps in diagnosis. Early recognition and definitive surgical management can prevent prolonged morbidity and restore functional capacity, as observed in our patient.

CONCLUSION

Tumor-induced osteomalacia is a rare but treatable cause of severe disability, with phosphaturic mesenchymal tumor being the most common underlying etiology. Early recognition and surgical management can restore function and quality of life. Resection under regional anesthesia, as in our case, helped the patient return to his normal life. An accurate diagnosis is the key to a simple solution for a drastic morbidity.

Ethical Consideration
Patient consent forms were obtained before manuscript submission.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
RM: Conceptualization, Writing – original draft preparation, Investigation; **SKP:** Conceptualization, Writing – original draft preparation, Investigation; **BKS:** Conceptualization, Writing – original draft preparation, Investigation; **AK, SS, AND, MCS:** Conceptualization, Writing – review and editing; **VS:** Conceptualization, Writing – review and editing, Supervision.

Data Availability Statement
No datasets were generated or analyzed for this study.

Author Disclosure
The authors declared no conflict of interest.

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CASE REPORT

Adrenocortical Carcinoma with Suspected Dual Cortisol and Aldosterone Secretion: A Case Report

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Abstract

Adrenocortical carcinoma (ACC) is a rare malignancy, accounting for 0.05-2% of all malignant tumors. Most cases are sporadic and asymptomatic, often discovered incidentally via imaging. However, 50-60% present with autonomous hormonal secretion, with 45% producing excess cortisol, and only 1% exhibiting mineralocorticoid excess.

We report a 43-year-old Filipino female with a 6-month history of abdominal bloating, proximal muscle weakness, edema, and hypertension. Laboratory tests showed hypokalemia (serum potassium 2.5-3.05 mmol/L; normal 3.3-5.0 mmol/L). Imaging revealed a neoplastic right suprarenal mass (adrenal origin vs confluent lymphadenopathy) described as an incidental, lipid–poor right adrenal mass measuring 4.7 x 3.6 x 6.1 cm, with contrast-enhanced Hounsfield units of 40, along with periportal and paraaortic lymphadenopathies.

Biochemical evaluation indicated an intermediate probability of primary aldosteronism: suppressed plasma renin at 0.97 ug/L/hr (0.97 ng/mL/hr), normal plasma aldosterone 599.46 pmol/L (21.61 ng/dl), and aldosterone-renin ratio of 618 (pmol/L)/ (ng/L/hr) (22.27 ng/dl/ng/mL/hr). Ideally, confirmatory testing with an aldosterone suppression test prior to imaging and adrenal vein sampling (AVS) should be performed to lateralize the lesion before surgery; however, the patient opted to proceed with surgery. The patient also had overt hypercortisolism, with non-suppressed serum cortisol of 31.88 µg/dL (reference <1.8 µg/dL) on a low-dose dexamethasone suppression test, suppressed ACTH at 2.81 pg/mL (reference 7.7–63.6 pg/mL), and clinical features of Cushing syndrome, including facial plethora, and proximal muscle weakness. While these findings support the diagnosis of an ACTH-independent hypercortisolism, current guidelines recommend confirmatory testing, including 24-hour urinary free cortisol or late-night salivary cortisol, before definitive evaluation to distinguish ACTH-dependent from ACTH-independent disease. Concomitant catecholamine and androgen excess were excluded with normal 24-hour urine metanephrines and serum DHEAS.

Surgical removal via open adrenalectomy was performed. Histopathology confirmed ACC, supported by immunohistochemistry. Postoperative treatment included radiotherapy and planned adjuvant mitotane therapy. During follow-up, the patient's blood glucose and blood pressure worsened, requiring medication adjustments. Unfortunately, the patient succumbed to the disease seven months post-surgery.

This case highlights the difficulties in assessing adrenal tumors that concurrently secrete cortisol and aldosterone, especially when biochemical results are inconclusive, emphasizing the need for careful assessment and prompt intervention in this rare coexistence.

Key words: adrenocortical carcinoma, hyperaldosteronism, hypercortisolism

INTRODUCTION

Adrenocortical carcinomas (ACC) are rare and highly malignant tumors, accounting for less than 2% of all malignant cancers. Most adult cases are sporadic, with many patients remaining asymptomatic and diagnosed incidentally during imaging.[1] However, some patients present with symptoms caused by autonomous hormone secretion or local effects from an abdominal or adrenal mass. Typically, 50 to 60% of ACCs manifest as functioning adrenal tumors. Symptoms of excess cortisol are observed in 45% of cases, while signs of mineralocorticoid excess are much less common, affecting only about 1% of patients.

Dual hormone-secreting ACCs, producing both cortisol and aldosterone, are rare and pose diagnostic challenges, as biochemical abnormalities may overlap and must be interpreted in the context of clinical features. Current

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guideline-based evaluation of primary aldosteronism involves screening with measurement of the aldosterone–renin ratio followed by confirmatory suppression testing, and localization with imaging or adrenal vein sampling.[2] On the other hand, assessment of cortisol excess requires two concordantly abnormal findings on dexamethasone suppression testing, 24-hour urinary free cortisol, or late-night salivary cortisol, followed by further evaluation for its cause via ACTH measurement.[3]

The diagnosis of ACCs involves biochemical testing, followed by surgical resection and histopathologic confirmation. Adjuvant therapies, such as radiotherapy and mitotane, and regular monitoring for disease progression or recurrence are recommended. This report describes a rare case of adrenocortical carcinoma that initially presented with clinical and biochemical findings suggestive of cortisol excess and possible aldosterone co-secretion, although confirmatory testing for aldosterone was not performed, highlighting the challenges in evaluating dual hormone-secreting tumors.

CASE

A 43-year-old female with no known comorbidities presented with a six-month history of facial swelling, bilateral lower extremity weakness, and bipedal edema, along with generalized bloating that was relieved with rest. The patient had no history of medication use and denied smoking or alcohol consumption. A cardiology consultation was performed six months before admission, which revealed hypertriglyceridemia; she was started on fenofibrate 200 mg once daily and was highly compliant. Follow-up history showed persistent bipedal edema, bilateral lower extremity weakness, and abdominal bloating; therefore, a gastroenterology consult was arranged, and an EGD showed signs of gastritis from *Helicobacter pylori* infection. The patient was sent home with 40 mg pantoprazole once daily, clarithromycin twice daily, and amoxicillin three times daily for 10 days.

During follow-up, the patient reported persistent bipedal edema, bilateral lower extremity weakness, and abdominal bloating, now accompanied by elevated blood pressure and blood glucose levels. Blood pressure was controlled with valsartan 80 mg once daily. Workup showed hypokalemia (serum potassium 3.05 mmol/L) and hepatomegaly with severe fatty changes on whole abdomen ultrasound. The patient was subsequently started on furosemide 20 mg once daily and spironolactone 25 mg once daily, with a recommendation for an endocrinology consult to evaluate the elevated blood glucose.

During follow-up with the cardiology service, the patient continued to have persistent bilateral lower extremity weakness, bilateral lower extremity edema, and abdominal bloating. Additionally, the patient's persistently elevated blood pressure levels necessitated an adjustment of medication to valsartan/amlodipine 160/10 mg once daily, while spironolactone was maintained. A whole abdominal CT scan with triple contrast was subsequently performed to evaluate the persistent abdominal bloating. The results showed an enhancing right suprarenal mass measuring 4.7 x 3.6 x 6.1 cm, likely neoplastic (adrenal origin versus confluent lymphadenopathy), and periportal and para-aortic lymphadenopathies likely indicating metastasis. It was identified as a lipid-poor soft-tissue mass with contrast-enhanced Hounsfield units of 40. Heterogeneous enhancement, non-contrast Hounsfield units, contrast washout values, and neovascularization were not evaluated because an adrenal protocol was not conducted during the initial imaging. The patient was referred to the endocrinology service for further evaluation.

From an endocrinology perspective, the patient denied any episodes of diplopia, increased shoe or ring size, or headache. The patient had no complaints of increased perspiration, heat or cold intolerance, tremors, or changes in BM. The patient had no history of steroid use and denies any episodes of easy bruising but reports episodes of proximal muscle weakness and weight gain (56 kg to 67 kg within one month). Physical examination revealed moon facies, a dorsocervical fat pad, and no violaceous striae over the abdomen.

In the case of an incidentally discovered adrenal mass, hypertension, and hypokalemia (serum potassium levels between 2.5 and 3.05 mmol/L), workup for primary aldosteronism was performed after correcting serum potassium levels and discontinuing spironolactone. Plasma renin activity was at the lower end of the reference range at 0.97 ug/L/hr (0.97 ng/mL/hr), while plasma aldosterone was 599.46 pmol/L (21.61 ng/dL). The aldosterone-renin ratio was elevated to 618 (pmol/L)/(ng/L/hr) (22.27 ng/dL/ng/mL/hr); therefore, it was considered a positive screening test for primary aldosteronism. Given these findings, the patient has an intermediate likelihood of primary aldosteronism. Ideally, confirmatory aldosterone suppression testing should be performed before adrenal computed tomography and adrenal venous sampling (AVS) to determine lateralization prior to surgical intervention in patients over 35 years old.[2] In this case, aldosterone suppression testing was recommended but not performed due to financial constraints, as the patient chose to proceed with surgery instead. Nevertheless, although AVS was discussed as part of the ideal guideline-directed workup for primary aldosteronism, proceeding with definitive surgical management was ultimately deemed more clinically appropriate than pursuing AVS for localization, given the clinical findings and radiographic features suggestive of adrenocortical carcinoma with possible nodal metastases.

In line with this, an important consideration in the diagnostic workup was to first rule out potentially life-threatening conditions, such as pheochromocytoma, prior to surgery, followed by optimizing blood pressure and metabolic control, and correcting hypokalemia before definitive intervention. Additional biochemical workup

Table 1. Biochemical testing results

Laboratory test	Result	Reference range
Plasma aldosterone	599.46 pmol/L (21.61 ng/dl)	111 – 860 pmol/L (4 – 31 ng/dl)
Plasma renin activity	0.97 ug/L/hr (0.97 ng/ml/hr)	0.39-3.94 ng/L/hr (0.39-3.94 ng/ml/hr)
Aldosterone – Renin ratio	618 pmol/L per ng/L/hr (22.27 ng/dl/ng/mL/hr)	<554 pmol/L per ng/L/hr (<20 ng/dl/ng/mL/hr)
Serum cortisol (1 mg dexamethasone suppression test)	31.88 mcg/dl	<1.8 mcg/dl
Serum ACTH	2.81 pg/ml	7.2-63.6 pg/ml
Dehydroepiandrosterone sulfate (DHEAS)	0.44 mg/L	0.27 – 2.4 mg/l
TSH	0.196 uIU/ml	0.27-4.20 uIU/ml
FT4	13.10	12-22 pmol/L
HbA1c	9.3%	
24-hour urine metanephrines	0.23 mg/ 24 hrs	0 – 1 mg/ 24 hours

was therefore performed, including evaluation for cortisol excess and pheochromocytoma. Catecholamine and androgen excess were ruled out with normal 24-hour urine metanephrines and DHEAS levels — 0.23 mg/24 hours and 0.44 mg/L, respectively. Serum cortisol after a low-dose dexamethasone suppression test was not suppressed (31.88 mcg/dL), and ACTH levels were 2.81 pg/mL, suggesting ACTH-independent Cushing syndrome secondary to an adrenal mass. Similarly, guideline recommendations for additional workup, including 24-hour urinary free cortisol or late-night salivary cortisol, were not performed before definitive evaluation to distinguish ACTH-dependent from ACTH-independent disease, as the patient opted to proceed with surgical management instead.[3]

The patient was subsequently referred to the urology service for eventual adrenalectomy. Clearances from cardiology and endocrinology were obtained, showing normal levels of creatinine, serum sodium, serum ionized calcium, and complete blood count. The 12-lead ECG indicated cardiomegaly. However, based on Simpson's criteria, 2D echocardiography results were within normal limits, with an ejection fraction of 71%.

The patient then underwent an open adrenalectomy, revealing the following intraoperative findings: a right adrenal mass measuring 6 cm adherent to the inferior vena cava, the superior pole of the kidney, the inferior surface of the liver, and the portal vein. The right adrenal mass was dissected from these structures, and 19 lymph nodes attached to the inferior vena cava were also removed. Histopathologic evaluation of the adrenal tumor under light microscopy demonstrated features consistent with a Weiss score of 3, indicating malignant behavior. Immunohistochemical studies showed a Ki-67 index of 30%, suggesting high proliferative activity. Additionally, the tumor was confirmed as adrenal cortical carcinoma through additional stains (calretinin and inhibin) (Figure 1). Given the malignant histopathologic features and elevated proliferative index, adjuvant therapy was recommended to lower the risk of recurrence and enhance disease management. The patient underwent 25 radiotherapy sessions, which were well tolerated. An oncology consultation was performed, and the patient was advised to undergo chemotherapy with mitotane. Postoperatively, there was early improvement in blood pressure and glucose control, along with reduced signs and symptoms of hypercortisolism. The patient was instructed to follow up regularly to monitor for tumor recurrence but was lost to follow-up. During subsequent visits, the patient's blood glucose and blood pressure increased, requiring medication adjustments. Unfortunately, the patient succumbed to the disease seven months after surgery.

DISCUSSION

Adrenocortical carcinoma (ACC) is a rare cancer occurring at a rate of 0.5-2 cases per million people per year, with the highest incidence between ages 40 and 60, primarily affecting women.[4] ACC typically presents as a functioning adrenal tumor in 50-60% of cases. Most patients exhibit symptoms of hypercortisolism, accounting for 45% of cases, while only 1% of the tumors produce aldosterone. The patient denied any episodes of easy bruising but reported proximal muscle weakness, weight gain (from 56 kg to 67 kg in 1 month), along with physical signs like moon facies, dorsocervical fat pad, and bipedal edema, which indicate hypercortisolism from Cushing Syndrome. Additionally, the combination of hypertension and hypokalemia in the presence of a unilateral adrenal mass should prompt evaluation for mineralocorticoid excess.

The diagnosis of ACC involves a combination of clinical, biochemical, and radiological assessments. A comprehensive hormonal workup is essential, as it can serve as a marker for tumor recurrence and help evaluate the patient's clinical features. Additionally, this workup aids in preoperative, intraoperative, and postoperative assessments.[5] The absence of autonomous steroid secretion decreases the likelihood that an adrenal mass is an adrenocortical cancer.[5]

Autonomous hormone co-secretion has emerged as a recurring feature in published case reports of ACC, highlighting the importance of thorough biochemical assessment in all patients with adrenal masses. Previous reports also suggest that cortisol-producing ACCs are associated with poorer clinical outcomes than nonfunctioning tumors, possibly due to the metabolic derangements and immunosuppressive effects of hypercortisolism.[6,7] A multivariate analysis from a study evaluating the prognostic

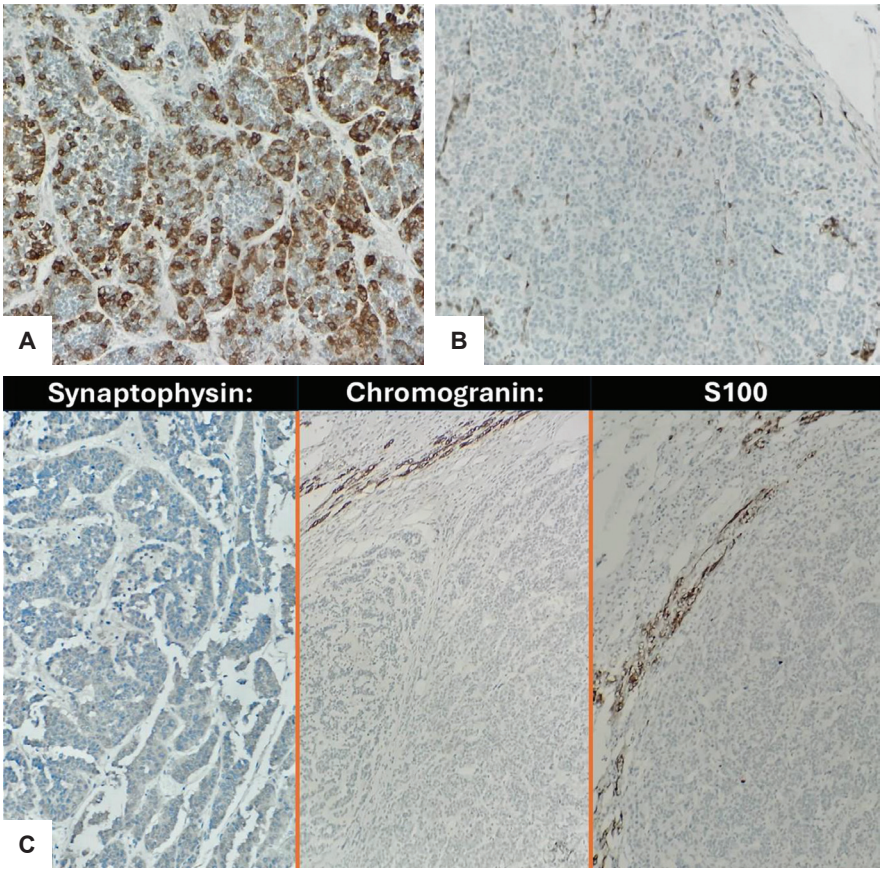

Figure 1. Immunohistochemical staining on low power magnification with inhibin, calretinin, synaptophysin, chromogranin and S100 to support the diagnosis. **(A)** Staining with inhibin shows positive membranous staining in the tumor cells. **(B)** Immunohistochemical staining with calretinin shows focal positive cytoplasmic staining in the tumor cells. **(C)** Immunohistochemical staining for synaptophysin, chromogranin and s100 all show negative findings.

role of overt hypercortisolism in completely operated ACC demonstrated that patients with hypercortisolism had decreased recurrence-free survival and overall survival, even after adjustment for established prognostic factors, including age, sex, tumor stage, and tumor size.[1,7] These findings further support that hypercortisolism is associated with a more aggressive behavior. As previously discussed, hormonal workup also aids in preoperative assessment. In this case, identifying hypercortisolism was crucial for anticipating and managing postoperative adrenal insufficiency, a potentially life-threatening complication.[5,6]

In contrast, the prognostic impact of concomitant aldosterone secretion remains uncertain because of the limited number of reported cases.[6]

Reported cases of aldosterone and cortisol co-secretion demonstrate a consistent biochemical profile characterized by hypokalemia, suppressed renin, elevated aldosterone levels, and non-suppressed cortisol.[5,8] Clinically, patients often initially present with abdominal pain or symptoms attributable to mass effect or hormone excess.[9] Additionally, most of the reported cases involved adrenal lesions measuring >5 cm, with a range of 6-22 cm, similar to the case of our patient.[8,9]

In this patient's case, plasma renin activity was suppressed below 1 ng/ml/hour, with a normal plasma aldosterone concentration of 599.46 pmol/L (21.61 ng/dl), and an elevated aldosterone-renin ratio of 618 (pmol/L)/ (ng/L/hr) (22.27 ng/dl/ng/mL/hr) indicating a positive screening for primary aldosteronism.[2] Following the 2025 clinical practice guideline of the Endocrine Society on primary aldosteronism, confirmatory aldosterone suppression testing is recommended in patients with intermediate probability prior to subtype classification. If confirmatory testing is positive, adrenal computed tomography followed by adrenal venous sampling (AVS) is advised to establish lateralization before surgical intervention, particularly in patients older than 35 years, given the limited reliability of imaging alone in distinguishing unilateral adenoma from bilateral adrenal hyperplasia.[2] However, testing was not done due to financial constraints; also, the patient was willing and was able to undergo surgery instead. Conversely, cortisol hypersecretion was evident, with non-suppressed cortisol levels at 31.88 mg/dl after a 1 mg dexamethasone suppression test. A low ACTH level of 2.81 pg/ml suggests an ACTH-independent hypercortisolism. Although the patient had a non-suppressed cortisol level after the 1 mg dexamethasone suppression test and an adrenal mass, she did not meet criteria for mild autonomous cortisol secretion (MACS), as she exhibited overt clinical features consistent with Cushing syndrome, indicating clinically significant hypercortisolism rather than subclinical disease.[8,10] Exclusion of pheochromocytoma before surgery is warranted, as preoperative preparation is necessary among patients with catecholamine excess.[5] The patient had normal 24-hour urine metanephrines; therefore, pheochromocytoma was not considered. Testing for adrenal androgen excess,

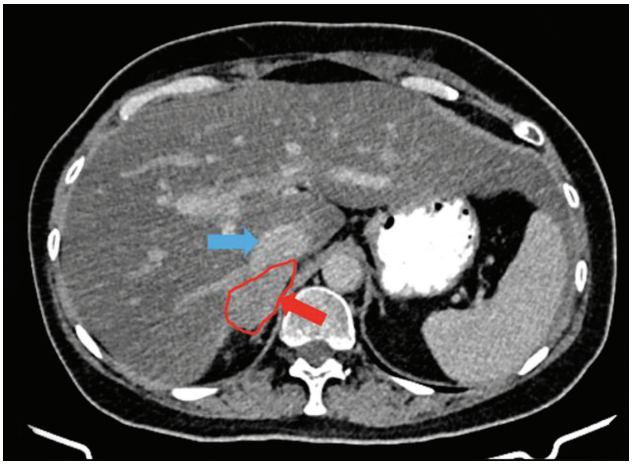

Figure 2. Axial contrast-enhanced CT image of the abdomen demonstrating a 4.7 × 3.6 × 6.1 cm enhancing right adrenal mass *(red arrow)* with post-contrast attenuation of 40 HU, consistent with a lipid-poor lesion. The mass abuts hepatic segments VI and VII and compresses the inferior vena cava *(blue arrow)*. The size (>4 cm) and imaging characteristics are suspicious for malignancy; the patient was subsequently diagnosed with adrenocortical carcinoma with suspected aldosterone and cortisol co-secretion.

for which the patient showed normal findings, was also performed since mixed cortisol and androgen secretion is highly suggestive of malignancy.[11]

The biochemical diagnosis is supported by imaging to differentiate between adrenal adenoma, adrenocortical carcinoma, pheochromocytoma, and metastatic lesions.[8] The patient was evaluated with an enhancing right suprarenal soft tissue and lipid-poor mass, measuring 4.7 x 3.6 x 6.1 cm, with Hounsfield units of 40, along with periportal and paraaortic lymphadenopathies that are likely indicative of metastasis (Figure 2). In this context, features suggestive of adrenal malignancy included a size of 4-6 cm and contrast-enhanced Hounsfield units greater than 10.[12] Heterogeneous enhancement, non-contrast Hounsfield units, contrast washout values, and neovascularization were not assessed, as an adrenal protocol was not performed during the initial imaging.

Given the high suspicion of adrenocortical carcinoma, based on a florid presentation of endocrine-related symptoms developing over six months and the onset of new metabolic comorbidities, including hypertension and Type 2 Diabetes Mellitus, along with imaging characteristics and tumor size suggestive of malignancy, an open adrenalectomy was performed to achieve complete tumor removal despite an indeterminate biochemical workup. Postoperative TNM staging is crucial for prognosis and evaluating treatment options.[1,8] In this case, the right adrenal mass was only partially resected due to its size; however, 19 locoregional lymph nodes were retrieved, categorizing it as TNM Stage III, with complete resection as the ideal treatment. Patients with advanced adrenal carcinomas may also show vascular invasion, primarily into the renal vein and inferior vena cava.[8] Grossly, ACC lesions are typically large and heterogeneous, often appearing brown, orange, or yellow due to their lipid content.

Histopathologic examination of the specimen after surgery confirms the diagnosis of ACC. The Weiss scoring system is also utilized, based on the identification of morphologic parameters under light microscopy. It classifies tumors based on morphologic and cytologic features and invasive properties.[13] The presence of three or more criteria from the Weiss score, including the following, strongly indicates malignant behavior: atypical mitoses (>33% of the tumor), capsular invasion, necrosis, and venous or sinusoidal invasion.[5,14] Histopathologic evaluation of the patient's tumor fulfilled three of the following criteria from the Weiss score, namely: atypical mitotic figures, suspicious capsule infiltration, and a diffuse architecture of more than 33% of the tumor characterized by atypical cuboidal to rounded cells arranged in nests visible at low magnification – corresponding to a Weiss score of 3 (Figure 3).

Furthermore, immunohistochemical stains play a role in differentiating primary adrenocortical tumors from non-adrenocortical tumors.[1,8] Immunohistochemical staining for the confirmation of dual secretion of aldosterone and cortisol was not conducted, as available resources were allocated towards investigations aimed at establishing the diagnosis of adrenocortical carcinoma. The immunohistochemical staining supportive of adrenocortical carcinoma diagnosis was positive, indicated by calretinin and inhibin. According to a 2022 study by Jorda et al., the mere detection of inhibin and calretinin alone does not provide sufficient sensitivity for diagnosing adrenocortical tumors, with sensitivities of 70% and 73%, respectively. However, the combined use of these two antigens enhances sensitivity to 94%.[15] Additional stains, including S100, Synaptophysin, and Chromogranin, which are markers for neuroendocrine tumors, were negative, ruling out pheochromocytoma (Figure 1).[5]

Postoperatively, prognosis is classified according to TNM ENSAT staging or GRAS criteria.[16,17] The TNM staging is evaluated both before and after surgery, with stage 1 defined as a localized adrenal tumor less than 5 cm in size, stage 2 as a localized tumor larger than 5 cm, stage 3 as a tumor invading the surrounding adipose tissue, adjacent organs, renal vein, or vena cava regardless of lymph node involvement, and finally, stage 4 as the presence of distant metastases regardless of tumor size and lymph node status.[1,15] The patient was classified as stage 3, which correlates with a 5-year survival rate of 19-54%.[16,18]

The GRAS criteria include four prognostic factors that independently predict relapse and overall survival: grade (Weiss scoring or Ki-67), primary resection status, patient's age, and presence of secretory syndrome. Resection status is classified as R0 (microscopically complete), R1 (microscopically incomplete), R2 (macroscopically incomplete), or Rx when unknown.[16] The adrenal lesion

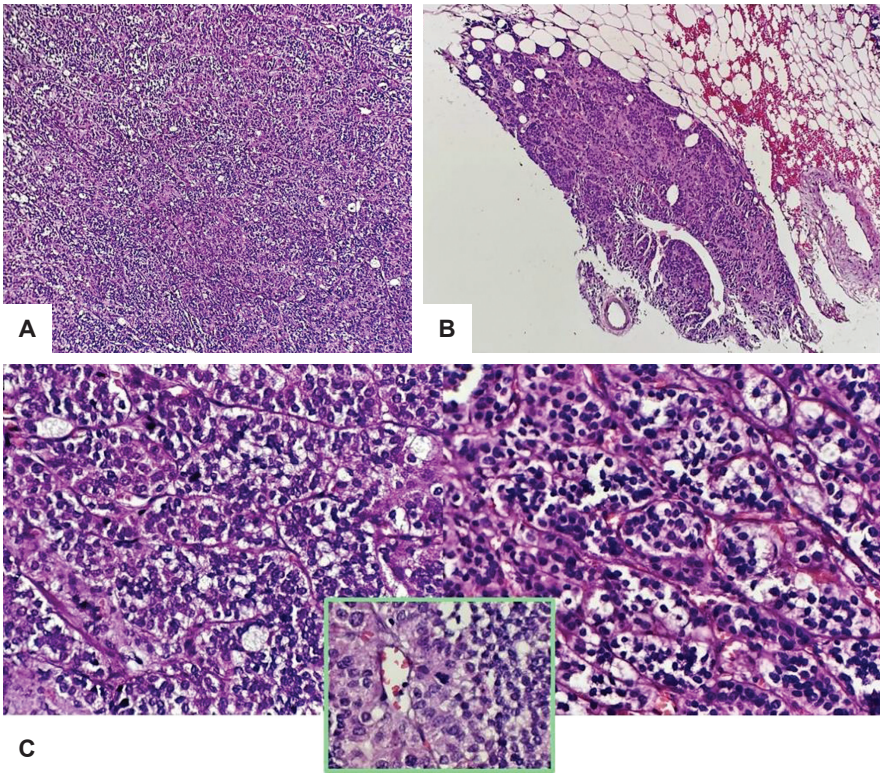

Figure 3. Histopathologic evaluation of the right adrenal gland. **(A)** Low power magnification of the adrenal mass shows atypical cuboidal to round cells disposed in nests (H&E, 10x). **(B)** Atypical cells are seen infiltrating into the peri-adrenal fat in other microsections (H&E, 10x). **(C)** High power magnification of the adrenal mass shows that the mildly pleomorphic, atypical cells have vesicular, hyperchromatic nuclei, some with prominent nucleoli. These atypical cells have moderate eosinophilic, granular to clear cytoplasm. Also noted in the picture insert is an atypical mitosis (H&E, 40x).

in our patient was incompletely resected, classified as R2, with an overall 5-year survival rate of 13%. The grade is determined by Ki-67 immunohistochemistry, which assesses cell proliferation; scores exceeding 10% indicate a poor prognosis, higher recurrence risk, and rapid disease progression.[8,16] The patient's Ki-67 was 30%, showing high proliferation and locally advanced ACC, which suggests a decreased overall survival. Due to the variable 5-year survival rates after resection, adjuvant therapy, radiotherapy, and mitotane were recommended, along with follow-up using cross-sectional imaging of the chest, abdomen, and pelvis to detect any new lesions, recurrence, or disease progression.

The patient completed 25 radiotherapy sessions without complications and was advised to start mitotane therapy; however, she was lost to follow-up. Her blood glucose and blood pressure levels rose during treatment, requiring medication adjustments. Seven months postoperatively, the patient died from the disease.

CONCLUSION

Adrenocortical carcinoma is a rare malignancy, with 50-60% of cases initially presenting as hypercortisolism and 1% exhibiting mineralocorticoid excess. To confirm the diagnosis, a detailed history, physical exam, and biochemical and imaging tests are essential in managing adrenocortical carcinoma. Symptoms can result from excess hormone production. Uncontrolled hypertension and hypokalemia should prompt evaluation for primary aldosteronism. Conversely, signs of excess cortisol, such as moon facies, dorsocervical fat pad, weight gain, and proximal muscle weakness, warrant assessment for Cushing syndrome. Features suggestive of malignancy in adrenal masses include tumor growth over 4-6 cm, neovascularization, heterogeneous enhancement with >20 HU, and invasion into nearby structures.

In this case, there was diagnostic uncertainty, as biochemical findings were indeterminate and limited resources precluded further confirmatory testing or additional pathologic evaluation to establish hormonal co-secretion definitively. This represents a limitation in fully characterizing the tumor's functional status. Nevertheless, given the florid clinical presentation, clear signs of hormone excess, and radiologic features worrisome for malignancy, the decision was made to proceed with complete surgical excision of the adrenal mass. Postoperative histopathologic examination remains essential for definitive diagnosis and prognostication. Subsequent management may include adjuvant therapies, such as mitotane or radiotherapy, along with regular monitoring for recurrence as clinically indicated.

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Ethical Consideration
Patient consent forms were obtained before manuscript submission.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

CFIJ: Conceptualization, Methodology, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **FRCG:** Conceptualization, Methodology, Investigation, Resources, Writing – review and editing, Visualization, Supervision, Project administration.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

VIPoma Presenting With Obstructive Jaundice: A Case Report

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Abstract

VIPoma is a rare pancreatic neuroendocrine tumor characterized by the overproduction of vasoactive intestinal peptide (VIP), typically manifesting as watery diarrhea, hypokalaemia and metabolic acidosis. Its presentation can be atypical, complicating diagnosis. We report the case of a 30-year-old male who initially presented with obstructive jaundice and fatigue, with imaging revealing a pancreatic head mass and liver metastases. Histopathological analysis confirmed a low-grade pancreatic neuroendocrine tumor. The clinical course was complicated by portal vein thrombosis and metastatic spread. Six months later, the patient developed persistent, refractory watery diarrhea with associated hypokalaemia. Elevated serum VIP levels and Gallium-68 DOTATATE positron-emission tomography and computed tomography (PET-CT) supported the diagnosis of VIPoma. Symptom resolution was achieved with subcutaneous octreotide, followed by transition to monthly long-acting release (LAR) octreotide. Approximately 60% of VIPoma cases are metastatic at the time of diagnosis, as demonstrated in this patient. The case highlighted the diagnostic challenges of VIPoma in the presence of atypical symptoms such as jaundice and absence of initial diarrhea. It also underscores the need for close multidisciplinary collaboration to determine the best course of action and to optimize patient outcomes.

Key words: VIPoma, diarrhea, pancreatic neuroendocrine tumor

INTRODUCTION

VIPoma is a rare neuroendocrine tumor (NET) that arises primarily in the pancreas but may also occur elsewhere in the gastrointestinal tract. It is most frequently associated with Verner-Morrison syndrome, characterized by the triad of profuse watery diarrhea, hypokalaemia and metabolic acidosis resulting from the overproduction of vasoactive intestinal peptide (VIP).[1] Although chronic diarrhea is the hallmark manifestation, presentation may be subtle or atypical, creating a diagnostic challenge.

We report a 30-year-old male who initially presented with obstructive jaundice and fatigue, suggestive of a primary hepatobiliary or gastrointestinal pathology. However, further investigation revealed a pancreatic mass, which was subsequently diagnosed as a VIP-secreting neuroendocrine tumor. His course was complicated by liver metastases and portal vein thrombosis. The case highlights the importance of a comprehensive diagnostic approach, including advanced imaging modalities and biochemical testing in patients with atypical presentations of pancreatic NETs. Early recognition and intervention in these complex cases significantly influence therapeutic strategies and patient prognosis.

CASE

A 30-year-old male presented with a 1-week history of progressive jaundice accompanied by dark-colored urine and pale stools. He denied any history of abdominal pain, nausea, or vomiting. He had no recent travel, alcohol use, or known liver disease, and his medical history was otherwise unremarkable. Laboratory results showed cholestatic jaundice (Table 1).

Hepatobiliary ultrasonography showed a well-defined hypoechoic lesion at the periportal region measuring 3.9 x 4.9 x 4.0 cm, with dilatation of the common bile duct and bilateral intrahepatic ducts. Computed tomography (CT) scan showed a suspected pancreatic carcinoma causing biliary obstruction, with abdominal lymph node and liver metastasis and portal vein thrombosis (Figure 1). Endoscopic ultrasound of the pancreas showed a hypoechoic lesion at the head of pancreas measuring 38 x 35 mm, causing upstream dilatation of the pancreatic duct and common bile duct. Endoscopic retrograde cholangio-pancreatography (ERCP) with sphincterotomy and metal stenting was performed. Fine-needle biopsy demonstrated a low grade neuroendocrine tumor with mitosis rarely seen and a Ki67 index of 1% - 2% (Figure 2). The patient was referred to oncology to discuss further management but was lost to follow-up.

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Table 1. Summary of investigations during first presentation

Investigations	Results	Unit	Normal range
Renal profile			
Urea	2.4	mmol/L	3.2-8.2
Creatinine	57	mmol/L	49-90
Sodium	136	mmol/L	136-145
Potassium	4.2	mmol/L	3.4-4.5
Calcium	2.4	mmol/L	1.5-3.0
Phosphate	0.9	mmol/L	0.8-1.7
Magnesium	1.0	mmol/L	0.66-1.07
Chloride	103	mmol/L	98-107
Liver function tests			
Total bilirubin	277.9	µmol/L	3-19
Direct bilirubin	205	µmol/L	0-5
Alkaline phosphatase	742	U/L	46-116
Gamma-glutamyl transferase	612	U/L	12-73
Alanine transaminase	69	U/L	10-49
Aspartate transaminase	51	U/L	0-34
Albumin	50	g/L	32-48
Tumor markers			
Carbohydrate Antigen 19.9 (CA19.9)	4.0	U/mL	0-37
Carcinoembryonic Antigen (CEA)	1.0	ng/mL	<5

Table 2. Summary of investigations during second admission

Investigations	Results	Unit	Normal range
Renal profile			
Urea	4.1	mmolL	3.2-8.2
Creatinine	74	mmol/L	49-90
Sodium	144	mmol/L	136-145
Potassium	1.5	mmol/L	3.4-4.5
Calcium	2.3	mmol/L	1.5-3.0
Phosphate	0.8	mmol/L	0.8-1.7
Magnesium	1.0	mmol/L	0.66-1.07
Chloride	108	mmol/L	98-107
Liver function tests			
Total bilirubin	19.4	µmol/L	3-19
Alkaline phosphatase	126	U/L	46-116
Alanine transaminase	15	U/L	10-49
Aspartate transaminase	27	U/L	0-34
Others			
Serum VIP	211	pg/mL	<86
24-hour urine 5 HIAA	12.96	µmol/L/day	3.66-42.89
Serum chromogranin A	96	ug/L	<101
Stool Ova and cyst	Negative		
Stool culture and sensitivity	No growth		

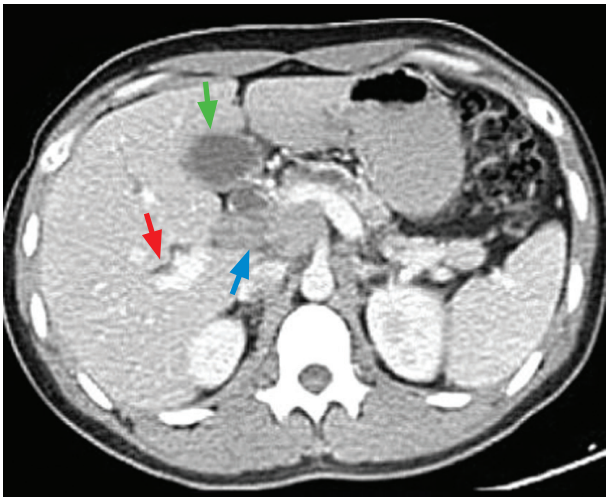

Figure 1. CT abdomen showed an ill-defined hypodense mass at pancreatic head measuring about 3.0 x 3.5 x 4.2 cm *(blue arrow)* with distended gallbladder *(green arrow)* and dilated intrahepatic duct *(red arrow)*.

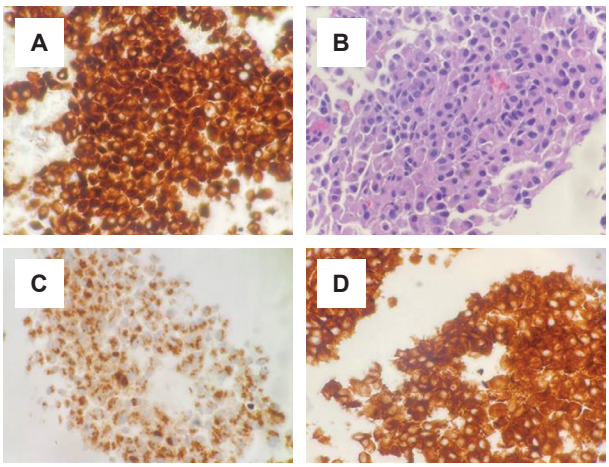

Figure 2. FNB head of pancreas: Scanty tumor tissue with neuroendocrine differentiation **(A)** cytokeratin stain (ck ae1/ae3, 400x); **(B)** H&E stain (400x); **(C)** Chromogranin A stain (400x); **(D)** Synaptophysin stain (400x).

Six months later, he was readmitted with a 2-week history of diarrhea. He reported frequent episodes of watery stools (5-6 times a day) over the past week, accompanied by muscle weakness, fatigue, and unintentional weight loss of approximately 8 kg over the past month. His diarrhea was continuous and had worsened over the past several days. He denied fever, abdominal pain, or intake of any new medications. On examination, he was mildly dehydrated, with dry mucous membranes and a reduced skin turgor. There was mild epigastric tenderness but no palpable masses.

Laboratory testing showed resolution of cholestasis but severe refractory hypokalaemia despite 3 days of intravenous potassium replacement (Table 2). There were normal calcium levels and a mildly elevated chloride level which is atypical as VIPomas are often associated with hypochloraemia due to bicarbonate loss. Stool studies excluded infectious causes, and 24-hour urine 5-hydroxyindoleaceticacid (5-HIAA) was normal. Following endocrinology referral, subcutaneous octreotide was initiated and titrated up to 100 mcg thrice a day, resulting in resolution of symptoms and hypokalaemia within 24 hours.

A fasting serum VIP sample obtained before treatment was elevated at 211 pg/mL (normal range <86 pg/mL). PET-CT with Gallium-68 DOTATATE showed a large focal DOTA-octreotide uptake over an ill-defined hypodense lesion at the pancreatic head and portal hepatic lymph node (maximum standardized uptake value, 19.09) measuring 3.34 x 3.06 x 5.51 cm with multifocal uptake in abdomino-pelvic lymph nodes and both hepatic lobes (Figure 3). In the setting of watery diarrhea, hypokalaemia, elevated VIP level, the PET CT results supported the diagnosis of VIPoma.

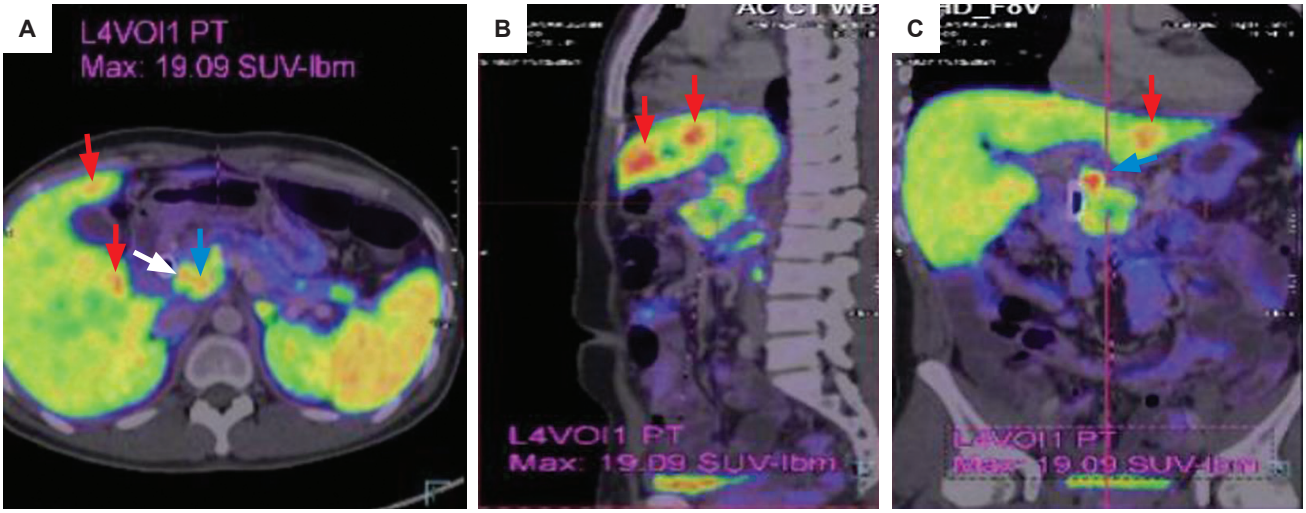

Figure 3. Gallium-68 DOTATATE PET-CT images show somatostatin receptor–expressing lesions: **(A)** adjacent porta hepatis lymph nodes *(white arrows)*; **(A, B and C)** multiple lesions in both hepatic lobes *(red arrows)*; and **(A and C)** a large focal lesion in the pancreatic head *(blue arrow)*.

He was then transitioned to long-acting release (LAR) octreotide 20 mg monthly, with an overlap period for symptom control. A multidisciplinary team comprising hepatobiliary surgeons, oncologists, and endocrinologists concluded that curative surgery was not feasible due to metastases and vascular involvement. He remains clinically stable and asymptomatic on octreotide LAR, at subsequent clinic visits and reports satisfaction with the current treatment outcome.

DISCUSSION

VIPoma, a rare pancreatic neuroendocrine tumor (pNET), presents a diagnostic challenge due to its often atypical and subtle clinical presentation. The classic syndrome associated with VIPoma, Verner-Morrison syndrome, is characterized by severe watery diarrhea, hypokalaemia, and metabolic acidosis caused by the excessive secretion of vasoactive intestinal peptide (VIP).[1] Symptoms at diagnosis are often varied and dependent in part on the site of tumors and also on whether the tumors are functioning in nature, which may cause significant delays in diagnosis.[2]

A recent systematic review of 65 patients with VIPoma reported that watery diarrhea was present in only 54.5% of cases at initial presentation, indicating that a substantial proportion of patients may lack the classic symptoms early in the disease course.[3] Furthermore, despite advanced disease, our patient's serum vasoactive intestinal peptide (VIP) concentration was only modestly elevated at 211 pg/mL when diarrhea developed, compared with the median serum VIP level of 636 pg/mL reported in the systematic review.[3] It is therefore plausible that the patient's VIP concentration was even lower at initial presentation and below the threshold required to induce clinically significant secretory diarrhea. The subsequent onset of diarrhea may have reflected progressive tumor growth and/or increased hormonal secretory activity over time. Although serial VIP measurements were unavailable to confirm this hypothesis, this explanation is consistent with the patient's clinical course and highlights the potential variability in the timing and severity of symptom development in VIPoma.

In approximately 60 to 80% of all VIPoma cases described to date, the patient presented with metastases at the initial VIPoma diagnosis.[4] The propensity for early metastasis underscores the importance of careful staging and imaging techniques. The metastases most commonly occur in the liver, lymph nodes, bones, and kidney.[5] Additionally, the presence of portal vein thrombosis in advanced cases can significantly complicate the clinical picture, leading to further diagnostic uncertainty. Portal vein involvement may contribute to worsening prognosis by causing portal hypertension, gastrointestinal bleeding, and ascites.[6]

Radiologic imaging plays a critical role in both the diagnosis and management of VIPomas.[7] Somatostatin receptor scintigraphy (SRS), a sensitive imaging modality for neuroendocrine tumors, has become a cornerstone in localizing the primary tumor and identifying metastatic sites.[8] Somatostatin analogues, such as octreotide, bind to the somatostatin receptors on the tumor cells, allowing for detailed visualization of the tumor's location and metastatic spread. In combination with computed tomography and magnetic resonance imaging, these imaging modalities offer a comprehensive assessment of the tumor's extent, guiding both surgical and non-surgical treatment strategies. In this case, somatostatin receptor scintigraphy confirmed the presence of a pancreatic mass and liver metastases, confirming the diagnosis of a metastatic VIPoma.

Surgical resection remains the mainstay of therapy for localized VIPomas.[9] However, metastatic disease requires a multidisciplinary approach. Somatostatin analogues, particularly octreotide, effectively control diarrhea and electrolyte disturbances by inhibiting VIP secretion, which

can improve the quality of life in patients with advanced disease.[10] Octreotide has also been shown to reduce tumor burden in some cases. Long-acting formulations of octreotide provide sustained symptom relief and improve treatment adherence, making them a preferred treatment option for many patients.

Overall, the diagnosis and management of VIPomas require a high degree of clinical suspicion, especially in patients with atypical presentations. Elevated serum VIP levels, in conjunction with imaging techniques such as somatostatin receptor scintigraphy, are crucial for confirming the diagnosis and guiding treatment decisions. Early diagnosis, combined with appropriate imaging and treatment, can dramatically enhance patient outcomes and quality of life.

CONCLUSION

This case illustrates VIPoma presenting with obstructive jaundice prior to the usual presentation of watery diarrhea and hypokalaemia. The delayed onset of diarrhea reinforces the need to consider functioning NETs in patients with pancreatic masses, even when characteristic symptoms are initially absent.

Management can be additionally challenging with metastatic disease. A multidisciplinary approach is essential to optimize care and therapeutic decision-making.

Ethical Consideration
Patient's consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
SYN: Conceptualization, Writing – original draft preparation, Visualization, Project administration; **KSC:** Conceptualization, Writing – review and editing, Visualization, Supervision.

Data Availability Statement
No datasets were generated or analyzed for this study.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Recurrent Syncope, Behavioral Changes and Weight Gain in an Elderly Filipino Woman: Successful Diagnosis and Management of Insulinoma With 13-Year Disease-Free Follow-up

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Abstract

Recurrent syncope and behavioral changes in the older population may suggest several disease entities associated with aging. Hypoglycemia is an often-missed potentially correctable underlying cause that should also be considered in the differential diagnosis. We present a case of a 62-year-old Filipino female who presented with recurrent syncopal attacks, behavioral changes and unintentional weight gain, associated with endogenous hyperinsulinemic hypoglycemia with no pancreatic mass seen on abdominal CT scan. A pancreatic head tumor was visualized through endoscopic ultrasound. Surgical removal of the mass resulted in resolution of her symptoms and restoration of her physical and functional well-being. This case is being reported to highlight that surgery cured her of the disease and she remains asymptomatic and well 13 years after her surgery.

Key words: hypoglycemia, insulinoma, pancreatic neoplasms, weight gain, syncope, blood glucose

INTRODUCTION

Recurrent syncope and behavioral changes in the older population may suggest several disease entities associated with aging. The most common of which are cerebrovascular diseases, complex seizures, Alzheimer's disease, and psychiatric illnesses among others. However, metabolic disorders which are potentially correctible underlying causes should also be considered in the differential diagnosis. Non-visualization of a pancreatic tumor on routine imaging should not deter the physician from doing extensive evaluation of a patient with high index of clinical suspicion. Definitive management of insulinoma may significantly improve the quality of life of the patient.

CASE

Recurrent syncope and behavioral changes in the older population may suggest several disease entities associated with aging. The most common of which are cerebrovascular diseases, complex seizures, Alzheimer's disease, and psychiatric illnesses. However, metabolic disorders which are potentially correctible underlying causes should also be considered in the differential diagnosis. Non-visualization of a pancreatic tumor on routine imaging should not deter the physician from doing extensive evaluation of a patient with high index of clinical suspicion. Definitive management of insulinoma may significantly improve the quality of life of the patient.

Clinical presentation

A 62-year-old Filipino female presented with light-headedness which later progressed to unresponsiveness. She had a history of recurrent dizziness for 5 years, relieved with food intake. It was associated with episodes of behavioral changes described as blank stares, inability to recognize family members, and repetitive washing or folding of clothes.

She had 3 similar episodes for the past 5 years all associated with low capillary blood glucose (CBG) (lowest level was 1.5 mmol/L), responsive to intravenous glucose infusion. Subsequent investigation done 3 months ago showed a low CBG at 1.5 mmol/L (normal range, 4.0-5.5 mmol/L), an insulin level of 41.8 IU/ml [normal value (NV) 0-23] and a C-peptide level of 5.282 ng/ml (NV 1.07-3.51). An upper abdominal CT did not reveal any pancreatic mass. There was an incidental finding of a 1.4 cm left renal cortical cyst. Plain computed tomography (CT) of the brain did not show mass any lesion or infarct.

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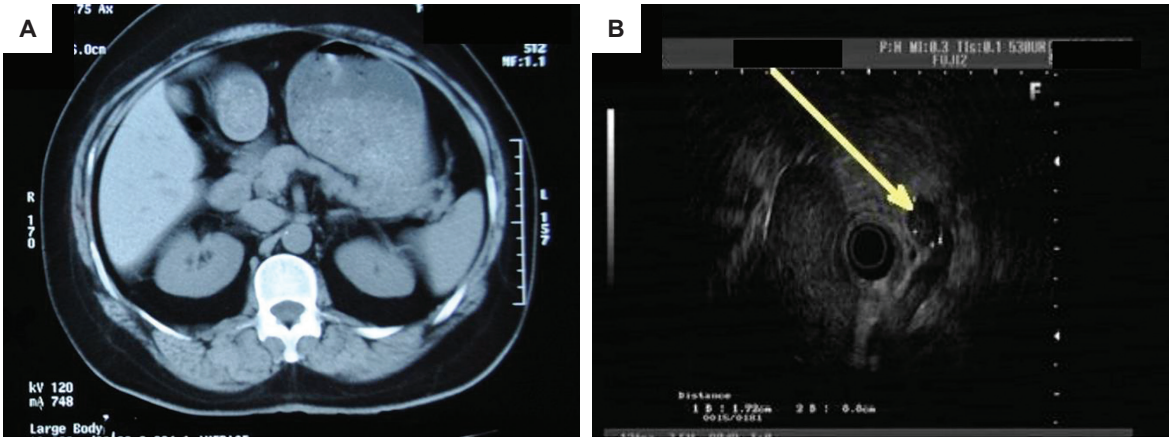

Figure 1. (A) Plain abdominal CT scan did not reveal pancreatic mass. **(B)** Endoscopic ultrasound showing a pancreatic head tumor *(yellow arrow)*.

She noticed an increase in appetite for the past few years leading to weight gain. However, she denied having headaches, blurring of vision, galactorrhea, heat or cold intolerance, or hyperpigmentation which may suggest pituitary disease. There was no history of fractures or nephrolithiasis which may suggest hyperparathyroidism. She had been hypertensive for the past 3 years, taking imidapril + hydrochlorothiazide. Medication history revealed intake of vitamin B complex and occasional use of herbal supplement (mangosteen extract). She denied insulin use or intake of oral hypoglycemic agents (OHA). All her previous hospitalizations were due to hypoglycemia.

On physical examination, she was lethargic but with normal vital signs. She was obese with a body mass index (BMI) of 30.5 kg/m^2. The rest of the physical findings were unremarkable. Neurologic evaluation revealed scanning speech, nystagmus, shallow left nasolabial fold, limb ataxia, positive Romberg's sign, and bilateral Babinski sign. The CBG on admission was 1.8 mmol/L which increased to 7.4 mmol/L after intravenous administration of 25 grams glucose solution.

Investigations

The admitting diagnosis was endogenous hyperinsulinemic hypoglycemia, recurrent and symptomatic (syncopal attacks) most probably from insulinoma, not visualized on abdominal CT scan.

Her laboratory work-up showed a very low fasting blood sugar (FBS) at 0.25 mmol/L, an elevated creatinine level of 162 umol/L (creatinine clearance of 34 mL/min), normal calcium at 2.31 mmol/L (NV 2.15 - 2.5) and a serum cortisol at 331.08 nmol/L (NV 160-620). Thyroid-stimulating hormone was also normal at 0.9 mIU/L (NV 0.3–3.8). Since a plain abdominal CT scan done in a previous hospital did not show any pancreatic mass, an endoscopic ultrasound (EUS) was pursued instead of doing a repeat CT with intravenous contrast. EUS showed a 1.7 x 1.3 cm, hypoechoic, heterogeneous, round pancreatic head mass abutting the splenic vein, with normal pancreatic duct, bile duct and other visualized areas of the liver. The impression was a pancreatic head mass, to consider a neuroendocrine tumor (Figure 1). She was then scheduled for enucleation.

Neurology referral was also done for dysarthria and other neurologic findings. A posterior circulation ischemia of the left ponto-cerebellar area was considered. A cranial CT scan was done to rule out stroke and other space-occupying lesions. Results showed microvascular ischemic changes, cerebro-cerebellar atrophy with ex-vacuo ventricular dilatation. There was no sellar-suprasellar mass noted. A 21-channel electroencephalogram (EEG) showed mild diffuse slowing of the background activity indicative of mild diffuse cerebral dysfunction of no specific etiology. An MRI of the brain was not pursued since the shallow left nasolabial fold, which was the lone lateralizing sign the patient manifested with, eventually resolved after normalization of blood glucose levels.

Differential diagnosis

Diseases which could also present with recurrent syncopal attacks and behavioral changes include psychiatric disorders, complex seizures, vascular dementias or cerebrovascular disease. Possible causes of hypoglycemia are surreptitious insulin or OHA use, nesidioblastosis, or presence of anti-insulin antibody. Multiple endocrine neoplasia 1 (MEN-1) may also be considered.

Normal psychiatric evaluation coupled with the absence of a mass lesion on cranial CT scan and diffuse slowing of background activity on EEG ruled out psychiatric and neurological disorders in this case. Extensive medical history and drug intake history made the surreptitious drug use less likely. A high C-peptide level of the patient is also not consistent with surreptitious insulin use. Nesidioblastosis or diffuse hyperplasia of the islets was also considered due to the initial non-visualization of the pancreatic mass on abdominal CT scan. However, most cases start during infancy and childhood, predominantly in males and

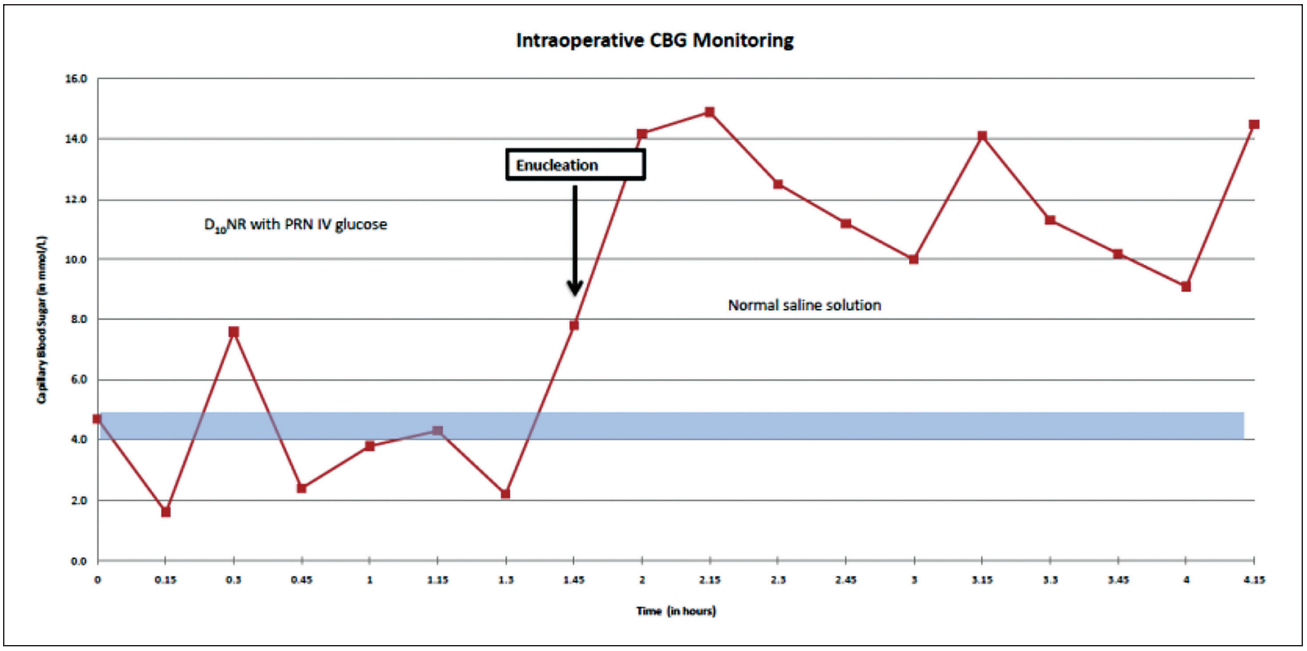

Figure 2. Intraoperative capillary blood glucose monitoring. Note the immediate rise in blood glucose levels post-enucleation of the pancreatic head tumor *(arrow signifies the time when the mass was removed)*. The blue bar represents the normal range of capillary blood glucose.

the episodes of hypoglycemia usually occur during the postprandial state. Hypoglycemia due to the development of native insulin antibodies is usually observed in the late postprandial period and is seen frequently in patients with history of autoimmune disease or exposure to sulfhydryl-containing drugs, which were not observed in this patient. MEN-1 was ruled out on the basis of the absence of pituitary involvement or parathyroid involvement as suggested by the normal cranial CT scan and normal serum calcium levels. However, this patient may have some degree of adrenal insufficiency based on the mid-normal serum cortisol levels in the setting of hypoglycemia, which is an inappropriate response. The expected response is an increased level of serum cortisol, being a counterregulatory hormone for hypoglycemia.

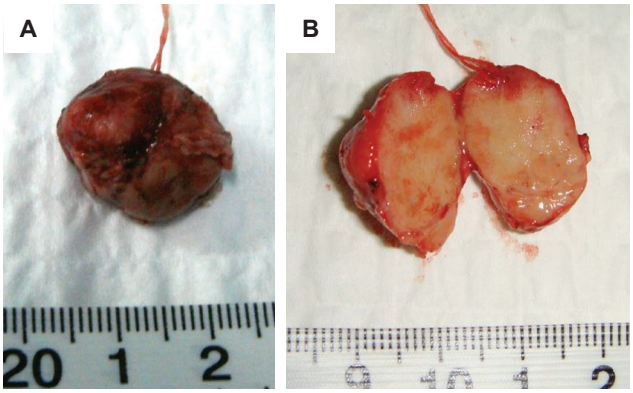

Figure 3. (A) Gross appearance of the 2-cm pancreatic head mass post-enucleation. **(B)** Cross-section of the mass.

Treatment

Enucleation of the pancreatic head mass after intraoperative ultrasound and palpation was done showing a 2 cm well-circumscribed, encapsulated pancreatic head tumor.

Upon enucleation of the tumor, CBGs immediately increased and values ranged between 8.9–14.4 mmol/L. Post-operatively, there was no episode of hypoglycemia noted (Figure 2).

Figure 3 shows the gross and cut section appearance of the tumor. Histopathology showed uniform cells in anastomosing cords consistent with an islet-cell tumor of the pancreas (pancreatic neuroendocrine tumor) (Figure 4). Immunohistochemical staining was positive for chromogranin A and synaptophysin proving the neuro-endocrine nature of the tumor (Figure 5). Insulin immuno-stain was contemplated but could not be done due to unavailability in the country.

Post-operatively, she developed acute pancreatitis, sepsis, acute kidney injury from ischemic acute tubular necrosis, and delirium. Careful hydration, imipenem, and other supportive treatment were given. She gradually improved in the subsequent days. There was no recurrence of syncope, behavioral changes or hypoglycemia. Her renal function improved. She was discharged on the 25th hospital day.

Outcome and follow-up

There were no episodes of behavioral or sensorial changes noted at home. Preprandial capillary blood sugars ranged from 6.1 – 7.2 mmol/L. The patient was consistently coherent and was able to resume her usual daily activities without assistance. On outpatient follow-up, she was comfortable,

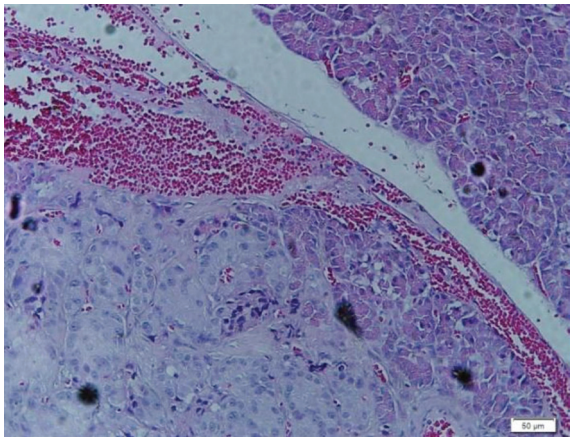

Figure 4. Normal pancreatic tissue on the right upper portion, with the pancreatic head mass (islet cell tumor / pancreatic neuroendocrine tumor) at the lower left side of the photomicrograph appearing as uniform cells in anastomosing cords (H&E, 40x).

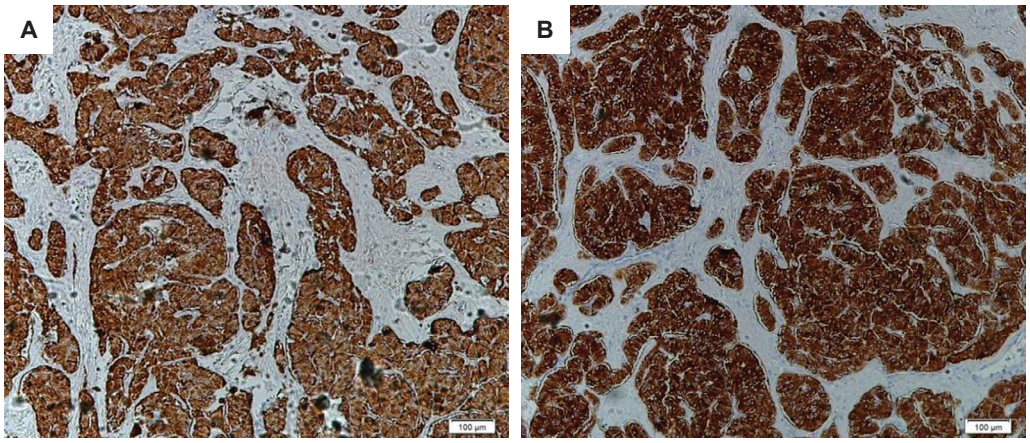

Figure 5. Positive chromogranin **(A)** and synaptophysin **(B)** immunohistochemical staining of the pancreatic head mass, 100x magnification.

generally felt better and had a positive outlook in life. Her BMI decreased from 30.5 kg/m^2 to 24 kg/m^2 two months after the surgery (Figure 6).

Thirteen years after surgery, there has still been no recurrence of hypoglycemic symptoms and she remains functionally independent at age 75. She weighs 42 kg with a BMI of 18.1 kg/m^2. Screening for fracture risk using FRAX Plus revealed a 10-year probability for major osteoporotic fractures of 4.3% and for hip fractures of 2.3%. These are above the therapeutic thresholds for Filipinos, hence anti-osteoporosis medications were recommended. She remains independent in all activities of daily living and is not frail using the Edmonton Frail Scale. She has yet to be screened for diabetes.

DISCUSSION

Insulinoma is a very rare disorder with an incidence rate of 4 per 1,000,000 persons. Among the endocrine pancreatic tumors, it is the most common functional neuroendocrine pancreatic neoplasm accounting for 70 to 80 percent.[1] The median age is estimated at 47 years (age range 30 – 70 years), with slight female predominance (59%). Insulinomas are usually solitary, benign and sporadic, 90% are less than 2 cm, 30% are less than 1 cm, 10% are multiple,

Figure 6. Photograph of the patient before surgery **(A)** with a BMI of 30.5 kg/m^2 and 2 months post-operatively **(B)** with a BMI of 24 kg/m^2.

10% are malignant, and 16% are associated with multiple endocrine neoplasia 1 (MEN-1).[1,2] The hypoglycemic symptoms are classified as either neuroglycopenic or adrenergic.[3] Neuroglycopenic symptoms include altered mental status, visual disturbance, amnesia/coma, abnormal behavior, and seizures. Adrenergic symptoms include sweating, weakness, obesity, tremors, hyperphagia, and palpitations. Symptoms that were present in our patient were altered mental status, abnormal behavior, obesity, and hyperphagia.

In the stepwise approach for the diagnosis of insulinoma, it is recommended to first confirm the hypoglycemia, followed by documentation of hyperinsulinism, differentiating endogenous from exogenous sources. Thereafter, localization studies of the tumor are performed, and appropriate treatment are done based on the diagnostic results.[4]

Localization studies include both non-invasive and invasive modalities. Non-invasive procedures include transabdominal ultrasonography, abdominal CT scan or MRI. Invasive procedures are employed only upon high suspicion for insulinoma and failure of all non-invasive imaging tests to detect the lesion. Among these are selective pancreatic arteriography, transhepatic portal venous sampling, intra-arterial calcium stimulation with hepatic vein catheterization, endoscopic ultrasound (EUS), and intraoperative ultrasonography. Newer modalities for localization are somatostatin receptor scintigraphy and GLP-1 receptor scintigraphy.[5,6]

An abdominal CT scan was initially done on this patient which was negative. The tumor was eventually localized using an EUS which showed a 1.7 x 1.3 cm tumor in the pancreatic head. Intraoperative ultrasound confirmed the presence of a 2-cm well-circumscribed, encapsulated pancreatic tumor.

After localization, our patient underwent tumor enucleation. Tumor enucleation is the procedure of choice for solitary benign tumors that are located in the pancreatic head. Those unsuitable for enucleation may have segmental resection of the pancreas, distal pancreatectomy, pancreaticoduodenectomy and formal resection for those suspicious for malignancy. Post-operative complications include pancreatic fistula, pseudocyst, intraabdominal abscess, pancreatitis, hemorrhage and diabetes.[5] According to a systematic review and meta-analysis, enucleation is a safe procedure, with a postoperative mortality of 1.1%, tumor recurrence rate of 3.1%, and acute pancreatitis occurrence rate of 1.7%.[7] Post-operative pancreatitis was observed in our patient.

Morbidity rate ranges from 10–43%, mortality rate at 0-4% and surgical cure rate was reported at 89-96%.[5] A multicenter study from Turkiye determined the remission rate at 91%.[8] Medical management may be done in those unsuitable for surgery, those awaiting surgery, those with unresectable disease, and those with unsuccessful operation. Dietary modification has a goal to prevent prolonged periods of fasting. Drugs used in the medical management include diazoxide, octreotide acetate, verapamil, propranolol, phenytoin, everolimus and sunitinib malate.[5] Our patient improved significantly with surgical management alone.

A study in Finland showed that the overall survival of non-metastatic insulinoma treated with curative-intent surgery was similar to controls.[9] Hence, our patient can expect normal life expectancy similar to control individuals, now that she has undergone enucleation.

This case has learning value for the following reasons. First, there are many causes of behavioral changes among senior citizens and hypoglycemia is not common. This teaches us to always check blood glucose levels in those with acute behavioral changes. Performing point-of-care capillary blood glucose determination is a rapid test that will make a primary care or emergency physician refer cases similar to this first to an internist-endocrinologist rather than to a neurologist.

Second, it is generally believed that metabolic causes of encephalopathy would not present with localizing neurologic deficits. Our patient had a shallow left nasolabial fold which would suggest a right frontal lobe lesion. Cranial CT scan, however, did not show a focal lesion. This, plus the resolution of the neurologic deficits upon correction of hypoglycemia, means that metabolic causes can cause transient “localizing” deficits.

Third, weight gain was very prominent in this case such that the patient was happy that she lost weight in as short as 2 months after surgery. Unintentional weight loss, which is part of frailty, is usually a problem in the elderly. However, the patient was the opposite and is an unusual symptom in her age group.

Fourth, the scan should not immediately exclude an insulinoma. In this case, we had to perform endoscopic ultrasound to localize the lesion preoperatively. Admittedly, this is a technology that may not be widely available in in our country and requires the expertise of a gastroenterologist capable of doing this procedure.

Fifth, this case shows that management of an insulinoma requires multidisciplinary teamwork. Physicians in the field of endocrinology, pancreatic surgery and gastroenterology had to work together to achieve a favorable outcome for this patient.

Sixth, the long duration of follow up is one of this case’s strength. The fact that she remains disease-free up to 13 years after surgery supports the knowledge that surgery can be curative. This can help physicians convince other similarly situated patients to undergo surgery so they can look forward to a cure and near-normal life expectancy.

Learning Points

- Insulinoma, though a rare and potentially reversible disorder, should be considered in the differential diagnosis of elderly patients presenting with recurrent syncope, behavioral changes and weight gain.
- Non-visualization of a pancreatic mass on routine imaging should not prevent the physician from pursuing the diagnosis of insulinoma in patients with a high index of clinical suspicion.
- Surgical enucleation of a solitary insulinoma has a high cure rate and may dramatically improve the metabolic status of the patient and his/her overall physical and functional well-being.
- Curative surgery can lead to disease-free survival for up to 13 years and counting.

Ethical Consideration

Patient consent forms were obtained before manuscript submission.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

EC: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Visualization; **MAS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – review and editing, Visualization, Supervision.

Data Availability Statement

No datasets were generated or analyzed for this study.

Author Disclosure

Both authors declared no conflict of interest.

Funding Source

None.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Challenges in Glycemic Monitoring: Undetectable HbA1c Level in an Asymptomatic Patient With Hemoglobin E and Beta-Thalassemia Minor: A Case Report

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Abstract

Glycated hemoglobin (HbA1c) is a laboratory examination recommended by the American Diabetes Association to monitor blood glucose levels in patients with diabetes mellitus. This gold standard method for testing HbA1c uses high-performance liquid chromatography (HPLC). One advantage of HbA1c testing with HPLC is the ability to detect Hb variants or hemoglobinopathies, although HbA1c results may become irrelevant in such conditions. A 49-year-old female patient came to the Ophthalmology Outpatient Clinic of Dr. Soetomo Hospital due to visual impairment in both eyes and plans for cryotherapy surgery. In preparation for the surgery, laboratory tests were performed with results of haemoglobin 12.1 g/dL, mean corpuscular volume 58.9 fL, mean corpuscular haemoglobin 19.3 pg, leukocytes 13,370/uL, platelets 399,000/uL and random blood glucose 127 mg/dL; however, HbA1c was not detected. In the HbA1c test, a 93.7% window variant was obtained. Based on blood smear evaluation, there was hypochromic microcytic anisopoikilocytosis with target cells. The electrophoresis results revealed HbA 0.7%, HbF 0.6%, HbE 94.9% and HbA2 4.7%, indicating the presence of beta thalassemia with hemoglobinopathy E. The diagnosis of hemoglobinopathy E is based on a complete blood count, peripheral blood smear and haemoglobin electrophoresis. HbA1c examination by HPLC can yield undetectable HbA1c levels in hemoglobinopathies. Monitoring blood glucose levels in such cases is also irrelevant when using HbA1c, because red blood cells have a shorter lifespan in the presence of Hb variants. Glucose monitoring in this condition can be done by periodic glucose examination, fructosamine, or glycated albumin. The HbA1c test cannot be used as a marker of glucose control in patients with hemoglobinopathy E.

Key words: hemoglobinopathy, HbA1c, HPLC, electrophoresis

INTRODUCTION

Glycated hemoglobin or hemoglobin A1c (HbA1c) is a hemoglobin fraction commonly used to evaluate long-term glycemic control and the risk of chronic complications in patients with diabetes mellitus. The American Diabetes Association (ADA) recommends HbA1c as one of the diagnostic criteria related to diabetes mellitus because it can reflect glucose bound to hemoglobin throughout the life of the erythrocyte (approximately 120 days), so that it can indirectly reflect clinical changes related to glucose exposure during this period, although factors that can affect hemoglobin concentration or erythrocyte turnover can also influence it.[1]

Several methods are known for HbA1c testing, including immunoassay, boronate affinity, enzymatic, capillary electrophoresis and ion-exchange high-performance liquid chromatography (HPLC). The latter two methods offer additional advantages beyond measuring HbA1c, as they can also detect various hemoglobin types and Hb variants. HPLC testing itself is known to have high sensitivity and specificity and can be used as an alternative to electrophoresis in identifying and measuring normal and abnormal hemoglobin fractions. The retention time obtained from HPLC testing can provide information about hemoglobin variants in a sample, both in measuring HbA1c, HbA2, and HbF levels. This allows for monitoring therapy and the progression of diabetes mellitus, as well as detecting recessively inherited hemoglobinopathies such as thalassemia and hemoglobinopathy E.[2,3]

Located in the thalassemia belt region, the prevalence of thalassemia carriers in Indonesia, according to WHO, is around 6-10% of the population, so it is estimated that there are 6-10 thalassemia carriers out of 100 residents.[4]

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More specifically, local estimates indicate that approximately 3.0–10.0% of the Indonesian population carries the beta-thalassemia trait and 2.6–11.0% carry the alpha-thalassemia trait, with around 2,500 infants born with beta-thalassemia major each year.[5] Hemoglobin E is also among the most common structural hemoglobin variants in Southeast Asia and is frequently co-inherited with beta-thalassemia.[5] Importantly, Indonesia's national newborn screening program is currently mandated only for congenital hypothyroidism and does not include hemoglobinopathies; consequently, individuals with beta-thalassemia minor or hemoglobin E commonly remain undetected until incidental laboratory testing later in life.[6] This makes hemoglobinopathy a condition that is not rarely encountered; however, due to the absence of significant clinical symptoms in sufferers, especially in carriers, the choice of examination method can be very decisive.

CASE

A 49-year-old female presented to the Eye Clinic at Dr. Soetomo General Hospital complaining of impaired vision in both eyes. She was reported to have blurred vision in her right eye and undetectable vision in her left eye. The patient did not complain of eye pain, fever, or impaired eye movement. She had no history of malignancy or metabolic disease, but had a history of hypertension and had not been taking her medication regularly. A physical examination revealed decreased visual acuity in both eyes and a leucocele over the entire surface of the left cornea. The attending physician diagnosed the patient with phthisis bulbi and left corneal leucocele and planned cryotherapy (CRI).

Prior to the surgical procedure, routine laboratory testing revealed a random blood glucose level of 127 mg/dL (N: <200 mg/dL) and an undetectable HbA1c result. HbA1c measurement was performed using the Bio-Rad D-10 high-performance liquid chromatography (HPLC) system. The chromatogram showed no detectable HbA1c peak at the expected retention time of approximately 2.0 to 2.2 minutes, with an abnormal chromatographic disturbance observed near this region. No variant window was initially identified (Figure 1). Because of this unexpected finding, the sample was diluted and reanalyzed. The repeated chromatogram again demonstrated the absence of the HbA1c peak at the expected retention time, while a prominent variant window peak occupying 93.7% of the total chromatogram area became evident, indicating the presence of a hemoglobin variant (Figure 2).

Other laboratory findings from the complete blood count are summarized in Table 1, demonstrating hemoglobin 12.1 g/dL, hematocrit 36.9%, erythrocytes 6,270,000/uL, mean corpuscular volume (MCV) 58.9 fL, mean corpuscular hemoglobin (MCH) 19.3 pg, leukocytes 13,370/uL, and platelets 399,000/uL (Figure 3). Based on the complete blood count, the patient's Mentzer index was 9.4, suggesting a possibility of thalassemia, as the number

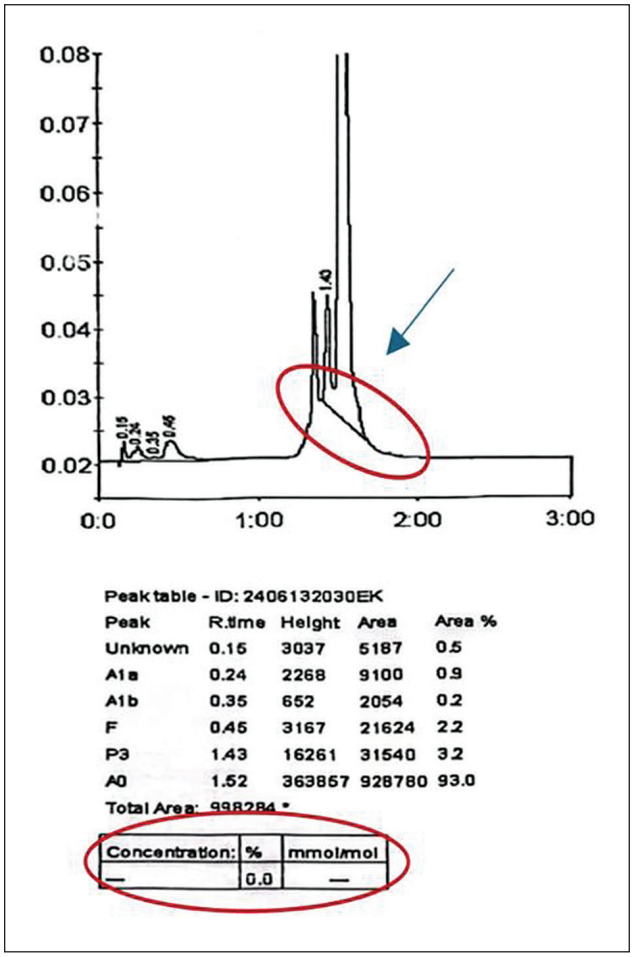

Figure 1. Pre-dilution HbA1c chromatogram using the Bio-Rad D-10 HPLC system. An undetectable HbA1c value is shown. The HbA1c peak, normally expected at a retention time of 0.79–1.01 seconds, was not identifiable in this chromatogram, likely due to masking by an extremely elevated hemoglobin variant that disrupted the normal elution pattern. The transverse line is visible, which may serve as an indirect diagnostic indicator of a high-concentration abnormal hemoglobin fraction. No variant window was detected.

of erythrocytes remained high despite a small size of the red blood cells. Peripheral blood smear examination was then carried out and revealed microcytic hypochromic erythrocytes with (+) target cells suspicious for thalassemia (Figure 4). Furthermore, electrophoresis was performed, and the results obtained were HbA 0.5% (N: 96.8-97.5%), HbF 0.6% (N: 0.0%), HbE 94.4% (N: not detected), HbA2 4.5% (N: 2.4-2.9%). Based on these results, a decrease in the HbA fraction and an increase in the HbF, HbE and HbA2 fractions were observed, suggesting beta thalassemia with hemoglobinopathy E (Figure 5).

Asymptomatic patients with no history of the disease in their family are advised to have a genetic consultation for screening for genetic disorders that may be transmitted through them to their offspring.

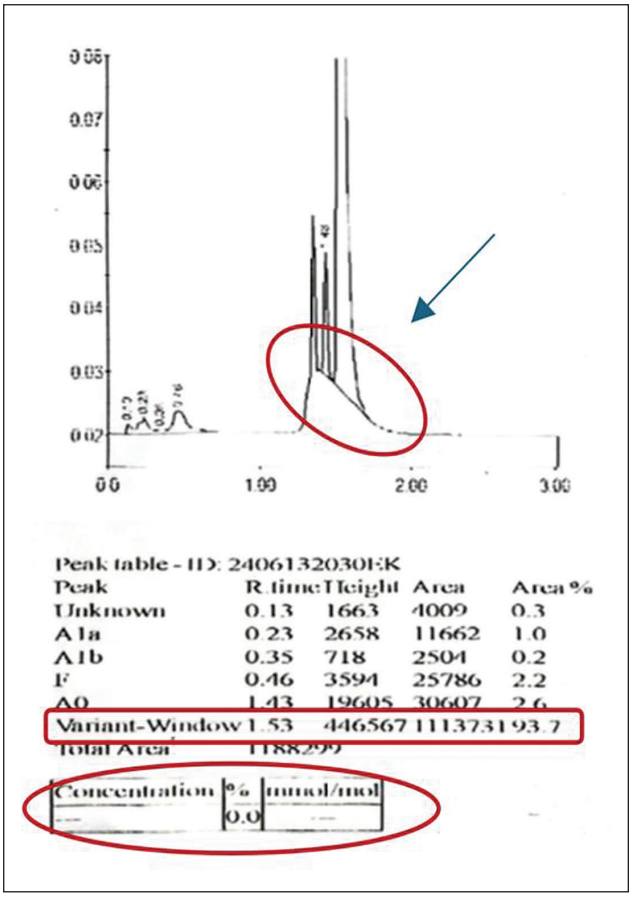

Figure 2. Post-dilution HbA1c chromatogram using the Bio-Rad D-10 HPLC system. An undetectable HbA1c value is still present after sample dilution. The HbA1c peak remains undetectable even sampel dilution. The transverse line is still visible on the chromatogram, and a variant window is present with a total area of 93.7%, consistent with a highly elevated hemoglobin variant.

Table 1. Complete blood count results

Parameter	Result	Unit	Reference range
Hemoglobin (Hb)	12.1	g/dL	Male: 13.3–16.6 Female: 11.0–14.7
Red Blood Cells (RBC)	6.27	$\times 10^6$/uL	3.69–5.46
Hematocrit (HCT)	36.9	%	Male: 41.3–52.1 Female: 35.2–46.7
Mean Corpuscular Volume (MCV)	58.9	fL	86.7–102.3
Mean Corpuscular Hemoglobin (MCH)	19.3	pg	27.1–32.4
Mean Corpuscular Hemoglobin Concentration (MCHC)	32.8	g/dL	29.7–33.1
RDW-SD	31.8	fL	41.2–53.6
RDW-CV	17.7	%	12.2–14.8
White Blood Cells (WBC)	13.37	$\times 10^3$/uL	3.37–10.0
Neutrophils	66.3	%	39.8–70.5
Lymphocytes	23.1	%	23.1–49.9
Monocytes	5.8	%	4.3–10.0
Eosinophils	4.4	%	0.6–5.4
Basophils	0.4	%	0.3–1.4
Platelets (PLT)	399	$\times 10^3$/uL	150–450
Mean Platelet Volume (MPV)	9.7	fL	9.2–12.0
Platelet Distribution Width (PDW)	11.7	fL	9.6–15.2
Plateletcrit (PCT)	0.39	%	0.19–0.39

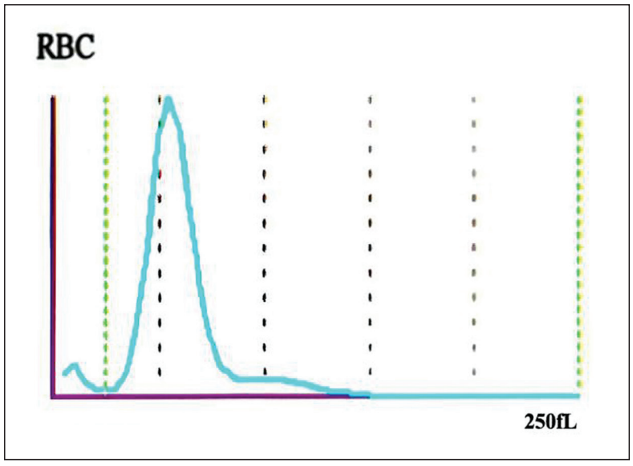

Figure 3. Red blood cell (RBC) histogram showing a left-ward shift consistent with microcytic red blood cells.

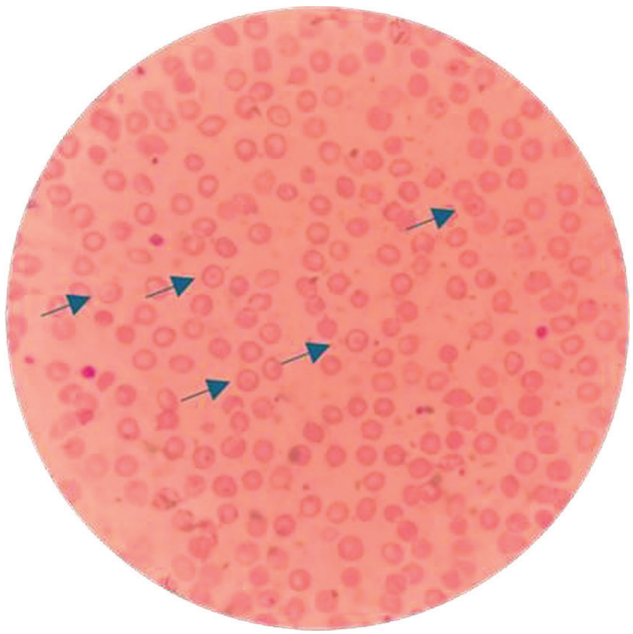

Figure 4. Examination of a peripheral blood smear with 1000x magnification showing the presence of target cells indicated by the blue arrows.

DISCUSSION

The diagnosis of hemoglobinopathy E is based on a complete blood count (CBC), specialized hematology tests, and DNA testing. A complete blood count (CBC) is the initial test commonly performed to screen for thalassemia or other hemoglobinopathies by assessing decreased MCV or MCH values, although iron deficiency anemia can also have similar symptoms. This means that the diagnosis of hemoglobinopathy cannot be based solely on MCV or MCH levels. It requires additional values, such as the MCV/RBC ratio or the Mentzer index, a peripheral blood smear, and other specialized tests such as HPLC (HbA1c) and electrophoresis, or, most effectively, DNA mutation analysis.[7]

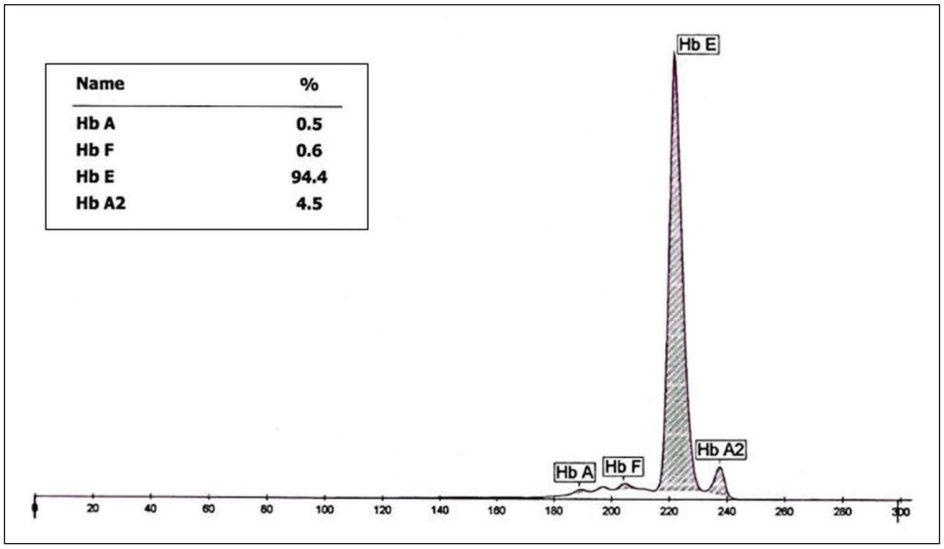

Figure 5. Electrophoresis examination showing high HbE values.

The HbA1c is a routine test for monitoring long-term blood sugar levels in patients with diabetes mellitus because it directly correlates with the risk of complications from the condition. Because it relates to hemoglobin, the HbA1c test can be influenced by factors such as erythrocyte survival time and the levels of certain hemoglobin fractions.[1,8] Because the HbA1c test is based on normal hemoglobin, the presence of other conditions such as hemoglobinopathies can affect the test results.[9] This is evident in the patient's HbA1c test results, which are still undetectable on the device even after repeating the test with dilution.

The undetectable HbA1c levels on the HPLC method used in this patient may be due to changes in the glycation process from HbA to A1c, resulting in abnormal peaks that make the A1c estimate unreliable. Hemoglobinopathy itself can make red blood cell production more susceptible to hemolysis, shortening glycosylation time, resulting in falsely low or even undetectable A1c results.[9] This is indicated by the appearance of transverse lines on two HbA1c test graphs, indicating this change (Figures 1 and 2).

Hemoglobinopathies are divided into two groups: thalassemia and hemoglobin variants.[1,8] In this patient, a high variant-window area of 93.7% was observed, with a decrease in the HbA fraction and an increase in the HbF, HbE, and HbA2 fractions, suggesting beta thalassemia with hemoglobinopathy E on the second test, after sample dilution. HPLC is an examination that separates various types of hemoglobin on a cation-exchange column and usually requires only a single sample injection. This examination is usually used as an alternative to electrophoresis examination but has the ability to identify and quantitatively measure low levels of HbA2 and HbF, although co-migration between HbA2 and HbE can occur, so that inaccurate HbA2 levels can occur due to the presence of other hemoglobin variants such as HbE, Lepore, DPunjab and S.[2,10]

The results of the HbA1c examination were then confirmed by the results of other laboratory tests, such as the patient's complete blood count, which showed a hemoglobin level of 12.1 g/dL, hematocrit 36.9%, erythrocytes 6,270,000/uL, MCV 58.9 fL, MCH 19.3 pg, leukocytes 13,370/uL, platelets 399,000/uL, and an increase in the RDW-CV value of 17.7%, indicating the possibility of variations in the shape of erythrocytes in the measured sample. Based on these results, a Mentzer index of less than 13 (9.4) indicated the possibility of the patient suffering from thalassemia. This is also supported by the peripheral blood smear, which showed hypochromic microcytic erythrocytes with target cells (+), suspicious for thalassemia. This result was further confirmed by electrophoresis, which showed a decrease in the HbA fraction, an increase in the HbF, HbE and HbA2 fractions, suggesting a beta thalassemia with hemoglobinopathy E. The uniqueness of this case is that the patient was asymptomatic, without a known family history, no signs of pancytopenia and no signs of hemolytic events or other complications, although this condition could possibly be caused by a variant form of the homozygous or heterozygous HbE E trait, which often causes clinicians to miss the attention of their diabetic patients with inappropriate HbA1c results.[11-13] The HbE condition is a thalassemic hemoglobinopathy with an abnormal HbE structure due to spontaneous point mutations in the beta-globin chain, causing substitution of lysine for glutamic acid, and the disease pattern is similar to that of beta thalassemia.[14,15]

In areas with high prevalence of Hb variants, clinical laboratory examinations need to consider various limitations of the examination, including those for HbA1c determination. The presence of other clinical conditions, such as hemoglobinopathies, can lead to silent conditions that make HbA1c levels determined by HPLC fail to reflect actual blood glucose levels, making treatment for diabetes patients becomes less appropriate.[15-17] On the other hand, HbA1c examination with HPLC is preferred

over other methods, such as immunoturbidity or point-of-care tests, because it can detect Hb variants, both homozygous and heterozygous, which can make HbA1c results less accurate.[17] Therefore, it is important to educate clinicians to avoid ordering HbA1c examinations in these patients. It is also worth noting that in regions within the thalassemia belt, such as Indonesia, hemoglobinopathy may remain undiagnosed well into adulthood in asymptomatic individuals.[6] In many individuals with HbE trait or beta-thalassemia minor, clinical manifestations may be minimal and therefore remain undiagnosed unless routine laboratory testing is performed. In this case, the hemoglobinopathy was incidentally detected during preoperative laboratory evaluation. On the other hand, the subtle microcytic picture of HbE is frequently attributed to iron deficiency, and neither electrophoresis nor HPLC is performed routinely in primary care, in the absence of clinical suspicion or family history, underscoring the need for heightened clinical awareness. Patients with Hb variants who have diabetes mellitus should be advised to use other methods of glucose monitoring that are not based on hemoglobin, such as fructosamine, glycated albumin or periodic glucose examinations to determine long-term glycemic control.[5,18-20]

CONCLUSION

Undetectable HbA1c values and the appearance of window variants on HPLC can be caused by hemoglobinopathies. This condition can be an initial indicator of Hb variants in patients with hemoglobinopathies or thalassemia traits who are clinically asymptomatic. Therefore, HbA1c testing cannot be used to monitor blood glucose levels in patients with hemoglobinopathies.

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Ethical Consideration
Patient's consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
DPS: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Visualization, Supervision, Project administration, Funding acquisition; **SZ:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing – review and editing, Visualization, Project administration, Funding acquisition; **MRF:** Methodology, Software, Validation, Formal analysis, Data curation, Writing – review and editing, Project administration, Funding acquisition.

Data Availability Statement
All data generated or analyzed during this study are included in this published article.

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CASE REPORT

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Hirata's Disease: A Case Report

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Abstract

Insulin Autoimmune Syndrome (IAS), also known as Hirata's disease, is a rare endocrine disorder characterized by recurrent hypoglycemia due to endogenous hyperinsulinemia and the presence of insulin autoantibodies (IAAs). We report a case of IAS successfully treated with corticosteroid therapy. Notably, the definitive diagnosis was established only during the second hospitalization, after multiple recurrent hypoglycemic episodes. The delayed diagnosis reflects the nonspecific presentation and the low initial suspicion for autoimmune hypoglycemia. In the first admission, although insulinoma had been excluded, the patient was discharged without a confirmed diagnosis. This case highlights the importance of early insulin autoantibody testing in patients with unexplained endogenous hyperinsulinemic hypoglycemia to prevent diagnostic delay and unnecessary investigations. Initial evaluation prioritized exclusion of insulinoma, the most common cause of endogenous hyperinsulinemic hypoglycemia, before autoimmune testing was pursued.

Key words: Insulin Autoimmune Syndrome, Hirata's disease, hypoglycemia

INTRODUCTION

Endogenous hyperinsulinemic hypoglycemia (EHH) is a condition characterized by low blood glucose levels resulting from excessive endogenous insulin secretion. The diagnosis of clinically significant hypoglycemia relies on Whipple's triad, which includes: (1) Symptoms consistent with hypoglycemia; (2) Documented low plasma glucose concentration; and (3) Relief of symptoms after glucose administration. Once Whipple's triad is fulfilled, biochemical evaluation is required to determine the underlying etiology. Endogenous hyperinsulinemic hypoglycemia is established when plasma insulin exceeds 3 μIU/mL, plasma C-peptide is greater than 0.6 ng/mL, and plasma glucose is less than 3.0 mmol/L.[1] Severe hypoglycemia due to EHH can significantly impair quality of life and may be life-threatening. The main causes of EHH include insulinoma, Insulin Autoimmune Syndrome (IAS), and type B insulin resistance syndrome (TBIRS), among which insulinoma is the most common etiology.[2] IAS, also known as Hirata's disease, was first described by Yukimasa Hirata and colleagues in Japan in 1970.[3] IAS represents an exceptionally uncommon condition in the general population. In Japan, the estimated incidence is approximately 0.017 cases per 100,000 population per year.[4] In China, despite its very large population, only a few dozen cases have been reported over several decades (84 cases within 30 years).[5] With increasing awareness, more cases have been found in Western countries.[4]

Due to its rarity and overlapping features with insulinoma, IAS is often misdiagnosed or diagnosed at a late stage. In Vietnam, Vu Bich Nga et al., reported a case of delayed diagnosis of IAS, initially mistaken for insulinoma.[6] Such diagnostic errors emphasize the need to raise awareness of this rare disorder. Herein, we present a case of IAS in a patient with recurrent hypoglycemia, emphasizing the importance of early recognition of endocrine causes to prevent diagnostic delay and guide appropriate management.

CASE

We report the case of a 64-year-old retired male who presented with repeated episodes of hypoglycemia. During the attacks, he typically experienced marked hunger, tremors of the extremities, and palpitations.

The patient had suffered from recurrent hypoglycemia since 2019 and was initially evaluated at another medical facility. A prolonged 72-hour fasting test was conducted but failed to reproduce a hypoglycemic event. Assessment at that time focused on excluding insulinoma. Given the rarity of insulin autoimmune syndrome and its overlapping clinical features with insulinoma, autoimmune causes were not prioritized. He was subsequently referred to our tertiary endocrine center for further evaluation. He had no past history of hepatic or renal disease. A detailed medication history revealed no exposure to sulfhydryl–

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Table 1. Biochemical findings during hypoglycemic episode

Test	Value	Reference range
Glucose (mmol/L)	2.05	3.9 – 5.6
Insulin (µIU /mL)	4128.6	2.6 – 24.9
C peptide (ng/mL)	8.69	0.78 – 5.19
IAA (%)	80.2	<7
HbA1c (%)	5.5	4-6.2
Cortisol 8h (nmol/L)	255	166-507
GOT (U/l)	37	11-34
GPT (U/l)	43	<45
Creatinin (µmol /L)	73	64-100

Table 2. HLA typing results

Locus	Alleles
HLA-DRB1*	04:05/04:06
HLA-DQA1*	03:01/03:01
HLA-DQB1*	03:02/04:02

containing medications, including methimazole, captopril or alpha-lipoic acid. Drug-induced IAS has been reported in association with medications such as carbimazole.[7] The patient had never received insulin therapy or oral hypoglycemic agents, particularly sulfonylureas. Although biochemical screening for sulfonylurea exposure was not available, detailed medication history did not suggest exogenous hypoglycemic agent use. Screening for associated autoimmune disorders was performed with negative results, including antinuclear antibodies (ANA), anti-double-stranded DNA antibodies, rheumatoid factor (RF) and thyroid function tests, all within normal limits.

On admission, he was fully conscious and interactive, and no abnormal findings were noted on physical examination. His hypoglycemic events generally developed in the post-absorptive period, with a frequency of three to four episodes per day, occurring consistently over the last six years.

Biochemical testing during a symptomatic episode demonstrated a plasma glucose level of 2.0 mmol/L, a C-peptide concentration of 8.69 ng/mL (reference 0.78–5.19), and a markedly elevated insulin level of 4128.6 µIU/mL (reference 2.6–24.9), confirming endogenous hyperinsulinemic hypoglycemia. Urine ketones were negative during the hypoglycemic episode, consistent with suppressed ketogenesis in the setting of hyperinsulinemia. Further evaluation to exclude alternative causes of hypoglycemia showed that morning serum cortisol was within normal limits, making adrenal insufficiency unlikely. Abdominal computed tomography did not reveal any pancreatic mass. Magnetic resonance imaging could not be performed due to cervical spine fixation hardware. In accordance with the common diagnostic approach prioritizing exclusion of insulinoma – the most frequent cause of EHH, imaging was undertaken before autoimmune testing. Subsequent immunological analysis revealed a striking elevation of insulin autoantibodies (IAA 80.2%, normal <7%). Taken together, the presence of endogenous hyperinsulinemia, the absence of pancreatic neoplasm on imaging, and the high titer of IAA supported the diagnosis of Insulin Autoimmune Syndrome (Hirata's disease).

To further investigate a potential genetic predisposition, high-resolution HLA class II typing was performed using PCR–sequence-specific oligonucleotide (PCR-SSO) methods. The analysis revealed the presence of HLA-DRB1*04:06, along with HLA-DQA1*03:01 and HLA-DQB1*03:02/04:02 alleles, which have been previously reported to be associated with Insulin Autoimmune Syndrome.

Therapeutically, the patient was first managed with an alpha-glucosidase inhibitor (50 mg three times daily before meals), but no clinical improvement was observed. Corticosteroid therapy with methylprednisolone was subsequently initiated at 32 mg daily and gradually tapered by 4 mg each month, leading to a marked reduction in the frequency and severity of hypoglycemic episodes. At one-year follow-up, the patient remained in good clinical condition with stable glycemic control while continuing on a low maintenance dose of methylprednisolone at 4 mg daily. Insulin autoantibody titers were not serially monitored during follow-up. However, the sustained clinical improvement after initiation of corticosteroid therapy supported an immune-mediated mechanism. Given the prolonged six-year history of recurrent hypoglycemia prior to treatment, spontaneous remission appeared unlikely in this case. The patient was maintained on a low dose of methylprednisolone and was closely monitored for potential steroid-related adverse effects, with no significant complications observed during follow-up.

DISCUSSION

Insulin Autoimmune Syndrome (IAS), also known as Hirata's disease, is a rare but clinically significant cause of endogenous hyperinsulinemic hypoglycemia. Although insulinoma remains the most common etiology of endogenous hyperinsulinism, IAS should be considered after pancreatic tumors have been excluded. This case is notable for its prolonged clinical course, atypical diagnostic features, and delayed diagnosis, highlighting the challenges of recognizing IAS in routine clinical practice.

Our patient experienced recurrent hypoglycemic episodes for approximately six years before a definitive diagnosis was established. Although insulinoma had been excluded during the first hospitalization, the absence of a confirmed alternative diagnosis resulted in delayed identification of the underlying cause. This prolonged diagnostic process reflects a common pitfall in clinical practice, in which

IAS may be overlooked after structural pancreatic disease has been ruled out and autoimmune etiologies are not adequately considered. Similar diagnostic delays have been reported previously. In a Southeast Asian case series, several patients with Insulin Autoimmune Syndrome were initially investigated for insulinoma before insulin autoantibodies were identified, underscoring the need to consider IAS after pancreatic tumors have been excluded.[8]

The pathophysiology of IAS involves sequestration of endogenous insulin by circulating autoantibodies after meals, followed by unregulated delayed insulin release, leading to late postprandial hypoglycemia.[4] In this case, a previously performed 72-hour fasting test failed to provoke hypoglycemia, a finding that is uncharacteristic of insulinoma and more consistent with IAS. As reported in the literature, hypoglycemia associated with IAS tends to occur predominantly in the postprandial or late post-absorptive period rather than during prolonged fasting. IAS is characterized by circulating insulin autoantibodies that bind endogenous insulin and cause its unpredictable release. This leads to disproportionately elevated measured insulin levels relative to C-peptide, often resulting in a high insulin-to-C-peptide ratio, which helps distinguish IAS from insulinoma. In our patient, the markedly elevated insulin level compared with the moderately increased C-peptide supported this mechanism.

Type B insulin resistance syndrome (TBIRS) should also be considered in antibody-mediated insulin disorders. However, TBIRS is typically characterized by severe insulin resistance and hyperglycemia due to anti-insulin receptor antibodies. In contrast, our patient presented with recurrent hypoglycemia without features of severe insulin resistance, findings more consistent with IAS.

Measurement of insulin autoantibodies (IAA) played a decisive role in establishing the diagnosis in this patient. The markedly elevated IAA level, together with biochemical evidence of endogenous hyperinsulinemia and the absence of a pancreatic mass on imaging, was sufficient to confirm IAS and avoid unnecessary invasive investigations.

The management of IAS differs fundamentally from that of insulinoma because the underlying mechanism is immune-mediated rather than tumor-related. Initial treatment strategies typically include dietary modification and agents aimed at reducing postprandial glucose excursions. In our patient, therapy with an alpha-glucosidase inhibitor was ineffective. In contrast, corticosteroid treatment resulted in rapid and sustained improvement in glycemic control. Glucocorticoids are thought to suppress autoantibody production and reduce insulin variability, thereby alleviating hypoglycemic episodes. In a case series of Hirata syndrome by Mudagall et al., corticosteroid therapy was also shown to improve hypoglycemic episodes.[8]

Although IAS is often described as self-limiting, with spontaneous resolution reported in 80-82% of cases, our patient had experienced recurrent hypoglycemia for six years prior to diagnosis, making spontaneous remission unlikely. The marked clinical improvement and sustained control achieved with a low maintenance dose of methylprednisolone suggest that corticosteroid therapy can be an appropriate option in prolonged and symptomatic cases. Similar clinical characteristics and favorable responses to corticosteroid therapy have been reported in recent case series, including the study by Mudagall et al., which further supports the role of immunomodulatory treatment in selected patients with Hirata syndrome.[8]

Genetic susceptibility plays an important role in the pathogenesis of Insulin Autoimmune Syndrome (IAS), with established associations between IAS and specific HLA class II alleles, particularly HLA-DRB1*04:06 and HLA-DRB1*04:03, which are prevalent in East Asian populations.[4,9] In the present case, high-resolution HLA typing identified HLA-DRB1*04:06 together with HLA-DQA1*03:01 and HLA-DQB1*03:02/04:02, alleles that have been reported as part of a high-risk haplotype for IAS. Although HLA typing is not routinely required for the diagnosis of IAS, these findings provided additional supportive evidence for an immune-mediated mechanism and helped strengthen the diagnosis in the context of a prolonged and atypical clinical course.

IAS has been reported more frequently in East Asian populations, particularly in Japan and China, whereas published cases from Vietnam remain scarce.[4,5] Recent reports from Southeast Asia, including a case series by Mudagall et al., have also highlighted the clinical heterogeneity of IAS and the need for increased clinical awareness in the region.[8] This case contributes to the limited regional data and demonstrates clinical features and treatment responses consistent with previous reports. These findings underscore the importance of increasing clinical awareness and considering early IAA testing in patients with unexplained endogenous hyperinsulinemic hypoglycemia after insulinoma has been excluded, in order to prevent diagnostic delay and unnecessary investigations.

CONCLUSION

Insulin Autoimmune Syndrome is a rare but important cause of endogenous hyperinsulinemic hypoglycemia that may be easily overlooked. This case underscores the need to consider autoimmune causes and to measure insulin autoantibodies early in patients with unexplained hypoglycemia after insulinoma has been excluded. Timely diagnosis allows appropriate treatment, with corticosteroids providing effective and sustained glycemic control.

Ethical Consideration

Patient's consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfillment of the ICMJE authorship criteria.

CRediT Author Statement

QTL: Writing – review and editing; **TTN, LTV, NBL, LTTN:** Investigation; **NHTP, MVN:** Visualization.

Data Availability Statement

The data supporting the findings of this case report are included within the article. Additional data are not publicly available due to patient confidentiality.

Author Disclosure

The authors declared no conflict of interest.

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Congenital Hyperinsulinism With Paternally Inherited *ABCC8* Variants: A Single Center Experience Over a Decade in Singapore

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Abstract

ABCC8 pathogenic variants have been found to cause neonatal diabetes mellitus (NDM), maturity-onset diabetes of the young (MODY) and congenital hyperinsulinism (CHI), depending on the nature of the mutation. Few studies have reported on the carrier frequency of CHI-related *ABCC8* variants. In Singapore, the carrier rate is 1 in 754. Paternally inherited *ABCC8* recessive variants have been classically associated with focal lesions causing CHI.

In our case series of five patients with paternally inherited *ABCC8* variants, one patient had a second maternally inherited recessive variant, making him a compound heterozygous genotype presenting with severe, neonatal onset, diffuse disease that was not responsive to diazoxide. The remaining four patients had a single paternally inherited *ABCC8* variant, of which three were previously reported to be recessive variants—only 1 had a focal lesion while the rest had diffuse disease. A comprehensive review of our cases suggests that patients with paternally inherited *ABCC8* variants, whether autosomal recessive, heterozygous, or associated with genetic syndromes, were heterogeneous in their clinical manifestations and cannot be reliably distinguished based on their initial clinical presentation.

A deeper understanding of the genotype-phenotype correlation of *ABCC8*-related CHI will require further research and functional analyses. Both a genetic diagnosis and imaging using ^{18}F-DOPA-PET should be pursued in a timely manner once diazoxide unresponsiveness has been established. Single-stage near-total pancreatectomy may be considered for patients with diffuse disease.

Key words: congenital hyperinsulinism, paternally inherited, ABCC8 gene, diazoxide, ^{18}F DOPA PET CT

INTRODUCTION

Neonatal diabetes mellitus (NDM), maturity-onset diabetes of the young (MODY) and congenital hyperinsulinism (CHI) form a spectrum of diseases that result from pathogenic variants in the *ABCC8* gene.[1] This gene encodes the sulphonylurea receptor (SUR1) subunit of the potassium adenosine triphosphate (K_{ATP}) channel involved in insulin synthesis within the pancreatic β-cell. A gain-of-function or loss-of-function mutation of the *ABCC8* gene leads to deficient or excessive insulin production, respectively.

The earliest report of CHI from loss-of-function *ABCC8* mutation dated back to 1995.[2] As the most severe form of hyperinsulinemic hypoglycemia (HH) in newborns, CHI is characterized by inappropriate secretion of insulin during an episode of hypoglycemia. Transient forms are commonly seen in infants of diabetic mothers, those born small or large for gestational age, or following perinatal stress. These cases are usually diazoxide-responsive and resolve without requiring long-term pharmacotherapy. When there is persistent severe hypoglycemia requiring high glucose infusion rates (GIR), patients should be evaluated for CHI. The most common genes responsible for CHI are the K_{ATP} channel regulating genes, *ABCC8* and *KCNJ11*, which lie on chromosome 11p15.1.[3,4] Variants in these genes lead to impaired K_{ATP} channel synthesis, defective trafficking within the cell and to the plasma membrane, or altered glucose sensitivity– resulting in persistent β-cell membrane depolarization and continuous insulin release,

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suppressing gluconeogenesis, glycogenolysis and lipolysis, culminating in non-ketotic hypoglycemia.[5,6] Timely diagnosis and management of CHI is important to prevent acute complications of hypoglycemia such as seizures and death, as well as long-term neurological sequelae including cerebral palsy.

The estimated incidence of CHI is between 1 in 27,000 and 1 in 50,000 live births, with higher incidences seen in communities that are isolated and with higher consanguinity rates.[7,8] Less is known regarding the carrier frequency of *ABCC8* variants. Still, Glaser et al., reported a mutation carrier rate of 1 in 52 amongst more than 21,000 Ashkenazi Jewish individuals who were genotyped, translating to an estimated incidence of 1 in 10,816 for homozygous or compound heterozygous *ABCC8*-related CHI.[9] Numerous studies have reported hundreds of pathogenic *ABCC8* variants to elucidate genotype-phenotype correlations in CHI.[7]

In a cohort study 300 CHI patients, Kapoor et al., identified 45.3% with a genetic diagnosis.[10] While majority of the diazoxide-responsive cases had no identifiable mutation, 92.8% of those unresponsive to diazoxide had either *ABCC8* or *KCNJ11* pathogenic variants. CHI patients with *ABCC8* variants may be homozygous, compound heterozygous or heterozygous. Most patients with homozygous or compound heterozygous mutations are diazoxide unresponsive and have diffuse disease. Those with heterozygous *ABCC8* mutations may exhibit diazoxide responsive or diazoxide unresponsive phenotypes. Majority of them are dominant mutations, but a smaller group of patients has been found to have paternally inherited *ABCC8* variants with clinically unaffected fathers.[10,11] Historically, paternally inherited *ABCC8* variants have been associated with focal lesions, with loss of heterozygosity of the maternal allele demonstrated within the focal disease region.[12,13] However, there have been rare reports of paternally inherited *ABCC8* variants (from unaffected fathers), without a second hit identified, resulting in diffuse disease.[14]

In this report, we describe five patients who have CHI with paternally inherited *ABCC8* variants. Three of the cases involve known recessive variants, and notably only one patient exhibited the classical association with a focal lesion while the others had diffuse disease. We discuss the possible reasons for the difference between what we found in our patients and that which has been previously reported. Our findings suggest that CHI arising from paternally inherited *ABCC8* variants present with different clinical phenotypes, thus highlighting the variability in genotype-phenotype correlation.

METHODOLOGY

Patient selection

We included patients diagnosed with CHI and paternally inherited *ABCC8* variants on genetic testing. These patients were either born at or transferred to our center, which has established a HH program since 2015. Each child fulfilled the biochemical criteria for HH and inherited *ABCC8* variants from their fathers.

Data collection

Data were collected retrospectively from electronic medical records. Relevant antenatal and birth history collected included birth gestational age, birth weight, delivery mode, presence of antenatal scan abnormalities, maternal gestational diabetes mellitus and consanguinity, the age at first documented hypoglycemia episode and accompanying symptoms. Biochemical parameters collected included plasma glucose, insulin, ketone, cortisol, free fatty acid and growth hormone levels. Radiological investigations, where available, included findings from ^{18}F-DOPA-PET scan. Treatment-related information was noted, including maximum GIR, age at initiation and maximum doses of oral diazoxide, subcutaneous octreotide and oral nifedipine. For patients who underwent surgery, the procedure performed and estimated percentage of pancreas removed were recorded. Long-term comorbidities and neurodevelopmental outcomes were documented from outpatient follow up records.

Genetic testing

Genetic testing was performed using blood samples collected in EDTA tubes. Patients 1, 2 and 3 underwent Invitae Hypoglycemia Panel testing (San Francisco, CA, USA, Test Code 98006, includes 120 genes); while patients 4 and 5 underwent Sanger sequencing of the *ABCC8* and *KCNJ11* genes at Exeter Molecular Genetics Laboratory (UK).

All patients underwent comprehensive genetic counseling provided by a trained genetic counselor in collaboration with a geneticist. A written informed consent was obtained from a parent before testing. Genetic test results were reviewed by a geneticist before discussion with patient's family. In cases where a pathogenic variant was identified, further parental testing was conducted to determine if the mutation was inherited or *de novo*.

Ethical considerations

The study was granted exemption from review and informed consent by the SingHealth Institutional Review Board (CIRB 2021/2166) due to its use of de-identified clinical data.

CASE

We present five patients who were diagnosed with CHI with paternally inherited *ABCC8* variants. Table 1 shows the patients' demographic and relevant perinatal information. Four of them were male and four were Asians. All were born to non-consanguineous parents. One patient was

Table 1. Patient's demographic information

Patient	1	2	3	4	5
Sex	Male	Female	Male	Male	Male
Ethnicity	Asian	Asian	Asian	Non-Asian	Asian
Gestational age (Weeks + days)	37+3	36+6	39+5	37+5	38+5
Birth weight (g), SDS, centile (%)	5038, +4.14, 100	4575, +3.30, 99.9	4585, +2.17, 99.5	3335, +0.73, 77.0	3230, -0.16, 50
Mode of delivery	LSCS	LSCS	LSCS	NVD	LSCS
Antenatal scan abnormality	Macrosomia	Macrosomia	Macrosomia	None	None
Gestational diabetes (Yes/No)	No	Yes	No	No	No
Parental consanguinity (Yes/No)	No	No	No	No	No

LSCS, lower section cesarean section; NVD, normal vaginal delivery

Table 2. Patient's biochemistry and radiological investigations results

Patient	1	2	3	4	5
First hypoglycemia					
Hours of life	2	6	Day 93	36	3
Symptomatic (Yes/No)	No	No	Yes	Yes	Yes
BG (mmol/L)	2.0	2.7	2.8	1.5	0.2
Critical blood samples					
Days of life	Day 3	Day 6	93	Day 18	Day 3
BG (mmol/L)	1.5	2.7	2.8	2.5	1.2
Ketones (mmol/L)	0.1	0	0.3	0.0	(N.D.)
Insulin (mU/L)	89.7	52.4	3	3.3	11.7
Free fatty acid (mmol/L)	<0.10	0.11	1.7	(N.D.)	(N.D.)
Imaging results					
^{18}F-DOPA scan	Diffuse	Diffuse	Diffuse	Focal	
^{68}G-DOTATATE-PET					Inconclusive
^{68}GA-NODAGA-Exendin-4 scan	No focal lesion				
Ultrasound					Small nodular focus at junction of pancreas body and medial tail
Pancreatectomy	Near total	Subtotal at 3-month-old Near total at 5-month-old	No surgical intervention	Focal lesionectomy	Partial at 4-month-old Near total at 6-month-old

BG, blood glucose; N.D., no data

born late preterm at 36 + 6 weeks gestation, while the rest were term. Their birth weights ranged between 3,230 g and 5,038 g; three of the patients were macrosomic and required delivery by caesarean section, while the other two had birth weight appropriate for gestational age. Only one patient was an infant of mother with gestational diabetes.

Results of the diagnostic evaluation and treatment information of each patient are presented in Tables 2 and 3, respectively. All except one child presented with hypoglycemia early, within the first 48 hours of life, with blood glucose ranging between 0.2 to 2.0 mmol/L. Half of these patients were symptomatic, and all of them required high GIR (16.4 to 26.6 mg/kg/min) to maintain normoglycemia. These four patients were treated with oral diazoxide at doses up to 15-20 mg/kg/day and subcutaneous octreotide 33-35 mcg/kg/day but continued to have persistent hypoglycemia. The child (Case 3) who presented later at 3 months of life was born in an external medical facility and early postnatal glucose levels were reportedly normal. He required a relatively lower GIR and was the only case who responded to diazoxide at the dose of 4.5 mg/kg/day.

Four patients underwent ^{18}F-DOPA scan, while one underwent ^{68}G-DOTATATE PET scan due to the unavailability of the ^{18}F-DOPA scan in our center at the time when the first case of CHI was diagnosed. Out of the four patients who underwent ^{18}F-DOPA scan, three showed diffuse disease and only one demonstrated a focal lesion that was typically associated with paternally inherited *ABCC8* variant.

Patients who were diazoxide-unresponsive and had diffuse disease were eventually managed with near total pancreatectomy, while the patient with a focal lesion underwent curative lesionectomy.

Case 3, the only patient who responded to diazoxide, was also found to have a pathogenic *ABCC9* variant and had clinical features consistent with Cantu Syndrome – coarse facial features, hypertrichosis, large patent ductus arteriosus, complex subarachnoid vasculature and a left-sided congenital pulmonary airway malformation. He was recently admitted with persistent hypoglycemia following a viral gastrointestinal illness which required careful titration of diazoxide to 7 mg/kg/day, without cardio-

Table 3. Pharmacological interventions and follow-up outcomes

Patient	1	2	3	4	5
Treatment from diagnosis					
Maximum GIR (mg/kg/min)	21	26.6	8.8	20	16.4
Diazoxide					
Days of life initiated	10	7	102	12	3
Initial dose (mg/kg/day)	4.8	5.3	3.0	5.0	6.0
Maximum dose (mg/kg/day)	15.0	11.0	4.5	20.0	20.0
Octreotide					
Days of life initiated	44	14	Nil	19	45
Initial dose (mcg/kg/day)	5.0	5.2		5.0	7.5
Maximum dose (mcg/kg/day)	33.0	33.0		35.0	33.0
Nifedipine					
Days of life initiated		74			65
Initial dose (mg/kg/day)		1.1			0.2
Maximum dose (mg/kg/day)		1.26			0.7
Treatment on discharge					
Diazoxide (mg/kg/day)			4.5		
Hydrochlorothiazide (mg/kg/day)			4.5		
Octreotide (mcg/kg/day)					10
Mode of feeding	Gastrostomy	Gastrostomy	Oral + NGT	No data	NGT
Follow up					
Age at time of writing in years	0.7	1.5	2	8	13
Neurodevelopment	Normal	Normal	Normal	Normal	Normal

GIR, glucose infusion rate; NGT, nasogastric tube feeding

Table 4. Genetic variant found in relation to clinical phenotype of CHI

Patient	1	2	3	4	5
First variant found	*ABCC8* c.4258C>T (p.Arg1420Cys)	*ABCC8* c.4400C>T (p.Pro1467Leu)	*ABCC8* c.4252C>T (p.Arg1418Cys)	*ABCC8* c.4480C>T (p.Arg1494Trp)	*ABCC8* c.4414G>A (p.Asp1472Asn)
Classification	Heterozygous pathogenic	Heterozygous, VUS	Heterozygous Likely pathogenic	Heterozygous pathogenic	Heterozygous pathogenic
Inheritance	Paternal	Paternal	Paternal	Paternal	Paternal
Other variant found	*ABCC8* Partial deletion on Exon 31	None	*ABCC9* c.3347G>A (p.Arg1116His)	None	None
Classification	Heterozygous pathogenic		Heterozygous pathogenic		
Inheritance	Maternal		*De novo*		
Pancreas involvement	Diffuse	Diffuse	Diffuse	Focal	Diffuse
Diazoxide response	Resistant	Resistant	Responsive	Resistant	Resistant
Age at diagnosis	Day 3	Day 6	Day 93	Day 2	Day 3
Surgical intervention	Near total pancreatectomy	Near total pancreatectomy	Nil required	Lesionectomy	Near total pancreatectomy
Risk of recurrence in next offspring	25%	Uncertain	Uncertain	Negligible	Uncertain

VUS, variant of uncertain significance

vascular compromise. Following recovery, diazoxide dose was weaned back to baseline.

Table 4 summarizes the salient clinical features of each patient in relation to their genetic variant. Each patient had a distinct paternally inherited *ABCC8* variant. One patient had a concomitant maternally inherited partial deletion of the *ABCC8* exon, which makes him a compound heterozygous genotype. Out of the four patients who had a single paternally inherited *ABCC8* variant – one was diazoxide-unresponsive and had a focal lesion, two were diazoxide-unresponsive and had diffuse disease, while the last one was diazoxide-responsive and had diffuse disease.

As of this writing, the patients are now between 8 months old and 13 years of age and remain on follow-up. All of them have normal neurodevelopmental outcomes thus far.

DISCUSSION

Reference genomic data from Singapore's National Precision Medicine (NPM) program has shown that the carrier rate of an *ABCC8* gene mutation in our local population is 1 in 754 and the carrier frequency is similar in both genders.[15] The average number of live births per year in Singapore in the past decade (between 2014 and 2023) was 31,000.[16] This translates to 41 new carriers of the *ABCC8* mutation each year. To the best of our knowledge, the five patients reported in this case series are the only documented cases of CHI with paternally inherited *ABCC8* variants in our country over the past decade. While most carriers are likely to have a recessive variant, some of the CHI-related paternally inherited *ABCC8* variants may be dominant forms with variable penetrance – a possible explanation accounting for CHI patients with only a single paternally

inherited *ABCC8* variant detected and asymptomatic fathers.

When managing a patient with CHI, determining diazoxide-responsiveness is a crucial step. Patients who do not respond to diazoxide may require somatostatin analogs (octreotide), but tachyphylaxis and suboptimal compliance due to multiple injections limit its acceptability and efficacy.[17] Surgical intervention may hence become inevitable to prevent recurrent hypoglycemia and its undesirable consequences, including neuro-disability. In such cases, genetic testing and imaging of the pancreas are key investigations that guide further management. Genetic forms of CHI are unlikely to resolve over time and are often resistant to diazoxide, unlike cases with an identified pathogenic variant.[17,18] ^{18}F-DOPA-PET is the imaging of choice to differentiate focal lesions from diffuse disease.

Focal lesions can be treated with a lesionectomy which is often curative. Post-operative complications are minimal and most patients maintain normoglycemia without requiring further medical intervention.[17,19-21] Diffuse disease often requires near-total pancreatectomy and has far less satisfactory post-operative outcomes. Some of these patients continue to experience hypoglycemia despite having most of their pancreas removed due to persistent overactivity of remnant β-cell – necessitating continued pharmacotherapy or even additional surgery.[6] Majority eventually develop post-pancreatectomy diabetes mellitus and exocrine insufficiency.[22-24]

Numerous studies have explored the genotypic-phenotypic correlation in CHI, as it has several important clinical implications. Understanding these correlations may: i) Allow us to anticipate the clinical behavior of the CHI based on genetic results and manage them pro-actively; ii) Aid in prenatal or antenatal counseling for individuals who are carriers and planning to conceive;[6] and iii) In resource-limited regions, surgical intervention may potentially be pursued without the absolute need for advanced imaging techniques (such as ^{18}F-DOPA-PET) which can be a logistical challenge that significantly delays definitive treatment.

Paternally inherited *ABCC8* heterozygous mutations have been classically associated with focal pancreatic lesions. In this study, we presented five CHI cases with paternally inherited *ABCC8* variants, with varying clinical characteristics. Of these cases, only one patient (patient 4) had a focal lesion, while the others had diffuse disease.

Patient 1 had a paternally inherited recessive missense *ABCC8* variant (c.4258C>T, p.Arg1420Cys),[25] as well as a maternally inherited recessive *ABCC8* variant that results in a partial deletion on exon 31 that is expected to disrupt RNA splicing and lead to loss of protein function. The latter is a novel variant that has not been previously reported. His clinical progress was consistent with what is expected of CHI arising from compound heterozygous recessively acting *ABCC8* mutations – diffuse disease with no response to diazoxide.[18] These patients tend to present early and have very recurrent hypoglycemia. In the case series by Kapoor et al., the median age of presentation for this genotype group was 1 day old. Between CHI patients with normal and poorer neurodevelopmental outcomes, the latter group was found to have significantly longer duration of intravenous glucose treatment and more severe symptoms at onset.[17] These patients invariably have diffuse disease and imaging may not be feasible or necessary especially in resource-limited settings.[6] Following knowledge of the genetic diagnosis, near total pancreatectomy may benefit the patients by avoiding further hypoglycemia and prolonged hospitalization.

Patients 2 and 5 had paternally inherited heterozygous *ABCC8* mutations, demonstrated no response to diazoxide, their ^{18}F-DOPA scan did not show any focal disease, and histopathological examination of their pancreas were conclusive of diffuse disease. Patient 2 had a missense variant of uncertain significance (c.4400C>T, p.Pro1467Leu) that had not been previously reported, while patient 5 had a missense variant (c.4414G>A, p.Asp1472Asn) that had been previously reported to be recessively acting.[14] Both patients' fathers carried the respective variants but were asymptomatic. Although paternally inherited recessive *ABCC8* variants are classically associated with focal lesions, both our patients had diffuse disease. Kapoor et al., had reported 6 out of 19 paternally inherited recessive *ABCC8* variants that were associated with diffuse disease, while another case series by Nessa et al., reported 3 out of 10 in their cohort. The exact mechanism that results in this phenomenon is unclear but possible explanations could include incomplete penetrance, presence of a second somatic recessive mutation within the pancreas that was not identified by sequencing, presence of other unknown genetic mutation (considering only around half of all CHI cases tested have an identifiable genetic mutation), or environmental influences.[12,13] We acknowledge our limitation which is the absence of further sequencing (such as Whole Genome Sequencing) to interrogate the intronic regions of CHI-related genes, that may potentially identify a second recessive variant. A less likely possibility would be a missed focal lesion at surgery.

Of note, the clinical presentations of patients 2 and 5 were not different from those of patient 1 (compound heterozygote) and patient 4 (focal disease). They presented with similar degrees of hypoglycemia within first few days of life and were not responsive to diazoxide or octreotide. A subtotal (80%) pancreatectomy was performed in both cases, with persistence of hypoglycemia post-operatively and they eventually went for second surgery to remove up to 95% of the pancreas. Both patients have normal neurodevelopmental outcomes to date.

Patient 3 was found to carry a paternally inherited recessive *ABCC8* variant (c.4252C>T, p.Arg1418Cys) and a *de novo* dominant *ABCC9* variant. The latter results in Cantu syndrome, a rare autosomal dominant disease that occurs

from a gain-of-function mutation in the *ABCC9* or *KCNJ8* gene, that encode the SUR2 and Kir6.1 subunits of the K_{ATP} channels respectively. While SUR1 is mainly expressed by pancreatic β-cell, SUR2 is found in cardiac, skeletal and smooth muscles. Increased K_{ATP} channel activity renders the cell in hyperpolarized state, leading to reduced excitability and contraction of the muscle cell. The clinical features of Cantu syndrome include cardiomegaly, large patent ductus arteriosus, pulmonary hypertension, vascular tortuosity in brain and retina, generalized edema, skeletal abnormalities, hypertrichosis, coarse facial features and developmental delay.[26] There is currently no pharmacotherapy found effective in treating patients with Cantu syndrome, although glibenclamide, a sulphonylurea that inhibits SUR1/2 activity, had been discussed as a potential drug.[27] Of note, the use of diazoxide can be potentially harmful for patients with Cantu syndrome because it works to increase K_{ATP} channel activity. This makes our case exceptionally interesting, because our patient has CHI resulting from coexisting *ABCC8* variant and he is diazoxide-responsive. Although this is a paternally inherited recessive variant from an unaffected father, it behaves atypically with a later onset, diffuse disease and was responsive to diazoxide. It is unclear whether the co-existence of the *ABCC9* variant has a role to play in contributing to its diazoxide-responsiveness. It is also with caution that diazoxide is used in the treatment of this patient's CHI, as close surveillance is required to ensure that the cardiovascular status of this child is not compromised.

CHI has been found to be associated with several genetic syndromes, but the mechanism through which the genetic defect results in dysregulation of insulin secretion and glucose metabolism are unclear in most. The syndromes that have been reported with CHI include overgrowth syndromes like Beckwith-Wiedemann and Sotos syndrome; monogenic developmental disorders such as Kabuki, Costello and CHARGE syndrome; chromosomal disorders such as Turner, Trisomy 13 and Trisomy 21; channelopathies like Timothy syndrome and Long QT; and metabolic disorders including congenital disorder of glycosylation, tyrosinemia and others.[28] To our knowledge, ours is the first case of Cantu syndrome with CHI.

Patient 4 had a paternally inherited recessive *ABCC8* variant (c.4480C>T, p.Arg1494Trp)[29,30] that has been previously reported in several cases of focal CHI where loss of heterozygosity of the corresponding maternal allele was demonstrated. His clinical presentation and findings were consistent with what has been observed.

A comprehensive review of our cases suggests that patients with paternally inherited *ABCC8* variants, whether autosomal recessive, heterozygous or associated with genetic syndromes, are heterogeneous in clinical phenotypes and cannot be reliably distinguished by their initial clinical presentation. Smith et al., described a pair of siblings with CHI who had the same paternally inherited *ABCC8* variant - the older sibling presented with persistent hypoglycemia that required GIR of 20.8 mg/kg/min and diazoxide, while the younger sibling had only transient hypoglycemia that resolved without high GIR requirement nor diazoxide.[31] Chang et al., presented 8 Chinese patients with CHI from *ABCC8* variants (most of them were paternally inherited heterozygous mutations with unaffected fathers) with variable clinical manifestations, suggesting that allelic expression imbalance (AEI) may be the underlying explanation for the phenotypic variations.[32]

Diazoxide-resistant disease may have focal or diffuse disease and can only be differentiated by functional imaging. Some focal lesions may still be missed on imaging.[21] While we acknowledge our limitations in the extent of genetic testing and the possibility of undiscovered CHI-causing mutations, paternally inherited heterozygous *ABCC8* variants do not necessarily indicate focal disease. Hence interpretation of ^{18}F-DOPA scan must be objective and unbiased. Furthermore, rare cases of CHI with multifocal lesions have been reported and curative treatment require removal of all the focal lesions.[33] This underscores the importance of pre- and intra-operative disease localization and careful planning of the surgical approach. A single-stage laparoscopic near-total pancreatectomy is the surgery of choice for these patients, as a subtotal pancreatectomy is unlikely to be successful in eliminating hypoglycemia in those with diffuse disease.

CONCLUSION

Patients with single paternally inherited *ABCC8* variants identified have variable clinical manifestations. They can have diffuse disease and may demonstrate diazoxide response. Their clinical presentations may not be distinguishable from the autosomal recessive, compound heterozygous, autosomal dominant or syndrome-associated forms of CHI. In this paper, we described cases of paternally inherited heterozygous *ABCC8* mutations with diffuse disease including one with a novel variant; a case with coexisting paternally inherited *ABCC8* and *ABCC9* variants with competing molecular mechanisms that have implications on medical therapy; and a case of compound heterozygous *ABCC8* mutations with a novel variant. Deeper understanding of the molecular mechanisms with functional analyses may help give us more information on the genotypic-phenotypic correlation in CHI cases related to *ABCC8*. From our experience, we advocate for prompt pursuit of a genetic diagnosis once diazoxide resistance is established or if there are atypical features (i.e., syndromic), followed by timely imaging with ^{18}F-DOPA-PET scan to detect focal or diffuse disease, and a single-stage near-total pancreatectomy may be considered in cases of diffuse disease. With this approach, we can avoid prolonged hospitalization and recurrent hypoglycemia and optimize neurodevelopmental outcomes in these patients.

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Patients' consent was obtained before submission of the manuscript.

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All authors certified fulfillment of ICMJE authorship criteria.

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CRediT Author Statement
CC: Conceptualization, Methodology, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **DC:** Conceptualization, Conceptualization, Resources, Data Curation, Writing – review and editing, Visualization, Project administration; **ALK:** Writing – review and editing, Visualization; **SC:** Conceptualization, Formal analysis, Resources, Data curation, Writing – review and editing, Visualization, Supervision, Project administration; **FY:** Conceptualization, Formal analysis, Resources, Data curation, Writing – review and editing, Visualization, Supervision, Project administration.

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Treatment of a Giant Prolactinoma With Bromocriptine Leads to Marked Improvement in Visual Field Defect

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Key words: prolactinoma, pituitary neoplasms, bromocriptine, dopamine agonists, visual fields, optic chiasm

A 48-year-old male had blurred vision, narrowed visual field and headache over 6 months. He lost consciousness for which he was brought to the emergency department. Pertinent in the neurologic examination was bitemporal hemianopsia. The rest of the physical and neurological examination was normal. A pituitary mass causing optic chiasmal compression was then suspected.

Serum prolactin was elevated at >100,000 mIU/L (>4,700 ng/mL). Cranial MRI (Figure 1) showed a lobulated T1-isointense and T2-heterogeneous pituitary mass, measuring 4.2 x 5.2 x 4.7 cm. There was compression of the third ventricle and foramen of Monro, obliteration of the optic nerves and chiasm, widened cavernous sinuses, and encasement of both internal carotid and left anterior cerebral arteries. A diagnosis of giant prolactin-secreting

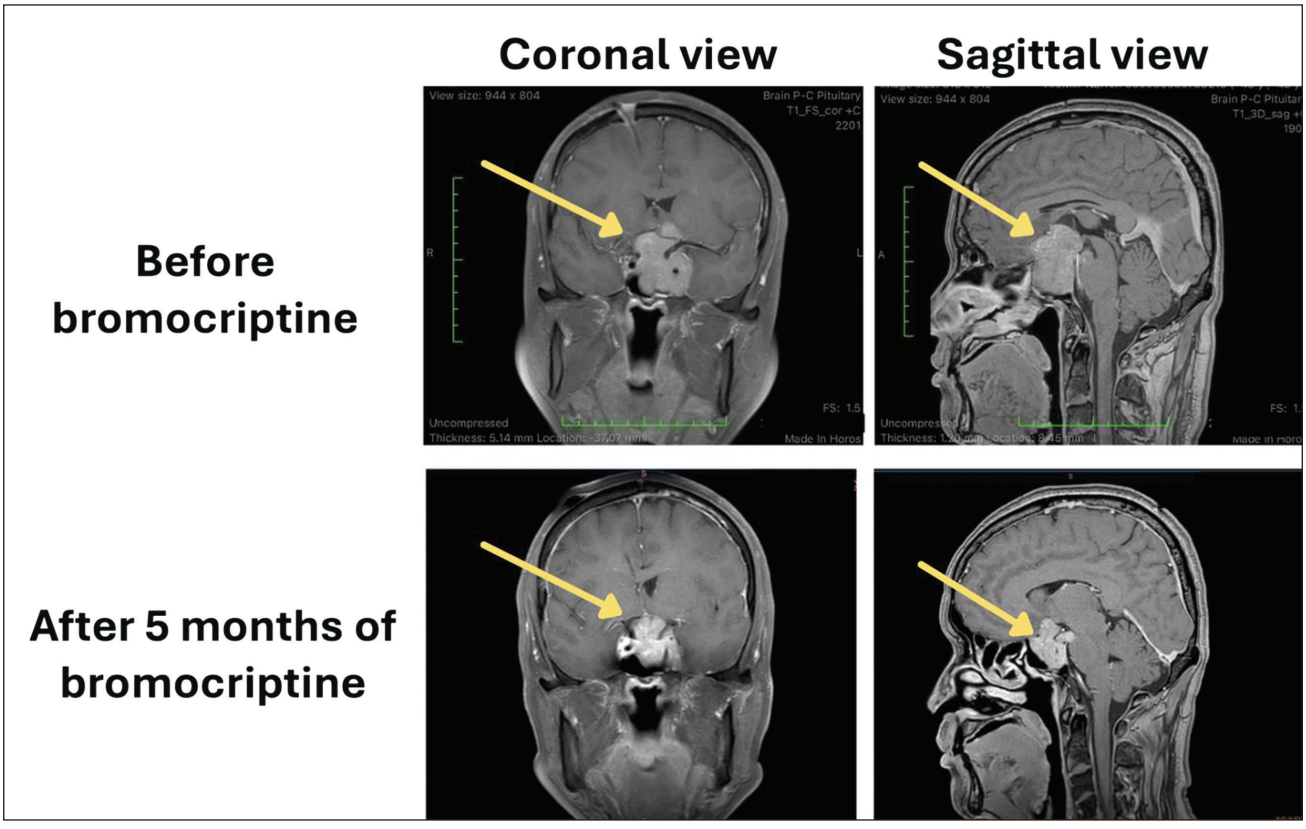

Figure 1. MRI showing the giant pituitary adenoma *(arrows)* before and 5 months after starting bromocriptine treatment.

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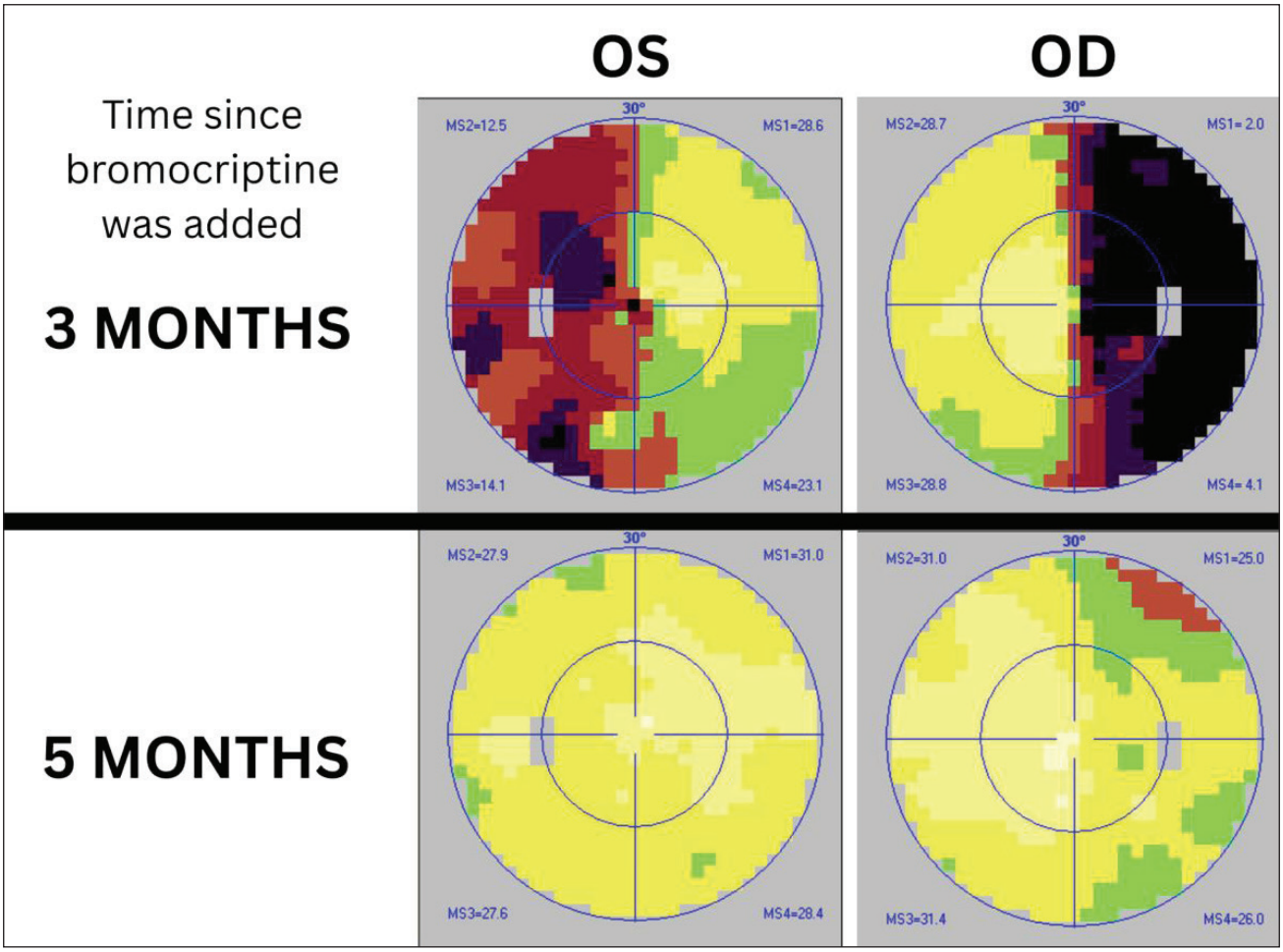

Figure 2. Visual field testing done 3 months after initiating bromocriptine showed moderate to severe depression of vision *(red and black)* in the entire temporal hemifield on the left eye (OS), and widespread severe depression of vision *(black)* of the entire temporal hemifield on the right eye (OD), respecting the vertical meridian (bitemporal hemianopsia). After 5 months, the left eye (OS) now shows very good field sensitivity *(yellow)* throughout. The right eye (OD) shows mild to moderate depression of vision *(green and red)* limited to the supero-temporal field.

pituitary macroadenoma was made. Due to obstructive hydrocephalus, he underwent emergency ventriculo-peritoneal shunt. Surgical removal of the tumor due to visual compromise was contemplated. However, since the pituitary mass was Knosp grade 4, surgical excision was expected to be incomplete. A multidisciplinary discussion involving the neurosurgeon, endocrinologist and the patient himself and his family was done. The goals of therapy were 1) Improvement in visual field (clinical); 2) Normalization of serum prolactin (biochemical); and 3) Reduction in size or complete resolution of the pituitary adenoma (radiologic/anatomic). It was emphasized to the patient that if there is no improvement in visual field with dopamine agonist (DA), surgery would eventually be resorted to. Treatment with DA was started based on prevailing recommendations.[1]

Cabergoline is not readily available and still has to be imported from overseas. Bromocriptine 2.5 mg/day was started since it is the locally available DA. Within 1 month, serum prolactin decreased to 10,746 mIU/L. Bromocriptine was increased to 3.75 mg/day and maintained at this level. Serum prolactin (mIU/L) further decreased to 3,031 to 2,465 then 1,722 at 2, 3 and 4 months (98% reduction), respectively. He tolerated bromocriptine and did not experience any adverse effects.

Visual field testing was done 3 months after initiating bromocriptine (Figure 2). It showed moderate to severe depression of vision *(red and black)* in the entire temporal hemifield on the left, and widespread severe depression of vision *(black)* of the entire temporal hemifield on the right, respecting the vertical meridian. This was interpreted as bitemporal hemianopsia, incongruous, from optic chiasm compression.

The characteristic visual field defect in large pituitary tumors is bitemporal hemianopsia. When large pituitary tumors extend superiorly, they compress on the optic chiasm - the site of decussation where the nerve fibers from the nasal portion of both retinas cross to the contralateral optic tract. The nerve fibers from the temporal portion of both retinas do not cross and continue on in the ipsilateral optic tract. The nasal portion of the retina allows us to see

the temporal field of vision. When these nerve fibers are compressed, the temporal field of vision on both sides are affected while the nasal visual fields remain clear.

Repeat cranial MRI at 5 months showed reduction in the size of adenoma to 3.2 x 3.2 x 3.4 cm. A follow-up perimetry done at this time showed very good field sensitivity (yellow) throughout the left eye while the right eye showed mild to moderate depression of vision (green and red) limited to the supero-temporal field.

LEARNING POINTS

Pharmacologic management with DA bromocriptine can be effective as first-line treatment in improving visual field defects even in a giant prolactinoma. Visual field defects should not compel doctors to immediately choose surgery over pharmacologic treatment for patients with prolactinomas.

Reduction in serum prolactin levels parallels the reduction in the size of the prolactinoma and improvement in visual field. Patients can be reassured that their vision may be restored medically without the need to undergo surgery if their giant pituitary adenoma is prolactin-secreting.

PATIENT'S PERSPECTIVE

For many years, I worked in a hospital where I was always the one caring for patients. I never imagined that one day, I would become a patient myself. Before I got diagnosed with giant prolactinoma, I often went to work deprived of sleep and food because of my lack of appetite. I also started forgetting things even right after doing them. I ignored these changes, thinking I was just tired, until I learned the real cause—a large tumor behind my eyes that was affecting my brain and vision.

First, I had my first surgery to remove fluid from my brain. I was later told I might need another major surgery to remove the tumor completely. But when I was referred to other physicians, they gave me hope. They explained that my case is still treatable through medications with strict monitoring, and if the treatment continues to work, I will no longer need another surgery.

With regular check-ups and close monitoring, the treatment has been successful. My hormone levels dropped by 98%, the tumor size has significantly decreased, and even my vision has started to improve! After 5 months of treatment, I was already fit to return to work.

As of this moment, I am still undergoing medication with constant guidance and help of my doctors. I remain hopeful that in time, I will be fully healed. This experience has taught me the true value of health, rest and self-care. I used to push myself too hard at work, but now I know our body has limits. Most of all, I learned to be truly grateful for the doctors who guided me, for my family and friends who supported me, and for God who gave me another chance at life. From the bottom of my heart, I am thankful for this second chance and for everyone who stood by me through this journey.

Ethical Consideration
The patient's consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Data Availability Statement
No datasets were generated or analyzed for this study.

CRediT Author Statement
MASS: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft presentation, Visualization, Supervision; **JSP**: Formal analysis, Investigation, Writing – review and editing; **SAL:** Formal analysis, Investigation, Writing – review and editing.

Author Disclosure
The authors declared no conflict of interest.

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BRIEF COMMUNICATIONS

Utilization and Impact of Diabetes Technology Among Type 1 Diabetes Patients at a Tertiary Hospital in Thailand

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Abstract

Background. While diabetes technologies such as insulin pumps, continuous glucose monitoring (CGM), and automated insulin delivery (AID) systems have demonstrated potential to improve glycemic control and reduce hypoglycemia, their utilization and effectiveness in Thailand remain underdocumented. This study aimed to assess the use and impact of diabetes technologies on glycemic outcomes at King Chulalongkorn Memorial Hospital (KCMH), a tertiary care center in Bangkok, Thailand.

Methodology. A cross-sectional study was conducted among T1D patients receiving care at the endocrinology clinic of KCMH between August 2023 and July 2024. Data were collected at each patient's most recent follow-up visit, and participants were classified into technology users and non-technology users. Data collection focused on demographics, diabetes technology use, and clinical parameters, including HbA1c, hypoglycemia events, and CGM metrics (Time in Range (TIR), Time Above Range (TAR), Time Below Range (TBR)).

Results. A total of 61 patients with T1D were included, of whom 49% were technology users (6% insulin pumps, 57% CGM, 37% AID). Technology users had a significantly higher mean HbA1c (8.1% ± 1.6) than non-technology users (7.2% ± 1.2, p = 0.011). AID users achieved a higher mean TIR (67.6% ± 16%) compared to CGM users (54.0% ± 23.8%), but the difference was not statistically significant. Both AID and CGM users maintained a low incidence of hypoglycemia (<54 mg/dL).

Conclusion. This study found a relatively high rate of diabetes technology adoption at our center compared to other Asian countries, highlighting its potential to reduce the risk of hypoglycemia and improve glycemic stability. However, technology users also had higher HbA1c levels, suggesting that diabetes technology is often prescribed to high-risk patients with poor glycemic control. Future research should focus on longitudinal studies to better understand and address barriers to optimal glycemic outcomes among diabetes technology users.

Key words: diabetes technology, type 1 diabetes, glycemic control

INTRODUCTION

Type 1 diabetes (T1D) requires intensive glucose management to prevent long-term complications.[1] Traditional methods, such as multiple daily insulin injections (MDI), are associated with an increased risk of hypoglycemia and may offer less lifestyle flexibility compared to advanced insulin delivery systems. Recent advancements, such as insulin pumps (CSII) and automated insulin delivery (AID) systems, have demonstrated potential in improving therapy optimization by enabling more precise, real-time adjustments to insulin delivery.[2] Similarly, self-monitoring of blood glucose (SMBG) provides only single-point measurements, potentially leading to unrecognized episodes of hyperglycemia or hypoglycemia. Recent advancements, such as insulin pumps, continuous glucose monitoring (CGM) and automated insulin delivery (AID) systems, have demonstrated potential to improve glycemic management by enabling better self-management and therapy optimization.[3] Meta-analyses have shown that CGM significantly reduces HbA1c levels by 0.24% compared to SMBG (95% CI: -0.34 to -0.13), while also lowering the risk of severe hypoglycemia.[4] Similarly, insulin pump therapy has been associated with a significant HbA1c reduction of 0.30% (95% CI: -0.58 to -0.02) compared to MDI, along with a decrease in severe hypoglycemic events.[5]

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Despite the benefits of diabetes technology, its utilization and effectiveness in Thailand remain underdocumented. This study aims to assess the use and impact of diabetes technologies on glycemic outcomes at King Chulalongkorn Memorial Hospital (KCMH), a tertiary care center in Bangkok, Thailand.

METHODOLOGY

This is a cross-sectional study conducted among T1D patients receiving care at the diabetes clinic of KCMH between August 2023 and July 2024. Patients aged 18 years or older with at least two follow-up visits were included, while those who were pregnant or lost to follow-up were excluded. We utilized a complete-case analysis approach, including only participants with complete clinical data for the outcomes in the final assessment. Individuals lost to follow-up were excluded. Baseline demographic data, micro- and macrovascular complications and treatment outcomes were collected from each patient's most recent follow-up visit. Participants were classified into two primary groups: technology users and non-technology users. Technology users were further categorized by their device type: Standalone CGM, Standalone insulin pumps (CSII) and Automated Insulin Delivery (AID) systems.

The data collection focused on the patient demographics, diabetes technology use and clinical parameters. For each participant, clinical data, including the most recent HbA1c reading, severe hypoglycemia events (hypoglycemia requiring assistance, emergency room visit or hospitalization) and CGM metrics collected from only technology users such as Time in Range (TIR 70-180 mg/dL), Time Above Range (TAR 181-250 mg/dL and >250 mg/dL), Time Below Range (TBR 54-69 mg/dL and <54 mg/dL) and glucose variability (% coefficient of variation), were collected from their latest follow-up visit within the study window.

Qualitative data were presented as frequencies and percentages. Prior to the analysis, the distribution of all continuous variables was assessed for normality using visual inspection of histograms and formal statistical testing (e.g., the Shapiro-Wilk test). Quantitative data with a normal distribution were expressed as mean ± SD and analyzed using the Student's t-test. Meanwhile, non-normally distributed data were expressed as median (IQR) and analyzed using the Wilcoxon rank-sum test. Categorical data were analyzed using the chi-square test or Fisher's exact test, as appropriate. A *p*-value of <0.05 was considered statistically significant.

This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand [IRB no.0459/68].

RESULTS

A total of 61 patients with T1D were included, with females comprising 67.2% of the participants, a median age of 35 years and a mean diabetes duration of 15 years. The mean body mass index (BMI) was 23.2 kg/m². Most participants held at least a bachelor's degree (77%) and were employed (72.1%). Regarding healthcare coverage, 56% of diabetes technology users were under the Universal Coverage Scheme, with fewer participants in the self-pay group. Comorbidities included dyslipidemia (39.3%), hypertension (8.2%) and thyroid disorders, including hypo-, hyperthyroidism, thyroid nodules and autoimmune thyroid diseases (16.4%). The prevalence of microvascular complications was 14.8% for diabetic retinopathy, 16.4% for diabetic nephropathy and 9.8% for diabetic neuropathy. Macrovascular complications were rare (Table 1).

Among the participants, 49% were technology users, while 51% were non-technology users. Among technology users, 6% used insulin pumps, 57% used CGM and 37% used AID systems. The median duration of technology use was 7.4 months. Technology users had a significantly higher mean HbA1c (8.1% ± 1.6) than non-technology users (7.2% ± 1.2, p = 0.011). Severe hypoglycemia occurred in 13.3% of technology users and 16.1% of non-technology users. Hyperglycemic crises (diabetic ketoacidosis or hyperglycemic hyperosmolar state) in the past year were rare, with only one patient affected in each group (Table 2).

CGM reports indicated that AID users achieved a higher mean TIR (67.6% ± 16%) compared to CGM users (54.0% ± 23.8%), although this difference was not statistically significant (p = 0.125). AID users also spent less time in hyperglycemia, with a lower time above range 181-250 mg/dL (23% ± 9.3%) and time above 250 mg/dL (10.6% ± 11%) compared to CGM users (27.9% ± 19.7% and 15.4% ± 16.1%, respectively). Furthermore, AID users had lower average glucose levels than CGM-only users (164.2 ± 28.2 versus 173.6 ± 46.3 mg/dL, respectively), whereas glucose variability was similar between the groups (35.8% ± 6.1% versus 35.6% ± 7.0%, respectively). Both AID and CGM users maintained low rates of hypoglycemia: time spent between 54–69 mg/dL was 1.5%–2.0% in both groups, while time spent below 54 mg/dL was 0% for all technology users (Table 3).

DISCUSSION

Our study identified a diabetes technology adoption rate of 49%. This figure is notably higher than reported data from other Asian regions, such as Singapore, China and Korea, where utilization of diabetes technology in T1D remains relatively low.[6-8] While our findings are comparable to adoption levels observed in Europe (>50%), they remain lower than those in high-income countries like the United States, where adoption rates reach up to 80%. Meanwhile, in countries like Japan, higher adoption rates (23% for insulin pumps and 41% for CGM) are driven by established reimbursement programs.[6-10] Our center's uptake likely reflects the impact of Thailand's Universal Coverage Scheme. Notably, while this scheme covered 56% of our technology users, the remaining 44% were self-

Table 1. Baseline characteristics of the T1D patients

Baseline characteristics	All (n = 61)	Technology users (n = 30)	Non-technology users (n = 31)
Female, n (%)	41 (67.2)	21 (70)	20 (64.5)
Age: median (IQR)	35 (26, 41)	32.5 (23.5, 37)	37 (29.5, 43.5)
Body weight(kg): mean ± SD	62.1 ± 12.1	63.9 ± 12.8	60.4 ± 11.4
Body mass index (kg/m²): mean ± SD	23.2 ± 3.6	23.8 ± 3.9	22.7 ± 3.3
Education level: n (%)			
High school	12 (19.7)	8 (26.7)	4 (12.9)
Bachelor's degree	47 (77)	21 (70)	26 (83.9)
Master's degree	2 (3.3)	1 (3.3)	1 (3.2)
Employment status: n (%)			
Yes	44 (72.1)	19 (63.3)	25 (80.6)
No	17 (27.9)	11 (36.7)	6 (19.4)
Healthcare entitlements: n (%)			
Universal coverage scheme	31 (50.8)	17 (56.7)	14 (45.2)
Social security scheme	24 (39.3)	10 (33.3)	14 (45.2)
Civil servants' direct payment entitlement	4 (6.6)	1 (3.3)	3 (9.7)
Self-pay	2 (3.3)	2 (6.7)	0 (0)
Comorbidities: n (%)			
Hypertension	5 (8.2)	3 (10)	2 (6.5)
Dyslipidemia	24 (39.3)	10 (33.3)	14 (45.2)
Graves' disease	4 (6.6)	2 (6.7)	2 (6.5)
Hashimoto's thyroiditis	6 (9.8)	2 (6.7)	4 (12.9)
Obstructive sleep apnea	1 (1.6)	1 (3.3)	0 (0)
MAFLD	3 (4.9)	2 (6.7)	1 (3.2)
PCOS	2 (3.3)	1 (3.3)	1 (3.2)
Depression	5 (8.2)	5 (16.7)	0 (0)
Coronary heart disease	2 (3.3)	1 (3.3)	1 (3.2)
Duration of T1DM - years: median (IQR)	15.5 (9.8)	15.1 (9.6)	15.8 (10.1)
HbA1C -%: mean ± SD	7.6 ± 1.4	8.1 ± 1.6	7.2 ± 1.2
Macrovascular complication: n (%)			
Myocardial infarction	2 (3.3)	1 (3.3)	1 (3.2)
Cerebrovascular disease	0 (0)	0 (0)	0 (0)
Peripheral arterial disease	0 (0)	0 (0)	0 (0)
Microvascular complication: n (%)			
Retinopathy	9 (14.8)	4 (13.3)	5 (16.1)
Nephropathy	10 (16.4)	2 (6.7)	8 (25.8)
Neuropathy	6 (9.8)	1 (3.3)	5 (16.1)
Diabetic technology: n (%)			
Continuous glucose monitoring alone	17 (27.9)	17 (57.3)	0 (0)
Insulin pump alone	2 (3.3)	2 (6)	0 (0)
Automated insulin delivery	11 (18.0)	11 (36.7)	0 (0)

Data are presented as n (%), median (IQR) and mean ± SD as described. MASLD = Metabolic-dysfunction associated steatotic liver disease, PCOS = polycystic ovarian syndrome

Table 2. Clinical outcomes and diabetic technology use

	Technology users (n = 30)	Non-technology users (n = 31)	*P*-value
HbA1c: Mean ± SD	8.1 ± 1.6	7.2 ± 1.2	
≤7%	4 (13.8)	13 (41.9)	0.011
>7%	25 (86.2)	18 (58.1)	0.033
Severe Hypoglycemia, n (%)			1.000
Yes	4 (13.3)	5 (16.1)	
No	25 (83.3)	25 (80.6)	
Hyperglycemic crisis, events per patient year			0.935
0	27 (90)	26 (83.8)	
1	1 (3.3)	1 (3.2)	
N/A	2 (6.7)	4 (13)	

payers, suggesting that individual affordability remains a significant factor in access to technology in our setting.

Interestingly, our study found that technology users had a significantly higher average HbA1c compared to non-technology users. While we acknowledge that technology users represent three distinct clinical groups — CGM, CSII and AID — the small size of our individual subgroups (specifically the standalone pump users at 6%) necessitated analyzing these participants as a single cohort to maintain sufficient statistical power. This disparity in HbA1c likely reflects several factors. First, advanced technology is often prioritized for high-risk patients with a history of poor glycemic control or clinically significant hypoglycemia, indicating a clinical selection bias. Second, the duration of technology use may play a role; since the median duration of technology use was approximately 7 months, new users face a steep learning curve in interpreting glucose trends and adjusting insulin, which can lead to suboptimal short-term results. Because our cross-sectional analysis focused

Table 3. Summary of CGM metrics of the technology-user T1D patients

Factor	CGM-only (n = 17)	AID (n = 11)	*P*-value
HbA1C: Median (IQR)	7.9 (7.0, 8.8)	7.6 (7.2, 8.0)	0.429
TIR (70 – 180 mg/dL) (%)	54.0 ± 23.8	67.6 ± 16.0	0.125
TAR (181-250 mg/dL) (%):	27.9 ± 19.7	23.0 ± 9.3	0.478
TAR (>250 mg/dL) (%)	15.4 ± 16.1	10.6 ± 11.0	0.417
TBR (54-69 mg/dL) (%): Median (IQR)	2.0 (1.0, 4.0)	1.5 (0.0, 2.8)	0.355
TBR (<54 mg/dL) (%) Median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.065
Average glucose, mg/dL	173.6 ± 46.3	164.2 ± 28.2	0.576
GMI,%	7.5 ± 1.2	7.2 ± 0.8	0.555
Glucose variability (%CV)	35.6 ± 7.0	35.8 ± 6.1	0.940

Data are presented as mean ± SD unless stated otherwise.
TIR = Time in range, TAR = Time above range, TBR = Time below range, GMI = Glucose management indicator

on the most recent clinical parameters, these findings might capture a population with more complex management needs that require ongoing, intensive support.

Consistent with established literature, our findings suggest that diabetes technology is effective in mitigating hypoglycemia risk.[11] In our cohort, severe hypoglycemia events—defined as episodes requiring external assistance—occurred less frequently among technology users (13.3%) compared to non-technology users (16.1%). This difference did not reach statistical significance. Furthermore, CGM data indicated that both AID and CGM users maintained a low incidence of time spent in the clinically significant hypoglycemic range (<54 mg/dL), supporting the role of these technologies in improving glycemic stability and preventing dangerous low blood sugar events.

Additionally, in our cohort, 56% of technology users were covered under Thailand's Universal Coverage Scheme, underscoring the expanding role of the National Health Security Office (NHSO) in improving access to advanced diabetes care. However, the remaining 44% of technology users relied on out-of-pocket payments or private insurance, suggesting that socioeconomic factors and individual affordability still play a major role in technology adoption in Thailand. This disparity highlights a potential selection bias whereby more affluent patients may be more likely to utilize these devices. Future policy efforts should focus on broader reimbursement to ensure that clinical need, rather than financial status, is the primary driver of technology use.[12]

The strengths of this study include a detailed exploration of demographic characteristics and CGM metrics among diabetes technology users. However, the limitations include a small sample size and the cross-sectional study design, which limit the ability to determine long-term glycemic improvements. In this study, a formal sample size calculation was not performed. Instead, a convenience sampling method was employed, including all 61 eligible patients with Type 1 Diabetes who attended the Diabetes clinic during the study period. We acknowledge this small sample size as a limitation that may impact the study's statistical power and the generalizability of the results. Moreover, the small sample size precluded the use of multivariable regression to adjust for potential confounders, such as duration of diabetes or baseline disease severity. Consequently, the observed associations remain unadjusted and should be interpreted with caution. Also, the cross-sectional design and use of convenience sampling may introduce selection bias, as patients with more complex management needs were more likely to be technology users. Specifically, the small number of standalone insulin pump users (6%) precluded a robust three-way subgroup analysis between CGM, CSII, and AID users. While these technologies are distinct, lumping them allowed for a broader assessment of the impact of technology adoption versus traditional management within our clinical context.

The study revealed that patients with more complex glycemic management needs primarily used advanced diabetes technologies as reflected by their higher HbA1c levels. AID systems demonstrated superior glycemic stability and a reduced risk of hypoglycemia, supporting their targeted use in high-risk patients. However, effective use of diabetes technology requires adequate training, continuous patient support and comprehensive education. Future research should focus on longitudinal studies to better understand and address barriers to optimal glycemic outcomes among diabetes technology users.

CONCLUSION

This study found a high rate of diabetes technology adoption at our center, highlighting its potential to reduce the risk of hypoglycemia and improve glycemic stability.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

JP: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing – original draft preparation, Visualization**; JJ:** Formal analysis, Investigation, Resources, Data curation, Project administration; **NL:** Conceptualization, Methodology, Formal analysis, Writing – review and editing, Supervision.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

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Corrigendum

Corrigendum on the article entitled, *'Thyroid Imaging Reporting and Data System (TIRADS) in Stratifying Risk of Thyroid Malignancy at The Medical City,'* by Dy et al., published in JAFES Vol. 32. No. 2.

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Description of error and impact

After the publication of this article, an internal database tracking review revealed that raw data spreadsheet columns had been cross-linked non-synchronously across multiple tracking matrices. This compilation oversight led to an inaccurate initial division of benign versus malignant historical groups. The overall study size remains fixed at 149 adult patients.

The corrected distribution confirms 68 malignant cases (45.64%) and 81 benign cases (54.36%), rather than the previously reported 50 malignant (33.56%) and 99 benign (66.44%) cases. These baseline tracking shifts alter corresponding numerical risks, crude and adjusted odds ratios, diagnostic performance metric percentages, and matching 95% confidence intervals across the text, figures, and tables.

The core clinical conclusions are updated to reflect that TIRADS categories 3–5 did not reach independent statistical significance in multivariable logistic regression analyses. These adjustments do not affect the clinical utility of ultrasound monitoring protocols, nor do they alter the academic validity of the study.

Corrections to the abstract

- **Results:** "Among the 149 nodules examined, 50 (33.56%) were confirmed to be malignant via histopathology, while 99 (66.44%) were benign... solid composition adjusted OR 4.912... Risk of malignancy for TIRADS categories 3, 4a, 4b, 4c and 5 were 12.50%, 12.82%, 26.19%, 53.70% and 66.67%, respectively... Crude OR for 4a, 4b, 4c, 5 were 1.03, 2.48, 8.12, 14.0... Sensitivity 98.00%, Specificity 7.07%, PPV 34.75%, NPV 87.50%, Accuracy 53%" is corrected to **"Among the 149 nodules examined, 68 (45.64%) were malignant and 81 (54.36%) were benign. Solid composition was significantly associated with malignancy. The overall diagnostic indices were as follows: sensitivity 95.59% (95% CI 87.64–99.08), specificity 7.41% (95% CI 2.77–15.43), PPV 46.43% (95% CI 37.97–55.05), NPV 66.67% (95% CI 29.93–92.51), positive LR 1.03 (95% CI 0.95–1.12), negative LR 0.60 (95% CI 0.15–2.29), and overall accuracy 47.65% (95% CI 39.41–55.98)."**
- **Conclusion:** "Higher TIRADS classification is associated with higher risk of thyroid malignancy. TIRADS is a sensitive classification in recognizing patients with thyroid cancer." is corrected to **"TIRADS categories 3–5 were not significantly associated with malignancy on logistic regression analysis. While TIRADS demonstrated high sensitivity (96%), its very low specificity (7%) limits its ability to reliably distinguish malignant from benign nodules, indicating that it should be used cautiously and in conjunction with other diagnostic tools."**

Corrections to the main text

- **Study Population and Clinico-Demographic Characteristics:** "Among these, 50 (33.56%) had histopathologically confirmed malignant nodules, while 99 (66.44%) had benign lesions" is corrected to **"Among these, 68 (45.64%) had histopathologically confirmed malignant nodules, while 81 (54.36%) had benign lesions (Figure 1)."**
- **Factors associated with malignancy and risk by TIRADS category:** "Malignancy risks for TIRADS categories 3, 4a, 4b, 4c, and 5 were 12.50%, 12.82%, 26.19%, 53.70%, and 66.67%, respectively... Crude OR for 4a, 4b, 4c, 5 were: 1.03, 2.48, 8.12, 14.0..." is corrected to **"Malignancy risks for TIRADS categories 3, 4a, 4b, 4c, and 5 were 33.33%, 36.84%, 38.10%, 57.41%, and 66.67%, respectively (Table 3). The cORs comparing TIRADS categories 4a, 4b, 4c, and 5 to category 3 were 1.17 (95% CI 0.26–6.21), 1.23 (95% CI 0.28–6.48), 2.70 (95% CI 0.64–13.85), and 4.00 (95% CI 0.48–44.25), respectively. Despite this apparent increase in risk, the differences in TIRADS grading distribution between malignant and benign nodules were not statistically significant (all p >0.05)."**
- **Diagnostic performance of TIRADS:** "On comparing TIRADS results and histopathology, we found that TIRADS 4a to 5 classes had approximately 98% sensitivity, 7.07% specificity, LR+ of 1.05, LR- of 0.28, PPV of 34.75%, NPV of 87.5%, and accuracy of 53%." is corrected to **"TIRADS categories 4a to 5 classified 93.96% of nodules, identifying 95.59% of malignant nodules but also labeling 92.59% of benign nodules**

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as high risk (Table 4). Sensitivity was high at 95.59% (95% CI 87.64–99.08); however, specificity was low at 7.41% (95% CI 2.77–15.43). The PPV, NPV, and overall accuracy were 46.43%, 66.67%, and 47.65%, respectively. The likelihood ratios indicated limited clinical utility (positive LR 1.03; negative LR 0.60), suggesting that TIRADS alone poorly distinguishes benign from malignant nodules despite its high sensitivity."

Corrections to figures and tables

- **Figure 1 flowchart:** The flowchart originally showed a cohort distribution of 99 benign cases and 50 malignant cases. This is corrected to display the updated stratification frequencies: **Benign Histopathology total is 81 patients (TIRADS 3 (6 patients), TIRADS 4a (24 patients), TIRADS 4b (26 patients), TIRADS 4c (23 patients), TIRADS 5 (2 patients)); Malignant Histopathology total is 68 patients (TIRADS 3 (3 patients), TIRADS 4a (14 patients), TIRADS 4b (16 patients), TIRADS 4c (31 patients), TIRADS 5 (4 patients)).**
- Tables 1 and 3 were removed.
- **Table 2.** Association of patient characteristics with malignancy at surgical histopathology (n = 149) corrected to: **Table 1.** Clinico-demographic profile of the patients **(n = 149).**

Table 1. Clinico-demographic profile of the patients (n = 149)

	CORRECTED				ORIGINAL		
	All (n = 149)	Benign (n = 81, 54.36%)	Malignant (n = 68, 45.64%)	*p*	Benign (n = 99)	Malignant (n = 50)	*p*
	Median (IQR); Frequency (%)						
Age (years)	47 (36-59)	49 (36-59)	44.50 (35.75-57.25)	0.304	47.13 ± 12.91	46.46 ± 14.93	0.775
<30	17 (11.41)	8 (9.88)	9 (13.24)	0.795	8 (8.08)	9 (18)	
30-39	34 (22.82)	16 (19.75)	18 (26.47)		26 (26.26)	8 (16)	0.040
40-49	33 (22.15)	18 (22.22)	15 (22.06)		22 (22.22)	11 (22)	0.184
50-59	33 (22.15)	21 (25.93)	12 (17.65)		22 (22.22)	11 (22)	0.184
60-69	29 (19.46)	16 (19.75)	13 (19.12)		19 (19.19)	10 (20)	0.223
≥70	3 (2.01)	2 (2.47)	1 (1.47)		2 (2.02)	1 (2)	0.538
Sex				0.432			0.883
Male	20 (13.42)	13 (16.05)	7 (10.29)		13 (13.13)	7 (14)	
Female	129 (86.58)	68 (83.95)	61 (89.71)		86 (86.87)	43 (86)	
Composition				<0.001			<0.001
Solid	93 (62.42)	40 (49.38)	53 (77.94)		49 (49.49)	44 (88)	
Mixed	56 (37.58)	41 (50.62)	15 (22.06)		50 (50.51)	6 (12)	
Echogenicity				0.041			
Hyperechoic or isoechoic	53 (35.57)	33 (40.74)	20 (29.41)		41 (41.41)	12 (24)	
Hypoechoic	56 (37.58)	33 (40.74)	23 (33.82)		38 (38.38)	18 (36)	0.269
Markedly hypoechoic	40 (26.85)	15 (18.52)	25 (36.76)		20 (20.20)	20 (40)	0.007
Margins				0.141			
Well-circumscribed	60 (40.27)	34 (41.98)	26 (38.24)		48 (48.48)	13 (26)	
Microlobulated	37 (24.83)	24 (29.63)	13 (19.12)		26 (26.26)	10 (20)	0.471
Irregular	52 (34.90)	23 (28.40)	29 (42.65)		25 (25.25)	27 (54)	0.001
Calcifications				0.011			
Microcalcifications	36 (24.16)	19 (23.46)	17 (25.00)		20 (20.20)	16 (32)	
Macrocalcifications	29 (19.46)	9 (11.11)	20 (29.41)		13 (13.13)	16 (32)	0.391
None	84 (56.38)	53 (65.43)	31 (45.59)		66 (66.67)	18 (36)	0.012
Shape				0.254			
Wider than tall	123 (82.55)	70 (86.42)	53 (77.94)		86 (86.87)	37 (74)	
Taller than wide	26 (17.45)	11 (13.58)	15 (22.06)		13 (13.13)	13 (26)	0.055
TIRADS Category				0.150			
3	9 (6.04)	6 (7.41)	3 (4.41)				
4a	38 (25.50)	24 (29.63)	14 (20.59)				
4b	42 (28.19)	26 (32.10)	16 (23.53)				
4c	54 (36.24)	23 (28.40)	31 (45.59)				
5	6 (4.03)	2 (2.47)	4 (5.88)				
Bethesda classification				<0.001			
I	13 (8.72)	11 (13.58)	2 (2.94)		82 (82.83)	13 (26)	
II	82 (55.03)	56 (69.14)	26 (38.24)				
III	12 (8.05)	4 (4.94)	8 (11.76)		5 (5.05)	7 (14)	0.001
IV	11 (7.38)	7 (8.64)	4 (5.88)		9 (9.09)	2 (4)	0.687
V	27 (18.12)	3 (3.70)	24 (35.29)		3 (3.03)	24 (48)	<0.001
VI	4 (2.68)	0	4 (5.88)		0	4 (8)	
Dimensions							
CC	2.67 (1.74-3.80)	3.09 (1.88-4.11)	2.14 (1.63-3.51)	0.008	3.06 ± 1.39	2.49 ± 1.20	0.016
W	1.94 (1.34-2.98)	2.29 (1.51-3.20)	1.66 (1.16-2.33)	0.008	2.34 ± 1.20	1.88 ± 0.98	0.023
AP	1.61 (1.06-2.46)	1.80 (1.19-2.69)	1.44 (1.00-2.01)	0.100	1.86 ± 0.95	1.66 ± 0.87	0.215

- Table 4. Clinical features associated with malignant thyroid nodules at surgical pathology (n = 149) corrected to: **Table 2.**
- Table 5. TIRADS categories and risk of malignancy of patients who underwent thyroidectomy (n = 149) corrected to: **Table 3.**

Table 2. Clinical features associated with malignant thyroid nodules at surgical pathology (n = 149)

	CORRECTED				ORIGINAL		
	cOR (95% CI)	*p*	aOR (95% CI)	*p*	aOR	95% CI	*p*-value
Age (years)	0.99 (0.96-1.01)	0.311					
<30	reference	-	reference	-	(reference)	-	-
30-39	1.00 (0.31-3.23)	>0.999	1.60 (0.39-6.96)	0.516	0.2823	0.0402 to 1.9818	0.203
40-49	0.74 (0.22-2.40)	0.616	0.86 (0.20-3.82)	0.845	0.4061	0.0612 to 2.6961	0.351
50-59	0.51 (0.15-1.66)	0.264	0.53 (0.11-2.54)	0.419	0.4125	0.0606 to 2.8058	0.365
60-69	0.72 (0.21-2.40)	0.595	0.40 (0.08-1.91)	0.253	0.1135	0.0146 to 0.8849	0.038
≥70	0.44 (0.02-5.53)	0.538	0.23 (0.00-5.34)	0.413	0.1076	0.0009 to 12.5138	0.358
Sex							
Female	reference	-	reference	-			
Male	0.60 (0.21-1.56)	0.308	0.29 (0.07-1.05)	0.059	0.6446	0.1113 to 3.7339	0.624
Composition							
Mixed	reference	-	reference	-			
Solid	3.62 (1.79-7.61)	<0.001	2.14 (0.90-5.26)	0.084	4.9122	1.3257 to 18.2011	0.017
Echogenicity							
Hyperechoic or isoechoic	reference	-	reference	-	reference	-	-
Hypoechoic	1.15 (0.53-2.50)	0.722	1.21 (0.49-3.08)	0.676	1.9757	0.6069 to 6.4319	0.258
Markedly hypoechoic	2.75 (1.19-6.54)	0.019	3.48 (1.16-11.47)	0.026	3.6708	0.8463 to 15.9214	0.082
Margins							
Well-circumscribed	reference	-	reference	-	reference	-	-
Microlobulated	0.71 (0.30-1.64)	0.425	0.77 (0.29-1.96)	0.582	2.0423	0.5823 to 7.1637	0.265
Irregular	1.65 (0.78- 3.51)	0.190	0.63 (0.23-1.67)	0.361	1.6792	0.4940 to 5.7073	0.406
Calcifications							
None	reference	-					
Microcalcifications	2.48 (0.91-7.14)	0.081					
Macrocalcifications	0.65 (0.30-1.45)	0.292					
Shape							
Wider than tall	reference	-					
Taller than wide	1.80 (0.77-4.33)	0.178					
Bethesda classification							
I or II	reference	-	reference	-	reference	-	-
III	4.47 (1.36-16.64)	0.013	4.04 (1.07-17.68)	0.039	7.4988	1.5572 to 36.1108	0.012
IV	1.42 (0.38-4.84)	0.586	1.78 (0.44-6.88)	0.405	1.9548	0.3329 to 11.4788	0.458
V	16.58 (5.56-65.78)	<0.001	13.95 (4.11-63.61)	<0.001	36.7881	8.1908 to 165.2305	<0.0001
VI	21.32 (2.17-2859.90)	0.006	17.42 (1.31-2510.29)	0.028	-	-	-
Dimensions							
CC	0.69 (0.53-0.89)	0.005					
W	0.65 (0.47-0.88)	0.007					
AP	0.72 (0.49-1.02)	0.071					

Table 3. TIRADS categories and risk of malignancy of patients who underwent thyroidectomy (n = 149)

TIRADS Category	CORRECTED					ORIGINAL				
	Histopathology		Risk of Malignancy (%)	cOR (95% CI)	*p*	Histopathology		Risk of Malignancy (%)	cOR (95% CI)	*p*
	Benign (n = 81)	Malignant (n = 68)				Benign (n = 99)	Malignant (n = 50)			
3	6/9	3/9	33.33%	reference	-	7/8	1/8	12.50%	reference	-
4a	24/38	14/38	36.84%	1.17 (0.26-6.21)	0.844	34/39	5/39	12.82%	1.03 (0.10 to 10.23)	0.980
4b	26/42	16/42	38.10%	1.23 (0.28-6.48)	0.789	31/42	11/42	38.10%	2.48 (0.27 to 22.54)	0.419
4c	23/54	31/54	57.41%	2.70 (0.64-13.85)	0.191	25/54	29/54	57.41%	8.12 (0.93 to 70.59)	0.059
5	2/6	4/6	66.67%	4.00 (0.48-44.25)	0.215	2/6	4/6	66.67%	14 (0.94 to 207.60)	0.055

Table 4. Accuracy of TIRADS in predicting a malignant thyroid nodule (n = 149)

TIRADS	CORRECTED			TIRADS	ORIGINAL		
	Malignant (n = 68)	Benign (n = 81)	Total		Malignant (n = 50)	Benign (n = 99)	Total
	Frequency (%)						
TIRADS 4 to 5	65 (95.59)	75 (92.59)	140 (93.96)	***TIRADS 4 to 5***	49 (98)	92 (92.93)	141 (94.63)
TIRADS 3	3 (4.41)	6 (7.41)	9 (6.04)	***TIRADS 3***	1 (2)	7 (7.07)	8 (5.37)
Total	68 (100)	81 (100)		***Total***	50 (100)	99 (100)	149 (100)
Sensitivity (%, 95% CI)	95.59 (87.64, 99.08)	Positive LR (LR, 95% CI)	1.03 (0.95, 1.12)	Sensitivity	98 (89.35-99.95)	Positive LR	1.05 (0.99 to 1.13)
Specificity (%, 95% CI)	7.41 (2.77, 15.43)	Negative LR (LR, 95% CI)	0.60 (0.15, 2.29)	Specificity	7.07 (2.89 to 14.03)	Negative LR	0.28 (0.04 to 2.24)
PPV (%, 95% CI)	46.43 (37.97, 55.05)	Accuracy (%, 95% CI)	47.65 (39.41, 55.98)	PPV	34.75 (33.24 to 36.29)	Accuracy	53%
NPV (%, 95% CI)	66.67 (29.93, 92.51)			NPV	87.5 (46.96 to 98.23)		

- Table 6. Accuracy of TIRADS in predicting a malignant thyroid nodule (n = 149) corrected to: **Table 4.**

Corrections to the References

The reference list is corrected from 26 to 18 entries. The following eight references were removed:

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Journal of the
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Endocrine Societies

Instructions to Authors

The **Journal of the ASEAN Federation of Endocrine Societies (JAFES)** is an open-access, peer-reviewed, English language, medical and health science journal that is published three times a year by the ASEAN Federation of Endocrine Societies (AFES). **Authors may include members and non-members of the AFES.**

Manuscripts, correspondences and other editorial matters should be sent via electronic mail to JAFES@asia.com or JAFES.editor@gmail.com.

Manuscripts are received with the understanding that the submitted manuscript represents original, exclusive and unpublished material, that it is not under simultaneous consideration for publication elsewhere, and that it will not be submitted for publication in another journal, until a decision is conveyed regarding its acceptability for publication in the JAFES. Furthermore, the submitted manuscript and supplemental materials do not infringe any copyright, violate any other intellectual property, data privacy rights of any person or entity, and have written permissions from copyright or intellectual property right owners for all copyrighted/patented works that are included in the manuscript; the study on which the manuscript is based had conformed to ethical standards and/or had been reviewed by the appropriate ethics committee; that no references or citations have been made to predatory/suspected predatory journals; and that the article had written/informed consent for publication from involved subjects.

ARTICLE TYPES

JAFES welcomes manuscripts on all aspects of endocrinology and metabolism in the form of original articles, review articles, case reports, feature articles (clinical practice guidelines, clinical case seminars, book reviews, et cetera), editorials, letters to the Editor, brief communications, images in endocrinology and special announcements. See Inset Box for descriptions and specific requirements per article type.

COVER LETTER

A cover letter must accompany each manuscript which should cite the title of the manuscript, the list of authors (complete names and affiliations and their specific role/s in writing the manuscript), with one (1) author clearly designated as correspondent, providing his/her complete postal/mailing address, telephone number, e-mail and fax number. The **JAFES cover letter template** must be used.

All authors are required to obtain an ORCID iD. To register, kindly follow this link: https://orcid.org/register.

AUTHOR FORM

For submissions to the JAFES to be accepted, all authors must read and accomplish the **JAFES Author Forms** consisting of: (1) the Authorship Certification, (2) the Author Declarations, (3) the Author Contribution Disclosure, (4) the Author Publishing Agreement and (5) the Conversion to Visual Abstract (optional for original articles only) to improve dissemination to practitioners and lay readers. The completely accomplished JAFES Author Forms shall be scanned and submitted along with the manuscript. No manuscript shall be received without the completely accomplished JAFES Author Forms.

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To improve and standardize reporting of findings depending on the study type, authors should ensure compliance with and submit the appropriate accomplished EQUATOR (Enhancing the QUAlity and Transparency of Research) Network Guidelines. These guidelines are freely available at: http://equator-network.org.

1. CONSORT (2010) Checklist for Reporting Clinical Trials
2. CARE (2013) Checklist for Reporting Case Reports
3. COREQ (2007) Checklist for Reporting Qualitative Research
4. PRISMA (2009) Checklist for Reporting Systematic Reviews and Meta-Analyses
5. STROBE (2007) Checklist for Reporting Observational Studies
6. STARD (2015) Checklist for Reporting Diagnostic Accuracy Studies
7. CHEERS (2013) Checklist for Reporting Economic Evaluation of Health Interventions
8. SQUIRE (2015) Checklist for Quality Improvement Reporting in Healthcare
9. ARRIVE (2013) Guidelines for Reporting Animal Research

ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

In order to ensure scientific objectivity and independence, the JAFES requires all authors to make a full disclosure of areas of potential conflict of interest. Such disclosure will indicate whether the person and/or his/her immediate family has any financial relationship with pharmaceutical companies, medical equipment manufacturers, biomedical device manufacturers, or any companies with significant involvement in the field of health care.

Examples of disclosures include but not limited to ownership, employment, research support (including provision of equipment or materials), involvement as speaker, consultant, or any other financial relationship or arrangement with manufacturers, companies or suppliers. With respect to any relationships identified, author(s) must provide sufficiently detailed information to permit assessment of the significance of the potential conflict of interest (for example, the amount of money involved and/or the identification of any value of goods and services).

The form is also downloadable at http://www.icmje.org/conflicts-of-interest/.

ETHICS REVIEW APPROVAL

For Original Articles, authors are required to submit a scanned soft copy of the Ethics Review Approval of their research. For manuscripts reporting data from studies involving animals, authors are required to submit a scanned copy of the Institutional Animal Care and Use Committee approval.

INFORMED CONSENT

For Case Reports, Images in Endocrinology and Clinical Case Seminars, authors are required to submit scanned soft copy of signed informed consent for publication from the involved subject/s ("Patient Consent Form"). In case the involved subject/s can no longer be contacted (i.e., retrospective studies, no contact information, et cetera) to obtain consent, the author must seek ethical clearance from the institutional board to publish the information about the subject/s.

DATA SHARING AND AVAILABILITY

For purposes of transparency and scientific integrity, JAFES requires that authors provide a statement on the availability of data described in the manuscript submission. Depending on the circumstances, one of the following data availability and sharing statements may be selected:

- Datasets generated and analyzed are included in the published article.
- No datasets were generated or analyzed for this study.
- Datasets for the study are publicly available in the data repositories* listed in References.**
- Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.
- Datasets analyzed in the study are under license and not publicly available for sharing.

If the above statements are not appropriate, the authors are asked to contact the JAFES Editorial Coordinator at jafes.editor@gmail.com.

Repositories for deposit of datasets may include institutional repositories or third-party repositories such as but not limited to:

- Figshare [https://figshare.com/]
- Dryad [https://datadryad.org/]
- Zenodo [https://zenodo.org/]
- Open Science Framework [https://osf.io/]
- Dataverse [https://dataverse.harvard.edu/]

Note: Deposited datasets should bear a persistent identifier (e.g., Digital Object Identifier or DOI; or accession number) and publicly available through a license (at least CC-BY 4.0).

ARTIFICIAL INTELLIGENCE (AI)-GENERATED CONTENT

Authors are required to disclose their use of generative artificial intelligence (AI) and AI-assisted technologies for all submissions to JAFES. This shall be described in the cover letter AND the submitted work in the appropriate section as to how it was used.

Authors are expected to exercise due diligence in reviewing, editing, and finalizing the output arising from use of such technologies, to include ensuring that there is appropriate attribution of all quoted material, including full citations.

Use of AI for data collection, analysis, or figure generation

The use of AI/AI-assisted technologies for data collection, analysis, or figure generation shall be described in sufficient detail as part of the Methodology.

Use of AI for manuscript preparation

A statement reflecting the use of AI/AI-assisted technologies shall be included as part of the Acknowledgments.

Example statement:

Acknowledgments

The author(s) used [NAME OF TOOL/SERVICE] to [OBJECTIVE OF USING AI/AI-ASSISTED TECHNOLOGY] and have duly overseen, reviewed, edited, and finalized the content.

GENERAL GUIDELINES

1. The manuscript should be encoded using Microsoft Word, double-spaced throughout with 1¼ cm (½ inch) paragraph indentation, with 3-cm margins (1¼ inch) all around on A4 size paper. The preferred font style and size is Times New Roman 12.
2. The manuscript should be arranged in sequence as follows: (1) Title Page, (2) Abstract, (3) Text, (4) References, (5) Tables, and (6) Figures and Illustrations.
3. References should pertain directly to the work being reported.
4. All the sheets of the manuscript should be labelled with the family name of the main author (all in capital letters) and page number (in Arabic Numerals) printed on the upper right corner.
5. All manuscripts not complying with the above shall be promptly returned for correction and resubmission.

Title Page

1. The title should be as concise as possible.
2. Only the full names of the authors directly affiliated with the work should be included (First name, Middle initial and Last name). There are 4 criteria for authorship (ICMJE recommendations):
   2.1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
   2.2. Drafting the work or revising it critically for important intellectual content; AND
   2.3. Final approval of the version to be published; AND
   2.4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
3. The highest educational attainment or title of the authors should be included as an attachment whenever appropriate.
4. Name and location of no more than one (1) institutional affiliation per author may be included.
5. If the paper has been presented in a scientific forum or convention, a note should be provided indicating the name, location and date of its presentation.

Abstract

For original articles, the abstract should contain no more than 500 words with a structured format consisting of the objective/s, methodology, results and conclusion. For feature articles, case reports, interhospital grand rounds, and brief communications, the abstract should be no more than 200 words and need not be structured.

Keywords

At least 3 keywords but no more than 6, preferably using terms from the Medical Subject Headings (MeSH) list of Index Medicus, should be listed horizontally under the abstract for cross-indexing of the article.

Text

1. Generally, the text should be organized consecutively as follows: Introduction, Methodology, Results and Discussion, and Conclusion (IMRAD format).
2. All references, tables, figures and illustrations should be cited in the text, in numerical order.
3. All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses. The same abbreviation may then be used subsequently instead of the long names.
4. All measurements and weights should preferably be in System International (SI) units.
5. If appropriate, information should be provided on institutional review board/ethics committee approval.
6. Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

References

1. References in the text should be identified by Arabic Numerals in superscript on the same line as the preceding sentence.
2. References should be typed double-spaced on a separate sheet. They should be numbered consecutively in the order by which they are mentioned in the text. They should not be alphabetized.
3. All references should provide inclusive page numbers.
4. Journal abbreviations should conform to those used in PubMed. Include PMID, PMCID and DOI of the references.
5. A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
6. The style/punctuation approved by JAFES conforms to that recommended by the International Committee of Medical Journal Editors (ICMJE) available at http://www.icmje.org. Follow the format of the examples shown below:

Journal Article

Padua FR, Paspe MG. Antinuclear antibody in the rheumatic and non-rheumatic diseases among Filipinos. Acta Med Philipp. 1990; 26(2):81-5.

One to Six Authors (Commentary, Online)

Krause RM. The origin of plagues: Old and new. Science. 1992;257:1073-8. PMID: 1509258 DOI: 10.1126/science.257.5073.1073.

Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. [Commentary]. J Translational Med. January 20, 2004; 2(3):1-4. http://www.translational-medicine.com/content/2/1/3. Accessed November 18, 2005.

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the US. JAMA. 2001;286(10):1195-200. PMID: 11559264 DOI: 10.1001/jama.286.10.1195.

More than Six Authors

McGlynn EA, M.Asch S, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med. 2003;348(26):2635-45. PMID: 12826639 DOI: 10.1056/NEJMsa022615.

Jasul Jr. GV, Paz-Pacheco E, Jimeno CA, et al. AFES A.S.-O.N.E.: ASEAN Survey Of Needs in Endocrinology in the time of the COVID-19 pandemic. J AFES Fed Endocr Soc.2020;35(1):5-13. PMID: 33790494 PMCID: PMC7992306 DOI: 10/15605/jafes.035.01.10.

Authors Representing a Group

Moher D, Schulz KF, Altman D; for the CONSORT Group. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987-91. PMID: 11308435 DOI: 10.1001/jama.285.15.1987.

Book

Byrne, DW. Publishing your medical research paper: What they don't teach in medical school. Baltimore: Williams & Wilkins, 1998.

World Wide Web

The key and critical objectives of JAMA. http://jama.ama-assn.org/misc/aboutjama.dtl. Accessed April 4, 2007.

Tables

1. Cite all tables consecutively in the text and number them accordingly.
2. Create tables, preferably using Microsoft Excel, with one table per worksheet.
3. Tables should not be saved as image files.
4. The content of tables should include a table number (Arabic) and title in capital letters above the table, and explanatory notes and legends as well as definitions of abbreviations used below.
5. Font should be Arial Narrow size 8.
6. Each table must be self-explanatory, being a supplement rather than a duplicate of information in the text.
5. Up to a maximum of five (5) tables are allowed.

Figures and Graphs

1. Figures or graphs should be identified by Arabic Numeral/s with titles and explanations underneath.
2. The numbers should correspond to the order in which the figures/graphs appear in the text. It is recommended that figures/graphs also be submitted as image files (preferably as .tif, .jpeg, or .png files) of high resolution (at least 300 dpi).
3. Editable figures or graphs can also be created using Microsoft Word.
4. Provide a title and brief caption for each figure or graph. Caption should not be longer than 15-20 words.
5. All identifying data of the subject/s or patient/s under study such as name or case numbers should be removed.
6. Up to a maximum of five (5) figures and graphs are allowed.

Illustrations and Photographs

1. Where appropriate, all illustrations/photographic images should be at least 600 dpi and submitted as image files (preferably as .tif, .jpeg, or .png files). All images should be checked for resolution. Right click on the image and click properties to see the resolution.
    1.1 There should be minimal processing of digital images submitted with a manuscript for review to the JAFES. A certain degree of image processing (lighting, color, contrast, size, orientation, cropping, placement of identifying markers and labels) is deemed acceptable only if the final image correctly and accurately represents the original information or data. Thus, JAFES requires all unprocessed, unaltered, and raw image files to be submitted with the manuscript to facilitate evaluation and review. These shall serve also as JAFES' records for issues that may arise after publication of the manuscript.
    1.2 Adjustments in brightness, color balance, or contrast should be applied equally to the whole image and should not result in the exclusion, hiding, obscuring, or deletion of any information that is present in the original image, enhancement of any particular portion of the image. Manipulations such as grouping of images for comparison should be indicated with image margins or clear demarcations, and must be described in the caption. Other types of manipulation such as copying and pasting of images and passing them off as multiple figures is not acceptable. Appropriate re-orientation of the whole image, as well as superimposition of arrows, markers, or other figures and labels is acceptable.
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    2.1 All image adjustment and processing tools/software used should be disclosed in the methodology section of original articles or described in the caption or description if in article types without a separate section on methods.
3. Computer-generated illustrations which are not suited for reproduction should be professionally redrawn and digitized (preferably as .tif, .jpeg, or.png files) at least 600 dpi. All letterings for illustrations should be done professionally and be of adequate size to remain readable ever after size reduction during layout.
4. All letterings for illustration should be done professionally and should be of adequate size to retain even after size reduction.
5. Figure legends should be numbered sequentially, typed double-spaced on a separate sheet of paper. Give the meaning of all symbols and abbreviations used in the figure.
6. Up to a maximum of five (5) illustrations/photographs are allowed.

N.B.: For tables, figures, graphs, illustrations, and photographs that have been previously published in another journal or book, a note must be placed on the specific item stating that such has been adapted or lifted from the original publication and referenced in the **References** portion. Appropriate copyrights and permissions should be secured from the original author/publisher.

SCREENING

Upon receipt of the manuscript, the Editorial Coordinator shall review the submission, check if it has met all submission requirements. The Editorial Coordinator shall communicate with the author/s should there be any clarifications or incomplete requirements.

INITIAL EDITORIAL ASSESSMENT

Once submission requirements are satisfactorily met, the Editor-in-Chief to decide whether it shall be considered for publication and proceed to peer review.

Authors shall be notified through e-mail that their manuscript either (a) shall be sent to referees for peer-review or (b) has been declined without review.

PAYMENT OF SUBMISSION FEES

All manuscripts deemed suitable for review must settle the Submission Fee before the review process begins.

PEER REVIEW

The JAFES implements a strict double blind peer review policy. Each manuscript is referred to two (2) peer reviewers who are deemed as subject experts. A third reviewer may be needed in case there is discordance in the peer reviewer recommendation.

The manuscript is routinely referred to a statistician/ method expert to check appropriateness and validity of data analysis and conclusions. In addition, the manuscript is also referred to the radiologists or pathologists for review if there are diagnostic imaging studies or microscopic images, respectively.

For manuscripts that are reviewed, authors can expect an initial decision within forty five (45) days after submission. There may be instances when decisions can take longer than 45 days, in such cases, the Editorial Coordinator shall inform the authors.

FINAL EDITORIAL DECISION

The Editor-in-Chief shall make the final decision for publication.

Editorial decisions shall be one of the following:

- **Acceptance without further revision**
- **Acceptance with minor revisions**
- **Major manuscript revision and resubmission**
- **Not accepted for publication**

COPYEDITING AND PRODUCTION

Accepted manuscripts are subject to copyediting and editorial modifications to bring them in conformity with the style of the journal.

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ARTICLE TYPES

Editorials
Articles that represent the scientific opinion and views of an author. Every issue of JAFES includes an Editorial by the Editor-in-Chief and may include one or two additional editorials from experts from the scientific community commenting on a particular field or issue on endocrinology.

No abstract or keywords necessary.

Letters to the Editor and Author Responses
JAFES welcomes Letters to the Editor that provide scholarly commentary on published articles, including constructive critique, clarification or alternative interpretation of findings.

When a Letter to the Editor raises substantive scientific, methodological, or interpretive concerns, the corresponding author of the original article will be invited to submit a formal response. While submission of a response is strongly encouraged to promote balanced academic discourse, publication of the Letter is not contingent upon receipt of an author reply.

Author responses must:
- Address the issues raised in a clear, professional, and evidence-based manner
- Adhere to the journal's word limits and formatting requirements
- Refrain from introducing new data unless explicitly permitted by the editor

All Letters to the Editor and corresponding author responses are subject to editorial review and may be edited for clarity, length, and tone. The Editor-in-Chief retains final authority over publication decisions.

No abstract or keywords necessary.

A Letter to the Editor must not exceed 2 typewritten pages or 500 words.

Feature Articles
JAFES may feature articles, either as part of an issue theme, such as Summary Clinical Practice Guidelines on endocrinology from each AFES country society, or a special topic on endocrinology by an international expert or authority.

A manuscript for feature articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Review Articles
Review articles provide information on the "state of the art." JAFES encourages that reviews not only summarize current understanding of a particular topic but also describe significant gaps in the research, and current debates.

A manuscript for reviews should not exceed 15 typewritten pages (including tables, figures, illustrations and references) or 4000 words.

Original Articles
The abstract should contain no more than 500 words with a structured format consisting of the objective/s, methodology, results and conclusion.

A manuscript for original articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Case Reports
A manuscript for case reports should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words.

Case Series
A case series, defined as a report describing more than one patient with similar clinical features, presentations, interventions, or outcomes, may be submitted as a distinct article type.

Manuscripts should not exceed 4,500 words or 15 typewritten pages, inclusive of tables, figures, illustrations, and references.

Authors are encouraged to present individual case details concisely, preferably using tables or summary formats where appropriate, and to avoid repetitive narration of similar clinical information. Greater emphasis should be placed on the comparative analysis, identification of patterns, and the clinical or scientific insights derived from the series.

The number of cases included should be sufficient to support meaningful observations, typically ranging from three to ten patients, although flexibility may be exercised depending on the rarity or significance of the condition.

Submissions that primarily describe a single patient should be submitted as a Case Report and must adhere to the corresponding limits.

Interhospital Grand Rounds
JAFES encourages submission of special articles that summarize and document the proceedings of endocrinology grand rounds, which includes presentation of medical problems of a particular patient, evaluation and work-up, treatment and clinical course, discussion of key diagnostic and management points, and commentaries by specialty experts. JAFES recognizes the importance of this type of article as an educational tool for physicians and health practitioners.

A manuscript for grand rounds should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Brief Communications
Brief Communications are short reports intended to either extend or expound on previously published research OR present new and significant findings which may have a major impact in current practice. If the former, authors must acknowledge and cite the research which they are building upon.

A manuscript for brief communications should not exceed 5 typewritten pages (including tables, figures, illustrations and references) or 1500 words.

Images in Endocrinology
Images may include photographs of clinical cases encountered and documented during practice. They may also include diagnostic images (e.g., photomicrographs of histopathologic diagnosis, radiographs) or special studies performed (e.g., spectral karyotype imaging, fluorescent microscope images, immunostains) that aided in diagnosis.

A 250-word text should accompany the images. Submissions to this category should comply with the journal's image integrity guidelines.

Special Announcements
Special announcements may include upcoming conventions, seminars or conferences relevant to endocrinology and metabolism. The Editors shall deliberate and decide on acceptance and publication of special announcements. Please coordinate with the Editorial Coordinator for any request for special announcements.

Checklist Guide for Submission of Manuscripts to JAFES	
Instructions to Authors	☐ Review manuscript submission guidelines
Cover Letter	☐ Include cover letter as an attachment ☐ Indicate in the letter the title of the work ☐ Indicate all the authors (complete names, affiliations, ORCID iD, specific role/s in writing the manuscript and e-mail address) ☐ Indicate in the letter the Corresponding author: and provide complete contact information (post address, telephone, fax number, e-mail address)
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References	☐ All references should be cited in the text, in numerical order. Use Arabic numerals ☐ Ensure all references follow the prescribed format
Tables, Figures, Illustrations and Photographs	☐ All tables, figures, illustrations and photographs should be cited in the text, in numerical order per type ☐ Provide separate files for tables, figures and illustrations ☐ Provide a title and legend (if appropriate) for each table ☐ Provide a title, legend (if appropriate), and caption for each figure and illustration (caption should be no longer than 15-20 words) ☐ If table, figure, or illustration is adapted, state so and include the reference.

Journal of the
ASEAN Federation of
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Editorial Policies

FOCUS AND SCOPE

The *Journal of the ASEAN Federation of Endocrine Societies (JAFES)* is a peer-reviewed, open-access journal dedicated to advancing knowledge and practice in endocrinology, diabetes, and metabolism within the ASEAN region and beyond. The journal publishes high-quality original research, reviews, clinical practice guidelines, case reports, and policy-relevant studies that address the unique epidemiologic, clinical, and health systems challenges of endocrine disorders in Southeast Asia.

It aims to serve as a platform for regional collaboration, promote locally generated evidence, and contribute to global scientific discourse by highlighting perspectives and innovations from ASEAN countries.

PUBLICATION FREQUENCY

Starting 2026, JAFES shall be published three (3) times a year. Articles are batched at the end of April, August, and December of each year and released as an issue on the JAFES website.

While awaiting assignment to an issue, articles are published as "Early Access" on the JAFES website as soon as the review and editing process is complete.

EDITORIAL INDEPENDENCE

The Journal of the ASEAN Federation of Endocrine Societies (JAFES) is committed to maintaining the highest standards of editorial integrity, transparency, and academic freedom. **This policy outlines the principles and safeguards that ensure editorial independence in all aspects of the journal's operations.**

JAFES upholds editorial independence as essential to the integrity and credibility of the journal. The Editor-in-Chief and the Editorial Board have full authority over the editorial content of the journal, including decisions on which manuscripts to accept, revise, or reject.

Editorial decisions are based on the quality, originality, scientific rigor, relevance, and clarity of the submitted manuscripts, and are not influenced by:

- The policies or positions of the ASEAN Federation of Endocrine Societies (AFES) or its member societies;
- The identity, affiliation, or position of authors, reviewers, or institutions;
- Commercial, political, or personal interests;
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While JAFES is the official publication of the AFES and supported by its member societies, the publisher or AFES leadership shall not interfere in the evaluation, selection, or editing of individual articles. Their role is limited to ensuring the journal's operational and financial sustainability, without infringing on editorial decisions.

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All editors, reviewers, and authors must declare any actual or potential conflicts of interest that could affect the objectivity of editorial decisions. Editors must recuse themselves from handling manuscripts in which they have a conflict of interest and delegate such submissions to another qualified editor.

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LIST OF AUTHORS

Complete Name	Position/ Designation	Institutional Affiliation	Role in writing the manuscript	Email address	ORCID iD

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