



Journal of the ASEAN Federation of Endocrine Societies

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FEATURE ARTICLES

The Recent 15 years of JAFES: 2010-2025

Philippine Clinical Practice Guidelines on Screening, Diagnosis, Management and Prevention of Primary Osteoporosis and Fragility Fractures Among Postmenopausal Women and Older Men

ORIGINAL ARTICLES

Acute Kidney Injury in Children with Type 1 Diabetes Mellitus Hospitalized for Diabetic Ketoacidosis: A Retrospective Study

Paediatric Type 2 Diabetes Presentation and Trends Four Years Pre- and Post-COVID-19 Pandemic in Klang Valley, Malaysia

Determinants of Cardiac Autonomic Neuropathy Among Patients with Diabetic Peripheral Neuropathy: A Facility-based Cross-Sectional Study

Prevalence of Hypogonadism Among Males with Type 2 Diabetes Mellitus in a Malaysian Tertiary Hospital: A Cross-Sectional Study

Prevalence of Hepatic Fibrosis and Performance of Non-invasive Liver Fibrosis Scores in an Eastern Indian Diabetic Population with NAFLD

Evaluating Serum Endosialin (CD248) Levels as a Diagnostic Marker in Gestational Diabetes: A Case-Control Study

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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 and special announcements. Authors may include members and non-members of the AFES.

Authors are required to accomplish, sign and submit scanned copies of the JAFES Author Form consisting of: (1) Authorship Certification, that the authors contributed substantially to the work; that the manuscript has been read and approved by all authors, and that the requirements for authorship have been met by each author; (2) the Author Declaration, that the article represents original material that is not being considered for publication or has not been published or accepted for publication elsewhere; that the article does not infringe or violate any copyrights or intellectual property rights, and that no references have been made to predatory/suspected journals; that the article is approved by the appropriate institutional review board and is adherent to the principles of the Declaration of Helsinki or that the article had written/informed consent for publication from involved subjects (for Case Report/series, Images in Endocrinology, Clinical Case Seminars); that use of artificial intelligence (AI) or AI-assisted technologies, whether for data collection, analysis, or figure generation, or for preparation of the manuscript, shall be declared to include the name of the AI tool or service used; and that the author(s) have duly overseen its use, reviewed the generated content for correctness and veracity, and ensured compliance to ethical publication standards; (3) the Author Contribution Disclosure, which lists the specific contributions of authors; (4) the Author Publishing Agreement which retains author copyright, grants publishing and distribution rights to JAFES, and allows JAFES to apply and enforce an Attribution Non-Commercial Creative Commons user license; and (5) Conversion to Visual Abstract to have the published work (*optional for original articles only) converted as visual abstract to improve dissemination to practitioners and lay readers. Authors are also required to submit the signed ICMJE form for Disclosure of Potential Conflicts of Interest. For original articles, authors are required to submit a scanned copy of the Ethics Review Approval of their research as well as registration in trial registries as appropriate. 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. Consent forms, as appropriate, have been secured for the publication of information about patients.

Articles and any other material published in the JAFES represent the work of the author(s) and should not be construed to reflect the opinions of the Editors or the Publisher. In 2025, JAFES implemented a minimal fee for article submissions to support its editorial office operations. JAFES remains fully open access, with no fees for downloading or subscriptions required to access scholarly content.

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The Recent Fifteen Years of JAFES (2010–2025): Places We Visited, Pathways We Blazed, and Networks We Multiplied



November 2025 will be remembered in a special way: a moment when we got to look back to the recent fifteen years, look in, and look forward again to the future.

The ASEAN Federation of Endocrine Societies (AFES) is an organization that has always been close to our hearts at the Philippine Society of Endocrinology and Metabolism or PSEM (later Philippine Society of Endocrinology, Diabetes and Endocrinology or PSEDM; and currently Philippine College of Endocrinology, Diabetes and Metabolism or PCEDM). Filipino endocrinologists have been active participants in AFES from the time of the founding in 1981, with our own founding member Dr. Augusto D. Litonjua. My active involvement as Immediate Past President of the PSEM in 2002 was marked by the launch of a commemorative coffee-table book during 12th AFES meeting in Singapore in 2003, entitled *AFES 1981-2003: Renewing our Commitment to the ASEAN Region* (Figure 1). Through then AFES President and the Endocrine and Metabolic Society of Singapore President Dr. Daphne Khoo, we shared this special historical token at that meeting.¹ It was a sentimental display of the strengths of each of the member organizations and a welcome to new member Vietnam, under the leadership of Professor Mai The Trach, Founding Member and then First Vice-President, Vietnam Association of Diabetes and Endocrinology, the first new member since the inception of the AFES.

How did JAFES get launched?

In the commemorative book in 2003, Malaysian founding member Professor Dato' Dr. Mustafa Embong detailed how JAFES was planned early on in 1981 and was first published in 1982 with articles sourced from the first AFES Congress. He wrote, "JAFES was one initiative taken by the Federation to promote exchange of knowledge among members and to provide a platform to encourage young ASEAN endocrinologists to undertake research and publish findings." As Editor-in-Chief since 1997, in 2003 he reported further: "... While financial constraint is an issue, the bigger challenge is to ensure that JAFES is published regularly and on time. ... We face two major problems: lack of articles and lack of reviewers. Many have complained that they are not keen to submit articles to JAFES because it is not in the *Index Medicus*. It is really a catch-22 situation... Perhaps it is time to pass the baton."

It came to pass in 2010 that AFES offered the Philippines to host the next editorial group of JAFES, with yours truly as the next Editor-in-Chief. Now as we revisit those recent fifteen years beginning 2010, we ask: "Has JAFES made a difference in our patients' lives?"

What were the places we visited in the recent 15 years?

With increasing rates of Diabetes Mellitus in the region, over the past 15 years, indeed nearly 40% of the articles focused on DM. Our opening issue in 2011 featured national Clinical Practice Guidelines (CPGs) for DM from Indonesia, Malaysia, the Philippines, and Singapore. Research through the years focused on prevalence, genetic associations, complications and management strategies. Gestational Diabetes Mellitus (GDM) was also a significant concern, with CPGs for diabetes in pregnancy from Indonesia and Myanmar, and studies on diagnostic markers and maternal/neonatal outcomes.²

Rising rates of obesity and metabolic syndrome led to 11% of the articles, including CPGs on obesity from Malaysia, Myanmar, Singapore, and Indonesia. The "double burden of malnutrition in Asia" is specifically mentioned as a phenomenon that should not be dismissed.

<https://doi.org/10.15605/jafes.040.02.01>

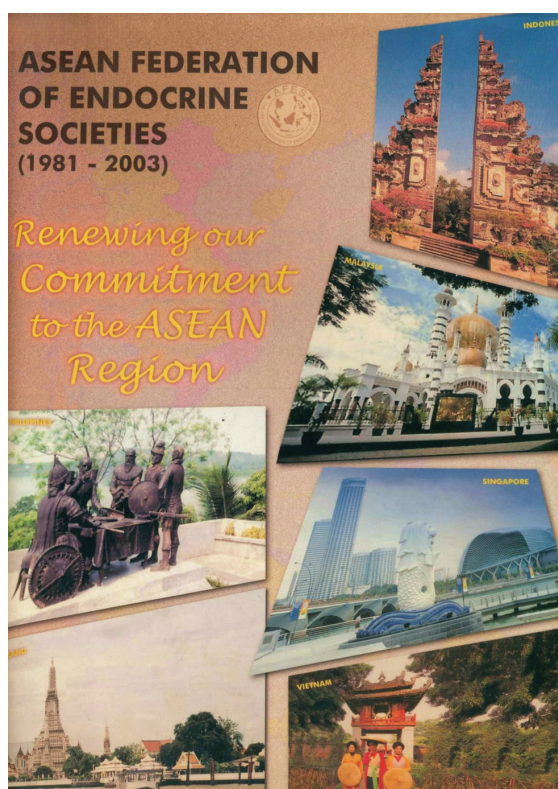


Figure 1. Cover of the 12th AFES Commemorative Book: ASEAN Federation of Endocrine Societies (1981–2003): Renewing Commitment to the ASEAN Region. Singapore; 2003.

Thyroid disorders comprise another huge endocrine problem in the region, accounting for 19% of the publications. National CPGs for thyroid disorders have been reported for hyperthyroidism in Indonesia, general management in Malaysia, disorders of thyroid function in Myanmar, and well-differentiated thyroid carcinoma in the Philippines.

Other major topics of articles include osteoporosis and bone disease, and dyslipidemia.

JAFES also went into less-explored territories of research gaps and emerging ideas: (1) impact of COVID-19 on endocrine disorders; (2) molecular, genetic, and precision medicine approaches; (3) digital health, telemedicine, and AI in endocrinology; (4) novel therapeutic and diagnostic modalities; (5) psychosocial aspects, quality of life, and patient-centered care; (6) enhancement of diagnostic and management guidelines and protocols; and similar areas that cut across multiple endocrine dysfunctions.

Yes, time and again we have been reminded in JAFES of many oft-forgotten challenges, which we can only overcome if there were genuine exchange of knowledge and regional collaboration and cooperation on endocrine issues. We need to continue pushing forward on such areas of concern as: (1) persistent public health issues; (2) implementation and adherence challenges; (3) need for culturally and linguistically validated tools; (4) addressing specific diabetes complications; (5) pediatric and young-onset endocrine issues; (6) understanding and managing rare or complex cases; or (7) addressing environmental and lifestyle factors.

What were the pathways that we blazed?

JAFES encouraged various ways of reporting on the endocrine research and practice, the better to cater to our mix of researchers, authors, and readers.

Publications from original work of authors in the region comprised 45% of the articles published, with case reports representing another 34%. As much as randomized controlled studies and analytical works provide greater evidence, we did find value in reporting uncommon cases from the region too. In one editorial we even wrote, “the case for case report.” Those rare or differentially presented cases were a great source of learning as well.

We were one of the first to do visual abstracts to disseminate information from articles published both for the scientific community and for the lay, shouting out from social media platforms, such as Facebook, Instagram and Twitter.

And in the process have we helped multiply the networks that the AFES set out to create since 1981?

Fundamentally, we worked on enhancing JAFES as the platform for advancing endocrine research in the ASEAN region, to be a voice of endocrinology in the region. Most submissions, particularly coming from non-English speaking countries that had difficulty getting acceptance in international journals, were nurtured by our peer reviewers and editors who assisted in transforming good ideas towards meaningful statements and reports. We championed the dissemination of clinical practice guidelines (CPGs) tailored for the Region for various topics, to understand our similarities and differences and to be a platform for not just learning from each other but also be an impetus to help each other.

We promoted and practiced open access to scientific information. Open access allowed every reader – researcher, practitioner or patient – a link to a full text of the article with no charges. Authors were able to submit and publish without major concern for financial cost.

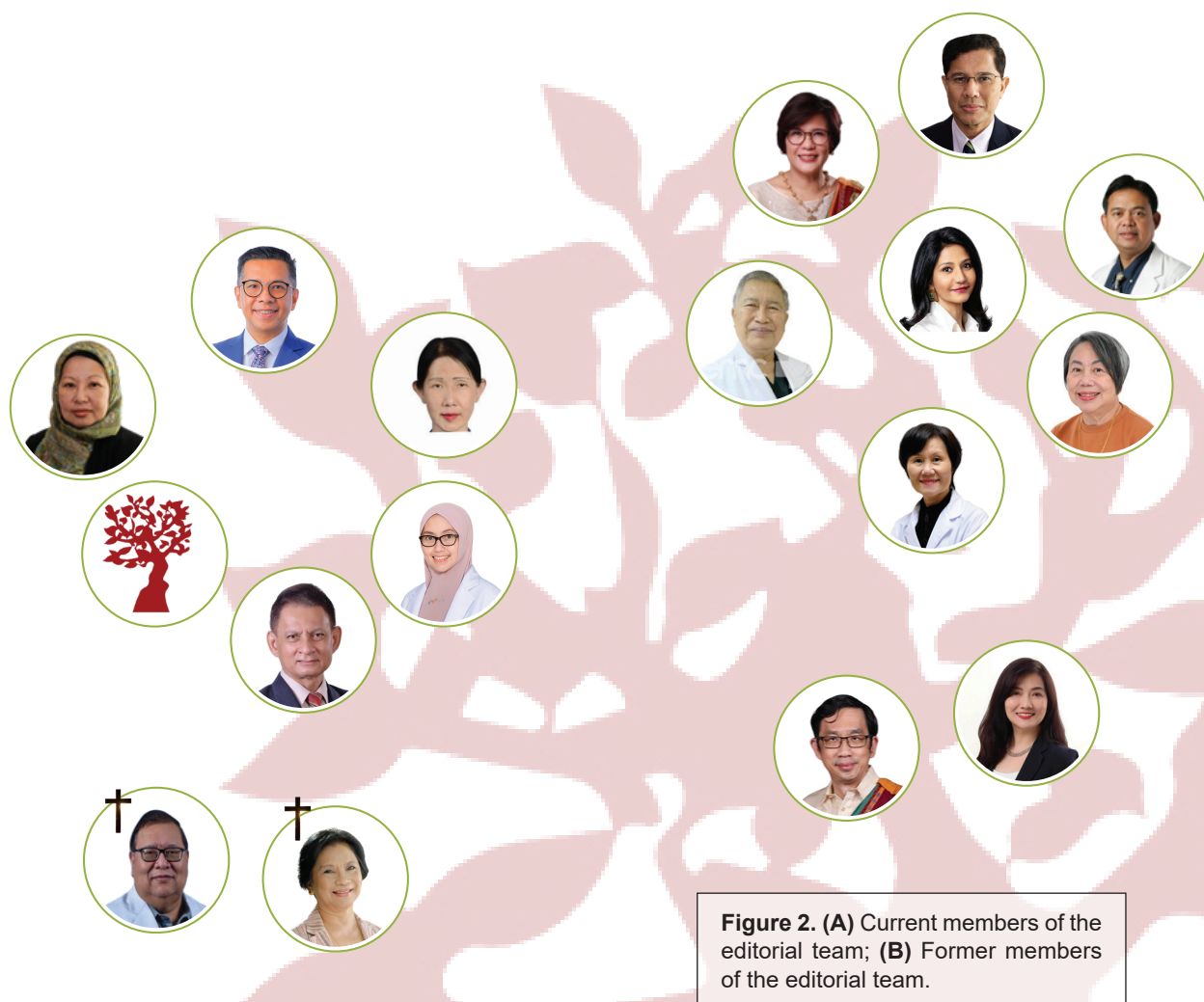
We did all that while making JAFES recognized in the most important online scientific indices and full-text archives like PubMed Central (which essentially replaced the role of in-print *Index Medicus* that was already discontinued in 2004), the better for our ASEAN work to be known – and referenced – not only in the ASEAN region but throughout the world.

The JAFES Editorial Team

2011 to present



Past Members



Our Clarivate Journal Impact Factor (JIF) now puts JAFES on the map, ensuring appropriate citations for our articles, and from here we can only expand our reach — better for our patients to access and for us, as healthcare providers, to deliver the most regionally appropriate care in endocrinology.

So indeed, it has been a full circle moment, too. I had the privilege to speak at the Diabetes Asia Conference 2025 led by Prof Mustaffa Embong in October 2025 in Kuala Lumpur, Malaysia. On behalf of the JAFES Editorial Team (Figure 2), I personally shared with him these successes of JAFES through the years of careful learnings and overcoming challenges.

This November, all our Societies gather in Vietnam (Da Nang) for the 2025 AFES, where we continue to collaborate in foreseeing better futures for JAFES as well, with our next Editor-in-Chief.

The vision to deliver an ASEAN perspective for patient care lives on. The journey endures; as we say it from the Philippines: *Mabuhay!* (Long live!) AFES and JAFES. And to all who have contributed to these efforts, *Salamat po* (Thank you).

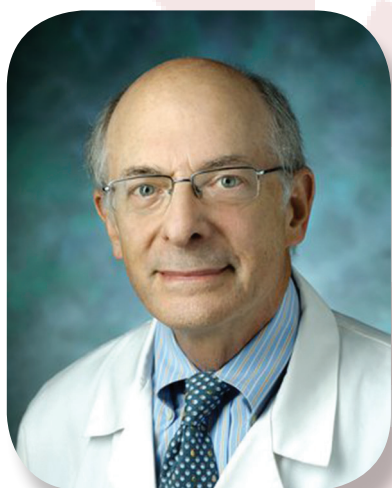
Elizabeth Paz-Pacheco
Editor-in-Chief

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Gratitude to Our Reviewers

The Journal of the ASEAN Federation of Endocrine Societies (JAFES) extends its deepest appreciation to all our reviewers who, through the years, have generously lent their time, expertise and unwavering commitment to the advancement of endocrinology scholarship in the region. Your rigorous evaluations, thoughtful insights and steadfast dedication have been integral to sustaining the quality and integrity of the journal.



We express our special thanks to **DAVID S. COOPER, MD, MACP**, Professor of Medicine and Radiology at the Johns Hopkins University School of Medicine and Professor of International Health at the Johns Hopkins Bloomberg School of Public Health, whose long-standing support and guidance have accompanied us through every stage of our journey.

His steadfast presence has been instrumental as we worked toward and ultimately achieved, our milestones and goals. We are profoundly grateful for his example of excellence, generosity and professionalism.

To all our reviewers, past and present, thank you for standing with JAFES and for helping us build a strong platform for regional endocrine research. Your contributions continue to shape the future of our scientific community and we remain deeply honored by your partnership.

The Recent 15 years of JAFES: 2010-2025

Amado O. Tandoc III, MD, FPSP, Melissa O. Tandoc, RN, Cecilia A. Jimeno, MD, FPCP, FPCEDM,
Benito M. Pacheco, PhD, Elizabeth Paz-Pacheco, MD, FPCP, FPCEDM

JAFES EVOLUTION OVER TIME

The Journal of the ASEAN Federation of Endocrine Societies (JAFES) has undergone significant evolution since its inception, marked by developments in its operational policies, content focus, and international recognition.

Planning and First Publication (Circa 1981-2010)

JAFES was planned in 1981. In 1982 the Indonesian Society of Endocrinology undertook the first publication, with articles sourced from the first AFES Congress held in 1981. In 1997 Malaysia volunteered to be the permanent secretariat for JAFES and Professor Dato Dr. Mustaffa Embong was appointed Editor-in-Chief. After almost seven years the EIC had reported at the time that while financial constraint was an issue, the bigger challenge was ensuring that JAFES was published regularly and on time. Two problems were faced: lack of articles and lack of reviewers. "Many have complained that they are not keen to submit articles to JAFES because it is not in the Index Medicus. It is really a catch-22 situation... Perhaps it is time to pass the baton."

Eventually, in 2010, the Philippine Society of Endocrinology and Metabolism (now the Philippine College of Endocrinology,

Diabetes and Metabolism) offered to host the JAFES editorial group and appointed Dr. Elizabeth Paz-Pacheco as Editor-in-Chief. Indeed among the early goals was qualifying JAFES for the major indexes for medical journals.

Foundational Aspects and Early Evolution (Circa 2010-2012)

JAFES is now an open-access, peer-reviewed, English language, medical and health science journal published bi-annually by the ASEAN Federation of Endocrine Societies (AFES). Its editorial policies are aligned with the International Committee of Medical Journal Editors (ICMJE) and it resolves ethical issues using recommendations from the Committee on Publication Ethics (COPE). JAFES is also a member of the World Association of Medical Editors (WAME) and CrossRef.

A 2012 editorial marked "the Second Year of the New JAFES," shared a significant re-launch or transformation in 2010. By 2011, JAFES was actively publishing content, with its May issue (Vol. 26 No. 1) focusing on "Advancing Endocrine Research in the ASEAN region," and including feature articles on the AFES's 30th anniversary (1981-2011) and national clinical practice guidelines for Diabetes Mellitus from various ASEAN countries. The November



Figure 1. First Editorial Board.



Figure 2. The JAFES successfully launched at Sofitel Manila, Philippines, on May 26, 2011.



Figure 3. Relaunch of JAFES at the 16th ASEAN Federation of Endocrine Societies (AFES) Congress, November 17–20, 2011, Ho Chi Minh City, Vietnam.

2011 issue (Vol. 26 No. 2) highlighted "Reducing Obesity and Metabolic Syndrome," and featured obesity clinical practice guidelines from several ASEAN nations. Subsequent issues in 2012 covered topics like thyroid disorders and bone disease in Southeast Asia, along with associated clinical practice guidelines. Editorials from this period consistently emphasized "Amplifying the Voice of ASEAN Endocrinology through JAFES and its Website" and focusing efforts towards indexing JAFES.

Commitment to Open Access and Publication Ethics (2013-2016)

An editorial in November 2013 specifically addressed "Open Access and Ethical Publication," and mentioned the Asia Pacific Association of Medical Editors (APAME) Tokyo Declaration, reinforcing JAFES's dedication to these principles. The journal continued to broaden its scope, featuring topics such as reproductive health in ASEAN in



Figure 4. First JAFES covers (Vol. 26 Nos. 1 and 2).



Figure 5. Rebranding of JAFES in 2016.

2013. By 2014, an editorial titled "Growing Pains, Evolution and Progress," acknowledged the journal's developmental journey. In 2015, JAFES emphasized the value of "Case Reports" as a resource and featured detailed "Diabetes Care Models" from Singapore, Malaysia, Myanmar, and the Philippines. The November 2016 editorial further reiterated "Our Commitment to Open Access and to Integrity in Scientific Publication."

Enhancement of Publication Standards and International Recognition (2015-2020)

JAFES demonstrated an evolution in its author guidelines by introducing EQUATOR Network checklists for various study types in 2015, including CONSORT for clinical trials, CARE for case reports, PRISMA for systematic reviews and meta-analyses, STROBE for observational studies, STARD for diagnostic accuracy studies, and CHEERS for economic evaluations. This move underscored a commitment to higher quality reporting. In 2017, the journal explicitly listed the ICMJE's "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals," in its author guidelines. An editorial in May 2018 titled "Collaboration Among Endocrinology Publications in Asia," signaled a drive towards regional cooperation.

A significant milestone occurred in November 2020 when JAFES announced its acceptance for indexing in PubMed Central. This was highlighted as a "Better Normal, A Silver Lining in 2020," in an editorial, marking a major achievement in its journey towards wider recognition and accessibility. The journal also demonstrated its responsiveness to contemporary health crises, dedicating its May 2020 issue to "Response in Southeast Asia: Managing diabetes and other endocrine disorders during the COVID-19 crisis," including consensus recommendations and position statements.

Continued Growth and Future Directions (2021-2025)

The May 2021 editorial, "A Decade of Growth," further reflected on the journal's progress. JAFES has also

expanded its content categories, including the addition of a special issue dedicated to "Molecular and Cellular Endocrinology," in March 2023, indicating a move into more specialized and fundamental research areas. The journal continues to adapt to the evolving landscape of scientific publishing, discussing "Generative Artificial Intelligence (AI) in Scientific Publications," in its May 2024 editorial and emphasizing "Sustainability," in November 2024. The 2024 Author Guidelines also include the "Sydney Declaration on Predatory or Pseudo Journals and Publishers," showing its ongoing commitment to ethical publishing practices.

By 2024, JAFES is already indexed in all of its target indexing services and databases: PubMed (Medline), PubMed Central (PMC), Scopus™ (Elsevier), Web of Science™ (Clarivate Analytics), Directory of Open Access Journals (DOAJ), Western Pacific Region Index Medicus (WPRIM). In 2025, JAFES finally had an Impact Factor (IF) of 0.6 (from Clarivate Analytics).

A notable future change, beginning in 2025, is the implementation of a minimal submission fee to support editorial office operations, while ensuring JAFES remains fully open access without fees for downloading or subscriptions. The Editor-in-Chief's reflections in the May 2025 issue, looking back on a "15-Year Journey," indicate a sustained and evolving leadership guiding the journal's trajectory.

CONTENT

Prevalent Endocrine and Metabolic Disorders in the ASEAN Region

Over the last 15 years, the most prevalent endocrine and metabolic health issues in the ASEAN region are Diabetes Mellitus (especially Type 2 Diabetes Mellitus), Obesity and Metabolic Syndrome, Thyroid Disorders, Osteoporosis and Bone Disease, and Dyslipidemia. These conditions are frequently addressed through national clinical practice guidelines and are subjects of numerous research articles across various ASEAN countries.

1. Diabetes Mellitus (especially Type 2 Diabetes Mellitus) and its Complications

- This is overwhelmingly the most frequently highlighted and researched issue. Multiple ASEAN countries have developed national clinical practice guidelines for Diabetes Mellitus (DM), including Indonesia, Malaysia, the Philippines, and Singapore. An editorial in 2011 explicitly discussed "Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region," indicating its widespread significance.
- Research extensively covers Type 2 Diabetes Mellitus (T2DM), with studies on its prevalence, genetic associations, management strategies, and complications across various populations in the region.
- Gestational Diabetes Mellitus (GDM) is also a significant concern, with CPGs for diabetes in pregnancy from Indonesia and Myanmar, and studies on diagnostic markers and maternal/neonatal outcomes.
- Common complications of diabetes frequently studied include Diabetic Peripheral Neuropathy, Diabetic Kidney Disease, Diabetic Retinopathy, and Diabetic Foot Ulcers.
- The impact of the COVID-19 pandemic on diabetes management and outcomes in the region is a recent and notable area of focus.
- Undiagnosed diabetes and factors associated with it are also examined in Indonesia.

2. Obesity and Metabolic Syndrome

- These are major public health challenges, explicitly addressed by national clinical practice guidelines on the Management of Obesity from Malaysia, Myanmar, Singapore, Indonesia, and the Philippines.
- Editorials from JAFES have highlighted the importance of "Reducing Obesity and Metabolic Syndrome," and the "Obesity Epidemic in the Asia-Oceania Region."
- Studies investigate the prevalence of obesity and metabolic syndrome in various groups, including in Bali, Indonesia, Filipino adolescents, and community-living older persons in the Philippines, as well as among community health workers and pediatric populations. The "double burden of malnutrition in Asia," is specifically mentioned as a phenomenon that should not be dismissed.
- Insulin resistance is a key pathophysiological feature studied in relation to obesity and T2DM.

3. Thyroid Disorders

- Thyroid conditions are widespread, with "The Philippine Thyroid Diseases Study (PhilTiDeS 1)" reporting on the prevalence of thyroid disorders among adults in the Philippines. Studies also cover the prevalence of thyroid dysfunction in specific groups, such as elderly Filipinos and young patients with T2DM.
- National CPGs for thyroid disorders exist for hyperthyroidism in Indonesia, general management in Malaysia, disorders of thyroid function in Myanmar, and well-differentiated thyroid carcinoma in the Philippines.

- Common conditions include Graves' disease, various forms of hypothyroidism (including congenital hypothyroidism, severe hypothyroidism, and subclinical hypothyroidism), and thyroid carcinoma (papillary, follicular, micropapillary).
- Iodine Deficiency Disorders (IDD) are explicitly stated to "Continue to be a Problem in the Asia Pacific Region."

4. Osteoporosis and Bone Disease

- This category is significant, as evidenced by national guidelines for osteoporosis prevention, diagnosis, and treatment from Indonesia, Myanmar, the Philippines, and Singapore. An editorial also specifically focuses on "Understanding Bone Disease in Southeast Asia."
- Research includes studies on Vitamin D levels in various populations and their association with bone health, as well as conditions like primary hyperparathyroidism.

5. Dyslipidemia

- The prevalence and management of dyslipidemia are addressed through clinical practice guidelines summarized from Myanmar and the Philippines. Studies also examine physician adherence to these guidelines and statin treatment algorithms.

While other endocrine conditions like pituitary disorders (e.g., pituitary adenomas) and adrenal disorders (e.g., primary aldosteronism, pheochromocytoma, congenital adrenal hyperplasia) are reported, they appear less frequently in prevalence studies or national guidelines compared to the top five issues listed above.

RESEARCH GAPS AND EMERGING TOPICS 2011-2025

JAFES' 15-year publication history highlights several research gaps and emerging topics in endocrinology and metabolism, with a particular focus on the ASEAN region. These can be broadly categorized into new diseases and external factors, advanced methodologies and diagnostics, novel therapeutic and preventative strategies, and improvements in patient-centered care and public health.

Explicit Research Gaps and Challenges

1. Persistent Public Health Issues

- Iodine Deficiency Disorders continue to be a problem in the Asia Pacific Region.
- The "double burden of malnutrition," in Asia is a phenomenon that should not be dismissed.
- There is a need to understand sociodemographic and lifestyle factors associated with undiagnosed diabetes to address public health screening gaps.

2. Implementation and Adherence Challenges

- Improving access to healthcare and effective implementation of guidelines in the ASEAN region, as indicated by challenges in diabetes care during COVID-19 and surveys on physician adherence to dyslipidemia guidelines.

- Addressing poor medication adherence among persons with T2DM in Malaysia.

3. Need for Culturally and Linguistically Validated Tools

- There is a recurring need for the development and validation of culturally appropriate questionnaires and screening instruments for various endocrine conditions in specific populations. Examples include a Filipino Eating Behavior Questionnaire, thyroid cancer-specific HRQoL questionnaire for Filipinos, oral health screening questionnaires, Michigan Neuropathy Screening Instrument for Filipinos, a questionnaire for impaired hypoglycemia awareness in Filipino T2DM patients, a GDM knowledge questionnaire for Filipinos, a Filipino version of the Diabetes Distress Scale, and a Vietnamese-translated Diabetes Knowledge Questionnaire.

4. Addressing Specific Diabetes Complications

- Improving wound healing rates in diabetic foot ulcers through individualized glycemic interventions and identifying predictors of outcomes for foot ulcers.
- Developing accurate and cost-effective screening for diabetic peripheral neuropathy and peripheral arterial disease.
- Understanding complications associated with newer drug classes, such as the prevalence of bacterial urinary tract infection among patients on SGLT2 inhibitors.

5. Pediatric and Young-Onset Endocrine Issues

- Research is needed on cardiometabolic risk factors leading to diabetes in young individuals, trends in pediatric T2DM pre and post COVID-19, early puberty trends, and endocrine disorders in childhood brain tumor survivors. The need for other diagnostic tests for young-onset T2DM is also mentioned.

6. Understanding and Managing Rare/Complex Cases

- Case reports frequently highlight diagnostic and management dilemmas in rare endocrine presentations, implicitly pointing to gaps in general knowledge or standardized approaches for such conditions (e.g., Hirata syndrome, occult ectopic ACTH syndrome, reninoma, Nelson's syndrome, congenital adrenal hyperplasia, acromegaly without imaging evidence, ROHHAD-NET syndrome).

7. Addressing Environmental and Lifestyle Factors

- Studies continue to explore the impact of lifestyle on metabolic health, including prevailing food intake, physical activity, and health beliefs in rural agricultural communities to inform diabetes prevention programs, and the association between betel quid chewing and metabolic syndrome.
- The effect of maternal iodine excess during pregnancy on neonatal thyroid function and neurodevelopmental status also highlights environmental factors.

Emerging Topics and Areas for Further Research

1. Impact of COVID-19 on Endocrine Disorders

A significant and recent emerging area of research is the effect of the COVID-19 pandemic on diabetes and other endocrine conditions. This includes:

- Managing diabetes and endocrine disorders during the crisis.
- Consensus recommendations for in-patient management of diabetes among COVID-19 patients.
- Challenges for research ethics committees in the time of COVID-19.
- The use of social media (e.g., Facebook) for disseminating health information during the pandemic.
- Specific studies on the relationship between COVID-19 and thyroid diseases, metformin use and mortality in diabetic COVID-19 patients, early puberty trends during the pandemic, and hypothalamic-pituitary-adrenal axis activity in SARS-CoV-2 infected patients.

2. Molecular, Genetic, and Precision Medicine Approaches

There is an explicit call for "Molecular Insights to Clinical Perspectives," and "Molecular Basis of Endocrine-Related Disorders." Key areas include:

- Pharmacogenomics: Investigating genetic variants associated with poor responsiveness to specific diabetes medications (e.g., sulfonylureas).
- Population-Specific Genetic Research: Studies on single nucleotide polymorphisms (SNPs) in specific genes (e.g., Transcription Factor 7-like 2 gene, adiponectin gene) and their association with Type 2 Diabetes Mellitus (T2DM) in various ethnic populations (e.g., Myanmar, Pashtun).
- Advanced Genetic Screening: Next-generation sequencing to identify genetic polymorphisms related to lifestyle and nutrition, such as those affecting serum Vitamin D levels.
- Research into the cellular mechanisms, such as the effect of glucocorticoids on TAF1 gene transcription, and the impact of endocrine disruptors like Bisphenol S on endometrial cells and Bisphenol A on reproductive manifestations in PCOS.

3. Digital Health, Telemedicine, and AI in Endocrinology

- The need for Ocular Telehealth Programs to address diabetic retinopathy in Southeast Asia is highlighted.
- Research into the effectiveness of Short Message Services (SMS) for diabetes management and improving postpartum follow-up for Gestational Diabetes Mellitus (GDM) patients.
- The development of interactive multimedia applications and nutrition game applications for patient education and intervention in T2DM and school-aged children.
- Generative Artificial Intelligence (AI) in scientific publications is recognized as an emerging topic, particularly concerning its ethical implications and role in scientific methodology.

4. Novel Therapeutic and Diagnostic Modalities

- **Pharmacological Interventions:** Investigating off-label uses of existing drugs (e.g., metformin beyond its anti-diabetic role), efficacy of heparinoid supplementation in diabetic kidney disease, magnesium supplementation for glycemic control, and real-world effectiveness of newer drugs like liraglutide and semaglutide for weight loss in obesity without diabetes. Studies also explore combination therapies (e.g., hydroxychloroquine with teneligliptin, curcumin and piperine supplementation, DPP4 inhibitors with premixed insulin) and adjunctive therapies like bromocriptine-QR.
- **Non-Pharmacological and Lifestyle Interventions:** Exploring interventions such as Repetitive Transcranial Magnetic Stimulation (rTMS) for weight loss and the impact of yoga and walking on glycemic control.
- **Biomarkers and Screening Tools:** The search for better diagnostic and prognostic markers, including serum Endosialin (CD248) for GDM, Echocardiographic Epicardial Adipose Tissue Thickness for insulin resistance, plasma Retinol-Binding Protein 4 levels for T2DM risk in abdominal obesity, Lipid Accumulation Product Index for T2DM, and the Glutamate-Serine-Glycine Index as a biomarker for Non-alcoholic Fatty Liver Disease (NAFLD) after bariatric surgery. The correlation of fructosamine and HbA1c is also studied, as is the assessment of various insulin resistance surrogate indices.
- **Advanced Diagnostic Techniques:** Utilizing methods like Corneal Confocal Microscopy to identify structural small fiber abnormalities in Type 1 Diabetes Mellitus (T1DM) patients with impaired awareness of hypoglycemia.
- **Gut Microbiome:** Exploring the possible role of *Akkermansia muciniphila* in the etiopathogenesis and therapy of T2DM.

5. Psychosocial Aspects, Quality of Life, and Patient-Centered Care

- **Research into Health-Related Quality of Life (HRQoL)** for patients with Graves' disease and the development of specific HRQoL questionnaires for thyroid cancer patients.
- **Studies addressing mental health and emotional distress** in diabetic patients, including the prevalence of depression, diabetes-related emotional distress and its impact on self-care and glycemic control, and behavioral/emotional problems in children and adolescents with T1DM.
- **Patient Decision Aids:** Development of tools to support patient decision-making in choosing diabetes medications and osteoporosis treatments.
- **Addressing overlooked issues** such as sexual dysfunction in women with T2DM and the impact of diabetes distress and socioeconomic factors on HRQoL.
- **Occupational health considerations** like intentional hyperglycemia at work, work-related diabetes distress, and work ability among workers with diabetes.

6. Refining Diagnostic and Management Guidelines/Protocols

- **The need for standardizing diagnosis**, such as for pituitary adenomas.
- **Development of clinical practice guidelines (CPGs)** for pre-diabetes management in the Asia-Pacific region and updated CPGs for dyslipidemia.
- **Establishing trimester-specific reference intervals** for thyroid function tests in pregnant women and improving diagnostic accuracy by comparing different thyroid imaging reporting and data systems (e.g., TIRADS vs. ATA guidelines).
- **Developing standardized protocols for critical care**, such as for Critical Illness-Related Corticosteroid Insufficiency (CIRCI).

Table 1. Article Type Analysis (2011-2025)

Article Type	Number of Articles	Percentage of Total (%)
<i>Original Article</i>	233	44.98
<i>Case Report</i>	139	26.83
<i>Feature Article</i>	54	10.42
<i>Editorial</i>	32	6.18
<i>Images in Endocrinology</i>	24	4.63
<i>Review Articles</i>	17	3.28
<i>Case Series</i>	9	1.74
<i>Letter to Editors</i>	4	0.77
<i>Others</i>	2	0.39
<i>Interhospital Grand Rounds</i>	2	0.39
<i>Brief Communications</i>	1	0.19
<i>Endocrine Perspectives</i>	1	0.19
Total	518	100.00

Table 2. Distribution of Articles by Endocrine Disorders (2011-2025)

Endocrine Disorder Category	Number of Articles	Percentage of Total (%)
<i>Diabetes</i>	174	33.59
<i>Thyroid</i>	97	18.72
<i>Obesity</i>	28	5.40
<i>Adrenal</i>	24	4.63
<i>Bone / Calcium</i>	20	3.86
<i>Pituitary</i>	13	2.51
<i>Reproductive</i>	3	0.16
<i>Other (Neuroendocrine, Pheochromocytoma, etc.)</i>	159	30.69
Total	518	100.00

* The authors used Google NotebookLM for the analysis of the JAFES issues from 2010 to the present.

FROM REVIVAL TO IMPACT

JAFES Impact in the Southeast Asian Region

The Journal of the ASEAN Federation of Endocrine Societies (JAFES) has undeniably made a significant impact on the Southeast Asian (ASEAN) region by serving as a crucial platform for advancing endocrine research, disseminating clinical practice guidelines, fostering regional collaboration, and addressing prevalent health issues specific to its member countries.

1. Platform for Advancing Regional Endocrine Research

- From its early years, JAFES explicitly aimed at "Advancing Endocrine Research in the ASEAN region" and "Amplifying the Voice of ASEAN Endocrinology through JAFES and its Website."
- It welcomes manuscripts from both members and non-members of the ASEAN Federation of Endocrine Societies (AFES), but a substantial portion of its content focuses on studies conducted within ASEAN countries. For example, recent issues feature original articles from the Philippines, Malaysia, Thailand, Indonesia, Brunei Darussalam, Myanmar, and Vietnam, covering a wide array of endocrine and metabolic conditions.

2. Dissemination of CPGs Tailored for the Region

- A primary impact of JAFES has been the widespread publication of national and regional Clinical Practice Guidelines (CPGs) for key endocrine and metabolic conditions. This directly influences patient care and health policy in Southeast Asia. Examples include:
- Diabetes Mellitus: Summaries of national CPGs from Indonesia, Malaysia, the Philippines, and Singapore were featured in 2011, explicitly labeled as "Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region."
- Obesity: National CPGs for the management of obesity from Malaysia, Myanmar, Singapore, Indonesia, and the Philippines were published in 2011, responding to the "Obesity Clinical Practice Guidelines (CPGs) for the ASEAN Region: Facing the Challenge of Malnutrition."
- Thyroid Disorders: CPGs for hyperthyroidism (Indonesia), general thyroid management (Malaysia, Myanmar), and well-differentiated thyroid carcinoma (Philippines) have been featured.
- Osteoporosis: Summaries of guidelines from Indonesia, Myanmar, the Philippines, and Singapore have been published, contributing to "Understanding Bone Disease in Southeast Asia."
- Diabetes in Pregnancy: Indonesian and Myanmar CPGs for diabetes in pregnancy were shared.
- Dyslipidemia: Myanmar and Philippine CPGs for dyslipidemia management have been reviewed.
- Pre-diabetes: A consensus of key opinion leaders on the management of pre-diabetes in the Asia-Pacific Region was published, involving experts from multiple ASEAN countries.

- Pituitary Adenoma: A consensus for pituitary adenoma diagnosis in Indonesia was published.

3. Addressing Region-Specific Health Challenges and Public Health Concerns

- JAFES proactively highlights health issues pertinent to the region, such as the "double burden of malnutrition in Asia."
- It has provided a platform to discuss persistent problems like "Iodine Deficiency Disorders," which "Continue to be a Problem in the Asia Pacific Region."
- The journal addresses challenges in healthcare delivery, for example, calling for "Ocular Telehealth Programs" to combat "Diabetic Retinopathy in Southeast Asia."
- During the COVID-19 pandemic, JAFES dedicated an entire issue to "Response in Southeast Asia: Managing diabetes and other endocrine disorders during the COVID-19 crisis," including consensus recommendations from the Philippines and Myanmar for inpatient diabetes management among COVID-19 patients, and an "ASEAN Survey of Needs in Endocrinology."

4. Fostering Collaboration and Knowledge Exchange

- As the official journal of the AFES, JAFES inherently promotes collaboration among endocrinologists and researchers across ASEAN member countries. Editorials have explicitly called for "Collaboration Among Endocrinology Publications in Asia."
- The frequent publication of research and guidelines from various ASEAN countries (e.g., Philippines, Malaysia, Indonesia, Myanmar, Singapore, Thailand, Vietnam, Brunei Darussalam) demonstrates active cross-regional participation and knowledge sharing.

5. Promoting Open Access to Scientific Information

- As an open-access journal, JAFES ensures that its scholarly content is freely available to readers throughout the region, which is particularly impactful in areas where access to expensive subscription journals may be limited. This broad accessibility supports education, clinical practice, and research in all ASEAN member countries and beyond.

CONCLUSION

JAFES has demonstrably impacted the Southeast Asian region by providing a vital, open-access platform for local research, the development and dissemination of regionally relevant clinical guidelines, and fostering a collaborative environment to address the unique endocrine and metabolic health challenges faced by the diverse populations of ASEAN.

In her reflection on Fifteen Years of JAFES, the Editor-in-Chief described the journal's evolution as a "journey of deliberate steps, from local beginnings to regional strength and international credibility." JAFES's development has been steady, collaborative, and principled, guided by a

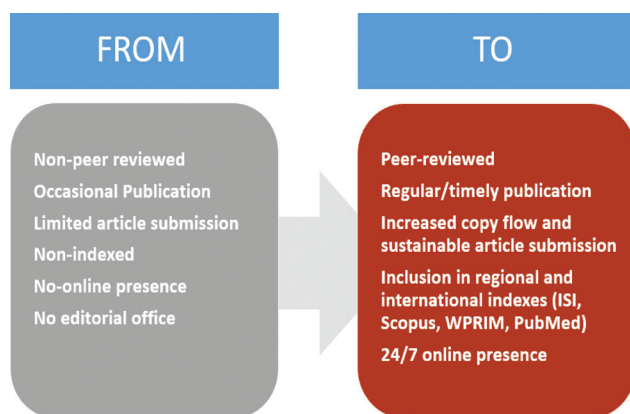


Figure 6. JAFES goals achieved.

consistent editorial vision and supported by a community of authors, reviewers, and society leaders across ASEAN.

Today, JAFES stands as both an archive and an advocate of regional endocrinology: a platform where Southeast Asian perspectives, data, and experiences are shared with the world. Its legacy is built not only on published articles but on the enduring ideals of integrity, inclusivity, and scientific excellence.

As JAFES moves forward, its mission remains unchanged: to serve as the collective voice of ASEAN endocrinology, advancing research, fostering collaboration, and sustaining the highest standards of ethical, open scientific communication.

Authors are required to accomplish, sign and submit scanned copies of the JAFES Author Form consisting of: (1) Authorship Certification, that authors contributed substantially to the work, that the manuscript has been read and approved by all authors, and that the requirements for authorship have been met by each author; (2) the Author Declaration, that the article represents original material that is not being considered for publication or has not been published or accepted for publication elsewhere, that the article does not infringe or violate any copyrights or intellectual property rights; that no references have been made to predatory/suspected predatory journals; and that use of artificial intelligence (AI) or AI-assisted technologies shall be declared to include the name of the AI tool or service used; (3) the Author Contribution Disclosure, which lists the specific contributions of authors; (4) the Author Publishing Agreement which retains author copyright, grants publishing and distribution rights to JAFES, and allows JAFES to apply and enforce an Attribution-Non-Commercial Creative Commons user license; and (5) the Conversion to Visual Abstracts (*optional for original articles only) to improve dissemination to practitioners and lay readers. Authors are also required to accomplish, sign, and submit the signed ICMJE form for Disclosure of Potential Conflicts of Interest. For original articles, authors are required to submit a scanned copy of the Ethics Review Approval of their research as well as registration in trial registries as appropriate. 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. For Case Reports or Series, and Images in Endocrinology, consent forms, are required for the publication of information about patients; otherwise, appropriate ethical clearance has been obtained from the institutional review board. Articles and any other material published in the JAFES represent the work of the author(s) and should not be construed to reflect the opinions of the Editors or the Publisher.



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Philippine Clinical Practice Guidelines on Screening, Diagnosis, Management and Prevention of Primary Osteoporosis and Fragility Fractures Among Postmenopausal Women and Older Men

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Abstract

Background. This first clinical practice guideline (CPG) on osteoporosis prevention and management in the Philippines is the output of a shared undertaking by a multidisciplinary CPG development team spearheaded by the Osteoporosis Society of the Philippines Foundation, Inc. and joined by the Philippine Academy of Family Physicians; the Philippine College of Endocrinology, Diabetes, and Metabolism; the Philippine Orthopedic Association; the Philippine Obstetrics and Gynecological Society and the Philippine Rheumatology Association. This guideline seeks to augment and update the "Consensus statements on osteoporosis diagnosis, prevention and management in the Philippines," initially published in 2011, incorporating evidence-based practices developed in the last decade.

Methodology. The steering committee formulated and prioritized clinical questions based on meetings and stakeholder consultations. A PICO (population, intervention, comparator, outcome) format was used to develop clinical questions and guide the systematic search for evidence. The development of guidelines followed the ADAPTE process. Once completed, panel discussions were done using the Evidence to Decision Framework. After the panel discussions, the final recommendations were revised.

Results. Thirty-four recommendations were formulated to address 27 clinical questions related to screening, prevention, diagnosis, pharmacologic and nonpharmacologic treatment, surgical management, follow-up, and continuity of care. With these recommendations, the developers aim to establish a standard of care in the prevention, diagnosis and management of osteoporosis and fragility fractures in both in-patient and out-patient cases that are appropriate to the Philippine context. Specifically, the CPG development group aims to use these recommendations to define the standard of care for osteoporosis as part of universal healthcare services once the program is implemented nationally. Relevant stakeholders may also use the recommendations to inform public and private payor policies for patients with fragility fractures, as well as by local government units or private companies looking to establish orthogeriatric centers with fracture liaison services.

Conclusion. This guideline is helpful for physicians and other allied health personnel in screening, diagnosis, management and prevention of primary osteoporosis and fragility fractures among postmenopausal women and older men.

Key words: Philippines, guidelines, osteoporosis, older men, postmenopausal women

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INTRODUCTION

Osteoporosis is a chronic bone disease that affects millions of individuals and constitutes a significant public health problem. As the global population continues to age, the burden of osteoporosis is projected to increase in the coming years due to increasing life expectancy, population aging, and the growing prevalence of noncommunicable diseases that impact negatively on osteoporosis risk factors.

METHODOLOGY

This clinical practice guideline is a systematic synthesis of scientific evidence related to primary, secondary and tertiary prevention strategies for osteoporosis in postmenopausal women. Guideline development followed the ADAPTE process, a validated and systematic approach to adapting existing guidelines for use in a specific organizational context or setting with limited time and resource commitments.¹ Developers also planned for a *de novo* systematic review and meta-analysis using the widely accepted grading of recommendations, assessment, development and evaluation (GRADE) approach for clinical questions that were unsuitable for adaptation.² Finally, the Evidence to Decision (EtD) Framework was used to guide panel discussions and inform decision-making when the final recommendations were formulated. For ease of interpretation and comparison across source CPGs, all recommendation statements and evidence ratings of the source CPGs (Table 3) were appraised and re-classified by the evidence review expert (ERE) using the GRADE approach, the rating system used for the present CPG (Tables 1 and 2).

RESULTS

After rigorous evidence reviews and panel discussions, the following clinical questions (Q) and recommendations (R) were formulated:

Q1: Among the adult population, who should be screened for osteoporosis?

R1: It is recommended that the following individuals be screened for osteoporosis: all postmenopausal women (PMW), men aged ≥ 50 years with clinical risk factors, and other adults with clinical risk factors (**Strong recommendation, moderate to high quality of evidence**).^{3,4}

Q2: Among the adult population, what factors increase the risk of osteoporosis?

R2: *Screening for the following risk factors is recommended:* advanced age (>70 years), previous fragility fracture, menopause or untreated early menopause, parental history of osteoporosis and/or fractures, excessive alcohol consumption (>3.5 units per day), smoking, frailty or low level of physical activity, coexisting illnesses, and certain medications. *Comorbidities:* diabetes, hyperparathyroidism or other endocrine diseases, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, malabsorption, institutionalized patients with epilepsy, chronic liver disease, neurological disease (Alzheimer's, Parkinson's, multiple sclerosis, stroke), moderate to severe chronic kidney disease (CKD), bronchial asthma, human immunodeficiency virus. *Medications:* glucocorticoids, antidepressants, anti-epileptic agents (i.e., enzyme-inducing drugs), aromatase inhibitors, gonadotrophin releasing hormone agonists for prostate cancer, proton pump inhibitors, thiazolidinediones, anticoagulants, methotrexate, thyroid hormones (**Strong recommendation, high quality of evidence**).^{3,4}

Q3: What tool should be used for osteoporosis screening?

R3: Osteoporosis screening should be performed using the fracture risk assessment (FRAX[®]) tool⁵ (Figure 1) (**Strong recommendation, high quality of evidence**).^{5,6}

Table 1. Rating quality of the evidence using the GRADE approach⁷

Quality of Evidence	Interpretation
High	We are confident that the actual effect is close to the effect estimate. Further research is unlikely to change our confidence in the effect estimate.
Moderate	We are moderately confident in the effect estimate. The actual effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research is expected to impact our confidence in the estimate of effect and may change the estimate.
Low	Our confidence in the effect estimate is limited. The actual effect may be substantially different from the estimate of the effect. Further research is very likely to impact our confidence in the estimate of effect and is expected to change the estimate.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect. Any estimate of the effect is very uncertain.

Table 2. Rating strength of recommendation using the GRADE approach⁷

Strength of Recommendation	Interpretation
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects (strong recommendation of an intervention). The undesirable effects of an intervention clearly outweigh the desirable effects (strong recommendation against an intervention).
Weak/Conditional	The trade-offs between desirable and undesirable effects are less certain, either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

R4: The Osteoporosis Self-assessment Tool for Asians (OSTA) tool⁷ may be used as an alternative to FRAX[®] for osteoporosis screening (Figure 1) (**Strong recommendation, high quality of evidence**).⁶

Q4: Among the adult population, what is the clinical presentation of osteoporosis?

R5: Patients who present with the following history, signs and symptoms should be suspected to have osteoporosis: acute onset back pain, height loss, previous fragility fracture, menopause or untreated early menopause, parental history of osteoporosis, and/or fractures. Physical examination findings include any of the following: low weight or body mass index (BMI) (<18.5 kg/m²), ≥4 cm height loss, or thoracic kyphosis (**Strong recommendation, high quality of evidence**).^{3,4}

Q5: Among at-risk PMW, should bone mineral density measurement using dual-energy x-ray absorptiometry be used to diagnose osteoporosis?

R6: Among at-risk PMW, it is recommended that a bone mineral densitometry (BMD) test using dual-energy x-ray absorptiometry (DXA) and WHO classification criteria be

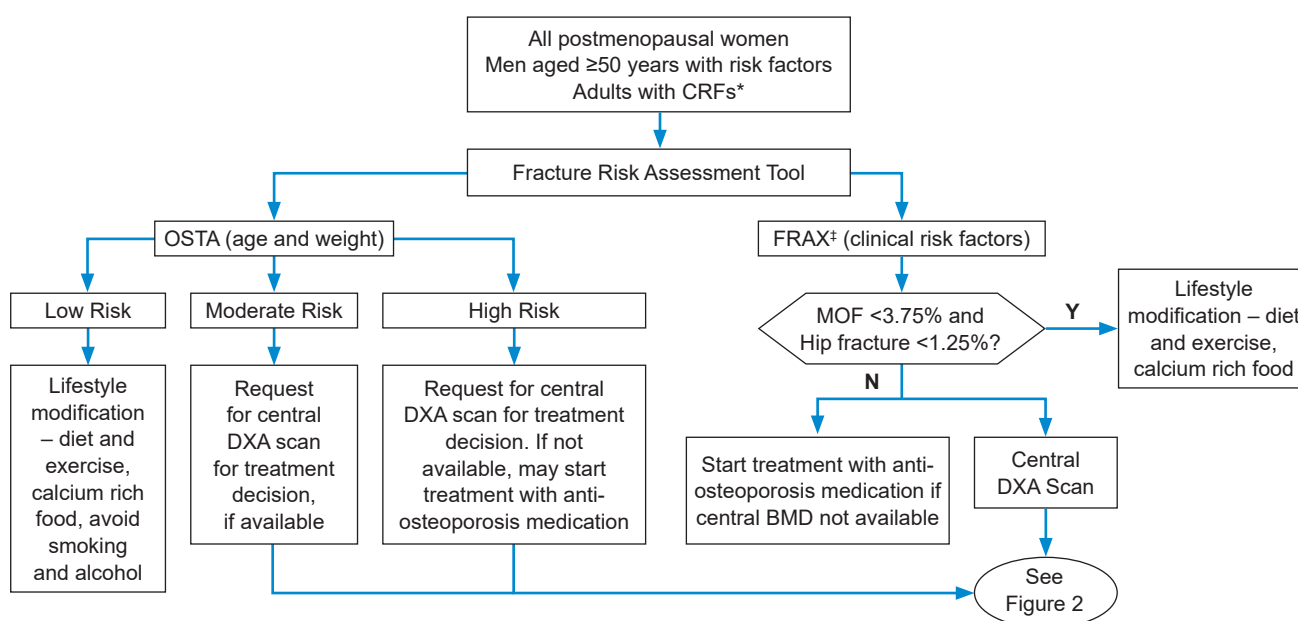
used for the diagnosis of osteoporosis (Figure 2) (**Strong recommendation, high quality of evidence**).^{3,8}

R7: Among at-risk PMW, it is recommended that the following criteria be used to diagnose osteoporosis: low bone mass (BMD T-score between <-1.0 and >-2.5) with a fragility fracture, or those at high fracture risk according to country-specific FRAX[®] (**Strong recommendation, high quality of evidence**).^{3,8}

R8: Among at-risk PMW of vertebral fracture, it is recommended that vertebral fracture assessment (VFA) using DXA or lateral spine radiograph be done (**Strong recommendation, high quality of evidence**).^{3,8}

R9: Among at-risk PMW without fracture, where BMD measurement via DXA is unavailable or not feasible, starting anti-osteoporosis therapy is suggested in the following:

- A fracture intervention threshold of 3.75% for major osteoporotic fractures and/or 1.25% for hip fractures using FRAX[®] tool, or
- Patients who fall under high risk category using Osteoporosis Screening Tool for Asians (**Strong recommendation, high quality of evidence**).^{3,8}



*Clinical Risk Factors that increase the risk of osteoporosis include: advanced age (>70 years), previous fragility fracture, menopause or untreated early menopause, parental history of osteoporosis and/or fractures, excessive alcohol consumption (>3.5 units per day), smoking, frailty or low level of physical activity, coexisting illnesses, and certain medications.

Comorbidities: diabetes, hyperparathyroidism or other endocrine diseases, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, malabsorption, institutionalized patients with epilepsy, chronic liver disease, neurological disease (Alzheimer's, Parkinson's, multiple sclerosis, stroke), moderate to severe chronic kidney disease, bronchial asthma, human immunodeficiency virus.

Medications: glucocorticoids, antidepressants, anti-epileptic agents (i.e. enzyme-inducing drugs), aromatase inhibitors, GnRH agonists for prostate cancer, PPIs, thiazolidinediones, anticoagulants, methotrexate, thyroid hormones.

†FRAX clinical risk factors: Age, gender, weight, height, parental history of hip fracture, personal history of fracture, glucocorticoid use, rheumatoid arthritis, secondary cause of bone loss, current smoking, alcohol intake of ≥3 units per day, ± femoral neck BMD using central DXA.

Figure 1. Primary prevention of bone loss.

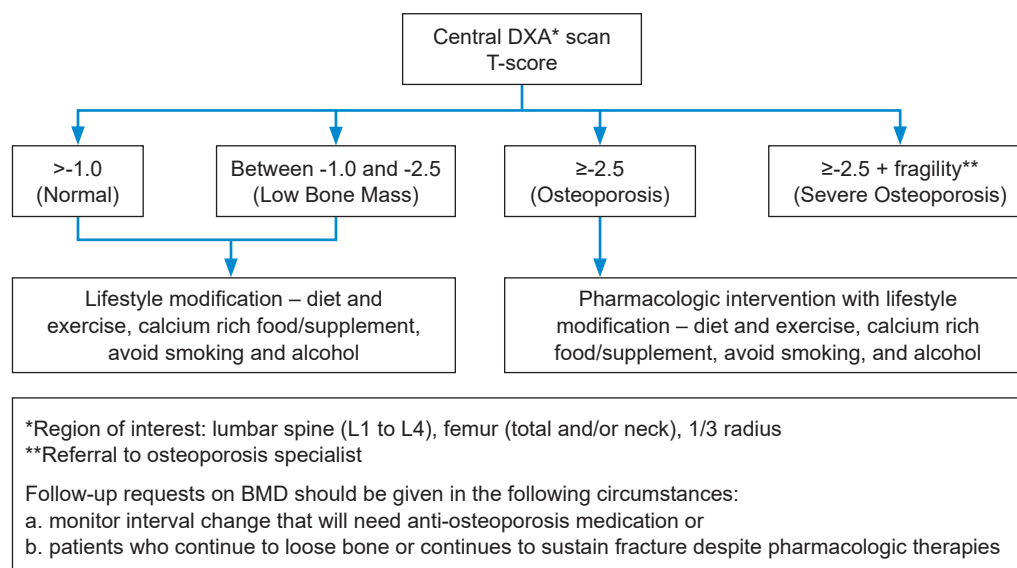


Figure 2. WHO classification criteria for BMD and management approach.

Q6: Among PMW with osteoporosis, are the anti-resorptive agents (e.g., alendronate, ibandronate, zoledronate, denosumab, raloxifene) effective in reducing vertebral, non-vertebral and hip fractures compared to placebo?

R10: Among PMW with osteoporosis, it is recommended that alendronate, denosumab, risedronate, and zoledronate be used as initial therapy to reduce vertebral, non-vertebral and hip fractures (**Strong recommendation, high quality of evidence**).⁶

R11: Ibandronate or raloxifene can be an alternative treatment in reducing vertebral fractures in certain cases (**Strong recommendation, moderate quality of evidence**).⁶

Q7: Among postmenopausal women with severe osteoporosis, are teriparatide, abaloparatide, and romosozumab effective in reducing vertebral, non-vertebral and hip fractures compared to placebo? How long should treatment duration be?

Severe osteoporosis is defined in any of the following situations:

- BMD T-score ≤ -2.5 plus fragility fractures
- BMD T-score ≤ -3.5
- Prior hip fracture
- Recent vertebral fracture (within the last two years)
- Two or more vertebral fractures (at anytime)

R12: Among PMW with severe osteoporosis, it is recommended that teriparatide, abaloparatide and romosozumab be used. Abaloparatide and romosozumab prevent vertebral, non-vertebral and hip fractures, while teriparatide reduces the risk of further vertebral and nonvertebral fractures. Treatment duration of bone forming agents for maximum treatment benefits is recommended to be referred to specialists. Teriparatide, abaloparatide and romosozumab are highly special drugs which should

be dispensed by bone specialists because of local availability and cost concerns (**Strong recommendation, high quality of evidence**).^{6,7}

Q8: Among postmenopausal women diagnosed with osteoporosis, should serum calcium and vitamin D levels be normal prior to initiating anti-resorptive therapy?

R13: Among PMW with osteoporosis, it is recommended that calcium insufficiency/deficiency be treated prior to initiation of anti-osteoporosis drugs (**Strong recommendation, moderate quality of evidence**).³

R14: It is also recommended that vitamin D insufficiency/deficiency should be addressed alongside the initiation of anti-osteoporosis drugs (**Strong recommendation, high quality of evidence**).³

Q9: Among PMW with osteoporosis, should calcium and vitamin D supplementation be given to reduce fragility fracture risk?

R15: Among PMW with osteoporosis, calcium and vitamin D supplementation is recommended along with anti-osteoporosis medication to reduce the risk of fragility fracture. The recommended dose for calcium is 700 to 1200 mg per day, and vitamin D at least 800 IU per day (**Strong recommendation, high quality of evidence**).⁸⁻¹⁰

Q10: Among patients with previous fragility fractures, what is the effect of pharmacologic intervention on the risk of having a subsequent or second fracture?

R16: Among patients with previous or prevalent fragility fractures (regardless if BMD is available or not), pharmacologic therapy, such as bisphosphonates and teriparatide, is recommended to reduce the risk of subsequent fractures (**Moderate quality of evidence, strong recommendation**).^{7,11}

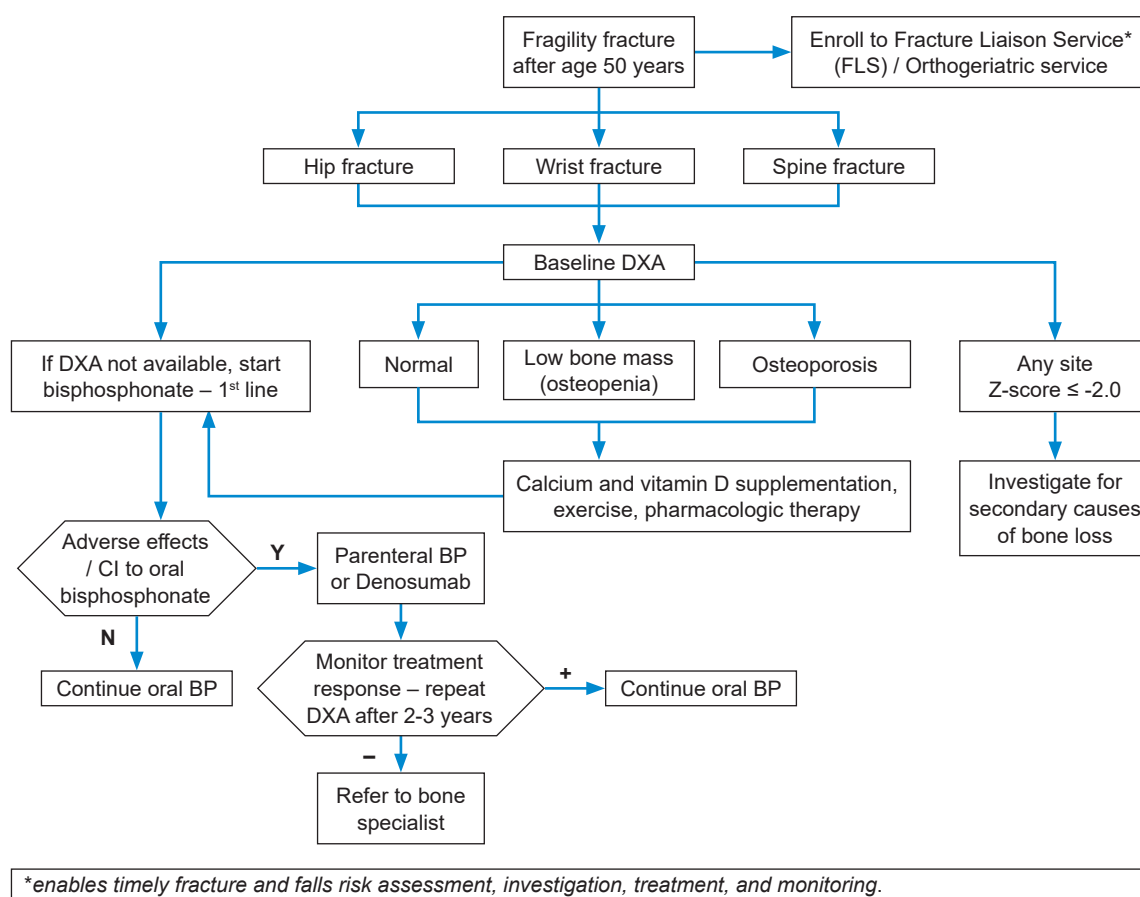


Figure 3. Algorithm on secondary fracture prevention.

Q11: Among patients with acute displaced fragility fractures of the distal radius, is early surgical intervention superior to conservative management for improving functionality?¹²

R17: Among patients 65 years old and older with acute displaced fragility fractures of the distal radius, it is not recommended to proceed with surgery to improve long-term patient functional outcomes (Figure 3) (Strong recommendation, high quality of evidence).⁹

Q12: Among patients who have painful osteoporotic compression fractures of the spine, is kyphoplasty superior to nonsurgical management for controlling pain and improving quality of life (QoL)?

R18: Among patients with recent-onset painful osteoporotic compression fractures of the spine refractory to conservative therapy, it is suggested that kyphoplasty be done over non-surgical treatment for acute pain control (six to eight weeks) and improvement of quality of life (Strong recommendation, moderate quality of evidence).⁷

Q13: Among patients who sustained fragility fractures of the hip, is early surgical intervention superior to delayed surgical intervention in improving overall survival, morbidity, mortality and functionality of patients?

R19: Among patients who sustained fragility fractures of the hip, it is suggested that early surgical management (within 24 to 48 hours) be done to reduce morbidity and improve survival (Strong recommendation, moderate quality of evidence).¹³

Q14: In patients with a previous osteoporotic fragility fracture, will enrollment in a secondary fracture prevention program or fracture liaison service (FLS) improve treatment adherence and prevent re-fractures?

R20: Among patients who have experienced fragility fracture, it is recommended that they be managed within a formal integrated system of care that incorporates a fracture liaison service to prevent re-fractures and improve adherence to osteoporosis treatment (Figure 3) (Strong recommendation, high quality of evidence).^{3,7}

R21: Among patients who have fragility fracture/s, it is recommended that appropriate interventions, including both pharmacologic and non-pharmacological approaches, be started (High quality of evidence, strong recommendation).^{3,7}

Q15: Among adults receiving osteoporosis treatment, what is the appropriate interval between central DXA scans in monitoring treatment response?

R22: Among adults receiving osteoporosis treatment, it is recommended that a central DXA test should be done every one to two years, especially in patients at high risk of fracture, then at longer intervals thereafter once a definite satisfactory treatment response is achieved (**Strong recommendation, moderate quality of evidence**).^{6,7}

Q16: Among patients with recent fragility fracture/s, should an immediate referral to a bone specialist be done for better evaluation and management?

R23: It is recommended that patients with the following risk factors/conditions be referred to an osteoporosis specialist: patients with fragility fracture and/or subsequent fragility fractures, BMD T-score ≤ -3.5 , treatment with high-dose glucocorticoids (≥ 7.5 mg/day of prednisolone or equivalent over three months), patients with comorbidities such as CKD, endocrine and rheumatic diseases (**Strong recommendation, high quality of evidence**).⁶

Q17: Should at-risk PMW and older men receive calcium supplementation and/or vitamin D supplementation for prevention of osteoporosis and fragility fractures?

R24: Among at-risk adults with normal FRAX[®] and BMD scores, calcium and vitamin D supplementation is recommended for those who do not meet country-specific reference standards. Potential hazards and adverse effects of calcium and vitamin D supplementation include increased risk for renal insufficiency, myocardial infarction, coronary artery disease and stroke (**Strong recommendation, moderate quality of evidence**).^{3,5,12}

Q18: Among PMW and older men, what doses of calcium and Vitamin D are associated with reduced fragility fracture risk?

R25: Among at-risk adults with normal FRAX[®] and BMD scores who do not meet country-specific reference standards, supplementation with vitamin D at 400 to 600 IU per day and calcium at 700 to 800 mg per day is recommended (**Strong recommendation, moderate quality of evidence**).^{3,12}

Q19: Among PMW and older men, what is the benefit of physical activity in the prevention of osteoporosis and fragility fractures?

R26: Among PMW and older men, regular physical activities using a combination of exercise types (such as weight bearing, balance training, flexibility or stretching exercises, endurance and progressive strengthening exercises) are recommended to increase BMD and reduce the risk of fragility fractures. Community-based programs may be sought through the respective Office of the Senior Citizens Affairs in each locality or community (**Strong recommendation, high quality of evidence**).^{3,7,15}

Q20: Among PMW and older men, does smoking cessation prevent osteoporosis and fragility fractures?

R27: Among PMW and old men, smoking cessation is recommended to reduce the risk of osteoporotic fractures. Specific guidelines on smoking cessation are outlined in the Philippine Guidelines on Periodic Health Examination – Lifestyle Advice CPG (**Strong recommendation, moderate quality of evidence**).^{3,7,12,14,15}

Q21: Among PMW and older men, what diet is effective in the prevention of osteoporosis?

R28: Among PMW and old men, a balanced diet or nutrient-dense diet (fruits, vegetables and whole grains) is recommended to prevent osteoporosis and fragility fractures (**Strong recommendation, moderate level of evidence**).^{3,7,12,15}

Q22: Should at-risk postmenopausal women receive menopausal hormone therapy (MHT) for the prevention of fragility fractures? What is the duration of use for MHT?

R29: Among at risk peri- and postmenopausal women with climacteric symptoms but without contraindications to MHT, it is recommended that MHT be given for a minimum duration of two years but not longer than three years to reduce fracture risk (**Strong recommendation, high quality of evidence**).¹⁶

R30: Among at-risk peri- and post-menopausal women with climacteric symptoms but with contraindications to MHT, MHT is not recommended (**Strong recommendation, high quality of evidence**).¹⁶

Q23: When should menopausal hormone therapy be initiated to reduce fracture risk?

R31: Among at-risk peri- and postmenopausal women with climacteric symptoms but without contraindications to MHT younger than 60 years of age, initiation of MHT may be of greater benefit in fracture risk reduction (**Strong recommendation, high quality of evidence**).¹⁶

Q24: Which hormone preparation should be used for fracture risk reduction?

R32: Among hysterectomized PMW, it is recommended to give estrogen-only replacement therapy for fracture risk reduction. Addition of progestins is recommended for women with intact uterus to prevent endometrial pathology (**Strong recommendation, high quality of evidence**).¹⁶

Q25: What are the safety issues of MHT?

R33: The safety issues of MHT include an increased risk for coronary events, stroke, venous thromboembolism (VTE), breast cancer and gallbladder disease. Among at-risk peri- and postmenopausal women with climacteric symptoms but without contraindications to MHT, transdermal estrogen (gel/patch) is recommended over oral estrogen to decrease the risk of VTE (**Strong recommendation, high quality of evidence**).¹⁶

Q26: Among at-risk postmenopausal women, should selective estrogen receptor modulators (SERMs) be considered an alternative to MHT for prevention of osteoporosis?

R34: Among women at-risk of breast cancer, raloxifene is recommended as an alternative to MHT to reduce the risk of vertebral fractures (**Strong recommendation, high quality of evidence**).¹⁶

Q27: How are adverse events monitored in women receiving MHT for osteoporosis prevention?

R35: Among women on MHT who are at risk of breast cancer, it is recommended for them to undergo annual mammograms. Among women with postmenopausal bleeding on MHT, it is recommended for them to undergo transvaginal ultrasound every six months for the first year and annually thereafter. Among women on MHT, it is recommended that they be monitored for signs and symptoms of venous thromboembolism, and cardiovascular and cerebrovascular diseases. (**Strong recommendation, high quality of evidence**).¹⁶

DISCUSSION

The burden of disease is expected to be more pronounced soon as the old population is expected to triple in size. Increasing education and dissemination of osteoporosis prevention, improving resource allocation, and paying more attention to screening and treatment of osteoporosis could help reduce the global burden of disease attributable to low bone mineral density and fracture, especially in low-middle and middle sociodemographic index countries and territories. The lack of high-quality, population-specific local data led to the adaptation of

CPGs from Asian and international sources. It is the best option at the time being to address the burden of osteoporosis in the Philippines. The authors of this CPG will spearhead local epidemiologic and cost-analysis studies that will help address the said knowledge gap. Future revisions of this CPG will focus on the said gaps to avoid the possibility of over-screening and over-treatment.

CONCLUSION

This guideline is helpful for physicians and other allied health personnel in the screening, diagnosis, management and prevention of primary osteoporosis and fragility fractures among postmenopausal women and older men. The guideline was submitted and accepted by the Department of Health in early 2024. The full text of the manuscript and supplementary appendix and references can be accessed via <https://doh.gov.ph/dpcb/doh-approved-cpg/>. Similarly, this guideline has been presented in conferences and annual conventions of various medical societies. This CPG will be updated after three years or earlier to present more recent evidence. Surveys and focused group discussions with end-users of this guideline will be also done to accurately capture their preferences and other views. Cost-evaluation, feasibility and health economic outcome studies will also be done in order to evaluate the impact of this guideline from a budget and financial standpoint. Lastly, to monitor and evaluate adherence of healthcare providers to evidence-based standards on the various domains of osteoporosis, possible key performance indicators include:

1. Screening and risk assessment: Percentage of eligible patients screened for osteoporosis using the validated fracture risk assessment tools (e.g., FRAX®, OSTA);
2. Diagnosis: Percentage of patients with fragility fractures assessed for osteoporosis, and time to diagnosis after incident fracture;
3. Prevention: Percentage of patients who engage in community exercise programs and on calcium and vitamin D supplementation;
4. Treatment initiation: Percentage of high-risk patients on anti-osteoporosis treatment; and
5. Fracture Liaison Service: Percentage of patients who are adherent to medications for 12 months or more, incidence of new fragility fractures in patients ongoing therapy, and time from fracture to osteoporosis care coordination.

Table 3. Summary of guideline content

A check (✓) indicates discussion of the clinical question in the source guideline

	1 AAOE ⁸	2 AAOS ¹³	3 AAOS ¹⁴	4 African ¹⁰	5 ASBMR	6 BBC ¹²	7 LatAm	8 NAMS ³	9 RAGCP ¹⁵	10 SIGN ⁹	11 UK NOGG ³	12 USPSTF ⁶
Screening												
Among the adult population, who should be screened for osteoporosis?											✓	
Among the adult population, what factors increase the risk for osteoporosis?											✓	
Among the adult population, what tool should be used for osteoporosis screening?												✓
Among the adult population, what is the clinical presentation of osteoporosis?											✓	
Diagnosis												
Among at-risk PMW, should bone mineral density measurement using dual energy x-ray absorptiometry be used to diagnose osteoporosis?	✓					✓				✓		✓
Management: Pharmacologic												
Among PMW with osteoporosis, are alendronate, ibandronate, zoledronate, denosumab, raloxifene effective in reducing vertebral, non-vertebral, hip fractures compared to placebo?	✓											
Among PMW with severe osteoporosis, are teriparatide, abaloparatide, and romosozumab effective in reducing vertebral, non-vertebral and hip fractures compared to placebo? How long should treatment duration be?	✓						✓			✓	✓	
Management: Non-Pharmacologic												
Among PMW women with osteoporosis, should calcium and vitamin D supplement be given to reduce the risk of fragility fractures?				✓	✓	✓						✓
Among PMW with osteoporosis, should serum calcium and vitamin D levels be normal before initiation of anti-osteoporosis medication?	✓									✓	✓	
Surgical Management												
Among patients with previous fragility fractures, what is the effect of pharmacologic intervention on the risk of having a subsequent or second fracture?										✓		
Among patients with acute displaced fragility fractures of the distal radius, is early surgical intervention superior to conservative management to improve functionality?		✓										
Among patients who have painful osteoporotic compression fractures of the spine, is kyphoplasty superior to nonsurgical management for controlling pain and improvement of quality of life (QOL)?										✓		
Among patients who sustained fragility fractures of the hip, is early surgical intervention superior to delayed surgical intervention in improving overall survival, morbidity, mortality and functionality of patients?			✓									
Among patients with previous osteoporotic fragility fracture, will enrollment in a secondary fracture prevention program or fracture liaison service (FLS) improve treatment adherence and prevent re-fractures?										✓	✓	
Follow-up Care												
Among PMW receiving osteoporosis treatment, what is the appropriate interval between central DXA scans in monitoring treatment response?	✓									✓		
Among patients with recent fragility fracture, should an immediate referral to an osteoporosis specialist be done for better evaluation and management?	✓										✓	
Prevention												
Among at-risk PMW and old men, should calcium and/or Vitamin D supplementation be recommended for prevention of osteoporosis and fragility fractures?									✓		✓	
Among PMW and old men, what doses of calcium and Vitamin D are associated with reduced fragility fracture risk?											✓	✓
Among PMW and old men, what is the benefit of physical activity in the prevention of osteoporosis and fragility fractures?									✓		✓	
Among PMW and old men, does smoking cessation prevent osteoporosis and fragility fractures?									✓	✓	✓	
Among PMW and old men, what diet is effective in the prevention of osteoporosis?									✓	✓	✓	
Prevention – MHT												
Among at-risk postmenopausal women, should menopausal hormone therapy (MHT) be recommended to prevent fragility fractures? For how long will the duration of use be?								✓				
Among at-risk postmenopausal women, when should MHT be initiated to reduce fracture risk?								✓				
Among at-risk postmenopausal women, what hormone preparation should be used for fracture risk reduction?								✓				
Among peri- and postmenopausal women, what are the safety issues of MHT?								✓				
Among at-risk PMW, should SERMS be given as an alternative to MHT for the prevention of osteoporosis?								✓				
Among at-risk PMW on MHT for osteoporosis prevention, what adverse events should be monitored?								✓				

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

JTYL: Conceptualization, Methodology, Investigation, Resources, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **ASA:** Conceptualization, Methodology, Investigation, Resources; **IAT:** Conceptualization, Methodology, Investigation, Resources; **JB:** Investigation, Resources, Writing – review and editing; **EVMC:** Investigation, Resources, Writing – review and editing; **SSE:** Investigation, Resources, Writing – review and editing; **MEF:** Investigation, Resources, Writing – review and editing; **JGT:** Investigation, Resources, Writing – review and editing; **TGB:** Investigation, Resources, Writing – review and editing; **LLL:** Investigation, Resources, Writing – review and editing; **EIYM:** Investigation, Resources, Writing – review and editing; **EM:** Investigation, Resources, Writing – review and editing; **DM:** Investigation, Resources, Writing – review and editing; **QNS:** Investigation, Resources, Writing – review and editing; **NSOJ:** Investigation, Resources, Writing – review and editing; **MRAP:** Investigation, Resources, Writing – review and editing; **JP:** Investigation, Resources, Writing – review and editing; **JR:** Investigation, Resources, Writing – review and editing; **MCARP:** Investigation, Resources, Writing – review and editing; **HUC:** Investigation, Resources, Writing – review and editing; **AWW:** Writing – review and editing; **IGP:** Writing – review and editing.

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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Acute Kidney Injury in Children with Type 1 Diabetes Mellitus Hospitalized for Diabetic Ketoacidosis: A Retrospective Study

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Abstract

Objectives. Diabetic ketoacidosis (DKA) is the most common initial presentation in children with newly diagnosed type 1 diabetes. Severe dehydration/acidosis, shock at admission, and hyperchloremia contribute to acute kidney injury (AKI). This retrospective study was done to determine the proportion of children hospitalized for DKA who had AKI and to compare clinical parameters between DKA children with AKI and without AKI to identify the risk factors associated with AKI.

Methodology. A retrospective review of all DKA admissions with type 1 diabetes was done. AKI was diagnosed as per KDIGO-2012 criteria. The analysis was done using a Chi-square test to assess the association between the status of AKI and other parameters. The Independent t-test was applied for comparison with the mean score between the No AKI / AKI group for numerical variables with normal distribution. A multivariate logistic regression analysis was performed to compare clinical parameters between both groups.

Results. Out of 32 children with DKA, 13 (40.63%) developed AKI. Among them, 9 had AKI at admission and 4 children developed AKI within the first 48 hours of admission. Optimum fluid management resolved AKI in 10 patients, but 3 of them required dialysis. Parameters like higher heart rate ($p = 0.0390$), higher respiratory rate ($p = 0.0402$), high leukocyte count ($p = 0.0005$), severe hyperglycemia ($p = 0.0204$), severe acidosis ($p = 0.0001$), hyperchloremia ($p = 0.016$) and shock at admission ($p = 0.0001$) were present in children with DKA and AKI.

Conclusion. In our study, a high proportion of children with DKA had AKI, which causes prolonged acidosis and hospital stay. Hence, comparing clinical parameters between both groups helps in identifying risk factors associated with AKI in persons with type 1 diabetes with DKA.

Key words: diabetic ketoacidosis, acute kidney injury, ketone bodies, hyperchloremia

INTRODUCTION

Diabetic ketoacidosis (DKA) is the most common initial presentation in new-onset type 1 diabetes in children with a frequency of around 15-70% across various populations.¹ Recurrence of DKA occurs in those with poor control, mismanagement during sick days, or interruption of delivery of insulin in insulin pumps. The leading cause of morbidity and mortality in DKA is due to cerebral injury. Cerebral edema accounts for about 60-90% of deaths, others being electrolyte imbalance, venous thrombosis, sepsis, renal injury, etc.¹ Acute kidney injury is associated with prolonged hospital stay and it can predispose to hypertension and chronic kidney disease (CKD). DKA with complications leads to prolonged hospital stay and higher treatment costs. Ketoacidosis resolves with correction by

fluid and insulin therapy. However, the presence of AKI leads to the persistence of acidosis as renal function gets compromised in severe and prolonged DKA. Several risk factors contribute to AKI in DKA. The most common being shock at admission, severe dehydration, severe acidosis, and hyperchloremia. There are no validated pharmacological interventions for AKI, hence prevention and early detection are key in management. Studies pertaining to the occurrence of AKI are less studied in DKA patients. Interpretation of creatinine varies in DKA as ketones interfere in creatinine measurement.² Even osmotic diuresis in DKA delays early diagnosis of oliguria. This retrospective study aimed to determine the proportion of children who develop AKI and to compare clinical parameters between children with DKA and AKI and those without AKI to identify the risk factors associated with AKI.

METHODOLOGY

A retrospective review of all case records of DKA admissions was done for children (<18 years) who were admitted from July 2018 to June 2021 at SDM College of Medical Sciences and Hospital, Dharwad. After ethical committee clearance (Ref. SDMIIEC/2021/83), data of all the cases admitted from the above 3-year period were collected. Diagnosis of DKA and its severity as mild, moderate, and severe DKA was defined as per ISPAD guidelines. The initial demographic details, clinical features (including vital signs and urine output), and anthropometry values were retrieved from case records in a structured format. Laboratory investigations like complete hemogram, venous blood gas analysis, and serum electrolytes were recorded at admission and were repeated after 4 to 6 hours and also on a case-to-case basis until recovery. An initial bolus of 10 - 20 ml/kg of normal saline (NS) followed by an additional 10 ml/kg infusion was given based on the presence of shock. Fluids were calculated according to severity of dehydration and maintenance fluids were added to replace the deficit over 24 to 48 hours (as per ISPAD 2018 guidelines). Inotropes and bicarbonates were considered in special situations as per standard guidelines.^{1,3} Intravenous insulin was used in all patients except in three children who were managed with subcutaneous insulin as they had mild DKA. Insulin infusion was started at 0.05 – 0.1 U/kg/hour after 1st hour of NS bolus. Intravenous fluids along with insulin infusion were adjusted as per serial serum electrolytes and blood sugar values during hospital stay. The duration of resolution of acidosis, duration of pediatric intensive care unit (PICU) and hospital stay were noted. Other associated complications like cerebral edema, deep vein thrombosis and foot drop were noted. Acute kidney injury was defined and staged as according to 2012 guidelines of Kidney Disease / Improving Global Outcomes Criteria (KDIGO). In the KDIGO criteria, AKI is defined as a creatinine level >1.5 times the expected baseline creatinine value.⁴ As we did not have baseline creatinine data of the patients at admission, we calculated the expected baseline creatinine values using an estimated glomerular filtration rate of 120 ml/min/1.73 sq. m. and patients height using Schwartz formula.⁵ Stage 0 AKI was defined as creatinine value <1.5 times, stage 1 AKI as creatinine 1.5-2 times, stage 2 AKI as 2-3 times and stage 3 AKI as creatinine >3 times the baseline creatinine. Those children who developed AKI during hospital stay were also taken into consideration and were staged based on progression. Creatinine estimation was done using the alkaline picrate-kinetic, International Federation of Clinical Chemistry-Isotope Dilution Mass Spectrometry (IFCC-IDMS) standardized method.

Statistical procedures

After the collection of data, the descriptive statistics with means/standard deviation were calculated for numerical variables; frequency, and percentages for categorical variables. The analysis was carried out by using Chi-square/Chi-square with the Yates correction test for association

between the status of AKI with other parameters. The Independent t-test was applied for comparison with mean score between with/without AKI group for numerical variables with normal distribution. The Kolmogorov-Smirnov test was performed and tested for the normality of all variables. Then the Mann-Whitney U test was used for numerical parameters with skewed distribution. The simple and multivariable logistic regression model was applied to compare clinical parameters between children with DKA and AKI and those without AKI to identify the risk factors associated with AKI. A statistical significance was set at a 5% level of significance ($p < 0.05$). The statistical software used are SPSS 20 and STATA 16.0.

RESULTS

A total of 62 children with type 1 diabetes were admitted to our hospital during the study period, but only 32 episodes of DKA were noted. Among those children without DKA ($n = 30$), few were newly diagnosed without ketosis and others were referred from other hospitals for post-DKA management.

Out of the 32 DKA episodes, 24 (75%) were new-onset diabetes and 8 (25%) were known diabetes cases (Table 1). Out of these 8 episodes, only one child had two episodes of DKA. The median age among patients with DKA was 10.2 years (range 1.58 – 13.92 years), with 15 (46.88%) being male and 17 (53.13%) being female (Table 1). Four of the 32 were diagnosed in another institution and they received appropriate IV fluids but not intravenous insulin bolus. All those old patients were on a basal-bolus regimen. The causes for the precipitation of DKA in established diabetes cases are poor compliance to medication and missed insulin doses. The majority of the children presented with severe DKA i.e., 24 (75%), mild and moderate being 3 (9.38%) and 5 (15.63%) respectively.

Out of 32 children, a total of 13 (40.63%) children were diagnosed with AKI. Among these, AKI was noted mainly in 1 (20%) case out of 5 moderate DKA and 12 (50%) cases in 24 severe DKA categories. Out of 13, 9 children had AKI at onset, others showed increasing creatinine within 48 hours of admission. The number of patients categorized into stages 0, 1, 2, and 3 of AKI as per KDIGO guidelines at admission were as follows: 4 (30.7%), 7 (53.84%), 1 (7.69%), and 1 (7.69%). The same at 48 hours were as follows: 6 (46.15%), 0 (0%), 4 (30.7%) and 3 (23.08%) respectively. Four patients with normal creatinine at admission being 0.73, 0.88, 1.01, and 0.91 showed increasing trends up to a maximum of 2.11, 5.77, 1.71, and 2.87 at 54, 108, 90, and 48 hours respectively. Oliguria was noted in only 4 patients. A total of 14 out of 32 (43.75%) patients presented in shock; 12 of these developed AKI (Yates corrected Chi-square – 32.00) ($p = 0.0001$) (Table 2).

AKI was managed by optimization of volume status in ten patients. Three of them required dialysis. Indications were as follows: persistence of low pH (less than 6.9) at 24 hours

in the first case, increase in creatinine and recurrence of acidosis in another case, and increase in creatinine along with oliguria which developed at 24 hours followed by hyperkalemia at 60 hours in the last case. The number of dialysis sessions was 5, 1, and 2, respectively.

A significant difference was observed between AKI and non-AKI groups for the following parameters by independent t-test (Table 3): higher heart rate ($p = 0.0390$), higher respiratory rate ($p = 0.0402$), high leukocyte count ($p = 0.0005$), severe hyperglycemia ($p = 0.0204$), severe acidosis ($p = 0.0001$), hyperchloremia ($p = 0.016$), time for resolution of acidosis ($p = 0.0002$), duration of PICU stay ($p = 0.0002$) and duration of hospital stay ($p = 0.0022$).

Multivariable regression analysis showed significance only for metabolic acidosis (low pH). However, other parameters didn't show any significance.

Other complications observed in our cases were as follows: cerebral edema in 3 patients, foot drop in 2 patients, and deep vein thrombosis in 1 patient. Foot drop was observed in 2 children who had AKI too. Phosphorus was very low (<0.5 mg/dl) in these children with CPK being 14,441 U/L and 3725 U/L respectively.

DISCUSSION

Diabetic ketoacidosis is the most often initial presentation in children with new-onset type 1 diabetes. The incidence of type 1 diabetes in children is on the rise as reported by various countries.¹ We found a higher incidence of DKA

Table 1. Association between gender and past episodes of DKA with AKI

	Without AKI	%	With AKI	%	Total	%	Chi-square	p-value
Gender								
Male	9	60.00	6	40.00	15	46.88	0.0050	0.9460
Female	10	58.82	7	41.18	17	53.13		
Past episodes of DKA								
No	12	50.00	12	50.00	24	75.00	2.1161*	0.1457
Yes	7	87.50	1	12.50	8	25.00		
Total	19	59.38	13	40.63	32	100.00		

*applied Yates corrected chi-square

Table 2. Association between AKI with shock at admission

Shock at admission	Without AKI	%	With AKI	%	Total	%	Yates corrected Chi-square	p-value
No	17	94.44	1	5.56	18	56.25	32.0000	0.0001*
Yes	2	14.29	12	85.71	14	43.75		

* $p < 0.05$

Table 3. Comparison of DKA without AKI and with AKI with different clinical parameters by independent group t test

Clinical parameters	Without AKI (n=19) Mean (SD)	With AKI (n=13) Mean (SD)	t-value	p-value
Age (years)	9.59 (3.15)	9.92 (3.17)	-0.2849	0.7777
Heart Rate (HR)	114.84 (22.05)	130.31 (16.14)	-2.1593	0.0390
Systolic Blood Pressure (SBP)	104.32 (10.78)	98.23 (14.56)	1.3602	0.1839
Diastolic Blood Pressure (DBP)	65.47 (7.24)	64.23 (15.97)	0.2989	0.7670
Respiratory Rate (RR)	34.42 (10.66)	42.08 (8.68)	-2.1451	0.0402
Haemoglobin (g/dl)	14.36 (1.33)	14.10 (1.48)	0.5322	0.5985
Packed Cell Volume (%) (PCV)	41.22 (3.87)	42.17 (4.60)	-0.6309	0.5329
Total Cell Count (TC) (cells/ μ L)	16975.2 (8676.7)	31863.0 (12805.5)	-3.9301	0.0005
Urea (mg/dl)	25.16 (7.79)	39.46 (18.21)	-3.0557	0.0047
Creatinine (mg/dl)	0.75 (0.13)	1.16 (0.67)	-2.6571	0.0125
Blood sugar at admission (mg/dl)	475.00 (172.19)	627.46 (174.27)	-2.4481	0.0204
Corrected sodium (mEq/L)	136.68 (3.44)	139.38 (6.78)	-1.4821	0.1487
Chloride (mEq/L)	91.37 (20.24)	96.62 (7.29)	-0.8917	0.3796
pH	7.17 (0.13)	6.87 (0.11)	6.5859	0.0001
Bicarbonate (mmol/L)	6.56 (5.19)	3.32 (2.20)	2.1165	0.0427
Glycated Hemoglobin (Hb%)	13.25 (2.85)	14.37 (2.08)	-1.2113	0.2352
Highest Chloride (mEq/L)	103.68 (5.19)	112.54 (9.25)	-3.4658	0.0016
Time for resolution of acidosis (hours)	19.63 (12.13)	73.77 (53.88)	-4.2550	0.0002
Duration Of PICU stay (days)	1.58 (0.69)	7.00 (5.58)	-4.2172	0.0002
Duration of hospital stay (days)	6.53 (3.08)	13.23 (7.96)	-3.3436	0.0022

* $p < 0.05$

among newly diagnosed cases i.e., in 24 (75 %) cases compared to various studies reporting incidence ranging from 47.9 % to 71%.⁶⁻⁹ Most episodes of DKA in known cases of diabetes was due to poor compliance and improper sick day management.

Organ dysfunction, commonly involving the brain and kidney in DKA has been reported by various authors.¹ Several theories proposed for cerebral injury include osmotic shifts, rapid rehydration, hypoxia/ischemia, severe acidosis, and inflammatory mechanisms.^{7,10} Normal saline is the most preferred solution in the initial 4 -6 hours of management as it is isotonic to plasma and use of lower osmolar solutions can precipitate cerebral injury.¹ However, it has a high concentration of chloride (154 mEq/L), which is 40-50% more than plasma.¹¹ This high chloride causes renal vasoconstriction predisposing to AKI. Proposed mechanisms for renal injury by hyperchloremia consist of renal vasoconstriction which causes cortical hypoperfusion, interstitial edema, intracapsular hypertension, and reduction of GFR.^{10,12,13} But, there is still no documented evidence to support the use of balanced fluid (chloride restrictive) in the initial management of DKA. An adequate balance of fluids is mandatory to avoid complications.

In our study, AKI was present at admission in 9 (69.2%) cases before treatment of DKA. The remaining 4 (30.8%) of them developed during hospital stay. The proportion of AKI in our study was 40.63%, which is almost similar to previous reports by others ranging from 35% to 64.2%.^{6,8,14} Most of the AKI was seen with new onset and severe DKA except for one who had past episodes of DKA. This finding was similar to other reports by Baalaaji M et al., and Tiwari LK et al.^{6,15}

Acute kidney injury has been reported to occur within 12-24 hours after DKA treatment similar to cerebral injury.¹⁶ The development of AKI during treatment even after improving hydration status is an indication to search for causes other than prerenal factors like hypovolemia.⁸ Our study found that AKI was associated with shock at admission, hyperchloremia during treatment, severe hyperglycemia, and severe acidosis.

Shock at admission showed a significant association with AKI (Table 2). Metabolic acidosis also showed a significant association with AKI (Table 4). None of the parameters showed any statistically significant association with AKI in multivariable analysis. The reason may be due to a smaller sample size. Hence, severe acidosis and shock at admission are important risk factors associated with AKI.

In our study, creatinine estimation was performed using the alkaline picrate-kinetic, IFCC-IDMS standardized method; however, it is not commonly done. Standardization of creatinine assay by Isotope Dilution Mass Spectrometry (IDMS) will improve the analysis and reduce the interference by interfering substances. Hence, creatinine estimation has to be standardized to appropriately compare

Table 4. Multivariable logistic regression analysis of the incidence of AKI by clinical parameters

Factors	Adjusted OR (95% CI)	p-value*
Heart Rate (HR)	1.16 (0.68 – 2.00)	0.5780
Respiratory Rate (RR)	1.21 (0.87 – 1.67)	0.2530
Highest chloride	1.17 (0.80 – 1.71)	0.4260
pH	0.00 (0.00 – 0.04)	0.010*
RBS	1.01 (0.99 – 1.03)	0.3910
Corrected sodium	1.00 (0.99 – 1.00)	0.3170

*p <0.05

the prevalence of AKI between various studies.¹⁷ Urine output may not be the sole criteria for diagnosis of AKI in DKA as these children have initial polyuria. Thus, diagnosis of AKI based on only urine output is difficult. Hence, studies of AKI in patients with DKA have to consider these factors for accurate diagnosis.

We observed a higher number of cases in severe DKA than in other categories. The study setting was in a tertiary referral hospital where in only sick children might have been referred. The higher number of AKI observed in our study could be due to late referral and severe DKA. Hence, early identification and management of shock and severe acidosis can prevent AKI. Early referral to the tertiary center may be considered in patients who have features that are harbingers of AKI progression like severe acidosis (pH <6.9) and shock at admission.

The variation in the incidence of AKI between various studies may be due to the use of different diagnostic criteria for AKI, the population studied, time of referral to the study center, regional referral guidelines, and sample size.

Identifying the root cause of AKI in DKA in resource-limited settings is highly relevant because of the increasing incidence of diabetes in children. Prospective, multi-center studies can identify the risk factors for AKI; management of DKA, and red flag signs in those children meriting early referral to a tertiary center. Other causes of AKI like the type of fluids used in the management and presence of sepsis were not included in our study. Smaller sample sizes from a single center are limitations of the study. Hence, the results regarding the risk factors need to be verified by other studies with larger populations of patients with DKA. Use of only KDIGO criteria can under or over-diagnose the AKI, hence employment of other criteria and their comparison with each other could have been done.

CONCLUSION

The management of DKA is very complex. Adequate fluid management is important to avoid complications. Severe acidosis predisposes to organ dysfunction. In our study, we found a high proportion of children with DKA had AKI, which causes prolonged acidosis and hospital stay. Hence, early identification of risk factors and prompt treatment prevent severe complications like AKI and limit the duration of hospital stay.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

SP: Conceptualization, Methodology, Formal analysis, Writing – original draft preparation, Writing – review and editing; **JK:** Conceptualization, Methodology, Writing – original draft preparation, Writing – review and editing; **MR:** Validation, Formal analysis, Writing – review and editing; **KK:** Writing – review and editing, Supervision, Project administration.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

The authors declared no conflict of interest.

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Paediatric Type 2 Diabetes Presentation and Trends Four Years Pre- and Post-COVID-19 Pandemic in Klang Valley, Malaysia

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Abstract

Background. The recent COVID-19 pandemic has led to a rise in the incidence of obesity both in children and adults. Studies on the effect of the pandemic on Type 2 diabetes mellitus (T2DM) trends in children are limited. In this study, we aim to evaluate the frequency, clinical characteristics and demographics of newly-diagnosed paediatric T2DM cases 4 years before and after the pandemic.

Methodology. The frequency and clinical data of patients aged ≤ 18 years with newly-diagnosed T2DM in 4 tertiary centers in urban Malaysia from 18 March 2016 until 17 March 2020 (pre-pandemic) and 18 March 2020 until 17 March 2024 (post-pandemic) was collected.

Results. Seventy-five (75) patients were recorded with newly-diagnosed T2DM pre-pandemic and fifty-four (54) patients were recorded with newly-diagnosed T2DM post-pandemic. There was no significant increase in T2DM cases and diabetic ketoacidosis (DKA) during pandemic and T2DM cases fell to below pre-pandemic levels in the 3rd and 4th year post-pandemic. HbA1c and serum glucose were lower post-pandemic than pre-pandemic: 10.1% vs 11.9%, $p = 0.008$ and 12.0 mmol/L vs 16.1 mmol/L, $p = 0.038$ respectively.

Conclusion. The incidence of T2DM and DKA did not increase during the pandemic and further declined in year 3 and 4 post-pandemic. Lower HbA1c and serum glucose in the post-pandemic group may suggest improved screening services and greater access to medical care.

Key words: COVID-19 pandemic, diabetic ketoacidosis, type 2 diabetes mellitus, obesity

INTRODUCTION

The COVID-19 pandemic was a global health crisis that significantly impacted the healthcare system worldwide in the year 2020 and 2021. One of the major health burdens observed was the unprecedented rise in the incidence of new onset type 1 diabetes mellitus (T1DM) and the surge in diabetic ketoacidosis (DKA) cases, especially severe DKA.¹⁻⁵ The rise in T1DM cases was hypothesised to be due to selective beta cell destruction led by the expression of SARS-CoV-2 main entry host receptor on pancreatic beta cells, though this could not be confirmed due to lack of COVID-19 screening in asymptomatic individuals and paucity of positive COVID-19 status among DM patients.⁵⁻⁷ The delay in seeking medical consultation during the pandemic may have also led to a surge in DKA cases with more severe presentations.⁶⁻⁹

Another concerning impact of the pandemic is the rise in the occurrence of obesity amongst children and adolescents during the pandemic lockdown. Recent data from the CDC had shown that the monthly rate of body mass index (BMI) increase in the paediatric population aged 2-19 years old in the United States had doubled in 2020 as compared to in 2018 and 2019 (pre-pandemic).¹⁰ In Malaysia, the incidence of obesity in adolescents aged 13-17 years old had risen from 10.6% in 2012 to 14.3% in 2022.¹¹ The trend of T2DM during the pandemic in 2020 and 2021 as well as after the pandemic has not yet been studied in Malaysia.

Studies on the effect of the COVID-19 pandemic on paediatric T2DM trends in other regions of the world have showed mixed findings, with the majority of studies showing an increase in T2DM cases during the pandemic.¹²⁻¹⁹ The increase in cases of T2DM and DKA were primarily

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reported in the United States.⁵ Studies in Asia are limited with mixed results.^{12,18} As most of the studies on T2DM only report the incident cases during the pandemic, the long-term trend of T2DM after the pandemic is still not known.⁵

Malaysia was under a movement control order (MCO) between 18 March 2020 and 3 May 2020 as well as between 1 June 2021 and 28 June 2021. During the MCO, most of the population were confined at home as education was provided virtually, resulting in unhealthy diets, lack of physical activities, and increased screen time. Social isolation had also caused higher stress levels promoting a state of insulin resistance in this population group. It is unknown if the social isolation experienced during the pandemic period had resulted in long-term increase in paediatric T2DM or DKA cases in Malaysia. The objective of this study is to evaluate the trends of T2DM and DKA cases during the 4-year period after the pandemic onset (18th March 2020 to 17th March 2024) as compared to the 4-year period before pandemic onset (18 March 2016 to 17 March 2020). 18th March 2020 was taken as the date of pandemic onset following the date when the MCO was first implemented. We also aim to determine the demographic and clinical characteristics of T2DM cases in children who presented during the 4-year period post-pandemic in comparison to the pre-pandemic period. Knowledge on the T2DM and DKA trends would be invaluable to strategise efforts to combat obesity and prevent metabolic syndrome. Evaluation of the demographics and clinical characteristics of T2DM patients during these two time periods will also enable identification of patients at risk of T2DM and DKA.

METHODOLOGY

Subjects

A retrospective study was conducted at 4 paediatric endocrine tertiary centres in Klang Valley, Malaysia during the 4-year period before the pandemic onset (18 March 2016 to 17 March 2020) and the 4-year period after the pandemic onset (18th March 2020 to 17th March 2024). These 4 tertiary centres are paediatric endocrine referral centers for Selangor and Wilayah Persekutuan in Malaysia. The sampling method used was universal sampling of all T2DM patients aged ≤ 18 years who had presented during these two time periods. The sample size for this study was estimated to be 96 using the formula for hypothesis testing for two proportions and was based on a study by Marks BE et al. wherein the DKA proportion during the pandemic was 0.234 and 1-year pre-pandemic was 0.04 among T2DM youths ≤ 21 years of age.^{15,20}

The diagnosis of T2DM included symptoms of hyperglycemia with the absence of diabetic autoantibodies and any one of the following: 1) fasting blood glucose ≥ 7 mmol/L, 2) 2-hour plasma glucose on OGTT ≥ 11.1 mmol/L, 3) random plasma glucose ≥ 11.1 mmol/L or 4) HbA1c $\geq 6.5\%$.²¹ Patients with maturity onset diabetes of the young (MODY), syndromic patients and patients with preexisting

conditions (e.g., Cushing's syndrome) or medications that could affect blood glucose (e.g., steroids or immunosuppressives), were excluded from the study. This study had obtained approval from the Malaysian Medical Research and Ethics Committee (NMRR ID 22-02002-OLV [IIR]).

MATERIAL AND METHODS

The demographic characteristics of T2DM patients at the initial presentation (gender, ethnicity, BMI z-score, BMI status and age of diagnosis) during the two time periods before and after the pandemic were retrieved. Information on the clinical characteristics (HbA1c, initial serum glucose, duration of symptoms, DKA proportion, DKA severity, pH, HCO₃, hospitalisation duration, PICU admission) was also reviewed. BMI status was categorised to obese (BMI $>95^{\text{th}}$ centile), overweight (85^{th} to 95^{th} centile) and normal (BMI $<85^{\text{th}}$ centile) by CDC growth charts. DKA was characterized by venous pH <7.3 or serum bicarbonate (HCO₃) <18 mmol/L; blood glucose >11 mmol/L and ketonemia or ketonuria.²¹ DKA severity was categorised as 1) mild: venous pH <7.3 or HCO₃ <18 mmol/L; 2) moderate: venous pH <7.2 or HCO₃ <10 mmol/L; and 3) severe: venous pH <7.1 or HCO₃ <5 mmol/L.²¹

Statistical analysis

Data analysis was performed with Statistical Package of Social Science (SPSS) Windows Version 29. Descriptive analysis was performed whereby continuous variables were presented as medians and interquartile ranges (IQR = Q25, Q75) or mean $\pm$ SD and categorical variables were presented as proportions (%). Continuous variables pre- and post-pandemic period were analysed by Mann-Whitney test if they were not normally distributed or student t-test if normally distributed. Chi Square test or Fisher's exact test were used for comparison of categorical variables in the two time periods. Missing data was checked and identified. Subjects with missing data were excluded from statistical analysis. A p value of <0.05 was considered statistically significant.

RESULT

T2DM and DKA frequency

There was a total of 129 children and adolescents with newly-diagnosed T2DM. Seventy-five (75) patients presented between 18 March 2016 and 17 March 2020 and 54 patients presented between 18 March 2020 and 17 March 2024. Compared to the 1-year pre-pandemic period wherein 17 T2DM cases were reported, there was only a slight increase of T2DM cases in the first 2 years of the pandemic (20 cases in the 1st year and 19 cases in the 2nd year). Subsequently, T2DM cases fell to below pre-pandemic levels in the 3rd and 4th year post-pandemic (Figure 1). We also did not observe any rise in DKA cases amongst our T2DM patients during the pandemic. There was only a total of 12 DKA cases throughout the two time periods; 7 presented before

the pandemic onset and 5 presented after the pandemic onset (Figure 1).

Clinical characteristics and demographics of T2DM patients

The demographic characteristics of the T2DM patients before and after the pandemic was shown in Table 1. There was no significant difference in the gender, ethnicity, age, BMI z-score and BMI status of the T2DM patients before and after the pandemic onset. A rise in BMI z-score was initially observed in the 1st 2 years post-pandemic, but this had reduced to pre-pandemic levels in the 3rd and 4th year post-pandemic (Figure 2).

The clinical characteristics of our T2DM patients are shown in Table 2. No difference was observed in the proportion of patients with DKA and in DKA severity before and after the pandemic onset. There was also no difference in the requirement for hospital or PICU admission and duration of hospitalisation between these two time periods. Patients who presented post-pandemic had a significantly lower HbA1c 10.1% (7.3%, 12.5%) compared to pre-pandemic 11.9% (9.4%, 14.0%), $p = 0.008$. The initial serum glucose at presentation was also significantly lower post-pandemic compared to pre-pandemic 12.0 mmol/L (8.1 mmol/L, 20.3 mmol/L) vs 16.1 mmol/L (12.2 mmol/L, 22.1 mmol/L), $p = 0.038$. The duration of symptoms was shorter

post-pandemic compared to pre-pandemic, 14 days (1, 30) vs 17.5 days (3, 60) even though this was not significant ($p = 0.064$).

In this study, COVID-19 screening was not uniformly performed during the post-pandemic period. Only one patient had been detected to be positive for the SARS-CoV-2, wherein he had presented with moderate DKA requiring PICU admission.

DISCUSSION

Diabetes and COVID-19 infection share a bidirectional relationship. Patients with diabetes are more prone to severe COVID-19 infections. Conversely, COVID-19 infection is linked to a deterioration of beta cell function and an inflammatory cytokine storm that can lead to the presentation of diabetes and DKA. In a previous study involving 180 patients in the same 4 tertiary centres in Malaysia, a marked increase in frequency of T1DM cases was observed after the pandemic onset as compared to pre-pandemic, i.e., 38 cases in 2020 and 58 cases in 2021 compared to 30 cases in 2018 and 27 cases in 2019. In the same study, a significantly higher proportion of T1DM patients presenting with DKA post-pandemic was reported compared to pre-pandemic (79.8 % vs 64.8%, $p = 0.025$).⁷ The proportion of severe DKA among these T1DM patients had also increased (46.8 % vs 28.2 %, $p = 0.012$).⁷

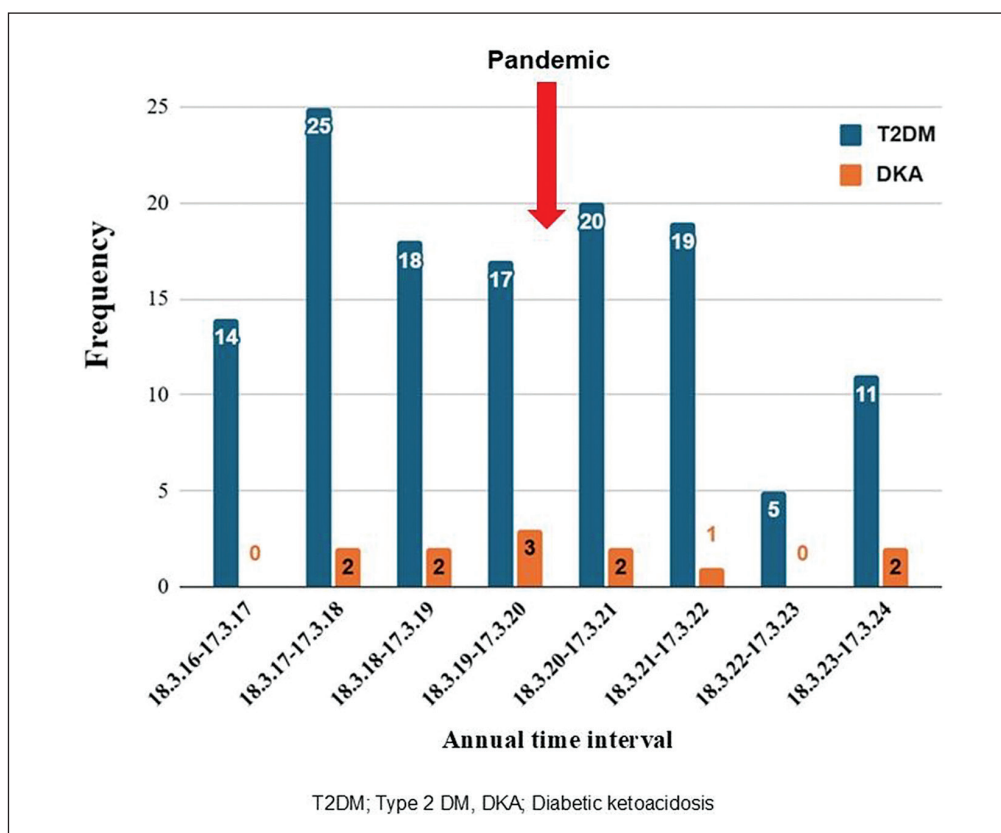


Figure 1. Frequency of T2DM and DKA at annual intervals pre- and post-pandemic. The blue bar indicates the annual frequency of T2DM. The orange bar indicates the annual frequency of DKA. The red arrow denotes the onset of the pandemic on 18.3.20, demarcating the 4-year pre-pandemic period and 4-year post-pandemic period.

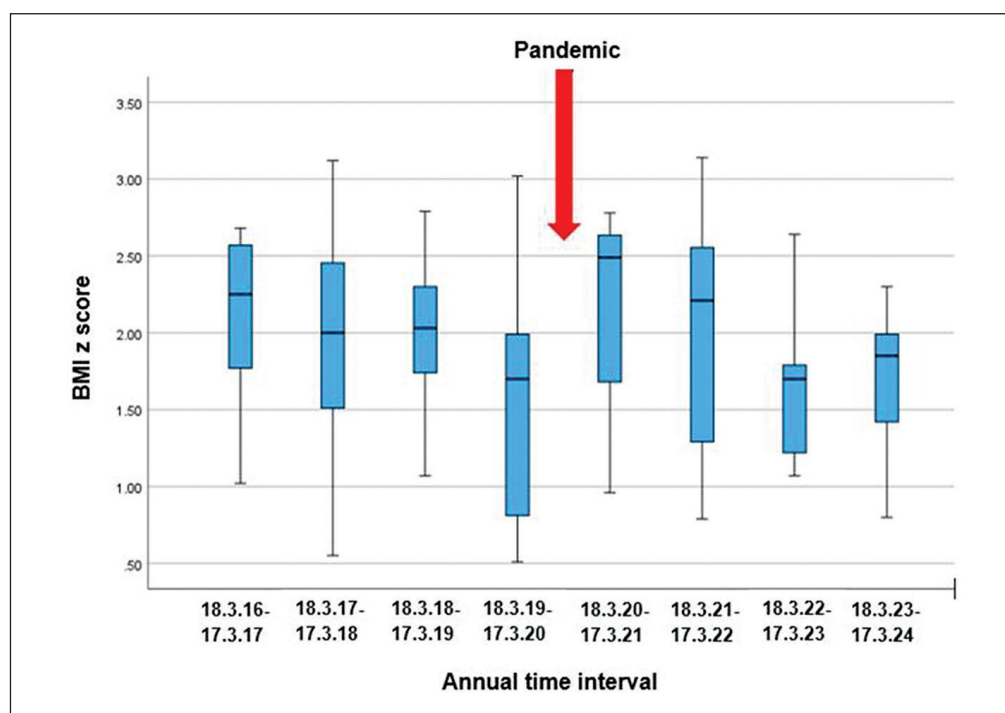


Figure 2. Median BMI z-score and range trends at annual intervals pre- and post-pandemic. The red arrow denotes the onset of the pandemic on the 18.3.20 and demarcates the 4-year pre-pandemic period and 4-year post-pandemic period.

In this present study, the increase in T2DM cases was only very marginal in the 1st and 2nd years of the pandemic and the T2DM frequency reduced to below pre-pandemic levels in the 3rd and 4th year post-pandemic. There was also no increase in DKA presentation amongst the study population during the pandemic. The rise of T1DM and DKA during the pandemic could be due to the underlying pathophysiological mechanism of SARS-CoV-2 which may precipitate beta cell failure. Type 2 DM occurs in the setting of insulin resistance in individuals who are overweight or obese and have a slower insidious course. In our population of T2DM patients, we observed an increase in BMI z-score in the first two years of the pandemic, likely due to the sedentary lifestyle and unhealthy eating habits due to the lockdown during the pandemic. The BMI z-scores, however, declined to pre-pandemic levels in the subsequent 3rd and

4th year post-pandemic. The decline in the BMI z-scores also coincided with the lower frequencies of T2DM cases in the 3rd and 4th year post pandemic.

The trend of T2DM post-pandemic in other regions of the world has been heterogenous. In contrast to our study findings, an increase in T2DM cases during the pandemic had been observed in the United States, especially among the non-Hispanic Black ethnic group.¹⁴⁻¹⁷ A higher BMI, higher serum glucose, lower pH and bicarbonate as well as higher proportion of DKA and hyperosmolar DKA were reported amongst T2DM in the American studies.¹⁴⁻¹⁷ Similarly, an increase in T2DM cases from 13 in 2017-2019 (pre-pandemic period) to 33 in 2020-2022 (pandemic period) was also observed in a multicenter regional study in Thailand.¹² The random blood glucose during the pandemic was higher

Table 1. Demographic characteristics of newly diagnosed T2DM patients (N = 129)

Variables	4-year period pre-pandemic (N = 75)	4-year period post-pandemic (N = 54)	P value
Age at diagnosis (years)	11.2 (10, 13.7)	11.5 (10, 13.2)	0.930 [†]
Gender n (%)			0.274 [†]
Male	31 (41.3%)	17 (31.5%)	
Female	44 (58.7%)	37 (68.5%)	
Ethnicity n (%)			0.361 [†]
Malay	40 (53.3%)	31 (57.4%)	
Chinese	9 (12%)	4 (7.4%)	
Indian	26 (34.7%)	17 (31.5%)	
Others	0 (0%)	2 (3.7%)	
BMI z score	1.9 (1.4, 2.4)	2.0 (1.5, 2.6)	0.323 [†]
BMI status			0.134 [†]
Normal weight	9 (12.2%)	2 (3.7%)	
Overweight	11 (14.9%)	13 (24.1%)	
Obese	54 (73%)	39 (72.2%)	

[†]Mann Whitney; [†]Chi Square test

Table 2. Clinical characteristics of newly diagnosed T2DM patients (N = 129)

Variables	4-year period pre-pandemic (N = 75)	4-year period post-pandemic (N = 54)	P value
Symptoms duration (days)	17.5 (3, 60)	14 (1,30)	0.064 [†]
HbA1c %	11.9 (9.4, 14)	10.1 (7.3, 12.5)	0.008 [†] *
DKA n(%)			1.000 [†]
Yes	7 (9.5%)	5 (9.3%)	
No	67 (90.5%)	49 (90.7%)	
DKA severity n (%)			0.867 [†]
No DKA	68 (90.7%)	49 (90.7%)	
Mild DKA	1 (1.3%)	0 (0%)	
Moderate DKA	1 (1.3%)	2 (3.7%)	
Severe DKA	5 (6.7%)	3 (5.6%)	
Initial serum glucose (mmol/L)	16.1 (12.2, 22.1)	12.0 (8.1, 20.3)	0.038 [†] *
pH	7.4 (7.3, 7.4)	7.4 (7.3, 7.4)	0.519 [†]
HCO₃ (mmol/L)	23 (19.8, 24.1)	22.4 (21.1, 25)	0.429 [†]
Hospital admission n (%)			0.350 [†]
Yes	51 (68%)	31 (58.5%)	
No	24 (32%)	22 (41.5%)	
Hospitalisation duration (days)	7 (5, 8)	7 (5, 10)	0.357 [†]
PICU admission n (%)			1.000 [†]
Yes	5 (6.7%)	4 (7.4%)	
No	70 (93.3%)	50 (92.6%)	
PICU duration (days)	3 (1.5, 11.5)	3 (1.3, 4.8)	1.000 [†]

[†] Mann Whitney; [†] Chi Square test; *P <0.05

but no difference was observed in DKA frequency, DKA severity, age, anthropometric data and symptom duration during the two periods.¹² A study from South Korea involving 4 academic centres shared similar findings to our study wherein there was no increase in T2DM cases during the pandemic (58 T2DM cases in 2018-2019 vs 33 cases in 2020), but a higher frequency of T1DM and DKA cases was reported during the pandemic.¹⁸ Reports on the incidence of insulin-treated T2DM in Australia also did not find a rise in cases in 2020 after the pandemic onset.¹⁹

Similar to our study, reduction in the T2DM trend in the 3rd year post-pandemic was also observed in other studies. A recent study in Germany demonstrated a 48.5% annual increase in T2DM from 2018 to 2021, followed by a 43% decrease in 2022.¹³ A single retrospective study conducted in the United States also showed that T2DM cases and DKA rates declined to pre-pandemic levels in the 3rd year of pandemic after an initial rise in the 1st two years.²² The downward trend of T2DM cases in the 3rd year post-pandemic may be due to the reduced infection rate and disease severity of SARS-CoV-2 attributable to prior infection and vaccination. In addition, the return to normalcy has allowed for adoption of more healthy lifestyle habits among children, such as increased physical activity, healthier eating habits, and reduced stress.

The recent introduction of the Malaysian Clinical Practice Guideline on management of obesity in 2023 was part of the Ministry of Health's initiatives to increase awareness and provide guidance in managing children and adolescents with obesity.²³ Greater emphasis on obesity multidisciplinary care and early screening for metabolic complications after the pandemic lockdown have led to patients with prediabetes and T2DM being diagnosed

earlier than before. This explained the shorter duration of symptoms, lower HbA1c and lower serum glucose levels in the post-pandemic period observed in our study. The recent availability of GLP1-agonist has also revolutionised the management of obesity and helped to prevent metabolic complications.

The lower frequency of T2DM cases and reduction in BMI z-score back to pre-pandemic levels in our study population in the 3rd and 4th year post-pandemic may reflect more effective obesity multidisciplinary care. In Australia, a return of BMI to pre-pandemic levels was also observed in two hospitals in New South Wales 21 months post-pandemic, after an initial spike at the pandemic onset, possibly attributed to state-wide policies aiming to curb childhood obesity. However, it is also likely that the reduction in the T2DM cases post-pandemic may also be due to the lack of presentation of these cases to the tertiary care hospitals as much of the public health services are still overwhelmed due to the aftereffects of the pandemic. As the course of T2DM in children is insidious, there is still a need for greater vigilance to detect this group of patients.

Limitations

Our study has several limitations. The retrospective design precludes the causative link between SARS-CoV-2 infection and T2DM. Furthermore, our study duration includes the 3rd and 4th year post-pandemic where routine screening of the SARS-CoV-2 infection is no longer compulsory. Thirdly, even though our study sites are referral centres for T2DM in Klang Valley, there may still be referral biases whereby patients may have presented to other healthcare facilities in Malaysia as this study was only based on the experiences in 4 centers in Klang Valley. There is also a

possibility that there are T2DM patients that have not yet been diagnosed due to being asymptomatic. The strength of our study is that it was conducted in 4 different hospitals in urban Klang Valley that caters for 40-44% of T2DM patients diagnosed in Malaysia and provided data on the T2DM trend and patient profile following the pandemic. The slow and insidious course of T2DM may however have a delayed presentation post-pandemic and warrants continuous surveillance amongst overweight and obese individuals.

CONCLUSION

The frequency of T2DM and DKA did not increase in our study population, and we observed a decline in T2DM in year 3 and 4 post-pandemic. The lower HbA1c and shorter duration of symptoms post-pandemic may reflect greater access to medical care and the effectiveness of screening among target population groups. However, it is uncertain whether these study findings can be generalised to other population cohorts. As T2DM has an insidious course, larger longer longitudinal studies are required to evaluate the long-term effect of the pandemic on T2DM trends.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

YLL: Conceptualisation, Methodology, Validation, Formal Analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **NMS:** Validation, Resources, Writing – review and editing; **FFWAN:** Conceptualisation, Investigation, Validation, Writing – review and editing; **AAZ:** Validation, Resources, Writing – review and editing; **NS:** Investigation, Validation, Writing – review and editing; **PGL:** Validation, Resources, Writing – review and editing; **MYJ:** Validation, Resources, Writing – review and editing.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Authors Disclosure

The authors declared no conflict of interest.

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None.

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Determinants of Cardiac Autonomic Neuropathy Among Patients with Diabetic Peripheral Neuropathy: A Facility-based Cross-Sectional Study

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Abstract

Introduction. Cardiac Autonomic Neuropathy (CAN) is frequently an underdiagnosed consequence of Diabetes Mellitus (DM), increasing the risk of cardiac arrhythmia, silent myocardial ischemia and sudden cardiac death. Diabetic Peripheral Neuropathy (DPN) is a common consequence of diabetes. We aimed to study the proportion of CAN among patients with DPN and identify the predictors of CAN in these patients.

Methodology. This is a hospital-based cross-sectional study conducted over a six-month period. A total of 60 DM patients with nerve conduction study-proven DPN, who fulfilled the inclusion and exclusion criteria, were enrolled in the study. CAN was assessed using both parasympathetic and sympathetic tests. A p -value of <0.05 was considered significant.

Results. The study included a total of 60 patients with diabetic peripheral neuropathy, out of whom 19 (32%) had CAN. Out of the 19 patients with CAN, 11 had severe CAN. There was no statistically significant association between the severity of DPN and CAN ($p = 0.162$). Logistic regression analysis (Model 3) showed that when adjusted for symptoms, risk factors, hypertension and a specific ECG finding (left atrial enlargement), the determinants of CAN were the presence of motor symptoms, being overweight or obesity and the presence of left atrial enlargement.

Conclusion. Among this cohort of persons with DM who all had DPN, CAN was found in one-third (32%) of the sample. Patients with DPN who are overweight/obese, have motor neuropathy or have left atrial enlargement have the most significant risk for developing CAN and may be recommended for its screening. Given that CAN is a frequently overlooked condition, each early diagnosis of CAN may potentially prevent its debilitating complications and even fatal outcomes.

Key words: cardiac autonomic neuropathy, diabetic peripheral neuropathy, diabetes mellitus, heart rate variability, orthostatic hypotension

INTRODUCTION

Diabetes Mellitus has become rampant and is the root cause of many complications. In comparison to people without the condition, those with diabetes have a roughly two-fold increased risk of cardiovascular disease and may lose about six to seven years of life.¹ Cardiac Autonomic Neuropathy (CAN) is a frequently underdiagnosed consequence of Diabetes. It is characterized by dysfunction of the autonomic nerves that innervate the heart, resulting in abnormalities in heart rate control, blood pressure regulation, and cardiac reflexes, leading to increased risk of mortality, arrhythmias, myocardial infarction, and sudden cardiac death.² Diabetic Peripheral Neuropathy (DPN) is a common consequence of diabetes that can present in many forms such as pain, numbness, tingling and burning sensation. It was found that the prevalence of CAN was relatively high in patients with DPN and its

severity worsens with worsening peripheral neuropathy.³ The studies on the prevalence of CAN and its predictors among patients with DPN are very few, and to the best of our knowledge, this study is probably the first in India. In this study, we have assessed the proportion of CAN among patients with DPN and its predictors.

METHODOLOGY

This is a hospital-based cross-sectional study conducted in a tertiary care hospital in Puducherry, India. A total of 90 patients aged 30-70 years, of both sexes, with proven type 2 diabetes mellitus (T2DM) (according to ADA criteria), who were either on or not on regular anti-diabetic drugs or insulin were sequentially enrolled in the study from our inpatient wards and outpatient General Medicine clinic. A minimum sample size of 60 patients was determined using a prevalence of 85.7% based on the study by Karthikeyan

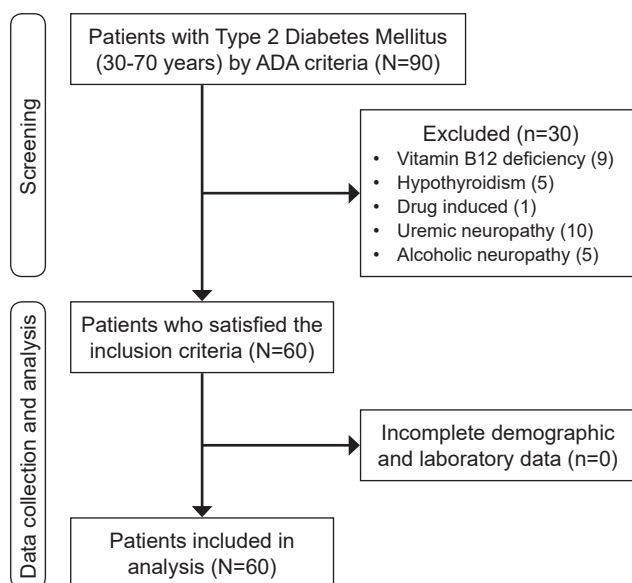


Figure 1. Flowchart of patient recruitment process.

et al.,² with a 95% confidence interval and an absolute precision of 8.86%, as calculated using Open Epi software. We sequentially recruited the patients from March 2023 to September 2023 using the inclusion criteria and identified patients with DPN using nerve conduction studies (NCS). Patients with other causes of peripheral neuropathy (such as vitamin B12 deficiency, hypothyroidism, drug-induced, toxin exposure, infections, alcohol consumption, uremic neuropathy and malignancy), those on pacemakers, those with sepsis and patients on anti-arrhythmic or antidepressant medications were excluded. A summary of the patient recruitment flowchart is shown in Figure 1.

After obtaining written consent, the patients were interviewed and examined by the principal investigator and a questionnaire with the required details was completed. The Toronto Clinical Scoring System (TCSS) was used both as a screening tool and to calculate the severity of Peripheral Neuropathy. The total score ranges from 0 to 19; a score of 0-5 means no PN, 6-8 is mild PN, 9-11 is moderate PN and 12-19 is severe PN.⁴ Fasting blood samples were collected and other evaluations were conducted at least 2 hours after waking up. HbA1c, serum lipid profile, serum urea, serum creatinine, liver function tests and thyroid-stimulating hormone (TSH) levels were determined from a 3 mL venous blood sample drawn from the patient by a trained nurse. The sample was sent to the biochemistry lab within 1 hour for analysis. The HbA1c estimation and serum lipid profile were done using the High-performance Liquid Chromatography method. The diagnosis of diabetes was based on the criteria established by the American Diabetes Association.⁵ After applying the exclusion criteria, the patients who had PN on the TCSS scale were subjected to nerve conduction studies. The patients with positive results in the NCS were included in our study.

Before being examined, the patients were asked to refrain from taking their anti-hypertensive drugs for the necessary

amount of time based on the duration of action of their drugs. Height was measured using a metal stadiometer with a precision of 0.5 cm in a typical standing posture without shoes. Meanwhile, weight was recorded using a digital scale with an accuracy of 100 g while wearing the least amount of clothing. The blood pressure was measured with a standard mercury sphygmomanometer after 15 minutes of rest. The heart rate and blood pressure were examined in the right hand in a supine and standing position.

A continuous electrocardiogram (ECG) was taken from each individual in two modes: the patient breathed deeply 6 times per minute and the ECG was recorded continuously for 1 minute in the supine position. The time of inspiration and expiration was marked on the ECG tape. The RR intervals were calculated based on the continuous ECG tape.⁶ The autonomic dysfunction was analyzed using parasympathetic and sympathetic cardiovascular reflex tests such as at-rest tachycardia (heart rate more than 100 beats per minute after 15 minutes of rest in a supine position); beat-to-beat heart rate variability (patient lies down and takes 6 breaths per minute and is considered abnormal when the expiration to inspiration RR interval ratio is more than 1.17); and, orthostatic hypotension (both systolic and diastolic blood pressures (BP) were measured with the patient in supine position and then repeated after standing for 3 minutes, whereby a reduction in systolic BP by 20 mmHg or diastolic BP by 10 mmHg after standing is considered abnormal).⁷ The criteria for diagnosis of CAN include:

1. Definite or confirmed CAN – the presence of any two abnormal cardiovascular reflex tests.
2. Severe or advanced CAN – definite CAN and the additional presence of orthostatic hypotension.⁸

Statistical analysis

Data was entered into Microsoft Excel and checked for errors. Descriptive statistics are presented as a mean $\pm$ standard deviation (SD) for continuous variables and as proportions or percentages for categorical variables. The Chi-square test was used to study the association between variables. The independent t-test was used to compare continuous variables between the two groups. Logistic regression was done to examine the predictors of CAN.

Ethics

This research has been reviewed and approved by the Institutional Ethics Committee of the tertiary care hospital where the study was conducted. The research has been designed and implemented in accordance with the committee's recommendations.

RESULTS

The study included a total of 60 patients with DPN who underwent testing for CAN. They were divided into two groups based on the presence of CAN: 41 (68%) patients

Table 1. Proportion of Cardiac Autonomic Neuropathy

Variables	Total = 60, n (%)
Cardiac Autonomic Neuropathy	
Definite CAN	8 (13.3)
Severe CAN	11 (18.3)
Total	19 (31.6)
Based on age distribution (in years)	
30-39	0 (0.0)
40-49	2 (3.3)
50-59	8 (13.3)
≥60	9 (15.0)
Gender	
Male	14 (23.3)
Female	5 (8.3)

with no CAN and 19 (32%) with CAN. Of the 19 patients with CAN, 11 (18%) had severe CAN (Table 1).

Among the study population, 42 (70%) were male and 18 (30%) were female. The mean age of the study population was 56.3 ± 9.6 years. The demographic profile showed no statistically significant difference in age distribution between the groups, with a mean age of 58.5 ± 7.8 years in the CAN group and 55.3 ± 10.3 years in the normal group ($p = 0.234$). Similarly, there was no statistically significant difference in gender distribution, with males constituting 73.7% (n=14) in the CAN group and 68.3% (n=28) in the normal group, and females constituting 26.3% (n=5) in the CAN group and 31.7% (n=13) in the normal group ($p = 0.672$) (Table 2).

The analysis of the duration of diabetes among the CAN group and the normal group did not show any statistically significant association ($p = 0.432$). Of the 60 patients who underwent TCSS scoring for DPN, 29 (48.3%) were found

to have mild, 28 (46.7%) moderate and 3 (5%) severe DPN. However, there was no statistically significant association between the severity of DPN and the occurrence or severity of CAN ($p = 0.162$) (Table 3).

The analysis of various symptoms of the patients did not show any statistically significant association with CAN. The motor symptoms were predominantly present in the CAN group (47.4%, n = 9) compared to the normal group (24.4%, n = 10) ($p = 0.075$). There was no statistically significant association between CAN and smoking ($p = 0.676$) or obesity ($p = 0.055$). The analysis of various comorbidities showed no statistically significant association between CAN and hypertension ($p = 0.337$) or dyslipidemia ($p = 0.631$). The prevalence of obesity was comparatively higher in the CAN group (33.3%, n = 6) than in the normal group (12.2%, n = 5). Orthostatic hypotension was present in 68.4% (n = 13) of the CAN group compared to only 9.8% (n = 4) of the normal group, a statistically significant difference ($p < 0.001$) (Table 4).

The analysis of laboratory parameters showed no statistically significant association between CAN and eGFR ($p = 0.470$), TyG index ($p = 0.494$), total cholesterol ($p = 0.965$), triglycerides ($p = 0.288$), HDL ($p = 0.906$) or LDL ($p = 0.904$). The mean HbA1c of the study population was 9.9 ± 1.9 , while the CAN group had a mean of 9.6 ± 1.8 and the normal group had a mean of 10.0 ± 2.0 . No statistically significant association was found between CAN and HbA1c ($p = 0.515$) (Table 5).

Analysis of the ECG showed that the following findings were predominantly observed in the CAN group: wide QRS (CAN 15.8% vs. normal 2.4%), left atrial enlargement (CAN 63.2% vs. normal 43.9%) and corrected QT interval ≥ 430 ms

Table 2. Age and gender profile of the participants

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Age (in years)	56.3 ± 9.6	58.5 ± 7.8	55.3 ± 10.3	0.234 [#]
Age distribution (in years)				
30-39	3 (5.0)	0 (0.0)	3 (7.3)	-
40-49	10 (16.7)	2 (10.5)	8 (19.5)	
50-59	21 (35.0)	8 (42.1)	13 (31.7)	
≥60	26 (43.3)	9 (47.4)	17 (41.5)	
Gender				
Male	42 (70.0)	14 (73.7)	28 (68.3)	0.672*
Female	18 (30.0)	5 (26.3)	13 (31.7)	
#Independent sample t-test; *Chi-square test				

[#]Independent sample t-test; ^{*}Chi-square test

Table 3. Diabetic status and severity of diabetic neuropathy according to TCSS

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Duration of diabetes (in years)				
<5	13 (21.7)	2 (10.5)	11 (26.8)	0.432*
5-10	32 (53.3)	11 (57.9)	21 (51.2)	
11-20	11 (18.3)	5 (26.3)	6 (14.6)	
>20	4 (6.7)	1 (5.3)	3 (7.3)	
TCSS Scoring				
Mild	29 (48.3)	6 (31.6)	23 (56.1)	0.162*
Moderate	28 (46.7)	13 (68.4)	15 (36.6)	
Severe	3 (5.0)	0 (0.0)	3 (7.3)	

*Chi-square test; ^Yates' corrected

^{*}Chi-square test; [^]Yates' corrected

(CAN 47.4% vs. normal 41.4%). However, no statistically significant association was found between CAN and any specific ECG findings in our study (Table 6).

The odds-ratio analysis using logistic regression revealed that males have 1.62 (95% CI 0.44-5.91) times the odds of developing CAN compared to females, but this difference was not statistically significant ($p = 0.461$). The odds of

Table 4. Symptoms, risk factors and comorbidity profile of participants

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Symptoms and risk factors				
Numbness	50 (83.3)	16 (84.2)	34 (82.9)	0.901
Pricking pain	17 (28.3)	4 (21.1)	13 (31.7)	0.394
Motor symptoms	19 (31.7)	9 (47.4)	10 (24.4)	0.075
Giddiness	7 (11.7)	3 (15.8)	4 (9.8)	0.498
Altered bowel/bladder	7 (11.7)	3 (15.8)	4 (9.8)	0.498
Overweight/obesity [§]	11 (18.6)	6 (33.3)	5 (12.2)	0.055
Smoking	5 (8.3)	2 (10.5)	3 (7.3)	0.676
Other comorbidities				
Hypertension	21 (35.0)	5 (26.3)	16 (39.0)	0.337
Dyslipidemia	15 (25.0)	4 (21.1)	11 (26.8)	0.631
Orthostatic hypotension	17 (28.3)	13 (68.4)	4 (9.8)	<0.001

*Chi-square test; [§]one missing value

Table 5. Laboratory parameters

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Estimated GFR				
≥100 ml/s	7 (11.7)	3 (15.8)	4 (9.7)	0.470 [^]
80-99 ml/s	18 (30.0)	3 (15.8)	15 (36.6)	
60-79 ml/s	17 (28.3)	8 (42.1)	9 (22.0)	
<60 ml/s	18 (30.0)	5 (26.3)	13 (31.7)	
TyG index				
4.0-4.9	28 (46.7)	11 (57.9)	17 (41.4)	0.494 [*]
5-5.4	20 (33.3)	5 (26.3)	15 (36.6)	
≥5.5	12 (20.0)	3 (15.8)	9 (22.0)	
HbA1c				
Mean ± SD	9.9 ± 1.9	9.6 ± 1.8	10.0 ± 2.0	0.515 [#]
6.6-9.5 %	29 (48.3)	11 (57.9)	18 (43.9)	0.600 [*]
9.6-12.5 %	23 (38.4)	6 (31.6)	17 (41.5)	
>12.5 %	8 (13.3)	2 (10.5)	6 (14.6)	
Lipid profile				
Total cholesterol	169.2 ± 55.1	169.7 ± 62.5	169.0 ± 52.2	0.965 [#]
Triglyceride	176.5 ± 100.6	156.1 ± 119.5	185.9 ± 90.5	0.288 [#]
HDL	37.1 ± 9.8	36.9 ± 8.3	37.2 ± 10.5	0.906 [#]
LDL	96.4 ± 38.4	95.5 ± 37.9	96.8 ± 39.1	0.904 [#]

[#]Independent sample t-test; ^{*}Chi-square test; [^]Yates' corrected

Table 6. ECG findings

Variables	Total (N = 60)	CAN (N = 19)	Normal (N = 41)	p-value
Normal ECG				
	52 (86.7)	16 (84.2)	36 (87.8)	0.974 [^]
Prolonged PR interval				
	0 (0.0)	0 (0.0)	0 (0.0)	-
QRS duration				
Narrow	56 (93.3)	16 (84.2)	40 (97.6)	0.169 [^]
Wide	4 (6.7)	3 (15.8)	1 (2.4)	
Left ventricular hypertrophy	3 (5.0)	1 (5.3)	2 (4.9)	0.566 [^]
Left atrium enlargement	30 (50.0)	12 (63.2)	18 (43.9)	0.165
Left axis deviation	17 (28.3)	4 (21.1)	13 (31.7)	0.394
Left bundle branch block	4 (6.7)	0 (0.0)	4 (9.8)	-
Other changes				
Poor R wave progression	6 (10.0)	2 (10.5)	4 (9.8)	0.711 [^]
T wave inversion in precordial leads	1 (1.7)	0 (0.0)	1 (2.4)	-
Low voltage complexes	1 (1.7)	1 (5.3)	0 (0.0)	-
Corrected QT interval (in ms)				
390-409	8 (13.4)	3 (15.8)	5 (12.2)	0.778
410-429	26 (43.3)	7 (36.8)	19 (46.4)	
≥430	26 (43.3)	9 (47.4)	17 (41.4)	

*Chi-square test; [^]Yates' corrected

Table 7. Predictors of Cardiac Autonomic Neuropathy

Variables		Unadjusted OR (95%CI)	p-value	Model 1 Adj. OR (95%CI)	p-value	Model 2 Adj. OR (95%CI)	p-value	Model 3 Adj. OR (95%CI)	p-value
Gender	Male	1.62 (0.44-5.91)	0.461	1.79 (0.45-7.14)	0.404				
	Female	Ref.	-	Ref.	-				
Duration of diabetes (in years)	<5	Ref.	-	Ref.	-				
	5-10	2.61 (0.48-14.11)	0.263	2.05 (0.32-13.08)	0.445				
	11-20	4.58 (0.67-31.19)	0.120	3.38 (0.40-28.40)	0.261				
	>20	1.83 (0.12-27.79)	0.662	1.38 (0.06-30.62)	0.836				
TCSS scoring	Mild	Ref.	-	Ref.	-				
	Moderate	3.06 (0.94-9.94)	0.062	2.41 (0.63-9.15)	0.194				
Symptoms									
	Numbness	1.02 (0.23-4.53)	0.969			0.99 (0.13-7.45)	0.998		
	Pricking pain	0.61 (0.16-2.23)	0.461			0.53 (0.09-2.93)	0.471	0.43 (0.08-2.27)	0.321
	Motor symptoms	3.10 (0.96-9.95)	0.057			8.40 (1.75-40.21)	0.008	7.11 (1.44-34.97)	0.016
	Giddiness	1.15 (0.19-6.96)	0.874			1.34 (0.14-12.14)	0.791		
	Altered bowel/bladder habits	1.85 (0.36-9.28)	0.455			0.96 (0.15-5.96)	0.972		
Risk factors									
	Smoking	1.58 (0.24-10.39)	0.632			0.15 (0.54-45.54)	0.157	2.87 (0.29-28.09)	0.363
	Overweight/obesity	3.64 (0.92-13.95)	0.064			10.80 (1.71-67.85)	0.011	21.83 (2.82-168.74)	0.003
Comorbidities									
	Hypertension	0.60 (0.17-2.01)	0.408			0.36 (0.05-2.28)	0.284	0.23 (0.04-1.14)	0.072
	Dyslipidemia	0.77 (0.21-2.88)	0.709			0.44 (0.05-3.37)	0.433		
ECG findings									
	Left atrium enlargement	2.55 (0.80-8.13)	0.112					6.07 (1.07-34.41)	0.041
	Left axis deviation	0.61 (0.16-2.23)	0.461						
	Left ventricular hypertrophy	1.14 (0.09-13.52)	0.913						

developing CAN were higher with a longer duration of diabetes of up to 20 years, with an OR of 2.61 for 5-10 years duration (95% CI 0.48-14.11) ($p = 0.263$) and an OR of 4.58 for diabetes duration of 11 to 20 years (95% CI 0.67-31.19) ($p = 0.120$). In contrast, the odds were lower in patients with diabetes for more than 20 years with an OR of 1.83 (95% CI 0.12-27.79) ($p = 0.662$). The odds of developing CAN were 3.06 (95% CI 0.94-9.94) times higher in patients with moderate DPN compared to those with mild DPN ($p = 0.062$). Among the symptoms, CAN was associated with increased odds of motor symptoms (OR 3.10, 95% CI 0.96-9.95, $p = 0.057$) and decreased odds of pricking pain (OR 0.61, 95% CI 0.16-2.23, $p = 0.461$). Smoking and overweight/obesity were associated with 1.58 times (95% CI 0.24-10.39, $p = 0.632$) and 3.64 times (95% CI 0.92-13.95, $p = 0.064$) the odds of developing CAN, respectively. Both hypertension (OR 0.60, 95% CI 0.17-2.01, $p = 0.408$) and dyslipidemia (OR 0.77, 95% CI 0.21-2.88, $p = 0.709$) were associated with decreased odds of developing CAN. ECG findings like LAE (OR 2.55, 95% CI 0.80-8.13, $p = 0.112$) and LVH (OR 1.14, 95% CI 0.09-13.52, $p = 0.913$) were associated with increased odds of developing CAN whereas left axis deviation (OR 0.61, 95% CI 0.16-2.23, $p = 0.461$) was associated with decreased odds of developing CAN. However, none of the above findings were statistically significant, as p -value was <0.05 (Table 7).

Model 1 of the adjusted odds-ratio analysis using logistic regression included adjustments for gender, duration of diabetes and TCSS scoring. It did not show any statistically significant association between these variables and CAN. Model 2 included adjustments for symptoms, risk factors and comorbidities. It revealed that CAN was significantly

Table 8. Model statistics for multivariable logistic regression

Model	Accuracy	Specificity	Sensitivity	AUC
Model 1	0.711	0.951	0.166	0.708
Model 2	0.779	0.853	0.611	0.804
Model 3	0.813	0.878	0.667	0.838

associated with increased odds of motor symptoms (OR 8.40, 95% CI 1.75-40.21, $p = 0.008$) and overweight/obesity (OR 10.80, 95% CI 1.71-67.85, $p = 0.011$). Model 3 included adjustments for symptoms (pricking pain and motor weakness), risk factors (smoking and overweight/obesity), comorbidities (hypertension) and ECG findings (left atrial enlargement or LAE). It was evident that CAN was significantly associated with increased odds of motor symptoms (OR 7.11, 95% CI 1.44-34.97, $p = 0.016$), overweight/obesity (OR 21.83, 95% CI 2.82-168.74, $p = 0.003$) and LAE (OR 6.07, 95% CI 1.07-34.41, $p = 0.041$) (Table 7).

Model statistics for multivariable logistic regression showed that Model 3 had the highest accuracy (81%), specificity (88%), sensitivity (67%) and AUC (0.838) among all three models (Table 8).

DISCUSSION

The study estimated the proportion of Cardiac Autonomic Neuropathy among patients with DPN and also the predictors of CAN among patients with DPN. The data of 60 DPN patients were studied, 70% of which are male, and the sample mean age was 56.3 ± 9.6 years. CAN was

found to be more prevalent among males; however, no statistically significant age or sex preponderance was seen. Neuropathy is the most prevalent complication of DM,⁹ and our study, based on cardiovascular reflexes, specifically determined the proportion of definite CAN among patients with DPN to be 32% (n = 19). Out of the 32%, 11 patients (18%) had severe CAN. Various studies have shown that the prevalence of CAN in DM patients ranges from 17% to 90% in patients with type 1 DM and 27.5% to 73% in patients with type 2 DM. This wide range is due to the varied study populations and differences in the criteria used to define CAN.¹⁰ The prevalence of CAN in this study was consistent with the overall prevalence of CAN in other studies. However, almost all of the available studies have shown the prevalence of CAN in diabetic patients, whereas our study assessed the proportion of CAN in patients with diabetic peripheral neuropathy. Using more precise instruments such as MIBG scans and PET scans may lead to a higher prevalence of CAN.¹¹⁻¹³ This study utilized a short-term continuous ECG, which is less accurate than 24-hour Holter monitoring of heart rate. Yet, it remains to be a straightforward and non-invasive procedure that can be performed at the bedside. Nevertheless, the tests utilized in our study have reasonably good sensitivity and specificity.¹³⁻¹⁶ The drawback of the tests is that they require the patient's active participation and complete cooperation.¹⁷ Additionally, there is a factor that heart rate variability generally declines with age.^{18,19}

Many studies have shown a direct relationship between the CAN and the duration of diabetes.³ Even though studies have shown that controlling diabetes can prevent or delay the onset of microvascular complications, our study revealed that there was no significant association between CAN and the duration of diabetes, glycemic control (HbA1c) or severity of peripheral neuropathy. This could be attributed to differences in study populations (i.e., patients with DPN and not all patients with diabetes), varying criteria used to define CAN or the underlying glycemic variability (as HbA1c only reflects the glycemic status in the last three months and does not indicate long-term glycemic control in diabetic patients).

QTc prolongation (by Bazett's formula) is a specific yet insensitive marker of Diabetic Autonomic Neuropathy. In our study, there was no significant association between CAN and any specific ECG finding independently of each other. Orthostatic hypotension was present in 68.4% (n = 13) of patients with CAN, which was statistically significant. Thus, orthostatic hypotension is indicative of severe CAN if considered along with other autonomic functions.

Logistic regression analysis (Model 3) showed that when adjusted for symptoms, risk factors, comorbidities (hypertension) and specific ECG findings (left atrial enlargement), the determinants of CAN were the presence of motor symptoms, being overweight or obese and the presence of left atrial enlargement. It was evident from the multivariate logistic regression analysis that Model 3

was the best among all the three models, with the highest accuracy (81%) and AUC (0.838).

Strengths and limitations

A key strength of the study is that all of the examinations and diagnostic procedures were conducted by a single examiner, increasing its internal validity. Limitations include the small sample size, single-center design and the lack of data on the long-term glycemic control and daily fluctuations in blood sugar levels of the patients and absence of follow-up.

CONCLUSION

Among this cohort of persons with T2D who all had DPN, CAN was found in one-third (32%) of the sample. Patients with DPN who are overweight/obese, have motor neuropathy or have left atrial enlargement in 2D-ECHO have the most significant risk for developing CAN and may be recommended for its screening. Given that CAN is a frequently overlooked condition, each early diagnosis of CAN may potentially prevent its debilitating complications and even fatal outcomes.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria

Author Disclosure

The authors declare no conflict of interest.

CRedit Author Statement

BM: Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data Curation, Writing – review and editing, Visualization, Project administration, Funding acquisition; **DG:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Funding acquisition; **SNH:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **Funding acquisition;** **BAK:** Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition

Data Availability Statement

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

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None.

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Prevalence of Hypogonadism Among Males with Type 2 Diabetes Mellitus in a Malaysian Tertiary Hospital: A Cross-Sectional Study

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Abstract

Objective. Previous studies have indicated that clinical hypogonadism is common among males with type 2 diabetes mellitus (T2DM). However, the reported prevalence varies due to the diverse diagnostic criteria used in these studies. This study aims to determine the prevalence of clinical hypogonadism among Malaysian T2DM males and their associated factors.

Methodology. A total of 360 participants who fulfilled the inclusion criteria were included in this study. Their socio-demographic and clinical parameters were documented and a total testosterone level was sampled from a morning fasting serum. Patients with serum total testosterone of 8-12 nmol/L had their serum total testosterone repeated and their symptoms assessed with the Aging Male Symptoms (AMS) scale. Clinical hypogonadism was diagnosed with total testosterone <12 nmol/L and cT <0.255 nmol/L, in addition to an AMS score of >26.

Results. The prevalence of clinical hypogonadism among Malaysian T2DM males was 17.5% (n = 63), with 55.6% of them having hypogonadotropic hypogonadism. There is a significant association between clinical hypogonadism with waist circumference >94 cm ($p < 0.001$), obesity ($p < 0.001$), hypertension ($p = 0.010$), coronary artery disease ($p = 0.014$) and peripheral artery disease ($p = 0.022$). There is a significant difference in the weight ($p = 0.001$), BMI ($p < 0.001$), waist circumference ($p < 0.001$), serum HDL-C levels ($p < 0.001$), serum triglycerides levels ($p = 0.001$) and serum TyG index ($p < 0.001$). Diabetic males with increasing age (adjusted OR = 1.070, 95% CI 1.004-1.146, $p = 0.038$), presence of coronary artery diseases (adjusted OR = 2.08, 95% CI 1.220-10.219, $p = 0.020$) and low total testosterone (adjusted OR = 2.451, 95% CI 1.908-3.155, $p < 0.001$) are at higher risk of developing clinical hypogonadism.

Conclusion. This study is the first in the Asian region to use stricter criteria for diagnosing hypogonadism. Despite these stringent criteria, the prevalence of hypogonadism remains significantly high among Malaysian T2DM males. It is particularly common in diabetic males over 35 years old with coronary artery disease, regardless of A1c control and the duration of diabetes.

Key words: hypogonadism, type 2 diabetes mellitus, testosterone, prevalence

INTRODUCTION

Low serum testosterone (T) levels have been shown to be present in males with type 2 diabetes mellitus (T2DM), with a prevalence ranging from 11.6 to 52.0%. This wide variation in prevalence occurs due to the different diagnostic criteria used to define low T levels.¹⁻²¹

Hypogonadism among T2DM males has been strongly linked to the dysglycaemic state, mainly contributed by insulin resistance and visceral adiposity. The dysglycaemic state further leads to a disruption of the hypothalamus-pituitary-gonadal axis characterised by increased pro-

inflammatory cytokines that reduce sex hormone binding globulin (SHBG) levels and cause negative feedback on the axis, as well as elevated leptin levels that are inhibitory to Leydig cell function.²²

It is pivotal to identify hypogonadal males with T2DM as both T2DM and low testosterone levels are independently associated with cardiovascular diseases.²³ T2DM is a known risk factor for coronary artery diseases (CAD) and the presence of hypogonadism further augments this risk. Low testosterone levels in men with diabetes have been shown to double the risk of cardiovascular events and deaths, whilst normalisation of testosterone in hypogonadal

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males reduces both outcomes.^{24,25} The question of whether hypogonadism is an independent risk factor or a surrogate marker for CAD is still being debated.^{11,12, 26,27}

Despite the high prevalence of T2DM in Malaysia, there has been only one study reporting the prevalence of hypogonadism among Malaysian males in the state of Sarawak, located on the Island of Borneo, which is limited by the utilisation of a single testosterone level.¹⁶ The scarcity of local data, especially in the Peninsula of Malaysia, diminishes the magnitude of this problem. This study aims to determine the prevalence of hypogonadism among males with T2DM in a Malaysian tertiary hospital.

METHODOLOGY

This cross-sectional study was approved by the hospital's institutional ethics and research committee. Employing a purposive sampling strategy, all male participants, aged 18-70 years with T2DM diagnosis, were screened during their scheduled diabetes clinic visits in a tertiary hospital between January 2018 and December 2021. Participants were screened using the inclusion criteria and excluded from the study if they had (1) established pituitary or testicular disorder; (2) acute or critical illness for the past 3 months; (3) liver cirrhosis, chronic kidney disease with estimated glomerular filtration rate (eGFR) <30 ml/min, severe heart failure, active malignancy; (4) receiving hormone replacement therapy; (5) current consumption of herbal or traditional medications where steroids or androgens as an ingredient cannot be excluded; and, (6) psychiatric illness.

Using the formula $n = [Z^2 P(1-P)]/d^2$, we calculated that the sample size of 360 participants was adequately powered for

this study, with $Z = 1.96$ (corresponding to 95% confidence interval) and $d = 0.05$, for an estimated prevalence of 35.2% by Zheng et al.⁷

Clinical and socio-demographic characteristics were collected using a semi-structured questionnaire. The participants' national registration card determined their ethnicity. Anthropometric parameters, such as height, weight, and waist circumference, were measured by trained nurses under the supervision of the investigators. Waist circumference was obtained with a measuring tape midway between the inferior angle of the ribs and the supra-iliac crest. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters.

The T2DM diagnosis was based on the American Diabetes Association criteria of abnormal fasting blood glucose or modified oral glucose tolerate test (mOGTT) or HbA1c >6.3%.^{28,29} Hypogonadism was defined as the presence of 1) low total testosterone (tT) level (<12 nmol/L), 2) low repeated calculated free testosterone (cFT) levels (<0.255 nmol/L) and 3) Aging Male Symptoms (AMS) score of ≥ 27 (Figure 1). Hypergonadotropic hypogonadism was defined if the patients with hypogonadism had luteinising hormone (LH) levels >8.6 mIU/mL, while hypogonadotropic hypogonadism was defined if LH levels ≤ 8.6 mIU/mL.³⁰

Insulin resistance was measured using the triglyceride and glucose index (TyG index) and calculated using the formula: $\ln [\text{fasting TG (mg/dL)} \times \text{fasting plasma glucose (mg/dL)}]/2$. TyG Index has been shown to be a useful surrogate marker for insulin resistance.^{31,32}

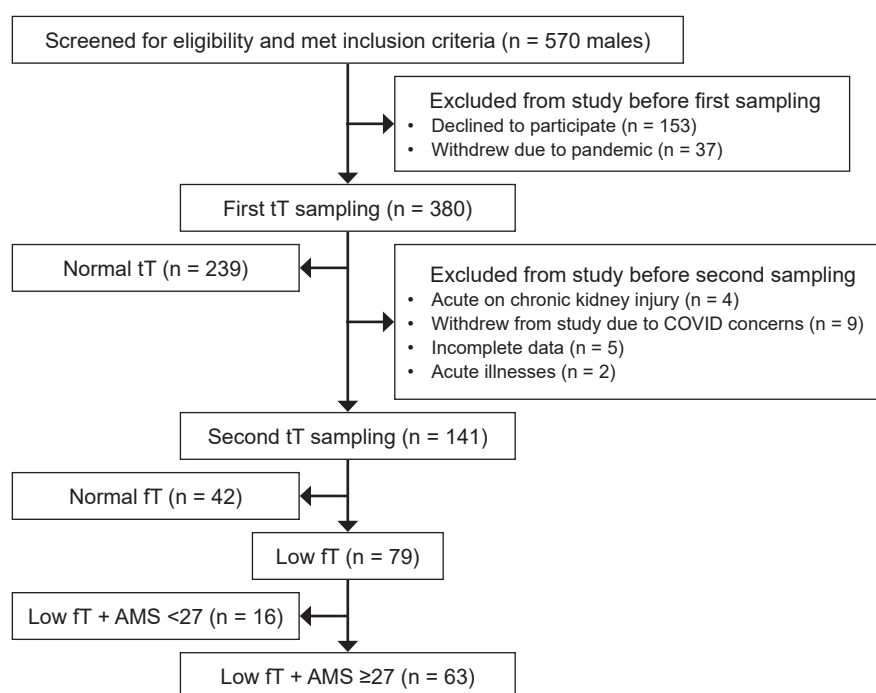


Figure 1. Flowchart of the patient recruitment process.

Hypertension and dyslipidaemia were considered present if the participants received medications for either of the above conditions or if there were abnormalities in the blood pressure levels or serum lipids. Coronary artery disease (CAD) was defined as a previous diagnosis of coronary vessel abnormalities by angiography or on current treatment for CAD. Echocardiography criteria confirmed heart failure, while proteinuria was defined as persistent microalbuminuria or proteinuria on more than one occasion. Chronic kidney disease was diagnosed based on the estimated glomerular filtration rate eGFR of <60 mL/min/1.73 m² for at least 3 months. Peripheral arterial disease (PAD) was defined as self-reported claudication pain, angiographically-confirmed PAD or the presence of erectile dysfunction (ED). Participants were classified as smokers (usual consumers in the last 3 months) or non-smokers.

All participants with low serum tT in the initial testing were assessed for hypogonadal symptoms and quality of life using the AMS questionnaire and sexual function using the International Index of Erectile Function (IIEF-5) questionnaire. The AMS questionnaire has been validated to assess the quality of life among hypogonadal males.³³ It includes three subcategories (somato-vegetative, psychological and sexual) of a defined set of items. Each question is rated on a scale of 1 to 5. Participants with an AMS score of <27 were classified as having few or no symptoms; 27-36 was as mild; 37-49 as moderate; and ≥50 as severe. The AMS scale has been translated and adapted into the Malay language.³⁴

Sample collection, preparation and analysis

Five millilitres of venous blood sample was drawn from each participant between 8 AM and 10 AM after an overnight fast. The blood samples were transferred into plain tubes, left to clot for 30 minutes and centrifuged at 3000 g for 10 minutes. The serum was aliquoted and stored at -20°C. Serum tT was measured using chemiluminescent immuno-metric assays (Roche Cobas e411; Roche Diagnostics GmbH, Mannheim, Germany). The reference values for T were 8-28 nmol/L; for LH: 1.7-8.6 mIU/mL; for oestradiol (E2): 11.3-

43.2 pg/mL; and for SHBG: 18.3-54.1 nmol/L. The laboratory technicians were blinded to the participants' information.

A tT level <12 nmol/L was considered as low. Participants with low tT levels were subjected to scoring of hypogonadal symptoms using the AMS scale and IIEF-5 questionnaires, as well as a repeated fasting morning tT, E2, LH, and SHBG. FT was calculated from SHBG, serum albumin and tT using the formula suggested by Vermeulen et al. with levels <0.255 nmol/L deemed low.³⁵

Statistical analysis

Statistical analysis was performed using SPSS 23 software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) Continuous data were presented as mean ± SE while categorical data were presented as frequencies and proportions. Data analysis showed that the variables were normally distributed; hence, the chi-square test and Fischer's exact test were used as a test of significance for qualitative categorical data, whilst the t-test was used as a test of significance to identify the mean difference between two quantitative variables.

RESULTS

A total of 570 T2DM participants were screened, and 380 who fulfilled the study criteria were recruited for the initial screening. (Table 1). However, due to incomplete data, acute illnesses and COVID-related concerns, only 360 out of 380 participants were included in the final data analysis. Based on the low tT and fT levels and AMS result, 63 participants were diagnosed to have hypogonadism (Figure 1).

Prevalence of hypogonadism

The prevalence of hypogonadism among T2DM participants was 17.5% (95% CI 0.139-0.218). Based on data from Table 2, the incidence of hypogonadism seems to start occurring by the age of 35 to 44 years, was highest among male participants 65-70 years old (21/101) (20.8%), and most common among participants of Chinese ethnicity (22/109)

Table 1. Clinical and biochemical characteristics of patients according to gonadal status (n = 360)

Variables	Total (n=360)	Hypogonadism (n=63)	Eugonadal (n=297)	p-value (t-test)
Age, year	56.8 ± 10.80	58.8 ± 9.92	56.4 ± 10.95	0.113
Duration of diabetes, year	14.3 ± 9.29	14.8 ± 10.51	14.2 ± 9.03	0.649
Weight, kg	83.2 ± 16.12	89.3 ± 18.00	81.9 ± 15.42	<0.001*
Waist circumference, cm	100.9 ± 12.46	106.6 ± 15.05	99.69 ± 11.51	<0.001*
BMI ^a , kg/m ²	29.1 ± 5.15	31.4 ± 6.50	28.7 ± 4.69	<0.001*
eGFR ^b , ml/min/1.73 m ²	74.6 ± 21.23	71.6 ± 21.89	75.3 ± 21.07	0.106
HbA1c, %	8.4 ± 1.97	8.5 ± 2.08	8.4 ± 1.95	0.365
HDL-C ^c , mmol/L	1.13 ± 0.259	1.03 ± 0.206	1.16 ± 0.264	<0.001*
Non-HDL-C ^c , mmol/L	3.40 ± 1.214	3.21 ± 0.984	3.44 ± 1.256	0.164
Tg ^d , mmol/L	1.68 ± 1.217	2.07 ± 1.802	1.59 ± 1.038	0.005*
ALT ^e , IU/L	32.4 ± 18.70	33.9 ± 19.1	32.1 ± 18.61	0.469
TyG ^f Index, mg ² /dL ²	4.87 ± 0.373	4.95 ± 0.417	4.85 ± 0.361	0.024*
tT ^g , nmol/L	14.90 ± 5.130	8.45 ± 2.783	16.26 ± 4.426	<0.001*

^a body mass index; ^b estimated glomerular filtration rate; ^c high-density lipoprotein-cholesterol; ^d triglyceride; ^e alanine transaminase; ^f triglyceride-glucose index; ^g total testosterone

(20.2%). Furthermore, the proportion of hypogonadism was significantly higher in males with abdominal obesity (21.1%), hypertension (19.5%) and coronary artery disease (26.7%). (Table 2)

Symptoms and sexual function in diabetic males with clinical hypogonadism

Almost all of the hypogonadal respondents had sexual symptoms, with 76.2% (48/63) complaining of severe symptoms such as reduced sexual performance, reduced erections and poor libido³⁹ (Figure 2). Most respondents (55.6%, 35/63) had moderate somato-vegetative symptoms like reduced facial hair growth or feeling burnt out. The

respondents mainly had mild to moderate psychological symptoms such as irritability and severe anxiety. Only 29 (46%) of the 63 hypogonadal males were sexually active (had sexual intercourse in the past 4 weeks). Based on the IIEF-5 score, almost one-third of these sexually active respondents had moderate to severe ED (Figure 3).

DISCUSSION

By far, this study is one of the few studies in the world evaluating the prevalence of hypogonadism in T2DM males using two persistent low total and free T levels, as well as the first in the Asian region to use stricter criteria to diagnose hypogonadism. With only one morning sample of tT <12

Table 2. Clinical and biochemical characteristics of patients according to hypogonadal status (n = 360)

Variable	Total (%) (n = 360)	Hypogonadism (%) (n = 63)	Eugonadal (%) (n = 297)	p-value
Age group				#0.606
18-24	4 (1.1)	0 (0)	4 (1.3)	
25-34	7 (1.9)	0 (0)	7 (2.4)	
35-44	48 (13.3)	9 (14.3)	39 (13.1)	
45-54	57 (15.8)	8 (12.7)	49 (16.5)	
55-64	143 (39.7)	25 (39.7)	118 (39.7)	
65-70	101 (28.1)	21 (33.3)	80 (26.9)	
Race				#0.318
Malay	196	36 (57.1)	160 (53.9)	
Chinese	109	22 (34.9)	87 (29.3)	
Indian	52	5 (7.9)	47 (15.8)	
Others	3	0 (0)	3 (1.0)	
Duration of diabetes				0.402
≤10 years	160 (44.4)	31 (49.2)	129 (43.4)	
>10 years	200 (55.6)	32 (50.8)	168 (56.6)	
Waist circumference				0.006*
≤94 cm	109 (30.3)	10 (15.9)	99 (33.3)	
>94 cm	251 (69.7)	53 (84.1)	198 (66.7)	
BMI^a group				#0.036*
<25	61 (16.9)	5 (7.9)	56 (18.9)	
≥25	299 (83.1)	58 (92.1)	241 (81.1)	
Hypertensive				#0.01*
Yes	313 (86.9)	61 (96.8)	252 (84.8)	
No	47 (13.1)	2 (3.2)	45 (15.2)	
Dyslipidaemia				#0.149
Yes	341 (94.7)	62 (98.4)	279 (93.9)	
No	19 (5.3)	1 (1.6)	18 (6.1)	
Smoking				##0.351
Yes	91 (25.3)	13 (20.6)	78 (26.3)	
No	269 (74.7)	50 (79.4)	219 (73.7)	
Heart failure				#0.882
Yes	5 (1.4)	1 (3.6)	4 (1.3)	
No	355 (98.6)	62 (98.4)	293 (98.7)	
CAD^b				##0.01*
Yes	86 (23.9)	23 (36.5)	63 (21.2)	
No	274 (76.1)	40 (63.5)	234 (78.8)	
CKD^c				##0.879
Stage 1	96 (26.7)	7 (25.0)	82 (27.6)	
Stage 2	169 (46.9)	13 (46.4)	139 (46.8)	
Stage 3	95 (26.4)	8 (28.6)	76 (25.6)	
Proteinuria				##0.190
Yes	173 (48.1)	35 (55.6)	138 (46.5)	
No	187 (51.9)	28 (44.4)	159 (53.5)	
PAD^d				##0.022*
Yes	170 (47.2)	38 (60.3)	132 (44.4)	
No	190 (52.8)	25 (39.7)	165 (55.6)	
HbA1c group				##0.849
≤7%	105 (29.2)	19 (30.2)	86 (29.0)	
>7%	255 (70.8)	44 (69.8)	211 (71.0)	
TyG^e				##0.491
>4.68 mg ² /dL ²	238 (66.1)	19 (30.2)	194 (65.3)	
≤4.68 mg ² /dL ²	122 (33.9)	44 (69.8)	103 (34.7)	

^a body mass index; ^b coronary artery disease; ^c chronic kidney disease; ^d peripheral arterial disease; ^e triglyceride-glucose index; # Fischer's exact test; ## chi-square test

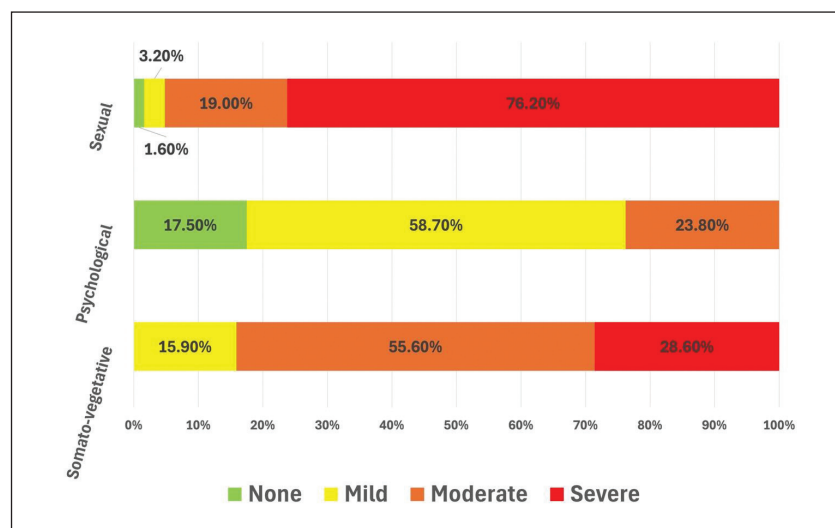


Figure 2. Hypogonadal symptoms among hypogonadal T2DM males (n = 63).

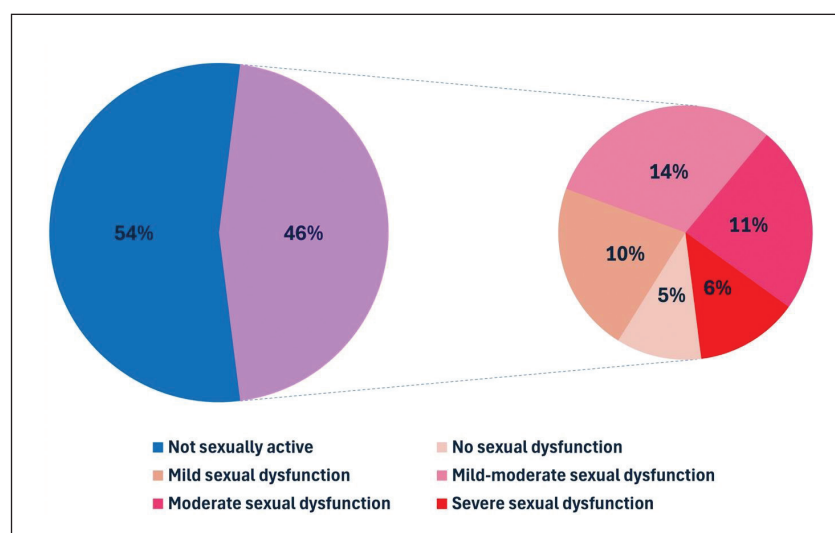


Figure 3. Sexual dysfunction among hypogonadal T2DM males (n = 63).

nmol/L, the prevalence of low tT was 37.1%, comparable to the other studies.^{1,7} Using a lower tT threshold of <8 nmol/L, the prevalence of hypogonadism further dropped to 8.1%, comparable with the 11.6% reported by Herrero et al.³⁷

From our 360 participants, 22.8% of T2DM males had hypogonadism if the criteria of an AMS score of ≥ 27 and a single tT of <12 nmol/L were applied. This result is consistent with the prevalence of 23.5% reported by an Ethiopian study which had used the similar criteria to diagnose hypogonadism among T2DM males.³⁸ Finally, using positive symptoms with one low tT and one repeated low cT, the prevalence of hypogonadism that we derived from our sample population was 17.5%, comparable to the prevalence of 20.7% by Agarwal et al., who had used positive symptoms and two consistent low T results as diagnostic criteria.¹³ Hence, we propose that hypogonadism among T2DM males should be diagnosed in the presence of hypogonadal symptoms and two consistently low T levels. In conjunction with this, fT should

also be tested at least once, given the high prevalence of obesity among T2DM males, which has falsely lowered fT levels due to low serum SHBG concentration.³⁰

To date, there has only been one prevalence study in Southeast Asia (Ahmad et al.) that reported a prevalence of 19.7% of hypogonadism among T2DM males attending a primary healthcare centre in the capital city of Sarawak. However, the diagnosis of hypogonadism utilised only a single reading of low total T levels with positive symptoms suggestive of hypogonadism.¹⁶ Comparing our study with that of Ahmad et al., the mean age in both study populations were almost similar (56.8 years vs 57.7 years), with similar proportions of obesity (83.1% vs 86.4%), visceral adiposity (69.7% vs 73.9%), hypertension (86.9% vs 88.1%) and dyslipidaemia (94.7% vs 95.8%). There are some differences in the study population's ethnicity, namely Malays (54.4% vs 44.7%), Chinese (30.3% vs 30.8%) and others (15.2% vs 24.4%), as there are more Ibans and indigenous ethnic groups in the state of Sarawak.

Table 3. Comparison of Asian studies on the prevalence of hypogonadism among type 2 diabetic males

Author (year of study)	Country and sample size	Sample population characteristic	Prevalence of hypogonadism using different criteria				
			1 tT + 1 cT + symptoms	2 cT + symptoms	1 tT or cT + symptoms	2 cT	1 tT or cT
<i>This study</i>	Malaysia 360	T2DM males, age 18-70 years	17.5%		22.8%		37.1%
<i>Waddankeri et al. (2024)</i> ²¹	India 250	T2DM males, age range unspecified			27.6% (tT)		
<i>Singh et al. (2023)</i> ²⁰	India 353	T2DM males, age 20-70			17.0% (cT)		
<i>Zhou et al. (2022)</i> ¹⁹	China 637	T2DM males, age 20-70					26.5% (tT or cT)
<i>Cai et al. (2021)</i> ⁵⁶	China 294	T2DM males, age range unspecified			21.7 (cT)		
<i>Kumari et al. (2021)</i> ¹⁸	India 200	T2DM males, age 30-69					45.5%
<i>Ahmad et al. (2020)</i> ¹⁶	Malaysia 360	T2DM males, 40-70 years			19.7% (tT)		
<i>Anupam et al. (2020)</i> ¹⁵	India 150	T2DM males, 25-70 years			17.3% (cT)		
<i>Cao et al. (2018)</i> ⁵⁷	China 205	T2DM males, age unspecified					34.1% (tT)
<i>Agarwal et al. (2017)</i> ¹³	India 900	T2DM males, 30-59 years		20.7%			
<i>Al Hayek et al. (2017)</i> ⁵⁸	Saudi Arabia 157	T2DM males, 30-70 years			22.9% (tT)		
<i>Li et al. (2017)</i> ³	China 122	T2DM males, age range unspecified					26.7-48% (tT)
<i>Madhu et al. (2017)</i> ¹²	India 150	T2DM males, age 30-70					32-40% (tT)
<i>Charan et al. (2017)</i> ¹¹	India 100	T2DM males, age >18 years					34% (tT)
<i>Zheng et al. (2016)</i> ⁷	China 2013	T2DM males, age unspecified					35.2% (tT)
<i>Cheung et al. (2016)</i> ^{6,10}	Hong Kong 1239	T2DM males, age 18-90					12.3% (tT)
<i>Mattack et al. (2015)</i> ⁶	India 80	T2DM males, age 31-71					31% (tT) 38% (cT)
<i>Liu et al. (2013)</i> ⁴	Taiwan 766	T2DM males, age unspecified					32.5 (tT)
<i>Mirzaei et al. (2012)</i> ⁵⁹	Iran 247	T2DM males, age >30 years			17.3% (tT)		
<i>Ganesh et al. (2009)</i> ⁹	India 100	T2DM males, age 25-50 years				15%	

In our study, we also noted a significant increase in the prevalence of hypogonadism as the patient reaches 35 years of age. The increase from 0% for those below the age of 35 to nearly 18.7% for those between the ages of 35 and 44 years demands further investigation. Interestingly, due to the high prevalence of T2DM in the country, anyone above the age of 35 has been recommended to have an annual screening of DM regardless of their risk factors. This recommendation is vital as the prevalence of T2DM approaches 5% in that age group, making screening cost-effective.

There has been a wide range of prevalence rates reported by previous authors, from 15-66%. However, most of these studies use different diagnostic criteria. Most guidelines recommend using two consistent low total or free T for a diagnosis of hypogonadism, as almost 30% of males with a low serum T level may be falsely diagnosed as hypogonadism, given that their repeated serum T will be normal.³⁹⁻⁴³ Furthermore, T levels are significantly affected by diurnal and day-to-day variations and food intake.

Hence, guidelines have recommended using two different morning fasting T levels, measured with an accurate and reliable method as suggested by the Center for Disease Control and Prevention (CDC) Hormone Standardization Program for Testosterone.^{39,44} The gold standard fT measurement should be from equilibrium dialysis assays or cT instead of direct analogue-based fT immunoassays, which are highly inaccurate.^{39,44} In males with DM and obesity, the SHBG is often low, leading to a high rate of falsely lowered tT levels.⁴⁵ However, in ageing males, SHBG will be elevated, resulting in a higher range of tT levels. Hence, males with borderline tT and a high likelihood of SHBG alterations are recommended to be assessed using fT.

Studies using only biochemical criteria of low tT or fT/cT reported a prevalence of 12.3%-40% and 19-50%, respectively.^{1,3-6,8,10,17,46-52} While studies that utilise two low fT/cT results to diagnose hypogonadism reported prevalence ranging from 15-20.7%^{9,13,53} (Table 3). Authors using the presence of hypogonadal symptoms in the

diagnosis, either positive Androgen Deficiency in the Aging Male (ADAM) or AMS scores with one reading of low fT/cfT, reported a prevalence of 17.3%. Meanwhile, the prevalence of hypogonadism using positive symptoms with one reading of low fT reported a prevalence of 17-32%. Studies utilising two T levels with symptomatology have a narrower prevalence range than those using biochemical criteria alone.^{1-16,21,38,54,55}

Sexual dysfunction is common among T2DM males.⁶⁰ Previous studies have reported that such symptoms may not be entirely due to low testosterone levels and can also be present among eugonadal T2DM males, especially when there are other comorbidities.^{17,52} Nonetheless, hypogonadal T2DM males have a higher prevalence of sexual dysfunction compared to eugonadal T2DM males.^{20,61} There have been many validated questionnaires used for screening of male hypogonadism. The most common screening tools used in T2DM research are the AMS and ADAM questionnaires, both showing a sensitivity of 83-97%.⁶²

Our study demonstrated a high prevalence of hypogonadism among Malaysian T2DM males. The latest Malaysian clinical practice guidelines have recommended that all diabetic males with sexual dysfunction should be screened for hypogonadism.⁶³ In tandem with other guidelines, hypogonadism should only be diagnosed if there are at least two low serum total testosterone levels (use fT level if the patient is obese or elderly). Subsequently, the cause of hypogonadism should be investigated to exclude other causes of hyper- or hypogonadotropic hypogonadism.

Limitations and strengths

Our study was not powered enough to individually analyse predictors for hypergonadotropic or hypogonadotropic hypogonadism among T2DM males. Given the long-standing duration of DM in our study population, the findings may not apply to those with diabetes of shorter duration. Several patients withdrew from the study or were unable to give repeated blood samples due to the movement restriction order imposed by the government during the COVID-19 pandemic. This curtailed the number of subjects who could complete both blood samplings.

The strength of our study is that this is the first study in the country and region that utilised stricter diagnostic criteria for hypogonadism, where both low tT and fT with the presence of hypogonadal symptoms were necessary for the diagnosis. In addition, the multi-racial configuration of the study population closely resembles the country's major ethnic distribution.

CONCLUSION

As the prevalence of T2DM in Malaysia increased to 18.3% (according to the 2019 National Health and Morbidity Survey), the number of T2DM males complicated with

clinical hypogonadism is expected to increase as well.⁶³ Our study confirmed that the prevalence of hypogonadism in T2DM males in Malaysia is 17.5% using a stricter criterion of two persistent low T levels (serum tT and serum fT level) and the presence of hypogonadal symptoms. Given that low testosterone levels are associated with various health outcomes, testing for clinical hypogonadism should be performed in diabetic males above the age of 35 years, regardless of the duration of diabetes and, especially in those with CAD. To date, there is no proven safe and effective treatment for clinical hypogonadism that exists other than weight loss.

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Statement of Authorship

All authors certified fulfilment of ICMJE authorship criteria.

CRedit Author Statement

KWH: Formal analysis, Investigation, Visualization; Supervision; **NAK:** Conceptualization, Methodology, Writing – review and editing; **NS:** Methodology, Investigation, Writing – original draft preparation, Writing – review and editing, Supervision.

Data Availability Statement

Datasets are not publicly available because participants in the study did not give written consent to share their data.

Conflict of Interest

The authors declared no conflict of interest.

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Prevalence of Hepatic Fibrosis and Performance of Non-invasive Liver Fibrosis Scores in an Eastern Indian Diabetic Population with NAFLD

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Abstract

Objectives. Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease, especially in patients with type 2 diabetes mellitus (T2DM). Significant prevalence of liver fibrosis has been observed in Indian diabetic patients with fatty liver. Early detection of liver fibrosis in persons with diabetes prevents serious problems. This study compares non-invasive liver fibrosis scores and vibration-controlled transient elastography (VCTE) utilising FIBROSCAN™ to assess fibrosis prevalence in patients with T2DM and NAFLD.

Methodology. This cross-sectional, observational study enrolled 351 patients with T2DM and NAFLD from September to October 2023 from eight West Bengal diabetes facilities. Liver stiffness measurement (LSM) via VCTE was used to detect fibrosis. Non-invasive tests (NITs), including fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), fibrotic NASH-index (FNI), and AST to platelet ratio index (APRI) were also calculated. To evaluate NIT diagnostic performance, AUROC curve calculations were used.

Results. Among patients with T2DM, 26.5% had fibrosis and 3.13% of individuals had advanced fibrosis ($\geq F3$), whereas 11.97% had significant fibrosis ($\geq F2$). Fibrotic NASH-index could detect fibrosis best with area under the curve (AUROC) >0.70 , whereas FIB-4 and NFS were better (AUROC >0.8) to identify advanced fibrosis, and APRI struggle to diagnose severe fibrosis.

Conclusion. In patients with T2DM with NAFLD, VCTE detects fibrosis. FNI is best tool for detection of fibrosis, whereas FNI and NFS are better for distinguishing advanced fibrosis in such patients. To increase fibrosis identification in this population, multiple diagnostic approaches are needed.

Key words: non-alcoholic fatty liver disease (NAFLD), vibration-controlled transient elastography (VCTE), fibrosis-4 index (FIB-4), NAFLD-fibrosis score (NFS), AST to platelet ratio index (APRI)

Clinical trial registration number (CTRI): CTRI/2023/08/056193 dated 7th August 2023

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), an important cause of chronic liver disease (CLD), is defined as excessive hepatic fat accumulation ($\geq 5\%$) with no secondary factors such as excessive alcohol use, hepatotoxic drugs, or other chronic liver disorders. Histological features of NAFLD may

vary from fatty liver to steatohepatitis, which can progress to fibrosis, cirrhosis, or even hepatocellular carcinoma.¹ Worldwide prevalence of NAFLD is reported to be 25.24%, with a recent meta-analysis reporting 29.62% prevalence in Asia and 28-32% in India.^{2,3} A significant regional variation (44.1% to 72.4%) in NAFLD prevalence exists between different parts of India.⁴⁻⁶

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When this condition is significantly associated with metabolic disorders such as type 2 diabetes mellitus (T2DM), obesity, and dyslipidaemia, it is known as metabolic dysfunction-associated steatohepatitis liver disease (MASLD).⁷ Non-alcoholic fatty liver disease in patients with T2DM is associated with increased mortality and cardiovascular risk.⁸ There is a high prevalence of NAFLD among Indian patients with T2DM ranging from 45% to 72%.^{9,10} In patients with T2DM, rapid progression of NAFLD to advanced fibrosis, cirrhosis, or increased hepatic and extrahepatic morbidity and mortality justify liver fibrosis screening in all patients with T2DM, as per most guidelines, including American Diabetes Association (ADA).^{11,12} The global prevalence of NASH and advanced fibrosis is reported to be 37.3% and 17%, respectively, in patients with T2DM and NAFLD.¹³

The assessment and staging of liver fibrosis remain the basis for clinical decision-making, prognosis, and therapeutic monitoring in patients with chronic liver disease. Although liver biopsy is the gold standard for identifying and staging liver fibrosis, its use is limited due to its invasive nature and intra- and interobserver variability.^{4,14} Prior research has assessed non-invasive methods, such as vibration-controlled transient elastography (VCTE) for evaluating liver fibrosis and steatosis in individuals with nonalcoholic fatty liver disease (NAFLD). The usefulness of VCTE in fibrosis assessment has been shown by research,¹⁵ and comparisons of several non-invasive procedures have revealed variations in diagnostic accuracy.¹⁶ Moreover, VCTE has been used in diabetic population research to screen for both liver fibrosis and steatosis.¹⁷

Alternative, non-invasive approaches to measure and stage liver fibrosis include imaging modalities (elastography-based or magnetic resonance imaging techniques) measuring liver stiffness or clinical predictive scores using serum biomarkers. The most reliable non-invasive screening method that can simultaneously measure liver steatosis and accurately assess the degree of fibrosis is vibration-controlled transient elastography (VCTE) with FIBROSCANTM (Echosense, Paris, France) utilizing controlled attenuation parameter (CAP) measurement.^{18,19} It is the first elastography method approved by the Food and Drug Administration (FDA).²⁰ Due to its higher sensitivity (80%–85% or more), VCTE is considered a more accurate approach for diagnosing even mild steatosis.^{19,21}

Non-invasive predictive scores are most feasible in clinics, especially when assessing a large number of patients. The most commonly used predictive scores or non-invasive tests (NITs) to evaluate fibrosis are fibrosis-4 index (FIB-4), NAFLD-fibrosis score (NFS), aspartate aminotransferase (AST) to platelet ratio index (APRI), body mass index (BMI), AST/ALT (alanine aminotransferase) ratio, diabetes score (BARD), fibrotic NASH-index (FNI), etc.^{22,23} Such NITs are easily accessible and reliable tools to differentiate patients with NAFLD in different stages of fibrosis. Also, NITs enable quick assessment of large numbers of patients,

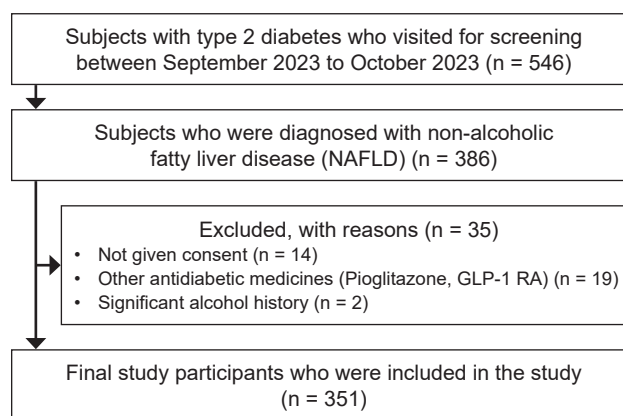


Figure 1. Flowchart of participants.

resulting to increased utility in clinical practice and clinical trials.^{24,25}

Fibrosis has been found to be independently associated with micro and macrovascular complications in patients with T2DM.¹⁸ Thus, such NITs help comprehensively evaluate patients with diabetes for hepatic and cardiovascular complications.

There is however a dearth of information about the diabetic population in Eastern India. By assessing the non-invasive fibrosis scores' performance in this particular cohort, this study seeks to close this gap. The present study evaluated the prevalence of fibrosis in MASLD diagnosed through transient elastography compared to various non-invasive liver fibrosis scores in the East Indian population with T2DM.

METHODOLOGY

Study design

A cross-sectional, observational, multicentric study was conducted on Indian patients with T2DM at eight diabetes centers in West Bengal, India. Patients who reported between September 2023 and October 2023 were screened, and those with NAFLD were included in the study (Figure 1).

Study objectives

The primary objective of the study was to evaluate the prevalence of fibrosis in T2DM through VCTE. The performance of different non-invasive liver fibrosis scores to diagnose the presence of fibrosis, significant fibrosis (SF), and advanced fibrosis (AF) in patients with diabetes was also assessed.

Study population

The study screened 546 patients with T2DM (HbA1c $\geq 6.5\%$) aged over 18 years, and enrolled 351 participants. Those who consented to fibrosis evaluation via VCTE

were included. A total of 195 patients were excluded due to chronic viral hepatitis, significant alcohol consumption, other liver diseases, prior use of medications such as pioglitazone and GLP-1 RA, or current use of saroglitazar, vitamin E, pentoxifylline, ursodeoxycholic acid (UDCA), or obeticholic acid (OCA).

Participants were recruited using a consecutive sampling method. Eligible patients visiting eight diabetes centers in West Bengal, India, between September and October 2023 were screened based on predefined inclusion and exclusion criteria. Those meeting the criteria were enrolled sequentially until the required sample size was achieved, ensuring a representative sample while minimizing selection bias.

Ethics committee approval

The study was approved by a central ethics committee (OrciVita Independent Ethics Committee – OIEC/07/01/2023 dated – 6th July 2023) and was conducted in line with the principles of the Helsinki Declaration. Clinical Trials Registry-India (CTRI) registration of the study was also carried out (CTRI registration no: CTRI/2023/08/056193 dated 7th August 2023). Written informed consent was obtained from all the participants before enrolment in the study.

Clinical assessment

Clinical and laboratory data were collected prospectively from all the included patients during VCTE. Past medical history included present medication use and alcohol use. Demographic measurements comprised of age, gender, BMI calculated as weight (in kilograms)/m², systolic and diastolic blood pressure, and duration of T2DM. On the day of the VCTE examination, a venous blood sample for laboratory parameters was obtained early in the morning following an overnight fast. Random blood sugar, HbA1c, ALT, AST, albumin and platelet count levels were analyzed. The laboratory parameters of patients at all eight study sites were submitted to one single laboratory to reduce variability in outcomes.

Liver stiffness measurement (LSM) using transient elastography

The LSM measurements were performed by trained technicians using FIBROSCAN™ (430 mini+, Echosense, Paris, France) as per the manufacturer's recommendations using either M or XL probes. The distance between the skin and liver capsule, known as a probe to liver capsule distance, was determined to establish the ideal probe size. The M probe was employed if it was <25 mm, while the XL probe was used if it was >25 mm. Measurement was done once all requirements were satisfied (proper layering on TM mode, an aligned line of imagination on A mode, and enough probe pressure). The patient was positioned supine with the right arm raised to its full height, and

the LSM of the right lobe of the liver was taken from the intercostal space. The median value was used to derive the LSM value, which was expressed in kilopascals (kPa). The VCTE examination was considered reliable for those with a median interquartile range value of less than 30% among 10 valid measurements and a success rate of at least 60%. Success rate was determined as the ratio of valid measurements to total measurements conducted.^{26,27}

The presence of liver fibrosis was graded based on LSM values provided by the manufacturer, i.e., absence of fibrosis (F0-≤7.0 kPa), mild (F1-≥7.1–10 kPa), moderate fibrosis (F2-≥10.1–13.0 kPa), severe fibrosis (F3-≥13.1–16.0 kPa) and cirrhosis (F4-≥16.1 kPa). The ≥F2 and ≥F3 scores were considered SF and AF, respectively. The CAP values obtained from the device were used when the VCTE examination was valid for that signal and expressed in decibels per meter (dB/m). The CAP scores of ≥238 dB/m were considered to have hepatic steatosis. Grading of hepatic steatosis was done based on the CAP value and was categorized as mild (S1 - 238–260 dB/m), moderate (S2 - 261–292 dB/m), and severe (S3 - ≥293 dB/m). Values were provided by the FIBROSCAN™ manufacturer.

Non-invasive tests

Various non-invasive scores such as FIB-4, NFS, FNI, and APRI were calculated using the collected data. Fibrosis-4 index, NFS and APRI were calculated using the formula described by Alqahtani and others,²² and FNI was calculated as per the formula described in the literature.²³ The rule-out and rule-in cut-off values of FIB-4, NFS, FNI, and APRI were 1.3 and 2.67, -1.455 and 0.676, 0.10 and 0.33, and 0.5 and 2.0, respectively.²⁵

Sample size

The sample size was initially determined based on prevalence estimation to ensure sufficient representation of patients with T2DM and NAFLD. With power at 85%, significance level of 0.05, and a reported T2DM prevalence of 11% in India, of which 70% have NAFLD, the required sample size was 546. This calculation was designed to provide robust prevalence estimates while accounting for potential exclusions and subgroup analyses.

To ensure adequate power for diagnostic accuracy assessment, a separate calculation was conducted using expected sensitivity (90%), specificity (90%), prevalence of 11%, precision of ±10%, 95% confidence level, and a 10% dropout rate. This resulted in a required minimum sample size of 350. After applying eligibility criteria and exclusions, 351 participants were included in the final analysis, ensuring sufficient power for both prevalence estimation and diagnostic accuracy evaluation. The study was conducted using the prevalence-based sample size determination, but the final sample size also met the requirements for diagnostic accuracy validation.

Statistical analysis

Categorical variables were expressed as percentages (%), while continuous variables were expressed as mean $\pm$ standard deviation (SD). The chi-square test was used to compare the categorical variables, while the independent t-test was used to compare continuous variables. Statistical significance was set at a value of $p < 0.05$. Receiver operating characteristic (ROC) curves with area under the ROC (AUROC) were calculated to determine the diagnostic utility of FIB-4, NFS, FNI, and APRI scores for non-invasive assessment of fibrosis or AF in diabetic patients with NAFLD. To generate the ROC curve, PROC logistic procedure in SAS software was used while the DeLong test²⁸ was utilized to compare each AUROC with the LSM value. The AUROC curve ranges from 0 to 1.0, with 0 indicating a perfectly inaccurate marker, while 1.0 represents a perfectly accurate marker. A value of 0.5 indicates that the tests cannot discriminate between patients with or without fibrosis.²⁹ In general, tests with an AUROC greater than 0.80 are thought to be clinically helpful.³⁰

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for FIB-4, NFS, FNI, and APRI scores with exact binomial 95% confidence interval (CI). All four NITs were also evaluated to select the optimal predicted probability cut-off using the Youden index (J value). The optimal probability cut-off is where J is the maximum. The SAS software (version 9.4; SAS Institute Inc., USA) was used to perform all the data analyses.

RESULTS

We prospectively included 351 (56% males) patients with T2DM and NAFLD in our study. The mean age and BMI

were 51 ± 9 years and 25.8 ± 4.2 kg/m², respectively. The total study population was categorised into two groups: absence (F0) and presence ($\geq$ F1) of fibrosis. Ninety-three (26.50%) subjects had liver fibrosis as per LSM by VCTE, while 258 (73.50%) subjects did not have fibrosis. The mean glycosylated haemoglobin in both groups was $7.6 \pm 1.8\%$, significantly different ($p = 0.0014$) among the groups. The demographic and laboratory parameters of the patients with T2DM and NAFLD with and without fibrosis are described in Table 1.

Prevalence of fibrosis based on LSM and CAP values

The prevalence of fibrosis among patients with T2DM was found to be 26.5% (F1 to F4), with a mean LSM of 10.2 ± 2.6 kPa (F1 to F4). Significant fibrosis (SF) ($\geq$ F2, LSM >10.0 kPa) was reported in 42 patients (11.97%), and 11 patients (3.13%) reported AF ($\geq$ F3, LSM >13.0 kPa). The prevalence of steatosis among patients with T2DM was 70.7% (S1 to S3), with a mean CAP of 293.4 ± 34 dB/m (S1 to S3). Significant steatosis (S2-S3) was found in 204 (58%) patients with a CAP score above 261 dB/m.

Performance of FIB-4, NFS, FNI, and APRI tests

The distributions of various parameters (FIB-4, NFS, FNI, and APRI) by the presence or absence of fibrosis are presented in Table 2. The mean score of FIB-4, NFS, FNI, and APRI was 1.8 ± 0.9 , -0.4 ± 1.1 , 0.6 ± 0.2 , and 0.5 ± 0.4 , respectively, in absence of fibrosis (F0) while 1.8 ± 1 , -0.5 ± 1.3 , 0.7 ± 0.2 , and 0.6 ± 0.4 , respectively in presence of fibrosis ($\geq$ F1).

The accuracy of these tests for detecting fibrosis, SF, or AF was measured using AUROC (Figure 2).

Table 1. Demographic and laboratory parameters of patients with type 2 diabetes with or without fibrosis based on LSM values

Demographics	Absence of Fibrosis (F0) (n = 258)	Presence of Fibrosis ($\geq$ F1) (n = 93)	Total (F0 to F4) (n = 351)	p-value
Age (mean $\pm$ SD), years	52 $\pm$ 8	50 $\pm$ 9	51 $\pm$ 9	0.0465 ^a
Gender, n(%)				0.0107 ^a
Male	156 (60%)	42 (45%)	198 (56%)	
Female	102 (40%)	51 (55%)	153 (44%)	
BMI (mean $\pm$ SD), kg/m ²	25.2 $\pm$ 3.8	27.3 $\pm$ 4.9	25.8 $\pm$ 4.2	<0.0001 ^a
T2DM (mean $\pm$ SD), duration in months	98 $\pm$ 85	85 $\pm$ 66	95 $\pm$ 81	0.1823
HbA1c (mean $\pm$ SD), %	7.4 $\pm$ 1.8	8.1 $\pm$ 1.8	7.6 $\pm$ 1.8	0.0014 ^a
AST (mean $\pm$ SD), U/L	32.2 $\pm$ 20	42.2 $\pm$ 24.5	34.8 $\pm$ 21.7	0.0001 ^a
ALT (mean $\pm$ SD), U/L	33.6 $\pm$ 18.8	50.7 $\pm$ 40.3	38.2 $\pm$ 27.3	<0.0001 ^a
Albumin (mean $\pm$ SD), g/dL	4.4 $\pm$ 0.3	4.3 $\pm$ 0.3	4.4 $\pm$ 0.3	0.0062 ^a
Platelet Count (mean $\pm$ SD), $\times 10^3 / \mu$ L	179.1 $\pm$ 67.8	195 $\pm$ 66	183.3 $\pm$ 67.6	0.0517
CAP (mean $\pm$ SD), dB/m	257.5 $\pm$ 49.2	291.9 $\pm$ 53.4	266.6 $\pm$ 52.5	<0.0001 ^a
LSM (mean $\pm$ SD), kPa	5 $\pm$ 1.1	10.2 $\pm$ 2.6	6.4 $\pm$ 2.8	<0.0001 ^a

The values are expressed as mean $\pm$ standard deviation (SD), count (n) and proportion (%)

^a p-value less than 0.05 is considered statistically significant measured by Chi-square test

AST: Aspartate aminotransferase; ALT: Alanine transaminase; BMI: Body mass index; CAP: Controlled attenuation parameter; DBP: Diastolic blood pressure; HbA1c: Glycosylated haemoglobin; HDL-C: High-density lipoprotein cholesterol; h/o: History of; LDL-C: Low-density lipoprotein cholesterol; LSM: Liver stiffness measurement; NAFLD: Non-alcoholic fatty liver disease; RBS: Random blood sugar; SBP: Systolic blood pressure; T2DM: Type 2 diabetes mellitus

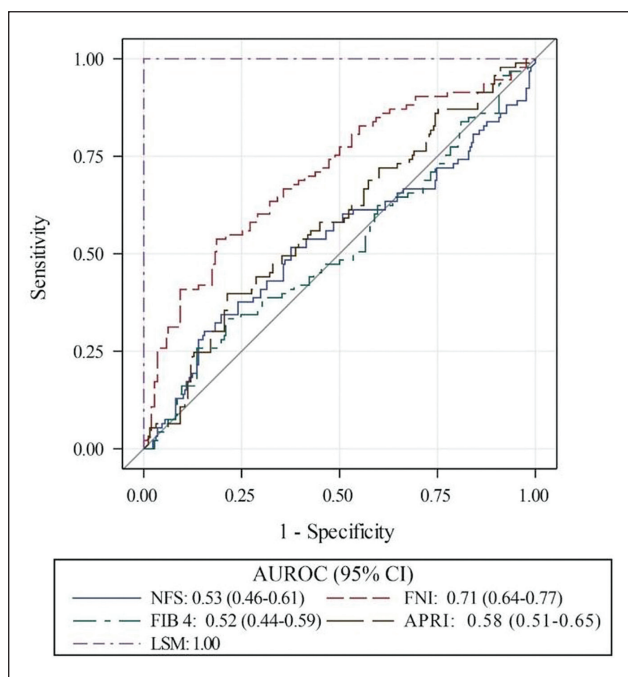


Figure 2A. Area under the receiver operator curves (AUROC) of non-invasive tests for presence of fibrosis.

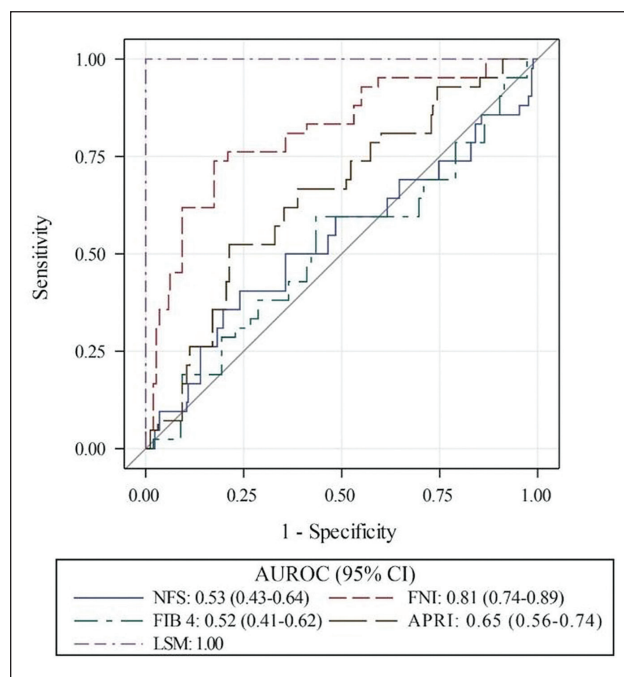


Figure 2B. Significant fibrosis (SF).

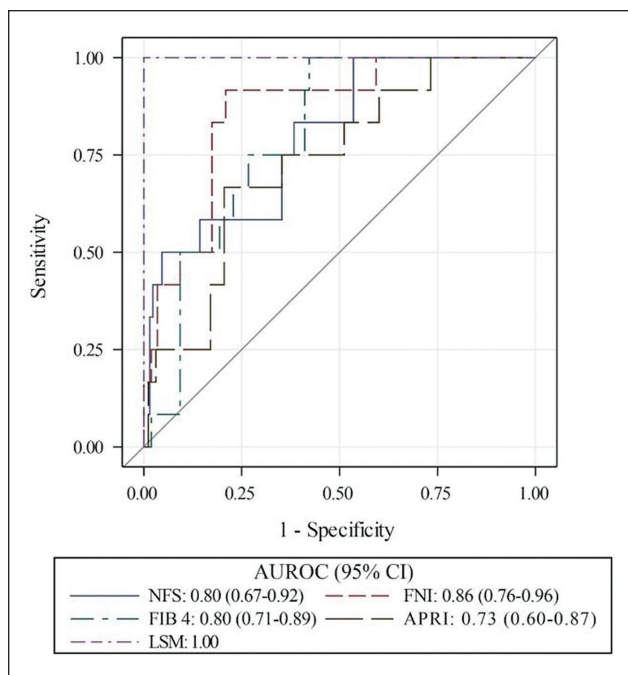


Figure 2C. Advanced fibrosis (AF).

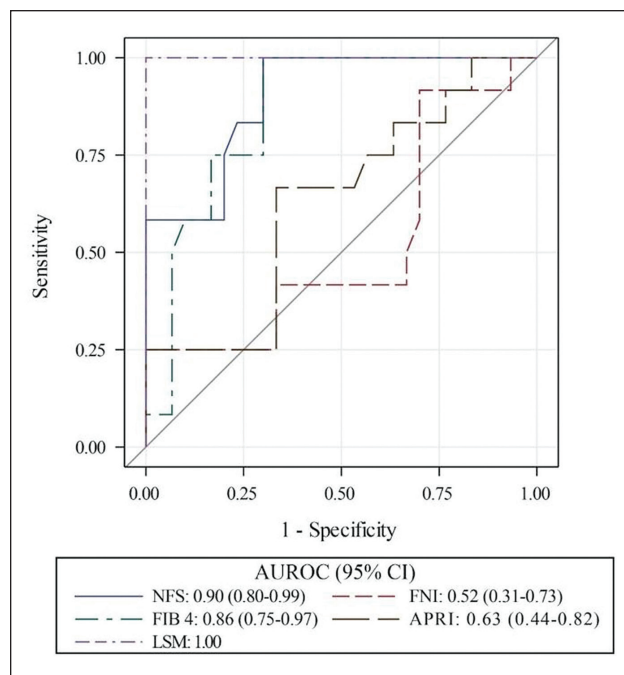


Figure 2D. Differentiating SF from AF in patients with type 2 diabetes.

DISCUSSION

As the landscape of liver diseases evolves, there is a growing recognition of the significant impact of metabolic dysfunction on liver health. While the term NAFLD remains widely used, there is a growing recognition of the critical role metabolic dysfunction plays in the development and progression of fatty liver disease. Metabolic dysfunction-associated steatotic liver disease, affecting a substantial

portion of the global population, highlights the complex nature of liver diseases, particularly in patients with advanced liver fibrosis.³⁴ Our study found a 26.5% fibrosis prevalence in patients with T2DM and NAFLD by VCTE via FIBROSCAN™. Significant fibrosis ($\geq$ F2, LSM >10.0 kPa) was found in 42 patients (11.97%), and 11 patients (3.13%) reported AF ($\geq$ F3, LSM >13.0 kPa). The mean score of FIB-4, NFA, FNI, and APRI was 1.8 ± 0.9 , -0.4 ± 1.1 , 0.6 ± 0.2 , and 0.5 ± 0.4 , respectively, in absence of fibrosis (F0)

while 1.8 ± 1 , -0.5 ± 1.3 , 0.7 ± 0.2 , and 0.6 ± 0.4 , respectively in presence of fibrosis ($\geq F1$). Although most patients with T2DM and NAFLD assessed to have fibrosis had high FIB-4, NFS, FNI, and APRI scores, a significant percentage had normal values.

Using the published cut-offs,²⁵⁻³⁰ the performance of FIB-4, NFS, and APRI for the diagnosis of fibrosis and SF were relatively poor with AUROC <0.64 , while that of FNI was acceptable (AUROC >0.70) (Table 3). On the other hand, the performance of FNI and APRI were poor (AUROC <0.64) for the diagnosis of AF, and that of FIB-4 and NFS were better (AUROC >0.8) (Table 3). Prasad et al., reported that

while the FIB-4 score demonstrated moderate diagnostic accuracy (AUROC: 0.634 for any fibrosis, 0.640 for advanced fibrosis), the NAFLD Fibrosis Score (NFS) showed lower discriminatory power, requiring further validation in Indian patients.³¹

Previous study in eastern India found similar (26%) hepatic fibrosis prevalence in patients with T2DM.⁹ Previous studies have indicated a higher risk of developing fibrosis in the presence of T2DM.^{8,31} Our study also found significantly higher age, HbA1c, BMI, AST, and ALT in patients with T2DM and fibrosis. This observation corroborates with previous studies indicating that age, obesity, and

Table 2. Percentage prevalence of different grades of liver fibrosis in patients with type 2 diabetes based on FIB-4, NFS, FNI, and APRI score cut-off values

NIT score cut-off values	F0	F1	F2	F3	F4
FIB-4					
<1.3 (n = 104)	72 (69.2)	19 (18.3)	13 (12.5)	0 (0)	0 (0)
1.3 to 2.67 (n = 204)	156 (76.5)	27 (13.2)	15 (7.4)	4 (2)	2 (1)
>2.67 (n = 43)	30 (69.8)	5 (11.6)	2 (4.7)	5 (11.6)	1 (2.3)
NFS					
<-1.455 (n = 65)	39 (60)	15 (23.1)	11 (16.9)	0 (0)	0 (0)
1.455 to 0.675 (n = 244)	192 (78.7)	27 (11.1)	19 (7.8)	5 (2)	1 (0.4)
≥ 0.676 (n = 42)	27 (64.3)	9 (21.4)	0 (0)	4 (9.5)	2 (4.8)
FNI					
<0.10 (n = 18)	15 (83.3)	3 (16.7)	0 (0)	0 (0)	0 (0)
0.10 to 0.33 (n = 99)	88 (88.9)	9 (9.1)	2 (2)	0 (0)	0 (0)
>0.33 (n = 234)	155 (66.2)	39 (16.7)	28 (12)	9 (3.8)	3 (1.3)
APRI					
<0.5 (n = 206)	159 (77.2)	31 (15)	13 (6.3)	2 (1)	1 (0.5)
0.5 to 2 (n = 138)	95 (68.8)	19 (13.8)	17 (12.3)	5 (3.6)	2 (1.4)
>2 (n = 7)	4 (57.1)	1 (14.3)	0 (0)	2 (28.6)	0 (0)

The values are expressed as n(%)

APRI: aspartate aminotransferase-to-platelet ratio; FIB-4: Fibrosis-4 index; FNI: fibrotic non-alcoholic steatohepatitis index; NAFLD: Non-alcoholic fatty liver disease; NFS: non-alcoholic fatty liver disease fibrosis score

Table 3. Sensitivity, specificity, and positive and negative predictive value of non-invasive tests for detection of presence of fibrosis (F1-F4), significant fibrosis - SF ($\geq F2$), advanced fibrosis - AF ($\geq F3$) and differentiation of SF and AF in patients with type 2 diabetes with non-alcoholic fatty liver disease

	Optimal Cut-offs	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value
Fibrosis								
FIB-4	1.17	0.52 (0.44-0.59)	33.33	79.07	36.47	76.69	66.95	0.8365
NFS	-1.16	0.53 (0.46-0.61)	34.41	80.23	38.55	77.24	68.09	0.6387
FNI	0.66	0.71 (0.64-0.77)	53.76	81.40	51.02	83.00	74.07	$<0.0001^a$
APRI	0.62	0.58 (0.51-0.65)	39.78	78.68	40.22	78.38	68.38	0.0764
Significant fibrosis (SF)								
FIB-4	1.77	0.52 (0.41-0.62)	59.52	56.59	18.25	89.57	57.00	0.9295
NFS	-1.04	0.53 (0.43-0.64)	40.48	75.97	21.52	88.69	71.00	0.6129
FNI	0.67	0.81 (0.74-0.89)	73.81	82.56	40.79	95.09	81.33	$<0.0001^a$
APRI	0.62	0.65 (0.56-0.74)	52.38	78.68	28.57	91.03	75.00	0.0487 ^a
Advanced fibrosis (AF)								
FIB-4	1.81	0.80 (0.71-0.89)	100.00	57.75	9.92	100.00	59.63	0.0084 ^a
NFS	-0.31	0.80 (0.67-0.92)	100.00	46.51	8.00	100.00	48.89	0.0001 ^a
FNI	0.62	0.86 (0.76-0.96)	91.67	79.07	16.92	99.51	79.63	$<0.0001^a$
APRI	0.63	0.73 (0.60-0.87)	66.67	79.46	13.11	98.09	78.89	0.0129 ^a
Significant vs. Advanced fibrosis								
FIB-4	1.81	0.86 (0.75-0.97)	100.00	70.00	57.14	10.00	78.57	0.0020 ^a
NFS	-0.31	0.90 (0.80-0.99)	100.00	70.00	57.14	10.00	78.57	0.0039 ^a
FNI	0.97	0.52 (0.31-0.73)	25.00	100.00	100.00	76.92	78.57	0.5278
APRI	0.63	0.63 (0.44-0.82)	66.67	66.67	44.44	83.33	66.67	0.0747

^a p-value less than 0.05 is considered statistically significant measured by Chi Square test.

APRI: aspartate aminotransferase-to-platelet ratio; AUROC: area under the receiver operating curves; CI: confidence interval; FIB-4: Fibrosis-4 index; FNI: fibrotic non-alcoholic steatohepatitis index; NFS: non-alcoholic fatty liver disease fibrosis score; NPV: negative predictive value; PPV: positive predictive value

higher levels of AST and ALT are independent predictors for the development of fibrosis.^{32,33}

Screening for fibrosis is challenging due to the high prevalence of NAFLD in the general population and more so in subjects with T2DM.³⁴ Magnetic resonance imaging, particularly MR elastography (MRE), offers superior accuracy for staging liver fibrosis and is considered the gold standard non-invasive imaging modality. However, VCTE is more accessible and cost-effective, making it a practical choice for widespread screening.³⁴ Vibration-controlled transient elastography by FIBROSCAN™ is an FDA-approved, effective, non-invasive tool for detecting steatosis and fibrosis. A meta-analysis reported the sensitivity and specificity of transient elastography (FIBROSCAN™) to be 83.7% and 78.2% for fibrosis stage F1, 87.5% and 78.4% for fibrosis stage F2, 93.7% and 91.1% for fibrosis stage F3 and 96.2% and 92.2% for fibrosis stage F4.³⁵ Thus, VCTE has good clinical usefulness in diagnosing fibrosis stages, ruling out advanced fibrosis, and may be an alternative to invasive liver biopsy.^{36,37} It has been found to be effective in screening for steatosis and fibrosis in patients with T2DM and has also been validated for diagnosing fibrosis in Indian patients.³⁸

However, this test is only appropriate for specialised medical settings because it entails training and expensive equipment, and inconsistent outcomes between observers may be seen. Thus, using NITs to stage liver steatosis and fibrosis is a significant advantage for patients with NAFLD, particularly for periodic assessments required for disease progression monitoring.³⁹

The present study investigated four different NITs or predictive scoring systems: FIB-4, NFS, FNI, and APRI. All these tests are based on measurements that are conducted in routine clinical practice. Many studies have been performed to validate the diagnostic accuracy of these tests for liver fibrosis. A recent meta-analysis concluded that simple NITs like FIB-4, NFS, and LSM-VCTE could be employed to predict clinical outcomes in patients with NAFLD without needing biopsies.⁴⁰ A meta-analysis of 64 studies reported pooled sensitivities and specificities of FIB-4, NFS, and APRI for detecting AF as 64.8% and 72.9%, 66.8% and 87.5%, and 59.7% and 78.9%, respectively. The summary AUROC at published cut-offs for FIB-4 and APRI were found to be 0.73 and 0.76, respectively, while that of NFS was unavailable due to few studies evaluated.²⁵ Most of these studies reported diagnostic accuracy in the general population, not the diabetic population. The sensitivity and specificity of FNI for detecting NASH were found to be 92% and 71%, with an AUROC of 0.93 in patients with NAFLD in general, while the same in the diabetic population was found to be 97% and 36%, respectively, with an AUROC of 0.89.⁴¹ Our study reports optimised AUROC for detecting the presence of fibrosis, SF, and AF as well as for differentiating SF and AF at previously published cut-offs (FIB-4:<1.3, NFS:<1.455, FNI:<0.10, APRI:<0.5).

We found that the sensitivity and specificity of FIB-4 and NFS were low for detecting fibrosis and SF compared to LSM. These results support previous studies wherein both these tests have reported <70% sensitivity and specificity for detecting fibrosis and SF compared to LSM.^{25,42} The optimised AUROC for detecting the presence of fibrosis were 0.52, 0.53, 0.71, and 0.58 for FIB-4, NFS, FNI, and APRI, respectively. The optimised AUROC for SF and AF were 0.52 and 0.80, 0.53 and 0.80, 0.81 and 0.86, and 0.65 and 0.73 for FIB-4, NFS, FNI and APRI, respectively.

However, FIB-4 and NFS effectively detect AF in T2DM patients at the cut-off of <1.3 and <1.455, respectively. Our results are consistent with earlier studies on the usefulness of FIB-4 and NFS in detecting AF.^{27,40} The accuracy of APRI for detecting fibrosis was not better than LSM; however, it was found to be more accurate than FIB-4 and NFS for detecting SF and AF, with a specificity of 75-80%. An earlier meta-analysis also reported the specificity of APRI at a cut-off of 0.43 for the detection of SF and AF to be more than 70%.²⁷

One important finding in our study is that FNI showed significantly better performance in detecting fibrosis, SF, and AF than LSM compared to FIB-4, NFS, or APRI. The specificity of FNI at a cut-off of <0.1 for detecting fibrosis, SF, and AF approximates 80%, while the sensitivity increases progressively for detection of fibrosis, SF, and AF from 50% to 90%. Previous studies also found FNI outperforming FIB-4 in detecting fibrosis.^{23,41}

The main finding of the present study was that all of these scores had a relatively high NPV (>85%) for detecting liver SF and AF in patients with T2DM, which was consistent with earlier research.⁴³ Thus, these NITs can be used reliably to rule out or exclude significant or advanced liver fibrosis in patients with T2DM. Testing the patients with one or more such NITs followed by LSM can increase the detection of fibrosis and decrease false positives. However, there is a chance that too many people may be referred to liver specialists by adopting this strategy; thus, these NITs should be used to rule out rather than diagnose fibrosis in patients with T2DM. This approach can help select patients requiring further investigations and referral to specialised liver clinics, to decrease the likelihood of developing cirrhosis in the future. Findings in the present study are in conjunction with the existing guidelines that recommend the usage of NITs for ruling out fibrosis.⁴⁴⁻⁴⁷ However, since the PPV and accuracy of the individual tests are low, they need to be utilized in conjunction with other complex tests to estimate the degree of fibrosis accurately.

Our study did encounter some limitations, such as the small sample size. A larger study population of patients with T2DM and NAFLD could have increased the reliability of these NITs. Furthermore, we compared the performance of these tests with VCTE and not with the gold standard recommended for detecting liver fibrosis, i.e., liver biopsy. Thus, further studies comparing the performance of

these NITs with liver biopsy could shed more light on the application of these tests for screening in large populations.

CONCLUSION

Our study found a 26.4% prevalence of fibrosis in patients with T2DM and NAFLD by FIBROSCAN™. Though most patients with T2DM and NAFLD afflicted with fibrosis had high FIB-4, NFS, FNI, and APRI scores, a significant percentage had normal values. Fibrosis-4 index, NFS and APRI had poor sensitivity for detecting the presence of fibrosis and SF, while FNI was acceptable. Fibrosis-4 index and NFS were better for detecting AF, while FNI and APRI performed poorly. A lower cut-off to detect fibrosis may be considered, especially for SF and AF by NITs.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

DS: Conceptualization, Formal analysis, Investigation, Data Curation, Writing – original; draft preparation, Supervision, Funding acquisition; **SC:** Methodology, Software, Validation, Resources, Visualization, Project administration; **SG:** Conceptualization; **AD:** Resources, Writing – review and editing, Supervision; **ASC:** Investigation, Writing – review and editing, Visualization; **SM:** Investigation, Writing – original draft preparation; **SB:** Software, Writing – review and editing, Projection; **SRC:** Methodology, Software, Validation, Resources, Visualization, Project administration; **MS:** Software, Writing – review and editing, Project administration.

Data Availability Statement

Datasets analyzed in the study are under license and not publicly available for sharing.

Author Disclosure

The authors declared no conflict of interest.

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Evaluating Serum Endosialin (CD248) Levels as a Diagnostic Marker in Gestational Diabetes: A Case-Control Study

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Abstract

Objectives. Gestational diabetes mellitus (GDM), a pregnancy-induced hyperglycemia, affects approximately 17% of pregnancies globally. Its pathophysiology remains unclear, with inflammation and vascular remodeling playing key roles. CD248, a glycoprotein linked to inflammation and vascular remodeling, has been implicated in various conditions, but its role in GDM is uncertain.

Methodology. A prospective case-control study was conducted with 169 pregnant women aged 18 to 49 at a tertiary hospital. Serum CD248 levels were assessed at 24 to 28 weeks of gestation prior to the oral glucose tolerance test (OGTT). Statistical analyses evaluated the association between CD248 levels, BMI and GDM status.

Results. Of the participants, 32 (18.9%) were diagnosed with GDM. CD248 levels were lower in GDM patients (8.15 ± 10.16 ng/mL) than in controls (11.42 ± 15.44 ng/mL), but the difference was not statistically significant ($p = 0.084$). Although CD248 levels did not correlate with OGTT values, it was positively associated with BMI ($p < 0.001$).

Conclusion. Unlike earlier findings associating elevated CD248 levels with early pregnancy GDM risk, this study found no significant relationship during later gestational stages. These results highlight a potentially complex and context-dependent role for CD248 in GDM pathophysiology.

Key words: CD248, Endosialin, Gestational Diabetes Mellitus, Inflammation, OGTT

INTRODUCTION

Gestational diabetes mellitus (GDM) is typically defined as hyperglycemia first identified during pregnancy, with blood glucose levels that are below the diagnostic thresholds for overt diabetes, whether during or outside of pregnancy. Based on the 2010 screening and diagnostic criteria established by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), the global prevalence of GDM is estimated to be 17%.¹ Increased maternal glucose concentration shows a linear correlation with perinatal complications in early (before 20 weeks) and late pregnancy (24 to 28 weeks). It is also linked to long-term cardiometabolic risks for both mother and offspring.²⁻⁴ The pathophysiology of GDM remains incompletely understood, but it is characterized by a pancreatic β -cell defect that fails to compensate for pregnancy-induced insulin resistance. This defect is influenced by factors such as genetic predisposition, epigenetic changes, placental hormones, adipokines, oxidative stress and inflammatory

cytokines. Notably, GDM has been linked to chronic, low-grade inflammation and angiogenesis, suggesting parallels with other conditions like cancer and atherosclerosis, where inflammation plays a central role.⁵⁻⁷ Vasculogenesis and angiogenesis are the two sequential processes involved in blood vessel formation during vascular development. In women with GDM, angiogenesis has been reported to be higher compared to those with type 1 diabetes mellitus and healthy controls.⁸

CD248, also referred to as endosialin or tumor endothelial marker 1, is a type I transmembrane glycoprotein that was initially identified on the blood vessels of various human tumors and subsequently recognized as an abnormally expressed marker of tumor endothelial cells, contributing to the reorganization of tumor blood vessels. In addition, CD248 is expressed in mesenchymal-derived cells, including pericytes, fibroblasts, vascular smooth muscle cells and osteoblasts.^{9,10} CD248 plays a critical role in vascular and extracellular remodeling, partly by promoting a pronounced

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hypoxic response.¹¹ It is significantly upregulated in the context of tumor growth, inflammation and injury-induced fibrosis in various organs, such as the liver and kidney.^{12,13} Global inactivation of the CD248 gene in mice reduces disease severity in various models of human diseases, including inflammatory arthritis and atherosclerosis. This reduction is characterized by decreased tissue infiltration of pro-inflammatory leukocytes and reduced circulating levels of cytokines and chemokines, such as IL-1 β , CCL2 and CCL5. Moreover, the absence of CD248 has been found to alleviate inflammation and fibrosis in models of both acute and chronic liver injury, as well as renal fibrosis.¹⁴ Elevated CD248 in early pregnancy was shown to predict development of GDM later on.¹⁵

We hypothesize that chronic low-grade inflammation and placental neovasculogenesis, may result in elevated levels of CD248, which could serve as a biomarker for identifying patients at increased risk of developing GDM. We aim to explore alternative diagnostic methods for GDM aside from oral glucose tolerance test which is the current gold standard.

METHODOLOGY

This prospective case-control study was conducted at Izmir Democracy University Buca Seyfi Demirsoy Research and Training Hospital from May to October 2024.

Patients aged 18 to 49 years, with no previous history of diabetes or systemic diseases, were included in the study. Exclusion criteria included multi-gestational pregnancies, alcohol consumption and the use of any medication other than those recommended by local health authorities for pregnancy supplementation, specifically 1200 IU of vitamin D and 30 mg of iron. Blood samples were collected from participants between the 24th and 28th week of pregnancy, just before the OGTT was done. The samples were collected between 8:30 AM and 10:00 AM on the day of the procedure while patients were in a fasting state. Blood samples were immediately stored at 4°C and left to clot for 4 to 6 hours. Following the clotting process, serum samples were centrifuged at 2000G for 10 minutes within a temperature range of 2 to 8°C. The resulting supernatant was portioned into 1 ml aliquots, transferred into cryotubes, and promptly frozen at -40°C for subsequent analysis. This freezing method and the selected temperature, which was not -80°C, were chosen as the only feasible option given the limited resources of our hospital. Before analysis, the samples were brought to room temperature (25°C) for thawing. Notably, the researcher responsible for the laboratory procedures was unaware of the patients' gestational diabetes status.

GDM was confirmed with a 75g OGTT. The diagnosis of GDM was made if any of the following conditions were met: fasting glucose levels of 92 mg/dL (5.1 mmol/L) or higher, 1-hour glucose levels of 180 mg/dL (10.0 mmol/L) or higher, or 2-hour glucose levels of 153 mg/dL (8.5 mmol/L) or higher. Initially, patients with GDM were treated with

dietary therapy whenever feasible. If dietary measures failed to meet the target glucose levels (fasting $\leq$ 95 mg/dL, 1 hour postprandial $\leq$ 140 mg/dL, 2 hours postprandial $\leq$ 120 mg/dL), insulin therapy was started with guidance from an endocrinologist.

The analysis was done using enzyme-linked immunosorbent assay (ELISA) kits specifically designed for CD248 (Ref: DZE201128848-LOT 202409, Shanghai Sunred Biological Technology Co.). To ensure precision and reliability in the measurements, the inter-assay and intra-assay coefficients of variation (CV) for CD248 were both determined to be less than 10%.

Ethics and statistical analysis

A total of 169 patients voluntarily agreed to participate in the study after providing informed consent. Ethical approval for the research was obtained from the Buca Seyfi Demirsoy Training and Research Hospital Ethics Committee under reference number 2024/275. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 23.0 (IBM Co., Chicago, IL). Kolmogorov-Smirnov analysis was used to assess data distribution. The independent sample t-test was applied for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. Chi-square tests, Pearson correlation tests and linear regression analyses were also conducted as appropriate. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Since a double-blinded method was used for patient selection, where neither the patients nor the researchers knew the OGTT results before sample collection, the groups were not matched in numbers. Thirty-two out of 169 patients who completed glucose testing were diagnosed with GDM. A post hoc analysis yielded a power of 0.81, with a significance level set at 0.05 and an effect size of 0.5. The incidence of GDM was 18.9%. The mean age of patients with GDM was 28.53 ± 6.05 years, while those without GDM was 28.74 ± 5.12 years ($p = 0.204$). Additional patient characteristics are detailed in Table 1.

It was determined that CD248 data does not follow a normal distribution ($p = 0.000$). Neither log nor square root transformation resulted in a normally distributed CD248 dataset; therefore, further analyses were conducted using non-parametric tests. The mean CD248 level was 8.15 ± 10.16 ng/mL in patients with GDM and 11.42 ± 15.44 ng/mL in patients without GDM. When comparing CD248 levels between the GDM and non-GDM groups, no significant difference was observed between the two groups ($p = 0.084$). A significant correlation was observed between BMI and hour-to-hour glucose values on the OGTT, while CD248 levels showed no correlation with glucose values on the OGTT. Further details are provided in Table 2.

Table 1. Characteristics of patients and comparison based on GDM status

	Patients with GDM (n = 32)	Control group (n = 137)	Significance (p)
Age	28.53 ± 6.05	28.74 ± 5.12	0.844
Gravida	2.47 ± 1.59	2.45 ± 1.55	0.958
Parity	1.00 ± 1.02	1.18 ± 1.28	0.454
Mean Gestational Week	25.94 ± 1.34	25.72 ± 1.59	0.464
Body Mass Index (BMI)	30.23 ± 5.80	27.44 ± 4.47	0.003
Smoking	Present	28 (16.6%)	0.172
	Absent	107 (63.3%)	

Student's T-test and Chi-square test were used where appropriate. Significant values are presented in bold.

Table 2. Correlations between CD248 levels, BMI and glucose levels on OGTT

		Fasting glucose	1-hour glucose	2-hour glucose
CD248	Correlation (r)	-0.091	-0.050	-0.064
	Significance (p)	0.242	0.515	0.408
BMI	Correlation (r)	0.320	0.281	0.104
	Significance (p)	0.000	0.000	0.179

Pearson correlation analysis performed. Significant values are presented in bold.

None of the variables—age, gravidity, parity, BMI, gestational week and smoking status—had a significant confounding effect on the relationship between GDM status and CD248 levels ($p = 0.444, 0.589, 0.354, 0.721, 0.211,$ and 0.437 , respectively).

DISCUSSION

This study evaluated the diagnostic potential of plasma CD248 levels in a cohort of 169 pregnant patients undergoing an OGTT. However, plasma CD248 levels did not exhibit a significant association with GDM status.

In a previous study, Wei et al., reported that elevated CD248 levels in early pregnancy were associated with an increased likelihood of developing GDM during gestational ages characterized by peak insulin resistance, with a reported range of 5–10 ng/mL for all patients, regardless of GDM status.¹⁵ In contrast, our study found that CD248 levels did not vary significantly in patients at 24 to 28 weeks gestational age and, notably, were lower in patients with GDM than those without. As the first study to evaluate CD248 levels specifically during the 24th–28th week of gestation, we propose that the previously observed elevation in early pregnancy may reflect increased placental inflammation and angiogenesis, which does not appear to continue alongside the rising insulin resistance later in pregnancy.

In murine models, CD248 knockout has been linked to enhanced insulin sensitivity, suggesting that CD248 may impede insulin signaling pathways.¹⁶ Conversely, our study observed that elevated serum CD248 levels in pregnant women correlated with improved insulin sensitivity. This discrepancy may be attributed to the complex and context-dependent roles of CD248 in humans, particularly during pregnancy, where it might interact with other physiological factors influencing insulin sensitivity.

BMI is widely recognized as a key factor influencing glucose metabolism and insulin resistance, particularly in the context of GDM. Our findings highlight the relationship between BMI and glucose levels at different time points during OGTT, and its association with CD248 levels. This suggests that higher BMI may contribute to impaired glucose regulation, especially in the early phases of the test. This aligns with existing evidence linking increased adiposity to reduced insulin sensitivity, often resulting in elevated postprandial glucose levels. Additionally, CD248 is known to play a role in adipose tissue physiology, further supporting its potential involvement in metabolic regulation. For instance, a study by Zhang et al. demonstrated that CD248 is abundantly expressed in mature white adipocytes and significantly correlates with BMI, suggesting its involvement in adipocyte function and obesity-related processes.¹⁷ Additionally, Patrick et al. reported that CD248 influences lipid metabolism in adipose tissue, further supporting its association with BMI and metabolic regulation.¹⁸ These studies corroborate our observations, underscoring the relevance of CD248 in adipose tissue dynamics and its potential impact on metabolic health.

CONCLUSION

This study is the first to investigate CD248 levels during the 24th–28th week of gestation and their association with GDM status. While our findings did not reveal a significant relationship between elevated CD248 levels and the development of GDM, they contribute valuable insights to a field with limited existing research. The lack of association highlights the need for further studies with larger, well-matched cohorts and optimal sample handling to better understand the role of CD248 in pregnancy-related metabolic changes. These results underscore the complexity of GDM pathophysiology and the potential for alternative biomarkers to improve diagnosis and management.

Limitations

A limitation of our study is the unequal distribution of case and control subject numbers, which was implemented to ensure researcher blinding; however, our findings on serum CD248 levels are consistent with previous literature. Additionally, preserving serum samples under optimal conditions, such as storage at -80°C, could yield more precise measurements and further validate the results.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

TBB: Conceptualization, Investigation, Resources, Data Curation, Writing – original draft preparation; **CA:** Validation, Investigation, Data Curation; **UA:** Software, Formal analysis; **HAA:** Formal analysis, Project administration; **SE:** Methodology, Writing – review and editing, Supervision.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Author Disclosure

The authors declared no conflict of interest.

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None.

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Sodium-Glucose Cotransporter-2 inhibitor (SGLT2i) Prescription Rates Amongst Diabetologists for Type 2 Diabetes Patients with Albuminuric Diabetic Kidney Disease: A Real-World Study at a Diabetes Center in Bangkok

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Abstract

Background. Despite the beneficial effects of SGLT2i in reducing kidney disease progression and mortality in people with diabetic kidney disease (DKD), the use of SGLT2i in this population remains low.

Objective. To explore the prescription rates of SGLT2i in type 2 diabetes (T2D) patients with albuminuric DKD and to assess clinician-perceived barriers to prescribing SGLT2i.

Methodology. A retrospective study of all medical records of T2D patients with albuminuric DKD and eGFR ≥ 20 mL/min/1.73m² in 2023 who had been treated by 13 diabetologists was conducted at Vimut-Theptarin Hospital, a private tertiary diabetes center in Bangkok. In cases of no documentation of non-prescribed SGLT2i, treating physicians were contacted to explore the reasons.

Result. A total of 282 medical records were reviewed (mean age 65.9 ± 10.0 years, A1C 7.5 ± 1.2 %, duration of diabetes 19.7 ± 10.4 years, mean eGFR 68.3 ± 24.1 mL/min/1.73 m², median UACR 151 (IQR 309) mg/g Cr, RAS inhibitors usage 80.1%). The SGLT2i prescription rate was 58.9% in 2023. Coronary artery disease, age ≥ 65 years, eGFR < 60 mL/min/1.73 m², optimal A1C and LDL control, use of thiazolidinedione were associated with SGLT2i prescription. Clinical inertia (31.9 %) was the most common reason for not prescribing SGLT2i in eligible patients, followed by cost concerns (18.1%) and frailty of patients (15.5%).

Conclusion. Prescribing SGLT2i to T2D patients with albuminuric DKD remains suboptimal among diabetologists due to clinical inertia, medication costs, and frailty. Our study underscores actions aimed at improving SGLT2i prescription rates in routine practice.

Key words: sodium-glucose cotransporter 2 inhibitors (SGLT2i), prescription rates, diabetic kidney disease, real-world data, Thai

INTRODUCTION

Over the last decade, sodium-glucose cotransporter 2 inhibitors (SGLT2i) which were initially developed as an anti-diabetic medication has transitioned to include organ protection in their action, particularly protection of the heart and kidney.¹ The results of landmark clinical trials demonstrated that various SGLT2is were associated with consistent reductions in kidney disease progression, as measured by a composite outcome comprised of progression to end-stage kidney disease (ESKD), doubling of creatinine, severity of albuminuria, and reductions in cardiovascular

events.²⁻⁹ The latest 2022 Kidney Disease Improving Global Outcomes (KDIGO) guideline for diabetes management in chronic kidney disease and 2024 KDIGO guideline for the evaluation and management of chronic kidney disease recommended SGLT2i as the preferred first-line pharmacologic therapy for patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) regardless of glycemic control based on high-quality evidences from randomized controlled trials.^{10,11} SGLT2i treatment should be initiated when the estimated glomerular filtration rate (eGFR) is ≥ 20 mL/min/1.73 m² and continued until renal replacement therapy. Nevertheless, in routine care,

multiple barriers hamper the adoption of guidelines as seen with earlier medications in cardiovascular diseases.¹²⁻¹⁴

While renin-angiotensin system (RAS) inhibitors, the standard of care in CKD patients for more than 3 decades, provide clear renoprotective effects by reducing systemic and intraglomerular pressures, the mechanisms in which SGLT2i improves renal hemodynamics are not completely understood. Evidences suggested that SGLT2i may act on many different cells inside the kidney and decrease energy consumption by proximal tubular cells.¹⁵ Interestingly, these benefits are observed in patients with or without diabetes and across a spectrum of renal function.¹⁶ Therefore, SGLT2i has been established as one of the four pillars of therapy in the management of CKD in people with T2D along with RAS inhibitors, finerenone, and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).¹⁷

Since its approval in Thailand in 2014, SGLT2i prescription rates have increased over time; however, estimates of SGLT2i use remain low in CKD people with diabetes due to various factors.¹⁸ When compared to the usage rate of RAS inhibitors which had been reported at about 40-60% in people with diabetes and CKD, it is estimated that the use of SGLT2i remains <20% in these population from previous reports all over the world.¹⁹⁻²² Moreover, there are disparities based on elderly, non-white race, gender, reimbursement system, and low-income eligible patients.²³⁻²⁵ Therefore, this study aimed to 1) explore prescription rates of SGLT2i in T2D with albuminuric diabetic kidney disease (DKD) 2) examine associated factors with receiving SGLT2i, and 3) assess clinician-perceived barriers to prescribing SGLT2i.

METHODOLOGY

The present study is a retrospective analysis of medical records obtained by 13 diabetologists at Vimut-Theptarin Hospital, a private diabetes center in Bangkok, Thailand. (Baseline characteristics of all diabetologists are shown in Supplement Data Table 1). Over 1,400 registered people with T2D follow-up regularly at our diabetes center in 2023. Inclusion criteria included T2D patients with albuminuric DKD who were regularly followed up at least 3 times in 2023. Patients ages <15 years or >80 years, patients with normoalbuminuria, eGFR <20 mL/min/1.73 m², patients with type 1 diabetes mellitus and other types of diabetes were excluded. Albuminuric DKD was defined as a diagnosis of T2D and CKD with increased albuminuria by urine albumin-creatinine ratio (UACR) ≥30 mg/g Cr. The severity of increased albuminuria was categorized into moderately increased albuminuria (UACR 30-300 mg/g Cr) and severely increased albuminuria (UACR >300 mg/g Cr). The CKD-EPI equations for eGFR were used to calculate glomerular filtrate rate from serum creatinine and eGFR was categorized per KDIGO guideline (Stage 1 – eGFR above 90 mL/min/1.73 m², Stage 2 – eGFR of 60 to 89 mL/min/1.73 m², stage 3a – eGFR of 45 to 59 mL/min/1.73 m², Stage 3b – eGFR of 30 to 44 mL/min/1.73 m², Stage 4 – eGFR of 16 to 29 mL/min/1.73 m²).²⁵ A subgroup analysis

was also conducted based on age group as more than 65 years, severity of albuminuria, and eGFR less than 60 mL/min/1.73 m². The clinical algorithm for the in-hospital use of SGLT2i and management of type 2 diabetes with diabetic kidney disease is presented in Supplement Data Figure 1.

Information on patient characteristics including demographics, comorbidities, prescribed medications, and laboratory data was retrieved from October to December 2023. Among albuminuric DKD patients who did not receive SGLT2i in 2023, the reason for not receiving SGLT2i was extracted from medical records. In cases of no documentation of non-prescribed SGLT2i, treating physicians were contacted for reasons. The proportion of SGLT2i prescriptions was re-assessed again at 6 and 12 months after the index visit in 2023 to see the trend of SGLT2i prescription. This study was approved by the Institutional Review Board (IRB) committee of Vimut-Theptarin Hospital (EC No.3-2024).

Statistical analyses

Continuous variables were summarized as mean ± standard deviation (SD) or median (interquartile range, IQR) while categorical variables were summarized using count and percentages. The *t*-test or analysis of variance was applied to compare differences in means among groups. The Chi-squared test was used to compare differences in percentages between groups. Variables analyzed in the univariate analysis included age ≥65 years, gender, A1C <7.0%, insulin usage, and eGFR based on previous literatures for associated factors in SGLT2i prescription.^{23,24} Factors achieving a *p*-value <0.1 were included in the multivariate models to determine associated factors with SGLT2i prescription among albuminuric DKD patients. A *p*-value of <0.05 was considered statistically significant. All analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 24 (IBM Corp., Armonk, NY, USA).

RESULT

A total of 1,196 medical records were screened in 2023 and 282 patients with albuminuric DKD were recruited based on inclusion criteria as shown in Figure 1. The details of studied patients (female 37.9%, mean age 65.9 ± 10.0 years, A1C 7.5 ± 1.2%, duration of diabetes 19.7 ± 10.4 years, mean eGFR 68.3 ± 24.1 mL/min/1.73 m², median UACR 151 (IQR 309) mg/g Cr, insulin usage 35.5%, RAS inhibitors usage 80.1%) are presented in Table 1.

The overall SGLT2i prescription rate in 2023 was 58.9% and was not changed during the study period as revealed in Figure 2. Only 12.8% of patients received RAS inhibitors, SGLT2i, and GLP-1 RAs as recommended in the KDIGO 2024 guideline. Elderly (ages of ≥65 years) and low A1C were associated with lower SGLT2i prescription rates as shown in Table 2. These factors also remained significant by multivariate analysis of associated factors in not receiving SGLT2i as shown in Table 3. Older ages of ≥65

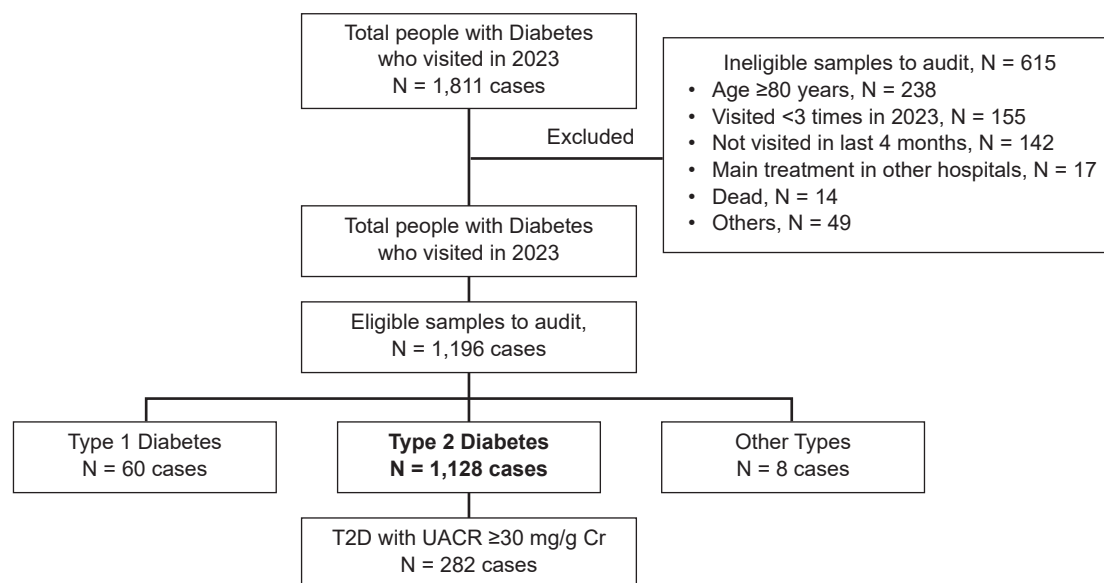


Figure 1. Flow of samples in SGLT2i study.

Table 1. Baseline characteristics of studied participants (N = 282 cases)

Variable	Mean (SD) / N (Percentage)
Female (%)	107 (37.9%)
Age (years)	65.9 (10.0)
<65	101 (35.8%)
65-74	136 (48.2%)
≥75	45 (16.0%)
Duration of diabetes (years)	19.7 (10.4)
BMI (kg/m²)	27.2 (5.1)
Active smoking (%)	23 (8.2%)
Hypertension (%)	217 (77.0%)
Coronary artery disease (%)	45 (16.0%)
Heart failure (%)	4 (1.4%)
Stroke (%)	18 (6.9%)
Peripheral artery disease (%)	29 (10.3%)
Diabetic retinopathy (%)	197 (69.9%)
A1C (%)	7.5 (1.2)
LDL (mg/dL)	79.4 (25.7)
Estimated GFR (mL/min/1.73 m²)	68.3 (24.1)
Stage 1 eGFR ≥90 mL/min/1.73 m ² (%)	68 (24.1%)
Stage 2 eGFR = 60-89 mL/min/1.73 m ² (%)	105 (37.2%)
Stage 3a eGFR = 45-59 mL/min/1.73 m ² (%)	58 (20.6%)
Stage 3b eGFR = 30-44 mL/min/1.73 m ² (%)	42 (14.9%)
Stage 4 eGFR = 15-29 mL/min/1.73 m ² (%)	9 (3.2%)
Albuminuria	
Moderately increased (30-300 mg/g Cr)	197 (69.9%)
Severely increased (>300 mg/g Cr)	85 (30.1%)
RAS inhibitors (%)	226 (80.1%)
Statin (%)	272 (96.5%)
Anti-diabetic medication (%)	
Metformin	229 (81.2%)
Sulfonylurea	103 (36.5%)
Thiazolidinedione	58 (20.6%)
DPP4 inhibitor	127 (45.0%)
GLP-1 RA	53 (18.8%)
Insulin	100 (35.5%)

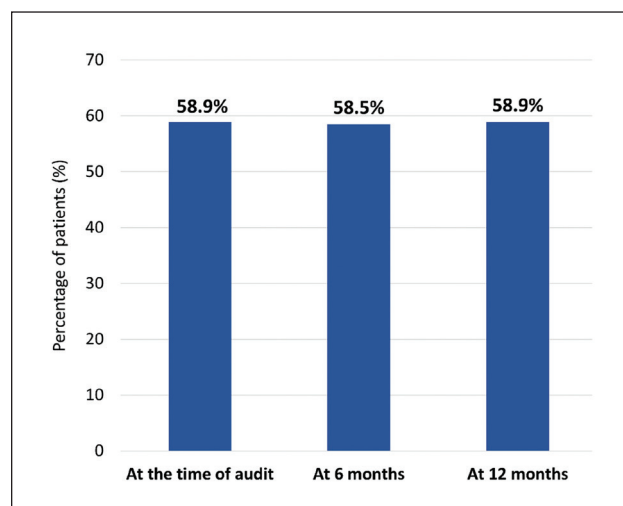


Figure 2. The overall SGLT2i prescription rate.

years and optimal A1C <7.0 % were less likely to receive SGLT2i (OR = 0.49; CI 95% 0.27-0.88, OR = 0.51; CI 95% 0.28-0.92, respectively). The details of SGLT2i prescription rates stratified by age group, eGFR categories, severity of albuminuria, and presence or absence of established atherosclerotic cardiovascular disease (ASCVD) were demonstrated in Figure 3. Notably, only 64.8% of DKD patients with established ASCVD received SGLT2i. Among patients not receiving SGLT2i, clinical inertia was the most common reason for not prescribing SGLT2i in eligible patients, followed by medication cost, frailty of patients with multiple comorbidities, and refusal from patients as revealed in Figure 4. Only 0.9% of non-prescribed SGLT2i patients were those with previous adverse events from SGLT2i.

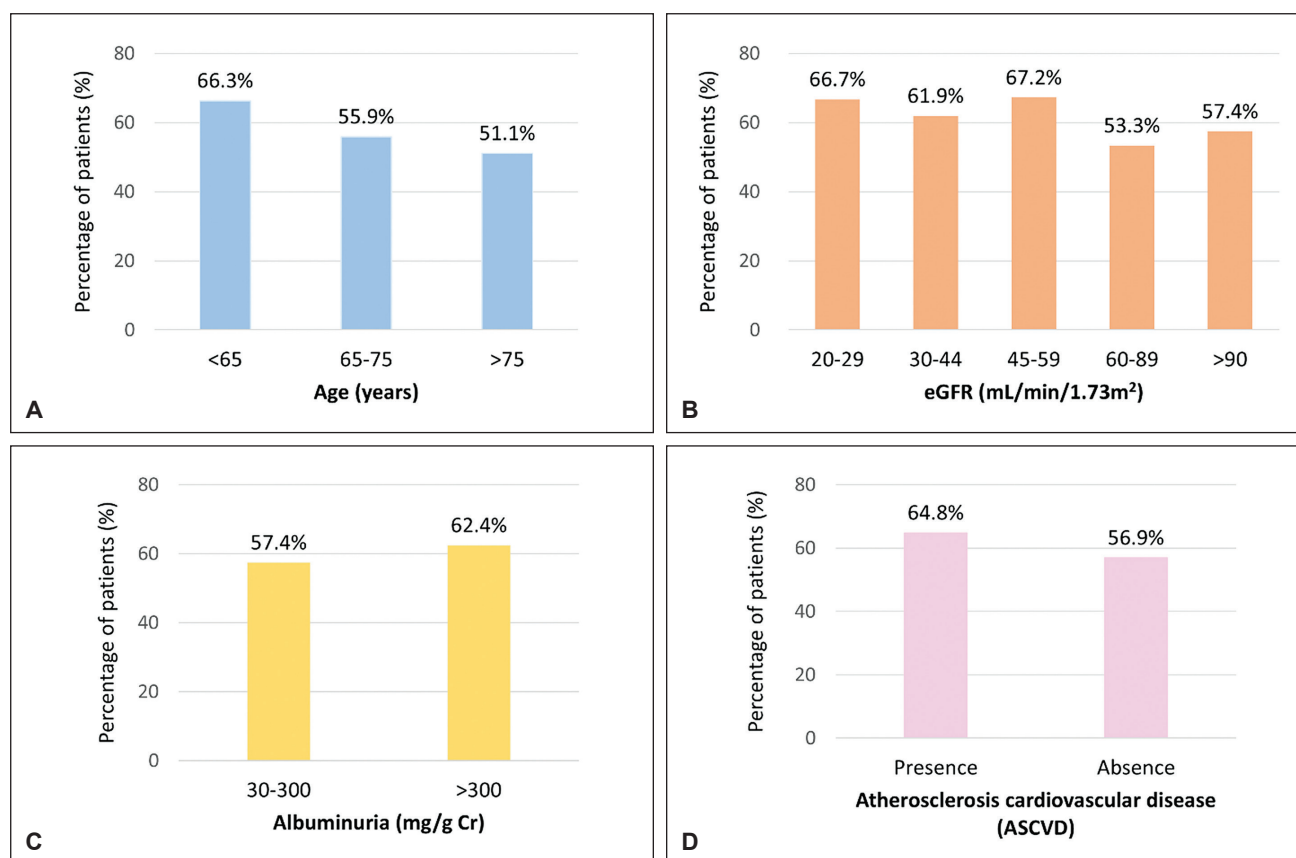


Figure 3. SGLT2i prescription rates stratified by (A) Age group; (B) eGFR categories; (C) Severity of albuminuria; (D) Presence or absence of established atherosclerotic cardiovascular disease (ASCVD).

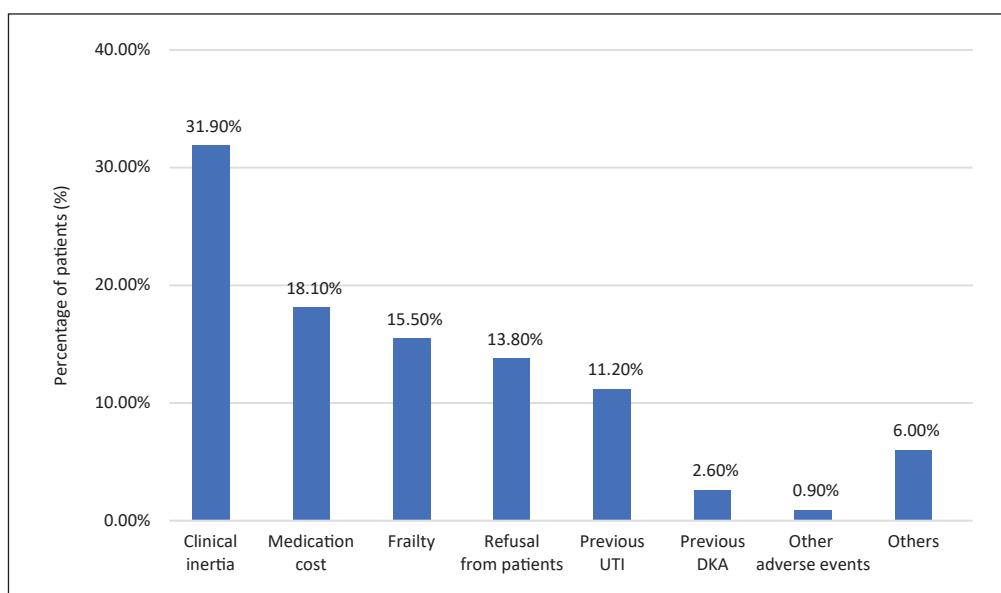


Figure 4. Reasons for not prescribing SGLT2i.

DISCUSSION

Our present study highlighted that prescribing SGLT2i to T2D patients with albuminuric DKD remained suboptimal among diabetologists in a private setting due to clinical inertia, medication costs and frailty.

SGLT2i use among DKD patients also showed a very low rate (10-20%) in diverse settings from primary care providers and specialties from previous reports all over the world.¹⁹⁻²⁵ These results underscore the need to develop interventions aimed at improving the SGLT2i prescription rates in routine practice. Even though prohibitive costs are a major issue, SGLT2i is subsidized by the government

Table 2. Comparison of patients who received SGLT2i (N = 166) and who did not receive SGLT2i (N = 116)

Variable	Patients who received SGLT2i Mean (SD) / N (Percentage)	Patients who did not receive SGLT2i Mean (SD) / N (Percentage)	p-value
Female	60 (36.1%)	47 (40.5%)	0.46 [†]
Age (years)	65.0 (10.1)	67.2 (9.6)	0.07 [‡]
<65 years	67 (40.4%)	34 (29.3%)	
65-74 years	76 (45.8%)	60 (51.7%)	
>75 years	23 (13.8%)	22 (19.0%)	
Duration of diabetes (years)	20.4 (10.3)	18.6 (10.4)	0.14 [‡]
BMI (kg/m²)	27.4 (5.2)	26.9 (4.9)	0.43 [‡]
Active smoking (%)	19 (11.4%)	4 (3.4%)	0.02 [†]
Hypertension (%)	123 (74.1%)	94 (81.0%)	0.18 [†]
Coronary artery disease (%)	33 (19.9%)	12 (10.3%)	0.03 [†]
Heart failure (%)	1 (0.6%)	3 (2.6%)	0.20 [†]
Stroke (%)	9 (5.4%)	9 (7.8%)	0.43 [†]
Peripheral artery disease (%)	15 (9.0%)	14 (12.1%)	0.41 [†]
Diabetic retinopathy (%)	116 (69.9%)	81 (69.8%)	0.99 [†]
A1C (%)	7.6 (1.2)	7.3 (1.2)	0.03 [‡]
LDL (mg/dL)	76.1 (22.9)	84.0 (28.8)	0.01 [‡]
Estimated GFR (mL/min/1.73 m²)	67.3 (24.6)	69.7 (23.4)	0.41 [‡]
Stage 1 eGFR ≥90 mL/min/1.73 m ² (%)	39 (23.5%)	29 (25.0%)	
Stage 2 eGFR = 60-89 mL/min/1.73 m ² (%)	56 (33.7%)	49 (42.2%)	
Stage 3a eGFR = 45-59 mL/min/1.73 m ² (%)	39 (23.5%)	19 (16.4%)	
Stage 3b eGFR = 30-44 mL/min/1.73 m ² (%)	26 (15.7%)	16 (13.8%)	
Stage 4 eGFR = 15-29 mL/min/1.73 m ² (%)	6 (3.6%)	3 (2.6%)	
Albuminuria (mg/g)			0.24 [‡]
Moderately increased (30-300 mg/g)	113 (68.1%)	84 (72.4%)	
Severely increased (>300 mg/g)	53 (31.9%)	32 (27.6%)	
RAS inhibitors (%)	139 (83.7%)	87 (75.0%)	0.07 [†]
Statin (%)	159 (95.7%)	113 (97.4%)	0.47 [†]
Anti-diabetic medication (%)			
Metformin	138 (83.1%)	91 (78.4%)	0.32 [†]
Sulfonylurea	52 (31.3%)	51 (44.0%)	0.03 [†]
Thiazolidinedione	40 (24.1%)	18 (15.5%)	0.08 [†]
DPP4 inhibitor	63 (38.0%)	64 (55.2%)	<0.01 [†]
GLP-1 RA	43 (25.9%)	10 (8.6%)	<0.01 [†]
Insulin	67 (40.4%)	33 (28.4%)	0.04 [†]

[†]t-test; [‡]Chi-squared test**Table 3.** Univariate and multivariate analysis of factors associated with receiving SGLT2i

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Female	1.20	0.74-1.96	0.46			
Age ≥65 years	0.61	0.37-1.02	0.06	0.49	0.27-0.88	0.02
Duration of diabetes	1.02	0.99-1.04	0.14			
BMI	1.02	0.97-1.07	0.43			
Active smoking	3.62	1.20-10.94	0.02	1.19	0.83-1.72	0.35
Hypertension	0.67	0.38-1.20	0.18			
Coronary artery disease	2.15	1.06-4.37	0.03	2.31	1.02-5.20	0.04
Heart failure	0.23	0.02-2.22	0.20			
Stroke	0.68	0.26-1.77	0.43			
Peripheral artery disease	0.72	0.34-1.56	0.41			
Diabetic retinopathy	1.00	0.60-1.68	0.99			
Optimal A1C <7.0 %	0.58	0.36-0.93	0.03	0.51	0.28-0.92	0.03
Optimal LDL <70 mg/dL	1.76	1.07-2.89	0.03	2.07	1.18-3.63	0.01
eGFR <60 mL/min/1.73 m²	1.53	0.94-2.52	0.09	1.87	1.06-3.31	0.03
Severely increased albuminuria	1.23	0.73-2.08	0.44			
RAS inhibitors	1.72	0.95-3.09	0.07	1.75	0.89-3.45	0.10
Statin	0.60	0.15-2.38	0.47			
Anti-diabetic medication						
Metformin	1.35	0.74-2.47	0.32			
Sulfonylurea	0.58	0.36-0.95	0.03	0.61	0.34-1.09	0.09
Thiazolidinedione	1.73	0.93-3.20	0.08	2.14	1.07-4.28	0.03
DPP4 inhibitor	0.50	0.31-0.81	<0.01	0.63	0.35-1.12	0.11
GLP-1 RA	3.71	1.78-7.73	<0.01	2.35	0.98-5.63	0.06
Insulin	1.70	1.02-2.83	0.04	0.73	0.37-1.43	0.36

or third-party payers in many countries. However, the adoption rate of SGLT2i by clinicians and patients was still low.

In this study, optimal A1C <7.0 % was an associated factor that was less likely to receive SGLT2i. The landmark trials supported the use of SGLT2i regardless of glycemic control in eligible patients, especially DKD patients.¹⁶ However, many practicing physicians considered this drug exclusively as anti-diabetic agent and limited its use in DKD patients due to its limited glucose-lowering effect despite its renoprotective action. Previous studies also suggested that clinical inertia, limited knowledge, and insufficient treatment review may have contributed to the low SGLT2i prescription rates.²⁶⁻²⁸ Collecting essential data regularly especially the use of organ protective drugs could be one of the possible solutions to leverage the use of SGLT2i among DKD patients.²⁹ Moreover, technology-assisted team-based care with regular feedback could reduce clinical inertia.³⁰ Management system with adding an alert to the electronic health record could significantly increase SGLT2i prescriptions as shown in a recent study in patients with heart failure.³¹

Based on our present study, an eGFR of <60 mL/min/1.73 m², underlying coronary artery disease, optimal LDL control, and use of thiazolidinedione were factors associated with SGLT2i prescription. Patients with DKD have a greater risk of cardiovascular complications, with DKD due to T2D becoming a major cause of ESKD requiring renal replacement therapy.³² It should be emphasized that most landmark clinical trials included participants with mainly an eGFR of 30–45 mL/min/1.73 m².²⁻⁹ In this study, optimal LDL control (LDL <70 mg/dL) and use of thiazolidinedione related with more prescription of SGLT2i could be explained by the features of patients in this study which required multiple drugs to control glucose, lipid and the higher proportion of established ASCVD.

Our study is similar to earlier studies in Caucasian populations in which older adults were less likely to be prescribed SGLT2i despite beneficial effects in reducing morbidity and mortality in comparison with younger patients with relatively preserved renal functions.²⁴ In the elderly population, the use of SGLT2i might be limited due to frailty, concern for side effects including euglycemic diabetic ketoacidosis, risk of genitourinary infection, and concerns for lower urinary tract infection. However, our present study highlighted clinical inertia among diabetologists as the most common barrier for low prescription rates. The safety and efficacy of SGLT2i in older adults is well established if a sick-day management plan as an integral part of the diabetes education program is enforced as a part of quality diabetes care.^{33,34} However, both direct costs from diabetes complications and indirect costs incurred through loss of productivity or earnings should be incorporated into decision-making when selecting medications to avoid clinical inertia.^{35,36}

Due to suboptimal prescription resulting mostly from clinical inertia amongst diabetologists of SGLT2i to T2D patients with albuminuric DKD, our study revealed that endocrinologists preferred use of SGLT2i more than internists. Further analysis of the characteristics of the diabetologists found that no significant difference in prescription rates of SGLT2i with regards to age, year of practice, subspecialties and number of cases per month as shown in Supplement Data Table 2.

There were limitations which influenced our results. First, the retrospective nature of the study and a single data source from a private diabetes center should be acknowledged. Second, we only included patients with albuminuric DKD with ages less than 80 years old from our inclusion criteria for annual audit diabetes care. Third, evaluated care gaps of SGLT2i prescription rates were done at one point in time. Some patients may have discontinued SGLT2i medications due to intolerance or adverse reactions from other hospitals before recruiting in this cohort. Fourth, this research included patients with at least 3 follow up visits per year, and may have excluded patients with well-controlled HbA1c who only come for visits 2 times per year based on ADA recommendations, and this might have potentially skewed the sample towards a slightly higher HbA1c. Finally, data on patient's socioeconomic status and healthcare payers were not available in this study.

CONCLUSION

Prescribing SGLT2i to T2D patients with albuminuric DKD remains suboptimal among diabetologists, with barriers including clinical inertia, medication costs, and concerns of adverse events and polypharmacy. Our findings emphasize that actions should be made to increase awareness and monitoring systems should be put in place to overcome barriers in prescribing SGLT2i among DKD patients.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

PC: Conceptualization, Software, Writing – original draft preparation; **YT:** Methodology, Writing – review and editing, Supervision; **WAC:** Formal analysis; **EW:** Investigation; **SB:** Data Curation, Project administration; **SN:** Resources, Visualization; **SK:** Writing – review and editing; **TH:** Writing – review and editing, Funding acquisition.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

The authors declared no conflict of interest.

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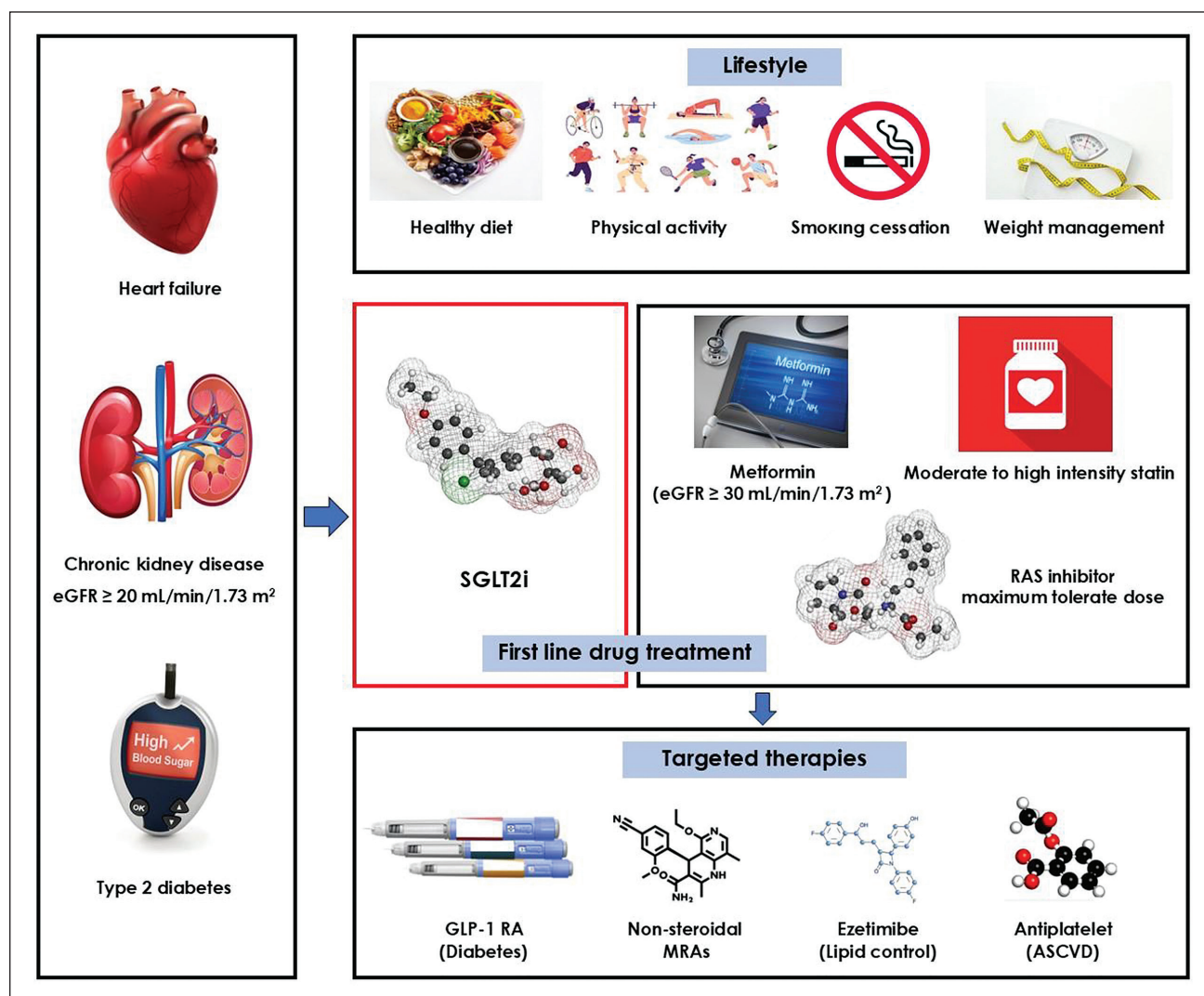
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SUPPLEMENT DATA



Supplement Data Figure 1. In hospital clinical algorithm for the use of SGLT2i and management of type 2 diabetes with diabetic kidney disease.

Adapted from KDIGO 2024 Clinical Practice Guideline for the evaluation and management of chronic kidney disease.

Supplement Data Table 1. Characteristics of all 13 diabetologists in Vimut-Theptarin Diabetes, Thyroid and Endocrine Center

Variable	Mean (SD) / N (Percentage)
Age (years)	58.2 (13.1)
Age group	
≤40 years	1 (7.7%)
41-50 years	3 (23.1%)
51-60 years	2 (15.4%)
61-70 years	5 (38.5%)
≥70 years	2 (15.4%)
Sex (Female)	4 (30.8%)
Subspecialties	
Endocrinologist	7 (53.8%)
Internist	6 (46.2%)
Years of practice in diabetology (%)	
≤5 years	0
6-10 years	2 (15.4%)
11-20 years	2 (15.4%)
21-30 years	2 (15.4%)
>30 years	7 (53.8%)
Estimated number of T2D patients per month (%)	
≤10 cases per month	2 (15.4%)
11-30 cases per month	2 (15.4%)
31-50 cases per month	3 (23.1%)
51-100 cases per month	4 (30.8%)
>100 cases per month	2 (15.4%)

Supplement Data Table 2. Comparison between diabetologists among high rate of SGLT2i prescription (rate ≥60%) and low rate of SGLT2i prescription (rate <60%)

Variable	Diabetologists with high rate of SGLT2i prescription (N = 8) Mean (SD) / N (Percentage)	Diabetologists with low rate of SGLT2i prescription (N = 5) Mean (SD) / N (Percentage)	P-value
Age (years)	57.4 (14.9)	59.4 (10.8)	0.79
Age group			0.83
≤40 years	1 (100%)	0	
41-50 years	2 (66.7%)	1 (33.3%)	
51-60 years	0	2 (100%)	
61-70 years	4 (80%)	1 (20%)	
≥70 years	1 (50%)	1 (50%)	
Sex (Female)	1 (25%)	3 (75%)	0.09
Subspecialties			0.07
Endocrinologist	6 (85.7%)	1 (14.3%)	
Internist	2 (33.3%)	4 (66.7%)	
Years of practice in diabetology			0.79
≤5 years	0	0	
6-10 years	2 (100%)	0	
11-20 years	1 (50%)	1 (50%)	
21-30 years	0	2 (100%)	
>30 years	5 (71.4%)	2 (28.6%)	
Estimated numbers of T2D patients			0.80
≤10 cases per month	2 (100%)	0	
11-30 cases per month	1 (50%)	1 (50%)	
31-50 cases per month	2 (66.7%)	1 (33.3%)	
51-100 cases per month	1 (25%)	3 (75%)	
>100 cases per month	2 (100%)	0	

Blood Glucose and Triglyceride Changes Following the Administration of Commercial Enteral Nutrition Solutions with Differing Glucose and Fat Contents

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Abstract

Objective. To clarify whether reducing the energy ratio of carbohydrates and increasing the ratio of fats contribute to suppressing blood glucose elevation not only under normal conditions, but also under the effects of glucocorticoids.

Methodology. Three test enteral nutrition solutions, differing in energy ratios and used in actual clinical settings, were given to rats: HINEX E-Gel (ST) with 20% fat and 64% carbohydrate content; HINEX E-Gel LC (LC) with 34% fat and 50% carbohydrate content; and HINEX Renute (RN) with 50% fat and 26% carbohydrate content. The time course data of plasma glucose, triglyceride, and insulin levels after a single oral administration of the test EN solution were obtained in normal rats (Experiment 1) and hyperglycemia model rats treated with dexamethasone (Experiment 2).

Result. In both normal and dexamethasone-induced hyperglycemic rats, plasma glucose levels were lower in the groups given RN than in the groups given ST. The differences in EN solutions did not significantly affect plasma triglyceride and insulin levels in both rat models.

Conclusion. This study suggested that the EN solution that is high in fat and low in carbohydrate suppressed the post-administration increase of blood glucose levels even in a state of steroid-induced hyperglycemia with insulin resistance.

Key words: enteral nutrition, blood glucose, steroid-induced hyperglycemia, surgical stress, triglycerides, plasma insulin

INTRODUCTION

In acute medical care, the control of blood glucose levels is considered important for patients with impaired glucose tolerance caused by underlying diseases or the use of steroids.^{1,2} Stress from surgical invasiveness or other causes increases plasma concentrations of corticosteroids, which then increase blood glucose levels.³⁻⁵ Particularly in brain surgery patients, a high blood glucose level is associated with a risk of poor neurological outcomes.⁶ The effect of nutrient administration on blood glucose levels is thus a matter of concern.

High-fat, low-carbohydrate enteral nutrition (EN) solutions slow the post-administration rise in the blood glucose level; therefore, they are presumed to be beneficial for patients in the acute stage of illness, particularly patients with serious internal medical diseases or stroke who require emergency medical care.² However, patients with such

conditions often demonstrate insulin resistance caused by upregulated stress hormones.⁷ Under these conditions, nutrients other than carbohydrates can serve as substrates for gluconeogenesis,⁸ making it difficult to assume that the nutritional composition of EN solutions will be directly reflected in blood glucose levels. A comprehensive understanding is required to determine how the composition of enteral nutrition impacts blood glucose levels in the context of steroid-induced hyperglycemia, whereas there is a lack of basic studies comparing EN solutions with different fat and carbohydrate compositions.

The aim of this study was to clarify whether reducing the energy ratio of carbohydrates and increasing the ratio of fats contribute to suppressing blood glucose elevation not only under normal conditions, but also under the effects of glucocorticoids. To confirm the basis for the benefits of high-fat, low-carbohydrate EN solutions in steroid-induced hyperglycemia, normal rats and dexamethasone-

Table 1. Main nutrient compositions of the test EN solutions

	ST (HINEX® E-Gel)	LC (HINEX® E-Gel LC)	RN (HINEX® Renute)
Calories (kcal/mL)	0.8	0.8	1
Protein (g/100 kcal)	4	4	6
Sugars (g/100 kcal)	15.4	11.8	5.9
Dietary fiber (g/100 kcal)	1.4	1.5	1.2
Fat (g/100 kcal)	2.2 (MCT 34%)	3.8 (MCT 34%)	5.6 (MCT 50%)
P:F:C	16:20:64	16:34:50	24:50:26
L-carnitine (mg/100 kcal)	0	25	40
Vitamin B1 (mg/100 kcal)	0.225	0.225	5

P:F:C indicates the energy ratio of protein, fat, and carbohydrates. The energy ratio of carbohydrates includes that of sugars and dietary fiber.

induced hyperglycemia model rats were used to compare the changes in blood glucose levels and other blood biochemistry indices after a single oral administration of three different EN solutions with varying proportions of carbohydrates and fats.

METHODOLOGY

This study was performed in accordance with the animal experiment guidelines of Otsuka Pharmaceutical Factory, Inc. (Tokushima, Japan) and conducted at its in-house research facilities. It was approved by the Otsuka Pharmaceutical Factory animal experiment review committee (approval numbers (Experiment 1): OPFCAE-2023219, (Experiment 2): OPFCAE-2023224).

Experiment 1

Experimental animals

Seven-week-old, male Wistar rats (The Jackson Laboratory Japan, Inc., Kanagawa, Japan) were used in the experiment. They were kept in an environment with room temperature of 23 ± 3 °C, humidity of $55 \pm 15\%$, and a 12-h light-dark cycle (light 07:00–19:00). An acclimation period of at least 7 days was set, and during the test period, they were given a standard chow (AIN-93G; Oriental Yeast Co., Ltd., Tokyo, Japan) and water ad libitum. Animals were fasted for 16 h before administration, and body weight and blood glucose levels were measured at 09:00 on the day of administration. Whole blood glucose levels were measured using a glucose analyzer, Glutest Mint (Sanwa Kagaku Kenkyusho Co., Ltd., Aichi, Japan), immediately after blood was collected prior to the administration of the test EN solution in each of the groups. Thirty-six rats were evenly assigned to three groups ($n = 12$ per group) through stratified randomization based on their pre-administration body weight and blood glucose levels. Each group of animals was then administered HINEX E-Gel (ST) (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), HINEX E-Gel LC (LC) (Otsuka Pharmaceutical Factory, Inc.), and HINEX Renute (RN) (Otsuka Pharmaceutical Factory, Inc.). The main nutrient compositions of the test EN solutions are shown in Table 1. The body weight of each group of rats used in Experiment 1 prior to the administration of each EN solution was 337.9 ± 12.6 g (ST group), 338.3 ± 11.1 g (LC group), and 337.7 ± 14.7 g (RN group). The doses

of ST, LC, and RN were 12.5 mL/kg, 12.5 mL/kg, and 10 mL/kg, respectively, so that the total calories of each of the test substances were the same in all three groups (10 kcal/kg). The animals in each group were given a single oral administration of the respective EN solution, and blood was collected at the prescribed times. In Experiment 1, there were no dropouts, and blood sampling was successfully conducted at all time points, resulting in no missing data. After the blood was collected, the animals were euthanized by cervical dislocation under isoflurane anesthesia.

Experiment 2

Adjustment of administered substances

Dexamethasone (Fujifilm Wako Pure Chemical Corp., Osaka, Japan) was dissolved to a concentration of 4 mg/mL using dimethyl sulfoxide (Fujifilm Wako Pure Chemical Corp.), and after sterilizing with a membrane filter (ADVANTEC DISMIC-28CP 0.20 μ m; Toyo Roshi Kaisha, Ltd., Tokyo, Japan), it was stored at -20 °C. Immediately before administration, a three-fold amount of physiological saline was added to the dexamethasone that had been returned to room temperature to make a 1 mg/mL dexamethasone solution. The prescribed solutions were administered subcutaneously once daily to the animals.

Experimental animals

Seven-week-old, male Wistar rats were used in the experiment. They were kept in an environment with room temperature of 23 ± 3 °C, humidity of $55 \pm 15\%$, and a 12-h light-dark cycle (light 07:00–19:00). An acclimation period of at least 7 days was set, and during the test period, they were given AIN-93G and water ad libitum. The dexamethasone solution was administered subcutaneously once a day from 4 days before the administration of the EN solution. After 16 h of fasting, body weight and blood glucose levels were measured at 09:00 on the day of administration of the EN solution. Whole blood glucose levels were measured using a glucose analyzer, Glutest Mint (Sanwa Kagaku Kenkyusho Co., Ltd.). Thirty-six rats were evenly assigned to three groups ($n = 12$ per group) through stratified randomization based on their pre-administration body weight and blood glucose levels. Each group of animals was then administered HINEX E-Gel (ST) (Otsuka Pharmaceutical Factory, Inc.), HINEX E-Gel LC (LC) (Otsuka Pharmaceutical Factory, Inc.), and HINEX Renute (RN) (Otsuka Pharmaceutical

Table 2. Results of nonparametric repeated measures ANOVA

Factor	df	Statistic	p-value
Experiment 1. Plasma glucose concentrations			
Between-subject factor: type of test EN solution	1.9346	28.3981	<0.0001
Within-subject factor: time from the administration of the EN solution	3.4528	244.7147	<0.0001
Interaction	5.9558	6.7364	<0.0001
Experiment 1. Plasma triglyceride concentrations			
Between-subject factor: type of test EN solution	1.9986	1.8981	0.1499
Within-subject factor: time from the administration of the EN solution	3.8829	89.6708	<0.0001
Interaction	7.1345	1.6804	0.1070
Experiment 1. Plasma insulin concentrations			
Between-subject factor: type of test EN solution	1.9302	1.5585	0.2112
Within-subject factor: time from the administration of the EN solution	3.1190	225.1788	<0.0001
Interaction	5.5430	0.5237	0.7769
Experiment 2. Plasma glucose concentrations			
Between-subject factor: type of test EN solution	1.8588	0.9174	0.3935
Within-subject factor: time from the administration of the EN solution	2.9440	26.3660	<0.0001
Interaction	5.2779	3.3618	0.0041
Experiment 2. Plasma triglyceride concentrations			
Between-subject factor: type of test EN solution	1.9672	0.2134	0.8042
Within-subject factor: time from the administration of the EN solution	2.2660	16.2958	<0.0001
Interaction	4.3450	1.1698	0.3218
Experiment 2. Plasma insulin concentrations			
Between-subject factor: type of test EN solution	1.9441	0.4323	0.6433
Within-subject factor: time from the administration of the EN solution	3.8731	41.9002	<0.0001
Interaction	6.9259	1.4160	0.1944

The approximate degrees of freedom (df), test statistics, and p-values were obtained from nonparametric repeated measures ANOVA.

Factory, Inc.). The main nutrient compositions of the test EN solutions are shown in Table 1. The body weight of each group of rats used in Experiment 2 prior to the administration of each EN solution was 236.8 ± 7.4 g (ST group), 243.0 ± 8.6 g (LC group), and 254.4 ± 9.9 g (RN group). A single oral administration of the respective test EN solution was given to each group, and blood was collected at the prescribed times after administration. In Experiment 2, there were no dropouts during either the dexamethasone administration period or the liquid diet administration trial. Blood sampling was successfully conducted at all time points, resulting in no missing data. After the blood was collected, the animals were euthanized by cervical dislocation under isoflurane anesthesia.

Blood analysis

Before (0 min) and 15, 30, 60, 90, and 120 min after administration of the test EN solution, 150 μ L of blood each time were collected from the subclavian vein without anesthesia. After treatment with heparin, the blood was centrifuged for 10 min at 3,000 g at 4 °C to obtain plasma. The plasma was frozen and stored in a freezer set at -80 °C until analysis. For all plasma specimens, the concentrations of blood glucose and triglycerides were measured by enzymatic methods using a Quick Auto Neo GLU-HK (Shino-Test Corp., Tokyo, Japan) and L-type Wako Triglyceride M (Fujifilm Wako Pure Chemical Corp., Osaka, Japan). Plasma insulin levels were determined by ELISA using a Morinaga Ultra Sensitive Rat Insulin ELISA Kit (Morinaga Institute of Biological Science, Inc., Kanagawa, Japan).

Statistical analysis

The results are shown as mean $\pm$ standard deviation values. In Experiments 1 and 2, the data for plasma glucose, triglyceride, and insulin concentrations in each group and at each time point were tested for normality using the Shapiro-Wilk test. Since the hypothesis of normality was rejected for all parameters, nonparametric repeated measures analysis of variance (ANOVA) was performed with type of test EN solution as a between-subject factor and time from the administration of the EN solution as the within-subject factor for each blood test item in the ST, LC, and RN groups. The approximate degrees of freedom, test statistics, and p-values obtained from the nonparametric repeated measures ANOVA test are shown in Table 2. Pairwise comparisons between each pair of groups at each time point were performed using the Brunner-Munzel test. The multiplicity of tests within and across time points was adjusted using the Benjamini-Hochberg method. The significance level was taken to be a two-tailed 5%. Statistical analysis and tests were performed using R software version 4.3.2. The nonparametric repeated measures ANOVA tests were performed using the nparLD package version 2.2 in R.

RESULT

Experiment 1

First, healthy normal rats were weighed, and an isocaloric dose of three different test EN solutions was administered orally based on their body weight ratios. Following the administration of each test EN solution, plasma glucose,

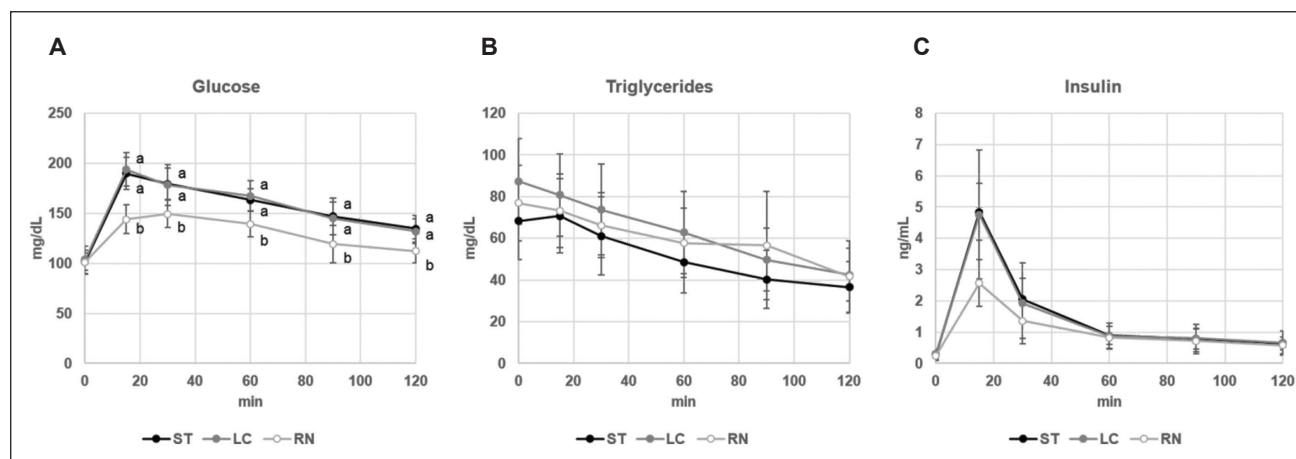


Figure 1. Changes in plasma glucose, triglyceride, and insulin levels in the normal rats.

Data are presented as mean $\pm$ standard deviation values. Different letters indicate a significant difference between groups (Brunner-Munzel test, $\alpha=0.05$).

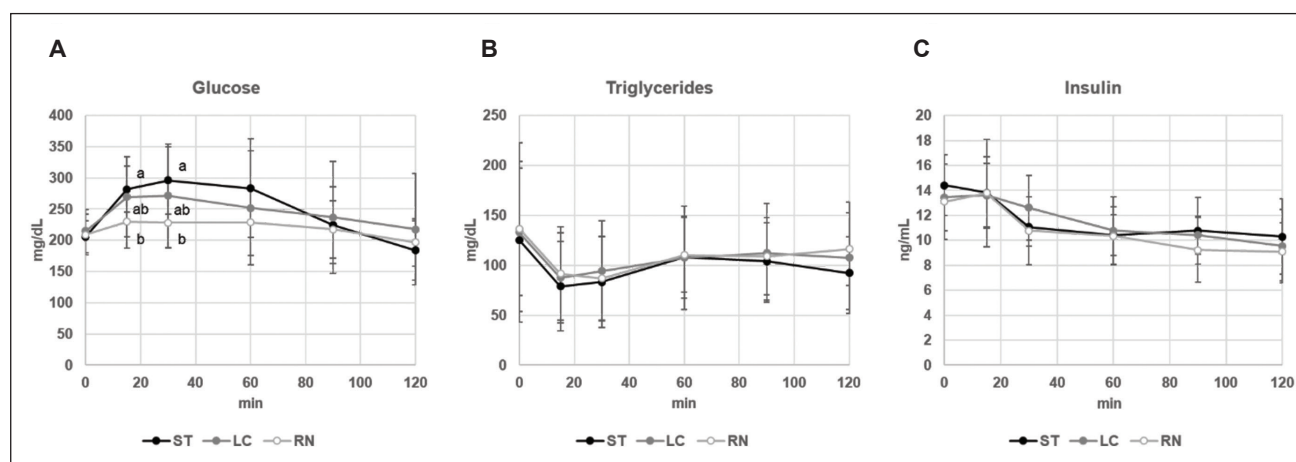


Figure 2. Changes in plasma glucose, triglyceride, and insulin levels in the dexamethasone-induced hyperglycemia model rats.

Data are presented as mean $\pm$ standard deviation values. Different letters indicate a significant difference between groups (Brunner-Munzel test, $\alpha=0.05$).

triglyceride, and insulin concentrations were measured through repeated blood sampling from the same individuals. The time courses of blood glucose levels in each group are shown in Figure 1A. The mean plasma glucose levels peaked at 15 min post-administration in the ST and LC groups, and at 30 min post-administration in the RN group, followed by a gradual decrease. The results of nonparametric repeated measures ANOVA showed main effects of both the type of test EN solution and time from administration of the EN solution, and interactions were significant. When compared at each time point, the blood glucose level was significantly lower in the RN group than in the two other groups at all time points more than 15 min after administration.

The plasma triglyceride levels in each group are shown in Figure 1B. The results of nonparametric repeated measures ANOVA showed that only the main effect of time from administration of the EN solution was significant; interactions were not significant.

The changes in plasma insulin levels in each group are shown in Figure 1C. The mean plasma insulin concentrations in all groups showed a transient increase. At the 15-min peak, the mean plasma insulin concentrations were lower in the RN group than in the ST and LC groups. The results of nonparametric repeated measures ANOVA showed that only the main effect of time from administration of the EN solution was significant; interactions were not significant.

Experiment 2

To elucidate whether reducing the energy ratio of carbohydrates contributes to the suppression of blood glucose elevation not only under normal conditions, but also under the influence of steroids, an investigation using hyperglycemic model rats induced by dexamethasone administration was conducted. The rats given dexamethasone at a dose of 1 mg/kg for 4 days showed lower body weights than the age-matched rats used in Experiment 1. In this experiment, there were no dropouts

during either the dexamethasone administration period or the liquid diet administration trial. Blood sampling was successfully conducted at all time points, resulting in no missing data. Following the administration of each test EN solution, plasma glucose, triglyceride, and insulin concentrations were measured in the same manner as in Experiment 1. The time course of blood glucose levels in each group at the time of administration of the test EN solution is shown in Figure 2A. Basal blood glucose levels were increased in rats administered dexamethasone. The results of nonparametric repeated measures ANOVA showed that the main effect of time from administration of the EN solution and interactions were significant. When compared at each time point, the blood glucose level after administration of the EN solution was significantly lower in the RN group than in the ST group at 15 and 30 min.

The plasma triglyceride level was increased in the animals that were given dexamethasone (Figure 2B). The results of nonparametric repeated measures ANOVA showed that only the main effect of time from administration of the EN solution was significant; interactions were not significant.

In the rats given dexamethasone, elevated plasma insulin levels were seen even before the administration of the EN solution. In contrast to normal rats, transient increases in plasma insulin concentrations following EN solution administration were not observed in dexamethasone-induced hyperglycemic model rats (Figure 2C). The results of nonparametric repeated measures ANOVA showed that only the main effect of time from the administration of the EN solution was significant; interactions were not significant.

DISCUSSION

It has been assumed that the energy ratio of enteral nutrition has an impact on post-administration blood glucose levels, but sufficient data have not been available on the fluctuations in blood glucose levels following administration of EN solutions with varying energy ratios of carbohydrates and fats in basic studies. In the experiment on normal rats, it was presumed that blood glucose levels after the administration of EN solution would be the lowest in the RN group, which received the EN solution with the lowest proportion of carbohydrate calories, but it was necessary to confirm whether the suppression of the rise in blood glucose levels was also exerted in the condition of steroid-induced hyperglycemia, with insulin resistance and elevated gluconeogenesis.

The results of blood tests in Experiment 1, as expected, showed that, in normal rats, the blood glucose levels were lower in the RN group than in the two other groups at all time points after administration of the EN solution. Although not significant, the mean plasma insulin levels were lower in the RN group than in the two other groups at 15 and 30 min after administration of the EN solution.

This was considered to reflect the more gradual increase in blood glucose levels observed in the RN group. In addition to having a low proportion of carbohydrates, the EN solution administered to the RN group also contains a high amount of vitamin B1 (Table 1), which is known to be involved in glucose metabolism and is reported to lower intracellular glucose levels under a glucose load.⁹ This suggests the possibility that the absorbed glucose was rapidly metabolized in cells.

For plasma triglyceride levels, despite the difference in fat contents of each EN solution, the main effect of type of test EN solution was not significant. The reasons for this may be that, although the EN solution administered to the RN group contains a large amount of fat, medium-chain triglycerides (MCTs) account for about 50% of its triglycerides. Both long-chain triglycerides (LCTs) and MCT are absorbed into intestinal epithelial cells and converted into fatty acids. However, unlike long-chain fatty acids (LCFAs), which are re-esterified to triglycerides, incorporated into chylomicrons, and secreted into the lymphatic system, medium-chain fatty acids (MCFAs) are directly secreted into the bloodstream as free fatty acids.^{10,11} MCFAs are also known to be more rapidly metabolized than LCFAs; whereas LCFAs require a membrane transporter to pass through the plasma membrane and a carnitine shuttle to traverse the mitochondrial membrane,^{12,13} MCFAs are directly transported to the mitochondrial intermembrane space without these systems.^{14,15} In addition, the amount of L-carnitine, which is known to promote the oxidative metabolism of long-chain fatty acids,¹⁶ was also highest in the EN solution administered to the RN group. These compositional differences were considered to contribute to the lack of significant differences in plasma triglyceride concentrations observed after administration.

In a previous study, we reproduced a condition of steroid-induced hyperglycemia with insulin resistance by administering dexamethasone subcutaneously at a dose of 1 mg/kg/day for 4 days to normal rats (data not shown). Dexamethasone is a synthetic glucocorticoid widely used in clinical settings as an anti-inflammatory drug,¹⁷ but dexamethasone and such glucocorticoids activate glucocorticoid receptors and enhance gluconeogenesis,^{18,19} and they are also known to induce whole-body insulin resistance.²⁰

In the blood test results in Experiment 2, the blood glucose levels 15 and 30 min after the administration of the EN solution were significantly lower in the RN group than in the ST groups, even in the dexamethasone-induced hyperglycemia model rats. Although no significant difference was observed, from 30 to 60 min after administration of the EN solution, the blood glucose levels in the LC group showed intermediate characteristics between those of the ST and RN groups, which were considered to reflect the carbohydrate content of the EN solution. For the plasma insulin levels, the main effect of the type of test EN solution was not significant, and there

was confirmed to be no transient, conspicuous rise in the insulin level, as was seen when the EN solutions were administered to normal rats. A possible reason was that these model rats were in a state of insulin resistance that showed higher blood glucose and higher insulin levels than normal rats even when fasting, resulting in saturation or malfunction of insulin secretion by pancreatic islet β -cells. Therefore, the lower blood glucose level in the RN group than in the ST groups was not due to insulin, but rather was thought to be due to the specific nutrient composition of the EN solution, including the low proportion of carbohydrate calories. The plasma triglyceride levels, as in Experiment 1, showed no significant difference by type of test EN solution, and the nutrient composition rich in MCTs and L-carnitine was thought to be able to promote the rapid absorption and metabolism of lipids even in a state of steroid-induced hyperglycemia.

In order to simulate clinical conditions, the test EN solutions used in this study were commercially available products. Therefore, not only the carbohydrates and fat, but also the composition of other nutrients in the test enteral nutrition did not match exactly. There was a possibility that in a state of enhanced gluconeogenesis, the different proportions of protein in the test EN solution affected the blood glucose levels. However, in Experiment 2, the blood glucose levels in the RN group, which received the EN solution with a high proportion of protein calories, were lower. From this, it was judged that the effects of the protein composition on blood glucose levels were negligible compared with those of the carbohydrate composition.

CONCLUSION

The results of this study showed that administration of an EN solution containing 50% fat and 26% carbohydrates decreased the post-administration increase in blood glucose levels compared with the product with 20% fat and 64% carbohydrate content, even in dexamethasone-induced hyperglycemic rats. This suggested that in states of steroid-induced hyperglycemia with insulin resistance, reducing the percentage of carbohydrates and increasing that of fats in EN solutions may be beneficial for proper blood glucose management.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

HK: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft preparation; **SM:** Formal analysis, Writing – original draft preparation, Writing – review and editing, Supervision; **IY:** Formal analysis, Writing – original draft preparation, Supervision, Project administration

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

HK, SM, IY are employees of Otsuka Pharmaceutical Factory, Inc.

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Overweight and Obesity and Multimorbidity in Community-Living Older Persons in the Philippines

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Abstract

Background. Overweight and obesity, as well as the coexistence of multimorbidity, have been recognized as global health challenges. However, less is known about the prevalence of obesity and multimorbidity among older people in the Philippines. This study sought to determine the prevalence of obesity and multimorbidity among community-living older people.

Methodology. A cross-sectional analysis of older persons ≥ 60 years from the Focused Intervention for Frail Older Adults Research and Development Program (FITforFrail). Height and weight were measured by body mass index as underweight, $< 18.5 \text{ kg/m}^2$; normal, $18.5\text{--}22.9 \text{ kg/m}^2$; overweight, $23\text{--}27.5 \text{ kg/m}^2$; and obese, $\geq 27.5 \text{ kg/m}^2$. Multimorbidity was defined as the presence of two or more chronic diseases, assessed as a self-reported physician's diagnosis.

Results. The prevalence of obesity was 15.4%, which was significantly more common among women ($p < 0.013$) and nonsmokers ($p < 0.006$). Multimorbidity, including overweight/obesity, was reported by 77.9% of older persons, and among older persons with overweight and obesity, multimorbidity was present in 76.5%. A higher number of chronic diseases were reported by older persons who were overweight and obese ($p < 0.006$). Significantly more overweight and obese older women reported having multimorbidity ($p < 0.049$) compared to older men. Hypertension, hyperlipidemia, musculoskeletal disorders and hyperuricemia were the most commonly reported chronic diseases among older persons with overweight and obesity.

Conclusion. The results of this study highlight the importance of overweight/obesity as a determinant of multimorbidity. Future research should look into gender differences in risk factors and multimorbidity patterns.

Key words: obesity, multimorbidity, older persons

INTRODUCTION

The prevalence of overweight and obesity has increased globally, prompting the World Health Organization (WHO) to declare 'globesity' as an escalating global health epidemic.¹ Thirty-eight percent of the world's population was reported to be overweight and 14% obese in 2020, which is projected to increase to 46% and 20%, respectively, in 2030.² A Global Burden of Disease Study on death and disability due to obesity reported an increase in death from 2.2 million in 1990 to 4.7 million in 2017 and disability-adjusted life years from 65 million in 1990 to 147.7 million in 2017.³ Obesity is significantly associated with premature death, increasing as the degree of obesity increases.⁴ While differences exist, obesity arises in both high and low to middle-income countries across age, social class, sex,

race and ethnicity.² Obesity speeds up the aging process, worsens the age-associated loss of lean body mass, impairs physical functioning and quality of life and increases the likelihood of hospitalization and length of hospital stay.⁵⁻⁷

Overweight and obesity are not merely defined as excessive gain in body weight against height. It is also related to excessive adiposity, leading to metabolic consequences such as hypertension, heart disease, diabetes, dyslipidemia, cardiovascular disease, nonalcoholic fatty liver disease, as well as osteoarthritis, respiratory disease, dementia, sleep apnea and some forms of cancer.⁸ It is significantly associated with multimorbidity, the presence of two or more chronic health conditions in the same individual, and increases with each degree of severity of obesity.⁸

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As the prevalence of obesity is increasing, so does the proportion of older persons. In 2023, the 60 years and older comprised 14.2% of the total population worldwide.⁹ This is projected to increase to 16.6% by 2030 and 22% by 2050, 80% of which will come from low to middle-income countries.^{10,11} In the Philippines, this age group, which comprised 8.8% of the population in 2023, is projected to increase to 10.5% by 2030 and 15.4% by 2050.⁹ Research on older persons in the Philippines is limited. Because of this looming public health crisis, an understanding of the epidemiology of overweight/obesity is critical for making informed healthcare policy planning for appropriate prevention and intervention. This study, therefore, aims to determine the prevalence of overweight and obesity among community-living older persons in the Philippines.

METHODOLOGY

The data for this study was obtained from the FITforFrail study, full details of which have been described previously.¹² Briefly, this was a cross-sectional study to determine community-living older adults' health and frailty status. Four communities from 4 provinces of 4 regions in the Philippines, namely, the National Capital Region, Cebu, Davao and Los Baños, were included in the study. Field listing was conducted, and records from the Office of Senior Citizens Affairs were obtained to ensure a wide coverage of older persons. The sample size was calculated based on the proportion of older persons in the four regions and over-sampled to account for nonresponse. A random selection of participants from each community, 60 years and older, who could communicate and respond to questions were invited to participate in the study. All the participants were informed of the purpose and procedures of the study upon their recruitment. The total sample included 405 of the eligible 424 participants. Complete information was obtained from 357 participants. No difference was seen regarding age, sex, and marital status between those with and without complete information. The University of the Philippines Manila Research Ethics Board has approved this study.

Data collection

This study used the Comprehensive Geriatric Assessment (CGA), a multidisciplinary evaluation program that uncovers, describes, and explains multiple problems of older persons while identifying their needs, resources, and strengths.¹³ The CGA was applied to create a coordinated care plan focusing on interventions for identified issues. Translation, pretesting, and pilot testing of the CGA were conducted in the language spoken by the participants in each identified community.

Study measures

Trained researchers collected data through face-to-face interviews and physical examinations in a designated health center and the participants' homes for those unable to travel. Sociodemographic information collected included

age, sex, civil status, living arrangement, location, and education. Lifestyle factors consisted of smoking, categorized as nonsmoker and smoker (previous and current); alcohol consumption, non-drinker and drinker (previous and current) and physical activity. Physical activity was measured by asking the participants if they exercised or did household chores. This was defined as exercising or doing household chores for at least 150 minutes per week. Basic activities of daily living assessed the absence or presence of difficulty in feeding, bathing, dressing up, transferring, toileting, and incontinence. Participants were considered dependent when they reported difficulty performing one or more tasks. Consultation with a health-care provider (doctor, dentist, nurse, community health worker, allied health professional, traditional healer) in the past year was also elicited.

Multimorbidity was defined as the presence of 2 or more chronic conditions or related health problems. The presence of a chronic condition was determined by self-report. Participants were asked if a doctor had ever diagnosed them with a chronic disease. This was then classified based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision published by the WHO. Body mass index (BMI) was calculated from weight and height measurements and classified following the proposed classification for Asian adults by the WHO as underweight, <18.5 kg/m²; normal, 18.5-22.9 kg/m²; overweight, 23-27.5 kg/m²; and obese, ≥27.5 kg/m².¹⁴

Statistical analyses

All analyses were performed using STATA (version 14). The distributional characteristic of continuous variables was examined using the P-P plot. Descriptive analyses were performed and expressed as means ± SD or median (IQR) and percentages with 95% sCI. Differences between continuous variables were examined using the Student's T-test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables. Differences between proportions were assessed using the Chi-square test or Fischer exact test. BMI was analyzed as a dichotomous variable, obesity (overweight and obese) and without obesity (underweight and normal) after analyses showed no differences among the independent variables, except for sex and smoking history or using the four categories.

RESULTS

The participants' age ranged from 60 to 91 years, median (IQR), 68 (64,75); 64.1% were females, and 52.4% were married. According to the WHO BMI classification, 14% were underweight, 34.2% normal, 36.4% overweight, and 15.4% obese. Table 1 shows the demographic characteristics according to BMI categories (overweight was merged with obese; underweight with normal BMI). Obesity was the most common among the 60-69 age group, which decreased with increasing age group. There were no differences

Table 1. Sociodemographic and selected characteristics of the sample population and BMI

		Total % (95%CI)		With Obesity ^a N=185, % (95%CI)		Without Obesity ^b N=172, % (95%CI)	p-value
Age [Median (IQR)]							0.667
60-69	214	59.9 (54.7, 64.9)	115	62.2 (55.0, 68.9)	99	57.6 (50.1, 64.7)	
70-79	105	29.4 (24.9, 34.3)	51	27.6 (21.2, 34.0)	54	31.4 (24.9, 38.7)	
80+	38	10.6 (7.8, 14.2)	19	10.3 (6.7, 15.6)	19	11.0 (7.2, 16.6)	
Sex							0.013
Women	229	64.1 (59.0, 68.9)	130	70.3 (63.4, 76.4)	99	57.7 (50.2, 64.8)	
Men	128	35.9 (31.1, 41.0)	55	29.7 (23.6, 36.6)	73	42.3 (35.2, 49.8)	
Civil status							0.538
Single	170	47.6 (42.5, 52.8)	91	49.2 (42, 56.4)	79	45.9 (38.6, 53.4)	
Married	187	52.4 (47.2, 57.5)	94	50.8 (43.7, 57.9)	93	54.1 (46.6, 61.4)	
Education							0.762
Primary	128	35.9 (31.1, 41.0)	63	34.1 (29.3, 43.0)	65	37.8 (30.9, 45.2)	
High school	111	31.1 (26.5, 36.1)	59	31.9 (25.6, 38.9)	52	30.2 (23.8, 37.4)	
College	118	33.1 (28.4, 38.1)	63	34.1 (27.7, 41.2)	55	32.0 (25.5, 39.2)	
Living arrangement							0.162
Alone	17	4.8 (2.6, 7.0)	6	3.2 (1.5, 6.8)	11	6.4 (3.6, 11.1)	
With others		95.2 (92.5, 97.0)		96.8 (93.2, 98.5)		93.6 (88.9, 96.4)	
Smoking history							0.006
Never smoker	207	58.0 (52.9, 63.1)	120	64.9 (57.8, 71.4)	87	50.6 (43.2, 58.0)	
Smoker	150	42.0 (36.9, 47.1)	65	35.1 (28.6, 42.2)	85	49.4 (42.0, 56.8)	
Alcohol consumption							0.866
Non drinker	149	41.7 (36.6, 46.8)	78	42.2 (35.3, 49.4)	71	41.3 (34.2, 48.8)	
Drinker	208	58.3 (53.2, 63.4)	107	57.8 (50.6, 64.7)	101	58.7 (51.2, 65.8)	
Physical activity							0.254
Yes	310	86.8 (83.3, 90.3)	157	84.6 (79.4, 89.8)	153	89.1 (83.6, 92.9)	
No	47	13.2 (9.7, 16.7)	28	15.4 (10.2, 20.6)	19	10.9 (7.1, 16.4)	
Self-rated health							0.800
Poor to fair	210	58.8 (53.7, 63.9)	110	59.5 (52.3, 66.3)	100	58.1 (50.6, 65.4)	
Good to excellent	147	41.2 (36.1, 46.3)	75	40.5 (33.7, 47.7)	72	41.9 (34.8, 49.4)	
Health consultation							0.082
Yes	299	83.8 (80.0, 87.6)	161	87.0 (81.4, 91.1)	138	80.2 (73.6, 85.5)	
No	58	16.2 (12.4, 20.0)	24	13.0 (8.9, 18.6)	34	19.8 (14.5, 26.4)	
^a overweight and obese							
^b underweight and normal BMI							

^a overweight and obese^b underweight and normal BMI

between older persons with and without obesity with regard to civil status, education, physical activity, ADL, alcohol consumption, self-rated health, and those seeking health consultation. Older persons with obesity were more commonly women, $p < 0.013$, and never smokers, $p < 0.012$.

Chronic diseases ranged from 0-12, median (IQR) of 3 (2,6). The prevalence of multimorbidity, including obesity, was 77.9%, while multimorbidity among older persons with obesity was 76.5%. There was no difference in multimorbidity between older persons with obesity (80.0%) and those without obesity (72.7%), with a p -value of 0.103. There were significantly more obese older women with multimorbidity compared to men (67.6% versus 32.4%, $p = 0.049$) (Table 2). Older persons with obesity reported a significantly higher number of chronic diseases than those without obesity ($p = 0.006$). No differences in multimorbidity were seen between older persons with and without obesity with regard to age, education, smoking, alcohol consumption, self-rated health, physical activity and health consultation.

Hypertension was the most commonly reported chronic disease by older persons with obesity ($p = 0.003$) (Table 3). Other chronic diseases more commonly reported were

hyperlipidemia ($p = 0.004$), musculoskeletal disorders ($p = 0.048$) and hyperuricemia ($p = 0.008$) (Table 3). In 51.4% of the participants, the most common multimorbidity in dyads reported by older persons with obesity was hypertension and visual impairment (95%CI, 43.4, 59.3) (Table 4). This was followed by hypertension and hyperlipidemia, visual impairment and hyperlipidemia and visual impairment and musculoskeletal disorders (24.3) (95%CI, 18.1, 31.8). The most common triadic combination consisted of hypertension, hyperlipidemia and visual impairment, as seen in 17.2% of the participants (95%CI, 13.2, 22.1).

DISCUSSION

This study investigated the prevalence of obesity in a sample of community-living older persons. The literature is replete with reports on the prevalence of obesity in older persons. However, the results vary due to age cut-off, data collection methods, data sources and settings, ascertainment and cut-off levels of obesity. In this study, the prevalence of obesity based on the WHO BMI for Asian populations category for obesity ($\geq 27.5 \text{ kg/m}^2$) was 15.4%. Using the same BMI threshold for obesity, other studies on older persons reveal a lower prevalence of 12.8% from the Singapore Chinese health study and an even lower 4.4% from Thailand's

Table 2. Multimorbidity of the sample population according to obesity

	Multimorbidity				P value
	n	With obesity ^a N=148, % (95%CI)	n	Without obesity ^b N=125, % (95%CI)	
Age [Median (IQR)]					0.873
60-69	90	60.8 (52.8, 68.3)	74	59.2 (50.4, 67.2)	
70-79	41	27.7 (21.1, 35.4)	38	30.4 (23.0, 38.9)	
80+	17	11.5 (7.3, 17.6)	13	10.4 (6.2, 17.0)	
Sex					0.049
Women	100	67.6 (59.7, 74.6)	70	56.0 (47.2, 64.4)	
Men	48	32.4 (25.4, 40.3)	55	44.0 (35.6, 52.8)	
Civil status					0.649
Single	68	45.9 (38.1, 53.9)	54	43.2 (34.8, 52.0)	
Married	80	54.1 (46.1, 61.9)	71	56.8 (48.0, 65.2)	
Education					0.785
Primary	43	29.1 (22.4, 36.9)	41	32.8 (25.2, 41.4)	
High school	51	34.5 (27.3, 42.5)	42	33.6 (25.9, 42.3)	
College	54	36.5 (29.2, 44.5)	42	33.6 (25.9, 42.3)	
Living arrangement					0.243
Alone	5	3.4 (1.5, 7.7)	8	6.4 (3.3, 12.1)	
With others	143	96.6 (94.7, 98.5)	117	93.6 (87.9, 97.9)	
Smoking history					0.071
No	93	62.8 (54.8, 70.2)	65	52.0 (43.1, 60.6)	
Yes	55	37.2 (29.4, 45.0)	60	48.0 (39.4, 56.7)	
Alcohol history					0.872
No	63	42.6 (34.9, 50.6)	52	41.6 (33.3, 50.4)	
Yes	85	57.4 (49.4, 65.1)	73	58.4 (49.5, 66.7)	
Physical activity					0.373
Yes	126	85.1 (78.5, 90.0)	111	88.8 (82.1, 93.2)	
No	22	14.9 (10.0, 20.6)	14	11.2 (6.8, 17.9)	
Self-rated health					0.859
Poor to fair	88	59.5 (51.6, 67.4)	73	58.4 (49.6, 66.7)	
Good to excellent	60	40.5 (32.9, 48.6)	52	41.6 (33.3, 50.4)	
Health consultation					0.283
Yes	134	90.5 (84.7, 95.2)	108	86.4 (79.3, 91.3)	
No	14	9.5 (5.8, 15.3)	17	13.6 (8.7, 20.7)	
No. of chronic diseases [median (IQR)]		3 (1, 5)		4 (2, 6)	0.006

^a overweight and obese^b underweight and normal BMI**Table 3.** Most commonly reported chronic diseases by obesity status

	n	Obese ^a % (95%CI)	n	Non-obese ^b % (95%CI)	p-value
Hypertension	121	65.1 (58.3, 71.9)	86	50.0 (42.6, 57.4)	0.003
Visual impairment^c	106	57.1 (50.1, 64.2)	81	47.2 (39.8, 54.5)	0.194
Hyperlipidemia	55	30.1 (23.6, 36.6)	32	19.3 (13.5, 25.1)	0.014
Diabetes	35	20.1 (14.4, 25.8)	33	19.9 (14.0, 25.7)	0.947
Musculoskeletal disorders^d	42	22.7 (17.3, 29.3)	25	15.3 (10.0, 20.6)	0.048
Hyperuricemia^e	37	20.6 (14.9, 26.3)	17	10.8 (6.3, 15.3)	0.008
Chronic lung disease^f	15	9.0 (5.0, 12.9)	14	9.0 (4.9, 13.2)	0.991
Cerebrovascular disease	11	6.8 (3.4, 10.3)	17	10.8 (6.3, 15.3)	0.167
Coronary heart disease	8	5.2 (2.2, 8.3)	13	8.5 (4.5, 12.5)	0.194
Tuberculosis	6	4.2 (1.5, 6.9)	12	7.9 (4.0, 11.8)	0.124

^a overweight and obese^b underweight and normal BMI^c includes cataracts, error of refraction, presbyopia, and glaucoma^d osteoporosis, arthritis and low back pain^e includes gout^f chronic bronchitis and asthma

Table 4. Multimorbidity patterns among older persons with obesity

	n	% (95%CI)
Dyads		
Hypertension + visual impairment	76	41.3 (34.2, 48.3)
Hypertension + hyperlipidemia	42	23.3 (17.3, 29.3)
Hyperlipidemia + visual impairment	39	21.7 (15.8, 27.5)
Visual impairment + musculoskeletal disorders	31	17.4 (12.1, 22.8)
Hypertension + musculoskeletal disorders	31	17.4 (12.1, 22.8)
Hyperlipidemia + hyperuricemia	30	16.9 (11.6, 22.2)
Hypertension + hyperuricemia	29	16.4 (11.1, 21.6)
Hypertension + diabetes mellitus	27	15.3 (10.2, 20.4)
Visual impairment + hyperuricemia	27	15.3 (10.2, 20.4)
Visual impairment + diabetes mellitus	25	14.3 (9.3, 19.2)
Hyperlipidemia + musculoskeletal disorders	17	10.0 (5.8, 14.2)
Hypertension + chronic lung disease	15	9.0 (5.0, 12.9)
Hypertension + cerebrovascular disease	11	6.8 (3.4, 10.3)
Visual impairment + chronic lung disease	10	6.3 (3.0, 9.7)
Triads		
Hypertension + hyperlipidemia + visual impairment	29	16.4 (11.1, 21.6)
Hypertension + musculoskeletal disorder + visual impairment	25	14.3 (9.3, 19.2)
Hypertension + hyperlipidemia + hyperuricemia	21	12.1 (7.6, 16.7)
Hypertension + hyperuricemia + visual impairment	21	12.1 (7.6, 16.7)
Hyperlipidemia + hyperuricemia + visual impairment	21	12.1 (7.6, 16.7)
Hypertension + diabetes + visual impairment	20	10.6 (7.5, 14.9)
Hypertension + visual impairment + hyperuricemia	20	10.6 (7.5, 14.9)
Hypertension + hyperlipidemia + diabetes	17	10.0 (5.8, 14.2)
Hyperlipidemia + diabetes + visual impairment	16	9.5 (5.4, 13.6)

national health examination survey.^{15,16} Meanwhile, the Malaysia Aging and Retirement Survey reported a higher prevalence of 30.8%.¹⁷ A previous local study, the University of the Philippines Wellness Initiative for Seniors and Elders, reported a prevalence of 28.4%.¹⁸ This study, however, included participants who were 55 years and older and classified obesity at a BMI of ≥ 25 kg/m².¹⁸

In this study, the prevalence of multimorbidity, including obesity, was 77.9%, and among older persons with obesity, 76.5%. These results are much higher than the 51% reported from a recent systematic review on the global and regional prevalence of older persons in community settings.¹⁹ An earlier systematic review on the prevalence of multimorbidity among older persons ranged from 55% to 98%.²⁰ In another systematic review of multimorbidity among community-living older persons from high- and low-middle-income countries, the prevalence ranged from 35.7% to 100%.²¹

There was no difference in the prevalence of multimorbidity between older persons with and without obesity. However, significantly more chronic diseases were reported by older persons with obesity in this study. The comparable prevalence of multimorbidity between older persons with and without obesity supports previous research that age is a significant risk factor for multimorbidity.^{20,22,23} Increasing age provides more room for chronic diseases to accumulate. Aging brings about a decline in organ and system functions, causing multiple hormonal dysregulation and proinflammatory states, increasing older persons' susceptibility to diseases and resulting in multimorbidity.^{23,24} Moreover, in a study to

determine the contribution of the hallmarks of aging, five of the nine hallmarks, namely, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication, contributed to the development of multimorbidity singly and jointly.²⁵ The higher number of chronic diseases among older persons with obesity is in line with previous research.^{9,26} Obesity plays a vital role in the pathophysiology of multimorbidity through the release of inflammatory cytokines and lipid intermediates, increased activation of sympathetic nervous and renin-angiotensin-aldosterone systems, and mechanical stress.²⁷

As with other reports, this study found obesity to be more common in older women.^{17,28} Body composition changes with age; decreases in lean body mass and increases in height are greater in women than in men.²⁹ Estrogen deficiency following menopause results in increased visceral adiposity.³⁰ Other factors reported to contribute to greater adiposity in women include being single, divorced or separated, limited socialization, physical inactivity and sleep problems.³¹⁻³³

This study also found more obese older women with multimorbidity, consistent with studies reporting a higher prevalence of multimorbidity among women with obesity than men.¹⁹⁻²¹ Being female is an independent risk factor for multimorbidity.²¹ Being a woman with obesity increases the risk of developing multimorbidity in older age, based on a study with a mean follow-up of 27.8 years compared to women without obesity.³⁴ Factors that are associated with obesity in women, such as physical inactivity, lifestyle and sleep problems, also increase the likelihood of multi-

morbidity.^{28,31,35} Additionally, longer life expectancy, poor self-rated health, socioeconomic disparity and health-care utilization contribute to a higher multimorbidity among older women.^{20,26,37} In the Philippines, older women have lower incomes and health care coverage and depend on their children for support.³⁸ An ADB study on gender differences in access to health care among older persons in the Philippines revealed that older women were more likely to report sickness or injury and seek consultation.³⁹ A study on aging and health in the Philippines reported that more older women are receiving outpatient care than men.⁴⁰

Nonsmokers were found to be more commonly obese than smokers. There is an inverse relationship between smoking and obesity. Smokers are more likely to be underweight or normal. At the same time, nonsmokers are more commonly obese or overweight.⁴¹ On the other hand, studies have reported that there was no association between obesity and increased amount of smoking.^{42,43} Nicotine, the major component of tobacco, is reported to increase resting metabolic rate and decrease appetite, causing body weight.⁴⁴ Smoking induces lipolysis and increases the 24-hour energy expenditure mediated by the sympathetic nervous.⁴⁵

Hypertension, hyperlipidemia, hyperuricemia and musculoskeletal disorders were the most commonly reported diseases by older persons with obesity, similar to previous research on the most common diseases in obesity, except hyperuricemia.^{9,16,22,26} These diseases also comprised most of the dyads and triads of multimorbidity in obesity. Hypertension, hyperlipidemia and obesity are essential components of the metabolic syndrome, the prevalence of which increases with increasing severity of obesity.⁴⁶ Hyperuricemia has also been linked to hypertension, obesity, and metabolic syndrome.⁴⁷ It is interesting to note that diabetes, which is significantly associated with obesity, was not common among older persons with obesity in this study. This may be because the Asian diabetes phenotype is less commonly associated with obesity.⁴⁸

Strengths and limitations

Chronic disease status was based on self-report, which is subject to response and recall bias. Older persons may have chronic conditions not listed in the questionnaire, which can lead to underreporting and underestimation of the prevalence of multimorbidity. However, self-reports have been considered a reliable measure of chronic disease.⁴⁹ The cross-sectional design of this study precludes causality. Whether obesity preceded multimorbidity or was preceded by multimorbidity cannot be determined. BMI, as a measure of obesity, has a limited ability to identify fat mass and lean body mass in older persons.

Despite these limitations, this study utilized information from a representative sample of community-living older persons with a high response rate. As far as the authors are aware, this is the first study to provide data on obesity and multimorbidity among community-living older persons in

the Philippines. Older persons will soon comprise a more significant proportion of the population in the country, as will the proportion of older persons with obesity and multimorbidity. The approach to older persons with obesity and multimorbidity could be challenging to health professionals because medical education, training and research, as well as clinical practice guidelines (CPGs), have been focused on single diseases.⁵⁰ Clinical trials often exclude older persons and those with multimorbidity; therefore, CPGs offer limited guidance in the management of older persons with multiple chronic diseases. A review on the applicability of CPGs on older persons with multimorbidity reported that only 4 (diabetes, osteoarthritis, atrial fibrillation and angina) of 9 CPGs discussed older persons and comorbid diseases.⁵¹ Multimorbidity in older persons with obesity is consequential because of its association with functional disability, poor quality of life, high healthcare utilization and cost, polypharmacy, higher rates of adverse events and increased risk of mortality.^{20,52,53}

CONCLUSION

This study identified the prevalence of overweight and obesity among community-living older persons and called attention to the importance of recognizing obesity as a determinant of multimorbidity. It is recommended that drivers of obesity be identified and that obesity prevention be a part of the public health agenda. Future research should look into sex differences in risk factors and multimorbidity patterns. Multimorbidity is considered the norm in older persons; therefore, understanding the epidemiology is warranted to plan for future resources and delivery of healthcare services and assist policymakers and public health planners in developing effective interventions.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

MSG: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **SADV:** Conceptualization, Methodology, Investigation, Resources, Writing – review and editing, Supervision, Project administration, Funding acquisition.

Data Availability Statement

The data supporting this study's findings are available on request from the corresponding author.

Author Disclosure

The authors declared no conflict of interest.

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Vitamin D Status and Dyslipidaemia Among Obese Individuals in Ibadan, Nigeria: A Pilot Study

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Abstract

Objective. Obesity is a major global health concern characterized by an accumulation of excessive body fat, dyslipidaemia and low vitamin D levels. This study aimed to assess the relationship between dyslipidaemia and vitamin D status in obese individuals and the risk of atherogenesis.

Methodology. In this cross-sectional study, 140 participants aged 18 to 65 years, were categorized into 4 equal groups of 35 each, based on their body mass index BMI. Baseline and demographic data were obtained using a semi-structured questionnaire. The serum levels of vitamin D, total cholesterol (TC), triglyceride (TG) and HDL-cholesterol (HDL-c) were measured using standard methods. Low-density lipoprotein cholesterol (LDL-c) and atherogenic index in plasma (AIP) were calculated.

Results. The vitamin D status was sufficient in all groups but its concentrations decline significantly as BMI increases. Serum TC, TG, LDL-c concentration significantly increases as BMI increases, but HDL-c concentration decreases. The AIP increases as BMI increases.

Conclusion. The study provided possible evidence to support the association between dyslipidaemia and inadequate vitamin D status in this cohort of adults with obesity in Ibadan, Nigeria.

Key words: obesity, dyslipidaemia, vitamin D status, atherogenic index

INTRODUCTION

Obesity is a multifaceted, long-term metabolic disorder characterized by an excessive buildup of body fat due to an imbalance between the amount of energy consumed and expended.¹ It is linked to the occurrence of cardiovascular diseases (CVD), hypertension, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), insulin resistance (IR), dyslipidaemia (which are features of metabolic syndrome) and different types of cancers. These factors are associated with increased rates of morbidity and mortality, worse quality of life, and societal stigmatization.² Dyslipidaemia is characterized by elevated concentrations of serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), as well as low concentrations of high-density lipoprotein cholesterol (HDL-c), thus, these lipid markers can be used to assess the presence of obesity.

Visceral obesity causes insulin resistance through the action of adipokines and free fatty acids (FFA). Adipokines, such as resistin and retinol-binding proteins, reduce insulin sensitivity; whereas leptin and adiponectin have the opposite impact. Obesity not only increases the likelihood of developing insulin resistance and diabetes mellitus, but it also plays a role in causing atherogenic dyslipidaemia. It directly contributes to inflammation and enhances the development of atherosclerosis, regardless of its impact on insulin resistance or lipoproteins.²

Vitamin D (25 [OH] D) is produced by the action of ultraviolet (UVB) rays on the skin where it converts 7-dehydrocholesterol to cholecalciferol (vitamin D3) or when ergocalciferol (vitamin D2) and vitamin D3 are consumed orally. The best method for determining a person's vitamin D status is to measure the amount of circulating 25(OH) vitamin D because of its longer half life.³ There is growing consensus that the ideal circulating

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25(OH) vitamin D level should be approximately 30.0–32.0 ng/ml or more, notwithstanding disagreements on the definition of low vitamin D status.⁴ Inadequate levels of vitamin D are also linked to metabolic derangements that negatively impact one's health.

Deficient/insufficient vitamin D status has recently been linked to several disorders, including metabolic syndrome, malignancies, autoimmune diseases, psychiatric disorders and neurodegenerative diseases. However, the exact mechanism of vitamin D deficiency in causing these disorders is still uncertain.⁵ Vitamin D deficiency in individuals may result in an increased susceptibility to obesity-related metabolic diseases due to the absence of potential anti-inflammatory effects on chronic low-grade inflammation.

Currently, the most likely explanation for the negative correlation between vitamin D serum levels and body mass index (BMI) is the process of volumetric dilution of vitamin D. Despite obese and lean individuals having comparable levels of vitamin D, overweight individuals have lower blood concentrations due to the higher distribution volume of vitamin D in their bodies. Specifically, 25 (OH) D is mostly distributed in the serum, muscle, fat, and liver compartments, which are found to be enhanced in individuals with obesity.⁶ Nevertheless, if the primary factor leading to low serum 25(OH) D levels in obese individuals is volumetric dilution, it implies that losing weight would subsequently elevate the levels of vitamin D in the bloodstream. However, researches on weight loss demonstrated contradictory findings.⁷ A group conducted a study to determine the levels of vitamin D in the plasma, omental, and subcutaneous tissue of individuals with obesity and a control group (normal weight).⁸ They discovered that the correlation between plasma vitamin D and concentrations of vitamin D in the subcutaneous and omental fat compartments was comparable in both groups. Additionally, they observed a similar distribution pattern of vitamin D between these two fat tissues. These findings suggest that adipose tissue does indeed function as a storage site for vitamin D.

Alternatively, the hypothesis of vitamin D sequestration in adipose tissue has been proposed.⁷ It has been reported that while the production of vitamin D in the skin does not vary between obese and normal weight individuals, individuals with obesity experience smaller increases in plasma levels of 25(OH) D after exposure to sunlight and oral intake of vitamin D compared to individuals with normal weight. It was proposed that vitamin D, being a fat-soluble vitamin, is stored and preserved in adipose tissue, resulting in reduced levels of vitamin D in the bloodstream of individuals with a significant amount of adipose tissue. The sequestration concept served as the foundation for the previously mentioned volumetric dilution hypothesis.⁷ However, when compared to volumetric dilution, the sequestration of the prohormones ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) is characterized

by their hydrophobic nature and ability to dissolve in adipose tissue. Additionally, sequestration refers to their inability to return to the circulation as a substrate for liver 25-hydroxylase, which converts these prohormones to 25(OH) D after they are stored.⁹

The lower levels of 25(OH) D observed in individuals with obesity can also be attributed to reduced sunlight exposure. This is likely due to their limited mobility and participation in outdoor activities, and different clothing habits compared to individuals with normal weight.¹⁰

However, the specific mechanisms behind the lower 25(OH) D concentrations in obesity are not fully understood, and there is uncertainty regarding the potential health consequences of these lower concentrations. This present study aims to elucidate the possible protective role of vitamin D against atherogenic lipids in individuals with obesity by assessing the relationship between vitamin D status and dyslipidaemia in this population.

METHODOLOGY

Study design

A cross-sectional study was carried out among 140 individuals aged 18 to 65 years, for a period of 4 months (March to July 2022). A convenient (non-random) sampling technique was used to select the study participants. The participants were recruited from the popular Bodija market, Ibadan, Nigeria and the University College Hospital, Ibadan, Nigeria. The individuals were grouped into 4 based on their BMI as normal weight i.e., controls (18.0 to 24.9 kg/m²), overweight (25.0 and 29.9 kg/m²), moderately obese (35.0 and 39.9 kg/m²) and severely obese (>40 kg/m²).

Inclusion/Exclusion criteria

Individuals with consent to participate were recruited into the study, while those with chronic illness (such as hypertension, diabetes mellitus, thyroid disorders) or on medication for chronic illness were excluded from the study because they have metabolic disorders that can affect the outcome of the study. Thyroid-stimulating hormone screening was done in all participants to rule out thyroid disorders while other chronic illnesses were excluded through the questionnaire.

Sample size

The minimum sample size for the study was calculated with the formula proposed by Charan and Biswas¹¹ which is as follows: $-Z_{1-\alpha/2}^2 p(1-p)/d^2$ where; $Z_{1-\alpha/2}$ = is the standard normal variate [at 5% type 1 error ($p < 0.005$) it is 1.96]; p = expected proportion in population based on previous studies or pilot studies (estimated as 8.1% from study by Chukwuonye et al., 2013);¹² d = absolute error or precision (this is chosen to be 5%). The minimum sample size calculated was 114.

Data and specimen collection

Following ethical approval from the University of Ibadan/ University College Hospital (UI/UCH) Joint Ethics Committee (UIUCH/EC/21/0726) and after obtaining informed consent from participants, a total of 10 ml of venous blood was withdrawn from each participant. The blood was withdrawn after an overnight fast through venipuncture using pyrogen-free disposable needles and syringes. Five milliliters of whole blood was dispensed into fluoride oxalate bottle and the obtained plasma after centrifugation was used for fasting plasma glucose measurement. The remaining 5 ml was dispensed into serum separator tubes (SST) and 30 minutes was allowed for clot retraction; and the obtained serum after centrifugation was used for vitamin D, TSH, fasting lipid profile assay. Each specimen bottle was assigned an identity number that will match the ID number on each data collection form used for participant recruitment. This separation process was achieved by spinning the specimen bottles in a centrifuge made by UNISCOPE at a speed of 4,000 revolutions per minute for duration of 10 minutes. The resultant plasma and serum were dispensed into their respective well-labeled plain bottle and stored at a temperature of -20°C until analysis was performed within 3 months of collection.

Assay methods

Fasting plasma glucose was determined using glucose oxidase method as described by Trinder¹³ on an automated chemistry analyzer, LandWind C-100 plus. The serum vitamin D concentration was quantitatively measured using an enzyme-linked immunosorbent assay (ELISA) as described by Holick MF¹⁵ on StatFax 400 ELISA reader. Vitamin D status is classified based on the ELISA kit manufacturers' manual (Calbiotech, Inc) as follows: levels <20 ng/ml, 21 ng/ml-29 ng/ml, 30 ng/ml-150 ng/ml, >150 ng/ml were considered as deficiency, insufficiency, sufficiency and intoxication respectively. Thyroid-stimulating hormone was assayed by ELISA method as described by Frank et al.¹⁶ The lipid profile (TC, TG and HDL-c) was done

using the enzymatic method as described by Fredrickson et al.,¹⁷ Hainline et al.,¹⁸ and Albers et al.,¹⁹ respectively on LandWind C-100 plus chemistry auto-analyzer. Low-density lipoprotein cholesterol was calculated using the using the formula described by Friedwald et al.²⁰ The equation is expressed as:

$$\text{LDL-c (mg/dl)} = \text{TC} - \text{VLDL-c} - \text{HDL-c}; \text{ where VLDL-c} = \text{TG}/5$$

Atherogenic index in plasma (AIP) was determined by a method proposed by Dabiasova and Frohlic in 2001;²¹ $\text{AIP} = \text{Log (TG/HDLc)}$, value is expressed in mmol/L.

Statistical analysis

The data analysis was conducted using the statistical package software for social scientists (SPSS) version 25.0. Kolmogorov-Smirnov test of normality was used to test the distribution of obtained data and non-Gaussian parameters were transformed. The data were presented as the mean value plus or minus the standard deviation (mean $\pm$ SD). The method of analysis of variance (ANOVA) was employed to assess and compare the differences in means among all groups, while the Duncan multiple range test was used to determine the differences within the BMI groups. The Pearson correlation coefficient was employed to ascertain the link between all parameters within each group. The level of significance was taken to be $p < 0.05$.

RESULTS

At the conclusion of the study, there was a total of 134 participants remaining, with 104 females and 30 males. Six (6) participants were excluded due to findings of thyroid disorders obtained from TSH screening and the remaining numbers for each group were described as follows: control (34), over-weight (33), moderately obese (32), and severely obese (34).

Figure 1 represents the mean vitamin D levels in all the participants and shows that the vitamin D concentration

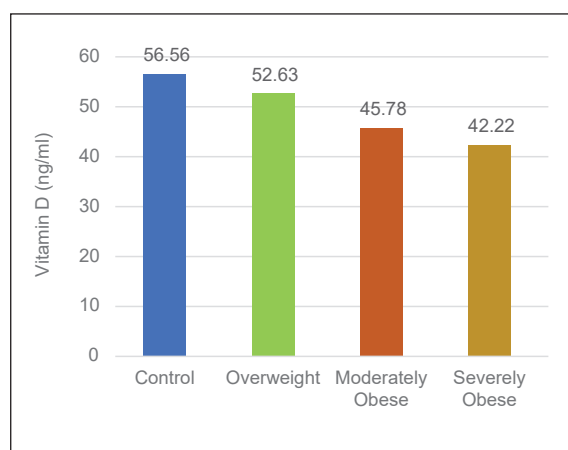


Figure 1. Mean serum vitamin D levels in the control, overweight, moderately obese and severely obese groups.

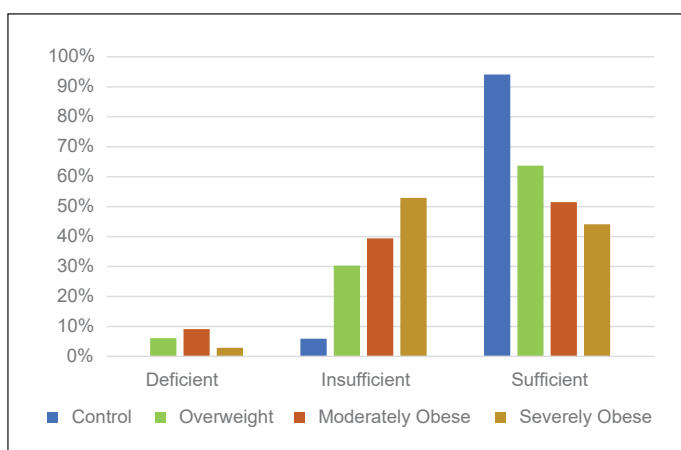


Figure 2. Classification of vitamin D status in the control, overweight, moderately obese and severely obese groups.

Table 1. Serum lipid profile levels in control, overweight, moderately obese and severely obese groups

Serum lipids	Control (n = 34)	Overweight (n = 33)	Moderately obese (n = 32)	Severely obese (n = 34)	p-value
T. Chol (mg/dl)	165.50 ± 24.15 ^a	191.80 ± 15.93 ^b	221.41 ± 15.17 ^c	241.53 ± 41.96 ^d	<0.001*
TG (mg/dl)	106.26 ± 27.21 ^a	129.06 ± 33.00 ^b	158.66 ± 17.35 ^c	189.32 ± 45.78 ^d	<0.001*
HDL (mg/dl)	67.35 ± 7.10 ^a	59.94 ± 11.14 ^b	39.09 ± 8.73 ^c	29.62 ± 13.37 ^d	<0.001*
LDL (mg/dl)	46.60 ± 22.65 ^a	67.33 ± 22.83 ^b	102.98 ± 18.45 ^c	118.72 ± 31.49 ^d	<0.001*

*p-value significance at $p \leq 0.05$

The Duncan multiple range test was used to determine the differences within the groups, with corresponding the compact letter display, a, b, c and d.

Values of the same superscript within the same column are not statistically different at $p > 0.05$ while values with different superscript are significantly different at $p < 0.05$. For all the lipid profile, $a \neq b \neq c \neq d$.

despite being sufficient in all the groups (≥ 30.0 ng/ml), declines significantly as BMI increases ($p = 0.000$). The serum vitamin D concentration is 56.56 ± 14.25 ng/ml, 52.63 ± 22.02 ng/ml, 45.78 ± 30.59 ng/ml and 42.22 ± 31.59 ng/ml in the controls, overweight, moderately obese and severely obese group respectively.

Figure 2 represents the classification of all the participants according to their vitamin D status (deficient/insufficient/sufficient), and it shows that 0%, 5.9 and 94.1% of the normal weight participants (controls) had vitamin D deficiency, insufficiency and sufficiency respectively; while 6.1%, 30.3% and 63.7% of the overweight participants had vitamin D deficiency, insufficiency and sufficiency respectively. 9.1%, 39.4% and 51.5% of the moderately obese group had vitamin D deficiency, insufficiency and sufficiency respectively; while 2.9%, 52.9% and 44.1% of the severely obese group had vitamin D deficiency, insufficiency and sufficiency respectively. Thus, the percentage of participants with vitamin D sufficiency decreases as BMI increases.

Table 1 shows the serum fasting lipid profile in the control, overweight, moderately obese and severely obese groups. It was observed that there were significant differences between the mean $\pm$ SD in the four BMI groups; where the serum concentrations of TC, triglyceride and LDL-c of normal weight (i.e., controls) is significantly lower than that of overweight ($p < 0.001$), that of overweight is significantly lower than that of moderately obese group ($p < 0.001$), that of moderately obese is significantly lower than that of severely obese group ($p < 0.001$). Meanwhile the serum concentration of HDL-c of the control is significantly higher than that of the overweight group ($p < 0.001$), that of the overweight is significantly higher than that of moderately obese group ($p < 0.001$) and that of moderately obese is significantly higher than that of severely obese group ($p < 0.001$). Therefore, the serum TC, triglycerides and LDL-c significantly increase across the four BMI groups with the severely obese group having the highest concentrations; while the opposite is observed for the serum HDL-c with the severely obese group having the lowest concentration.

The correlation between BMI and lipid profile in the severely obese group is shown in Table 2. There is a positive significant correlation ($p = 0.001$) between BMI and TC ($r = 0.685$), BMI and TG ($r = 0.656$), BMI and LDL-c ($r = 0.645$), and a significant negative correlation ($p = 0.001$) between BMI and HDL-c ($r = -0.654$) in the severely obese group.

Table 2. Correlation between BMI and Lipid Profile in severely obese group, n=34

Parameters	r	P Value
BMI vs T. Chol	0.685**	0.001**
BMI vs TG	0.656**	0.001**
BMI vs HDL-c	-0.654**	0.001**
BMI vs LDL-c	0.645**	0.001**

** Correlation is significant at the p -value ≤ 0.01 level (2-tailed).

Table 3. Correlation between vitamin D and lipid profile in control, overweight, moderately obese and severely obese groups

Parameters	Control (n = 34)	Overweight (n = 33)	Moderately obese (n = 32)	Severely obese (n = 34)
Vit. D vs T. Chol	-0.113	-0.040	0.060	-0.189
Vit. D vs TG	-0.261	-0.176	-0.044	-0.145
Vit. D vs HDL-c	-0.092	-0.051	-0.215	0.160
Vit. D vs LDL-c	0.107	0.125	0.171	-0.179

** Correlation is significant at the p -value ≤ 0.01 level (2-tailed).

Table 4. Atherogenic index in plasma (AIP) level in all participants

BMI	N	Mean	SD
Normal	34	-0.19	0.22
Overweight	33	-0.05	0.25
Moderately obese	32	0.25	0.11
Severely obese	34	0.37	0.20

Correlation between serum vitamin D and lipid profile in the control, overweight, moderately obese and severely obese groups is shown in Table 3. There is no significant correlation between vitamin D and lipid profile parameters (TC, TG, LDL-c and HDL-c) in all the 4 groups studied.

Table 4 shows the level of atherogenic index in plasma (AIP) in all the participants, and there is increasing value of AIP from the normal weight participants (-0.19 ± 0.22), to the overweight group (-0.05 ± 0.25), to the moderately obese group (0.25 ± 0.11) and severely obese participants (0.36 ± 0.20). Thus, the AIP increases as BMI increases.

DISCUSSION

The aetiology of obesity is multifactorial. It is a subject of controversy whether vitamin D deficiency is a consequence of obesity or a factor predisposing to obesity.²² In recent

years, the correlation between vitamin D and obesity has attracted considerable attention in the world, in which individuals with obesity might present with inadequate vitamin D status. Dyslipidaemia is a major feature of obesity and a major risk factor for atherogenesis and insulin resistance; thus, this present study explored the relationship between serum vitamin D levels and dyslipidaemia in obesity states, with the intent of determining the possible role of vitamin D in the management of lipid disorders in individuals with obesity.

In our study, though the mean serum vitamin D concentration in all the participants is sufficient (≥ 30 ng/ml), approximately half of the moderately obese and severely obese individuals have inadequate vitamin D status; this observation could be due to regular exposure to sunlight in the participants from this region, South-Western Nigeria. Most of these participants are sedentary traders who are exposed to sunlight for almost eight (8) hours a day. Sunlight exposure on the skin triggers the synthesis of vitamin D, which is crucial for maintaining optimal levels in the body and ameliorates vitamin D deficiency.

The inadequate vitamin D level found in half of the moderately and severely obese individuals might be as a result of the volumetric dilution principle in obesity.⁷ The more obese an individual is, the more likely vitamin D becomes insufficient or deficient because vitamin D is trapped in the adipose tissue. It was reported by Gonzalez et al., that the lower levels of 25(OH) vitamin D were associated with higher BMI,²³ suggesting that vitamin D might play an important regulatory role in the development of obesity. This present study found that vitamin D levels decrease significantly as BMI increases; this is consistent with the finding of Orce in 2019, which indicated that low vitamin D status is likely to contribute to the development of overweight/obesity.²⁴

Decreased vitamin D levels might not only lead to obesity. It has been proposed that as the weight of an individual increases, the likelihood of dyslipidaemia becomes higher. As seen in this present study, the TC, TG and LDL-c are significantly elevated in individuals with obesity compared with normal weight individuals; while the "good cholesterol" HDL-c is significantly lower in the obese group compared to normal weight participants. This trend occurs because obesity is considered to be potentially linked with abnormal lipid levels which can contribute to dyslipidaemia and an increase in cardiovascular risk outcomes. Thus, the observation from our study validates the findings of Xiongjing et al., and the prospective cohort studies of Wang et al., where they reported association between low vitamin D levels and dyslipidaemia.^{25,26}

A positive correlation was observed in this study between BMI and the lipid profile especially in the severely obese individuals; this observation concurs with the findings of Ofori and Angmortherh, where a positive correlation between BMI and lipid profile was also reported.² Thus, as

BMI increases, there is a tendency for lipid parameters to exhibit less favorable values. The mechanism underlying the positive correlation between BMI and lipid profile is considered multifactorial and complex. Such factors include increased adipose tissue mass, insulin resistance and altered lipoprotein metabolism.

In this present study, there was no significant correlation found between the levels of vitamin D and lipid profile in the different categories of all participants studied. This can be explained by different factors such as dietary habits, sunlight exposure, physical activity levels, and individual metabolic variations. These factors interact in intricate ways, providing the body with a substantial amount of vitamin D which mitigates the elevation of lipids.

It was found in this study that as an individual's BMI increases, AIP, a marker of CVD risk also increases, with higher values in the moderately and severely obese groups. The high prevalence of insulin resistance, adipose tissue inflammation, changes in lipoprotein composition and dyslipidaemia in obesity could explain this finding. AIP is calculated based on the ratio of triglyceride to HDL cholesterol,¹⁹ thus an increase in triglyceride and decrease in HDL cholesterol could contribute to an elevated AIP. Nevertheless, findings by Fernandez et al., and Niroumand et al., revealed why a better biomarker, such as AIP, is needed to predict cardiovascular disease (CVD) compared with conventional biomarkers.^{26,27} For instance, abnormally increased LDL-c levels indicate higher risk of coronary artery disease (CAD) events. However, many CVD patients do not exhibit elevated LDL-c levels. A similar finding was observed in this present study that as the mean LDL-c concentrations in the moderately and severely obese participants were at low risk rather than high risk category level. Therefore, it is not sufficient to use merely conventional lipid profiles to predict CVD. Rather, a calculated AIP based on the ratio of triglyceride to HDL is better used to predict cardiovascular disease.

In general, this present study highlights that, participants who maintained a healthy diet, engaged in outdoor activities, who are often exposed to sunlight and engage in physical exercise, who are not overweight or obese, would have sufficient 25(OH) vitamin D level with lipid profile within optimal limits and will be at low risk for cardiovascular diseases; this is shown by the AIP result of this study. However, some of those who are overweight and obese, who are also engaged in outdoor activities, who occasionally are exposed to sunlight and maintained a healthy diet from time to time, would have inadequate 25 (OH) vitamin D levels as well as some degree of derangement in lipid profile. These groups can be referred to as healthy obese as the exposure to sunlight ameliorates dyslipidaemia and increases vitamin D level. Also, individuals with sedentary lifestyle, indoor occupational activities, who do not engage in physical activities, who wore covered clothes when they went outside and who have genetic predisposition, would have deficient vitamin

D concentration, abnormal lipid levels and will be at higher risk for cardiovascular diseases. This is also in agreement with the work of Lagunova et al., and Nejabat et al., expressing the possible association between low vitamin D status, BMI and cardiovascular diseases.^{28,29}

CONCLUSION

The study provided possible evidence to support the association between dyslipidaemia and inadequate vitamin D status in this cohort of adults with obesity in Ibadan, Nigeria. It also supports the hypothesis that individuals with obesity who often expose themselves to sunlight are rarely vitamin D deficient but rather have inadequate vitamin D status. As individuals with obesity expose themselves to sunlight, the exposure prevents them from being at risk of vitamin D deficiency regardless of their vitamin D status. Exposure to sunlight mitigates the effect of sedentary lifestyle and dyslipidaemia by raising the serum vitamin D (25[OH] D) levels.

Recommendations

More attention needs to be focused on the approaches to prevention of dyslipidaemia in obesity, through proper dietary modifications, exercise and deliberate exposure to sunlight. Vitamin D nutritional fortifiers should be supplemented properly when indicated to prevent dyslipidaemia and other cardiovascular abnormalities caused by vitamin D deficiency.

Anthropometric measurement is important in the evaluation of patients with obesity. It is a cheap, non-invasive objective monitoring index for patients with this condition; thus it should be maintained as a standard practice.

Study limitation

This study did not investigate the advantages of vitamin D supplementation in raising the vitamin D level in the body and its effect on reducing the body weight as well as metabolic abnormalities. It was observed that the study population consists mostly of females, which may limit generalization; underscoring the need to recruit more males into the study to be conclusive. A larger sample size and a longer study duration to examine an interventional arm of participants with insufficient vitamin D levels, and the effect of weight management strategies in improving metabolic health outcomes in individuals with obesity would be optimal.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

OOS: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **ZOS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation,

Writing – review and editing, Visualization, Project administration, Funding acquisition; **AAS:** Software, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **KSA:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **CFA:** Methodology, Investigation, Resources, Project administration.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

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A Visualization Analysis of Hotspots and Frontiers in Obesity-Related Executive Functions Research: A Bibliometric Study

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Abstract

Objective. This study aims to provide a visual analysis of the research hotspots and frontiers in the field of obesity-related executive functions using bibliometric methods.

Methodology. Our analysis is based on 5814 English-language documents retrieved from the Web of Science Core Collection database. CiteSpace 6.2.R4 software was utilized to conduct bibliometric analysis. The study examines the trends, key players, and thematic evolution in obesity-related executive function research over the past decade.

Results. The number of publications in this domain has exhibited a steady linear growth trend, with American institutions and scholars leading in research contributions. The current research focus encompasses co-occurrence and cluster analysis of keywords and references, as well as the brain and associated cognitive functions. Our bibliometric analysis reveals a shift in focus towards the brain, cognition, executive functions, the prefrontal cortex and other related topics in obese individuals, in addition to established areas such as metabolic syndromes, insulin resistance, diabetes, gut microbiota, and dietary intake.

Conclusion. This study highlights new entry points for aspiring researchers in the field of obesity and executive functions. Future research directions may include a deeper exploration of the relationship between obesity and specific components of executive functions, such as working memory, inhibitory control, cognitive flexibility, and planning.

Key words: obesity, executive functions, bibliometric study, working memory, inhibition control, cognitive flexibility

INTRODUCTION

The increasing prevalence of obesity in developing countries has led to its emergence as one of the most significant global health problems.¹ Obesity is associated with several chronic conditions, including cardiovascular diseases, several types of cancers and an increased risk of all-cause mortality.² Moreover, several studies have provided evidence that obesity may have deleterious effects on the brain, making it a major risk factor for cognitive impairment. Midlife obesity is associated with an increased risk of dementia and accelerated brain atrophy in older patients.³ Given the widespread prevalence of obesity, identifying the pathogenic mechanisms underlying the deleterious cognitive effects of obesity is a growing public health problem. Traditionally, the effect of obesity on cognition was attributed to cardiovascular risk factors such as diabetes and hypertension. However, many reports have

shown that there may be a direct link between obesity and cognitive decline beyond the influence of cardiovascular risk factors, implying that obesity itself may be detrimental to the functioning of the central nervous system (CNS).

Relationship between obesity and executive functions

Overall, existing theories acknowledge that obesity is associated with impaired executive functions. A meta-analysis⁴ found that obese participants demonstrated a wide range of impairments in executive functions such as inhibitory control, cognitive flexibility, working memory, decision-making, verbal fluency and task-planning. However, the underlying mechanisms remain unclear. This association can be partially explained by the Body Mass Index (BMI)-related reduction in the thickness of the prefrontal cortex (PFC), which leads to impaired executive functions.⁵ Children with obesity and impaired

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executive functions may exhibit a dysregulated behavioural phenotype ranging from internalizing to externalizing behaviours and weight-related symptoms.⁶ Muscle strength, speed dexterity and cardiorespiratory fitness also correlated with executive functions in overweight and obese children. Further, cognitive flexibility appears to be more closely related to all fitness components during obesity treatment, whereas planning capacity and inhibition may depend on the analyzed components.⁷ Poor executive functions may hinder the efficacy of obesity treatment in children, while improvements in executive functions are associated with increased weight loss efficacy.⁸ Relatedly, obese adults with higher executive functions regain a certain amount of weight; however, younger adults with executive function deficits have a greater risk of severe obesity.⁹ Furthermore, recent studies have shown that there may be a weak but positive association between executive functions and eating behavior among obese individuals,¹⁰ that obesity and unhealthy lifestyles among adolescents are associated with poor executive functions¹¹ and that executive dysfunction in obese youths may be related to behavioral eating disorders.¹²

The majority of studies on obesity-related executive functions used questionnaires such as executive function-related psychological tests that typically examined small, local sample sizes, Statistical Package for the Social Sciences (SPSS) software, and meta-analyses. Therefore, developing a macroscopic grasp of the status of current research and hotspots in research on obesity-related executive functions is difficult. Although SPSS analysis and meta-analysis were utilized in many papers, national areas, keywords, author and institutional partnerships, publications and references could not be studied. It is vital to search for national regions, keywords, author and institutional collaborations, journals and references to identify the research hotspots and frontiers of obesity-related executive functions.

Unique role of bibliometrics in discovering the laws of scientific development

Bibliometrics is a type of metrology method based on the analysis of published literature in disciplines such as mathematics and statistics catalyzed in the digital era. It evaluates and predicts the research status and development trends in certain core research areas, explores characteristic laws that are implicit in a particular subject area, predicts future research trends in medicine and engineering, and provides intelligence analysis in fields such as agronomy and management and in software for robust knowledge network analysis, such as CiteSpace.¹³ The bibliometric tool VOSviewer,¹⁴ which has the advantages of rich graphic presentation, clear hierarchy and simple interpretation of analysis results, is widely recognized and cited in science metrology and knowledge mapping. Although obesity-related executive functions have been widely studied, there is no systematic understanding of research hotspots and evolutionary trends. Thus, the present study primarily used the Web of Science (WOS) core collection's full-text

database to search the literature and relevant publicly published research articles on obesity and executive functions, including inhibitory control, working memory and cognitive flexibility. These articles were used to draw CiteSpace and Bibliometrix webpages to construct a knowledge co-occurrence network and visualization map. This study aimed to refine and summarize the hidden connotations and laws in the literature and reveal the course of development, research progress, current status, hotspots of cutting-edge research and trends in the field to provide a reference for further research on obesity and executive functions.

METHODOLOGY

Data sources

The relevant literature was sourced from the Web of Science (WOS) Core Collection database. Overall, scholars agree that executive functions include inhibitory control, cognitive flexibility, working memory, decision-making, verbal fluency and planning.¹⁵ A search was conducted using the keywords 'Executive function' SAME obesity or 'Working Memory' SAME Obesity or Inhibition SAME obesity or 'Cognitive flexibility' SAME obesity. The included studies should be published in English, resulting in 15104 articles. Setting the time period from January 1, 2013 to December 31, 2022, excluding 4615 articles, there were 10489 remaining. The article type was selected for refinement, with 1385 excluded and 9104 remaining. Upon selecting 'open access' and excluding 3290 articles, the search results showed 5814 relevant literature (Figure 1).

Analytical method

The 5,814 articles retrieved and screened were imported into the software Citespace 6.2.R4 in Refworks format for

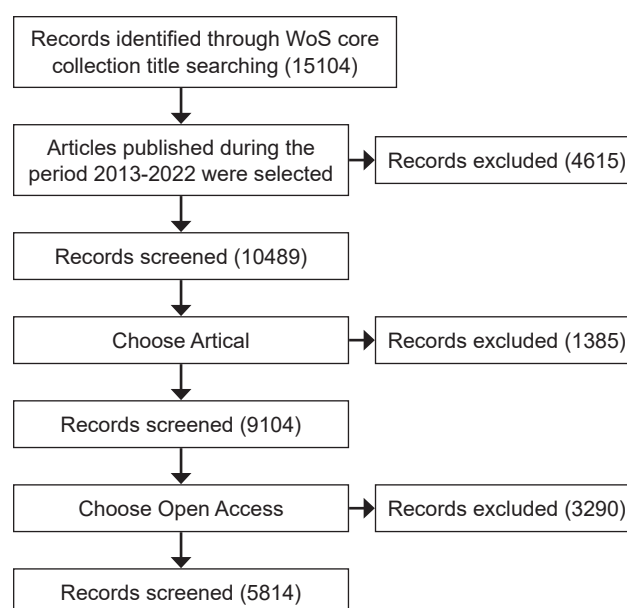


Figure 1. Data source retrieval process.

visualization analysis, where the authors, research institutions, countries and keywords were extracted. The time period was set from January 2013 to December 2022 with a partition length of 1 year, and the time slice selected was "1." The threshold setting selected the top 50 frequent occurrences within each time slice. Descriptive statistics were used to discuss the authors, countries and the number of articles published. The influence of the articles was evaluated through citation analysis and co-occurrence analysis, while the keywords' conceptual relevance and academic interaction were assessed. Furthermore, content analysis based on keyword clustering clarified the main themes, hot topics and development trends.

In the analysis diagram of the issuing organization and author, the higher the density, the closer the cooperation between the author or organization; in the co-occurrence analysis diagram of keywords, the higher the density, the higher the degree of closeness between the keywords.

RESULTS

Overall description

Volume is an extrinsic indicator of the field, and the inter-annual change in the volume of a publication can be used to observe and understand the development dynamics of the field. The search method retrieved a total of 5814 articles published on the topic "obesity and executive functions," during the period 2013–2022. Figure 2 indicates that the annual publication volume in the field of executive functions in obesity over the last decade (i.e., between 2013 and 2019) showed a steady linear increasing trend. The number of journals published in 2020 was significantly higher than in 2019; however, the growth rate slowed in 2021 relative to 2020, and the volume of journals showed a downtrend in 2022. This data illustrates international scholars' increasing emphasis on studying obesity and executive functions.

International concern

An analysis of countries where the literature was published shows that the volume of publications produced on a given subject area reflects the overall level of concern and international influence of a country/region on that issue.

A total of 2,290 articles were published in the United States (US), representing 39.39% of the overall count. This was nearly 1.89 times more than the number of articles published in China, which ranked second (1210 articles), and 4.94 times more than the number of articles published in South Korea, which ranked third (464 articles). Thus, US research contributions in obesity and executive functions are much higher than in other countries. Research by Chinese scholars on obesity and executive functions is gradually gaining importance and is ranked second in terms in the volume of publications (Figure 3).

As seen in Figure 4, the US contributes the most to this research area (larger dots indicate greater contributions), followed by China, South Korea, Germany and Japan. As shown in the relationship network (Figure 5), the US showed the largest cooperative strength with other countries, followed by South Korea, Germany, Japan, England, Spain and Australia (data not given). For instance, the more connected the network, the greater the cooperative strength; similarly, numerous partial connections with other countries indicate greater cooperative strength (Figure 5). The intensity of cooperation between China and other countries was significantly much lower than that of other countries, such as the US and South Korea, illustrating that scientific cooperation between China and other countries in the field of obesity and executive functions should be enhanced.

Analysis of article sources

Academic journals are important vectors for displaying the results of scientific research. A total of 1188 journals and 5814 relevant literature sources on obesity and executive functions from 2013 to 2022 were screened by statistical analysis from the WOS. Owing to the large number of journals, only the journal volume of the ten top-rated journals was considered (Table 1). Among the top ten journals (Table 1), PLoS One had the highest volume with 237 articles, representing 4.08% of the total literature sample, with a journal impact factor of 3.752 (JIF 2021) and journal citation reports (JCR) partition of Q2.

Scientific Reports and International Journal of Molecular Sciences came second and third, with 217 articles (3.73%; JIF 2021 = 4.997, Q2) and 138 articles (2.37%; JIF 2021 =

Table 1. Journal name before article source (Top 10) and number published in the journal and the journal impact factor

Order	Journal name	Number	JCR partition	IF (2021)	IF (5 years)
1	PLOS ONE	237	Q2	3.752	4.096
2	SCIENTIFIC REPORTS	217	Q2	4.997	5.516
3	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	138	Q1/Q2	6.208	6.628
4	NUTRIENTS	126	Q1	6.706	7.185
5	DIABETES	112	Q1	9.305	10.493
6	MOLECULES	85	Q2	4.927	5.110
7	JOURNAL OF BIOLOGICAL CHEMISTRY	82	Q2	5.485	5.294
8	MOLECULAR METABOLISM	82	Q1	8.568	8.928
9	NATURE COMMUNICATIONS	73	Q1	17.694	17.764
10	APPETITE	59	Q1/Q2	5.016	5.653

6.208, Q1), respectively. They were followed by Nutrients (JIF 2021 = 6.706, Q1) and Diabetes (JIF 2021 = 9.305, Q1) with 126 and 112 articles, respectively, and the remaining journals had published under 100 articles. Among them, Nature Communications had the highest impact factor (JIF 2021 = 17.694); however, its journal volume was not high at 30.8% (73 articles). In contrast, PLoS One had the lowest impact factor (JIF 2021 = 3.752), but its journal volume was the highest. Thus, the number of journal articles did not correspond to influence, which may relate to the topic-journal fit, highlights of journal articles and the submission cycle. The analysis of the main research areas of the top ten journals in this field showed that studies focused on nutrition, diabetes, molecular metabolism, biochemistry, diet and other disciplines, indicating a multi-disciplinary approach.

Analysis of institutions and authors

Institutions reflect the distribution of research units in the field, as indicated by the analysis of institutions with

emphasis on obesity and executive functions (Table 2). The institutional publications that ranked among the top 20 were not only tertiary institutes and institutes of science but also medical research centers and veterans' health management institutions, of which the University of California System, Harvard University and Harvard University of Texas System were ranked as the top three with 217, 163 and 150 publications, respectively. Inserm, or the *Institut national de la Sante et de la recherche medical* (National Institute for Health and Medical Research), ranked fourth with 145 publications. Chinese institutions ranked among the top 20, including the Chinese Academy of Sciences and Shanghai Jiao Tong University, with 95 and 72 publications, respectively.

Visual relationship maps (Figure 6) were obtained using CiteSpace 6.1. R6 Basic. The authors John Gunstad, Mary Beth Spitznagel, Gladys Strain, James E. Mitchell, Ross D. Crossby, Michael Devlin and Ronald Cohen – all from colleges or institutes in the US – showed close academic communication and cooperation (the blue dots and

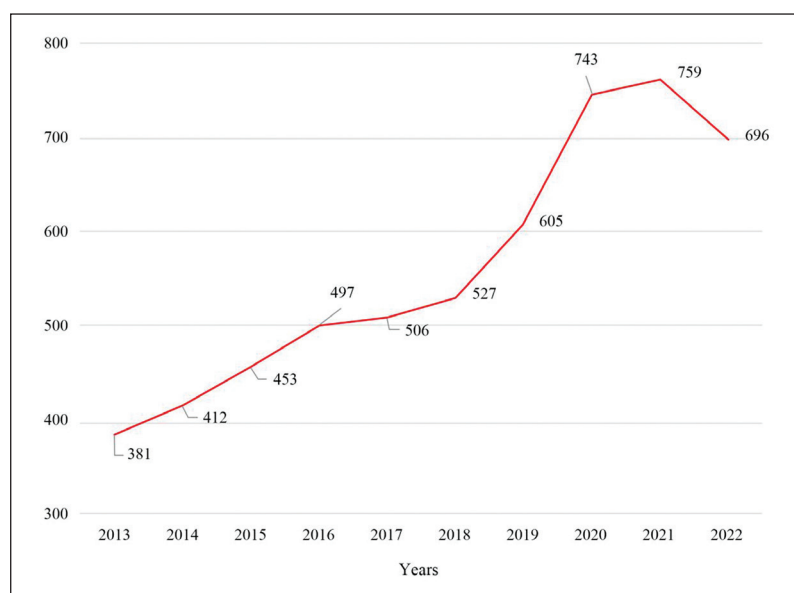


Figure 2. Annual scientific production growth chart.

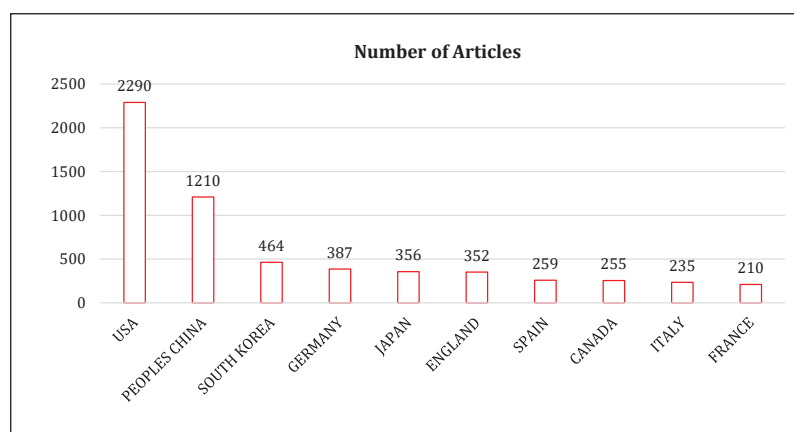


Figure 3. Top ten countries by publication volume.

Table 2. Top 20 institutional publications

Order	Institution name	Numbers
1	UNIVERSITY OF CALIFORNIA SYSTEM	217
2	HARVARD UNIVERSITY	163
3	UNIVERSITY OF TEXAS SYSTEM	150
4	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE INSERM	145
5	US DEPARTMENT OF VETERANS AFFAIRS	141
6	VETERANS HEALTH ADMINISTRATION VHA	140
7	UDICE FRENCH RESEARCH UNIVERSITIES	128
8	NATIONAL INSTITUTES OF HEALTH NIH USA	120
9	CIBER CENTRO DE INVESTIGACION BIOMEDICA EN RED	117
10	HARVARD MEDICAL SCHOOL	117
11	PENNSYLVANIA COMMONWEALTH SYSTEM OF HIGHER EDUCATION PCSHE	112
12	UNIVERSITY SYSTEM OF OHIO	98
13	CHINESE ACADEMY OF SCIENCES	95
14	UNIVERSITY OF LONDON	90
15	UNIVERSITY OF CALIFORNIA SAN DIEGO	85
16	UNIVERSITY OF MICHIGAN	81
17	UNIVERSITY OF MICHIGAN SYSTEM	81
18	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS	80
19	SHANGHAI JIAO TONG UNIVERSITY	72
20	YALE UNIVERSITY	72



Figure 4. A visualization of the national knowledge map of publication volume.

Table 3. Top 20 authors and their corresponding number of articles

Order	Author	Number
1	Gunstad, John	20
2	Spitznagel, Mary Beth	14
3	Strain, Gladys	13
4	Mitchell, James E	13
5	Crosby, Ross D	12
6	Devlin, Michael	11
7	Cohen, Ronald	11
8	Wang, Wei	11
9	Jiang, Changtao	11
10	Lee, In-Kyu	10
11	Gonzalez, Frank J	10
12	Dieguez, Carlos	10
13	Blueher, Matthias	9
14	Tinahones, Francisco J	9
15	Alosco, Michael L	9
16	Drucker, Daniel J	8
17	Bae-jump, Victoria L	8
18	Al-mulla, Fahd	8
19	Ahmad, Rasheed	7
20	Demarco, Vincent G	7

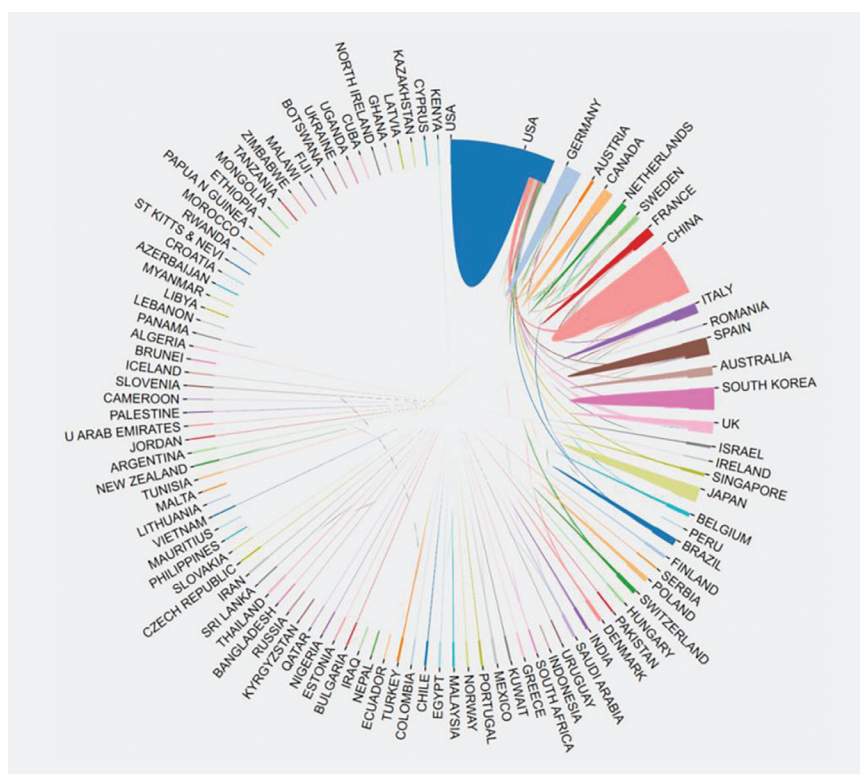


Figure 5. National publication visual map: the relationship network of countries.

connections in Figure 6). Based on an author relationship map, Gunstad et al., formed a core team of authors in the field and contributed significantly. We found no evidence of similar cooperative networks among the other authors.

Analysis of research hotspot

Keyword analysis allows for a better understanding of important issues in the research field. The analyzed key-

words included keyword co-occurrence, keyword cluster analysis, keyword timeline plots, and keyword convex atlas.

Co-occurrence of keywords

Running CiteSpace, setting the year slice to one year, and ticking keywords at node types resulted in a keyword co-occurrence map. Among them, Tables 4 and 5 present statistics on the frequency and betweenness centrality

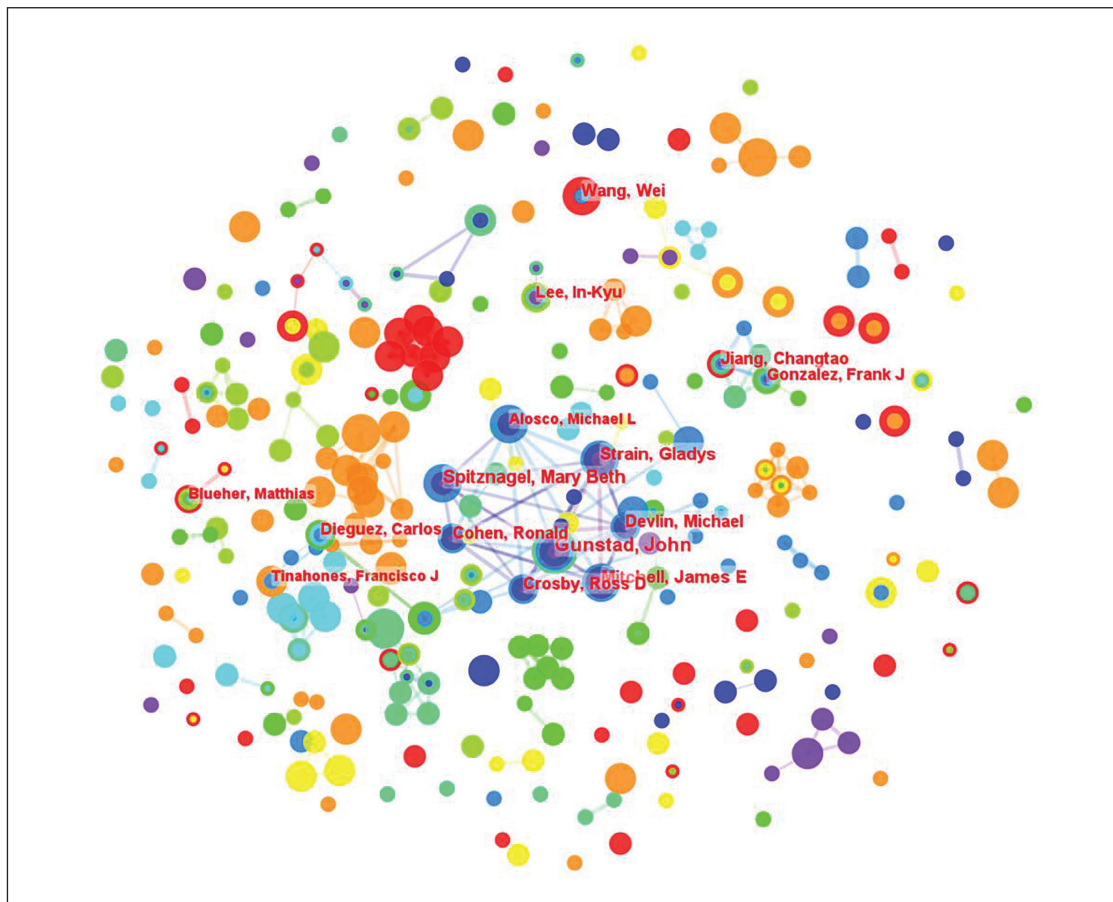


Figure 6. Author co-occurrence map.

Table 4. Keyword frequency

Order	Keyword	Frequency
1	obesity	2160
2	inhibition	1233
3	insulin resistance	1170
4	expression	915
5	activation	635
6	adipose tissue	634
7	inflammation	618
8	mice	434
9	metabolism	430
10	metabolic syndrome	378
11	mechanism	374
12	oxidative stress	372
13	cell	370
14	gene expression	319
15	receptor	302
16	body mass index	289
17	disease	285
18	risk	262
19	resistance	262
20	protein	246
21	glucose	242
22	pathway	238
23	diet-induced obesity	235
24	differentiation	229
25	executive functions	227
26	association	223
27	dysfunction	214
28	skeletal muscle	206
29	ppar gamma	205
30	food intake	204

Table 5. Keyword centrality

Order	Keyword	Centrality
1	glucose metabolism	0.06
2	adiposity	0.05
3	system	0.04
4	polyphenol	0.04
5	secretion	0.03
6	nlrp3 inflammasome	0.03
7	nitric oxide synthase	0.03
8	mouse model	0.03
9	messenger rna	0.03
10	memory	0.03
11	macrophage	0.03
12	kinase	0.03
13	kappa b	0.03
14	impairment	0.03
15	hyperglycemia	0.03
16	health	0.03
17	glucose tolerance	0.03
18	energy expenditure	0.03
19	endothelial dysfunction	0.03
20	down regulation	0.03
21	chronic kidney disease	0.03
22	cancer cell	0.03
23	breast cancer	0.03
24	binding	0.03
25	beta	0.03
26	bariatric surgery	0.03
27	activated receptor gamma	0.03
28	3t3 l1 adipocyte	0.02
29	abdominal obesity	0.02
30	absorption	0.02

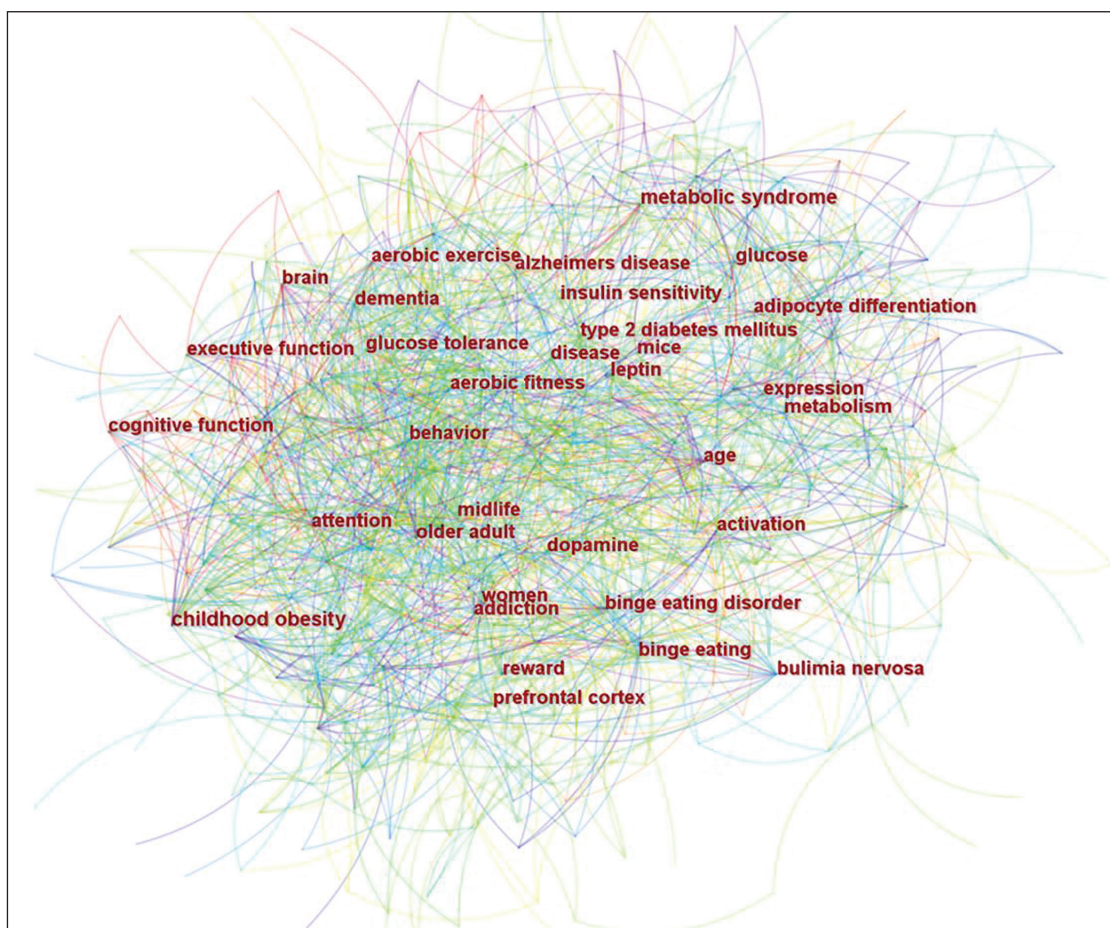


Figure 7. Keyword co-occurrence plot.

of the keywords. The top 30 keywords were selected for each frequency and betweenness centrality based on comprehensive consideration. Diversity in research themes was evident from the frequency of keywords. Specifically, excluding the subject heading obesity, suppression of inhibition was the highest (1233 times), followed by insulin resistance (1170), expression (915), activation (635), adipose tissue (634) and inflammation (618). In terms of the betweenness centrality of the keywords, the highest centrality was for glucose metabolism, with a centrality of up to 0.06, which was collinear with all other keywords, followed by systems (0.04), polyphenols (0.04) and secretion (0.04).

The atlas structure showed that these keywords were important hub nodes. Together with the other keywords in surrounding nodes, they constituted a popular research topic in the field (Figure 7). Researchers mainly focused on insulin resistance, adipose tissue, and inflammation in obese people, which may be inseparable from the glucose metabolism function in obese people. Among the atlas keywords, psychologically relevant keywords, such as brain, cognitive function, prefrontal cortex, attention, behavior, reward and addiction, received much attention. In terms of age, there was a greater focus on obesity in children and women than in men.

Analysis of keyword clusters

Running the CiteSpace software, the time was set from January 2013 to December 2022, the year slice was set to one year, the log-likelihood ratio (LLR) was employed for clustering keywords with high frequencies and clear keyword clustering profiles were obtained using multiple adjustment thresholds (Figure 8). The modular clustering

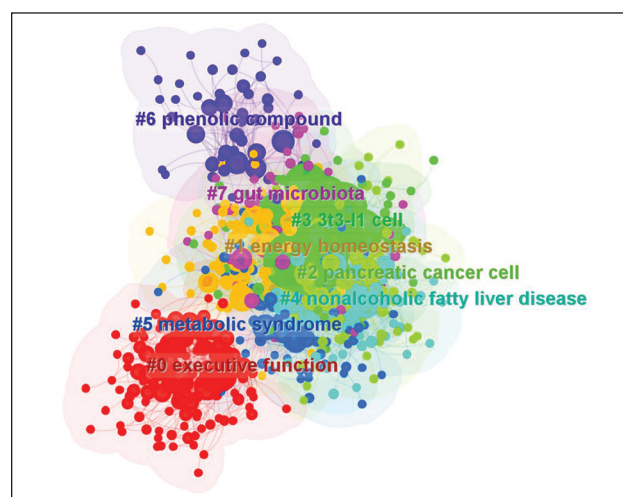


Figure 8. Keyword extraction and visual map construction of WOS data set from 2013–2022.

value (Q-value) was 0.4435 ($Q > 0.3$ implies a significant clustering structure). The silhouette cluster average profile value (s-value) was 0.7349 ($s > 0.5$ indicates that the clustering is generally considered reasonable, and $s > 0.7$ indicates that the clustering is convincing). The results of the keyword cluster analysis for the cluster structure of obesity and executive functions (Figure 8) were significant and compelling. The clustering order was 0–7, and the lower the clustering order, the higher the number of keywords included in the clustering. Each cluster was comprised of multiple closely related words. The core keyword cluster map (Figure 8) can be divided into eight research hotspot directions: (1) those with the smallest clustering order (#0) are executive functions (e.g. inhibition, working memory, cognitive flexibility, cognitive control, etc.); (2) clustering order #1, energy homeostasis; (3) clustering order #2, pancreatic cancer cells; (4) clustering order #3, 3T3-L1 cells (a type of cell associated with fat metabolism);¹⁶ (5) clustering order #4, non-alcoholic fatty liver disease; (6) clustering order #5, metabolic syndrome; (7) clustering order #6, phenolic compounds, which have some inhibitory effects on adipose tissue formation; and (8) clustering order #7, gut microbiota.

Timeline diagram of keywords

Based on the keyword clustering, we drew a keyword timeline diagram (Figure 9) using CiteSpace 6.1. R6 Basic to depict the keyword evolution process under each cluster on the relationship between obesity and executive functions from a temporal perspective, thereby enabling a deeper understanding of the thematic changes in this topic. Eight clusters emerged in 2013 and included BMI, glucose resistance, NF-kappa B, high-fat diet, insulin resistance, diet-induced obesity and oxidative stress, indicating that this area was explored from a weight, nutritional, biological and clinical perspective in 2013. Research results on the clustering of #0 executive functions, #3 adipogenesis, #5 oxidative stress, #4 oxidative stress and #7 gut microbiota increased across the study's timeframe and continued to receive considerable attention. Researchers paid less

attention to clustering #1 food intake, #2 NF kappa B, #4 endoplasmic reticulum stress, and #6 pancreatic lipase levels after 2020.

Keyword prominence atlas

Words for the top 25 bursts of intensity (Figure 10) were obtained using CiteSpace 6.1. R6 Basic, all of which were greater than five in burst intensity. Overall, research on the relationship between obesity and executive functions was conducted mainly from 2013 to 2022. Burst words for induced insulin resistance and fatty acid oxidation had the longest duration of four years, and the remaining burst words had a duration of one to three years. Keywords with the strongest burst intensity were “metabolic syndrome” (12.34), followed by “induced insulin resistance” (8.72), “growth factor” (7.12), “fatty acid oxidation” (7), and “gene expression” (6.32), and so on. Interestingly, “non-alcoholic fatty liver disease,” “diabetes mellitus,” “sex difference,” “interleukin-6,” and “mellitus-6,” which presented higher outbreak intensity in recent years, and are expected to become new areas of research focus in this field.

Analysis of the references

References were analyzed to help determine influential literature and authors in the research field. Keywords, including analysis of frequency, betweenness centrality, co-citation co-occurrence map of the literature, and the clustering map of keywords in the co-cited literature, were plotted against a timeline.

Running CiteSpace and setting the year slice to one year and the literature reference tick at node types resulted in a literature co-occurrence map (Figure 11A). Tables 6 and 7 show statistics for the citation frequency and betweenness centrality of references, and the top 10 articles ranked for frequency and betweenness centrality were selected for each review. Based on citation frequency, the top three ranked articles were those by Yang,⁴ Blüher¹⁷ and Ng,¹⁸ with frequencies of 75, 57, and 49, respectively. From

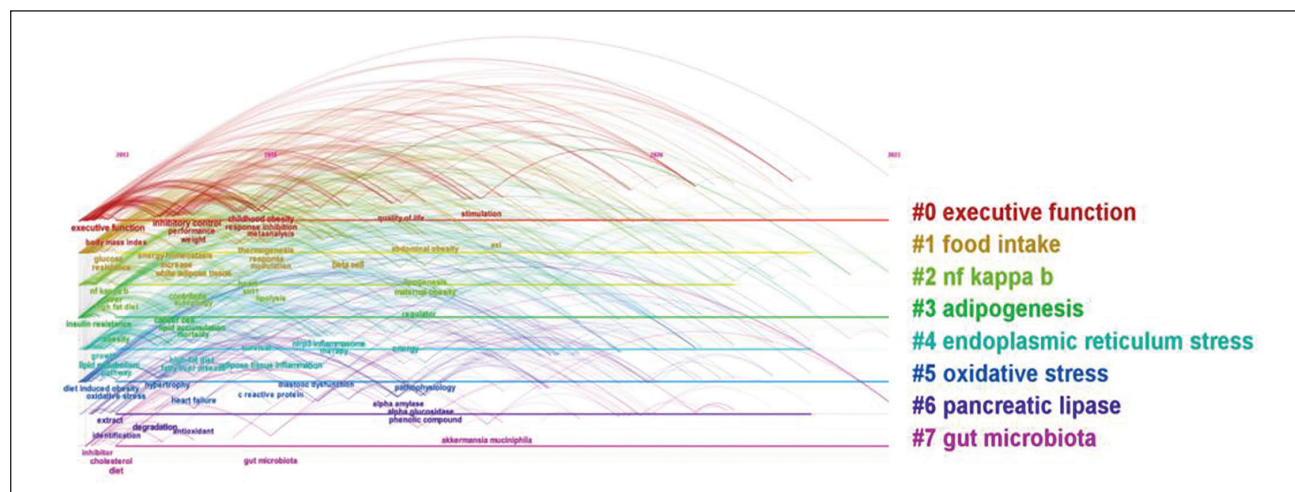


Figure 9. Keyword timeline plot.

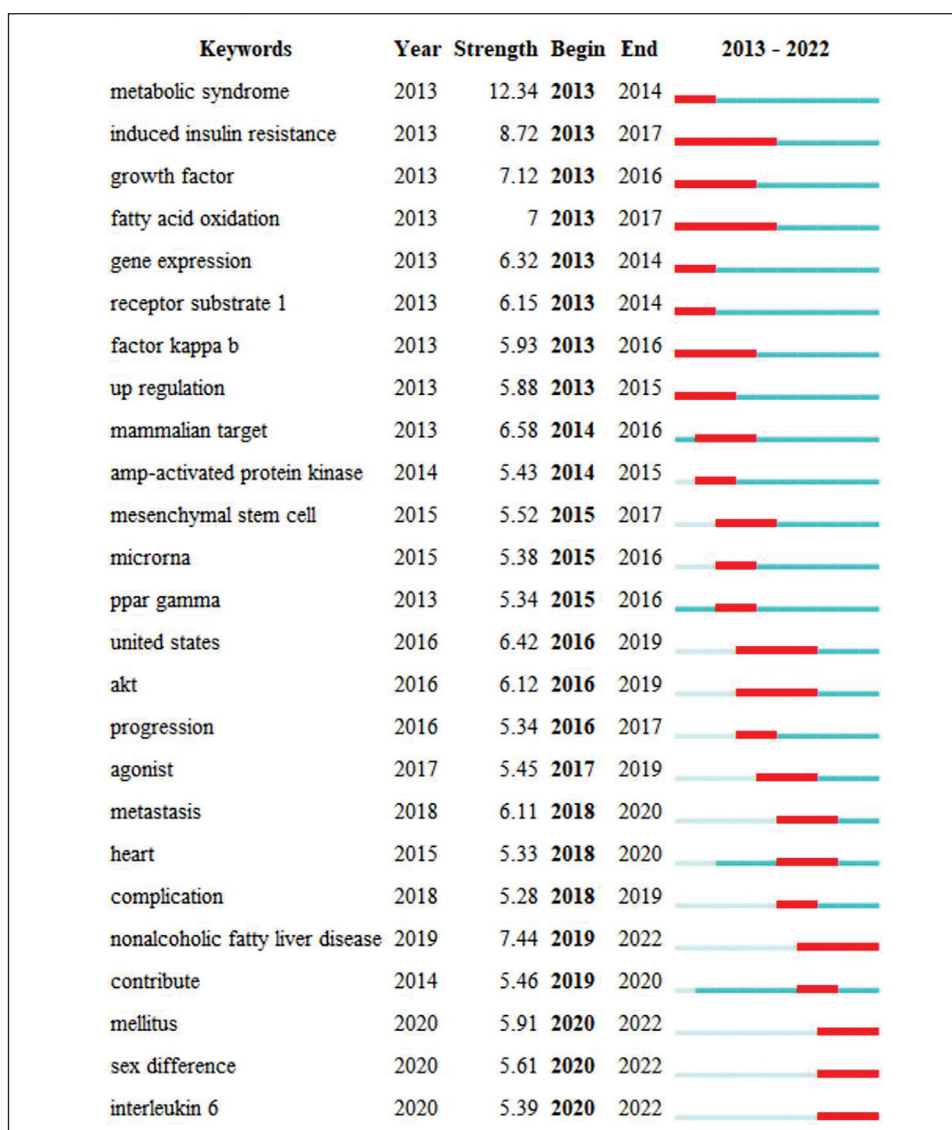


Figure 10. Top 25 keywords with the strongest citation bursts.

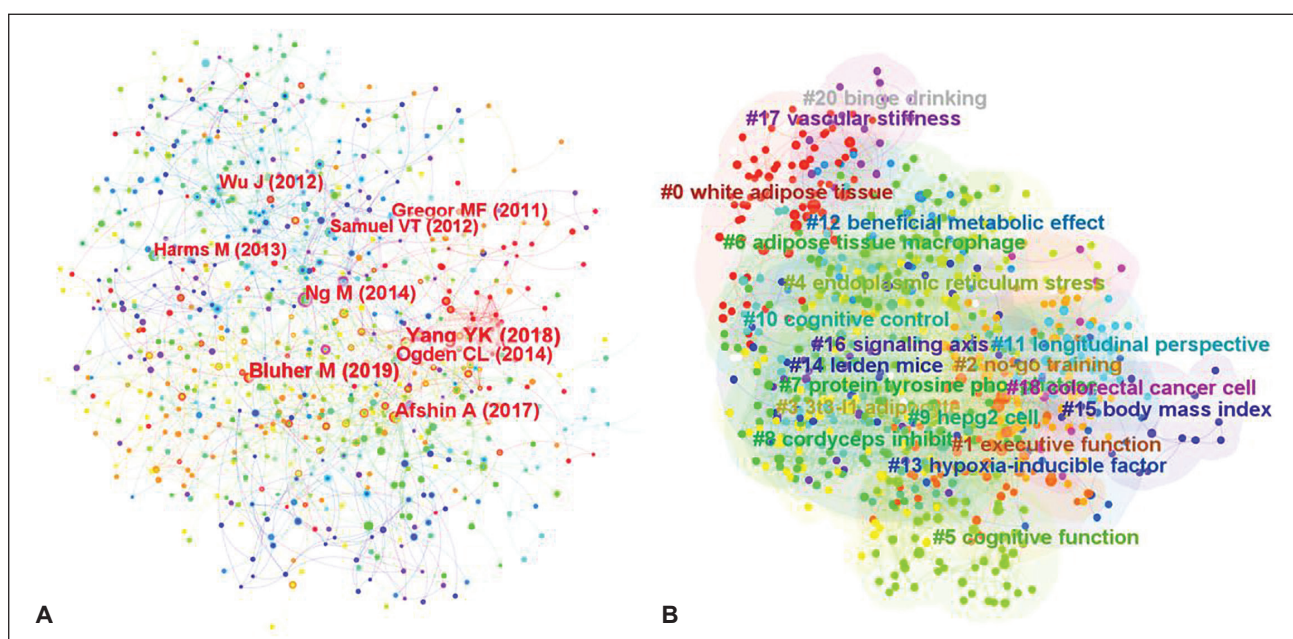


Figure 11. (A) The cited literature co-occurrence map; (B) The cited cluster plot.

the perspective of betweenness centrality, the top three ranked articles were by Ng,¹⁸ Chavez¹⁹ and Gettens,²⁰ with betweenness centralities of 0.16, 0.14, and 0.13, respectively. Among them, the article by Ng¹⁸ was ranked among the top three for both frequency and betweenness centrality, illustrating that this is a research paper with important implications in the field.

Consistent with the literature co-occurrence map structure (Figure 11A), the highlighted authors were among the top ten ranked authors. The cited cluster map (Figure 11B) presents 20 keyword clusters. The modular clustering value (Q-value) was 0.7789 (Q >0.3 implies a significant clustering structure). The silhouette cluster average

profile value (s-value) was 0.8384 (s >0.5 implies that the clustering is generally considered reasonable; s >0.7 implies that the clustering is convincing). There were 20 research hotspot directions for 'co-clustering': #0 white adipose tissue, #1 executive functions, #2 go/no-go training, #3 3T3-L1 adipocytes, #4 endoplasmic reticulum stress, and #5 cognitive function.

Based on the clustering of references, a literature timeline diagram (Figure 12) was created to gain more insight into subject changes in the field from a temporal perspective.

Taking 2013 as the community, the direction of keywords cited in the literature before 2013 was: #11 longitudinal

Table 6. Frequency of cited articles

Order	Cited references	Count
1	Yang YK, 2018, NEUROSCI BIOBEHAV R, V84, P225, DOI 10.1016/j.neubiorev.2017.11.020	75
2	Bluhner M, 2019, NAT REV ENDOCRINOL, V15, P288, DOI 10.1038/s41574-019-0176-8	57
3	Ng M, 2014, LANCET, V384, P766, DOI 10.1016/S0140-6736(14)60460-8	49
4	Afshin A, 2017, NEW ENGL J MED, V377, P13, DOI 10.1056/NEJMoa1614362	49
5	Ogden CL, 2014, JAMA-J AM MED ASSOC, V311, P806, DOI 10.1001/jama.2014.732	48
6	Gregor MF, 2011, ANNU REV IMMUNOL, V29, P415, DOI 10.1146/annurev-immunol-031210-101322	39
7	Wu J, 2012, CELL, V150, P366, DOI 10.1016/j.cell.2012.05.016	35
8	Samuel VT, 2012, CELL, V148, P852, DOI 10.1016/j.cell.2012.02.017	33
9	Harms M, 2013, NAT MED, V19, P1252, DOI 10.1038/nm.3361	32
10	Rosen ED, 2014, CELL, V156, P20, DOI 10.1016/j.cell.2013.12.012	29

Table 7. Centrality of references

Order	Cited references	Centrality
1	Ng M, 2014, LANCET, V384, P766, DOI 10.1016/S0140-6736(14)60460-8	0.16
2	Chavez JA, 2012, CELL METAB, V15, P585, DOI 10.1016/j.cmet.2012.04.002	0.14
3	Gettens KM, 2017, J BEHAV MED, V40, P687, DOI 10.1007/s10865-017-9831-5	0.13
4	Lackey DE, 2016, NAT REV ENDOCRINOL, V12, P15, DOI 10.1038/nrendo.2015.189	0.11
5	Flegal KM, 2010, JAMA-J AM MED ASSOC, V303, P235, DOI 10.1001/jama.2009.2014	0.10
6	Alosco ML, 2014, AM J SURG, V207, P870, DOI 10.1016/j.amjsurg.2013.05.018	0.10
7	Czech MP, 2017, NAT MED, V23, P804, DOI 10.1038/nm.4350	0.10
8	Samuel VT, 2012, CELL, V148, P852, DOI 10.1016/j.cell.2012.02.017	0.09
9	Emery RL, 2017, PSYCHOL BULL, V143, P868, DOI 10.1037/bul0000105	0.09
10	Bluhner M, 2019, NAT REV ENDOCRINOL, V15, P288, DOI 10.1038/s41574-019-0176-8	0.08

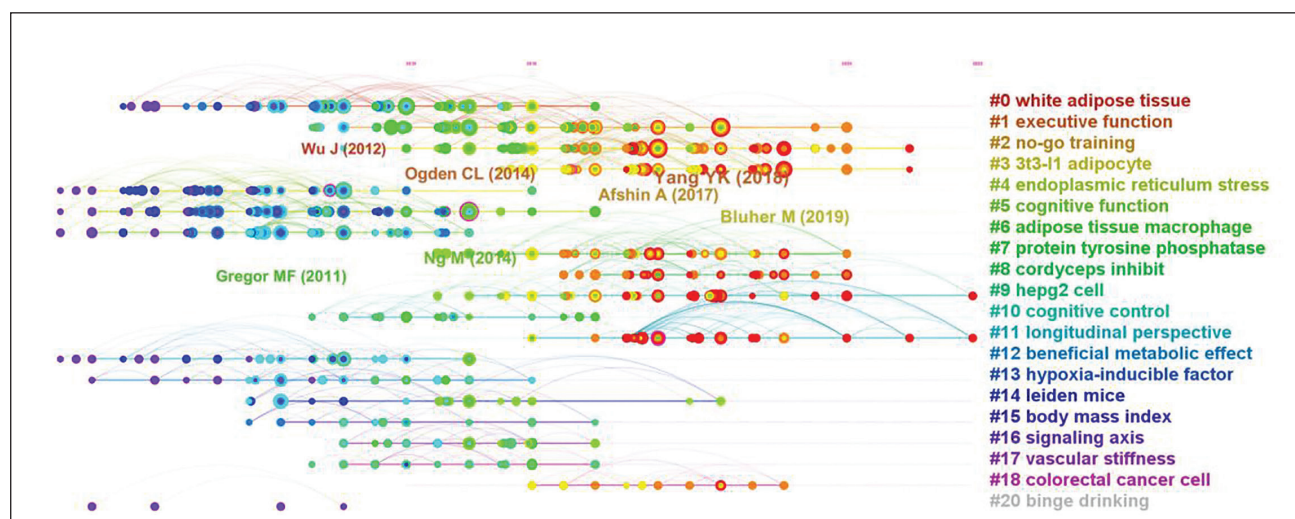


Figure 12. Reference timeline map.

perspective, #12 beneficial metabolic effects, #13 hypoxia-inducible factor, #14 Leiden mice, #15 BMI, #16 signaling axis, #17 vascular stiffness, #18 colorectal cancer cell, and #20 binge drinking. The direction of keywords cited in the literature during the period 2013–2016 was: #10 cognitive control, #9 HepG2 cell, #8 Cordyceps inhibit, #7 protein tyrosine phosphatase, and #6 adipose tissue macrophage. During 2016–2022, the literature had the following keyword directions: #5 cognitive function, #4 endoplasmic reticulum stress, #3 3T3-L1adipose, #2 go/no-go training, #1 executive function, and #0 white adipose tissue. Among these, researchers' focus on #0 white adipose tissue and #1 executive functions is ongoing.

DISCUSSION

This study conducted an internationally focused analysis and examined the relationship between obesity and executive functions using bibliometric methods, study characteristics, keywords and references, and found that the performance of executive functions in the obese population is still a topic of intense research. This may be because scholars have paid increasing attention to brain structure and CNS changes in obese people. Executive functions, which are higher cognitive abilities closely related to brain structure and the nervous system, are a series of operational processes through which individuals supervise and control their consciousness and behavior; they play an important role in cognitive processes. Researchers generally agree that executive functions include inhibitory control, cognitive flexibility, working memory, decision-making, verbal fluency and planning.¹⁵ Chronic stress induces preclinical changes in the metabolic, cardiovascular and immune systems. This phenomenon, known as allostatic load (AL), can impair executive functions (EF), which may be even more affected in individuals with excess weight due to their characteristic inflammatory state and cardiometabolic changes.²¹ Obese adolescents had impaired EF, as evidenced by low inhibition and cognitive flexibility levels compared to healthy-weight adolescents.²² We tested interactions between emotion regulation and executive functioning in relation to eating pathology in AwO/O while considering stimuli-specific deficits (e.g., food-specific deficits) in behavioral task performance. The result shows²³ that among adults with AwO/O, emotion regulation difficulties are closely related to eating pathology, regardless of performance on working memory and inhibitory control tasks.

However, a more influential model argues that executive functions encompass three key dimensions: (1) inhibitory control, which refers to the ability to suppress impulses or automatic (preponderant) responses; (2) cognitive flexibility, which is the ability to shift attention, adjust solutions, or find resources in appropriate circumstances when difficulties are encountered; and (3) working memory, which refers to the ability to monitor the relevance of incoming stimuli and memorize updated information.²⁴

Relationship between obesity and suppressive control

Wang et al.,²⁵ found that P3 could serve as an important neural marker for the future development of novel therapeutic strategies to improve the suppressive control of obesity. One such strategy is using mobile apps employing sweet food-specific inhibitory control training (SF-ICT), which may effectively change the eating behavior of children who overeat sweet foods.²⁶ Identifying individuals with low inhibitory control (IC) may facilitate early detection of adolescents at risk for obesity.²⁷ Moreover, food-specific inhibitory control training is particularly effective in individuals with low IC and a high BMI.²⁸ However, in a randomized controlled study of event-related potentials, Carbine et al.,²⁹ found that multiple food-specific or universal IC training over four weeks did not affect overall weight loss, calorie intake, or N2 ERP amplitude. In addition, pubertal obesity is associated with a decline in the ability to mediate cognitive conflict during inhibitory control³⁰ and individual differences in conflict monitoring may explain binge eating behavior among obese adolescents in situations where more inhibitory control efforts are required.³⁰ Neuroimaging studies in obesity have shown that reduced prefrontal cortical activity affects inhibitory control and BMI,³¹ and the findings of Brockmeyer et al.,³² highlight the relevance of the interplay between inhibitory control and food reward assessment in maintaining obesity.

Relationship between obesity and working memory

In the general population, the adult BMI polygenic genetic risk scores are associated with working memory in children,³³ however, all genetic risks are not modulated by childhood BMI per se and may relate directly to working memory deficits.³³ Sánchez-SanSegundo et al.,³⁴ found that obese individuals had lower working memory performance than overweight individuals, providing evidence for the influence of obesity on cognitive functioning. Inflammation may mediate the relationship between obesity and impaired working memory.³⁵ Obesity hinders working memory via gut microbial metabolism of aromatic amino acids, according to research.³⁶ Obesity is associated with impaired working memory in women but not males, according to a study based on a nationally representative dataset of US adults.³⁷ In a similar vein, stereotype threat has been linked to decreased working memory in obese women.³⁸ Furthermore, Wu et al.,³⁹ found that obese children had domain-specific working memory deficiencies and remembered more items than children of normal weight during food-and-drink-related working memory tasks. Obese individuals exhibit decreased working memory and stimulus-reward learning.⁴⁰ Youth with Children with loss of control (LOC) eating and overweight/obesity demonstrated difficulties mentally retaining and manipulating numerical information in daily life, replicating prior laboratory-based research. Overeating may be related to improved working memory (WM), regardless of LOC status, but temporality and causality should be further explored.⁴¹

Association of obesity with cognitive flexibility

Cognition underpins the flexibility of human eating and disruption to higher cognitive processes, such as inhibitory control and memory, resulting in increased food intake, which could result in weight gain in the long term. Data from longitudinal and interventional studies and non-human animal models suggest a reciprocal relationship exists between obesity and cognitive function. However, whether disruption to higher cognitive processes is a primary cause of obesity in humans remains unclear.⁴² In a sample of overweight and obese adults, greater dietary intake of choline, lutein, and zeaxanthin was associated with rapid performance in cognitive flexibility tasks.⁴³ Further, reduced cognitive flexibility may lead to behavioral rigidity that induces a disordered eating state and, subsequently, obesity.⁴⁴ The cognitive reserve that accumulates over one's lifetime and cognitive flexibility can reduce the detrimental effects of obesity on cognitive functioning during old age.⁴⁵

Executive functions training for obese individuals

The clinical relevance of executive functions in diagnosis, treatment, and prognosis cannot be overlooked; therefore, La Marra et al.,⁴⁶ proposed that executive functions should be included in managing obese patients. The effects of executive functions related to training activities have also been examined in individuals with obesity. Obesity treatments that combine cognitive training, particularly those that train compensatory strategies, may improve weight loss.⁴⁷ Executive function training approaches improve weight control and comorbidity in obese children.⁴⁸ Further, by administering cognitive remediation therapy to obese individuals, weight loss effectiveness may improve because any improvement in executive functions may disrupt unhealthy lifestyle habits.^{49,50} Riggs et al.,⁵⁰ suggested that obesity interventions must include programs that promote executive functions tailored for potential groups of adolescents with different levels of obesity risk.

Limitations

Regarding data collection, the resulting database source was limited to the WOS, and studies on Chinese and English databases, excluding the WOS, were not performed. Additionally, in data processing, considering the possibility of duplication between theses and academic journals, which may affect the integration and analysis of information such as final authors, institutions, and keywords, this study selected only articles for the data source. Reviews, theses, and other content were not included. A more comprehensive integrative analysis of Chinese and English databases could be considered in subsequent studies.

CONCLUSIONS

This study used bibliometric approaches to facilitate in-depth and quantitative analysis of the relationship structure between obesity-related executive functions and scientific

findings over the past decade. The findings show that US institutions and academia are leading in terms of the current volume and impact of literature contributions to the field. The analysis of research hotspots showed that in addition to focusing on metabolic syndromes, insulin resistance, diabetes, gut flora and dietary intake, researchers have also focused in recent years on related topics such as the brain, cognition, executive functions and the prefrontal cortex of obese people. These topics can provide a reference point for aspiring scientific researchers. Future researchers must consider providing insights into the relationship between obesity and specific components of executive functions, such as working memory, inhibitory control, cognitive flexibility and planning.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

SQ: Conceptualization, Supervision; **LS:** Conceptualization, Investigation, Writing – original draft preparation; **JH:** Methodology, Writing – original draft preparation, Writing – review and editing; **YX:** Resources, Data Curation, Visualization; **XH:** Software, Visualization; **RS:** Formal analysis, Investigation; **XW:** Resources; **YST:** Project administration

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

The authors declared no conflict of interest.

Funding Source

None.

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Post-operative Outcomes of Pituitary Macroadenoma Patients in a Tertiary Hospital in the Philippines

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Abstract

Background. Pituitary adenomas comprise approximately 20% of surgically resected intracranial tumors. This study aimed to collect local data on the post-operative neurologic, visual and endocrine outcomes of patients with pituitary macroadenoma.

Methodology. This is a retrospective study of patients with pituitary macroadenoma who underwent neurosurgery at the Philippine General Hospital between 2017 to 2022. Data on demographics, clinical signs and symptoms, neuro-ophthalmologic examination findings, hormonal and radiologic studies, type of surgery, and post-operative outcomes were collected. Statistical analyses were done to compare the neurologic, ophthalmologic and endocrine status pre- and post-operatively.

Results. A total of 122 patients were included. The mean age was 44.18 years, and majority (50.82%) were female. The most common presentation was blurring of vision. Most tumors were non-functioning (77.87%). Among the functioning adenomas, the most common was acromegaly. The median tumor size was 3.5 cm, and the median time to surgery was 18 months. Microscopic transsphenoidal surgery was the most common approach (60.83%) followed by endoscopic resection (24.17%). There was significant improvement in visual acuity post-operatively ($p > 0.05$), by approximately one line in the Snellen chart. There was also some improvement in post-operative endocrine function, manifested as a significant decrease in the use of hormone replacement therapy. Factors such as age, sex, type of adenoma, tumor size, timing of surgery, surgical approach, post-operative complications and adjuvant radiation were not significantly associated with the visual and endocrine outcomes ($p > 0.005$).

Conclusion. This is the first local study to comprehensively assess the entirety of post-operative outcomes among pituitary macroadenoma patients. Our results showed that even patients with longstanding visual and endocrine deficits may still improve with surgery.

Key words: pituitary macroadenoma, pituitary surgery, post-operative outcomes, Philippines

INTRODUCTION

Pituitary adenomas comprise approximately 20% of all surgically resected intracranial tumors.¹⁻³ While epidemiologic data vary due to different factors, the estimated annual incidence is 3 to 94 cases per 100,000, with an overall estimated prevalence of 16.7%.^{1,3,4} Despite its benign characteristics, this tumor exerts significant medical and socioeconomic burden on patients, especially since it commonly affects those in the working age group (second to fourth decade of life).⁵ The most common clinical presentations are visual impairment and endocrino-

pathy, due to the proximity of the tumor to the optic chiasm and effects on other functions of the pituitary gland.³ This holds true particularly for pituitary macroadenomas, which are tumors that are at least 1 cm in greatest diameter.^{1,3} Without prompt and adequate treatment, pituitary adenomas can increase in size, causing further compression of the optic apparatus and leading to complete blindness in some cases.^{4,6,7}

In high-income countries, early detection and treatment are feasible due to access to health coverage, social security and advanced neurosurgical care, making it

easier for patients to seek consult even if they only have mild signs and symptoms.⁸ On the other hand, in low- and middle-income countries (LMIC) like the Philippines, socioeconomic factors come into play, affecting health-seeking behavior and contributing to delay in treatment.⁸ In addition, pituitary surgery is usually performed in larger tertiary centers, limiting the number of operations performed in the country.

There is paucity of local data regarding the post-operative outcomes of patients with pituitary macroadenoma. In this study, we determined the neurologic, visual, and endocrine outcomes of patients who underwent surgery for pituitary macroadenoma, quantified the amount of delay between symptom appearance and treatment, and correlated it with the visual and endocrine outcomes. To the authors' knowledge, this is the first local study to comprehensively assess the entirety of post-operative outcomes among pituitary macroadenoma patients.

METHODOLOGY

This is a retrospective study describing the demographic and clinical characteristics and outcomes of pituitary macroadenoma patients who underwent neurosurgery at the Philippine General Hospital between 2017 to 2022. Total enumeration of all eligible samples was done. All pituitary macroadenoma patients of pediatric to adult age seen by the neurosurgery service in the period specified were included in the study. Histopathology results were reviewed to ascertain the diagnosis of pituitary macroadenoma. Patients diagnosed with pituitary microadenoma, presented with a recurrent tumor, underwent surgery at another institution, underwent medical management only, or had missing medical records were excluded. Patients with final histopathology results other than pituitary macroadenoma (sellar-suprasellar meningioma, craniopharyngioma, glioma and adenocarcinoma) were likewise excluded in the study. This study was approved by the University of the Philippines Manila Research Ethics Board (UPMREB 2023-0650-01). Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Patient information was obtained from the databases of the multidisciplinary team managing pituitary tumor patients (neurosurgery, endocrinology, and ophthalmology), after which chart review was performed. Data on age, sex, clinical signs and symptoms, neuro-ophthalmologic examination findings [visual acuity, visual field perimetry, optical coherence tomography (OCT)], hormonal and radiographic studies, type of surgery, extent of resection, post-operative complications, and post-operative outcomes were collected. The timing of surgery in relation to symptom onset was recorded, in order to quantify delays. Post-operative clinical status, ophthalmologic examination findings and hormonal levels were assessed at two time points: at the immediate post-operative period (within 48 hours) and on the latest follow-up date.

- Pre- and post-operative visual conditions were determined using the best corrected visual acuity classification used by the World Health Organization. These were categorized as mild (visual acuity 20/40 to 20/60),
- moderate (worse than 20/60 to 20/200),
- severe (worse than 20/200 to 20/400), and
- blind (worse than 20/400).⁹

The best corrected visual acuity was recorded in both Snellen and logMAR notation. Pre- and post-operative visual field defects were also compared.

Endocrine assessments were based on comparison of baseline pre- and post-operative pituitary panels and use of medications. Since majority of pre-operative hormonal tests were done in laboratories outside the hospital, results were based on the available normal reference range. Different hormonal panels were evaluated for the pituitary hormonal axes: serum cortisol and plasma adrenocorticotrophic hormone (ACTH) for corticotrophs; luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol and testosterone for gonadotrophs; serum thyroid-stimulating hormone (TSH), free T4 and T3 for thyrotrophs; serum growth hormone (GH) and insulin-like growth factor-1 (IGF-1) for somatotrophs; serum prolactin (PRL) levels for lactotrophs; and posterior pituitary function based on the presence of diabetes insipidus (DI). Dynamic testing of hypothalamic-pituitary axes such as 1 mg dexamethasone suppression test or growth hormone test with 75 g oral glucose were done by the endocrinology team in cases where there was a consideration of hyperfunctioning pituitary tumors. Assessment and characterization of hormonal dysfunction were based on pre-operative hormonal levels and diagnosis of the endocrinology team. In addition, patients were classified with pre-operative hypopituitarism if there is partial loss of anterior and posterior pituitary gland function leading to at least one abnormal endocrine axis prior to surgery, and with panhypopituitarism if three or more endocrine axes were deranged.

The diagnostic criteria for DI consisted of polyuria (≥ 250 mL for two consecutive hours), hypernatremia (serum Na level >145 mEq/L) and urine specific gravity (USG) of ≤ 1.005 .¹⁰ A patient was diagnosed with DI if there were clinical evidence of documented polyuria and low USG. The presence of hypernatremia is supportive but not required to make the diagnosis. Pre-operative hormonal medications were also taken into consideration and was compared post-operatively as an indirect measurement of endocrine outcomes.

Post-operative complications such as diabetes insipidus, cerebrospinal fluid (CSF) leak, and post-operative meningitis were reported. Post-operative meningitis was diagnosed based on clinical presentation of fever, nuchal rigidity and altered mental status, in conjunction with CSF analysis, peripheral blood leukocytosis and response to meningitic doses of antibiotics.¹¹

Statistical analyses were performed using STATA MP – Parallel Edition Statistical Software, Version 18 (StataCorp LP, TX, USA). A p -value ≤ 0.05 was considered statistically significant. Data normality was analyzed using Shapiro-Wilk's test. Descriptive statistics included mean and standard deviation (SD) for normally distributed, continuous data; median and interquartile range for ordinal data and non-normal, continuous data; and frequency and proportion for nominal data. Within-group comparisons of the different neurologic, ophthalmologic and endocrine outcomes from pre- to post-operative periods were conducted using McNemar's test for categorical variables; Wilcoxon signed-rank test for ordinal and non-normally distributed, continuous data; and paired t -test for normally distributed, continuous data. On the other hand, the associations of different factors with visual outcomes and change in hormonal changes were conducted using Cramer's V for nominal factors and eta correlation for continuous-level factors.¹²

RESULTS

All cases were acquired from a retrospective database from 2017 to 2022. A total of 188 patients with pituitary macroadenoma fulfilled the inclusion criteria, but 66 patients had missing charts and were excluded. Thus, only 122 patients were included in our sample. The baseline characteristics are summarized in Table 1. Multiple neurosurgeons performed the operations over the study period, mostly neurosurgery residents in training, although a few cases were performed by general and subspecialty consultant neurosurgeons. The level of expertise of the surgeon was not included in the variables analyzed, since they were mostly neurosurgery trainees and represented a relatively homogeneous group.

The mean age of the patients in our study was 44.18 years (SD $\pm$ 12.07), and majority (50.82%) were females. Nearly 40% had hypertension and 30% had diabetes mellitus. Most patients (77.87%) had non-functioning pituitary macroadenoma. Among those with functioning adenomas, the most prevalent was acromegaly (59.26%). The most common signs and symptoms overall were blurring of vision (59.02%) and headache (15.57%), while the most common symptom for functioning tumors was galactorrhea (15.57%).

The median maximum tumor diameter was 3.5 cm (IQR 3 to 4.3), with most tumors being 2.1 to 4 cm in maximum diameter (61.05%). Cavernous sinus involvement was seen in 28.38%, while hydrocephalus was present pre-operatively in 9.26% of patients.

Indications for surgery included visual compromise (68.85%), headache (15.37%), and functioning adenomas (10.66%). The most common surgical approach was microscopic transsphenoidal excision (TSE) (60.83%), followed by endoscopic TSE (24.17%) and transcranial excision (14.17%). Gross total tumor resection was achieved in

70.59%. The most common post-operative complications were transient DI (24.59%) and post-operative hematoma (4.92%), a third of which required reoperation (Table 2). The median length of hospital stay was 12 days (IQR 8 to 16). Nine patients (7.38%) underwent adjuvant radiotherapy for residual tumor.

Table 1. Demographic, clinical and radiographic characteristics of patients with pituitary macroadenoma

Characteristic	Frequency	Percentage (%)	Mean (SD ^a) or Median (IQR ^b)
Age, years (SD^a)			44.18 (12.07)
Sex			
Male	60	49.18	
Female	62	50.82	
Comorbidities			
Hypertension	36	29.51	
Diabetes mellitus	25	20.49	
Cardiac disease	3	2.46	
Pulmonary disease	2	1.64	
Tumor size, cm (median, IQR^b, n = 95)			3.50 (3.00–4.30)
≤ 2.0	7	7.37	
2.1 to 4.0	58	61.05	
> 4.0	30	31.58	
With cavernous sinus involvement (n = 74)	32	28.38	
With hydrocephalus (n = 108)	10	9.26	
Type of pituitary macroadenoma			
Non-functioning	95	77.87	
Functioning	27	22.13	
Acromegaly	16	59.26	
Prolactinoma	9	33.33	
Cushing's disease	1	3.70	
TSH-secreting	1	3.70	
Signs and symptoms			
Blurring of vision	72	59.02	
Headache	19	15.57	
Galactorrhea	19	15.57	
Visual field cuts	12	9.84	
Acromegalic features	9	7.38	
Amenorrhea	2	1.64	

^a SD, standard deviation

^b IQR, interquartile range

Table 2. Surgical indication, approach, extent of resection and post-operative complications of patients with pituitary macroadenoma

Characteristics	Frequency	Percentage (%)
Indications for surgery		
Visual compromise	84	68.85
Headache	19	15.37
Functioning adenoma	13	10.66
Treatment failure	9	7.38
Surgical approach (n=120)		
Transsphenoidal excision (microscopic)	73	60.83
Transsphenoidal excision (endoscopic)	29	24.17
Craniotomy for tumor excision	17	14.16
Ventriculoperitoneal shunt	1	0.83
Extent of resection (n=120)		
Gross total	84	70.59
Subtotal	35	29.41
Post-operative complications		
Transient diabetes insipidus	30	24.59
Post-operative hematoma	6	4.92
Meningitis	5	4.10
Cerebrospinal fluid leak	3	2.46
Pneumonia	3	2.46
Internal carotid artery injury	1	0.82

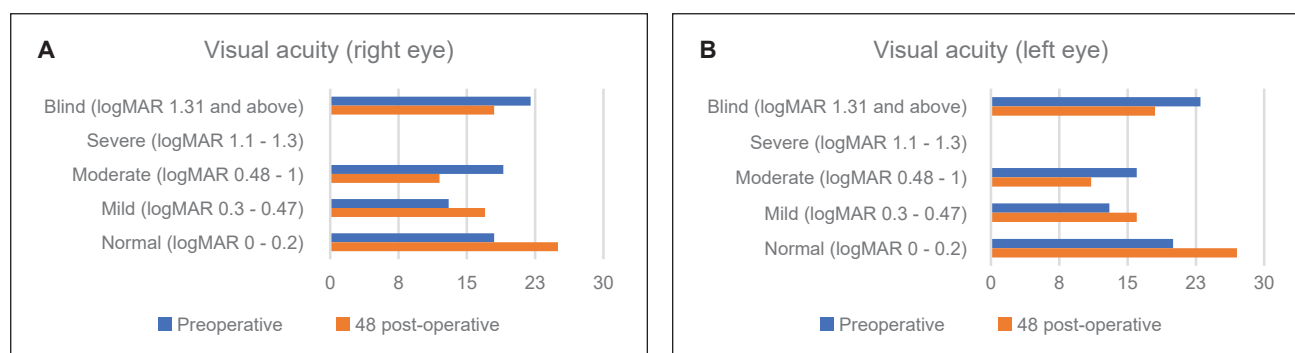


Figure 1. Pre-operative and 48-hour post-operative visual acuity [(A) right eye and (B) left eye] among patients with pituitary macroadenoma.

The median time from symptom onset to initial physician consult and neurosurgery consult were 2.96 months (IQR 0.00 to 12.00) and 12.00 months (IQR 4.44 to 35.86), respectively. Moreover, the interval from symptom onset to surgery was a median of 18.67 months (IQR 9.27 to 44.44). Majority of patients (31.25%) were seen by a neurosurgeon within 6 months of symptom onset, but most (27.35%) waited more than 3 years before they underwent surgery (Table 3).

Pre-operatively, the median Glasgow Coma Scale (GCS) score was 15. Only 5.15% of patients had neurological deficits, the most common of which was cranial nerve palsy (2.06%). Mean pre-operative visual acuities were 20/70, logMAR 0.54 (IQR 0.24 to 2.00) and 20/70, logMAR 0.54 (IQR 0.18 to 2.00) for the right and left eyes, respectively. Pre-operatively, 30.56% of patients were already blind (logMAR 1.31 and above) in the right eye, 31.94% in the left eye, and 2.78% bilaterally. Majority (60.56%) also exhibited bitemporal hemianopsia on confrontation test pre-operatively, while 16.90% had unilateral hemianopsia and 22.54% had normal visual fields.

Table 3. Descriptive statistics of the interval periods of events among patients with pituitary macroadenoma

Interval of events	Median (IQR ^a)	Frequency	Percentage (%)
Symptom onset to initial physician consult (n=115)	2.96 (0.00-12.00)		
Less than 6 months		67	58.26
6 months to 1 year		22	19.13
1 to 2 years		7	6.09
2 to 3 years		6	5.22
More than 3 years		13	11.30
Symptom onset to neurosurgery consult (n=112)	12.00 (4.44-35.86)		
Less than 6 months		35	31.25
6 months to 1 year		24	21.43
1 to 2 years		16	14.29
2 to 3 years		14	12.50
More than 3 years		23	20.54
Symptom onset to surgery (n=117)	18.67 (9.27-44.41)		
Less than 6 months		16	13.68
6 months to 1 year		24	20.51
1 to 2 years		29	24.79
2 to 3 years		16	13.68
More than 3 years		32	27.35

^a IQR, interquartile range

Of the 21.13% with functioning macroadenoma, acromegaly (59.26%) and prolactinoma (33.33%) were the most common. On the other end of the spectrum, 15.29% (13/85) had hypopituitarism, 22.09% (19/86) had hypocortisolism, 22.73% (25/110) had hypothyroidism, and 5.49% (5/91) had secondary hyperprolactinemia pre-operatively. One patient had pre-operative DI. The difference in the denominators was due to incomplete workup or missing information for some patients. Majority of patients with hypopituitarism were on levothyroxine (36.07%) and prednisone (22.13%).

Post-operatively, all patients remained GCS 15. Only 72 patients in our study had ophthalmologic data that could be compared pre- and post-operatively. After pituitary decompression surgery, the mean post-operative visual acuity was 0.40 logMAR (Snellen equivalent 20/50) for both eyes, from 0.54 logMAR (Snellen equivalent 20/70) pre-operatively. The improvement in the visual acuity scores for both eyes was statistically significant ($p=0.001$). In terms of visual fields, 60.56% reported subjective improvement; 38.03%, no change; and 1.41%, worsening.

Postoperative hormonal levels are described in Table 4 and Figure 2. Majority of patients with pituitary hypofunction did not exhibit any change in hormonal status from the pre-operative to the latest follow-up period. A smaller group of patients showed improvement in hypopituitarism (21.74%), hypothyroidism (19.35%) and hypocortisolism (8.33%). Data on hypogonadism was not estimated due to insufficient data. Proportions of patients who were on levothyroxine (36.07 vs. 17.21%, $p = 0.001$) and hydrocortisone (21.31 vs. 3.28%, $p = 0.001$) significantly decreased pre- and post-operatively. Initially, there were two time periods identified for follow-up: follow up number 1 (within 48 hours post-surgery) and number 2 (latest follow-up). Due to inconsistencies and lack of post-operative data including hormonal levels on follow up beyond the 48-hour period, results could not be properly accrued.

Correlation analyses of the different factors showed that age, sex, type of pituitary macroadenoma, size of tumor, timing of surgery, interval from symptom onset to surgery, surgical approach, post-operative complications and adju-

vant radiation therapy were not significantly associated with either the visual or endocrine outcomes of the patients (Appendices A and B). Outcomes associated with the level

of expertise of the surgeons who performed each procedure were not analyzed and were deemed beyond the scope of the study.

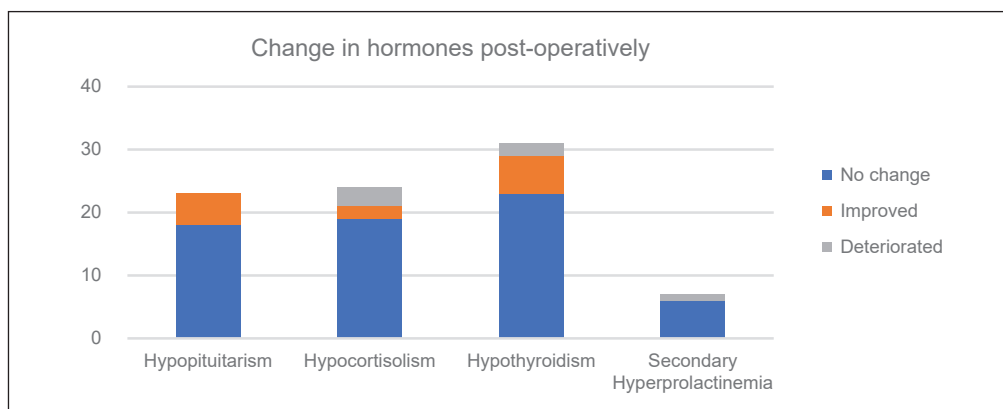


Figure 2. Post-operative hormonal status among patients with pituitary macroadenoma.

Table 4. Descriptive statistics of the neurologic, ophthalmologic, and endocrinologic outcomes of patients with pituitary macroadenoma

Outcome	Timeframe				p-value (two-tailed)
	Pre-operative		Latest Follow-up		
	n	Summary Statistic	n	Summary Statistic	
Neurologic outcomes					
Deficits, frequency (%)	97	5 (5.15)	40	3 (7.50)	0.625 ^a
Palsy		2 (2.06)		1 (2.50)	1.000 ^a
Paresis and plegia		1 (1.03)		1 (2.50)	1.000 ^a
Ptosis		1 (1.03)		0	1.000 ^a
Glasgow coma scale, median (IQR)	119	15 (15-15)	119	15 (15-15)	0.250 ^b
Ophthalmologic outcomes					
Visual acuity (logMAR)					
Right eye	72	0.54 (0.18-2.00)	72	0.40 (0.10-1.15)	0.001 ^{b*}
Normal (logMAR 0-0.2)		18 (25.00)		25 (34.72)	0.001 ^{a*}
Mild (logMAR 0.3-0.47)		13 (18.06)		17 (23.61)	
Moderate (logMAR 0.48-1.0)		19 (26.39)		12 (16.67)	
Severe (logMAR 1.1-1.3)		0		0	
Blind (logMAR 1.31 and above)		22 (30.56)		18 (25.00)	
Left eye	72	0.54 (0.18-2.0)	72	0.40 (0.10-1.15)	0.001 ^{b*}
Normal (logMAR 0-0.2)		20 (27.78)		27 (37.50)	0.001 ^{a*}
Mild (logMAR 0.3-0.47)		13 (18.06)		16 (22.22)	
Moderate (logMAR 0.48-1.0)		16 (22.22)		11 (15.28)	
Severe (logMAR 1.1-1.3)		0		0	
Blind (logMAR 1.31 and above)		23 (31.94)		18 (25.00)	
Visual field cuts	71		—	—	—
Normal		16 (22.54)			
Unilateral		12 (16.90)			
Bilateral		43 (60.56)			
Blind		0			
Visual field cuts change	—	—	71		—
No change				27 (38.03)	
Improved				43 (60.56)	
Worsened				1 (1.41)	
Endocrine outcomes (%)					
Hormonal function					
Hypopituitarism	31	13 (15.29)		1 (3.12)	
Hypocortisolism	23	19 (22.09)		9 (28.12)	
Hypothyroidism	24	25 (22.73)		4 (11.43)	
Secondary hyperprolactinemia	7	5 (5.49)		2 (18.18)	
Medication					
Levothyroxine	122	44 (36.07)	122	21 (17.21)	0.001 ^{a*}
Prednisone	122	27 (22.13)	122	21 (17.21)	0.334 ^{a*}
Hydrocortisone	122	26 (21.31)	122	4 (3.28)	0.001 ^{a*}
Metformin	122	2 (1.64)	122	5 (4.10)	0.250 ^{a*}
Bromocriptine	122	5 (4.10)	122	2 (1.64)	0.250 ^{a*}
Desmopressin	122	3 (2.46)	122	1 (0.82)	0.313 ^{a*}
Medroxyprogesterone	0	—	122	1 (0.82)	0.316 ^{a*}

Comparative analyses were conducted using the following:

^a Chi-square test of homogeneity or Fisher's exact test

^b Mann-Whitney U test

^c Independent t-test

DISCUSSION

This is the first local in-depth study on the post-operative neurologic, ophthalmologic and endocrine outcomes of pituitary macroadenoma, as well as the delay from symptom onset to surgery.

Delay in diagnosis and treatment

Our study showed that it took three months for a patient to see a physician, 12 months to see a neurosurgeon and 18 months before they could undergo surgery. This supported the finding that timely diagnosis and universal access to treatment for pituitary adenoma patients remain difficult in our population. Contributing factors include the lack of specialists and equipment in local hospitals and the high cost of diagnostic examinations and treatment.¹³ Waiting time for surgery differ according to country-level income, with high income countries (HICs) reporting an average wait time of four to 30 days, depending on the surgical urgency of each case.¹⁴ Brain tumor patients tended to wait longer in LMICs than HICs, due to healthcare costs, lack of universal healthcare insurance programs, limited neurosurgery workforce, and lack of facilities such as operating rooms and hospital beds.¹⁴

Aside from socioeconomic factors, the benign nature of pituitary adenomas may have led to delay in diagnosis. Most of our patients presented with a large tumor size due to indolent growth and benign characteristics; hence, nearly one-third were already blind in one eye pre-operatively.¹⁵ This finding was similar to the experience in Ghana, where 38.9% of patients were blind pre-operatively.¹⁶ Furthermore, despite being one of the most common intracranial tumors, pituitary adenoma are fairly not known by the general public.¹⁷ Since the patients' presenting symptoms were mainly visual problems, their first consult would be with ophthalmology, contributing to delay in surgical treatment.¹⁷

Timing of surgery and surgical approach

Almost one-third of our patients underwent surgery more than three years from symptom onset, but our results showed that the timing of surgery had no significant association with visual and endocrine outcomes. This was in contrast to a study that reported that the duration and severity of pre-operative visual symptoms may dictate the post-operative outcome; hence, the dictum is to treat early to preserve and correct visual deficits.^{2,16} A meta-analysis found that symptom duration was one of the predictive factors affecting visual recovery after surgery, while other studies reported inconsistent results.^{8,18} In our cohort, several of our patients were already blind pre-operatively, which may have affected the analysis.

Surgery is the mainstay treatment for pituitary macroadenoma, and endoscopic transsphenoidal excision (TSE) has been the technique of choice in most centers inter-

nationally since it was introduced more than 20 years ago.¹⁶ Furthermore, surgery is indicated in patients with functioning pituitary macroadenoma who are refractory to medical treatment. In a meta-analysis comparing microscopic and endoscopic TSE, the endoscopic arm showed higher gross total resection rates and visual recovery among patients.¹⁹ In our cohort, microscopic TSE was performed more than twice as often as endoscopic TSE. This was due to the lack of equipment and specialists that only became available fairly recently in our center.

Post-operative outcomes

Ophthalmologic

There was a statistically significant improvement of approximately one line of visual acuity in our patients post-operatively. Most patients also demonstrated subjective improvement in their visual field. This phenomenon was due to the biological response of the optic nerve to decompression during surgery, which may take place within ten minutes of decompression.^{6,20}

The pattern of visual field defect depends on the growth pattern of the tumor.²¹ Compression of the optic chiasm produces visual pathology directly due to its mass effect upon the axons, impairing axonal transport and signal transmission. It may also produce pathology indirectly through the compression of perivascular structures that supply the chiasm, producing ischemia. In animal models, chronic nerve compression has demonstrated a direct dose-response relationship, in which the duration of compression correlated with the degree of nerve injury. Histopathologic evidence demonstrated initial breakdown of the blood-nerve barrier, followed by perineural edema and subsequent gliosis. With loss of trophic stimuli, diffuse demyelination was then observed, with subsequent Wallerian degeneration.²²

This retrograde degeneration of axons from the optic chiasm was directly observed during funduscopy examination as optic atrophy. Objective measurement of the retinal nerve fiber layer (RNFL) thickness through OCT has been found to demonstrate prognostic value for immediate visual recovery after pituitary decompression.²³ Patients with a RNFL thickness of ≥ 80 microns were found to have greater visual recovery post-operatively compared to those with thinner RNFL at presentation.²⁴

Visual recovery was postulated to be divided into three phases: rapid recovery (within minutes to one week post-operatively), early slow phase (one to four months) where improvement was more evident, and late phase (six months to three years) where there was only minimal improvement.⁶ Clinical studies reported progressive improvement in visual acuity, which usually ranged from one to two years and even as late as five years post-operatively.^{6,16,25} For visual field recovery, most of the improvement occurred within three to six months after surgery.²⁶ Other authors observed that the majority of visual improvement occurred within

the first six to ten weeks, with continued improvement up to one year post-operatively. Immediate improvement occurs due to the removal of the physiologic conduction block,^{6,27} and visual evoked responses were documented to improve as early as 10 minutes after surgical pituitary decompression.²⁰ Over time, limited remyelination and resumption of axoplasmic flow may produce guarded visual recovery.^{6,27} Our study adds to the current neuro-ophthalmologic evidence that pituitary decompression surgery may still demonstrate potential visual benefit.

Endocrine

The incidence of individual endocrine deficits in our study was consistent with that reported in the local literature, where adrenal insufficiency (22.09%) and hypothyroidism (22.73%) were found to be the most common endocrinopathies, followed by secondary hyperprolactinemia (19.35%).²⁸ However, the lack of routine assessment of growth hormone (GH) and luteinizing hormone/follicle-stimulating hormone (LH/FSH) axes in all patients at admission prevented accurate estimate of GH deficit and hypogonadism. Since we did not have complete data about the patients' hormonal status, the use of hormone replacement therapy was used as an indirect way to assess the improvement of the endocrine axis among our patients post-operatively. The study demonstrated significant decrease in use of levothyroxine and hydrocortisone/prednisone among patients who underwent surgery, which suggested resolution of hormonal deficiencies.

After uneventful surgery, pituitary function is usually evaluated four to six weeks post-operatively, since earlier evaluation may falsely reflect the hormonal status.²⁹ Jahangiri et al., reported that the three anterior pituitary axes (hypogonadism, hypothyroidism, and hyposomatotropism) showed delayed normalization of laboratory values, occurring between six weeks to six months.³⁰ Hence, our findings that 74-85% of our patients exhibited persistent pituitary hypofunction post-operatively may be overestimated due to poor patient follow-up.

However, pre-operative hypopituitarism was unlikely to be corrected with surgery.³¹ This may be due to the destructive effect of tumor compression on the pituitary gland or from the disturbance in the portal circulation which causes ischemic processes and cell necrosis, leading to pituitary hypofunction.³⁰ Similar to the compressive effect of pituitary tumors on the optic nerve and subsequent visual outcomes, longstanding tumors may lead to limited endocrine recovery because the pituitary gland has little capacity for regeneration.³¹ This was consistent with our findings; majority of our patients did not show any endocrine improvement post-operatively. Younger age, absence of hypertension, and absence of intra-operative CSF leak were identified as the strongest clinical predictors of hormonal recovery.³² Tumor size and baseline pituitary gland volume were also thought to affect the recovery of hypopituitarism after surgery,³² but other authors reported that there was no significant association.³³

Functioning adenoma comprises 22% of the total population in the study with prolactinoma and acromegaly as the most common hypersecreting pituitary tumors. Although medical management has been previously the treatment of choice for prolactinoma, this study reflects increasing utilization of surgery for this subgroup. Treatment with bromocriptine or cabergoline showed remission rate of 90% with microprolactinoma and 70% with macroprolactinoma.³⁴ For those patients who underwent surgical resection of prolactinoma, the cure rate was at 70% among microprolactinomas, and only 30% among macroprolactinomas, especially if the cavernous sinus is involved.³⁵ Prolactin levels are closely followed up for the first year after surgery, and increasing levels suggest tumor recurrence, or tumor progression in cases of residual tumor.³⁵ Outcomes of prolactinoma patients who underwent surgery were not demonstrated due to insufficient data on post operative hormonal levels among the patients included. However, indirect measures such as the use of dopamine agonist therapy were remarkably decreased among these post-operative patients.

Acromegaly, on the other hand, was one of the most common hypersecreting pituitary tumors in our study. Trial of medical therapy has been the first line treatment for acromegaly, especially in cases with only moderate clinical symptoms. Medical treatment include somatostatin analogue, pegvisomant, and dopamine agonist such as cabergoline, in cases of modest biochemical abnormality and minimal metabolic symptoms.³⁵ In our experience, medical treatment can be challenging due to its unsustainable cost among patients.¹³ In fact, our data showed that none of the acromegalic patients were able to start any of the first line medical treatment, and instead, all of which opted to undergo surgical resection as this was more feasible rather than the hormonal treatment available.

Acromegalic patients who underwent surgical tumor resection would have immediate improvement in metabolic parameters within hours of resection.³⁵ With insufficient data on post-operative hormonal levels among our patients, an accurate measurement of outcomes among this subset of patients were unlikely.

Surgical complications and length of hospital stay

Transient DI was the most common complication in our cohort, similar to other studies but in contrast to others, wherein CSF leak was the most common.^{34,36,37} The incidence of transient DI in our study (24.59%) was slightly higher compared to other centers, which ranged from 18.3% to 24%.^{1,32,38} These results may be confounded by the retrospective nature of some studies, as well as the surgical technique and experience of the surgeons involved.³⁶ It was also reported that patients who had CSF leak intra-operatively had a higher risk of transient DI post-operatively due to more aggressive resection.³⁸ Fortunately, the rate of permanent DI is low, ranging from 0-2%.^{30,32,38}

The most common type of complication influenced the median length of hospital stay (12 days), since patients who developed transient DI had to stay longer for serial monitoring of serum sodium, urine output, and urine specific gravity. Our length of stay was slightly longer than the median of five to eight days after uneventful surgery in most centers.³⁹ Stratified fast-track care in pituitary surgery was also being explored. Patients were discharged two to three days after uneventful surgery and followed up regularly at home by a case manager, decreasing overall costs.⁴⁰

Follow up

Poor patient follow-up and inconsistencies with pre- and post-operative outcome measures were evident in our study. In fact, 36% of the initial cohort were excluded due to incomplete charts. Geographic and socioeconomic factors likely played a role in the poor follow-up. Since the country is an archipelago, patients may find it challenging to seek medical consult due to transportation difficulties, especially those in isolated rural areas.¹³ They would also have to shoulder the cost of transportation, adding to the cost of medical care.

The latter part of the study period coincided with the coronavirus-19 (COVID-19) pandemic which resulted in lockdowns, travel restrictions, and closure of non-urgent services such as the outpatient department. Even after the telemedicine service was implemented, patient follow-up was still very poor. For the pituitary adenoma patients who were able to participate in telemedicine, there was an incomplete assessment of neurological and visual outcomes due to the inability of physicians to examine patients face-to-face.

Another sequela of the pandemic was the rapid transition to electronic medical records in our institution. This process may have contributed to the incomplete data on post-operative outcomes in our study, particularly in the years 2020 to 2021, due to clinicians' inexperience with the new platform and intrinsic errors in the new system.

Due to the retrospective design of our study, there was no regular follow-up interval aside from the first 48 hours post-operatively. A systematic review on the topic showed that there was heterogeneity in the length of follow-up across studies due to income level, availability of resources, and the multidisciplinary nature of the disease. In fact, the authors highlighted that lost patient data might have been a more common problem than a patient being lost to follow-up, hence they suggested a more centralized and standardized method in evaluating outcomes following treatment.³⁹ As for the timing of post-operative imaging, there is no standard at present. Kunigelis et al.^g suggested performing cranial imaging at least three months post-operatively, since earlier scans were equivocal and resulted in increased reoperation rates but did not show any difference in the long-term clinical outcomes.⁴¹

Recommendations

We recommend establishing a centralized patient database that could be accessed by the different specialty services in the multidisciplinary pituitary team. This will include uniform pre- and post-operative neurologic, ophthalmologic and endocrine assessments in order to accurately compare and quantify the outcomes of our patients. Pre- and post-operative diagnostic examinations (automated visual perimetry, OCT and hormonal workup) should be standardized. A uniform follow-up schedule should also be implemented to facilitate comparison of visual and endocrine changes pre- and post-operatively.

Limitations

The limitations of our study included the following: it was retrospective in nature, involved only a single center, and had incomplete data due to missing charts. In addition, we may have overlooked any potential significance in the correlational analysis due to missing charts and inconsistent post-operative data.

CONCLUSION

This is the first local study to comprehensively assess the entirety of post-operative outcomes among pituitary macroadenoma patients. Our results showed that the median tumor size was 3.5 cm and the median time to surgery was 18 months. Despite these, there was subjective improvement in the patients' visual fields, and the mean visual acuity improved by approximately one line in the Snellen chart post-operatively. There was also some improvement in endocrine function post-operatively. This showed that even patients with longstanding visual and endocrine deficits may still improve with surgery. Improvements are needed to decrease surgical delays, achieve better post-operative outcomes, encourage patient follow-up and standardize pre- and post-operative treatment protocols.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

MUH: Conceptualization, Resource, Data Curation, Writing – original draft preparation, Writing – review and editing; **DJL and JAN:** Conceptualization, Resource, Data Curation, Writing – original draft preparation, Writing – review and editing; **KSS:** Writing – review and editing, Supervision, Project administration. **KOK:** Conceptualization, Writing – original draft preparation, Writing – review and editing, Supervision, Project Administration.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

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APPENDICES

Appendix A. Correlation analyses of the association of the different factors with the visual outcome among patients with pituitary macroadenoma (N = 122)

Characteristic	Visual acuity change						Visual field cut change											
	Right Eye			Left Eye			No change			Improved			Worsened			p-value		
	N	No change	Improved	Worsened	p-value	N	No change	Improved	Worsened	p-value	N	No change	Improved	Worsened	p-value			
Age, year	72	42.38 (10.72)	47.5 (15.81)	45.33 (12.82)	0.535	72	43.25 (11.69)	48.0 (11.78)	43.22 (11.85)	0.656	71	45.15 (14.89)	44.26 (10.46)	31.0 (0)	0.530			
Sex (%)	72	18 (40.91)	14 (8.33)	2 (50.0)	0.382	72	25 (58.14)	8 (34.78)	1 (16.67)	0.067	71	13 (48.15)	23 (53.49)	1 (100)	0.571			
Male	26 (59.09)	10 (41.67)	2 (50.0)			18 (41.86)	15 (65.22)	5 (83.33)			14 (51.85)	20 (46.51)	0					
Female																		
Macroadenoma type	72	30 (16.18)	24 (100.0)	4 (100.0)	0.002*	72	34 (79.07)	19 (82.61)	5 (83.33)	1.000	71	19 (70.37)	38 (88.37)	1 (100.0)	0.148			
Non-functioning	14 (31.82)	0				9 (20.93)	4 (17.39)	1 (16.67)			71	8 (29.63)	5 (11.63)	0				
Functioning	72	9 (20.45)	0			8 (18.6)	1 (4.35)	0		0.227	71	7 (25.93)	3 (6.98)	0	0.079			
Acromegaly	72	4 (9.09)	0			0	3 (13.04)	1 (16.67)		0.024*	71	0	2 (4.65)	0	0.512			
Prolactinoma	72	1 (2.27)	0			1 (2.33)	0	0		1.000	71	1 (3.7)	0	0	0.438			
Cushing's disease	72	0	0			0	0	0		-	71	0	0	0	-			
TSH-secreting	62	2 (5.41)	0	1 (4.55)	0.862	62	2 (5.13)	0	1 (5.0)	0.973	65	4 (17.39)	0	0	0.063			
Tumor size (%)	23 (62.16)	3 (100.0)	15 (68.18)			23 (63.89)	4 (66.67)	14 (70.0)			11 (47.83)	28 (68.29)	1 (100.0)					
≤2 cm	12 (32.43)	0	6 (27.27)			11 (30.56)	2 (33.33)	5 (25.0)			8 (34.78)	13 (31.71)	0					
2.1 to 4.0 cm																		
>4.0 cm																		
Timing of surgery	72	6 (13.64)	4 (16.67)	1 (25.0)	0.176	72	8 (18.6)	3 (13.04)	0	0.229	71	4 (14.81)	3 (6.98)	1 (100.0)	0.120			
<6 months	9 (20.45)	3 (12.5)	1 (25.0)			7 (16.28)	5 (21.74)	1 (16.67)			3 (11.11)	7 (16.28)	0					
6 months to 1 year	10 (22.73)	6 (25.0)	0			10 (23.26)	6 (26.09)	0			5 (18.52)	10 (23.26)	0					
1 to 2 years	3 (6.82)	7 (29.17)	1 (25.0)			5 (11.63)	2 (8.7)	4 (66.67)			3 (11.11)	8 (18.6)	0					
2 to 3 years	16 (36.36)	4 (16.67)	1 (25.0)			13 (30.23)	7 (30.43)	1 (16.67)			12 (44.44)	15 (34.88)	0					
>3 years																		
Symptom onset to initial consult	67	20 (48.78)	10 (45.45)	2 (50.0)	0.659	67	16 (40.0)	13 (61.9)	3 (50.0)	0.336	67	9 (33.33)	18 (47.37)	1 (100.0)	0.574			
<6 months	11 (26.83)	5 (22.73)	0			11 (27.5)	5 (23.81)	0			9 (33.33)	8 (21.05)	0					
6 months to 1 year	4 (9.76)	2 (9.09)	1 (25.0)			4 (10.0)	2 (9.52)	1 (16.67)			1 (3.7)	6 (15.79)	0					
1 to 2 years	2 (4.88)	1 (4.55)	1 (25.0)			4 (10.0)	0	0			3 (11.11)	2 (5.26)	0					
2 to 3 years	4 (9.76)	4 (18.18)	0			5 (12.5)	1 (4.76)	2 (33.33)			5 (18.52)	4 (10.53)	0					
>3 years																		
Symptom onset to neurosurgery consult	67	13 (31.71)	5 (22.73)	0	0.088	67	10 (24.39)	7 (35.0)	1 (16.67)	0.878	64	4 (16.0)	11 (28.95)	1 (100.0)	0.187			
<6 months	9 (21.95)	6 (27.27)	1 (25.0)			10 (24.39)	4 (20.0)	2 (33.33)			6 (24.0)	9 (23.68)	0					
6 months to 1 year	5 (12.2)	5 (22.73)	0			7 (17.07)	2 (10.0)	1 (16.67)			3 (12.0)	6 (15.79)	0					
1 to 2 years	3 (7.32)	1 (4.55)	3 (75.0)			6 (14.63)	1 (5.0)	0			7 (28.0)	2 (5.26)	0					
2 to 3 years	11 (26.83)	5 (22.73)	0			8 (19.51)	6 (30.0)	2 (33.33)			5 (20.0)	10 (26.32)	0					
>3 years																		
Surgical approach	71	26 (59.09)	11 (47.83)	1 (25.0)	0.447	71	24 (57.14)	13 (56.52)	1 (16.67)	0.044*	70	14 (51.85)	20 (47.62)	0	0.836			
TSE ^a (microscopic)	13 (29.55)	10 (43.48)	2 (50.0)			16 (38.1)	7 (30.43)	2 (33.33)			9 (33.33)	16 (38.1)	1 (100.0)					
TSE ^a (endoscopic)	5 (11.36)	2 (8.7)	1 (25.0)			2 (4.76)	3 (13.04)	3 (50.0)			4 (14.81)	6 (14.29)	0					
Craniotomy																		
Post-operative complications	72	1 (2.27)	2 (8.33)	0	0.397	72	2 (4.65)	1 (4.35)	0	1.000	71	1 (3.7)	0	2 (4.65)	1.000			
CSF ^b leak	72	1 (2.27)	0		1.000	72	1 (2.33)	0	0	1.000	71	3 (11.11)	0	0	0.093			
Hematoma	72	13 (29.55)	7 (29.17)	1 (25.0)	1.000	72	12 (27.91)	7 (30.43)	2 (33.33)	1.000	71	5 (18.52)	15 (34.88)	0	0.293			
Transient DI ^c	72	4 (9.09)	0	0	0.437	72	4 (9.3)	0	0	0.381	71	1 (3.7)	0	3 (6.98)	1.000			
Meningitis																		
Adjuvant radiation therapy	36	5 (21.74)	2 (16.67)	0	1.000	36	4 (15.38)	2 (25.0)	1 (50.0)	0.433	35	1 (7.69)	0	5 (22.73)	0.377			
Note: Analysis for ventriculothoracic shunt (surgical approach), internal carotid artery injury (post-operative complications), permanent diabetes insipidus (post-operative complications), and pneumocephalus (post-operative complications).																		

Note: Analysis for ventriculoperitoneal shunt (surgical approach), internal carotid artery injury (post-operative complications), permanent diabetes insipidus (post-operative complications), and pneumonia (post-operative complications) were not feasible due to insufficient cases.

Analyses were conducted using the following: Eta Correlation, Cramer V

* Significant at 0.05

^a TSE, transsphenoidal excision; CSF, cerebrospinal fluid; ^c DI, diabetes insipidus

Appendix B. Correlation analyses of the association of the different factors with the endocrine outcome among patients with pituitary macroadenoma (n = 122)

Characteristic	Change in hormonal level									
	Hypopituitarism					Hypocortisolism				
	N	No change	Improved	Worsened	p-value	N	No change	Improved	Worsened	p-value
Age, year^a	23	40.06 (11.89)	45.0 (10.8)	44.89 (12.13)	0.412	24	41.0 (1.26)	43.0 (8.49)	43.33 (8.74)	0.923
Sex (%)	23	6 (33.33) 12 (66.67)	3 (60.0) 2 (40.0)	0 0	0.280	24	8 (42.11) 11 (57.89)	0 2 (100.0)	2 (66.67) 1 (33.33)	0.333
Macroadenoma type^b	23	11 (61.11) 7 (38.89)	2 (100.0) 0	3 (100.0) 0	0.095	24	11 (57.89) 8 (42.11)	2 (100.0) 0	3 (100.0) 0	0.206
Non-functioning	23	3 (16.67) 2 (11.11)	0 0	0 0	0.328	24	4 (21.05) 2 (10.53)	0 0	0 0	0.532
Acromegaly	23	2 (11.11) 1 (5.56)	0 0	0 0	0.435	24	2 (10.53) 1 (5.26)	0 0	0 0	0.750
Prolactinoma	23	1 (5.56) 1 (5.56)	0 0	0 0	0.590	24	1 (5.26) 1 (5.26)	0 0	0 0	0.872
Cushing's disease	23	1 (5.56) 1 (5.56)	0 0	0 0	0.590	24	1 (5.26) 1 (5.26)	0 0	0 0	0.872
TSH-secreting	23	1 (5.56) 1 (5.56)	0 0	0 0	0.590	24	1 (5.26) 1 (5.26)	0 0	0 0	0.872
Tumor size (%)	20	2 (11.76) 0	0 0	0 0	0.211	21	2 (11.76) 0	0 0	0 0	0.768
≤2 cm	20	2 (11.76) 0	0 0	0 0	0.211	21	2 (11.76) 0	0 0	0 0	0.768
2.1 to 4.0 cm	20	2 (11.76) 0	0 0	0 0	0.211	21	2 (11.76) 0	0 0	0 0	0.768
>4.0 cm	20	15 (88.24) 4 (22.22)	2 (100.0) 0	3 (100.0) 0	0.120	24	15 (88.24) 2 (10.53)	2 (100.0) 0	3 (100.0) 0	0.047*
Timing of surgery (%)^b	23	4 (22.22) 1 (5.56)	0 2 (40.0)	0 0	0.120	24	2 (10.53) 2 (10.53)	0 1 (50.0)	2 (66.67) 0	0.047*
<6 months	23	4 (22.22) 1 (5.56)	0 2 (40.0)	0 0	0.120	24	2 (10.53) 2 (10.53)	0 1 (50.0)	2 (66.67) 0	0.047*
6 months to 1 year	23	6 (33.33) 1 (5.56)	2 (40.0) 1 (20.0)	0 0	0.120	24	8 (42.11) 6 (31.58)	0 0	0 0	0.047*
1 to 2 years	23	6 (33.33) 1 (5.56)	2 (40.0) 1 (20.0)	0 0	0.120	24	8 (42.11) 6 (31.58)	0 0	0 0	0.047*
2 to 3 years	23	6 (33.33) 1 (5.56)	2 (40.0) 1 (20.0)	0 0	0.120	24	8 (42.11) 6 (31.58)	0 0	0 0	0.047*
>3 years	23	6 (33.33) 1 (5.56)	2 (40.0) 1 (20.0)	0 0	0.120	24	8 (42.11) 6 (31.58)	0 0	0 0	0.047*
Symptom onset to initial consult (%)^b	22	9 (52.94) 4 (23.53)	3 (60.0) 0	0 0	0.249	23	12 (66.67) 4 (22.22)	1 (50.0) 0	1 (33.33) 0	0.245
<6 months	22	9 (52.94) 4 (23.53)	3 (60.0) 0	0 0	0.249	23	12 (66.67) 4 (22.22)	1 (50.0) 0	1 (33.33) 0	0.245
6 months to 1 year	22	4 (23.53) 2 (11.76)	0 1 (5.88)	0 0	0.249	23	4 (22.22) 1 (5.56)	0 0	0 0	0.245
1 to 2 years	22	2 (11.76) 1 (5.88)	0 1 (5.88)	0 0	0.249	23	1 (5.56) 1 (5.88)	0 0	0 0	0.245
2 to 3 years	22	1 (5.88) 1 (5.88)	0 1 (5.88)	0 0	0.249	23	0 1 (5.88)	0 1 (5.00)	0 1 (33.33)	0.245
>3 years	22	1 (5.88) 1 (5.88)	0 1 (5.88)	0 0	0.249	23	1 (5.56) 1 (5.88)	1 (50.0) 1 (33.33)	1 (33.33) 0	0.245
Symptom onset to neurosurgery consult (%)^b	21	6 (35.29) 5 (29.41)	1 (50.0) 0	0 1 (33.33)	0.380	22	6 (35.29) 5 (29.41)	1 (50.0) 0	0 1 (33.33)	0.716
<6 months	21	6 (35.29) 5 (29.41)	1 (50.0) 0	0 1 (33.33)	0.380	22	6 (35.29) 5 (29.41)	1 (50.0) 0	0 1 (33.33)	0.716
6 months to 1 year	21	5 (29.41) 2 (11.76)	0 0	0 0	0.380	22	5 (29.41) 2 (11.76)	0 0	0 0	0.716
1 to 2 years	21	2 (11.76) 1 (5.88)	0 1 (5.88)	0 0	0.380	22	2 (11.76) 1 (5.88)	0 0	0 0	0.716
2 to 3 years	21	1 (5.88) 1 (5.88)	0 1 (5.88)	0 0	0.380	22	1 (5.88) 1 (5.88)	0 1 (50.0)	0 2 (66.67)	0.716
>3 years	21	3 (17.65) 10 (55.56)	1 (50.0) 3 (60.0)	2 (66.67) 0	0.380	24	3 (17.65) 9 (47.37)	1 (50.0) 1 (50.0)	2 (66.67) 2 (66.67)	0.156
Surgical approach (%)^b	23	10 (55.56) 7 (38.89)	1 (20.0) 3 (60.0)	0 0	0.305	24	9 (47.37) 9 (47.37)	1 (50.0) 0	2 (66.67) 0	0.156
TSE ^c (microscopic)	23	10 (55.56) 7 (38.89)	1 (20.0) 3 (60.0)	0 0	0.305	24	9 (47.37) 9 (47.37)	1 (50.0) 0	2 (66.67) 0	0.156
TSE ^c (endoscopic)	23	7 (38.89) 1 (5.56)	3 (60.0) 1 (20.0)	0 0	0.305	24	9 (47.37) 1 (5.26)	0 1 (50.0)	0 1 (33.33)	0.156
Craniotomy	23	1 (5.56) 1 (5.56)	0 1 (20.0)	0 0	0.305	24	1 (5.26) 1 (5.26)	0 1 (50.0)	0 1 (33.33)	0.156
Post-operative complications (%)^b	23	1 (5.56) 0	0 0	2 (2.02) 0	0.590	24	1 (5.26) 0	0 0	0 0	0.872
CSF ^d leak	23	1 (5.56) 0	0 0	2 (2.02) 0	0.590	24	1 (5.26) 0	0 0	0 0	0.872
Hematoma	23	0 4 (22.22)	0 1 (20.0)	0 0	-	24	0 5 (26.32)	0 0	0 1 (33.33)	-
Transient DI ^e	23	4 (22.22) 1 (5.56)	1 (20.0) 0	0 0	0.915	24	5 (26.32) 1 (5.26)	0 0	1 (33.33) 0	0.762
Meningitis	23	1 (5.56) 1 (5.56)	0 0	0 0	0.590	24	1 (5.26) 1 (5.26)	0 0	0 0	0.872
Adjuvant radiation therapy	18	1 (7.69) 1 (7.69)	2 (40.0) 2 (40.0)	0 0	0.099	18	3 (21.43) 3 (21.43)	1 (50.0) 1 (50.0)	0 0	0.480

Note: Analysis for ventriculoperitoneal shunt (surgical approach), internal carotid artery injury (post-operative complications), permanent diabetes insipidus (post-operative complications), and pneumonia (post-operative complications) were not feasible due to insufficient cases.

* Significant at 0.05

Analyses were conducted using the following: ^a Eta Correlation; ^b Cramer V

^c TSE, transphenoidal excision; ^d CSF, cerebrospinal fluid; ^e DI, diabetes insipidus

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Effectiveness of Adrenal Venous Sampling in the Management of Primary Aldosteronism: Single-Centered Cross-Sectional Study at a Tertiary Care Hospital in Sri Lanka

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Abstract

Introduction. Adrenal venous sampling (AVS) is the gold standard procedure to discriminate unilateral primary aldosteronism (UPA) from bilateral disease (BPA). AVS is technically demanding and is only performed in a limited number of centers in Sri Lanka. This study aimed to evaluate the effectiveness of AVS in the management of primary aldosteronism.

Methodology. Thirty-two patients who underwent AVS at the National Hospital of Sri Lanka from April 2021 to April 2023 were enrolled. Continuous and categorical variables were summarized with mean $\pm$ SD and proportions, respectively. Mean and standard deviation of contralateral suppression index (CSI) were estimated with an intercept-only Bayesian inference model.

Results. The adrenal veins were successfully cannulated in 12 (37.5%). Lateralization was established in 11 (91.7%), and one was diagnosed as having bilateral disease. There were no total failures. Right AV cannulation was unsuccessful in 18 (56.25%), out of which lateralization was demonstrated in 9 (50%), while the rest were considered inconclusive. Left AV cannulation was unsuccessful only in 2 (6.25%); one was lateralized, while the other remained inconclusive. Among patients classified as having unilateral disease, the estimated mean of the CSI was 0.33 (89% credible interval: 0.11–0.86).

Conclusion. Despite failure due to procedural difficulties, AVS remained useful in the management of patients with PA. CSI remains a useful tool when cannulation is unsuccessful, especially on the right side.

Key words: adrenal venous sampling, lateralization, contralateral suppression index

INTRODUCTION

Primary aldosteronism (PA) is highly prevalent among patients with drug-resistant hypertension¹ and may be diagnosed in >11% of the patients referred to specialized hypertension centres.² Though it is common, it is still underdiagnosed.³

There is strong evidence indicating that PA increases the risk of organ damage, including cardiorenal complications, if left untreated. Hence, early diagnosis of affected patients and prompt initiation of specific treatment are crucial for preventing cardiovascular events and reversing damage.⁴

It is essential to differentiate unilateral PA [aldosterone-producing adenoma (APA)] from bilateral PA (idiopathic hyperaldosteronism [IHA]) as the former warrants

adrenalectomy, whereas the latter needs lifelong treatment with mineralocorticoid receptor (MR) blockers.⁵

Historically, adrenal computed tomography played a crucial role in diagnosing the culprit lesion in PA.⁵ With the increasing identification of non-functional adrenal tumours leading to unnecessary interventions, adrenal vein sampling (AVS) became the gold standard investigation to localize and lateralise the lesion. The only exceptions are in younger patients below 35 years of age with florid disease and the presence of a clear one-sided adrenal adenoma with a normal contralateral gland.⁵ Current clinical practice guidelines advocate the use of AVS with measurement of plasma cortisol concentration (PCC) and plasma aldosterone concentration (PAC).⁵ Though AVS is a straightforward diagnostic test, globally it is used only in a few centres due to the technical challenges, especially in a developing country like Sri Lanka.

However, apart from very few studies conducted in India, research studies on this area are scarce. So far, no studies have been done on AVS and its impact on PA management in Sri Lanka. Hence, we aimed to evaluate the effectiveness of AVS in the management of primary aldosteronism at a tertiary care hospital in Sri Lanka.

METHODOLOGY

Study design

We conducted a retrospective cross-sectional study from April 2021 to April 2023 at the National Hospital of Sri Lanka (NHSL), a tertiary referral centre for AVS in Sri Lanka.

Data collection and its analysis were approved by the ethics review committee at NHSL.

Study population

A total of 32 patients who underwent AVS at the National Hospital of Sri Lanka from April 2021 to April 2023 were enrolled in the study. The diagnostic work-up for primary aldosteronism was done according to the established guidelines.^{5,6}

Demographic, clinical, and laboratory data were obtained retrospectively from the electronic records in the Department of Chemical Pathology, NHSL. Study variables collected include (1) patient demographics (age and gender), (2) clinical characteristics (blood pressure, potassium level, aldosterone and renin concentrations, post-saline loading aldosterone concentration), (3) radiological imaging findings, and (4) adrenal venous sampling data.

Radiological imaging

Images from the most recent CT or MRI reports reported by the consultant radiologist prior to AVS were evaluated. Imaging reports were categorized in one of four ways: left-sided lesion, right-sided lesion, bilateral lesions, or no lesion. If a lesion was observed on one adrenal gland and the contralateral gland appeared completely normal, the finding was classified as unilateral, either as left-sided or right-sided, depending on the side of the lesion.

Adrenal venous sampling

Adrenal vein sampling (AVS) was performed in either a sequential non-stimulated or, in one case, a stimulated manner, depending on the availability of cosyntropin (synthetic ACTH). Due to the economic crisis in Sri Lanka, cosyntropin was not routinely accessible through the public healthcare system, and patients were required to self-fund it if stimulation was deemed necessary. As a result, non-stimulated AVS was the standard approach, with only one patient undergoing stimulated AVS after independently securing cosyntropin.

The procedure was carried out in a dedicated interventional radiology suite by a consultant interventional radiologist, with real-time support from the endocrinology and chemical pathology teams. After local anesthesia, vascular access was obtained through the common femoral vein using a 5F or 6F sheath under aseptic technique. A hydrophilic guidewire and a diagnostic catheter (typically a Simmons or Cobra catheter for the right adrenal vein and a renal double curve or multipurpose catheter for the left) were advanced under fluoroscopic guidance to selectively cannulate each adrenal vein. AVS was performed in a sequential manner — first the right adrenal vein, followed by the left — with blood samples collected from each adrenal vein and a peripheral vein (usually the inferior vena cava at the level of the renal veins or right atrium) for cortisol and aldosterone measurement.

Samples were immediately handed over to the chemical pathology team present on site to ensure rapid processing and minimize pre-analytical variability.

A cortisol gradient across each adrenal vein and IVC of >5 in a stimulated AVS and that of ≥ 2 in a non-stimulated AVS was used to establish successful cannulation. The procedure was considered successful when both the right and left adrenal veins were successfully cannulated.

Lateralization index (LI) was defined as the ratio of the high to low cortisol-corrected aldosterone ratio. LI of ≥ 4 in stimulated AVS and that of ≥ 2 in a non-stimulated AVS indicated unilateral aldosterone excess, while the values between 3 and 4 were assumed borderline in stimulated AVS.

Contralateral suppression index (CSI) is calculated as the ratio of aldosterone/cortisol in the nondominant side to the periphery (IVC). CSI of <0.5 is highly predictive of contralateral disease.⁷

Serum aldosterone was measured with a competitive two-step chemiluminescent microparticle immunoassay in a Diasorin-Liason fully automated analyser at the Medical Research Institute, Sri Lanka.

Serum cortisol was measured by a competitive two-step chemiluminescent microparticle immunoassay in the ADVIA Centaur XP fully automated analyser at NHSL.

All the samples were transported to relevant laboratories at room temperature and analysed on the day of the collection.

Statistical analysis

The distribution of continuous variables was visualized with kernel density plots and histograms. These variables were summarized using the mean and standard deviation (SD) when they demonstrated a near-normal distribution, and the median and interquartile range (IQR) when they did not. Categorical variables were summarized with frequency tables and presented as percentages.

The inter-observer agreement between AVS and CT was assessed with Cohen's kappa statistic and percentage agreement.

Due to the limited sample size and the nature of the data, a Bayesian statistical approach was adopted to estimate the distribution parameters of the CSI. Given that CSI is a non-negative continuous ratio, a lognormal likelihood function was chosen, as it is a maximum entropy distribution appropriate for modelling positive values. An intercept-only Bayesian inference model was implemented using Markov Chain Monte Carlo (MCMC) sampling. Weakly informative priors were applied for the mean (μ) and standard deviation (σ) of the log-transformed CSI values. This choice was made to provide sufficient regularization while allowing the data to primarily inform the posterior estimates, especially in the context of a small sample size and lack of strong prior knowledge. All patients included in this analysis ($n = 12$) had successful bilateral AVS.

CSI $\sim$ lognormal(μ, σ)	[Likelihood function]
log(μ) = a	[intercept-only model]
a $\sim$ N(0,1) and $\sigma \sim$ uniform(0,10)	[prior distributions]

Four MCMC chains were used with 50% warm-up samples. Chain mixing patterns were visualized with trace plots.

Analysis was conducted using R language 4.1.2 and Stan Modelling Language through *rstan* and *rethinking* interface packages.

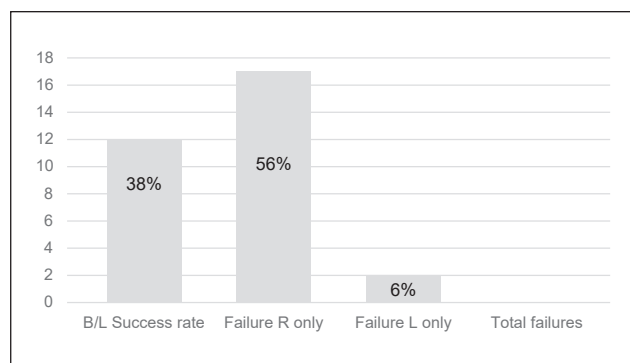


Figure 1. Success and failure rates of AVS.

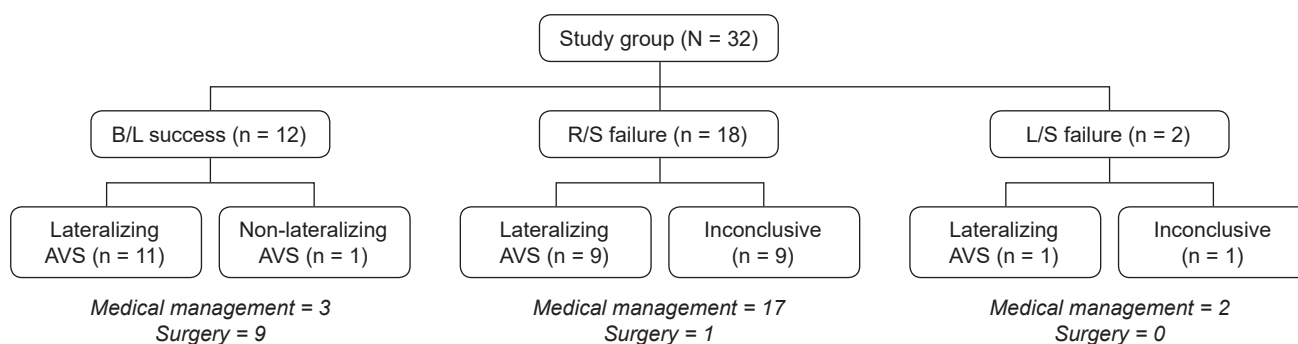


Figure 2. Study profile.

RESULTS

A total of 32 patients who underwent AVS at the National Hospital of Sri Lanka from April 2021 to April 2023 were included. The mean age of the study population was 52.47 ± 26.14 years, with 19 (59.4%) of them being men. All had hypertension, and 28 (87.5%) had at least one episode of spontaneous hypokalemia.

Of the 32 patients who underwent CT adrenal imaging, 10 had left-sided adenomas, 7 had right-sided adenomas, and 15 had normal adrenal imaging findings.

Success and failure rates

Out of 32 patients, only one underwent stimulated AVS.

There were no total failures in adrenal vein cannulation. Successful cannulation of both adrenal veins was demonstrated (Figure 1) in 12 (37.5%), including the patient who underwent stimulated AVS. Cannulation was unsuccessful on the right in 18 patients (56.25%), compared to 2 patients (6.25%) on the left.

Among those with successful bilateral cannulation, 92% ($n = 11$) demonstrated lateralization, proving they had unilateral disease, while one patient had bilateral disease. In the group with failed right adrenal vein cannulation ($n = 18$), 50% ($n = 9$) showed lateralization according to the CSI. Of the two patients with unsuccessful left adrenal vein cannulation, one showed lateralization, and the other had inconclusive results based on the CSI (Figure 2).

No significant procedure-related complications were noted.

Seven patients underwent unilateral adrenalectomy. Histological analysis revealed left-sided adrenal adenomas in five patients and right-sided adrenal adenomas in two. All demonstrated significant improvement in aldosterone and renin values as well as in blood pressure during follow-up. Two patients are awaiting surgery, while the remaining patients are being managed medically.

Agreement between AVS and CT findings

CT and AVS results were compared in 12 patients with bilaterally successful AVS, excluding cases with failure in cannulation of either side. The agreement between the two diagnostic methods was 42%. Cohen's kappa statistic was 0.168, indicating a slight agreement. This is depicted in Figure 3.

Estimation of the contralateral suppression index

The Bayesian model demonstrated good convergence, with all four Markov chains showing adequate mixing, as evidenced by trace plot evaluations (Supplementary Figure 1). Among patients classified as having unilateral disease based on adrenal vein sampling, the posterior mean of the CSI was estimated at 0.33, with an 89% credible interval ranging from 0.11 to 0.86 (Figure 4). This distribution supports the utility of CSI in distinguishing unilateral from bilateral aldosterone secretion patterns and aligns with previously suggested thresholds in the literature, though further validation in larger cohorts is warranted.

DISCUSSION

The present study provides a critical understanding of the implementation of AVS in the management of PA at the NHSL. The overall success rate for AVS during this period was 38%, which is on par with the German Conn's registry, which reported successful bilateral adrenal vein cannulation in only 30.5% of patients. Furthermore, success rates in centres performing a small number of AVS are reported to be as low as 8%–10%. However, the successful cannulation rate of both adrenal veins was as high as 95.6% in high-volume centers.⁸

The main challenge in successful AVS is the failure to cannulate the right adrenal vein, which results from either the inability to identify the vessel or the misidentification of the vessel.

In this study, the failure rates of the right and left adrenal veins were 56% and 6%, respectively. This finding is consistent with previous studies, which have shown that the right adrenal vein cannulation failure rate is typically higher, ranging from 30% to 60%.^{9,10}

In our study, the endocrinology team opted for surgery in only one patient who lateralized on CSI but had successful cannulation on only one side. For cases involving unsuccessful unilateral cannulation and discordant findings between imaging and CSI results, the team deferred surgery and recommended repeating AVS at a later time.

We found a strikingly high rate (58%) of disagreement between CT/MRI results and AVS results, assuming AVS is 100% accurate in detecting the lateralization of aldosterone secretion. Among patients with successful bilateral cannulation ($n = 12$), a unilateral abnormality was reported

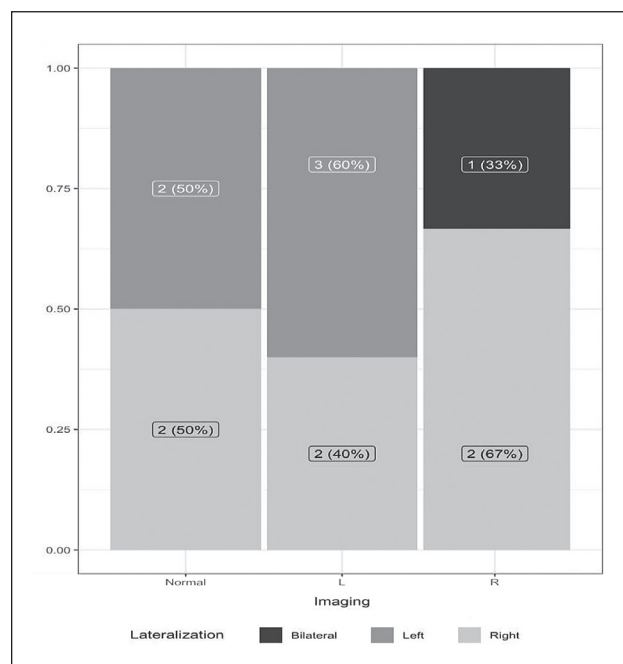


Figure 3. Agreement between adrenal vein sampling (AVS) and CT findings depicted with a width-stacked column chart.

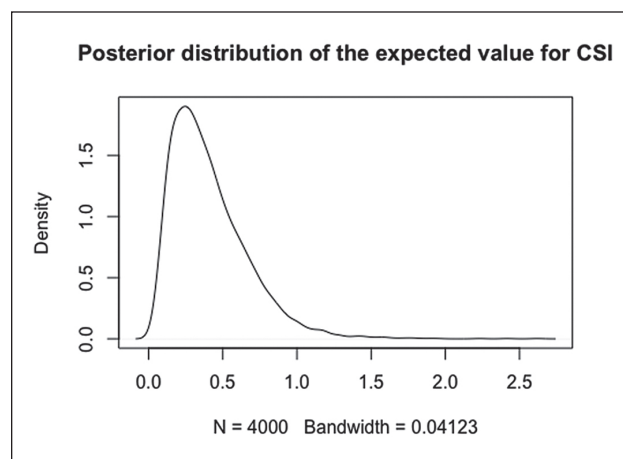


Figure 4. Posterior distribution of the expected value for CSI.

by CT/MRI in 66.6% ($n = 8$) and by AVS in 91.7% ($n = 11$). Agreement between CT/MRI and AVS on the involved side was found in only 42% of patients, indicated by a Cohen's kappa statistic of 0.168 (slight agreement). This finding aligns with previous studies that reported a discrepancy between CT/MRI and AVS ranging from 35% to 52%.^{8,11}

CT/MRI may detect non-functioning adenomas or nodules, or may fail to detect small functional adenomas, leading to false positive or false negative results. Conceptually, AVS is an attractive procedure because it detects the origin of the abnormality on a biochemical basis in a primarily biochemical disease.

The estimated mean of the posterior CSI distribution was 0.33, which is consistent with the findings by Pasternak

Table 1. Baseline patient data including Contralateral Suppression Index (CSI)

ID	Age	Gender	HT	Hypokalemia	Aldo	Renin	ARR	AVS (S/NS)	Right Cannulation	Left Cannulation	CSI	Lateralized (from AVS)	Imaging
1	71	F	Y	Y			>30	NS	N	Y			L/S lesion
2	34	F	Y	Y	45	0.38	118	NS	Y	Y	0.225	R/S	R/S lesion
3	49	M	Y	Y	30.3	0.12	252	NS	N	Y			L/S lesion
4	60	M	Y	Y	14	0.2	71	NS	Y	Y	2.3	B/L	R/S lesion
5	66	M	Y	Y	20.1	1.3		NS	Y	Y	0.2	L/S	L/S lesion
6	46	M	Y	Y	18.6	0.11	169	NS	N	Y			Normal
7	48	F	Y	Y			>30	NS	Y	Y	0.48		normal
8	64	M	Y	N	14.3	0.07	204	S	Y	Y	1.5	R/S	L/S
9	46	M	Y	Y	12.9	0.48	26.9	NS	N	Y			normal
10	63	M	Y	Y	10.2	<0.5		NS	N	Y			normal
11	44	F	Y	Y	32	0.5	>30	NS	Y	Y	0.5	L/S	L/S
12	65	F	Y	Y	22.3	0.5	44.6	NS	Y	Y	0.83	L/S	L/S
13	27	F	Y	Y	31.8	0.12	265	NS	N	Y			normal
14	78	F	Y	N	24.3	1	24.3	NS	Y	N			R/S lesion
15	63	M	Y	Y	10.2	<0.5		NS	N	Y			normal
16	46	M	Y	Y	17	<0.5		NS	N	Y			normal
17	33	F	Y	Y	10.2	0.6	18	Ns	Y	Y	7.88	R/S	normal
18	48	M	Y	N	28.4	0.32	88.8	Ns	N	Y			normal
19	49	F	Y	Y	11.6	0.67	17.3	NS	N	Y			normal
20	58	M	Y	N	27.5	0.07	330	NS	Y	Y	0.29	R/S	R/S
21	34	F	Y	Y	12.6	0.57	22.1	NS	Y	Y	4.6	R/S	L/S
22	73	M	Y	Y	57.3	<0.5		NS	N	Y			L/S lesion
23	33	M	Y	Y	10.2	0.6	17	NS	Y	Y	7.88		normal
24	47	F	Y	Y	40.2	0.11		NS	Y	Y	0.47	R/S	normal
25	50	F	Y	Y	26.5	0.9	29.2	NS	N	Y		L/S	R/S lesion
26	54	M	Y	Y	37.3	2.0	18.6	NS	N	Y			R/S lesion
27	70	M	Y	Y	24	0.2	120	NS	N	Y			normal
28	50	M	Y	Y	32	1.9		NS	N	Y			R/S lesion
29	39	F	Y	Y	28.1	0.25	112	NS	N	Y			L/S lesion
30	64	M	Y	Y	22.8	0.16	143	NS	Y	N			L/S lesion
31	47	M	Y	Y	28.4	0.3	88.8	NS	N	Y			normal
32	60	M	Y	Y	30	<0.5	>60	Ns	N	Y			normal

et al., and William Young et al. It appears that a cut-off of ≤ 0.5 is reliable for avoiding the misclassification of bilateral disease as contralateral unilateral disease. This cut-off value performed well in identifying either left or right unilateral disease.^{6,7}

The limitation of this single-centre study is the generalizability of its results to other centres performing AVS, mainly due to differences in procedural technique, cosyntropin infusion use, and aldosterone and cortisol assays. Stimulated AVS was not routinely available in Sri Lanka, except for patients who could afford cosyntropin, owing to the economic crisis. Furthermore, the outcomes were based on the retrospective analysis.

The main strength of our study is that its results were derived from a well-defined national cohort. Patient management was standardized according to the Endocrine Society clinical guidelines whenever feasible, and we used the LI and cut-off values recommended by the most recent Endocrine Society guidelines, which have been shown to be most reliable. Nonetheless, this is the first study reporting the effectiveness of AVS in the management of PA from Sri Lanka.

CONCLUSION

The high diagnostic accuracy of AVS compared to imaging studies further supports the suggestion that AVS should serve as the gold standard diagnostic test for the subtyping of PA. Furthermore, successful cannulation of both adrenal veins is critical for reliable subtype characterization.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

CB: Conceptualization, Methodology, Writing – Original draft preparation; **SM:** Software, validation, Data curation; **SN:** Conceptualization, Methodology; **SO:** Investigations, resources; **JL:** Investigations, Resources; **GK:** Supervision, Writing – Reviewing and Editing.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

The authors declared no conflict of interest.

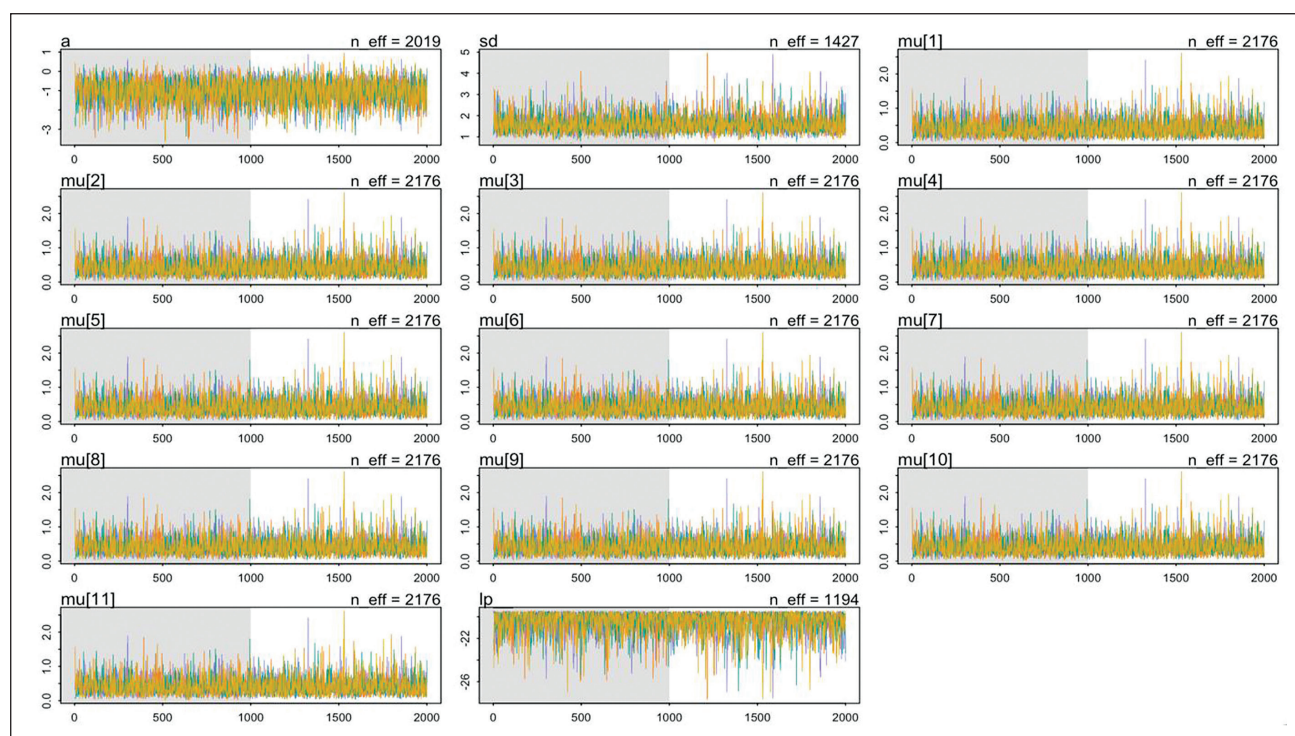
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SUPPLEMENTARY MATERIAL

Supplementary Figure. Trace plot of the parameter estimations of the grand intercept (a), standard deviation (sd) and the means of each of the observations (mu[1] to lp).

Clinical and Genotypic Insights into Turner Syndrome: Emphasis on Cardiovascular Abnormalities

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Abstract

Objective. Turner syndrome (TS) is a genetic disorder characterized by X chromosome abnormalities in females. It presents with various clinical features, including short stature and cardiovascular anomalies. Limited awareness and diagnostic facilities contribute to the underdiagnosis of TS in India. The current study aims to explore genotype-phenotype associations with clinical characteristics and cardiovascular abnormalities in TS patients in India.

Methodology. A cross-sectional study involving 40 TS patients underwent clinical assessments and karyotyping. Data on demographics, anthropometry, Turner stigmata, cardiovascular evaluation, neurocognitive assessment and biochemical parameters were collected. The statistical analysis was conducted utilizing Statistical Package for Social Sciences (SPSS) version 27.0.

Results. Monosomy 45, X (55%) was the most prevalent genotype, with notable differences in age at diagnosis and height standard deviation score among genotypes. Thirty-five percent (35%) of participants had cardiovascular abnormalities, with a higher prevalence in the monosomy group. Lower IQ scores and increased thyroid autoimmunity were associated with specific genotypes. Additionally, a greater occurrence of skeletal and cutaneous stigmata, including cubitus valgus and multiple nevi, was observed in the monosomy group.

Conclusion. The study underscores the significance of genotype-phenotype associations in TS, emphasizing personalized management strategies. Early detection using sophisticated technologies like MRI, comprehensive assessments and assisted personalized management strategies to individual genetic profiles may improve cardiovascular and overall health outcomes in Turner syndrome patients.

Key words: Turner syndrome, genotype-phenotype associations, cardiovascular abnormalities, karyotyping, clinical characteristics

BACKGROUND

Turner syndrome (TS) is the sole survivable monomer syndrome in humans resulting from complete or partial absence of the X chromosome in females. It is relatively common, occurring in approximately 1 in 2,500 live female births.¹ Despite India's birth rate and the estimated incidence of TS, many cases likely go undetected due to limited awareness and diagnostic facilities.²

The primary phenotypic hallmark of TS is short stature, accompanied by characteristic features like a short neck, broad chest, genu valgum and nail dysplasia.³ Of the complications associated with TS, non-congenital cardiovascular disease emerges as a major threat, responsible for over 40% of deaths, while congenital cardiovascular

anomalies contribute around 8% to mortality.⁴ Intriguingly, individuals with 45, XO monosomy exhibit a substantially higher prevalence of cardiovascular anomalies (38%) compared to those with 45, X/46, XX mosaicism (11%), consequently leading to elevated mortality rates.⁵ Cardiovascular abnormalities such as aortic dissection, represent a significant concern in TS, contributing to a mortality rate three times higher than that of the general population.⁶ Additionally, autoimmune diseases, notably thyroiditis,⁷ and skeletal issues like osteoporosis elevate health risks, particularly in adult women with TS.³

Given the diverse clinical presentations of TS, contingent upon the patient's karyotype, this study aims to investigate the influence of various chromosomal irregularities on clinical and biochemical characteristics in TS patients.

METHODOLOGY

Study design

This observational, cross-sectional study spanned 18 months from February 2020 to July 2021 in a tertiary care center in India. It focused on patients clinically diagnosed with TS attending the Endocrinology Department of Nil Ratan Sircar (NRS) Medical College Hospital, Kolkata. The diagnosis was confirmed through karyotypic analysis once they had provided informed consent.

Inclusion and exclusion criteria

Participants included patients with TS whose karyotyping was validated by examining 20 to 50 metaphase cells using the Giemsa-Trypsin-Giemsa (GTG) banding technique in a certified genetics laboratory. Patients with Noonan syndrome and those lacking karyotypic confirmation despite exhibiting features suggestive of TS were excluded.

Measurements and assessments

Anthropometric measurements, detailed clinical examination and pubertal status were recorded. Cardiovascular evaluation included electrocardiogram, echocardiography with colour Doppler and Magnetic Resonance Imaging (MRI). A cardiac MRI with aortography was done on a Siemens 3 Tesla MAGNETOM Verio dot machine done by a single operator to look for different cardiac and aortic anomalies. The aortic size index (ASI) is the ratio of the aortic diameter to body surface area. The diameter is usually taken at the level of the ascending aorta or the part of the aorta near the right pulmonary artery. The elongated transverse aortic arch was also noted, if present, which is a kinking of the inferior aortic contour at the aortic isthmus and/or left subclavian artery originating from a position posterior to the trachea in the horizontal plane and/or an increased distance between the left common carotid and left subclavian artery.

Neurocognitive evaluation included the Weschler Adult Intelligence Score⁸ for subjects aged 15 and above, and the Malin's Intelligence Scale for Indian Children for those aged 5-15.

Routine biochemical parameters and hormonal parameters were analysed in an autoanalyzer and a Siemens immunoassay system (IMMULITE 1000), respectively, in our institution laboratory.

Sample size estimation

Previous studies done on genotype-phenotype associations in TS patients had sample sizes ranging from 16 to 52 participants.^{9,10}

Considering $\alpha=0.05$, $\beta = 0.85$, the sample size is estimated to be 43.

Similarly, considering an $\alpha=0.05$, $\beta = 0.80$, the sample size is estimated to be 25.

Therefore, we considered a sample size of 40 in our study.

Ethical clearance

Written informed consent was obtained from all participants, and confidentiality was maintained. The study was conducted in accordance with the Declaration of Helsinki (1964) and approved by the Institutional Research Ethics Committee.

Statistical analysis

The study participants were classified into three groups based on their karyotypic profile: Monosomy (Genotype A), Mosaicism (Genotype B) and Structural defects (Genotype C). Continuous data were displayed as mean with standard deviation (SD), and categorical variables were represented as frequency (N) and percentage (%). The data was entered into a Microsoft Excel sheet and analyzed utilizing Statistical Package for Social Sciences (SPSS) (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Demographics, clinical features and biochemical parameters were compared using Chi-square test (for categorical variables) or one-way ANOVA (for continuous variables). The differences in the prevalence of cardiovascular abnormalities were compared between the groups A, B and C using Chi-square test. The association between the aortic size index and the genotypes identified were compared using One-way ANOVA. A p-value of ≤ 0.05 was deemed statistically significant.

RESULTS

The study comprised forty (N = 40) subjects diagnosed with TS, confirmed through clinical stigmata assessment and karyotypic analysis. Among the participants, fifty-five percent (n=22) exhibited monosomy, denoted as Genotype A, while twenty-five percent (n=10) presented with structural defects, including seven isochromosomes, two ring chromosomes, and one deletion at Xp22.3, categorized as Genotype C. Additionally, twenty percent (n=8) displayed mosaicism, categorized as Genotype B (Figure 1).

Significant differences were observed in the mean age at diagnosis across genotypes, with individuals of Genotype A diagnosed at an average age of 7.4 years, while those of Genotypes B or C were diagnosed at 11.8 years ($P<0.05$). Similarly, there was notable variability in mean height SDS, with the monosomy genotype exhibiting the lowest value (-4.4 ± 1.33), followed by the structural defect genotype (-3.80 ± 1.18), and the mosaic genotype showing the least decrease in height (-3.13 ± 0.86) ($P<0.05$). No significant differences in the IQ scores have been observed between individuals with Genotype A (83.7 ± 10.8), Genotype B (87 ± 10.2) and Genotype C (87.4 ± 14.4). For a comprehensive overview of additional characteristics, refer to Table 1.

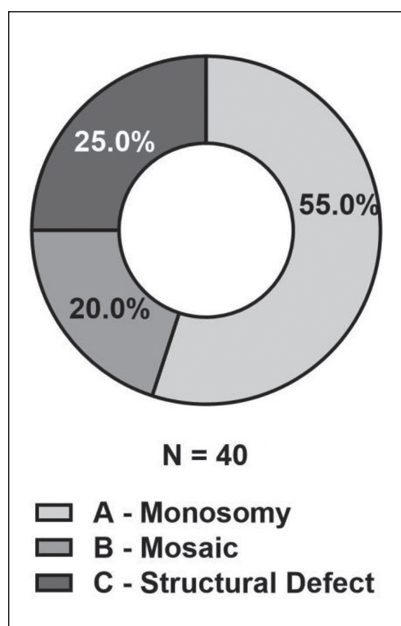


Figure 1. Distribution of karyotypes among subjects with Turner syndrome (n = 40).

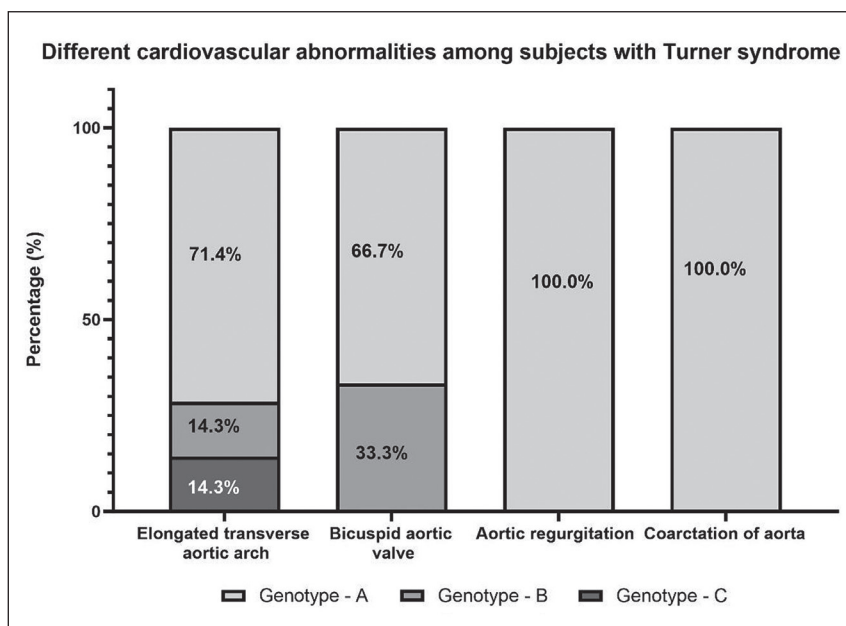


Figure 2. Different cardiovascular abnormalities among subjects with Turner syndrome (n = 40).



Figure 3. Cardiac MRI showing cardiovascular abnormalities in subjects with Turner syndrome. **(A)** Dilated subclavian artery (blue arrow) and elongated transverse aortic arch (orange arrow); **(B)** Coarctation of aorta (blue arrow) and dilated subclavian artery (red arrow); **(C)** Coarctation of aorta (red arrow) and dilated subclavian artery (blue arrow).

Among the study participants, 14 cases exhibited cardiac abnormalities, accounting for 35% of the total cohort (Figure 1 and Table 2). Additional analysis indicated that the monosomy group exhibited a higher percentage of cardiovascular abnormalities than the other genotype groups (Figure 2). Figure 3 shows a representative image suggestive of an elongated transverse aortic arch.

Additionally, the mean aortic size index in the monosomy group was 2.7 cm/m² in the monosomy group, while it measured 2.3 cm/m² in the non-monosomy group (Table 3).

DISCUSSION

This study examined the correlation between genotypes and the diverse clinical and biochemical characteristics in individuals of Indian descent diagnosed with TS, with a specific focus on cardiovascular abnormalities. Our study revealed significant associations between genotypes and certain clinical and biochemical features.

The distribution of genotypes among the 40 patients with TS in our study closely resembles that reported in existing

literature. Monosomy 45, X (45, XO) was the most prevalent genotype, comprising 55% of the cases, followed by structural defects and mosaic genotypes. A previous study in Indian TS patients observed monosomy in 69% of cases, followed by mosaic genotypes (12%) and structural defects (19%).¹¹ Similarly, studies across the globe have reported monosomy to be the most common (~50%) genetic defect, followed by mosaic genotypes (10-30%) and structural defects (10 to 38%).^{12,13}

Monosomy X in Turner syndrome increases the risk of heart defects due to the loss of genes on the second X chromosome, which are critical for normal cardiovascular development.¹⁴ For example, a haploinsufficiency of *TIMP1* has been associated with increased risk for bicuspid aortic valve, aortic aneurysm formation and dissection.^{15,16} This highlights the need for early cardiac screening and lifelong monitoring to prevent severe complications.

Our study revealed a lower mean age at diagnosis, particularly in the monosomy group, compared to the non-monosomy groups. This finding aligns with recent Indian studies reporting a mean age at presentation of approxi-

Table 1. Prevalence of different clinical and biochemical features among subjects with Turner syndrome (n = 40)

Abnormalities	Genotype-A (N = 22) n (%) or mean $\pm$ SD	Genotype-B (N = 8) n (%) or mean $\pm$ SD	Genotype-C (N = 10) n (%) or mean $\pm$ SD	p-value
Age at diagnosis (yr)	7.4 $\pm$ 2.1	12 $\pm$ 5	11.8 $\pm$ 2.7	0.0002***
Height SDS	-4.4 $\pm$ 1.3	-3.12 $\pm$ 0.86	-3.8 $\pm$ 1.2	0.03*
Weight SDS	-1.67 $\pm$ 0.7	-1.09 $\pm$ 0.83	-1.12 $\pm$ 0.6	0.05
TPO positive	13 (59.1%)	0 (0%)	7 (70%)	0.01*
FSH (mIU/mL)	86.4 $\pm$ 18.7	60.8 $\pm$ 42.6	62.5 $\pm$ 28.3	0.02*
Estradiol (pg/mL)	7.2 $\pm$ 1	19.5 $\pm$ 6.8	16.4 $\pm$ 3.5	0.0001***
AMH (ng/mL)	1.6 $\pm$ 0.7	4 $\pm$ 1.8	2.9 $\pm$ 2	0.0007***
IQ Scores	83.7 $\pm$ 10.8	87 $\pm$ 10.2	87.4 $\pm$ 14.4	0.64
Verbal-Performance IQ	11.4 $\pm$ 1.9	12.5 $\pm$ 0.5	15.2 $\pm$ 1.4	<0.0001****
Multiple pigmented nevi	18 (81.8%)	2 (25%)	6 (40%)	0.01*
Cubitus valgus	19 (86.4%)	2 (25%)	6 (60%)	0.01*
Short 4th Metacarpal	19 (86.4%)	2 (25%)	6 (60%)	0.01*
Low posterior hairline	19 (86.4%)	2 (25%)	6 (60%)	0.01*
Shield chest	4 (18.2%)	4 (50%)	0 (0%)	0.03*
Low set ears	17 (77.3%)	6 (75%)	4 (40%)	0.1
Short/webbed neck	11 (50%)	2 (25%)	4 (40%)	0.46
Scoliosis	3 (13.6%)	0 (0%)	2 (20%)	0.43
High arched palate	16 (72.7%)	2 (25%)	6 (60%)	0.06

OR: Odds Ratio; SDS: Standard Deviation Score; TPO: Thyroid Peroxidase; FSH: Follicle-Stimulating Hormone; AMH: Anti-Müllerian Hormone. *, ***, **** represents $P < 0.05$, $P < 0.001$, $P < 0.0001$ respectively.

Table 2. Association between different cardiovascular abnormalities among subjects with Turner syndrome and the genotype

Abnormalities	Genotype-A (N = 22) n (%)	Genotype-B (N = 8) n (%)	Genotype-C (N = 10) n (%)	p-value	Picked up by Echocardiography	Picked up by Cardiac MRI
Bicuspid aortic valve	2 (9.1%)	1 (12.5%)	0 (0%)	0.5545	Yes	Yes
Elongated transverse aortic arch	5 (22.7%)	1 (12.5%)	1 (10%)	0.6236	No	Yes
Aortic regurgitation	3 (100%)	0 (0%)	0 (0%)	-	Yes	Yes
Coarctation of aorta	1 (100%)	0 (0%)	0 (0%)	-	Yes	Yes

Table 3. Association between ASI: Genotype

ASI	Number	Mean	SD	Minimum	Maximum	Median	p-value
Genotype-A	11	2.7009	0.1053	2.4500	2.8000	2.7100	0.0013
Genotype-B	2	2.3500	0.0707	2.3000	2.4000	2.3500	
Genotype-C	1	2.3800	0.0000	2.3800	2.3800	2.3800	

ASI – Aortic Size Index

mately 14 years, with many patients primarily presenting with gonadal failure.¹⁷ This discrepancy in age at diagnosis may reflect varying clinical presentations influenced by karyotype. Therefore, healthcare providers must be vigilant to facilitate early detection of TS in adolescents, particularly among those presenting with gonadal issues.¹⁷

Additionally, the mean height Standard Deviation Score (SDS) across all ages was notably shorter (between -3.12 and -4.4) than that found in international studies (~ -2.0 to -3.0),¹⁸ suggesting a characteristic of the Indian TS population.¹⁹

The shorter stature observed in the current study may be attributed to delayed diagnosis and a subsequent delay in initiating growth-promoting therapies, certain ethnic and genetic factors specific to the Indian population, and associated comorbidities such as renal anomalies and

cardiac defects. Additionally, factors such as access to healthcare resources and nutritional status could influence growth outcomes in this group.¹¹ In our study, individuals with monosomy (45, X) had a lower mean height SDS than other genotypes. This could be attributed to the additional effect of haploinsufficiency of genes such as SHOX on the X chromosome.¹¹

The current study also observed an increased frequency of skeletal and cutaneous markers, with cubitus valgus and multiple nevi being the most prevalent (Table 1). Previous studies have also observed that the clinical manifestations of TS are most pronounced in individuals with monosomy 45, X, least severe in those with mosaicism 45, X/46, XX, and intermediate in individuals with iso-chromosome and Y-material genotypes.^{20,21}

The observed variation in clinical severity among TS karyotypes suggests differential gene expression and epigenetic influences. Unique genetic makeup and interactions between X chromosome genes and other factors likely contribute to phenotypic variability.^{20,21} In the current study, stigmata were more common in the monosomy group, particularly cubitus valgus, short fourth metacarpal, low posterior hairline, multiple pigmented nevi, and shield chest.

Early detection of cardiovascular abnormalities in TS is crucial due to their potential impact on morbidity and mortality. In the current study, a slightly higher prevalence (35%) was observed compared to previous reports of 25 – 30%, consistent with findings from a Taiwanese cohort that noted these abnormalities predominantly in the classical 45, XO TS group.²² This highlights the importance of cardiac MRI over echocardiography, particularly for detecting abnormalities like elongated transverse aortic arch (ETAA) and cardiac lesions.^{23,24} While cardiac MRI offers detailed imaging, accessibility and cost can limit its widespread use, necessitating a balanced approach in integrating both techniques for comprehensive cardiovascular assessment in TS patients.²³

Examining IQ scores in TS patients reveals potential cognitive impairments, impacting academic, social and daily functioning, reflecting the importance of tailored interventions for improved quality of life.²⁵ Regarding cognitive function, we found lower IQ scores in our TS patients (Avg. IQ – 83.7) compared to previous studies.^{25,26} This observation is consistent with research indicating an increased incidence of intellectual disability, particularly in patients with ring chromosome r(X).²⁷ Additionally, hypothyroidism was found to be most common in isochromosomes, possibly due to enhanced autoimmunity involving the thyroid gland.^{17,28}

Limitations

The study's small sample size limits the generalizability of findings to the broader TS population. Limited awareness and diagnostic facilities in India may contribute to a biased sample that does not fully represent the spectrum of TS, particularly milder cases. Lack of information on confounding variables and significant delays in diagnosing TS in patients could impact the observed phenotype and the severity of cardiovascular abnormalities.

CONCLUSION

Our cohort revealed that classic monosomy is the most common form of Turner Syndrome. This group had the lowest SDS height and had more cardiac defects, the most common being an elongated transverse aortic arch. Advanced imaging techniques like cardiac MRI are crucial for accurately diagnosing cardiovascular abnormalities. Additionally, our findings highlight lower IQ scores and increased thyroid autoimmunity in certain genotypes,

emphasizing the need for comprehensive assessments and targeted interventions. Early detection and appropriate management are essential for improving outcomes in TS patients.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

MC: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **AM:** Validation, Formal analysis, Data Curation, Writing – review and editing; **PKS:** Conceptualization, Methodology, Validation, Resources, Data Curation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

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Resistance Patterns of Urinary Tract Pathogens Isolated from Patients with Type 2 Diabetes Mellitus on Sodium Glucose Co-transporter 2 Inhibitors Admitted in a Tertiary Hospital in the Philippines: A Single-Center Retrospective Cohort Study

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Abstract

Background. Congruent with the increasing prevalence of diabetes, a growing armamentarium of anti-diabetes medications has been introduced. Among these are sodium glucose co-transporter-2 inhibitors (SGLT2i).

Objectives. SGLT2i use has been linked to an increased incidence of urogenital infections. The study aims to compare resistance patterns of urinary tract isolates among patients with diabetes who are on SGLT2i and not on SGLT2i.

Methodology. Single-center retrospective cohort study. A total of 464 patients (75 on SGLT2i, 389 not on SGLT2i) with DM type 2 and urinary tract infection were included. Urine culture results were compared.

Results. A similar pattern of urinary tract isolates was found between groups except for *C. albicans* being more common in the SGLT2i group. There was no significant association between the presence of resistant urinary tract pathogens and the use of SGLT2i. There was no statistically significant difference in resistance rates between groups, except for imipenem ($p = 0.015$).

Conclusion. SGLT2i use per se does not play a pivotal role in mediating bacterial resistance in urinary tract pathogens among patients with DM type 2. We do not recommend for or against the use of specific antimicrobials based on SGLT2 inhibitor alone. Patient's clinical profile along with urine culture test results remain key factors in patient management.

Key words: diabetes, SGLT2 inhibitors, urinary tract infection, urine culture, resistance

INTRODUCTION

Diabetes mellitus (DM) type 2 is a progressive and debilitating disease associated with various macrovascular and microvascular complications. Patients with DM type 2 are at high risk for a multitude of infections including asymptomatic bacteriuria (ASB), urinary tract infections (UTI) and non-sexually transmitted genital infections (vulvo-vaginal infections and balanitis).^{1,2} There are "pathogen"-related mechanisms such as an increased bacterial adherence to uroepithelial cells (particularly *E. coli*-expressing type-1 fimbriae) which would explain the increased prevalence of bacteriuria in patients with diabetes, and the "host"-related mechanisms such as an alteration in polymorphonuclear function and adhesion, chemotaxis and phagocytosis.³ These factors, plus glucosuria and/or diabetes-associated bladder dysfunction, would explain the increase in the prevalence of UTI in patients with type 2 diabetes.

Sodium glucose co-transporter-2 inhibitors

Congruent with the increasing prevalence of DM type 2 globally, a growing armamentarium of anti-diabetes medications has been introduced to target different organ systems that play a role in the pathophysiology of DM type 2. Among these, sodium glucose co-transporter-2 inhibitors (SGLT2i) are relatively new treatment options for diabetes. These drugs promote the renal excretion of glucose by inhibiting glucose reabsorption in the proximal convoluted tubules. Moreover, SGLT2i have demonstrated beneficial outcomes in patients with cardiac and renal comorbidities.⁴⁻⁶ Thus, in addition to glycemic control, its proven cardiorenal benefit makes this class of drugs very promising. However, SGLT2i have been linked to an increased incidence of urogenital infections, which may limit their utility in some patients.

While most UTIs caused by SGLT2i were of mild to moderate severity, the US FDA had revised labels for all SGLT2i by adding a warning for severe UTI in 2015. This warning was prompted by post-marketing adverse event reports of urosepsis and pyelonephritis in patients using these agents. Literature on SGLT2i and UTI have been inconsistent, as older meta-analyses with fewer clinical trials showed a higher UTI risk,⁷ while more recent meta-analyses did not demonstrate an increased risk of severe or non-severe UTI with SGLT2i use.⁸⁻¹¹ However, the generalizability of the above meta-analyses may be limited as these participants may be part of clinical trials and/or have insurance claims, in which glycemic control may be better. In our setting, in which the majority of patients have poor diabetes control, recurrent mild to moderate UTI secondary to SGLT2i use may be more common,¹² possibly underreported, and are more likely to have received a multitude of antibiotics as outpatient.

Despite the higher frequency of UTI among patients with diabetes on SGLT2i and the higher risk of antibiotic resistance due to repeated use of antibiotics as outpatient, there are currently no studies that specifically identify resistance patterns of urinary tract pathogens among diabetic patients on SGLT2i. The study therefore will provide relevant information regarding the characterization and antimicrobial susceptibility patterns of urinary tract pathogens among type 2 DM patients on SGLT2i. The study will also specifically compare the urine isolate resistance patterns among patients on SGLT2i and those not on SGLT2i.

OBJECTIVES

The study compared the resistance patterns of urinary tract pathogens among patients with type 2 diabetes on SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) and those not on SGLT2 inhibitors. Specifically, this study:

1. Compared the incidence of resistant urinary tract pathogens among admitted DM type 2 patients on SGLT2i therapy and those not on SGLT2i therapy. Resistant urinary tract pathogens will be categorized as follows:
 - a. ESBL + enterobacteriaceae
 - b. Fluoroquinolone-resistant urinary tract pathogens
 - c. Carbapenem-resistant enterobacteriaceae
 - d. Vancomycin-resistant enterococcus
 - e. Fluconazole-resistant fungal infection
 - f. Methicillin-resistant *Staphylococcus* sp.
2. Determined and compared the antibiotic resistance patterns of the isolated urinary tract pathogens among admitted DM type 2 patients on SGLT2i therapy and those not on SGLT2i.
3. Determined the association of the following factors to resistant urinary tract pathogens among DM type 2 patients on SGLT2i therapy:
 - a. Age, sex, body mass index (BMI), duration of diabetes, HbA1c and estimated glomerular filtration rate (eGFR) at time of treatment initiation, func-

tional status (chairbound/bedridden), duration of SGLT2i therapy, the use of concomitant oral hypoglycemic agents and presence of concomitant comorbidities such as chronic kidney disease (CKD), congestive heart failure (CHF) and stroke.

METHODOLOGY

This is a retrospective cohort study. Medical chart reviews of all patients with type 2 diabetes mellitus admitted from January 2021 to October 2023 in Chong Hua Hospital, a tertiary private hospital in Cebu City, were done. All patients with a diagnosis of type 2 diabetes mellitus and urinary tract infection were included in the study. Review and approval of the study protocol by the Chong Hua Hospital Institutional Ethics Review Board (CHH IERB) was obtained prior to initiation of the study.

Study population and data collection

The study specifically included the following patients:

1. Admitted at Chong Hua Hospital under the Department of Internal Medicine from January 2021 to October 2023
2. Patients greater than 18 years old, diagnosed with type 2 diabetes mellitus based on ADA criteria
3. Diagnosed with urinary tract infection (*presence of one or more of the following: dysuria, frequency, urgency, hematuria, lower abdominal pain, flank pain, nocturia, fever with or without chills, costovertebral angle tenderness*) with urine culture and sensitivity test result

The study excluded the following patients:

1. Newly diagnosed with Type 2 DM during admission
2. Incomplete and inaccessible medical charts
3. Unavailable urine culture and sensitivity test results

The study was limited to a review of medical charts. The following data were collected:

1. SGLT2 inhibitor used: canagliflozin, dapagliflozin, empagliflozin
2. Urine culture and sensitivity test results (to include the number of isolated pathogens, identification of the isolated pathogen and its antibiotic susceptibility pattern)
3. Patient demographics: age, sex, height, weight, diabetes duration, HbA1c, eGFR, functional status, SGLT2i therapy, use of other DM medications, concomitant comorbidities and diagnosis of sepsis

Statistical analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables (nominal/ordinal), mean and standard deviation for normally distributed interval/ratio variables, and median and interquartile range for non-normally distributed interval/ratio variables.

Mann-Whitney U test was used to compare the median values of continuous variables between groups (SGLT2i vs. no SGLT2i) and absence vs. presence of resistant urinary tract pathogens). Chi-square test was used to compare the frequency of categorical variables between groups. Fisher's exact test was used in place of the Chi-square test for comparisons with small samples that were not fit for Chi-square.

Odds ratios and the corresponding 95% confidence intervals from binary logistic regression were computed to determine the association between patient characteristics and the presence of resistant urinary tract pathogens.

Missing observations were not inputted and were excluded from the analysis. Implausible values, including extreme outliers, were identified during data cleaning and corrected as necessary. All statistical analyses were performed using a 5% level of significance. Data analysis was conducted using Stata version 15.0 (StataCorp, 2017).

RESULTS

A total of 464 patients (Figure 1) with diabetes mellitus type 2 and a diagnosis of urinary tract infection were included. Of these, 75 patients were in the SGLT2i therapy group and 389 patients in the non-SGLT2i therapy group.

Patient characteristics

The demographic and clinical characteristics of patients on SGLT2i therapy versus those not receiving the treatment were compared (Table 1). The median age of the included patients was 70 years (IQR: 61-80 years). Significant differences were noted between the two groups in terms of gender distribution and biguanide use. The SGLT2i group had a notably higher proportion of males (40%) compared

to the non-SGLT2i group (17.5%). Furthermore, the use of biguanides was lower among patients receiving SGLT2i (38.7%) compared to those not on this therapy (52.7%). Beyond these differences, the two patient groups exhibited comparable demographics and clinical variables across several parameters, including age distribution, duration of diabetes and baseline HbA1c levels, with all *p*-values >0.05.

Isolated urinary tract pathogens

E. coli was the most prevalent pathogen across both cohorts (Table 2.1). Further comparison of both groups showed that *C. albicans* was found more frequently in the SGLT2i therapy group than in the non-SGLT2i therapy group (19.61% vs. 7.22%), and is the second most common isolated pathogen in this group. Other pathogens, including *K. pneumoniae*, *P. mirabilis*, *E. faecalis* and *C. koseri*, demonstrated variability in prevalence between the groups, with *P. aeruginosa* only detected in the non-SGLT2i therapy group.

Resistant urinary tract pathogens

The incidence of resistant urinary tract pathogens, identified as the growth of the following in culture: ESBL + *Enterobacteriaceae*, Fluoroquinolone-resistant uropathogens, Carbapenem-resistant *Enterobacteriaceae*, Vancomycin-resistant *enterococcus*, Fluconazole-resistant fungal infection and Methicillin-resistant *Staphylococcus* sp., was also compared between the 2 groups (Table 2.2).

In the SGLT2i group, ESBL-producing *Enterobacteriaceae* was observed to be more prevalent (17.6%) compared to the non-SGLT2i group (13.1%). This finding may indicate that although SGLT2i doesn't increase the overall risk for antibiotic resistance in urinary pathogens, it may have the potential to foster the growth of the more resistant strains, probably due to a higher risk of recurrent UTI.

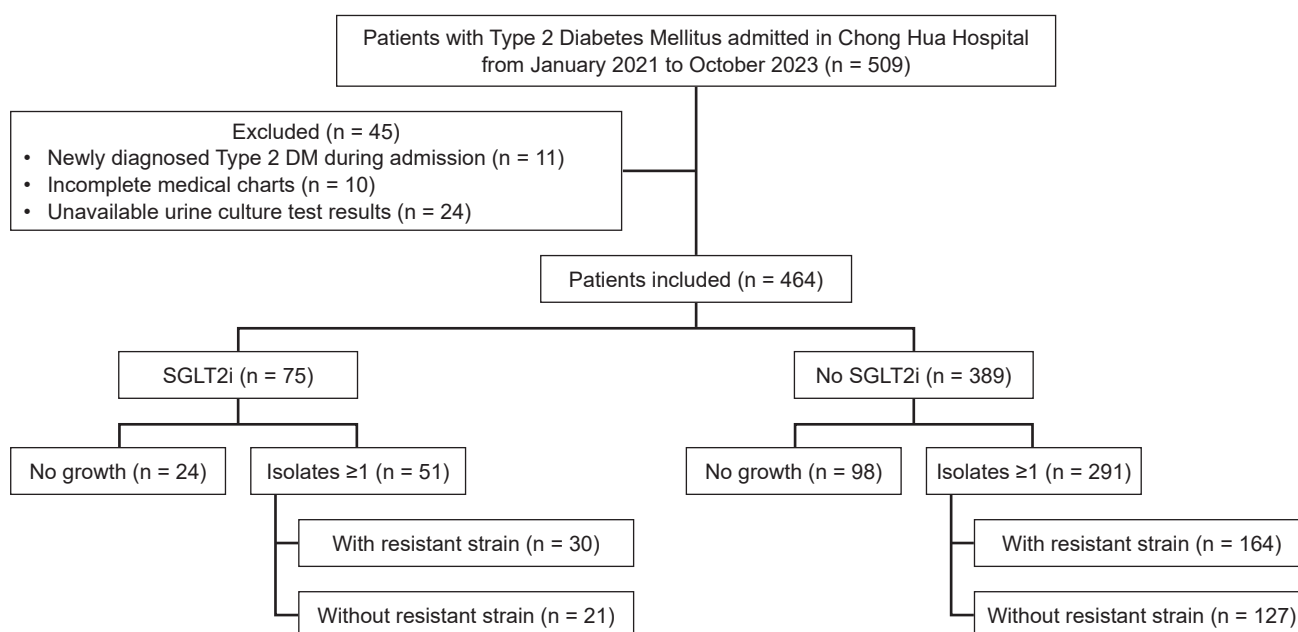


Figure 1. Diagram of the study population as further categorized to those on SGLT2i therapy and not on SGLT2i therapy.

Table 1. Clinical demographic data of patients on SGLT2 inhibitor and not on SGLT2 inhibitor therapy

Variables	Total (n = 464)	SGLT2i (n = 75)	Non-SGLT2i (n = 389)	p-value
Median (IQR) Frequency (%)				
Age (years)	70 (61-80)	70 (63-81)	70 (60-79)	0.466 [‡] ; 0.415 [†]
<40	10 (2.16)	0	10 (2.57)	
40-54	49 (10.56)	6 (8)	43 (11.05)	
55-69	168 (36.21)	30 (40)	138 (35.48)	
≥70	237 (51.08)	39 (52)	198 (50.9)	
Sex				<0.001 [†]
Male	98 (21.12)	30 (40)	68 (17.48)	
Female	366 (78.88)	45 (60)	321 (82.52)	
BMI (kg/m²)				0.587 [†]
<18.5	20 (4.4)	2 (2.7)	18 (4.72)	
18.5-22.9	123 (27.03)	18 (24.32)	105 (27.56)	
≥23	312 (68.57)	54 (72.97)	258 (67.72)	
Duration of diabetes (years)				0.697 [†]
1-5	151 (37.94)	22 (33.33)	129 (38.86)	
6-10	66 (16.58)	12 (18.18)	54 (16.27)	
>10	181 (45.48)	32 (48.48)	149 (44.88)	
Baseline HbA1c (%)				0.157 [†]
<7.0	228 (51.94)	37 (52.86)	191 (51.76)	
≥7.0 - <8.0	68 (15.49)	13 (18.57)	55 (14.91)	
≥8.0 - <9.0	42 (9.57)	10 (14.29)	32 (8.67)	
>9.0	101 (23.01)	10 (14.29)	91 (24.66)	
eGFR (ml/min)				0.929 [†]
>60	187 (40.39)	30 (40)	157 (40.46)	
30-60	196 (42.33)	33 (44)	163 (42.01)	
<30	80 (17.28)	12 (16)	68 (17.53)	
Concomitant oral hypoglycemics				
DPPIV Inhibitor	269 (57.97)	37 (49.33)	232 (59.64)	0.098 [†]
Biguanide	234 (50.43)	29 (38.67)	205 (52.7)	0.026 [†]
SUR	115 (24.78)	18 (24)	97 (24.94)	0.864 [†]
TZD	11 (2.37)	1 (1.33)	10 (2.57)	0.519 [†]
Insulin	144 (31.03)	18 (24)	126 (32.39)	0.150 [†]
GLP1 agonist	7 (1.51)	3 (4)	4 (1.03)	0.053 [†]
Menopausal status (n = 123)				0.768 [†]
Pre-menopause	10 (8.13)	1 (6.25)	9 (8.41)	
Post-menopause	113 (91.87)	15 (93.75)	98 (91.59)	
Concomitant comorbidities				
CAD/CHF	363 (78.23)	61 (81.33)	302 (77.63)	0.477 [†]
CKD	67 (14.44)	11 (14.67)	56 (14.4)	0.951 [†]
Stroke	65 (14.01)	8 (10.67)	57 (14.65)	0.362 [†]
BPH	16 (3.45)	3 (4)	13 (3.34)	0.775 [†]
Nephrolithiasis, urolithiasis, obstructive uropathy	21 (4.53)	4 (5.33)	17 (4.37)	0.713 [†]
Chairbound/ bedridden functional status	94 (20.26)	9 (12)	85 (21.85)	0.052 [†]
Sepsis	78 (16.81)	14 (18.67)	64 (16.45)	0.639 [†]

Statistical tests used: *Mann-Whitney U test; †Chi-square test

Table 2.1. Isolated urinary tract pathogens among patients on SGLT2i therapy and not on SGLT2i therapy

Isolated pathogens	SGLT2 (n = 51)	Non-SGLT (n = 291)	p-value
Frequency (%)			
<i>Escherichia coli</i>	17 (33.33)	133 (45.7)	0.101 [†]
<i>Candida albicans</i>	10 (19.61)	21 (7.22)	0.014 [§]
<i>Klebsiella pneumoniae</i>	6 (11.76)	41 (14.09)	0.657 [†]
<i>Proteus mirabilis</i>	1 (1.96)	15 (5.15)	0.483 [§]
<i>Enterococcus faecalis</i>	4 (7.84)	14 (4.81)	0.323 [§]
<i>Citrobacter koseri</i>	3 (5.88)	8 (2.75)	0.216 [§]
<i>Staphylococcus haemolyticus</i>	0	2 (0.69)	>0.999 [§]
<i>Pseudomonas aeruginosa</i>	0	7 (2.41)	0.599 [§]

Statistical tests used: *Mann-Whitney U test; †Chi-square test; §Fisher's exact test

Table 2.2. Incidence of resistant urinary tract pathogens among type 2 DM patients on SGLT2 inhibitor therapy and not on SGLT2 inhibitor therapy

Variables	SGLT2i (n = 51)	Non-SGLT2i (n = 291)	p-value
Frequency (%)			
Overall Incidence of resistant strains*	40%	42.5%	
ESBL + Enterobacteriaceae	9 (17.6)	38 (13.06)	0.380 [†]
Fluoroquinolone resistant uropathogens	17 (33.3)	101 (34.71)	0.849 [†]
Carbapenem resistant Enterobacteriaceae	1 (1.96)	4 (1.37)	0.556 [§]
Vancomycin resistant Enterococcus	1 (1.96)	0	0.149 [§]
Fluconazole resistant Fungal infection	0	0	-
Methicillin-Resistant Staphylococcus sp.	5 (9.8)	23 (7.90)	0.587 [§]
Extensively drug resistant Pseudomonas	1 (1.96)	0	0.149 [§]

Statistical tests used: *Mann-Whitney U test; †Chi-square test; §Fisher's exact test

*Note: Incidence is calculated based on the number of patients with one or more resistant strains over the total number of patients on SGLT2i (and total number of patients not on SGLT2i in the second column)

Antimicrobial susceptibility patterns

Antimicrobial resistance patterns were also compared between the two groups (Table 3). For gram-negative bacteria, no significant differences in resistance rates were

observed between the two groups for most antibiotics, including amoxicillin/clavulanic acid, piperacillin/tazobactam, cefoxitin, cefuroxime, ceftazidime, ceftriaxone, cefepime, amikacin, gentamicin, ciprofloxacin and trimethoprim-sulfamethoxazole. The resistance rates for

Table 3. Antimicrobial susceptibility patterns among Type 2 DM patients on SGLT2i and not on SGLT2i therapy

	SGLT2i			Non-SGLT2i			p-value
Culture							0.220
No growth		24 (32)			98 (25.19)		
One or more isolate		51 (68)			291 (74.81)		
	S	I	R	S	I	R	
Gram negative							
Penicillin							
Amoxicillin/ clavulanic	31 (79.5)	4 (10.3)	4 (10.3)	170 (70.8)	23 (9.6)	47 (19.6)	0.187
Piperacillin/ tazobactam	32 (84.2)	0	6 (15.8)	221 (89.5)	5 (2)	21 (8.5)	0.227
Ampicillin	0	0	5 (100)	9 (16.7)	2 (3.7)	43 (79.6)	0.582
Cephalosporins							
Cefoxitin	31 (83.8)	2 (5.4)	4 (10.8)	205 (82.3)	9 (3.6)	35 (14.1)	0.798
Cefuroxime	19 (50)	3 (7.9)	16 (42.1)	149 (60.6)	17 (6.9)	80 (32.5)	0.271
Ceftazidime	27 (65.9)	1 (2.4)	13 (31.7)	195 (76.5)	1 (0.4)	59 (23.1)	0.243
Ceftriaxone	21 (67.7)	0	10 (32.3)	156 (76.8)	0	47 (23.2)	0.269
Cefepime	31 (79.5)	0	8 (20.5)	215 (85.3)	1 (0.4)	36 (14.3)	0.337
Aminoglycosides							
Amikacin	37 (97.4)	1 (2.6)	0	245 (99.2)	0	2 (0.8)	>0.999
Gentamicin	36 (92.3)	1 (2.6)	2 (5.1)	224 (87.8)	2 (0.8)	29 (11.4)	0.398
Fluoroquinolones							
Ciprofloxacin	22 (57.9)	1 (2.6)	15 (39.5)	159 (62.6)	1 (0.4)	94 (37)	0.858
Others							
Imipenem	32 (84.2)	1 (2.6)	5 (13.2)	226 (95.4)	4 (1.7)	7 (2.9)	0.015
Trimethoprim- Sulfamethoxazole	25 (67.6)	0	12 (32.4)	153 (64)	0	86 (36)	0.716
Nitrofurantoin	2 (40)	1 (20)	2 (40)	0	0	0	-
Tobramycin	1 (100)	0	0	0	0	0	-
Colistin	0	0	0	1 (33.3)	1 (33.3)	1 (33.3)	-
Polymyxin b	0	0	0	0	1 (100)	0	-
Gram positive							
Penicillin	3 (60)	0	2 (40)	16 (80)	0	4 (20)	0.562
Tetracycline	2 (22.2)	0	7 (77.8)	23 (60.5)	0	15 (39.5)	0.063
Vancomycin	8 (88.9)	0	1 (11.1)	43 (100)	0	0	0.173
Linezolid	7 (100)	0	0	32 (100)	0	0	-
Ampicillin	3 (60)	0	2 (40)	16 (100)	0	0	0.048
Amoxicillin	2 (50)	0	2 (50)	11 (100)	0	0	0.057
Piperacillin/ Tazobactam	2 (50)	0	2 (50)	10 (100)	0	0	0.066
Oxacillin	1 (20)	0	4 (80)	1 (3.8)	0	25 (96.2)	0.301
Ciprofloxacin	4 (57.1)	0	3 (42.9)	28 (77.8)	0	8 (22.2)	0.347
Levofloxacin	0	0	0	2 (100)	0	0	-
Tigecycline	4 (100)	0	0	15 (100)	0	0	-
Cefoxitin	1 (25)	0	3 (75)	1 (3.8)	0	25 (96.2)	0.253
Erythromycin	4 (80)	0	1 (20)	13 (46.4)	1 (3.6)	14 (50)	0.346
Clindamycin							
Streptomycin	1 (100)	0	0	2 (100)	0	0	-
Gentamicin							
TMS	5 (100)	0	0	17 (63)	0	10 (37)	0.155
Chloramphenicol	0	0	0	1 (100)	0	0	-
Rifampicin	0	0	0	1 (25)	0	3 (75)	-
Ertapenem	0	0	0	2 (100)	0	0	-
Nitrofurantoin	2 (40)	1 (20)	2 (40)	0	0	0	-
Fungal							
Fluconazole	10 (100)	0	0	19 (95)	0	1 (5)	>0.999
Flucytosine	11 (100)	0	0	17 (89.5)	0	2 (10.5)	>0.999
Caspofungin	11 (100)	0	0	20 (95.2)	0	1 (4.8)	>0.999
Micafungin	11 (100)	0	0	20 (95.2)	0	1 (4.8)	>0.999
Amphotericin B	2 (66.7)	0	1 (33.3)	5 (100)	0	0	0.375
Voriconazole	9 (100)	0	0	19 (95)	0	1 (5)	>0.999

S – susceptible; I – Intermediate; R – Resistant

p-value for the sensitivity testing was based on "resistance"

Critical region with multiple comparison adjustment is 0.0125

these antibiotics were broadly similar across both groups ($p > 0.05$). However, there was a significant difference in imipenem resistance, with a resistance rate of 13.2% in the SGLT2i group compared to 2.9% in the non-SGLT2i group ($p = 0.015$). This suggests that patients on SGLT2i therapy might have a higher risk of harboring imipenem-resistant bacteria. For gram-positive bacteria, the resistance patterns for penicillin, tetracycline, vancomycin and linezolid showed no significant differences between the two groups ($p > 0.05$). Similarly, no significant difference was observed in the resistance to fluconazole for fungal isolates ($p > 0.05$).

It is also worth noting that in both groups, resistance rates were highest with ampicillin (79%-100%), cefuroxime (32%-42%), ciprofloxacin (37%-39.5%), nitrofurantoin, trimethoprim-sulfamethoxazole, ceftriaxone and ceftazidime.

Table 4 presents the clinical and demographic profile between patients with and without growth of resistant strains on urine culture. Age appeared to be a statistically significant factor, with older patients having resistant strains compared to those without resistant strains (71.5 vs. 68

Table 4. Patient factors associated with and without growth of resistant strains on urine culture (n = 464)

Variables	With resistant strain (n = 194)	Without resistant strain (n = 270)	p-value
	Median (IQR)	frequency (%)	
Age (years)	71.5 (62-82)	68 (60-79)	0.046 [‡] ; 0.045 [†]
<40	2 (1.03)	8 (2.96)	
40-54	13 (6.7)	36 (13.33)	
55-69	71 (36.6)	97 (35.93)	
≥70	108 (55.67)	129 (47.78)	
Sex			0.108 [†]
Male	34 (17.53)	64 (23.7)	
Female	160 (82.47)	206 (76.3)	
BMI (kg/m²)			0.141 [†]
<18.5	5 (2.63)	15 (5.66)	
18.5-22.9	58 (30.53)	65 (24.53)	
≥23	127 (66.84)	185 (69.81)	
Duration of diabetes (years)			0.322 [†]
1-5	59 (36.88)	92 (38.66)	
6-10	22 (13.75)	44 (18.49)	
>10	79 (49.38)	102 (42.86)	
Baseline HbA1c (%)			0.522 [†]
<7.0	95 (51.35)	133 (52.36)	
≥7.0 - <8.0	31 (16.76)	37 (14.57)	
≥8.0 - <9.0	21 (11.35)	21 (8.27)	
>9.0	38 (20.54)	63 (24.8)	
eGFR (ml/min)			0.242 [†]
>60	83 (43.01)	104 (38.52)	
30 - 60	73 (37.82)	123 (45.56)	
<30	37 (19.17)	43 (15.93)	
Concomitant oral hypoglycemic			
DPPIV Inhibitor	110 (56.7)	159 (58.89)	0.638 [†]
Biguanide	93 (47.94)	141 (52.22)	0.363 [†]
SUR	50 (25.77)	65 (24.07)	0.676 [†]
TZD	6 (3.09)	5 (1.85)	0.386 [†]
Insulin	56 (28.87)	88 (32.59)	0.392 [†]
GLP1 agonist	4 (2.06)	3 (1.11)	0.407 [†]
Menopausal status (n = 123)			0.879 [†]
Pre-menopause	4 (7.69)	6 (8.45)	
Post-menopause	48 (92.31)	65 (91.55)	
Concomitant comorbidities			
CAD/CHF	154 (79.38)	209 (77.41)	0.611 [†]
CKD	29 (14.95)	38 (14.07)	0.792 [†]
Stroke	26 (13.4)	39 (14.44)	0.750 [†]
BPH	6 (3.09)	10 (3.7)	0.722 [†]
Nephrolithiasis, urolithiasis, obstructive uropathy	8 (4.12)	13 (4.81)	0.724 [†]
Chairbound/ bedridden functional status	41 (21.13)	53 (19.63)	0.691 [†]
Sepsis	34 (17.53)	44 (16.3)	0.727 [†]
SGLT2 use			0.728 [†]
Without SGLT2	164 (84.54)	225 (83.33)	
With SGLT2	30 (15.46)	45 (16.67)	
Drug class (n = 75)			0.919 [†]
Empagliflozin	21 (70)	31 (68.89)	
Dapagliflozin	9 (30)	14 (31.11)	

Statistical tests used: *Mann-Whitney U test; †Chi-square test

years, $p = 0.046$). Other demographic and clinical variables were comparable between the two groups ($p > 0.05$).

Table 5 presents an analysis of the association between SGLT2i use and specific patient characteristics with the presence of resistant urinary tract pathogens. Among the variables included, age was found to be significantly associated with the presence of resistant urinary tract pathogens among DM type 2 patients. Specifically, each additional year of age slightly increased the likelihood of having a resistant urinary tract pathogen (OR = 1.02, 95% CI [1.00, 1.03], $p = 0.027$). Other variables also did not show a significant association with the presence of resistant pathogens in this patient population.

Table 5. Association of SGLT2i use, patient characteristics with presence of resistant urinary tract pathogens

Variables	OR (95% CI)	p-value
Age (years)	1.02 (1.00 – 1.03)	0.027
Sex		
Male	Reference	-
Female	1.46 (0.92 – 2.33)	0.109
BMI (kg/m²)		
18.5–22.9	Reference	-
<18.5	0.37 (0.13 – 1.09)	0.072
≥23	0.77 (0.51 – 1.17)	0.221
Duration of diabetes (years)		
1–5	Reference	-
6–10	0.78 (0.42 – 1.43)	0.422
>10	1.21 (0.78 – 1.87)	0.400
Baseline HbA1c (%)		
<7.0	Reference	-
≥7.0 – <8.0	1.17 (0.68 – 2.02)	0.566
≥8.0 – <9.0	1.40 (0.72 – 2.71)	0.317
>9.0	0.84 (0.52 – 1.37)	0.491
eGFR (ml/min)		
>60	Reference	-
30 – 60	0.74 (0.49 – 1.12)	0.156
<30	1.08 (0.64 – 1.82)	0.779
Concomitant oral hypoglycemic		
DPPIV Inhibitor	0.91 (0.63 – 1.33)	0.638
Biguanide	0.84 (0.58 – 1.22)	0.363
SUR	1.10 (0.72 – 1.68)	0.676
TZD	1.69 (0.51 – 5.62)	0.391
Insulin	0.84 (0.56 – 1.25)	0.392
GLP1 agonist	1.87 (0.41 – 8.47)	0.415
Menopausal status (n = 123)		
Pre-menopause	Reference	-
Post-menopause	1.25 (0.35 – 4.53)	0.730
Concomitant comorbidities		
CAD/CHF	1.12 (0.72 – 1.76)	0.611
CKD	1.07 (0.64 – 1.81)	0.792
Stroke	0.92 (0.54 – 1.56)	0.750
BPH	0.83 (0.30 – 2.32)	0.722
Nephrolithiasis, urolithiasis, obstructive uropathy	0.85 (0.35 – 2.09)	0.724
Chairbound/ bedridden functional status	1.10 (0.69 – 1.73)	0.691
Sepsis	1.09 (0.67 – 1.78)	0.727
SGLT2 use		
Without SGLT2	Reference	-
With SGLT2	0.91 (0.55 – 1.51)	0.729
Drug class (n = 75)		
Empagliflozin	1.05 (0.39 – 2.88)	0.919
Dapagliflozin	0.95 (0.35 – 2.59)	0.919

DISCUSSION

Urinary tract infection is highly prevalent among patients with diabetes.^{13–15} A recent descriptive cross-sectional study in a tertiary hospital in India has shown the prevalence of UTI at 75.4%. Additionally, the overall multidrug resistance (defined as an isolate resistant to two or more antimicrobial agents) was observed in 87.4% of the bacterial isolates.¹⁶ This can be explained by several mechanisms, including an increase in urinary glucose concentration, promoting growth of microorganisms, incomplete bladder emptying and subsequent urologic manipulation, immunologic alterations and the history of multiple antibiotic use common in patients with diabetes.^{17–23} The pharmacologically-induced increased urinary glucose concentrations with SGLT2i might then provide a favorable growth environment for genitourinary microorganisms.³ However, literature regarding the association of SGLT2i and UTI is conflicting.^{24–29} Yet since its debut in 2013, with the increasing use of SGLT2i, we are currently seeing an increase in the reported prevalence of urinary tract infections with these agents. A recent study by Tanriverdi et al., has shown a 54.9% urine culture positivity rate among patients on SGLT2i therapy compared to 16% in the non-SGLT2 inhibitor therapy group. Among those with positive urine cultures, *Escherichia coli* was isolated in 83.3%, and both *E. coli* and *K. pneumoniae* were isolated in 16.7%.³⁰

In the present study, across both cohorts, *E. coli* was the most frequently isolated pathogen. A similar pattern of common urinary pathogen isolates was also noted in existing literature, with the most common being: *E. coli*, *Enterococcus* spp., *Klebsiella* spp.^{16,31} Upon further comparison of both groups, *C. albicans* was found to be more common in the SGLT2i group (19.61% vs. 7.22%) and is the second most common pathogen isolated in the group. This observation could be explained by a study by Hiyama et al., wherein the effect of glucosuria on the growth of *Candida* spp. was investigated, showing that viable cell numbers of *Candida* spp. was more than tenfold higher in the urine added with 3000 mg/dL glucose as compared to that in plain urine.³²

In terms of the presence of resistant urinary tract pathogens, there seems to be no significant difference in the incidence between those on SGLT2i (40%) and those not on SGLT2i (42%). This implies that SGLT2i use by itself does not play a pivotal role in mediating bacterial resistance in urinary tract pathogens. SGLT2i group however had a slightly increased prevalence of ESBL-producing *Enterobacteriaceae* (17.6% vs 13.1%) and Methicillin-resistant *Staphylococcus* species (9.8% vs 7.9%). Due to its association with higher risk of recurrent urinary tract infections, its potential influence on fostering the more prevalent resistant strains cannot be undermined. The mechanism of these observed differences is beyond the scope of the study.

Antimicrobial susceptibility patterns were also analyzed, with most antibiotics demonstrating no significant difference in resistance rates between groups. In general, the increased resistance rates to commonly used antibiotics reflect its possible frequent usage in outpatient settings. Alarming, the resistance rate to imipenem was significantly higher in the SGLT2i group (1.9% vs. 1.37%, $p < 0.015$), demonstrating a pronounced risk of imipenem-resistant bacterial infections among these patients. Whether this could be due to frequent use of carbapenems from recurrent admissions for UTI is beyond the scope of this study and perhaps may be an avenue for future research.

The association between SGLT2i use and patient-specific characteristics with the presence of resistant strains was also examined. Among the various factors included, age was the only significant factor, with each additional year increasing the likelihood of harboring resistant strains (OR = 1.02, 95% CI [1.00,1.03], $p = 0.027$), pointing to the heightened susceptibility of older individuals to harboring UTI with resistant strains. The association of increasing age and harboring of resistant strains could be influenced by multiple factors, including incomplete bladder emptying (e.g., autonomic neuropathy), prior history of multiple antibiotic use and hospital admissions in the elderly group. Data did not show a statistically significant overall impact of SGLT2i on the propensity for developing resistant pathogens as mentioned above.

CONCLUSION

In the study, we examined the resistance patterns of urinary tract pathogens among DM type 2 patients, categorizing them into those receiving SGLT2i and those who were not receiving SGLT2i. A similar pattern of urinary tract isolates was found between the two groups except for *C. albicans*, which was more common in the SGLT2i group. No significant association was established between the presence of resistant urinary tract pathogens and the use of SGLT2i. There was also no difference in antimicrobial resistance rates between groups except for imipenem.

In conclusion, it has been shown that among DM type 2 patients, SGLT2i use is not associated with a higher risk of antimicrobial resistance as compared to those not on SGLT2i therapy. Thus, the study would not recommend for or against the use of specific antimicrobials based on SGLT2i use alone. Rather, the patient's history and clinical condition, along with urine culture and sensitivity test results, should remain the main factors in determining patient management.

The strength of this research lies in its thorough investigation of antimicrobial resistance within a targeted DM type 2 patient cohort, providing real world evidence on SGLT2i treatment and resistance patterns against urinary tract pathogens in a local setting. Nevertheless, its observational design constrains the ability to establish causative links between observed associations. Future research, adopting

long-term, prospective methodologies and larger populations, is warranted to confirm these observations and explore the underlying mechanisms of resistance development.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

CRCC: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - original draft preparation, Writing - review and editing, Visualization, Supervision, Project administration, Funding acquisition; **CCYT:** Conceptualization, Methodology, Validation, Resources, Writing - original draft preparation, Writing - review and editing, Supervision, Project administration

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Datasets generated and analyzed are included in the published article.

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Multiple Therapeutic Applications of Metformin Moving Beyond Its Anti-Diabetic Role: A Systematic Review

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Abstract

Introduction. Metformin is a commonly used anti-diabetic drug due to its safety, low cost, and strong glucose-lowering effects. Recent research studies have identified novel molecular targets and pathways for metformin, thereby expanding its potential beyond the treatment of Type 2 diabetes.

Methodology. This systematic review provides the latest updates on the therapeutic applications of metformin in multiple diseases. This systematic review follows the PRISMA guidelines, focusing on experimental studies systematic reviews and meta-analyses from PubMed, Scopus, Web of Science and Google scholar, the search terms ("Metformin"[MeSH] OR "Metformin") AND ("Cancer" OR "Cardiovascular Disease" OR "Neurodegenerative Disease" OR "Aging") AND ("Therapeutic Use" OR "Non-diabetic"). A comprehensive search yielded numerous studies, from which relevant and up-to-date papers were carefully selected.

Results. The review highlights the multifaceted applications of metformin in various diseases. Evidence demonstrates its positive effects on cardiovascular diseases, obesity, different types of cancer, and liver and kidney disorders. These findings suggest that metformin acts through diverse molecular mechanisms, exerting benefits that extend beyond glycemic control.

Conclusion. Based on the current literature, metformin exhibits a broad spectrum of therapeutic benefits, extending beyond its primary use in diabetes management. Its role in treating multiple diseases has marked it as a multifaceted agent in modern medicine. Further research is warranted to fully explore its capabilities and optimize its use in different clinical settings.

Key words: multiple therapeutic uses, metformin, cancer, obesity, cardiovascular diseases, anti-aging effect

Metformin

Metformin is a commonly used anti-diabetic drug due to its safety, low-cost, and strong glucose-lowering effects. Recent research studies identified novel molecular targets and pathways for metformin that extend its potential beyond type 2 diabetes.

The present systematic review provides the latest updates on metformin therapeutic applications in multiple diseases.



Therapeutic applications



Cardiovascular diseases



Obesity



Cancer



Liver and kidney disorders

Metformin demonstrates a broad spectrum of therapeutic benefits beyond diabetes management.

Graphical Abstract

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INTRODUCTION

Metformin, an oral antidiabetic agent, functions by enhancing insulin sensitivity, reducing hepatic glucose production and limiting intestinal glucose absorption. Due to its efficacious glycemic control and established safety profile, metformin is frequently prescribed as the initial pharmacological intervention for patients diagnosed with Type 2 Diabetes Mellitus (T2DM).¹

Beyond its role in managing blood sugar levels in T2DM, metformin also provides health benefits in various other areas. A growing number of studies suggest that metformin lowers the risk of cardiovascular diseases (CVD), breast and endometrial cancers, obesity, liver and kidney conditions, and may also offer anti-aging effects.² Metformin exhibits a variety of biological effects, suggesting that it can influence different cellular processes. Studies have identified several cellular targets with which metformin interacts, resulting in its therapeutic effects. These interactions highlight the complex pathways by which metformin operates within the body, affecting not only blood sugar regulation but also other essential cellular functions that enhance its overall health benefits.³⁻⁵

Metformin suppresses high blood glucose levels mainly by two pathways: either through the AMPK (Adenosine Monophosphate-Activated Protein Kinase) dependent pathway⁶ or the AMPK independent pathway.⁷ In the case of the AMPK-dependent pathway, metformin works by blocking mitochondrial complex I in the liver, leading to the activation of AMPK. This activation enhances insulin sensitivity by modulating fat metabolism and reducing cAMP levels. The decreased cAMP levels have a negative/inhibitory effect on gluconeogenic enzymes involved in glucose synthesis in the liver. Recent studies suggest that metformin may also activate AMPK through a lysosomal pathway called the v-ATPase Regulator pathway.⁵ This review article sheds light on the off-label uses of metformin, extending beyond its well-established role in the management of diabetes. It explores the drug's multifaceted impacts on various biological processes and its potential applications in areas such as cardiovascular health, cancer prevention, anti-inflammatory activities, weight management, and aging. By highlighting the multifaceted pharmacological profile, offering insights into its mechanisms of action, and paving the way for future research into its use in non-diabetic conditions.

METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist is provided in Supplementary Table S1. Relevant studies were identified through a comprehensive search of PubMed, Scopus, Google Scholar and Web of Science databases. The search strategy included a combination of targeted keywords such as ("Metformin"[MeSH] OR

"Metformin") AND ("Cancer" OR "Cardiovascular Disease" OR "Neurodegenerative Disease" OR "Aging") AND ("Therapeutic Use" OR "Non-diabetic"). The details of the MeSH terms searched across all databases are given in Supplementary Table S2. The inclusion criteria for the studies were: (1) studies investigated the effects of metformin beyond its primary use in diabetes management; (2) peer-reviewed articles published in English; and (3) studies providing details on metformin's role in cancer treatment, cardiovascular protection, obesity management and other non-diabetic conditions. Studies were excluded if they: (1) focused exclusively on metformin's role in glycemic control without addressing the additional therapeutic effects; (2) were conference abstracts, case reports, editorials or letters to the editor; or (3) lacked sufficient methodological details or relevance to the study objective. Eligible studies underwent a detailed data extraction process, focusing on key findings related to the multifaceted applications of metformin. The extracted data were then systematically analyzed and categorized to provide insights into the potential applications of the drug in cancer therapy, obesity management, cardiovascular protection and other non-diabetic conditions. The risk of bias was assessed using the Cochrane Tool for Randomized Controlled Trials (RCTs) and the Newcastle Ottawa Scale (NOS) for observational studies (Supplementary Table S1). The overall quality of evidence was moderate with heterogeneity in study designs. Findings were interpreted considering these limitations. Due to the significant heterogeneity in interventions (e.g., metformin dosages, combination therapies) and outcomes across studies, a meta-analysis was deemed inappropriate. A narrative synthesis was conducted to summarize key findings thematically.

Risk of bias assessment

Two reviewers (AU and AJ) independently assessed the risk of bias for each outcome measure using Cochrane RoB 2.0 (for RCTs) and NOS (for observational studies), with discrepancies resolved by a third reviewer (WAS). Rayan software aided the screening. Complete assessments are in Supplementary Table S1.

The PRISMA flowchart, shown in Figure 1, illustrates the detailed study selection process.

Metformin in obesity

A growing number of studies have reported the potential use of metformin in controlling obesity and associated comorbidities. Metformin has demonstrated modest yet significant effects on weight reduction in individuals without diabetes. In preclinical studies, metformin effectively mitigated obesity induced by high-fat diets. This effect is attributed to an increased expression of fibroblast growth factor 21 (FGF-21), a pivotal metabolic hormone that stimulates lipolysis in white adipose tissue, consequently reducing adipose accumulation.⁸ Additionally, metformin enhances the brown adipose tissue (BAT) metabolic activity

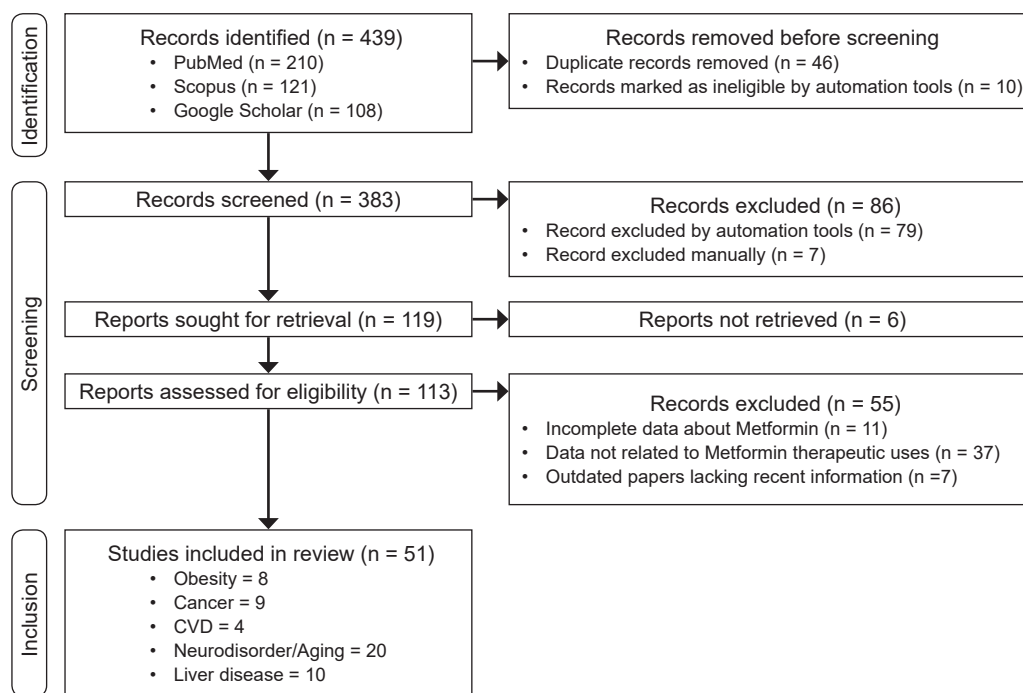


Figure 1. PRISMA flowchart.

Table 1. Detailed description of included studies

Author and publication year	Study type	Study duration	Study subjects	Age (years)	BMI (kg/m ²)	Treatment groups
Jensterle et al. 2014 ¹³	RCT	15 weeks	32	27.6 ± 7.2	39.5 ± 6.2	Metformin 1000 mg BD (n = 15), Liraglutide 1.2 mg OD (n = 17)
Feng et al. 2015 ¹⁴	RCT	16 weeks	50	18–40	BMI ≥25	Metformin 500 mg TID or combination therapy
Nylander et al. 2017 ¹⁵	RCT	46 weeks	92	18–45	>30	Liraglutide 3 mg, Placebo
Kesavan et al. 2023 ¹⁶	Open-label RCT	22 weeks	176	18–40	>24	Exenatide 10 µg BD, Metformin 1000 mg BD
Ling et al. 2025 ¹⁷	RCT	36 weeks	72	29.9 ± 6.1	25	Liraglutide 1.8 mg OD, Placebo
Jensterle et al. 2016 ¹⁸	Prospective RCT	10 weeks	44	33.3 ± 4.4	37.2 ± 4.5	Combination therapy (Metformin 1g BD + Liraglutide 1.2 mg OD), Liraglutide 1.2 mg OD
Jensterle et al. 2017 ¹⁹	Open-label RCT	26 weeks	30	33.1 ± 6.1	38.3 ± 5.4	Liraglutide 3 mg OD (n = 15), Combination therapy (Metformin 1000 mg BD + Liraglutide 1.2 mg OD, n = 15)
Salamun et al. 2018 ²⁰	Open-label RCT	14 weeks	28	31.07 ± 4.75	36.7 ± 3.5	Metformin 1000 mg BD, Combination therapy (Metformin 1000 mg BID + Liraglutide 1.2 mg)

BMI: Body Mass Index; RCT: Randomized Controlled Trial; BD: twice daily; OD: once daily; TID: thrice daily

that prevents obesity in mice. BAT contributes to energy dissipation through thermogenesis, a process facilitated by the uncoupling protein 1 (UCP1). Using PET/CT imaging, researchers found that metformin accumulates in BAT likely due to increased expression of organic cation transporters (OCT).⁹ Further studies have shown that metformin combats obesity effects by reducing fatty acid uptake, increasing mitochondrial biogenesis and stimulating thermogenesis.^{10,11} Animal studies indicate that metformin influences gut microbiota, reducing fat uptake and decreasing the development of fat-induced obesity.¹² Table 1 illustrates an overview of different randomized clinical trials and other studies examining metformin as a treatment for obesity, including the study design, participant characteristics and interventions. The studies listed in Table 1 encompass a diverse range of study designs, including randomized, open-label and double-

blind placebo-controlled trials. The study participants have met various diagnostic criteria, including the Rotterdam criteria for PCOS and the National Institutes of Health (NIH) 1990 criteria for obesity. The studies' duration spans from 12 to 32 weeks, with sample sizes ranging from 28 to 176 participants. The age range of the participants is 18 to 45 years, and the baseline BMI values generally fall within the range of 24 and 39 kg/m². Regarding interventions, metformin was evaluated both as monotherapy and in combination with other pharmacological agents such as Liraglutide, Exenatide or combinations thereof. The metformin dosage ranged from 500 to 1000 mg daily (BID, TID, or QD). Table 2 presents the clinical outcomes of the investigations listed in Table 1, with a focus on anthropometric measurements, including BMI, body weight, waist circumference (WC) and fat mass. In the study by Jensterle et al., patients receiving metformin 1000

mg BID exhibited a notable decrease in BMI (37.4 ± 6.4 to 36.5 ± 6.3) and body weight (103.6 ± 19.7 kg to 101.3 ± 19.8 kg) following a 12-week intervention.¹³ Comparable results were observed by Ma et al. using metformin 500 mg TID, with reductions in BMI (30.8 ± 3.4 to 29.4 ± 3.3) and body weight (82.3 ± 11.4 kg to 78.6 ± 10.9 kg).¹⁴ Elkind-Hirsch et al., reported that liraglutide 3 mg substantially reduced BMI and WC, while the control group receiving a placebo showed minimal changes.¹⁵ Figure 2 depicts the comparative impact of metformin on body mass index (BMI) across different study groups. The data elucidate variations

in BMI before and after metformin administration, demonstrating its potential for weight modulation. Error bars represent standard deviation.

Metformin in cancer

An increasing number of scientific studies suggest that metformin shows therapeutic potential for various cancer types, including breast cancer,¹⁵ hematologic malignancies,¹⁷ bone cancer,¹⁸ colorectal cancer,¹⁹ endometrial cancer, and melanoma²⁰ The anticancer effects of

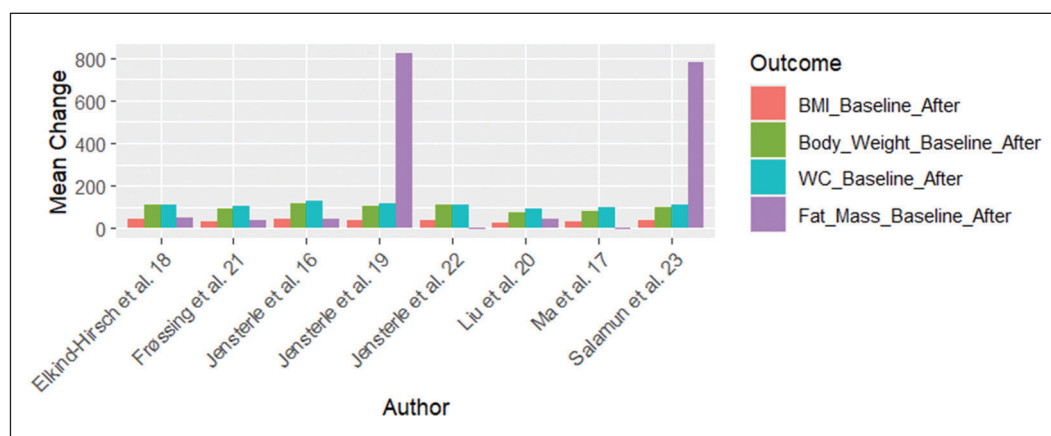


Figure 2. Effect of metformin on Body Mass Index (BMI).

Table 2. Clinical studies with anthropometrical outcomes

Author and publication year	Group for intervention	Baseline for BMI after	Baseline for body weight after	Baseline for WC after	Baseline for body mass after	Baseline after
Jensterle et al. 2015 ¹³	Liraglutide (1.2 mg)	41.6 ± 5.3 / 40.5 ± 5.1	113.7 ± 18.7 / 110.7 ± 18.1	128.5 ± 13.9 / 124.1 ± 11.7	42.5 ± 2.8 / 40.8 ± 3.2	-3.0 / -2.3
	Metformin (1000 mg BID)	38.4 ± 6.4 / 36.5 ± 6.3	103.6 ± 19.7 / 101.3 ± 19.8	121.6 ± 17.1 / 119 ± 18	43.3 ± 6.4 / 45.2 ± 4.2	-6.2 ± 2.4 / -3.8 ± 3.5
Ma et al. 2021 ¹⁴	Metformin (500 mg TID) + Exenatide 2 mg	30.8 ± 3.4 / 29.4 ± 3.3	82.3 ± 11.4 / 78.6 ± 10.9	97.3 ± 9.6 / 92.7 ± 8.7	-3.8 ± 2.4 / -2.1 ± 3.0	-5.7 ± 0.75 / -3.8 ± 3.5
	Metformin (500 mg TID)	32.4 ± 3.2 / 29.6 ± 2.8	79.1 ± 10.8 / 77.0 ± 9.7	96.6 ± 9.1 / 95.0 ± 8.1	(p < 0.01) / (p = 0.008)	-4.3 ± 1.3 / -2.3 ± 0.6
Elkind-Hirsch et al. 2022 ¹⁵	Liraglutide (3 mg)	41.6 ± 1.1 / 39.1 ± 1.1	111 ± 2.8 / 104.7 ± 2.9	111 ± 2.2 / 101 ± 2.0	47.6 ± 0.8 / 46.0 ± 0.9	-7.0 ± 6.0 / -7.5 ± 3.9
	Placebo	43.9 ± 1.7 / 43.4 ± 1.8	119 ± 4.7 / 117.9 ± 5	116 ± 3.3 / 110 ± 3.3	48.2 ± 0.8 / 47.9 ± 0.9	-7.0 ± 6.0 / -7.5 ± 3.9
Liu et al. 2017 ¹⁶	Exenatide (10 µg)	29.1 ± 3.1 / 26.0 ± 3.5	72.9 ± 9.8 / 68.7 ± 9.7	92.9 ± 10.1 / 83.9 ± 9.7	44.1 ± 3.8 / 39.4 ± 3.7	-7.0 ± 6.0 / -7.5 ± 3.9
	Metformin (1000 mg BID)	27.3 ± 1.8 / 27.2 ± 1.8	70.4 ± 4.6 / 68.2 ± 4.6	89.4 ± 6.6 / 84.4 ± 5.3	41.3 ± 2.7 / 40.2 ± 2.9	-7.0 ± 6.0 / -7.5 ± 3.9
Frøssing et al. 2018 ¹⁷	Liraglutide (1.8 mg)	33.3 ± 5.1 / 33.3 ± 4.6	94.2 ± 15.4 / 91.3 ± 13.6	102.6 ± 10.8 / 102.6 ± 11.1	35.9 ± 8.5 / 35.7 ± 7.2	NA
	Placebo	33.3 ± 4.6 / 33.3 ± 4.6	91.3 ± 13.6 / 91.3 ± 13.6	102.6 ± 11.1 / 102.6 ± 11.1	35.7 ± 7.2 / 35.7 ± 7.2	NA
Jensterle et al. 2017 ¹⁸	Metformin (1000 mg BID) + Liraglutide (1.2 mg)	37.7 ± 4.0 / 35.5 ± 4.2	105.8 ± 15.8 / 99.6 ± 15.9	117.2 ± 14.5 / 105.2 ± 27.0	824.2 ± 254.7 / 735.3 ± 227.5	-5.2 / 0.2
	Liraglutide (1.2 mg)	36.7 ± 5.1 / 35.3 ± 5.1	102.6 ± 17.9 / 98.8 ± 17.6	113.0 ± 13.9 / 107.5 ± 15.4	-6.2 ± 2.4 / -3.8 ± 3.5	-6.3 ± 3.7 / 3.6 ± 2.5
Jensterle et al. 2015 ¹⁹	Liraglutide (3 mg)	39.2 ± 5.5 / 37.0 ± 5.5	111.1 ± 14.8 / 104.7 ± 14.8	110.1 ± 12 / 105.9 ± 12.8	-6.3 ± 3.7 / 3.6 ± 2.5	NA
	Liraglutide (1.2 mg) + Metformin (1000 mg BID)	37.5 ± 5.3 / 36.2 ± 5.5	102.5 ± 9 / 98.9 ± 10.3	105.2 ± 10.7 / 103.0 ± 8.2	-5.2 ± 2.5 / -4.4 ± 3.2	NA
Salamun et al. 2018 ²⁰	Metformin (1000 mg BID)	35.5 ± 4.9 / 33.0 ± 3.3	99.6 ± 17.8 / 92.6 ± 18	108.8 ± 14.5 / 97.5 ± 11	779.4 ± 247.3 / 698.1 ± 292.8	NA
	Metformin (1000 mg BID) + Liraglutide (1.2 mg)	NA	NA	NA	NA	NA

BMI: Body Mass Index; BID: twice daily; TID: thrice daily; NA: Not Applicable WC: waist circumference

metformin stem from its capacity to directly and indirectly modulate cellular metabolism. It exerts its influence through two primary signaling pathways: the AMPK-dependent and the AMPK-independent. In the AMPK-dependent pathway, metformin triggers AMPK activation, which subsequently suppresses the mTOR (mammalian target of rapamycin) signaling pathway. This interference with mTOR activity impacts protein synthesis, consequently decelerating cell growth and division.²¹

Table 3 presents an overview of the studies examining metformin's role in cancer treatment, highlighting various treatment protocols, patient profiles and dosing strategies. The studies encompassed prospective cohort, randomized clinical, and retrospective designs with diverse sample sizes and treatment approaches, including MPA, MA and LNG-IUD in conjunction with metformin. Treatment efficacy, measured by complete response (CR) and partial response (PR), differed across studies, with the majority demonstrating favorable outcomes for the progestin-metformin combination. BMI and age information were also documented, revealing comparable baseline values among groups. Table 4 outlines the diagnostic and reproductive outcomes for patients in studies investigating metformin usage. These investigations compared progestin monotherapy to progestin-metformin combination therapy, assessing outcomes such as complete response (CR), partial response (PR), non-response (NR) and pregnancy rates. Reproductive outcomes varied, with some studies reporting pregnancy and live birth rates, while others omitted reproductive data. In general, the progestin-metformin combination showed promising results regarding response rates, although reproductive outcomes were not consistently reported across studies.

Metformin in cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity worldwide. Multiple factors contribute to the development of CVDs, including lifestyle choices and medical conditions such as tobacco use, diabetes mellitus, obesity, hyperlipidemia and hypertension. Among these risk factors, diabetes mellitus demonstrates a strong association with CVDs (including coronary artery disease, atherosclerosis and heart failure) and frequently presents

as a comorbid condition.³¹ Elevated blood glucose levels (hyperglycemia) induce oxidative stress, which can lead to endothelial dysfunction and a lipoprotein imbalance, thereby increasing the risk of CVDs. Metformin has demonstrated efficacy in reducing CVD incidence among individuals with diabetes. Metformin prevents deleterious modifications of apolipoprotein residues caused by alpha-dicarbonyl compounds through the activation of AMPK. This mechanism contributes to the restoration of high-density lipoprotein (HDL) function and mitigates alterations in low-density lipoprotein (LDL). Enhanced HDL function facilitates cholesterol transport and diminishes the risk of cardiovascular disorders. Furthermore, metformin attenuates oxidative stress in blood vessels and mitigates inflammation induced by hyperglycemia, further reducing the risk of CVDs. Type 2 diabetes mellitus (T2DM) elevates the risk of heart failure, with approximately one-third of heart failure cases reported in patients with diabetes. Metformin has been shown to enhance cardiac energy metabolism, which is necessary for normal heart function, by improving lipid and glucose metabolism through AMPK activation.³² Table 5 presents an overview of the study characteristics included in the review, evaluating incident heart failure outcomes in patients with preserved left ventricular ejection fraction (LVEF $\geq 50\%$). The table outlines the study design, demographic details of the populations and follow-up durations. Figure 3 illustrates a forest plot summarizing the effect of metformin treatment across four studies on HFpEF. Individual effect sizes ranged from 0.68 (95% CI: 0.51, 0.85) to 0.88 (95% CI: 0.83, 0.93), with a pooled random-effects model estimate of 0.82 (95% CI: 0.74, 0.90), demonstrating a statistically significant beneficial effect.

Metformin in neurodegenerative disorders

Neurodegenerative disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), are characterized by progressive neuronal loss and cognitive or motor impairments. Parkinson's disease primarily affects the dopaminergic neurons in the substantia nigra, resulting in tremors, bradykinesia, and rigidity. Genetic and environmental factors contribute to its pathogenesis.^{33,34} Metformin has been demonstrated to decelerate the progression of neurodegenerative disorders, mitigate age-related diseases, and extend lifespan.³⁵⁻³⁹ Table 6 summarizes the characteris-

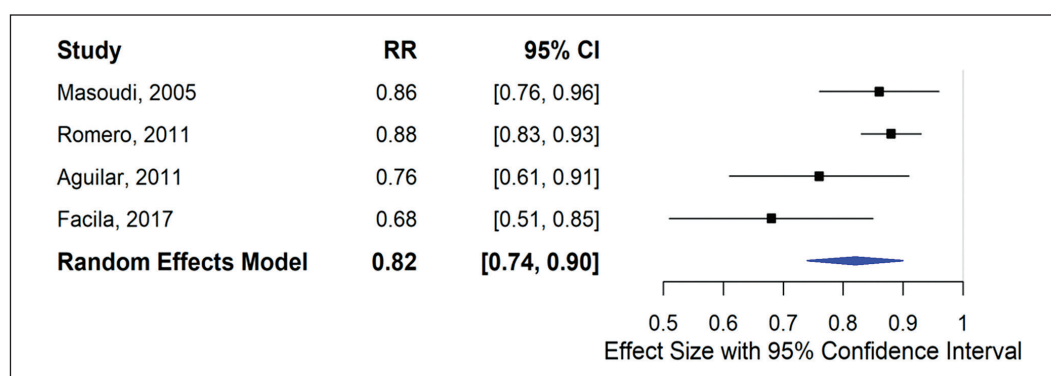


Figure 3. Effect of metformin in patients with heart failure with preserved ejection fraction (HFpEF).

Table 3. Overview of studies on metformin use in cancer treatment, including patient demographics, treatment methods and outcomes

Author and publication year	Study Type	BMI (mean, baseline)	Number of patients (groups)	Treatment methods	Diagnosis groups	%	Age (mean, baseline)
<i>Shao et al. 2023</i> ²²	Prospective cohort study	PROG: 26.33 ± 4.30 / PROG + MET: 27.01 ± 4.43	Total = 219, PROG = 138, CAH = 81	MPA or MA + Metformin	CAH+PROG = 35.5, MET+PROG = 35.8	PROG: 35.05 ± 5.14, PROG + MET: 32.00 ± 4.58	PROG: 32.00 ± 4.58
<i>Janda et al. 2021</i> ²³	3 arm open-label RCT	3-arm: 48.0 ± 9.7, 2-arm: 43.1 ± 9.6	Total = 165, PROG = 118, Met = 47	LNG-IUD + Metformin	EAC = 58%, EHA = 42%	3-arm: 51.5 ± 14.1, 2-arm: 60.6 ± 13.8	3-arm: 51.5 ± 14.1, 2-arm: 60.6 ± 13.8
<i>Acosta-Torres et al. 2020</i> ²⁴	Retrospective study	PROG: 34.7 (26.9–45.3) / PROG + MET: 41.5 (32.7–53.1)	Total = 92, PROG = 58, PROG + MET = 34	MPA or MA or Prometrium or LNG-IUD + Metformin	AH/EIN: 54 (59%), EC: 38 (41%)	PROG: 36.0 (30.0–38.5), PROG + MET: 32.0 (29.0–35.0)	PROG: 32.0 (29.0–35.0)
<i>Mandelbaum et al. 2020</i> ²⁵	Retrospective study	PROG: 38.3 (31.2–45.0), PROG + MET: 37.1 (32.7–46.3)	Total = 245, CAH = 176, Local progestin group = 69	MPA or MA or norethindrone or depo-medroxyprogesterone acetate (systemic); LNG-IUD (local) + Metformin	CAH: all patients	PROG: 32.9 (32.2–46.3), PROG + MET: 42.0 (38.0–60.5)	PROG: 42.0 (38.0–60.5)
<i>Factor et al. 2024</i> ²⁶	Randomized, single-center	PROG: 24.6 ± 4.1 / PROG + MET: 24.7 ± 5.2	Total = 150, PROG = 74, PROG + MET = 76	MA + Metformin	PROG: 62 (AEH) + 12 (EEC), PROG + MET: 61 (AEH) + 15 (EEC)	PROG: 34.4 ± 5.2, PROG + MET: 32.0 ± 4.5	PROG: 32.0 ± 4.5
<i>Yuan et al. 2022</i> ²⁷	No data	PROG: 33.37 ± 4.49, PROG + MET: 34.43 ± 4.24	All = 120, EAC: all patients	MPA + Metformin	EEC: all patients	PROG: 36.12 ± 8.41, PROG + MET: 33.73 ± 7.47	PROG: 33.73 ± 7.47
<i>Shan et al. 2014</i> ²⁸	Controlled, single-blind	No data	All = 16, PROG = 8, PROG + MET = 8	MA + Metformin	EAH: all patients	All patients: 35.2 ± 5.8, PROG: 34 ± 7.1, PROG + MET: 36.4 ± 4.2	PROG + MET: 36.4 ± 4.2
<i>Shiwani et al. 2024</i> ²⁹	Retrospective study	All patients: 26.7 (17.6–36.0)	All = 32, PROG = 23, PROG + MET = 32	MPA or MA + Metformin	AH: 13/32 (40.6%), G1EC: 19/32 (59.4%)	All patients: 30.4 (20–40)	All patients: 30.4 (20–40)
<i>Mitsuhashi et al. 2019</i> ³⁰	Retrospective study	PROG: 23.3 (21.6–27.1), PROG + MET: 29.7 (27.3–32.0)	All = 63, PROG = 23, PROG + MET = 42	MPA + Metformin	AEH/CAH: 21/63, EC: 42/63	All patients: 35 (26–44)	All patients: 35 (26–44)

BMI: Body mass index; EAC: endometrial adenocarcinoma; EIN: endometrial intraepithelial hyperplasia; M: oral metformin; WL: weight loss intervention; CR: complete response; PROG: progestin; MA: megestrol acetate; PROG+MET: Progestin+Metformin; CH: complex hyperplasia; AH: atypical hyperplasia; AEH: Atypical Endometrial Hyperplasia; CAH: Complex Atypical Hyperplasia

Table 4. Reproductive and treatment outcomes comparing progestin + metformin versus progestin alone across different studies

Author (year)	Diagnostic method	Patients (total)	Groups (PROG + MET vs. PROG)	Intervention	Comparison	Treatment outcomes	Reproductive outcomes
<i>Shao et al. 2023</i> ²²	Hysteroscopic surgery	219	Group 1: 81, Group 2: 138	MPA or MA + MET, MPA or MA	Group 1: MET + PROG, Group 2: PROG	CR: 93.8% (Group 1), 84.1% (Group 2); PR: 3.7% (Group 1), 3.6% (Group 2); NR: 2.5% (Group 1), 11.6% (Group 2)	Pregnancies: Group 1: 37%, Group 2: 36.8% Live births: Group 1: 22.2%, Group 2: 23.7% Abortions: Group 1: 40%, Group 2: 35.7%
<i>Janda et al. 2021</i> ²³	Endometrial biopsy or D&C	165	Group 1: 47, Group 2: 118	LNG-IUD + MET, LNG-IUD	Group 1: PROG + MET, Group 2: PROG	CR: 61% (Group 1), 67% (Group 2); PR: 6% (Group 1), 12% (Group 2); NR: 24% (Group 1), 18% (Group 2)	No data on pregnancies, abortions, or live births
<i>Acosta-Torres et al. 2020</i> ²⁴	Endometrial biopsy or D&C	92	Group 1: 34, Group 2: 58	MPA/MA/Prometrium/ LNG-IUD + MET	Group 1: PROG + MET, Group 2: PROG	CR: 68% (Group 1), 69% (Group 2); Relapse Rate: 4 cases on treatment, 10 off treatment	Pregnancies: Group 1: 6%, Group 2: 24% Live births: Group 1: 6%, Group 2: 24%
<i>Mandelbaum et al. 2020</i> ²⁵	Endometrial biopsy	245	Systemic Progestin Group: 176, Local Progestin Group: 69	MPA or MA + MET	Systemic Progestin: Group 1 + MET, Group 2: PROG	CR: 34.1% (Systemic), 84.1% (Local); PR: 10.2% (Systemic), 1.4% (Local)	No data on pregnancies, abortions, or live births
<i>Factor et al. 2024</i> ²⁶	D&C +/- hysteroscopy	150	Group 1: 76, Group 2: 74	MA + MET	Group 1: PROG + Metformin, Group 2: PROG	CR at 16 weeks: 34.3% (Group 1), 20.7% (Group 2) CR at 36 weeks: 74.3% (Group 1), 68.2% (Group 2)	Pregnancies: Group 1: 51.3%, Group 2: 48.4% Live births: Group 1: 21.6%, Group 2: 41.9%
<i>Yuan et al. 2022</i> ²⁷	Histopathological exam	120	Group 1: 60, Group 2: 60	MPA + MET	Group 1: PROG + MET, Group 2: PROG	CR: 26.7% (Group 1), 20% (Group 2); PR: 45% (Group 1), 33.3% (Group 2)	Pregnancies: Group 1: 81.7%, Group 2: 61.7% ART: Group 1: 32.7%, Group 2: 37.8%
<i>Adamyant et al. 2024</i> ²⁸	D&C	16	Group 1: 8, Group 2: 8	MA + MET	Group 1: PROG + MET, Group 2: PROG	CR: 75% (Group 1), 25% (Group 2); NR: 37.5% (Group 1), 67.7% (Group 2)	No data on pregnancies, abortions, or live births
<i>Zhou et al. 2015</i> ²⁹	Hysteroscopic biopsy or D&C	32	Group 1: 9, Group 2: 23	MPA or MA + MET	Group 1: PROG + MET, Group 2: PROG	CR: 88.9% (Group 1), 84.4% (Group 2)	Pregnancies: Group 1: 55.6%; ART: Group 1: 88.9%
<i>Mitsuhashi et al. 2019</i> ³⁰	D&C	63	Group 1: 42, Group 2: 23	MPA + MET	Group 1: PROG + MET, Group 2: PROG	CR: 97% (Group 1), 61% (Group 2); Relapse: 13.1%	Pregnancies: Group 1: 45%; ART: 83% of pregnancies occurred within 12 months

PROG: Progesterone; MET: Metformin; MPA: Medroxyprogesterone Acetate; MA: Megestrol Acetate; D&C: Dilation and Curettage; CR: Complete Response; PR: Partial Response; NR: Non-Response; ART: Assisted Reproductive Technology

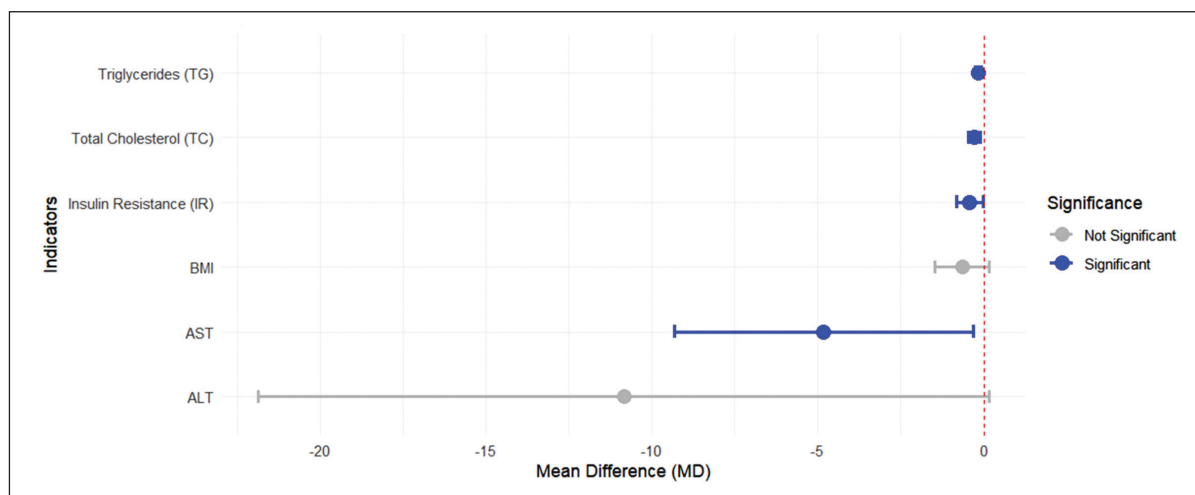


Figure 4. Impact of metformin on clinical and biochemical indicators in MASLD patients.

Table 5. Study characteristics on the incident heart failure outcomes in patients with left ventricular ejection fraction $\geq 50\%$

Study	Design	Sample size	Mean age (years)	% of Patients with LVEF $\geq 50\%$	Follow-up duration (years)
<i>Lupon et al. 2018</i> ³³	Retrospective study	13,930	76	23%	1.0
<i>Ziao et al. 2024</i> ³⁴	Prospective study	1,519	72	51%	4.7
<i>Lee et al. 1993</i> ³⁵	Retrospective study	835	72	49%	2.4
<i>Ohno et al. 2025</i> ³⁶	Retrospective study	6,185	68	45%	2.2

LVEF: Left Ventricular Ejection Fraction

Table 6. Characteristics and quality of included studies assessing the risk of neurodegenerative diseases with metformin use

Study	Design	Study period	Outcome	Sample size (exposure vs control)	Adjusted OR (95% CI)	Quality score
<i>Wang et al. 2024</i> ⁴¹	Cross-sectional	2008–2012	Cognitive dysfunction (FAB)	2304 (318 vs 1986)	1.29 (0.96 – 1.74)	7/11 (AHRQ)
<i>Laurie-Anne et al. 2023</i> ⁴²	Cohort	2004–2009	Dementia (ICD-9-CM)	1829 (1033 vs 796)	0.82 (0.52 – 1.28)	7/9 (NOS)
<i>Fang et al. 2023</i> ⁴³	Cohort	1996–2007	Parkinson's Disease (ICD-9-CM or A-code)	3758 (1879 vs 1879)	1.30 (0.69 – 2.46)	7/9 (NOS)
<i>Villani et al. 2022</i> ⁴⁴	Cohort	2000–2007	Dementia (ICD-9-CM or A-code)	12,383 (1864 vs 10,519)	0.76 (0.58 – 0.98)	7/9 (NOS)
<i>Garcia-Ptacek et al. 2016</i> ⁴⁵	Cohort	2000–2010	Parkinson's Disease (ICD-9-CM)	9302 (4651 vs 4651)	2.27 (1.68 – 3.07); Dementia: 1.66 (1.35 – 2.04)	7/9 (NOS)
<i>Emre et al. 2003</i> ⁴⁶	Cohort	2003–2005	Cognitive dysfunction (MMSE)	365	0.49 (0.25 – 0.95)	5/9 (NOS)
<i>Canet et al. 2003</i> ⁴⁷	Case-control	1998–2008	Alzheimer's Disease	14,172 (7086 vs 7086)	1.73 (1.11 – 2.68)	7/9 (NOS)
<i>Armstrong et al. 2019</i> ⁴⁸	Cohort	2004–2010	Dementia (ICD-10)	5332 (1478 vs 3854)	0.96 (0.89 – 1.03)	7/9 (NOS)
<i>Gorelick et al. 2010</i> ⁴⁹	Case-control	2006	Alzheimer's or Cognitive Dysfunction	126 (35 vs 91)	1.75 (0.81 – 3.78)	8/9 (NOS)
<i>Bamford et al. 2021</i> ⁵⁰	Cohort	2005–2014	Parkinson's Disease (ICD-10)	102,745 (94,349 vs 8396)	1.39 (1.06 – 1.82)	7/9 (NOS)
<i>Connor et al. 2020</i> ⁵¹	Cohort	2001–2012	Dementia (ICD-9)	14,562 (10,437 vs 4125)	<75 yrs: 0.89 (0.79–0.99); ≥75 yrs: 0.96 (0.87–1.05)	8/9 (NOS)
<i>Ruan et al. 2025</i> ⁵²	Cross-sectional	2014	Cognitive dysfunction (RCS)	198	0.52 (0.24 – 1.00)	5/11 (AHRQ)
<i>Silvija et al. 2025</i> ⁵³	Cross-sectional	2012	Cognitive dysfunction (MMSE)	1323	0.59 (0.35 – 0.99)	4/11 (AHRQ)
<i>Ordoobadi et al. 2024</i> ⁵⁴	Cohort	2004–2012	Dementia (ICD-10)	22,841 (NA)	0.58 (0.39 – 0.88)	8/9 (NOS)
<i>Negru et al. 2025</i> ⁵⁵	Cohort	1998–2011	Alzheimer's (NINCDS-ADRDA)	5894 (2120 vs 3774)	1.60 (0.87 – 2.93); Dementia: 1.42 (1.02 – 1.98)	8/9 (NOS)
<i>Friedman et al. 2011</i> ⁵⁶	Cohort	2011–2014	Cognitive dysfunction (MMSE)	757	2.47 (1.10 – 5.57)	6/9 (NOS)
<i>Riedel-Heller et al. 2001</i> ⁵⁷	Case-control	2013–2017	Dementia (ICD-10)	16,522 (8276 vs 8276)	0.96 (0.88 – 1.04)	8/9 (NOS)
<i>Du et al. 2023</i> ⁵⁸	Cohort	1997–2007	Alzheimer's (ICD-9)	30,170 (4978 vs 25,192)	Mono: 0.69 (0.28 – 1.71); Combo: 0.57 (0.26–1.26)	7/9 (NOS)
<i>Hsiao et al. 2015</i> ⁵⁹	Cohort	1999–2011	Dementia (ICD-9)	31,352 (15,676 vs 15,676)	0.71 (0.63–0.79)	7/9 (NOS)

SU: sulfonylurea; MET: Metformin; AD: Alzheimer's disease; FAB: Frontal Assessment Battery; FBG: Fasting blood glucose; RCS: Rapid cognitive screen; RCS: Rapid cognitive screen; AHRQ: Agency for Healthcare Research and Quality; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; NOS: Newcastle–Ottawa Scale; MMSE: Mini-Mental State Examination; AHRQ: Agency for Healthcare Research and Quality; NA: Not Applicable; Mono: monotherapy; Combo: combination therapy

tics and quality of studies assessing the association between metformin use and the risk of neurodegenerative diseases, including dementia, Alzheimer's disease (AD), and Parkinson's disease (PD). It elucidates variations in study design, population demographics, outcome measurements, and quality scores. The findings demonstrate heterogeneous results, with some studies suggesting that metformin has protective effects, while others report an increased risk or no significant association.⁴⁰

Metformin in liver diseases

Table 7 summarizes the characteristics of studies evaluating the effects of metformin on liver health, highlighting the diverse study designs, diagnostic methods and covariate adjustments employed. The varied metformin doses administered (ranging from 500 mg to 3000 mg) reflect individualized treatment approaches. Figure 4 illustrates the effects of metformin on key clinical and biochemical indicators in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Metformin significantly reduces Triglycerides (TG), Total Cholesterol (TC) and Insulin Resistance (IR), as indicated by the blue markers. Non-significant changes are observed for BMI,

AST and ALT as indicated by gray markers with confidence intervals crossing the line of no effect.⁶⁰⁻⁶² These findings elucidate the role of metformin in improving metabolic parameters in patients with MASLD.

The widespread use of metformin for non-diabetic purposes has gained significant attention in recent years. This shift in usage patterns reflects the drug's potential therapeutic benefits across various medical domains. Among these non-diabetic applications, liver disease stands out as the most prominent, accounting for 30% of the non-diabetes indications of metformin use. This suggests a growing recognition of metformin's hepatoprotective properties and its potential role in managing liver disorders. Following closely, cognitive dysfunction represents 15% of non-diabetes indications of metformin use, indicating an emerging interest in the drug's neuroprotective effects and its potential to mitigate cognitive decline. While cancer treatment and prevention still represent a significant area of research and clinical interest, they account for only 5%. The timeline plot presented in Figure 5 provides a chronological perspective on the evolution of metformin research across these different applications. This visual representation enables a comprehensive understanding

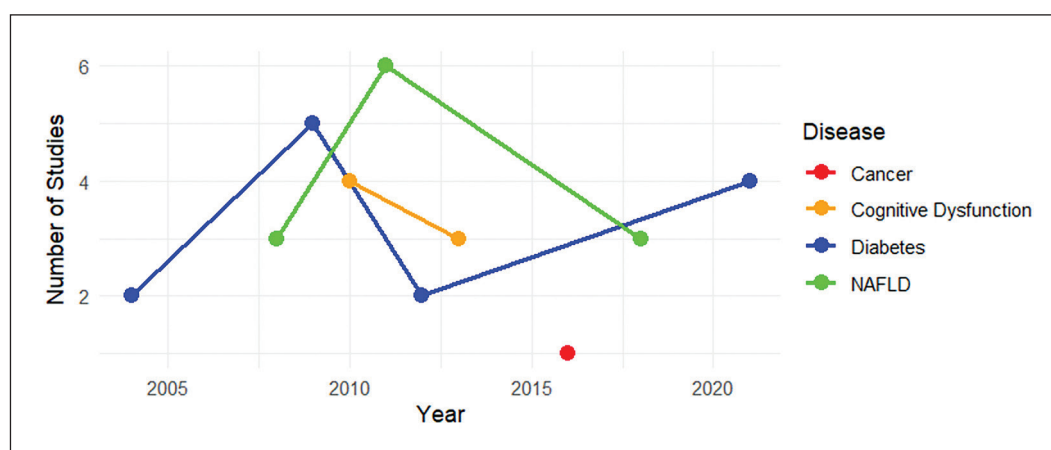


Figure 5. Timeline of research on metformin by disease.

Table 7. Characteristics of studies evaluating the effects of metformin on liver health

Study	Study Design	Case Count	Study Duration (Months)	Diagnostic Method	Metformin Dosage (Treatment Group)	NOS
Brackett et al. 2010 ⁶³	RCT	93	24	Ultrasonography	250 mg first week, 500 mg second week, and 1000 mg third week	8
Pinyopornpanish et al. 2021 ⁶⁴	Prospective cohort	50	6	Ultrasonography	1000 mg/day	7
Federica et al. 2024 ⁶⁵	RCT	42	6	Ultrasound	500 mg first week, 2000 mg second week	8
Idilman et al. 2008 ⁶⁶	Cohort	44	6	Biopsy	500 – 3000 mg/day	7
Ramanathan et al. 2022 ⁶⁷	Prospective	129	6	Biochemical, radiological, and histological criteria	850 mg/day	9
Nar et al. 2008 ⁶⁸	Open label RCT	28	12	MRI, CT, imaging, and liver biopsy	500 mg once daily (first week), 500 mg twice daily (second to third weeks), 1000 mg twice daily thereafter	8
Lee 2020 ⁶⁹	Prospective cohort study	34	6	Ultrasonography	850 – 1700 mg/day	7
Woo et al. 2014 ⁷⁰	Prospective	57	24	Biopsy and ultrasonography	1.5 g/day	8
García-Compeán et al. 2022 ⁷¹	RCT	36	6	Ultrasonography	850 mg/day	7
Hesen et al. 2017 ⁷²	Cohort	63	4	Ultrasonography	850 – 1700 mg/day	8

of how scientific interest in metformin's non-diabetes indications has evolved over time. The timeline likely reveals key milestones, breakthrough studies, and shifting trends in research focus, offering valuable insights into the drug's expanding therapeutic potential. By examining this timeline, researchers and clinicians can better appreciate the progression of metformin's applications, from its traditional role in diabetes management to its current status as a multifaceted therapeutic agent with diverse clinical implications.

CONCLUSION

The findings of this systematic review underscore the multifaceted therapeutic potential of metformin, extending well beyond its established role in managing type 2 diabetes. The analysis of recent literature reveals a growing body of evidence supporting metformin's efficacy in various health conditions, including cardiovascular diseases,⁷³ different types of cancers,⁷⁴ neurodegenerative diseases, and obesity. This review aims to synthesize these findings, explore the implications for clinical practice, and highlight areas for future research. The positive effects of metformin on cardiovascular health are significant. Multiple studies have demonstrated that metformin not only improves glycemic control but also exerts beneficial effects on lipid profiles and blood pressure, thereby reducing cardiovascular risk factors. The drug's ability to enhance insulin sensitivity and exert anti-inflammatory effects may contribute to these cardiovascular benefits. Given the high prevalence of CVD among diabetes patients, the integration of metformin into CVD management protocols could be a valuable therapeutic strategy. Metformin's cardiovascular benefits extend beyond diabetes management, suggesting potential applications in non-diabetic populations for the prevention and treatment of heart disease. Long-term studies show reduced cardiovascular events and mortality in type 2 diabetes patients using metformin. The drug's diverse effects on metabolic pathways make it promising for further cardiovascular medicine research.

Evidence suggests that metformin inhibits cancer cell proliferation and induces apoptosis through various mechanisms, including activation of the AMP-activated protein kinase (AMPK) pathway. This review elucidates that metformin has demonstrated efficacy in treating several types of cancer, including breast, colorectal, and endometrial cancers. These findings indicate that metformin may be considered an adjunctive therapy in oncology, particularly for patients with insulin resistance or metabolic syndrome.

Emerging research suggests that metformin may play a potential role in reducing the risk of neurodegenerative diseases. The reviewed data suggest a potential association between metformin use and improved cognitive function, particularly in individuals with hyperglycemia. The neuroprotective effects of metformin can be attributed to its ability to mitigate oxidative stress and inflammation, which are critical factors in the pathogenesis of neurodegenerative

disorders. However, additional longitudinal studies are necessary to establish causality and elucidate the underlying mechanisms involved.

Metformin's role in obesity management represents a further area of research interest. The medication has demonstrated efficacy in promoting weight reduction and enhancing metabolic parameters in overweight and obese individuals, particularly those exhibiting insulin resistance. Looking at the fact that obesity increases risk for diabetes and cardiovascular problems, the application of metformin in obesity for weight management could have significant public health implications.

In summary, metformin demonstrates a broad spectrum of therapeutic benefits that extend well beyond diabetes management. Its roles in treating cardiovascular diseases, various cancers, neurodegenerative diseases, and obesity position it as a multifaceted agent in modern medicine. As research continues to evolve, it is essential to optimize the use of metformin in clinical settings and explore its full potential in improving patient outcomes across a range of health conditions.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

AJ: Conceptualization, Methodology, Validation, Formal analysis, Data Curation, Writing – original draft preparation, Writing – review and editing; **AU:** Methodology, Writing – original draft preparation, Writing – review and editing; **SSA:** Methodology, Data Curation; **RA:** Formal analysis, Investigation.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Disclosure

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Hirata Syndrome Clinical Presentation and Management: A Single-Centre Experience

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Abstract

Background. Hirata syndrome, or Insulin Autoimmune Syndrome (IAS), is a rare condition characterized by hyperinsulinemic hypoglycemia due to autoantibodies targeting endogenous insulin. Its rarity and unique presentation make diagnosis and management challenging.

Objective. To analyze the clinical presentation, diagnostic methods, and management of IAS based on a single-center experience

Methodology. This was a case series, conducted at a tertiary care center in northeast India, involving six cases diagnosed between January 2022 and April 2024. Clinical histories, including drug use and comorbidities, were reviewed. Laboratory analyses during hypoglycemic episodes assessed insulin, C-peptide, β -hydroxybutyrate, and cortisol levels. Extended OGTT and 72-hour fasting tests were used when spontaneous hypoglycemia was absent. Insulin autoantibodies (IAA) confirmed the diagnosis.

Results. Six IAS cases were identified, with most linked to α -lipoic acid in multivitamins and one to methimazole. Patients experienced recurrent postprandial hypoglycemia. Elevated insulin, C-peptide, and IAA levels confirmed the diagnosis. Management included discontinuation of causative drugs, dietary changes with frequent complex carbohydrate meals, and pharmacotherapy (acarbose or prednisolone). Follow-up showed resolution of hypoglycemia and normalization of IAA levels in all patients.

Conclusion. IAS should be considered in patients with hypoglycemia and a history of sulfhydryl-containing medications. Early diagnosis using IAA measurement and appropriate management, including drug discontinuation, dietary adjustments, and pharmacotherapy, is essential. Further research is needed to refine treatment strategies and understand the pathogenesis of this rare syndrome.

Key words: *Hirata syndrome, insulin autoantibody syndrome, insulin autoantibody, hypoglycemia*

INTRODUCTION

Hirata syndrome, also known as Insulin Autoimmune Syndrome (IAS), presents a unique challenge in Endocrinology. First identified by Yukimasa Hirata and colleagues in Japan in 1970, this rare condition manifests as hyperinsulinemic hypoglycemia due to autoantibodies targeting endogenous insulin. The cornerstone of IAS diagnosis is the presence of circulating insulin autoantibodies (IAA), which play a pivotal role in its pathogenesis.¹ Symptoms and signs of hypoglycaemia are nonspecific and are classified into neurogenic and neuroglycopenic symptoms. Neurogenic (autonomic) symptoms include adrenergic (palpitations, tremors and anxiety) and cholinergic (diaphoresis, hunger and

paresthesias) symptoms. Neuroglycopenic symptoms are due to glucose deprivation in brain, these symptoms include cognitive impairment, psychomotor abnormalities and in severe cases seizures, and coma.²

IAS primarily arises as a result of medication-induced autoimmune responses, with methimazole being the most common trigger. Other implicated medications include captopril, d-penicillamine, propranolol, and α -lipoic acid. Furthermore, genetic predisposition, particularly HLA associations such as HLA-DRB1 *0406, DQB1 *0302, DQA1 *0301, DRB1 *0415, and DRB1 *13:01, have been observed in the majority of IAS cases. This condition can coexist with other autoimmune disorders such as Graves' disease, systemic lupus erythematosus (SLE), rheumatoid

arthritis, and chronic hepatitis. Additionally, less common associations include ankylosing spondylitis, anti-neutrophil cytoplasmic antibody-associated glomerulonephritis, polymyositis, systemic sclerosis, psoriasis, multiple myeloma, and monoclonal gammopathy.³ IAS are usually self-limiting once the triggering medication is stopped but immune-suppressants may be required in some.⁴

METHODOLOGY

This case series was conducted in the Department of Endocrinology at a tertiary care center in northeast India (Gauhati Medical College and Hospital, Guwahati, Assam, India). Ethical clearance for the study was obtained from the Institutional Ethics Committee (Approval No. MC No-190/2007/pt-II/oct-2024/7). Our study was conducted over a period of 28 months, from January 2022 to April 2024, covering all cases diagnosed and treated during this period. Our study employed a consecutive sampling approach and all patients presenting with hypoglycemia at the Endocrinology Department of our center between January 2022 and April 2024 were screened. Eligible patients meeting the inclusion criteria were enrolled in the study, ensuring no selection bias.

Inclusion criteria

Patients diagnosed with Hirata syndrome (Insulin Autoimmune Syndrome) based on clinical presentation of recurrent hypoglycemia (blood glucose <55 mg/dl) with elevated insulin autoantibody (IAA) levels confirmed by laboratory testing after excluding other common causes of hypoglycemia, such as insulinoma or exogenous insulin administration.

Exclusion criteria

1. Patients with hypoglycemia secondary to non-auto-immune causes, including insulinoma, critical illness, or malnutrition.
2. Individuals with incomplete diagnostic workup or insufficient data for analysis.
3. Patients who refused or withdrew consent during the study period.

A detailed history of the clinical features, drug intake, and associated comorbidities were assessed. At the height of hypoglycemia (Blood glucose <55 mg/dl), critical samples were collected and sent for analyzing serum insulin, serum C-peptide, plasma β -hydroxybutyrate and serum cortisol. If spontaneous hypoglycemia was not present, then a 72-hour fast test and Extended OGTT tests were done (up to 6 hours after 75 gm OGTT) to induce hypoglycemia. The samples were analyzed by Electrochemiluminescent immunoassay (ECLIA) by Roche Cobas e411 analyzer. Serum levels of insulin >3 μ IU/ml, C-peptide >0.6 ng/ml, and IAA >10 IU/ml were used as a cut-off for the diagnosis of hyperinsulinemic hypoglycaemia secondary to insulin

autoimmune syndrome. A written informed consent was taken from all of the cases. The total number of cases was 6 considering the rarity of the disorder; the descriptive observational data are presented below.

The observations obtained through clinical evaluation, laboratory investigations, and diagnostic procedures are presented descriptively in the Results section. Each case is detailed individually to highlight variations in clinical presentation, diagnostic findings, treatment approaches, and patient outcomes. This case-wise presentation format ensures that the methods employed for diagnosis and management are directly linked to the reported outcomes, offering a clear understanding of how each case was assessed and treated based on the outlined methodology.

RESULTS

During the study period, out of the 25 patients presenting with recurrent hypoglycemia, only 6 were diagnosed with Hirata syndrome. The details of the individual patients are as follows:

Case 1

A 48-year-old male presented with recurrent hypoglycemic episodes for 2 months occurring both in the fasting state as well as four to five hours after a major meal. This man complained of palpitation, tremors, and one episode of altered sensorium requiring hospitalization and intravenous (IV) dextrose therapy. The blood glucose measured during the episodes varied between 27-60 mg/dl. The critical sampling taken at a blood glucose (BG) level of 40 mg/dl revealed serum insulin >1000 μ IU/ml, serum C-peptide 32.3 ng/ml, serum cortisol 5.4 μ g/dl, serum GH 0.7 ng/ml and absent ketone bodies. The Computed tomography (CT) scan imaging of the abdomen was normal and since suspicion was high, insulin autoantibodies were sent which were more than four times elevated (85.3 IU/ml, normal <18 IU/ml). A diagnosis of Hirata syndrome was made based on the high insulin antibody levels and history of taking α -lipoic acid for a long duration. The patient was started on 2-hourly frequent complex carbohydrate meals along with acarbose (25 mg three times daily with meals) and α -lipoic acid was stopped. The patient did not develop any further episodes of hypoglycemia after the initiation of treatment. On follow-up after 3 months, the insulin antibodies were reassessed and were found to be negative. Acarbose was stopped and there had been no further hypoglycemia to date.

Case 2

A 38-year-old female presented with recurrent hypoglycemia for 1 month, which was typically post-prandial and occurring usually 3-4 hours after taking food. On evaluation, the critical sampling at a blood glucose level of 29 mg/dl revealed serum insulin >1000 μ IU/ml, serum C-peptide 23.96 ng/ml, serum cortisol 11.8 μ g/dl, and

negative urine ketones. The patient recovered after IV dextrose. A diagnosis of hyperinsulinemic hypoglycemia was made and an MRI (Magnetic resonance imaging) of the pancreas was done which was not suggestive of any tumor. Then anti-insulin autoantibodies were sent and were found to be 10 times elevated (188 IU/ml). Later the patient revealed a history of taking multivitamin tablets for a long duration which contained α -lipoic acid. The patient was started on a frequent complex carbohydrate diet and prednisolone (40 mg/day), which was tapered over 1 month. The patient responded well with no further hypoglycemic episodes even after stopping therapy.

Case 3

A 42-year-old female presented with multiple episodes of hypoglycemia for 5 months, which usually occurred 4-5 hrs after having food and relieved by taking food. The patient underwent an extended oral glucose tolerance test which resulted in hypoglycemia after 4 hours of taking 75 grams of glucose. Critical sampling at BG 20 mg/dl was done and the results showed serum insulin 600 μ IU/ml, serum C-peptide 5.5 ng/ml, and serum cortisol 19.6 μ g/dl. The CT scan of the abdomen was normal and insulin autoantibody levels were high (78.7 IU/ml). This patient also revealed a history of taking multivitamins containing α -lipoic acid. The patient was started on a complex carbohydrate diet with acarbose (25 mg three times daily with meals) and prednisolone (40 mg/day).

Case 4

A 60-year-old female presented with multiple hypoglycemic episodes for 20 days. The patient had a history of kidney stones for which she received multiple medications along with multivitamins containing α -lipoic acid. Hypoglycemic episodes were mainly post-prandial usually occurring after 2-3 hours after having food. The patient underwent a 72-hour fast test during which the patient did not have hypoglycemia, hence an extended OGTT was done during which the patient developed hypoglycemia after 3.5 hours. During hypoglycemia (BG 20 mg/dl) the serum insulin was >1000 μ IU/ml, C-peptide 23.02 ng/ml, cortisol 20 μ g/dl and GH 11.54 ng/ml. CT abdomen was normal whereas the anti-insulin autoantibody level was high (98 IU/ml). The patient was started on acarbose (25 mg three times daily with meals) with frequent complex carbohydrate-containing meals. The patient was discharged after 5 days. After 6 months of follow-up patient's antibody levels became negative and the patient did not have any more hypoglycemic episodes even after stopping acarbose.

Case 5

A 64-year-old non-diabetic male presented with recurrent hypoglycemia (lowest BG 34 mg/dl) for 1 month. Whipple's triad was documented when the case was admitted to the hospital. He was hypertensive and was taking telmisartan, amlodipine, and chlorthalidone. All hypoglycemia episodes

usually occur after 4-5 hours of taking a carbohydrate meal. He was also taking a multivitamin tablet for 2 months which contained α -lipoic acid. His critical sampling during hypoglycemia (BG 34 mg/dl) revealed adequate cortisol response (20.61 μ g/dl) and very high insulin (>1000 μ IU/ml) and C-peptide (23.27 ng/ml) levels. His CT abdomen was normal except for a small mesenteric lipoma. The anti-insulin autoantibody levels were high (93 IU/ml; normal range <18 IU/ml). The multivitamin tablet was stopped and he was started on acarbose (25 mg three times daily with meals) with a frequent complex carbohydrate-containing diet. The patient responded after the first dose without any further hypoglycemia episodes. After 3 months, during the follow-up, the patient's insulin autoantibody disappeared and acarbose was tapered off. There was no episode of hypoglycemia thereafter to date.

Case 6

A 60-year-old female presented with recurrent postprandial hypoglycemia for the last 1 month, 4 to 5 episodes in a week. She gave a history of thyroid disease and intake of antithyroid medication (methimazole 10 mg once daily) for the last 2 months, which she had stopped 1 week before presentation. The critical sampling during hypoglycemia (BG 42 mg/dl) revealed high serum insulin (>1000 μ IU/ml), high C-peptide (12.35 ng/ml), and serum cortisol of 28.20 μ g/dl with absent ketosis. Her thyroid function test was within normal limits (TSH 3.8 mIU/L) and a negative anti-TSH receptor antibody which ruled out Graves' disease. Her abdominal and thyroid imaging were normal. On further evaluation, her insulin autoantibody levels were found to be very high (68 IU/ml). A diagnosis of Hirata syndrome was made with methimazole being the possible culprit. This patient was treated with acarbose (25 mg three times daily) and she responded well without further episodes of hypoglycemia. The acarbose treatment was continued for 3 months and when her insulin antibody levels became negative, acarbose was tapered and stopped.

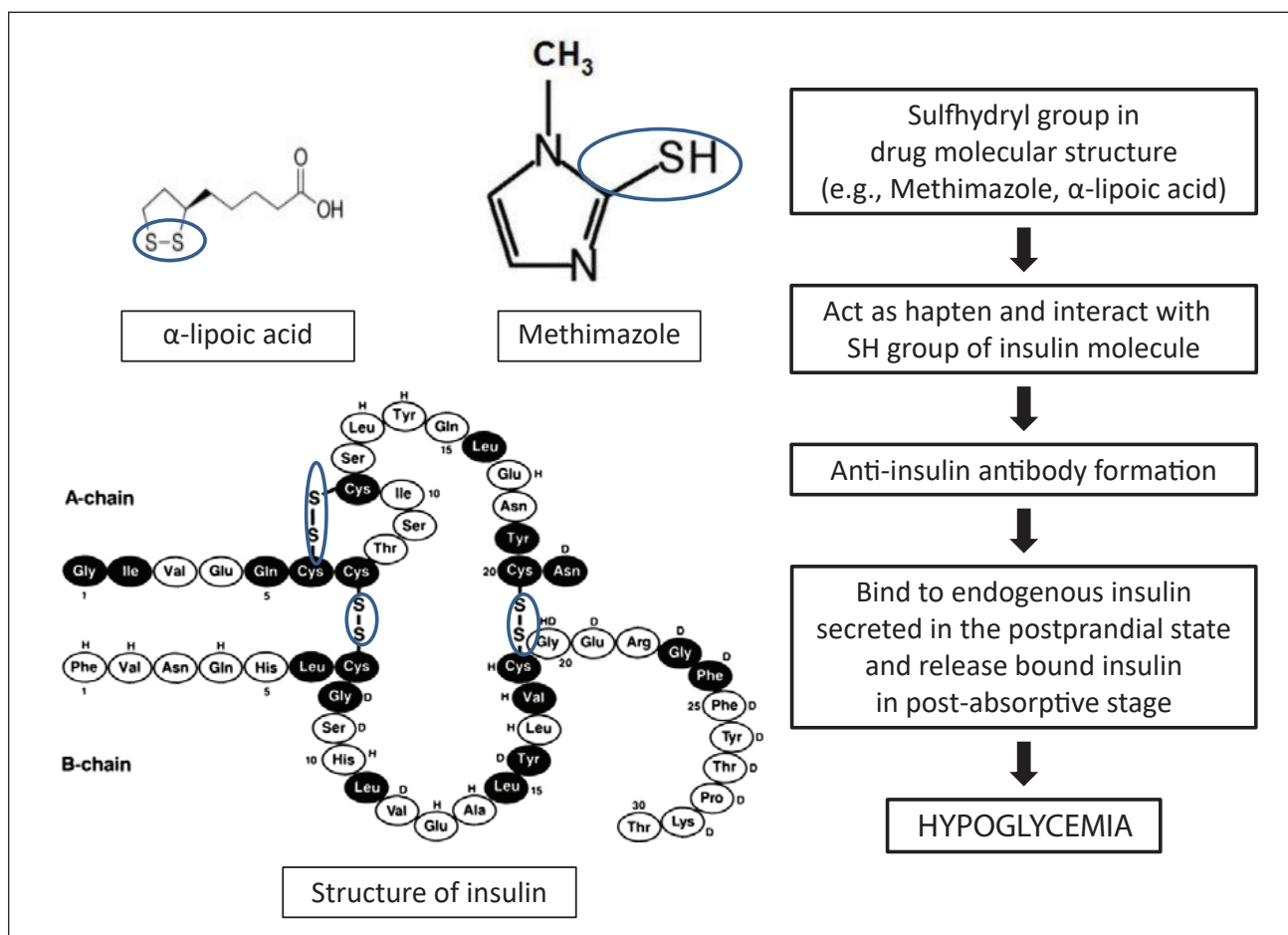
DISCUSSION

IAS is an autoimmune condition without any gender predilection. The mean age of presentation varies across different studies, ranging from 8 to 62 years. In our series, patients belonged to the age group of 42 to 64 years. Hypoglycemic episodes predominantly occur during the post-absorptive phase, although instances of fasting and exercise-induced hypoglycemia have also been reported. The underlying mechanism of hypoglycemia in IAS is attributed to the presence of substantial levels of insulin autoantibodies (IAA). When a person eats a meal, there is a surge in blood glucose levels which subsequently leads to increased insulin secretion from the pancreatic beta cells. However, when IAA is present, it binds to the insulin molecules and reduces the efficacy of insulin, resulting in postprandial hyperglycemia. This, in turn, stimulates heightened production of insulin and C-peptide to counteract the hyperglycemic state. The complexes formed between

Table 1. Summary of all six patients in tabular form

S.N	Age (Years)	Sex	Timing of hypoglycemia	Triggering drug	Insulin ($\mu\text{IU/ml}$)	C-peptide (ng/ml)	IAA (IU/ml)	Treatment
1	48	M	Fasting and postprandial	α lipoic acid	>1000	32.3	85.3	Acarbose
2	38	F	Fasting	α lipoic acid	>1000	23.96	188.0	Prednisolone
3	42	F	Fasting	α lipoic acid	>600	5.5	78.7	Acarbose and Prednisolone
4	60	F	Fasting	α lipoic acid	>1000	23.02	98.0	Acarbose
5	64	M	Fasting	α lipoic acid	>1000	23.27	93.0	Acarbose
6	42	F	Fasting and postprandial	Carbimazole	>1000	12.35	68.0	Acarbose

IAA – Insulin autoantibody



insulin and IAA serve as a reservoir of insulin which upon dissociation at a later post-absorptive phase act as a source of sustained free insulin release leading to prolonged and severe hypoglycemia. Any drug that contains a sulfhydryl group in its molecular structure can act as a hapten because of a similar sulfhydryl group in the insulin chains. These drugs can induce immunogenicity by interacting with the disulfide bonds in insulin and lead to formation of antibodies (Figure 1). Patients usually presented after 4-6 weeks of initiating the offending drug which was similar to other case series.^{4,6} In this study, the offending drug other than methimazole causing IAS was α -lipoic acid which is usually present in different types of multivitamins and health supplements. This study highlights that prolonged inadvertent use of such medications can lead to a serious side effect like IAS and the use of such supplements without

any indication should be avoided. Moreover, this study also emphasizes that IAS should be included in the differential diagnosis in evaluating a case of hypoglycemia. IAS can be differentiated from insulinoma by the insulin levels which are usually very high in IAS (above 1000 $\mu\text{IU/ml}$) compared to insulinoma (below 1000 $\mu\text{IU/ml}$). Hiya et al. published a case series on Hirata syndrome, reporting that insulin levels exceeded 1000 $\mu\text{IU/ml}$ in the two cases studied, with the insulin-to-C-peptide molar ratio also being greater than 1.⁴ Sehgal et al., published a case of Hirata syndrome which had similar high insulin levels.⁷ Hirata Syndrome can also be confused with Type B Insulin Resistance (TBIR), another rare autoimmune disorder causing hyperinsulinemia. However, while Hirata Syndrome is caused by autoantibodies against insulin, TBIR results from autoantibodies targeting insulin receptors, leading to

extreme insulin resistance. TBIR is strongly associated with SLE, Sjogren's, or systemic sclerosis and usually presents with persistent hyperglycemia with occasional paradoxical hypoglycemia. TBIR usually requires aggressive immunosuppression (steroids, cyclophosphamide or rituximab).

The assessment of insulin autoantibody titers is imperative for diagnosing IAS. Nevertheless, a prevailing limitation in many commercially-available assays is their capability to solely detect the immunoglobulin-G class of insulin autoantibodies. The molar ratio of insulin to C-peptide serves as a diagnostic marker for IAS, with values exceeding 1 indicating either IAS or exogenous insulin usage, where C-peptide is suppressed. Most instances of IAS exhibit a self-limiting course, with resolution of symptoms occurring within 3–6 months of initial diagnosis.⁸

In our study, our patients were treated with small frequent meals, acarbose, and steroids and they have proven to be effective as the disease is self-limiting. Ashraf et al. published a case report in which they found frequent small feeds and steroids to be effective in preventing hypoglycemia.⁹ Censi et al., found frequent small meals to be effective in preventing hypoglycemia in patients with Hirata syndrome.¹⁰

Continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) provide real-time glucose tracking, enabling early hypoglycemia detection, trend analysis, and pattern recognition. These tools help prevent severe episodes, guide dietary and pharmacologic adjustments (e.g., acarbose, steroids), and improve patient quality of life by reducing the need for frequent fingerstick testing. Their integration into Hirata syndrome management enhances safety and optimizes treatment strategies. However, in our series, CGM could not be utilized due to cost constraints, though its use would have significantly improved management.

For patients experiencing intractable hypoglycemia, initial treatment involves consuming small, frequent meals low in carbohydrates to mitigate postprandial hyperglycemia and subsequent insulin spikes. Short courses of corticosteroids, such as oral prednisolone (30–60 mg), may be employed as adjunct therapy. Additional therapeutic options encompass acarbose (to diminish carbohydrate absorption), diazoxide, octreotide, partial pancreatectomy (to restrict insulin release), and plasmapheresis (to reduce insulin autoantibody titers). Immunosuppressants like azathioprine, cyclophosphamide, and mycophenolate mofetil have also been explored in IAS management. In refractory cases, rituximab, an anti-CD20 monoclonal antibody, has demonstrated efficacy, particularly when steroid therapy proves ineffective.³

CONCLUSION

Our study highlights the diverse clinical presentations and diagnostic challenges encountered in patients with Hirata

syndrome. Despite its rarity, clinicians should maintain a high index of suspicion for IAS, especially in individuals presenting with recurrent hypoglycemia associated with autoimmune disorders or a history of sulfhydryl-containing medication use. Prompt diagnosis, through measurement of insulin autoantibodies and comprehensive evaluation is crucial for initiating appropriate management strategies, including dietary modifications, pharmacotherapy, and addressing underlying autoimmune conditions. Further research is warranted to elucidate the underlying mechanisms and optimize therapeutic approaches for this rare but clinically significant syndrome.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

GM: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **UKS:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **AKB:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **AB:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition.

Data Availability Statement

Datasets generated and analyzed are included in the published article

Author Disclosure

The authors declared no conflict of interest.

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None.

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Reninoma: A Rare Cause of Surgically Curable Hypertension and Secondary Hyperaldosteronism

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Abstract

Reninoma is a rare cause of renin-induced hypertension commonly seen in young adults and adolescents. Here, we describe a case of reninoma presenting with hypertension in the young. Further investigation revealed elevated renin and aldosterone levels. Computed tomography of the kidneys showed a right-sided renal mass. A diagnosis of reninoma was made, and the patient underwent nephron-sparing surgery, which rendered her normotensive post-operatively.

Key words: *reninoma, renin-induced hypertension*

INTRODUCTION

Reninoma is an extremely rare cause of hypertension, with less than 200 cases reported so far.¹ It is a tumour of the juxtaglomerular apparatus which secretes renin, leading to secondary hyperaldosteronism, ultimately causing hypertension. This disease is commonly seen in adolescents and young adults and has a female preponderance. Patients with reninoma mostly present with hypokalaemia although they can also be normokalaemic. Most reninomas are benign, and surgical resection can render the patient normotensive.² Here we report a case of reninoma in a young girl who presented with hypertension and palpitations. The patient underwent nephron-sparing surgery, resulting in the cure of her hypertension and palpitations.

CASE

A 23-year-old female was referred to our clinic for hypertension in the young. She has initially presented to a general practitioner with complaints of headache with palpitations for one year. She was found to have a home ambulatory blood pressure reading ranging between 130-180 mmHg (systolic) and 85-120 mmHg (diastolic). She was diagnosed with hypertension and started on doxazosin tablets. On further history, she complained of paroxysms of sweating with palpitations. She did not have symptoms of heat intolerance or diarrhoea. There was no history of weight gain, easy bruising or thinning of skin. She denied consumption of any supplements or over-the-counter medications. She had normal development and growth and had attained menarche at age 12 with regular menses. Her family history was unremarkable.

On examination, she was a moderately-built girl with a body mass index of 20.4 kg/m². Her pulse rate was 100 beats per minute and her blood pressure was 153/100 mmHg. She did not appear Cushingoid, there were no features of acromegaly and there was no goitre or exophthalmos. She had a regular pulse with no radio-radial or radio-femoral delay. Her apex beat was on the mid-clavicular line at the 5th intercostal space, with normal heart sounds. Her lungs were clear, and abdomen was soft with no organomegaly. There was no carotid or renal bruit heard. Tanner staging of her breast and pubic hair was appropriate for age.

Her routine blood investigations were normal. Thyroid function and urine metanephrines were within normal limits. Urine test revealed proteinuria of 1+, this was not quantified. Her electrocardiography (ECG) fulfilled voltage criteria for left ventricular hypertrophy (LVH). Transthoracic echocardiogram was normal and 24-hour Holter monitoring showed episodes of sinus tachycardia of up to 120 beats per minute. There were no arrhythmia detected. Her aldosterone and renin levels revealed an elevated renin level at 518 mU/L (4.4- 46.1 mU/L) with an elevated aldosterone of 998 pmol/L (61.2- 997.8 pmol/L).

A contrasted computed tomography (CT) of abdomen and pelvis was performed and this found a well-encapsulated heterogeneously-enhancing mass on the upper pole of the right kidney measuring 2.7 × 3 × 3.3 cm (Figure 1) with no other lesions elsewhere. Both adrenal glands were normal, and there was no evidence of renal artery stenosis. Given the raised renin and aldosterone values, a renin producing tumour was suspected. We proceeded with a biopsy of the renal mass to confirm the diagnosis. The histopathologic

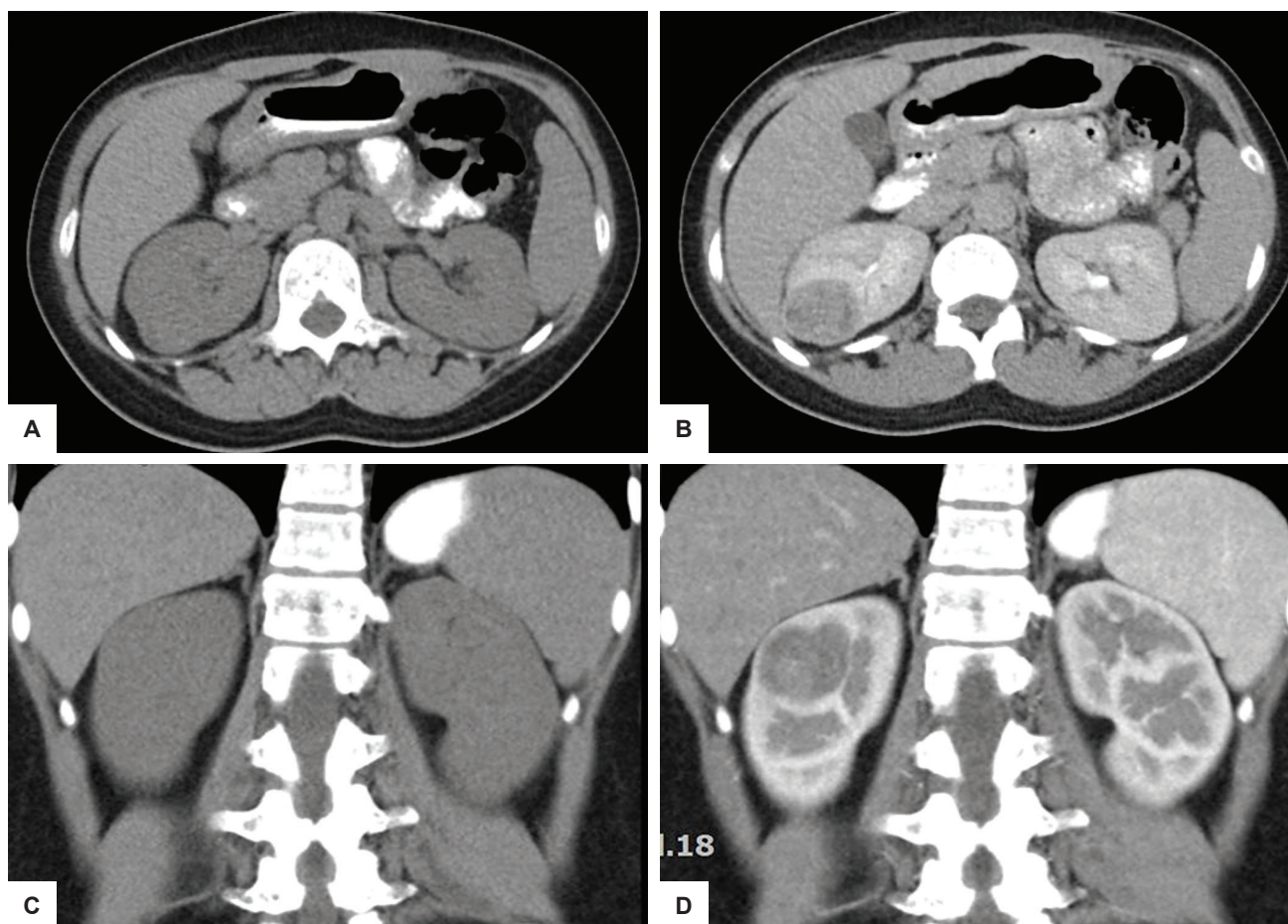


Figure 1. Contrast computed tomography (CT) of abdomen and pelvis demonstrated a well-encapsulated heterogeneously-enhancing mass on the upper pole of the right kidney. **(A)** Pre-contrast, mass appears isodense; **(B)** post-contrast, mass appears hypodense compared to renal cortex; **(C)** pre-contrast, mass appears isodense; **(D)** post-contrast, mass appears hypodense compared to renal cortex.

examination of the biopsy showed neoplastic cells that stained positive for smooth muscle actin, caldesmon and negative for beta-catenin. Examination under electron microscopy was not done due to resource limitations. Overall, these features were suggestive of a reninoma.

She was then switched to an angiotensin-converting enzyme inhibitor (perindopril) and a mineralocorticoid receptor antagonist (spironolactone) for adequate blood pressure control. She reported experiencing fewer episodes of palpitations after the switch of medications were made. She was referred to the urology team and underwent a partial nephrectomy of the right kidney. Her surgery was uneventful, with no fluctuations in blood pressure intraoperatively.

Post operatively, her blood pressure ranged from 100-117 mmHg (systolic) and 75-90 mmHg (diastolic) and both anti-hypertensive medications were withheld. She was reviewed for 2 months post-surgery in our clinic. She no longer complained of palpitations and her heart rate was between 75-86 beats per minute. Her home blood pressure monitoring was within normal limits. ECG revealed resolution of left ventricular hypertrophy, urine dipstick

was negative for protein and renal profile done showed normokalaemia. Histopathological examination of the resected tumour revealed an encapsulated lesion that stained positive for CD 34 (Figure 2A), CD 117 (Figure 2B), vimentin (Figure 2C) with absence of mitotic figures, confirming the diagnosis of reninoma with benign features.

DISCUSSION

In general, all patients with reninomas were found to have a high renin and aldosterone levels, while some cases have reported high renin levels with a normal aldosterone level,² albeit methods of sampling renin and aldosterone were not specified in most case reports. Typically, reninomas are small in size and have a cortical or subcortical location.³ There is also evidence that these tumours grow in size with time, suggesting that repeated interval scanning maybe useful in cases of uncertainty or when initial scan fails to identify a lesion.⁴ In the presence of renin-mediated hypertension, a reninoma should be suspected in the absence of renovascular disease. In our patient, in addition to high blood pressure, she also had palpitations and was found to have sinus tachycardia. Activation of sympathetic nervous system by the renin-angiotensin aldosterone

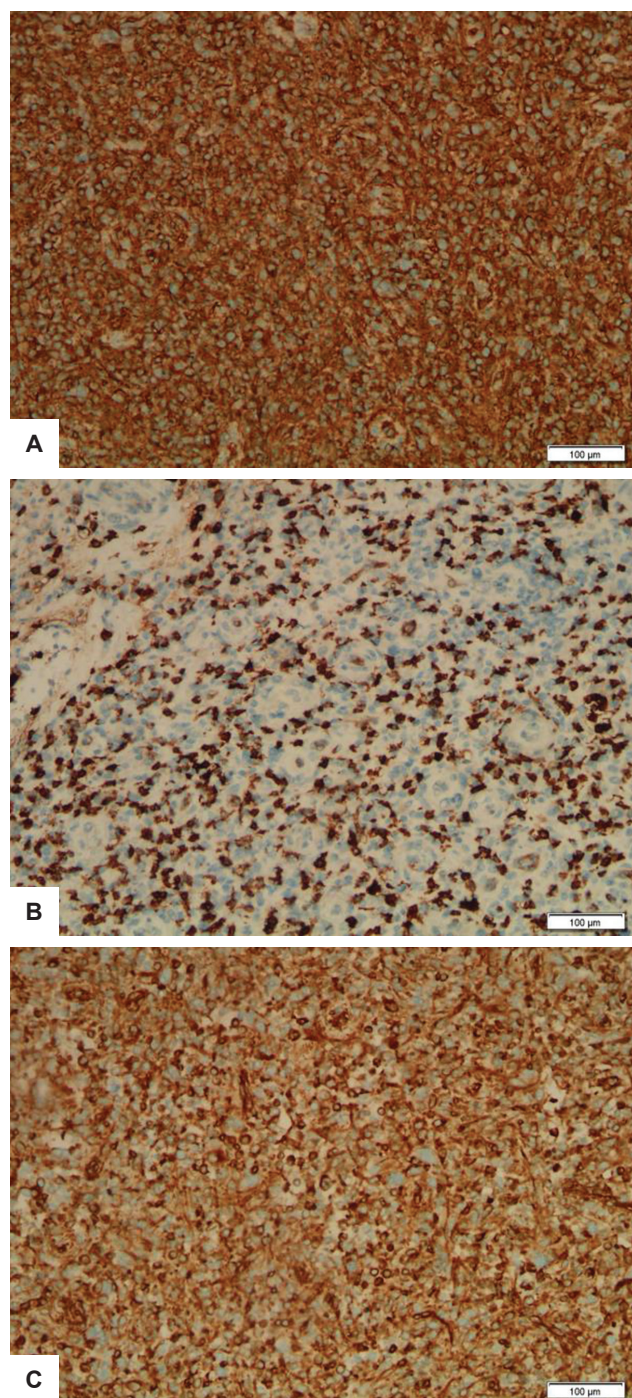


Figure 2. Histopathologic staining of the resected tumour (Immunohistochemistry, 200×): (A) CD34; (B) CD117; (C) vimentin.

system (RAAS) via angiotensin 2 has been well studied and is likely the reason for tachycardia in our patient, although other cases have not reported the same.⁵ Her tachycardia had significantly reduced with the ACE inhibitors and MR antagonists and had resolved completely post-operatively. Recommended medical management of reninomas are medications directly inhibiting the RAAS pathway such as ACE inhibitors and MRAs.² In one case report, aliskiren, a direct renin inhibitor at doses of 300 mg daily successfully controlled the blood pressure in a patient awaiting surgery.⁶

However, resistance to aliskiren after 5-6 months of usage was reported.⁶ Hypertensive organ damage has been commonly associated with reninomas. In a case series of 9 patients, 3 had severe hypertensive damage resulting in fetal demise in one pregnant patient, intracranial bleed in the second patient and severe retinopathy in the third patient.⁷ There is insufficient evidence to conclude if hypertensive complications are reversible post-surgery. In our patient, however, there was resolution of LVH and proteinuria seen post-operatively. The best diagnostic imaging is a contrasted computed tomography (CT) scan, which has shown 100% sensitivity.⁸ Reninomas generally are isodense or hypodense pre-contrast, with delayed enhancement seen post-contrast. Renal vein sampling (RVS) has been used as an adjunct to aid with diagnosis of reninomas. It is done by cannulating both renal veins and comparing renin values on both sides. A review of previous renal vein sampling found a sensitivity and specificity of a lateralizing ratio of 1.5 to be 56% and 94% respectively.² In a small case series of 3 patients with reninoma, RVS has successfully lateralized the lesion in all 3 patients. These patients were meticulously prepared pre-procedure; interfering medications were withheld; patients were put on a low sodium diet of less than 40 mmol/day and were maintained in a recumbent position overnight and during the procedure. Patients were also given captopril, and renin values were sampled 15 minutes after, which increased the sensitivity of the test.⁸ Overall, this suggests that if renal vein sampling were to be performed, good patient preparation and administration of captopril may yield a better sensitivity of RVS. In our case, due to the lack of resources and the rarity of this disease, a biopsy of the lesion was undertaken to ascertain the diagnosis prior to subjecting the patient to surgery. While most cases of reninomas are benign, there have been very few cases of malignant reninomas in the literature. In one case report, there was metastatic disease in a paraaortic lymph node with a recurrent mass seen 1 year post initial resection of a reninoma, and histopathological examination revealed a high mitotic index with perivascular invasion.³ Histologically, these tumours are made of closely packed polygonal cells with oval to round nuclei. Although moderate nuclear atypia is seen, mitotic figures are usually absent. The diagnosis is made with the demonstration of renin positivity in the cytoplasm, although this feature may also be observed in other disease such as renal cell carcinoma and Wilms tumour. Most reninomas stained diffusely for vimentin and CD 34, while CD 117 positivity has been reported in most but not all cases.⁹ Presence of rhomboid-shaped renin protogranules via an electron microscopy is diagnostic.¹ Ideally, a nephron-sparing surgery is the mainstay of treatment for reninomas. However, in very large tumours or centrally located tumours, a total nephrectomy may be required. Generally, blood pressure fluctuations are not seen intraoperatively, but there has been hypotension reported intraoperatively during a resection of a large reninoma.³ Radiofrequency ablation use has also been reported in 2 patients by Ru et al, however one patient developed hypertension post ablation requiring treatment.¹⁰

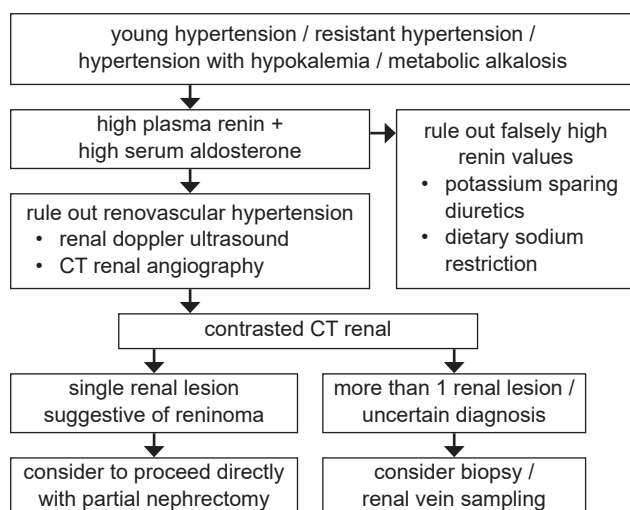


Figure 3. Approach to Reninoma.

CONCLUSION

Reninomas are mostly benign neoplasms that can lead to hypertension and severe end organ damage. Despite primary aldosteronism being the more common cause of young hypertension, when faced with elevated renin alongside an elevated aldosterone, a reninoma should be considered a possibility and renal imaging should be performed. A high clinical suspicion is required to diagnose this disease and to avoid unwarranted imaging and procedures. Nephron-sparing surgery can render the patient normotensive.

Ethical Consideration

Patient consent forms were obtained before manuscript submission.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

GK: Writing – original draft, Writing – review and editing; **LJL:** Writing – original draft, Writing – review and editing; **THC:** Supervision; **SK:** Supervision.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

The authors declared no conflict of interest.

Table 1. Imaging modalities and treatment options for Reninomas

	Medical management	Imaging modality	Treatment options
Preferred	Mineralocorticoid receptor antagonist (MRA)	Computed tomography of the kidneys	Partial nephrectomy or total if large reninoma or centrally located
Alternative/ Additional	Angiotensin converting enzyme inhibitors (ACE)	Renal MRI Renal vein sampling	Radiofrequency ablation

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Adrenergic Storm with Obstructive Hydrocephalus: Atypical Neurological Presentation of Von Hippel-Lindau Disease with Bilateral Pheochromocytoma in an Adolescent

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Abstract

Pheochromocytoma is often not the first diagnosis considered for many neurological complaints, especially obstructive hydrocephalus. We report a case of Von Hippel-Lindau disease in an adolescent presenting with obstructive hydrocephalus due to adrenergic storm requiring emergency ventriculoperitoneal shunt. This vignette emphasizes the importance of an integral approach, particularly accurate diagnosis that would lead to targeted pharmacological therapy focusing on alpha-adrenergic receptor blockade, which was followed by total curative excision of pheochromocytoma in a timely fashion.

Key words: adolescent, germline mutation, obstructive hydrocephalus, Von Hippel-Lindau disease, pheochromocytoma, posterior reversible encephalopathy syndrome

INTRODUCTION

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare chromaffin cell tumors that secrete catecholamine with an annual incidence of approximately 2-8 million person-years.^{1,2} The classic triad of symptoms in patients with PCC consists of episodic headache, sweating and tachycardia. It has an atypical presentation in 9%-10% of patients which includes cerebrovascular events.³ To date, cerebral infarction, intracranial hemorrhage, posterior reversible encephalopathy syndrome (PRES) and catecholamine-induced central nervous system (CNS) vasculitis have all been identified as unusual neurological manifestation of PCC.⁴ Herein, we report a case of a PRES with atypical features in a 12-year-old male, newly diagnosed with bilateral PCC and VHL disease.

CASE

A 12-year-old male presented to the emergency department (ED) with a 3-day history of severe headache (pain score 8/10), accompanied by visual disturbances and an unintentional weight loss of 4 kg over three months. He denied fever, constitutional symptoms, or contact with tuberculosis. On examination, he was conscious but markedly hypertensive (BP: 180/120 mmHg) and tachycardic (HR: 155 bpm). Fundoscopic evaluation revealed bilateral grade 4 hypertensive retinopathy with

papilledema. Electrocardiogram demonstrated sinus tachycardia with evidence of left ventricular hypertrophy. Laboratory parameters, including complete blood count, renal, hepatic and coagulation profiles, were within normal limits. CT scan with contrast of the brain revealed obstructive hydrocephalus with diffuse cerebellar edema and tonsillar herniation (Figure 1A). The provisional diagnosis at this juncture was obstructive hydrocephalus secondary to posterior fossa mass. Emergency ventriculoperitoneal (VP) shunt was performed after stabilization with intravenous labetalol, which was successfully tapered off within 4 hours postoperatively.

MRI of the brain performed on day 3 post-VP shunt showed diffuse cerebellitis without evidence of a posterior fossa mass. Given the abrupt neurological manifestation and typical neuroimaging findings of obstructive hydrocephalus, empirical treatment for tuberculous (TB) meningitis with anti-TB medications and intravenous dexamethasone were initiated after multidisciplinary discussion with intensivist and neurologist due to regional prevalence. Nonetheless, the cerebrospinal fluid (CSF) findings later did not support TB meningitis because the MTB GeneXpert was negative and CSF biochemistry was normal. Autoimmune screening, including anti-nuclear antibody and complement levels were within the normal range. Anti-TB therapy was discontinued on day 4. Despite initial improvement, the patient remained hypertensive

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(SBP: 160–190 mmHg, DBP: 90–110 mmHg) and tachycardic despite being treated with oral metoprolol 50 mg twice daily and oral prazosin 1mg thrice daily. He was referred to the endocrinology service for evaluation of secondary hypertension in a pediatric patient.

A detailed history uncovered intermittent episodes of headache, diaphoresis and visual blurring for the past three months. Physical examination revealed a thin male with growth parameters below the 25th percentile. There were no cutaneous stigmata of neurofibromatosis or features suggestive of multiple endocrine neoplasia (MEN) syndromes. Birth and developmental histories were unremarkable. Family history, including a detailed three-generation pedigree, was negative for endocrinopathies, pheochromocytoma, renal tumors, or central nervous system (CNS) neoplasms. Both parents and a 16-year-old sister were healthy. The maternal side of the family, including six siblings of the mother, had no significant medical conditions. The paternal side, including four siblings of the father, were similarly unaffected. The paternal grandmother had end-stage renal disease in her 60s of unclear etiology, but there was no documented history of PCC, renal cell carcinoma, or CNS tumors.

Endocrinological evaluation revealed markedly elevated urinary normetanephrine (101.8 μ mol/day; reference range: 2.46–23.0) and 3-methoxytyramine (4.9 μ mol/day; reference range: 0.10–1.79). The aldosterone-renin ratio (ARR) was low, with a direct renin level of 106.3 mU/L (reference range: 3–66), plasma aldosterone of 582.3 pmol/L (reference range: 102.5–1196) and ARR of 5 (Table 1). Thyroid function, serum calcium and phosphate levels were within normal limits, excluding other common endocrine causes of secondary hypertension. A suppressed morning cortisol level (<13.8 mmol/L) was noted, though interpretation was limited due to prior dexamethasone therapy. Cross-sectional imaging via contrast-enhanced CT of the thorax, abdomen and pelvis revealed bilateral adrenal masses (right: 3.2 $\times$ 2.6 $\times$ 4.2 cm; left: 3.1 $\times$ 4.6 $\times$ 6.3 cm) with associated abdominal lymphadenopathy (Figure 2). Functional imaging with Ga-68 DOTATATE PET/CT confirmed intense somatostatin receptor expression in both adrenal lesions, while the lymph nodes remained non-avid (Figure 3).

Initial alpha-blockade with prazosin was transitioned to terazosin and subsequently to oral phenoxybenzamine, which was titrated up to 10 mg three times daily based on body weight, symptomatology and blood pressure targets

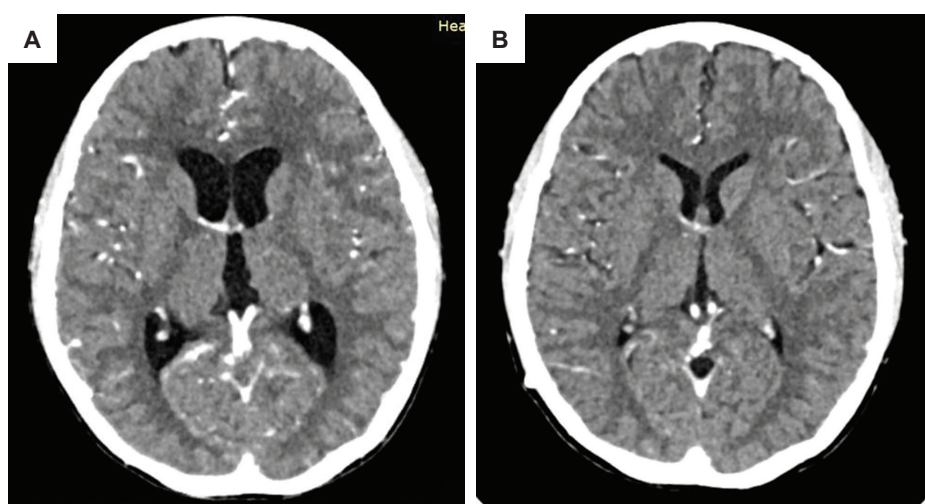


Figure 1. (A) Contrast CT of the brain on admission demonstrating diffuse bilateral cerebellar oedema with obstructive hydrocephalus. (B) Repeat Contrast CT of the brain showed resolved cerebellar edema and obstructive hydrocephalus.

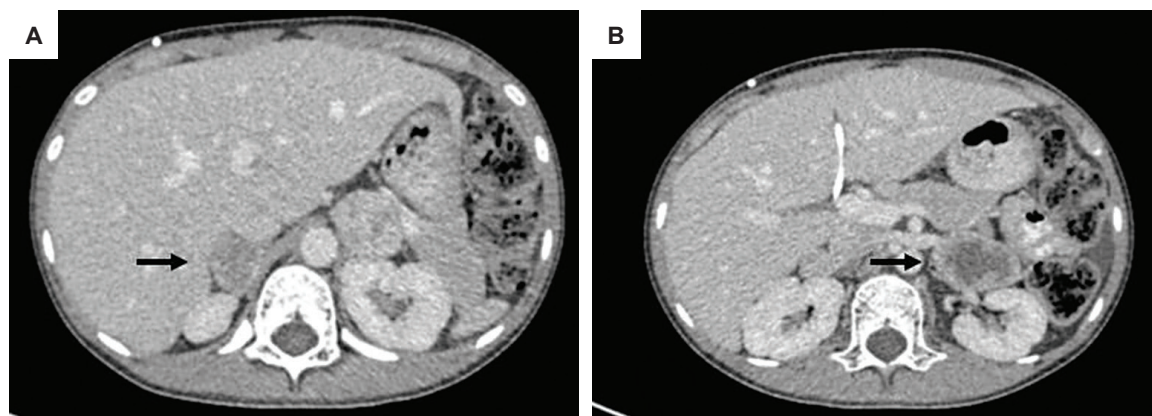


Figure 2. (A) Lobulated right suprarenal soft tissue lesion measuring 3.6 $\times$ 2.9 $\times$ 4.7 cm with central necrosis (black arrow). No clear fat plane is seen between the lesion and segment VII/VI/V of liver; (B) Lobulated left suprarenal soft tissue lesion measuring 3.1 $\times$ 4.6 $\times$ 6.3 cm with central necrosis (black arrow). Poor demarcation is seen between the lesion and body of the pancreas as well as the adjacent small bowel.

Table 1. Laboratory results

Investigations	Results	Normal range
24 hour urine metanephrine		
Normetanephrine	101.8 µmol/day	2.46 – 2.30
Metanephrine	0.6 µmol/day	0.30 – 0.95
3-methoxytyramine	4.9 µmol/day	0.10 – 1.79
Aldosterone renin ratio		
Direct renin level	106.3 mIU/L	3 – 66
Plasma aldosterone concentration	582.3 pmol/L	102.6 – 1196
ARR	5	
Thyroid function test		
TSH	1.1 mIU/L	0.55 – 4.78
FT4	12.1 mmol/L	12.2 – 22
Cerebrospinal fluid analysis		
Appearance	Clear and colorless	
Cell count	0	
Acid Fast Bacilli direct smear	Negative	
Mycobacterium tuberculosis	Negative	
GeneXpert	Negative	
Protein	0.159 mmol/L	
Glucose	5 g/dL	

(<130/80 mmHg). The patient underwent successful bilateral adrenalectomy. Intraoperatively, both adrenal glands were found to contain well-encapsulated, lobulated tumors (right: 6 × 2.5 × 3 cm; left: 6.5 × 5 × 2 cm) (Figure 4). Histopathological analysis confirmed bilateral pheochromocytomas, exhibiting classical zellballen architecture with evidence of both capsular and vascular invasion. Immunohistochemistry was positive for chromogranin A and synaptophysin, consistent with neuroendocrine differentiation.

Given the bilateral presentation at a young age, genetic testing was conducted and identified a heterozygous pathogenic variant in the VHL gene (c.482G>A; p.Arg161Gln), confirming a diagnosis of von Hippel-Lindau (VHL) syndrome. Predictive genetic testing of both parents and the proband's sister yielded negative results, indicating a likely *de novo* mutation.

Follow-up contrast-enhanced CT of the brain performed three weeks after initiation of alpha-adrenergic blockade and effective blood pressure control showed complete resolution of cerebellar edema, hydrocephalus and no evidence of leptomeningeal enhancement (Figure 1B). Postoperatively, the patient's symptoms resolved entirely and he remained normotensive without the need for antihypertensive therapy. Electrolytes and glucose levels remained stable and steroid replacement was initiated as per protocol. Surveillance evaluations, including ophthalmologic and otolaryngologic assessments, revealed no evidence of other VHL-associated lesions such as retinal hemangioblastomas, renal cell carcinoma, pancreatic cysts or neuroendocrine tumors.

DISCUSSION

Acute neurological crises as the initial presentation of PCC often led to delay in the PCC work-up as the initial pursuit would be focusing on stabilizing the neurological emergency.^{3,4} According to Anderson et al., who had retrospectively reviewed 93 patients with PCC aged 9-84

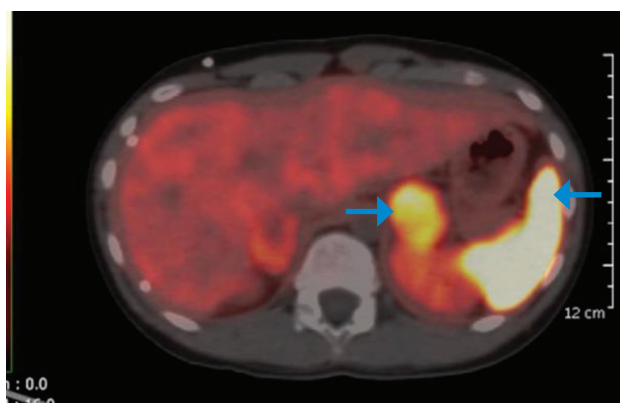


Figure 3. Ga-68 DOTATATE showing scan evidence of somatostatin receptor avid disease in bilateral supranrenal lesions with SUV_{max} 9.7 on the right supranrenal soft tissue and SUV_{max} 17.7 on the lobulated left supranrenal soft tissue (blue arrows).

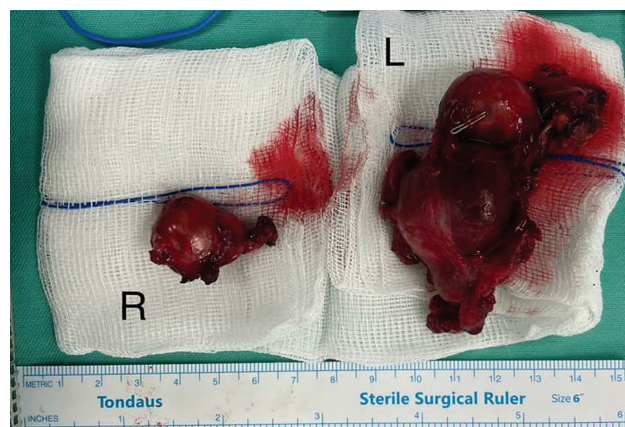


Figure 4. Gross pathology showing bilateral pheochromocytoma. The right adrenal tumor shows multilobulated with the main tissue mass measuring 6.0 × 2.5 × 3.0 cm with disrupted capsule. The left adrenal tumor shows nodular brownish tumor with smooth capsule, measuring 6.5 × 5.0 × 2.0 cm.

years, the common neurological crises were headache, seizures, strokes, delirium and subarachnoid haemorrhage.⁵ To note, neurological manifestation with PRES is an exceedingly rare phenomenon among the pediatric population, albeit PRES occurs extensively in adults. The pathophysiology of PRES involve catecholamine-induced hypertensive surges overwhelming cerebral autoregulation, especially in the posterior circulation, leading to profound vasogenic oedema.^{6,7} Furthermore, catecholamine excess could directly cause endothelial dysfunction and cerebral vasoconstriction, increasing the risk of both hemorrhagic and ischemic events.^{3,7} In essence, this vignette adds to the limited literature of PCC with atypical neurological manifestations, reinforcing the need for early endocrine and pediatric evaluation in pediatric hypertensive crises.

PRES is a time-sensitive disease and the prognosis depends on a timely detection which would translate into delivery of appropriate therapy before the occurrence of irreversible

or even fatal neurological complications. The cornerstone of PRES management comprises of control of hypertension and treatment of the underlying cause. In another note, the outcomes of PRES associated with PCC varied with some patients experiencing significant neurological recovery, while others faced severe complications. Powell et al., reported a young man who presented with clinical features of PRES secondary to PCC crisis, diagnosed as MEN2A syndrome, which had a good outcome after prompt treatment.⁸ Callao et al., reported a male patient who had left adrenalectomy done due to PCC who also presented with PRES but succumb due to complication of liver failure.⁹ In our case, PRES induced by PCC had extended to the cerebellum and brainstem resulting cerebrospinal fluid outflow obstruction with ongoing tonsillar herniation due to cerebellar edema. In contradistinction to the typical parieto-occipital involvement in PRES, our case demonstrated an isolated posterior fossa involvement which is exceedingly rare among adolescent population and these findings mimicked posterior fossa mass on initial CT imaging.^{10,11} This observation was also reported by Ogino et al., and Grossbach et al., who described acute obstructive hydrocephalus caused by PRES.^{12,13} Despite in extremis presentation, the prompt neurosurgical intervention and intensive care in our case had successfully relieved the intracranial pressure and demonstrated a satisfactory neurological recovery.

Although pheochromocytoma-paragangliomas (PPGLs) are rare in children accounting for 0.2–0.5 cases per million population annually, they remain the most common endocrine tumors in this age group and are implicated in approximately 0.5–1% of pediatric hypertensive cases.¹⁴ Compared to adults in whom paroxysmal hypertension is more characteristic, adolescent presentations often feature persistent hypertension as the dominant symptom. Up to 91% of PCC patients present with classic symptoms such as episodic headache, diaphoresis, palpitations and hypertension.¹⁵ However, atypical and severe neurological presentations, including PRES, cerebral infarction, CNS vasculitis and even hemorrhagic stroke, have been documented in children and adolescents with PPGL.^{3,7}

PCC associated with VHL syndrome, categorized under Cluster 1B of PPGL classification, typically demonstrate a noradrenergic biochemical phenotype.^{16,17} In this patient, 24-hour urinary catecholamine metabolite analysis showed markedly elevated normetanephrine (101.8 $\mu\text{mol/day}$; >40 times the upper limit of normal), a moderate increase in 3-methoxytyramine and normal metanephrine levels. This biochemical profile aligns with the characteristic pattern seen in VHL-related tumors. The underlying mechanism involves VHL gene mutations leading to stabilization of hypoxia-inducible factor 2- α (HIF-2 α), which regulates genes involved in catecholamine biosynthesis. HIF-2 α suppresses phenylethanolamine N-methyltransferase (PNMT), the enzyme responsible for converting norepinephrine to epinephrine, resulting in a predominant noradrenergic phenotype. Additionally, a modest elevation

in 3-methoxytyramine, a dopamine metabolite, may reflect minor dopaminergic activity, consistent with the biochemical spectrum of VHL-associated pheochromocytomas.¹⁷ Notably, the low aldosterone-to-renin ratio observed in our case can be attributed to the elevated plasma renin activity commonly seen in pheochromocytoma. This phenomenon is primarily driven by chronic catecholamine excess, which induces sustained vasoconstriction and leads to reduced circulating plasma volume. The resulting hypovolemia stimulates renin release via activation of β 1-adrenergic receptors. Additionally, catecholamines directly enhance renin secretion through β 1-adrenergic receptor-mediated pathways. These mechanisms collectively explain the increased plasma renin activity and consequently, the low aldosterone-to-renin ratio in patients with PCC.¹⁸

Cross-sectional imaging with contrast-enhanced CT of the thorax, abdomen and pelvis revealed bilateral adrenal masses and abdominal lymphadenopathy. The right adrenal mass measured 3.6 $\times$ 2.9 $\times$ 4.7 cm and the left measured 3.9 $\times$ 4.8 $\times$ 6.0 cm. Both lesions were heterogeneous, well-circumscribed and confined to the adrenal glands, without evidence of local invasion or distant metastases. Cluster 1B VHL/EPAS1-related PPGLs specifically PCC seem to show stronger expression of the L-type amino-acid transporter and less SSTR2 expression. Therefore, PET/CT imaging based on [18F]FDOPA is more sensitive than [68Ga]-DOTA-SSA PET/CT in VHL/EPAS1-related PPGLs.^{19,20} However, this modality was not available in our setting. Consequently, Ga-68 DOTATATE PET/CT was selected as the next best available molecular imaging tool, allowing functional assessment of the adrenal lesions. Ga-68 DOTATATE PET/CT has demonstrated sensitivity of 92–100% and specificity of 88–100% in various studies particularly for detecting extra-adrenal and metastatic disease in VHL-associated pheochromocytoma.¹⁷

Genetic analysis identified a *de novo* germline VHL mutation, with no pathogenic variants detected in either parent or sibling. While VHL syndrome is autosomal dominant, approximately 20% of cases result from *de novo* mutations.²¹ Genetic testing in all pediatric PPGL cases is essential, regardless of family history, as germline mutations underlie 50–70% of pediatric cases.¹ Syndromes such as MEN2, VHL, NF1, and SDHx mutations remain the most common etiologies. In children, VHL is the most frequently implicated genetic syndrome in bilateral adrenal PCC, consistent with our patient's presentation.¹⁴

Management of hypertension in PCC requires careful and sequential pharmacologic intervention. Our patient initially received intravenous labetalol which is a combined α - and β -adrenergic blocker in the Emergency Department as part of standard care for hypertensive emergency with obstructive hydrocephalus. However, in undiagnosed PCC, beta-blockade without adequate prior alpha-blockade may exacerbate hypertension due to unopposed α -adrenergic receptor stimulation.²² This phenomenon was observed in our case: despite treatment with oral metoprolol and low-

dose prazosin (1 mg TID), the patient remained significantly hypertensive. Blood pressure control was only achieved following the initiation of phenoxybenzamine, a non-selective and non-competitive α_1 - and α_2 -adrenergic receptor blocker, which remains the cornerstone of preoperative management in PPGL. Dosage must be individualized, accounting for body weight and hemodynamic targets. In this 36-kg patient, phenoxybenzamine at 10 mg TID effectively achieved normotension, targeting a preoperative blood pressure of <130/80 mmHg. This case highlights the essential principle that adequate alpha-blockade must precede beta-blockade in the management of PPGL to avoid life-threatening cardiovascular complications. Beta-blockers may be added subsequently to manage reflex tachycardia, but only after sufficient α -blockade has been established. Long-term follow-up is crucial in patients with *VHL*-associated PPGLs due to the risk of multisystem involvement, including retinal hemangioblastomas, renal cell carcinoma and pancreatic cysts or neuroendocrine tumors.²³ Multidisciplinary surveillance involving endocrinology, oncology, ophthalmology and genetics is essential for optimal patient management.

CONCLUSION

Adolescents with neurological manifestation warrant detailed and vigorous diagnostic evaluation, especially in the presence of *de novo* onset hypertension. Investigations should gravitate towards the exclusion of PCC because adrenergic storm could be its initial manifestation as exemplified in this vignette. Importantly, timely diagnosis establishment allows alignment with multi-disciplinary teams that ultimately lead to curative PCC excision. Bespoke treatment via genetic testing allows further management strategy, familial screening and prognostication, though this vignette represents a case of sporadic *VHL* disease.

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Ethical Approval

This case report has obtained approval from National Medical Research Register (NMRR), Ministry of Health Malaysia: NMRR-ID-23-03447-BEA

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

JMC: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **TLT:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **YHL:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision, Project administration; **SKYH:** Conceptualization, Methodology, Formal analysis,

Investigation, Resources, Supervision, Project administration; **FBY:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision, Project administration; **SWL:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision, Project administration; **XYO:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision, Project administration; **HCW:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision, Project administration; **SLY:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision, Project administration.

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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Diabetic Striatopathy as a Presenting Symptom in Newly Diagnosed Type 2 Diabetes Mellitus: A Case Report

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Abstract

Diabetic striatopathy is a rare, acute neurological complication of diabetes mellitus which presents with non-ketotic hyperglycemia and involuntary movements, specifically hemichorea or hemiballismus. Striatal abnormalities on neuroimaging have been reported in most, but not all cases. This case report aims to increase awareness that diabetic striatopathy can be a presenting symptom of diabetes mellitus.

A 92-year-old Filipino female with no history of diabetes presented with acute onset of focal clonic flexion of the left upper extremity for a few hours, which progressed to right hemifacial spasm. She was diagnosed with a hyperosmolar hyperglycemic state and was treated accordingly. Cranial CT scan findings were unremarkable. There was an immediate resolution of her neurologic symptoms after the correction of hyperglycemia.

The diagnosis of diabetic striatopathy highlights the importance of increasing awareness and understanding of this condition among clinicians to prevent delayed diagnosis and treatment. Screening for hyperglycemia is advisable for patients with involuntary movements. The prognosis for diabetic striatopathy is good with prompt glycemic control in most cases.

Key words: hyperkinetic movement disorder, nonketotic hyperglycemia, involuntary movement, neurologic complication

INTRODUCTION

The central and peripheral nervous system can be affected by diabetes mellitus. There are different associated neurological complications such as neuropathy, coma and seizures. Abnormal movements, which are found in increased frequency among persons with diabetes, can occur as the initial presentation of diabetes in those with poor glycemic control. The exact pathophysiology is still unknown.¹

Diabetic striatopathy (DS) is a rare acute hyperkinetic movement disorder due to nonketotic hyperglycemia. The reported prevalence rate of DS is 1 in 100,000. Despite the very dramatic and obvious clonic flexion of the extremity, the rarity of the disorder and the unfamiliarity of physicians with this condition hinders the recognition of the symptom as DS, leading to misdiagnosis.² Diabetic striatopathy usually occurs in elderly Asian women with type 2 diabetes mellitus with poor glycemic control. It is rarely seen in type 1 diabetes mellitus.³

CASE PRESENTATION

A 92-year-old Filipino nun from Manila was admitted due to involuntary movements of the left upper extremity and right hemifacial spasm. These symptoms, noted as myoclonic movements of the left upper extremity with hemifacial spasm described as twitching of the right side of the face started acutely 12 hours prior to admission while she was sleeping. There was no loss of consciousness and the patient was able to recall the events.

Hypertension was noted in the past medical history. There was no known history of diabetes. Six months ago, she was diagnosed with allergic dermatitis and was given oral steroids with tapering doses. During physical examination at the emergency room, an episode of myoclonic movements of a few seconds involving the left upper extremity was observed. Amidst such episode, she was coherent and oriented to time, place and person with intact recent and remote memory. Manual muscle testing of all extremities revealed a full range of motion against gravity

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with minimal resistance. No sensory deficit was observed on all extremities. All deep tendon reflexes were +2. Vital signs were normal. Weight was 43 kilograms. No signs of dehydration were seen.

At the time of the occurrence of the involuntary movements, capillary blood glucose taken using a glucometer was noted to be high. Confirmatory venous blood glucose testing performed in the laboratory yielded a value of 671 mg/dL. Laboratory results were as follows: HbA1c of 13.40%, serum ketones less than 0.5 mmol/L, serum osmolality of 328 mOsm/kg and serum WBC of 16,000/ μ L. Urinalysis revealed: glucose +3, negative for ketones, positive nitrite, WBC of 43/hpf and bacteria of 69/hpf. The blood pH was 7.489 and arterial bicarbonate was 24.4 mmol/L. Creatinine was 103.6 μ mol/L with estimated glomerular filtration rate was 43 ml/min/1.73 m². The patient was managed as a case of hyperglycemic hyperosmolar state initially with hydration with intravenous fluid, and administration of intravenous insulin glulisine. Insulin glargine 20 units subcutaneously once daily was eventually started. Ceftriaxone was started for the urinary tract infection. Bedside electroencephalogram was unremarkable. Plain cranial CT scan revealed no evidence of acute hemorrhage, acute or chronic infarct or focal mass lesion. The basal ganglia were physiologically calcified bilaterally. MRI was not performed due to lack of consent.

The patient was discharged with improved glycemic control and with no recurrence of hemiballismus nor hemifacial spasm. Fixed doses of insulin glulisine pre meals and linagliptin 5 mg tablet once daily were given as home medications.

DISCUSSION

Hyperglycemia can present with abnormal movements. The movements tend to acutely develop on one side of the body and usually disappear when the patient sleeps. Other neurologic deficits include weakness, pyramidal tract signs and hypotonia.¹

Diabetic striatopathy is an uncommon complication of type 2 diabetes mellitus which manifests as involuntary movements such as hemichorea or hemiballismus. The associated risk factors were elderly Asian females with type 2 diabetes mellitus with poor glycemic control. The mean age of patients affected according to a meta-analysis was 71 years of age. Signs of diabetic striatopathy include non-ketotic hyperglycemia, unilateral limb dyskinesia and striatal abnormalities on neuroimaging.³ Unilateral chorea is commonly seen in patients with hyperglycemia compared to bilateral chorea. Not all patients with diabetic striatopathy manifest with involuntary movements, some have impaired consciousness instead.⁴ Neuroimaging tests typically reveal a contralateral basal ganglia lesion. Magnetic resonance imaging is more sensitive in detecting these lesions with a sensitivity of 95% while CT scan has a lower sensitivity of 78%.⁵ Common neuroradiologic

findings in diabetic striatopathy are striatal hyperdensity on CT scan and striatal hyperintensity on T1-weighted MR imaging.⁶ However, it is also not uncommon for DS cases to have an unremarkable neuroimaging.^{7,8} In a study by Dubey et al which included 59 persons with diabetes with acute dyskinesia, majority of the patients (55.9%) did not have any abnormal striatal findings in neuroimaging tests.⁷

The pathophysiology of diabetic striatopathy is still unclear but mainly involves different mechanisms in the basal ganglia, an important structure involved in the production of movement in the body. Two proposed theories are the microvascular disease theory and infection or autoimmune inflammatory response theory.³ In the microvascular disease theory, uncontrolled hyperglycemia causes patchy necrosis and edema, lymphocyte infiltration, reactive astrocytosis, with macrophage and erythrocyte extravasation in basal ganglia.⁹ The second theory implicates the role of infection and autoimmune inflammatory response in basal ganglia dysfunction. Some studies have shown that in DS cases, there was lymphocytic infiltration around the blood vessels of the basal ganglia.¹⁰

Another theory explores the imbalance in the biochemical substrates in the brain. In non-ketotic hyperglycemia, the brain metabolism shifts to an anaerobic pathway which utilizes and depletes GABA, consequently decreasing acetylcholine levels. This decrease in GABA and acetylcholine, which are normal substrates in basal ganglia circuitry, causes basal ganglia dysfunction leading to involuntary movements.¹¹

Treatment is mainly control of hyperglycemia. It has a good prognosis, with resolution of involuntary movements once there is adequate glycemic control. Only 13% of patients have been reported to have recurrence of involuntary movements associated with hyperglycemia.¹²

VIDEO OF THE CASE



CONCLUSION

There is an increasing number of patients with diabetes diagnosed incidentally because of the onset of complications. As clinicians, we should be aware of the rare neurologic complications of uncontrolled diabetes mellitus to be able

to properly diagnose and treat the patient. In our case, the patient had no previous history of diabetes mellitus and was incidentally diagnosed because of her admission for involuntary movements. Diabetic striatopathy has a good prognosis hence proper diagnosis can lead to resolution of involuntary movements upon attaining blood sugar control.

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

PDCS: Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing – original draft preparation, Visualization; **TFR**: Conceptualization, Investigation, Resources, Data Curation, Writing – review and editing; **JMIC**: Conceptualization, Investigation, Resources, Data Curation, Writing – review and editing, Supervision, Project administration.

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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None.

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A Difficult Case of Ectopic ACTH Syndrome: Is Treatment Possible Even Without Accurate Localization?

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Abstract

Occult ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) is a relatively rare form of ACTH-dependent Cushing's Syndrome (CS). We describe a middle-aged female with symptomatic CS, where despite thorough investigations including hormone suppression testing, multiple imaging modalities, and inferior petrosal sinus sampling (IPSS), an ectopic source could not be demonstrated. Our case demonstrates that ketoconazole can be an effective therapeutic to suppress cortisol production even when the source of ectopic ACTH production is unknown. However, long-term evaluation is required.

Key words: ectopic ACTH syndrome, Cushing syndrome, hypercortisolism, ketoconazole

INTRODUCTION

Ectopic adrenocorticotrophic hormone (ACTH) Syndrome (EAS) accounts for up to 12% of all Cushing's Syndrome (CS)¹, and 10-20% of ACTH dependent CS cases.² Removal of the ectopic ACTH source results in potential cure and resolution of the excess cortisol production, and improvement in the sequelae.³ Improved imaging techniques have shown a wide spectrum of malignancies associated with EAS, with the most frequent aetiology being neuroendocrine tumours (NET).² Localising the ectopic source of ACTH can be difficult, and if untreated, it can have a significant impact on morbidity and mortality. Up to 20% of EAS cases do not have a lesion identified, even after long-term monitoring.^{2,4} The currently recorded prevalence is approximately 12%, with a risk of malignancy. It is necessary to detect and monitor the effects of therapy and prevent the unpredictable risk of recurrence. This case explores occult EAS and the challenges encountered when the primary lesion cannot be identified.

CASE

A 62-year-old female had recurrent hospital presentations due to dyspnoea, lower limb oedema and reduced mobility with falls. She was being treated for heart failure with preserved ejection fraction (HFpEF), with a past medical history of hypertension, hypercholesterolaemia, type-II diabetes mellitus, obesity, functional neurological disorder, generalised anxiety disorder, and prior thyroidectomy. Her

medications included apixaban 5 mg BD, empagliflozin 10 mg mane, frusemide 80 mg BD, hydrochlorothiazide 12.5 mg mane, insulin aspart 30-units TDS, insulin glargine 75-units nocte, metformin MR 500 mg BD, metoprolol 25 mg BD, simvastatin 80 mg nocte, spironolactone 25 mg mane, and thyroxine 150 mcg daily. She also presented with hyperglycaemia, recurrent severe hypokalaemia and worsening mental health.

Physical examination revealed moderate hypertension, Cushingoid features such as facial roundness and central adiposity, and fluid overload. She had never been on a prolonged course of a corticosteroid and had no family history of NET or CS.

Her midnight serum cortisol was elevated at 506 nmol/L with elevated ACTH 95.1 ng/L (7.2-63.3), elevated 24-hour urine free cortisol 1411 nmol (<270), and elevated salivary cortisol 37 nmol/L (<8). Cortisol was not sufficiently suppressed with overnight high-dose 8 mg dexamethasone, suggestive of ectopic ACTH production. Endocrine biochemistry and baseline renal and liver function are summarised in Table 1.

CT imaging of the adrenal glands demonstrated a 15 x 13 mm nodule in the lateral limb of the left adrenal (unchanged in size in two years) with <10 Hounsfield units (HU), consistent with a left benign adrenal lipoma. The medial limb was bulky in appearance, measuring 12 x 11 mm with a focal low-density nodule of <10 HU, radiologically considered to represent another adrenal adenoma, also

Table 1. Baseline hormonal panel and cortisol testing

Test	Results ^a	Laboratory reference range
Body weight	110.9 kg	-
Morning serum cortisol	764 nmol/L	100 - 535
Midnight serum cortisol	506 nmol/L	<206
Serum ACTH	95.1 ng/L	7.2 - 63.3
24-hr urine free cortisol	1411 nmol/24hr	<270
Midnight salivary cortisol	37 nmol/L	<8
Cortisol pre-dexamethasone ^a	942 nmol/L	100 - 535
Cortisol post-dexamethasone ^a	560 nmol/L	<50
Fasting glucose	13.2 mmol/L	3.0 - 5.4
HbA1c	75 mmol/mol (9.1%)	23 - 43 (4.0 - 6.0)
Total daily insulin (exogenous)	165 units	-
TSH	0.98 mIU/L	0.40 - 4.00
FT4	14.9 pmol	9.0 - 19.0
Chromogranin A	133.5 ng/mL	0.0 - 101.9
Growth hormone	<0.1 ug/L	<8.0
FSH	0.3 IU/L	26.7 - 133
LH	<0.2 IU/L	5.2 - 62.0
Prolactin	176 mIU/L	110 - 560
IGF-1	11.4 nmol/L	7.0 - 27.0
eGFR	>90 mL/min/1.73 m ²	>90
Creatinine	61 umol/L	45 - 90
Bilirubin	8 umol/L	<20
Alanine aminotransferase	53 u/L	10 - 35
Aspartate aminotransferase	45 u/L	10 - 35
Alkaline phosphatase	38 u/L	30 - 110
Gamma-glutamyl transferase	553 u/L	5 - 35

^a 8 mg overnight dexamethasone suppression test^b Baseline results compiled from various hospital presentations over 2022–2023

unchanged from previous imaging. Right adrenal gland was unremarkable. Pituitary MRI demonstrated a 2 mm area of hypoenhancement in the posterior portion of the pituitary, suggesting a possible pituitary microadenoma. Due to suspicion for hypercortisolaemia of pituitary origin, inferior petrosal sinus sampling (IPSS) was done, which

demonstrated low central peripheral ACTH gradients in both basal conditions and following corticotrophin-releasing hormone administration, with ratios of <2 and <3, respectively. This was suggestive of ectopic (non-pituitary) ACTH production.

To search for an ectopic source including possible NET, CT chest/abdomen/pelvis and 187 MBq Ga68 DOTATATE PET scan were conducted, which demonstrated a 14-15 mm non-enhancing and non-avid left lingula nodule and known benign left adrenal lesion (non-avid), with no definite DOTATATE-avid lesion identified. In the absence of an identified NET, a biopsy of the lingula nodule was done, which demonstrated unremarkable alveolar lung tissue with negative ACTH histology. Finally, a nuclear medicine bone scan demonstrated no bone metastases.

She was diagnosed with occult ectopic CS. Due to financial inaccessibility of metyrapone, she was commenced on ketoconazole 200 mg BD (subsequently increased to 300 mg BD). This resulted in significant biochemical improvement with a reduction in 24-hour urine free cortisol (453 nmol after 2-weeks of therapy; 41 nmol after 2 months) and a significantly suppressed cortisol following overnight dexamethasone testing after one week of ketoconazole (cortisol levels: 456 nmol/L pre-dexamethasone; 43 nmol/L post-dexamethasone). Serum (morning) cortisol levels before and after ketoconazole therapy are illustrated in Figure 1.

Most recent follow-up results are summarised in Table 2, demonstrating continued efficacy of ketoconazole. The patient continues to be monitored by an endocrinologist, with ongoing biochemical and imaging surveillance. The patient management plan involves continuous investigation of the underlying cause of ectopic ACTH production, with the aim of cure when its location becomes apparent.

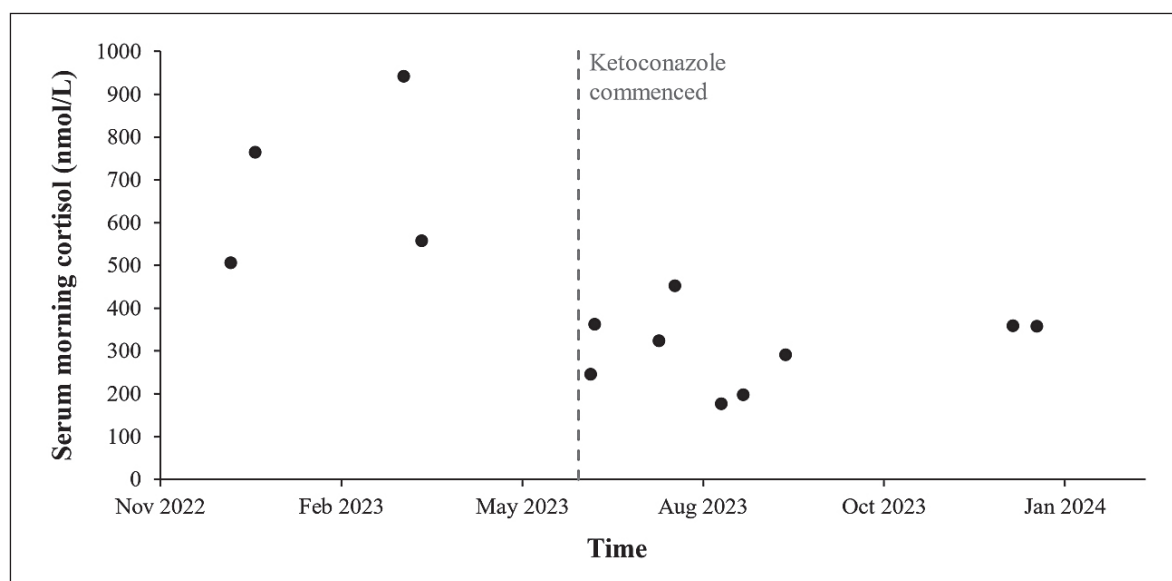


Figure 1. Serum morning cortisol (nmol/L) concentrations over time from initial presentation to January 2024. The commencement of ketoconazole is illustrated by the dashed grey vertical lines.

Table 2. Biochemistry results after 7 months of continuous ketoconazole therapy

Test	Result	Laboratory reference range
Body weight	90 kg	-
24-hour urine free cortisol	88 nmol/24 hr	<270
Morning serum cortisol	358 nmol/L	100 - 535
Serum ACTH	57 ng/L	7.2 - 63.3
Fasting glucose	9.2 mmol/L	3.0 - 5.4
HbA1c	41 mmol/mol (5.8%)	23 - 43 (4.0 - 6.0)
Total daily insulin (exogenous)	78 units	-
TSH	6.41 mIU/L	0.40 - 4.00
FT4	17.2 pmol/L	9.0 - 19.0
eGFR	73 mL/min/1.73 m ²	>90
Creatinine	71 µmol/L	45 - 90
Bilirubin	16 µmol/L	<20
Alanine aminotransferase	27 u/L	10 - 35
Aspartate aminotransferase	28 u/L	10 - 35
Alkaline phosphatase	91 u/L	30 - 110
Gamma-glutamyl transferase	488 u/L	5 - 35

DISCUSSION

EAS presents a complex diagnostic and therapeutic challenge to clinicians. Thorough and targeted clinical history taking and examination remain paramount to initial assessment. Several clinical signs of hypercortisolism may be missed, therefore, if there is high suspicion for hypercortisolism, clinical examination should investigate for signs such as central adiposity, rounded face, dorsocervical fat pad, proximal myopathy, cutaneous striae, and thinning of skin among others. Distinction between EAS and pseudo-Cushing's states such as obesity, chronic alcohol misuse, polycystic ovarian syndrome and psychiatric disorders where there is activation of the hypothalamus-pituitary-adrenal-axis, can be difficult on history and examination alone; targeted dynamic hormonal testing may assist further diagnosis.⁵

An important distinguishing feature of EAS from other forms of CS is the presentation of symptoms – muscle weakness as the most common, followed by hypertension, infections and peripheral oedema. Intriguingly, it has been found that weight loss is more prevalent than weight gain³ and hypokalaemia is often present as demonstrated in our case.⁶ The onset of predominant mineralocorticoid signs should signal a high degree of suspicion for EAS.⁷ It has been found that an ACTH level >148 pmol/L is more indicative of EAS than CS.⁸ The gold standard for diagnosing EAS is IPSS, which allows for the differentiation of the ACTH excess – either from a pituitary to an ectopic source.⁹ Once EAS is diagnosed, a combination of different modality techniques, including a DOTATATE and PET/CT, are important for localising the source.¹⁰

Treatment of occult EAS often involves control of hypercortisolaemia through use of adrenal steroidogenesis inhibitors such as ketoconazole and metyrapone, glucocorticoid receptor antagonist such as mifepristone, or bilateral

adrenalectomy in patients with severe hypercortisolism where medical control of CS is not feasible.¹¹ In our case, the patient responded well to ketoconazole. Ketoconazole is effective due to enzyme inhibition involved in cortisol synthesis. However, due to the rare hepatotoxicity risk with oral ketoconazole use, regular monitoring of liver enzyme levels is recommended.⁸ If identified, the definitive treatment is resection of the causative tumour, however other therapies may include chemotherapy, radiotherapy, or a long-acting somatostatin analogue.³ In refractory cases of occult EAS, bilateral adrenalectomy can be considered for cure of CS, however, the underlying ectopic source of ACTH remains. Due to the biochemical success and patient tolerance of continued medical therapy, surgical risks involved in bilateral adrenalectomy, lifelong glucocorticoid and mineralocorticoid replacement, and patient preference for non-surgical management pending identification of the underlying ectopic source, adrenalectomy was not undertaken in this case.

Management of occult EAS is seldom reported in the literature, though published cases have highlighted the difficulty of managing occult EAS. One similar case initially tried ketoconazole, however therapy was ceased after 2 weeks due to new liver enzyme derangement.¹² The patient was then commenced on metyrapone before eventually requiring urgent percutaneous adrenal ablation as salvage therapy in the setting of severe refractory hypercortisolemia with the patient not deemed fit for laparoscopic bilateral adrenalectomy. Another case of occult EAS was presented by Cannon and Doherty.¹³ Similarly, ketoconazole therapy was initially used while investigating the source of ectopic production, resulting in a reported 50% reduction in cortisol levels. However, due to suspicion of an intra-abdominal ectopic source, the authors undertook surgical exploration with intraoperative ultrasonography, identifying a pancreatic neuroendocrine tumor with metastatic disease. Distal pancreatectomy, splenectomy and left adrenalectomy were undertaken. Due to persistently elevated ACTH, right adrenalectomy was additionally required, with subsequent glucocorticoid and mineralocorticoid replacement therapy. Compared to these cases, our patient remains stable on medical management and we plan to continue surveillance with periodic imaging.

Additionally, the combination of type 2 diabetes mellitus accompanied by central obesity in middle-aged and elderly patients can be suspicious for hypercortisolism, which further worsens pre-existing diabetes. Use of exogenous insulin, an anabolic hormone, is associated with weight gain which increases cardiovascular complications, particularly in patients with metabolic syndrome. In patients with type 2 diabetes where weight loss would be medically beneficial, therapy with GLP-1 receptor agonists should be considered.¹⁴

Compared to computed tomography and magnetic resonance imaging, DOTATATE and PET/CT scans provide a higher degree of sensitivity and specificity, and are

often able to identify lymph node and bone metastases.² Peptide receptor radionuclide therapy is a novel management option for EAS, and the aforementioned imaging modalities can help indicate if this will be effective as evidenced by considerable uptake in the tumour burden.^{2,3}

CONCLUSION

Occult EAS is an important subset of CS which presents a diagnostic and management dilemma for physicians. This case demonstrates a methodical investigation of hypercortisolaemia, highlighting the difficulty of localising an ectopic source of ACTH. Ultimately, this case demonstrates a strong biochemical response to ketoconazole treatment in the absence of ectopic identification.

Ethical Consideration

Patient consent forms were obtained before manuscript submission.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

AIK: Conceptualization, Methodology, Formal analysis, Writing – original draft preparation, Writing – review and editing, Visualization; **LC:** Conceptualization, Methodology, Formal analysis, Writing – original draft preparation, Writing – review and editing, Supervision; **AW:** Conceptualization, Methodology, Formal analysis, 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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Parathyroid Adenoma with Macrofollicular Growth Pattern: A Rare Histopathological Entity

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Abstract

The majority of parathyroid adenomas can be localized preoperatively using various imaging techniques. The success rate of focused parathyroidectomy exceeds 95% when performed by an experienced surgeon. Here, we report an apparent failure of focused right inferior parathyroidectomy performed for a preoperatively detected parathyroid adenoma. This misinterpretation arose due to macrofollicular growth pattern of the resected parathyroid adenoma, which mimicked thyroid tissue. The patient subsequently underwent re-exploration, including intraoperative ultrasound, which revealed that the culprit gland had, in fact, been successfully removed during the initial surgery. This finding was also supported by a significant decrease in the intraoperative parathyroid hormone level, as compared to the pre-operative level. This case highlights the rare macrofollicular histology of parathyroid adenoma and underscores the importance of a multidisciplinary team in successfully treating the condition.

Key words: parathyroid adenoma, macrofollicular growth pattern, parathyroidectomy

INTRODUCTION

Hyperfunctioning parathyroid adenoma is the most common cause of primary hyperparathyroidism (PHPT).¹ Classically, PHPT presents with nonspecific features of hypercalcemia such as vague abdominal pain, neuromuscular weakness, bone disease, osteoporosis, neuropsychiatric manifestations, recurrent nephrolithiasis, or rarely, pancreatitis. Recently, with the increasing use of biochemical tests and ultrasonography, the diagnosis of asymptomatic disease is increasing.¹

We discuss a 29-year-old female who was diagnosed to have PHPT (high serum calcium with raised intact parathyroid hormone (iPTH), while being evaluated for nephrolithiasis. Preoperative imaging studies localized a single right inferior parathyroid adenoma. Despite preoperative diagnosis and localization, the tissue diagnosis of parathyroid adenoma could only be made after two surgical attempts. In this case, the frozen section of the excised tissue exhibited macrofollicular growth pattern, morphologically resembling normal thyroid parenchyma. As a result, the tissue diagnosis was missed, leading to a repeat neck exploration to identify the culprit gland.

CASE

A 29-year-old female presented with sudden onset flank pain radiating to the groin at a local hospital seven months ago. There was no history of fever, polyuria, or dysuria. No neuropsychiatric symptoms, or history of fractures or bone pains were noted. Ultrasonography of the abdomen revealed bilateral renal calculi, measuring 14 mm and 16 mm. Computed tomography (CT) urography confirmed bilateral renal calculi with dilated right pelvicalyceal system. Blood investigations including complete blood counts and renal function tests were normal except for raised serum calcium levels [10.8 mg/dL (normal range: 8.4-10.2 mg/dL)]. On further evaluation, iPTH level was found to be markedly elevated (213 pg/mL, normal range: 13.6-85.6 pg/mL) and serum 25-hydroxy vitamin D level was not deficient (28.3 ng/dL, normal range: 10 – 44 ng/dL), suggestive of PHPT. Subsequently, the patient was referred to our institution for further management.

Parathyroid localization with an initial neck ultrasound was done which revealed a hypoechoic lesion inferior to the right lobe of thyroid measuring 9 × 6 mm, suggestive of right inferior parathyroid adenoma. Subsequently, ^{99m}Tc sestamibi scintigraphy was performed, which was

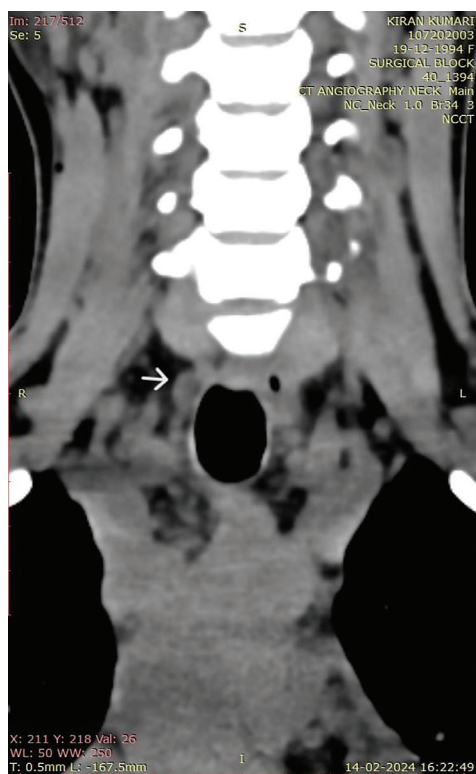


Figure 1. 4D-CT showing right inferior parathyroid adenoma (white arrow) immediately below the lower pole of right thyroid lobe.

inconclusive. As there was discordance between the above two imaging findings, four-dimensional CT (4D-CT) neck was done which showed a well circumscribed nodular soft tissue lesion lying posterior to the lower pole of right lobe of thyroid gland in paratracheal location, measuring $10 \times 7 \times 13$ mm in size. There was enhancement in the arterial phase and washout during delayed phase suggestive of right inferior parathyroid adenoma (Figure 1).

As it was a pre-operatively localized parathyroid adenoma involving a single gland, focused right inferior parathyroidectomy was planned. During surgery, a suspicious lesion immediately below the right inferior thyroid artery was found and excised along with surrounding pad of fat and sent for frozen section. Intraoperative iPTH and serum calcium were also sent. The frozen section report indicated presence of tissue with macrofollicular growth pattern suggestive of thyroid tissue, without any evidence of parathyroid adenoma (Figure 2). In view of the possibility of failed surgery, re-exploration was done. However, there was no abnormal lymphoid or fatty tissue in the suspected area. To optimize localization, an intraoperative ultrasound was performed by an experienced radiologist who also concluded absence of any suspicious tissue at the site of the right inferior parathyroid adenoma. The post-resection iPTH and calcium levels reflected a marked decline in iPTH levels to 5 pg/mL, and normalization of serum calcium to 9.4 mg/dL. Such findings pointed towards an evidence of successful removal of parathyroid adenoma during initial exploration and resection itself.

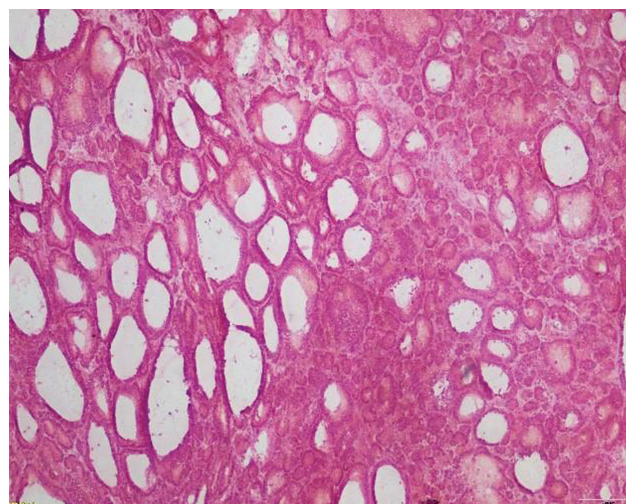


Figure 2. H&E-stained frozen section (40x) shows a lesion predominantly arranged in a follicular pattern.

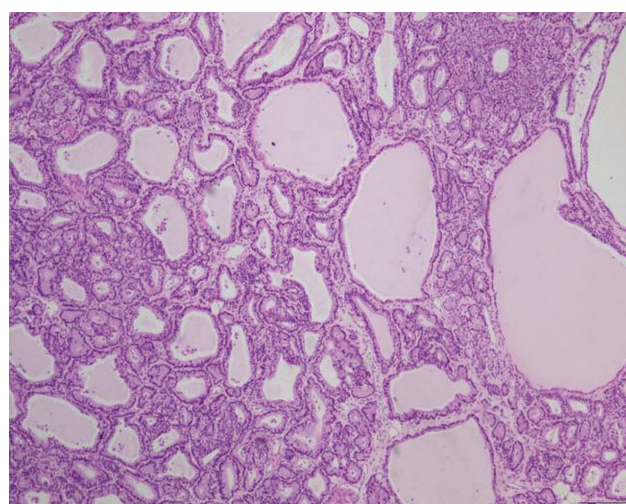


Figure 3. H&E-stained slide from a formalin-fixed, paraffin-embedded section shows a similar lesion predominantly arranged in a follicular pattern, with monomorphic nuclei and abundant clear cytoplasm (40x).

To resolve the enigma, the findings of re-exploration, intraoperative ultrasound and iPTH, and serum calcium were discussed with the pathologist. The frozen section slides of the surgery were reviewed again, and histopathology revealed an unusual morphology comprising of a tissue with monomorphic round nucleus and abundant clear cytoplasm having columnar appearance, arranged in comprehensive follicular pattern (Figure 2). The morphology of the parathyroid gland closely resembled that of the thyroid, leading to diagnostic uncertainty. Finally, histopathological report of formalin fixed paraffin embedded specimen confirmed parathyroid adenoma with macrofollicular growth pattern with adjacent normal parathyroid parenchyma (Figure 3). Immunohistochemistry was performed on formalin fixed paraffin embedded section and the cells were found to be immunopositive for parafibromin (Figure 4) and GATA 3. Cells were negative for TTF 1 and the Ki 67 index was less than 1 %.

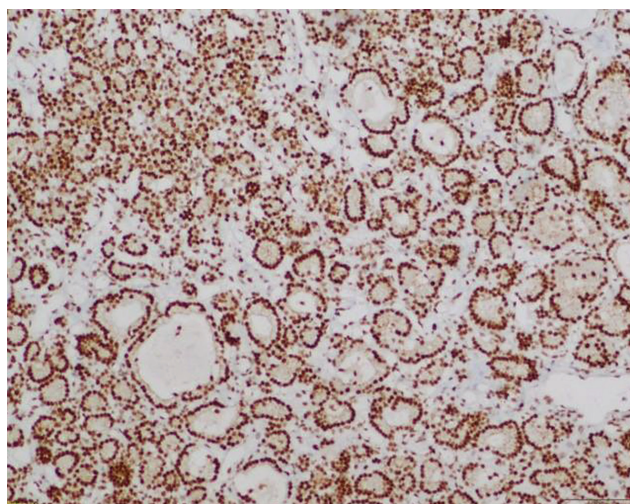


Figure 4. Immunohistochemical staining for parafibromin shows diffuse nuclear positivity (parafibromin IHC, 100x).

DISCUSSION

This case report highlights the challenges of distinguishing parathyroid gland lesions from thyroid lesions cytopathologically in a clinical setting. Our patient manifested with classical features of PHPT with right inferior parathyroid adenoma localized preoperatively by ultrasonography and 4D-CT. However, despite successful removal of the adenoma during the surgery, as confirmed by intraoperative biochemical findings, re-exploration had to be done in light of frozen section biopsy findings mimicking a follicular thyroid lesion.

Previous pathologic reports have highlighted the difficulty in differentiating parathyroid from thyroid lesions on fine needle aspiration cytology. However, combination of cytological features may point towards a parathyroid lesion rather than thyroid tissue as described by Kimberley et al.² Approximately 40% of the cases of parathyroid adenoma may exhibit microfollicular structure like that of a thyroid adenoma,³ however, thyroid follicular lesions also have macrofollicles.² In addition, intracytoplasmic fat vacuolation, high cellularity, small dark nuclei, bare nuclei, nuclear molding and overlapping are features more suggestive of parathyroid lesion.^{2,4,5} The presence of predominant follicular structures in a parathyroid adenoma is an atypical finding which may unexpectedly challenge histopathological interpretation. In such cases, the absence of birefringent calcium oxalate crystals, and the presence of well-defined cell membranes can help in the differentiation from the thyroid tissue.⁶ The documentation of such characteristics in real-time clinical practice is essential to prevent unnecessary delays in establishing an accurate diagnosis. These cytologic features, along with PTH immunoassay and/or immunostainings for GATA3 and parafibromin on cytologic specimens, aid in differentiating parathyroid from thyroid lesions.⁷

Only a handful of case reports in the past have described misdiagnosis of parathyroid adenoma as thyroid lesion in the clinical setting.⁸⁻¹⁰ In a patient with neck mass and hypercalcemia, aspiration cytology findings of cohesive clusters of monomorphic hyperchromatic cells resembling follicular cells, and papillary formation and follicle-like arrangements suggested the diagnosis of papillary carcinoma of the thyroid. Finally, histopathologic examination of the excised mass revealed parathyroid adenoma.⁹ In a report by Peterson et al, a 57-year-old female was conservatively managed for 8 years by repeated fine needle aspiration biopsy of a mildly suspicious thyroid nodule that showed atypical thyroid epithelial cells and the nodule was categorized as an atypical/follicular thyroid lesion Bethesda Class III. This thyroid nodule was not accurately diagnosed as parathyroid adenoma until the patient developed pathological hip fracture, with subsequent biochemical evaluation also suggestive of PHPT. Focused parathyroidectomy resulted in complete resolution of the symptoms in the patient.¹⁰ Although follicular growth pattern has been reported in parathyroid adenomas, macrofollicular growth pattern of parathyroid tissue, as observed in our case, has not been documented in the literature.

CONCLUSION

The appropriate management of parathyroid adenoma requires close coordination among an experienced surgeon, pathologist, and radiologist. The role of biochemical investigations in both the preoperative diagnosis and intraoperative assessment for confirming successful gland removal is paramount. Lastly, challenges in histological diagnosis can be resolved through ancillary tests, including PTH immunoassay and immunostaining for GATA3, and parafibromin.

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

RM: Conceptualization, Investigation, Writing – original draft preparation; **BKS:** Conceptualization, Investigation, Writing – original draft preparation; **AN:** Conceptualization, Writing – original draft preparation; **AK:** Conceptualization, Writing – review and editing; **DK:** Conceptualization, Writing – review and editing; **SS:** 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

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In response to the article, 'Interrelationship of Sarcopenia and Cardiovascular Diseases: A Review of Potential Mechanisms and Management,' by Rivera, et al., published in JAFES Vol. 39 No. 1.

Sarcopenia in Patients with Cardiovascular Disease Can Also Be Triggered by Other Risk Factors

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Key words: sarcopenia, muscle wasting, cardiovascular disease, medications, risk factors

We read with interest the review article by Rivera et al. on the influence of cardiovascular disease on the development of sarcopenia.¹ The aim of the review was to explore the pathophysiological mechanisms that explain the relationship between sarcopenia and cardiovascular disease, as well as its clinical assessment and associated management.¹ Inflammation, oxidative stress, endothelial dysfunction, neuronal and hormonal changes and other metabolic disturbances have been identified as factors responsible for sarcopenia in patients with cardiovascular disease.¹ The overview is impressive, but some points still need to be discussed as several causes of sarcopenia associated with cardiovascular disease were not considered in the review.¹

The first point is that there is evidence that sarcopenia is associated with low hemoglobin levels, so patients with sarcopenia should also be screened for anemia.² Other studies also indicate that anemia is associated with sarcopenia, so it has been suggested that these patients should switch to a diet rich in antioxidants, high-quality proteins and micronutrients, as well as engage in moderate physical activity and maintain a healthy weight.³ Sarcopenia can also occur in survivors of severe aplastic anemia treated after allogeneic hematopoietic stem cell transplantation.⁴ The effects of anemia on skeletal muscle can be exacerbated by heart failure.

The second point is that arterial hypotension or lowering blood pressure with beta-blockers was not mentioned in the review as being associated with sarcopenia.⁵ Inadequate blood supply to skeletal muscle due to chronic hypotension

may reduce skeletal muscle mass and lead to progression of sarcopenia, as adequate blood flow is required to maintain skeletal muscle mass.⁶ One factor that may contribute to the development of sarcopenia in this context is low capillarization of skeletal muscle, which leads to restricted diffusion of substrates, oxygen, hormones and nutrients.⁶

The third point is that medications that are frequently taken over a long period of time have not been discussed in detail as a cause of sarcopenia. These include statins, which are known to cause myopathy as a side effect in about one percent of cases, sulfonylureas and glinides.⁷ There is also evidence that GLP-1 receptor agonists, SGLT2 inhibitors, glucocorticoids, antineoplastics, immune checkpoint inhibitors, antiandrogens, chloroquine/hydroxychloroquine, colchicine, nucleoside analogs, loop diuretics and D-penicillamine can cause sarcopenia.⁸

The fourth point is that hemodialysis, which is often associated with cardiovascular disease, was not mentioned in the review as a recognized cause of sarcopenia.⁹ Sarcopenia in patients with end-stage renal disease undergoing maintenance hemodialysis can be explained by accelerated protein depletion, multiple metabolic disturbances and nutrient deficiencies.¹⁰

Fifth, we disagree with the statement that beta-blockers have a beneficial effect on sarcopenia.¹ On the contrary, several studies have found that beta-blockers are associated with an increased risk of sarcopenia.⁵ Another argument in favor of the sarcopenic effect of beta-blockers is that at least some beta-agonists increase muscle mass and strength.

In summary, it can be said that this interesting review has some limitations that relativize the results and their interpretation. Taking these limitations into account could strengthen the conclusions and increase the validity of the review. The causes of sarcopenia in cardiovascular disease are multifactorial and may be exacerbated or caused by genetic influences, immobility or disuse, hematologic diseases, medications and treatments such as dialysis, endocrine factors, inflammation, and nutritional deficiencies.

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Lateral Flare Sign of Thyroid-Associated Eye Disease

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Key words: thyroid eye disease, Graves' disease, temporal flare, ophthalmopathy

A 44-year-old male smoker presented with a six-month history of bulging and redness in his right eye. He also reported intermittent binocular double vision, which was more noticeable on upward gaze. There was no history of trauma, headache, vision loss, or tachycardia. Systemic examination was unremarkable. On examination, the patient had conjunctival redness, hyperemia, proptosis, and swelling with temporal flaring of the right upper eyelid (Figure 1A). Ocular motility and visual acuity were within normal limits. Thyroid function tests revealed TSH: 0.81 (reference range: 0.35–5.50), Free T4: 1.7 (0.80–2.19), and T3: 1.58 (0.87–1.78). Orbital MRI showed right eye proptosis and significant thickening with edema of the right inferior rectus muscle, without involvement of other extraocular muscles (Figure 1B). The TSH receptor antibody (TRAb) level was elevated at 2.38 IU/L (reference: <1.22).

A diagnosis of thyroid-associated eye disease (TED) was made, and the patient was closely monitored. At a subsequent visit, TSH was found to be suppressed and TRAb levels had increased further. The patient was started on low dose carbimazole, advised to strictly avoid smoking, and treated with intravenous methylprednisolone therapy.

TED is associated with hyperthyroidism in about 90% of cases.^{1,2} Orbital involvement in TED is typically bilateral.³ Euthyroid and unilateral presentations are uncommon and should prompt consideration of other causes, such as orbital pseudotumor, mucocoele, malignant lymphoma, leukemia, hemangioma, or lacrimal gland tumors.⁴

In this context, the presence of upper eyelid retraction with a 'lateral flare sign' may suggest TED.⁵ While increased sympathetic stimulation of Müller's muscle is usually

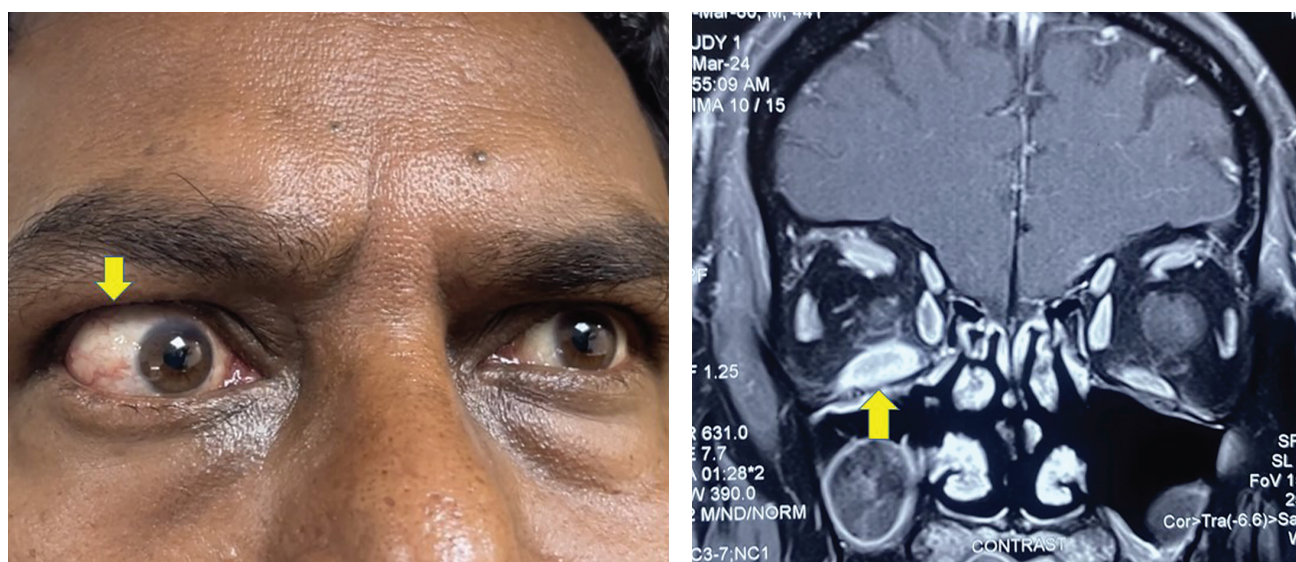


Figure 1. (A) Thyroid associated eye disease with lid retraction and 'lateral flare sign' in right eye. **(B)** Magnetic resonance imaging (MRI) with T2 contrast image showing thickening and oedematous changes in right inferior rectus muscle.

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responsible for lid retraction in these cases, the 'lateral flare' observed in TED can be attributed to enlargement or fibrosis of the levator muscle, resulting from its increased activity to compensate for the ipsilateral tight inferior rectus muscle. Additionally, scarring between the levator aponeurosis and the inflamed lacrimal gland fascia or adjacent soft tissues may contribute to this clinical sign.^{2,5}

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

SS: Conceptualization, Validation, Formal analysis, Investigation, Data curation, Writing – original draft preparation; **TA:** Conceptualization, Validation, Formal analysis, Investigation, Data curation, Writing – original draft preparation; **MB:** Investigation, Writing – review and editing, Supervision.

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Thymic Hyperplasia-Associated Myasthenia Gravis in the Setting of Coexisting Graves' Disease

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Key words: thymic hyperplasia, myasthenia gravis, Graves' disease

Thymic hyperplasia secondary to Graves' disease (GD) is a well-recognized entity.¹ Still, other causes of thymic hyperplasia in the presence of euthyroidism, especially the occurrence of massive thymic hyperplasia, should be investigated.² The clinical features of myasthenia gravis (MG) and thyroid eye disease (TED) may be similar, while thymic hyperplasia may occur in both conditions. Herein, we report an interesting case of the coexistence of severe TED and MG.

A 40-year-old Thai female diagnosed with severe TED requiring orbital decompression and intravenous methylprednisolone presented with left eye ptosis and chewing weakness for one month. Physical examination showed bilateral proptosis (19 mm in right eye, 21 mm in left eye) with eyelid retraction, erythema and edema of the eyelids and left eye ptosis. She denied limb muscle weakness, hoarse voice, or difficulty breathing. Her previous history included hypothyroidism after thyroidectomy for GD 18

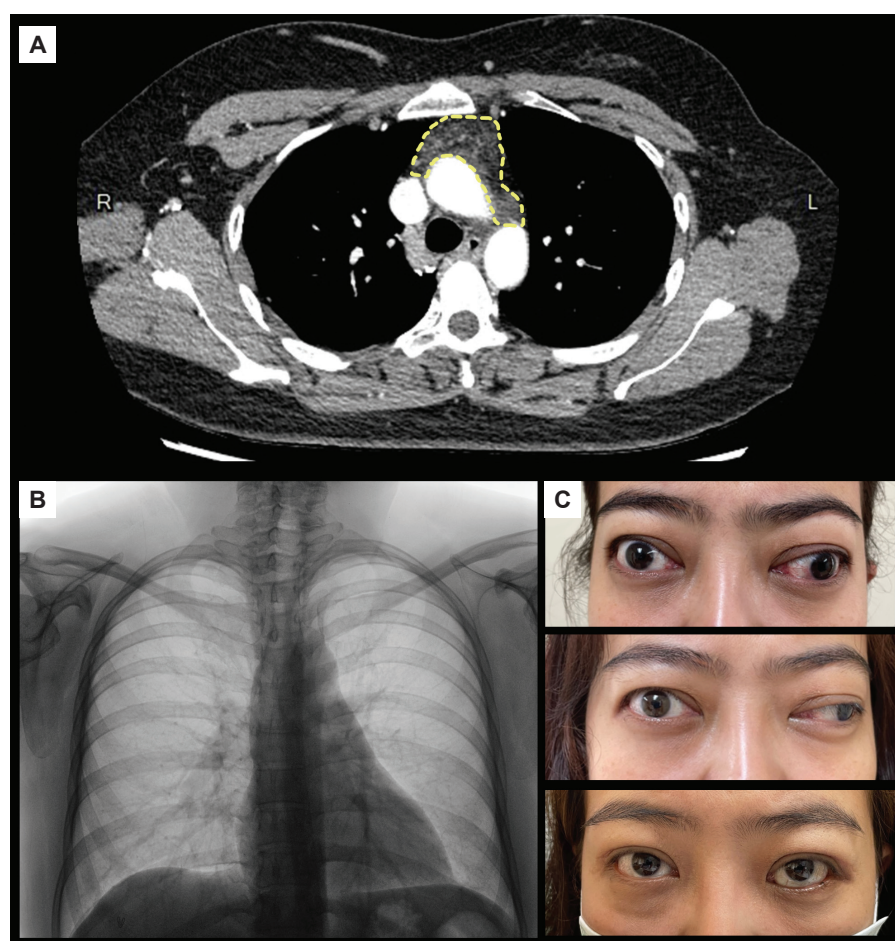


Figure 1. (A) Computed tomography images demonstrated a 10 × 9 × 1.6 cm thymic enlargement (thymic hyperplasia outline as shown in Figure 1A). (B) Chest X-ray at the time of thyroidectomy revealed no widening mediastinum (the brightness of the image is adjusted to enhance visibility). (C) Clinical course of severe thyroid eye disease from the initial presentation (18 months prior to the diagnosis of myasthenia gravis) which demonstrated inflamed bulging of both eyes and strabismus at left eye, new-onset left eye ptosis at the time of myasthenia gravis diagnosis, and after multiple surgical procedures including decompression surgery followed by strabismus surgeries.

months earlier. At the initial diagnosis of GD, laboratory tests were notable for highly elevated serum thyrotropin receptor antibody (TRAb) at 14.5 U/L (normal range <1.75 U/L). Anti-acetylcholine receptor antibody was positive, confirming the diagnosis of MG. A chest computed tomography scan showed a 10 × 9 × 1.6 cm thymic enlargement with a well-demarcated margin and mild homogeneous enhancement. The patient was euthyroid at the time, on LT4 replacement for surgical hypothyroidism. Serum TRAb was decreased at 1.39 U/L. There was no mediastinal widening on the previous chest X-ray (CXR) at the time of thyroidectomy. The patient underwent video-assisted thoracoscopic thymectomy. The pathologic results revealed non-neoplastic thymic tissue with focal thymic epithelial hyperplasia. One year after thymectomy, her symptoms had significantly improved and she was prescribed oral azathioprine 50 mg/day without prednisolone. Once her TED became inactive, strabismus and eyelid surgeries were performed.

Our case highlights a diagnostic dilemma in the background of coexisting GD and MG. Thymic hyperplasia could be secondary to both GD and MG.³ However, the previous CXR and clinical course of hyperthyroidism in this patient were essential to differentiate between both conditions. This present case emphasized that clues from all relevant imaging must be obtained to accurately determine the etiology of thymic hyperplasia in cases of coexistent GD and MG.

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfilment of ICMJE authorship criteria.

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YT: Conceptualization, Methodology, Investigation, Writing – original draft preparation, Project administration; **VV:** Resources, Data Curation, Writing – review and editing, Visualization; **TH:** Writing – review and editing, Supervision, Funding acquisition.

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The following were disclosed as of May 2025:

ELIZABETH PAZ-PACHECO | Editor-in-Chief

Prof. Pacheco receives grants for Metabolomics of DM Nephropathy from the Philippine Council for Health Research Development. She is a Past President of the Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM).

CECILIA A. JIMENO | Vice Editor-in-Chief

Prof. Jimeno receives honoraria for lectures on lipid lowering drugs (Atorvastatin, Rosuvastatin, Ezetimibe, Insulin Glargine) from Organon, AstraZeneca, Merck, Menarini, Sanofi). She also receives support for attending meetings on various antidiabetic medications from GX Pharmaceuticals, LG Chem, Corbridge. She is the Treasurer/Member of the Board of Directors of the Philippine Lipid and Atherosclerosis Society (PLAS). She is a stockholder of the Metro Pasay Medical Center.

GABRIEL V. JASUL JR. | Associate Editor

Prof. Jasul received honoraria for lectures from Sanofi Aventis, Novo Nordisk, MSD, Boehringer Ingelheim, Abbott Nutrition, AstraZeneca, LRI- Therapharma, UMed and Woerwag.

MADE RATNA SARASWATI | Associate Editor

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THAN THAN AYE | Associate Editor

Prof. Aye has nothing to disclose.

CHAICHARN DEEROCHANAWONG | Associate Editor

Prof. Deerochanawong has nothing to disclose.

NGUYEN THY KHUE | Associate Editor

Assoc. Prof. Khue receives consulting fees from Merck. She receives honoraria for lectures from Servier, Boehringer Ingelheim and Novo Nordisk. She is an Advisory Board of Merck Serono.

MARY ANN R. ABACAN | Editorial Board Member

Prof. Abacan receives grants as principal investigator of the Registry of Lysosomal Storage Disorders from Sanofi Genzyme (2014 to present) and as co-investigator of the SHP-ELA-401 - A Long-Term, Open-Label, Multicenter, Phase IV Study to Assess Longitudinal Changes on Height and Weight in Patients with MPS II who are receiving Elaprase and started Treatment with Elaprase at <6 Years of Age - Shire (2015-present). She is a Consultant Medical Specialist at the Institute of Human Genetics at the University of the Philippines-National Institutes of Health. She received honoraria as a lecturer of the Acute and Chronic Management of Organic and Amino Acidurias Training by Nutricia and Workshop for Dietitians (April 26, 2025). She is a co-chair of the National Transplant Ethics Committee of the Department of Health and of the Metabolic Experts Panel at the Newborn Screening Reference Center of the National Institutes of Health.

LORNA F. RAMOS-ABAD | Editorial Board Member

Prof. Abad has nothing to disclose.

MARISSA M. ALEJANDRIA | Editorial Board Member

Prof. Alejandria received research grants from the Department of Science and Technology – Philippine Council for Health Research and Development and from CRDF Global.

PIA D. BAGAMASBAD | Editorial Board Member

Prof. Bagamasbad received grant funding from the Department of Science and Technology-Philippine Council for Health Research Development (DOST-PCHRD) to conduct research on prostate cancer and SARS-CoV-2 and the DOST-National Academy of Science and Technology (NAST) to conduct research on prostate cancer. She received honoraria as a plenary speaker of the Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM) and the Philippine Society of Medical Oncology (PSMO). She is a member of the Endocrine (ENDO) Society (no financial involvement).

SARAT SUNTHORNYOTHIN | Editorial Board Member

Prof. Sarat has nothing to disclose.

NATTAPOL SATHAVARODOM | Editorial Board Member

Prof. Nattapol has nothing to disclose.

CHIAW LING CHNG | Editorial Board Member

Dr. Chng has nothing to disclose.

TINT SWE LATT | Editorial Board Member

Prof. Latt has nothing to disclose.

KHOO CHIN MENG | Editorial Board Member

Dr. Meng has nothing to disclose.

NURAIN MOHD NOOR | Editorial Board Member

Dr. Noor is the current President of the Malaysian Endocrine and Metabolic Society (MEMS).

NATHANIEL S. ORILLAZA JR. | Editorial Board Member

Dr. Orillaza receives research grants from the Department of Science and Technology to establish the Discovery and Innovation Hub. He also receives innovation grant research from the Philippine General Hospital. He receives honoraria as Advisory Board and member of the Speakers Bureau of Viatrix. He is also a member of the Speakers Bureau of Menarini and Taisho. He receives support from Viatrix and AO Foundation to attend lecture meetings. He has a pending patent for medical devices. He is a Research Officer of AO Foundation.

PAUL MATTHEW D. PASCO | Editorial Board Member

Dr. Pasco has nothing to disclose.

CATHERINE LYNN T. SILAO | Editorial Board Member

Dr. Silao receives research grants from the Newborn Screening Reference Center, National Institutes of Health, Department of Science and Technology-Philippine Council for Health Research Development (DOST-PCHRD). She receives honoraria for lectures and manuscript writing from Nestle Nutrition Institute. She receives support for attending meetings at the Asia Pacific Society of Human Genetics, Medical Genetics and Genomics Association in Thailand and Universitas Yarsi in Indonesia. She is part of the research group for the Methods and Means for Prognosticating the Occurrence of Pulmonary Complications in Leptospirosis and Early Diagnosis and Prognosis of Complicated Leptospirosis using Molecular Markers. She is the Secretary/Board of Director of the Asia Pacific Society of Human Genetics (no financial involvement) and member of the Human Genome Education Committee (no financial involvement). She is a stockholder of the Clinical Genetics and Genomic Counseling Care Services (CGGCCS) Inc.

ROGELIO V. TANGCO | Editorial Board Member

Dr. Tangco has nothing to disclose.

NGUYEN VAN TUAN | Editorial Board Member

Prof. Van Tuan received financial support from the Australian National Health and Medical Research Council for his research. He also received a grant from Amgen to conduct research in osteoporosis. He is a member of Healthy Bone Australia (no financial involvement).

MYO WIN | Editorial Board Member

Prof. Win has nothing to disclose.

MARITA V.T. REYES | Ethics Adviser

Dr. Reyes received a research grant to the Women's Health Care Foundation from the Philippine Council for Health Research and Development. She receives honoraria as Department of Science and Technology-Philippine Council (DOST-PCHRD) Philippine Health Research Ethics Board. She is the President and Chair of the Board of Trustees of the Women's Health Care Foundation (WHCF), Inc. She is a stockholder of Makati Medical Center, Manila Doctors Hospital, The Medical City.

AMADO O. TANDOC III | Editorial Coordinator

Dr. Tandoc receives fees as a Consultant Editor of the Scientific Proceedings of the Lung Center of the Philippines, Philippine Journal of Orthopaedics and the Philippine Journal of Allergy, Asthma and Immunology. He is also the Editor-in-Chief of the Philippine Journal of Pathology. He is a speaker and Treasurer of the Philippine Association of Medical Journal Editors (PAMJE).

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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.

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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/mailling address, telephone number, e-mail and fax number. The **JAFES cover letter template** must be used.

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2. The manuscript should be arranged in sequence as follows: (1) Title Page, (2) Abstract, (3) Text, (4) References, (5) Tables, and (6) Figures & Illustrations.
3. References should pertain directly to the work being reported.
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3. The highest educational attainment or title of the authors should be included as an attachment whenever appropriate.
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For original articles, the abstract should contain no more than 200 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 from 50 to 75 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.

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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.
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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.
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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.
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4. Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal.

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ARTICLE TYPES

Original Articles

The abstract should contain no more than 200 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.

Reviews

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. The abstract should be from 50 to 75 words and should not be structured. A manuscript for reviews should not exceed 15 typewritten pages (including tables, figures, illustrations and references) or 4000 words.

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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. The abstract should be from 50 to 75 words and should not be structured. A manuscript for feature articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

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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. The abstract should be from 50 to 75 words and should not be structured. A manuscript for grand rounds should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

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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.

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JAFES welcomes feedback and comments on previously published articles in the form of Letters to the Editor. No abstract or keywords necessary. A Letter to the Editor must not exceed 2 typewritten pages or 500 words.

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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.

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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)
EQUATOR Network Guidelines	☐ Review manuscript if compliant with appropriate EQUATOR Network Guidelines and submit checklist (e.g., CONSORT for clinical trials, CARE for case reports)
Author Form	☐ Ensure all authors have read and agreed to the following: (1) the Authorship Certification, (2) the Author Declarations, (3) the Author Contribution Disclosure, and (4) the Author Publishing Agreement, and (5) the Conversion to Visual Abstract (*optional for original articles) ☐ Submit a scanned copy of the fully accomplished form
ICMJE Form for Disclosure of Potential Conflicts of Interest	☐ Ensure all authors have read and agreed to disclose potential Conflicts of Interest ☐ Submit the PDF copy of the fully accomplished form *The form is also downloadable at: http://www.icmje.org/conflicts-of-interest/
Ethics Review Approval	☐ For Original articles, submit a scanned copy of the Ethics Review Approval of research ☐ For manuscripts reporting data from studies involving animals, submit a scanned copy of the Institutional Animal Care and Use Committee approval
Patient Consent Form (if applicable)	☐ For Case Reports, Images in Endocrinology and Clinical Case Seminars, submit a scanned copy of the fully accomplished form; otherwise, obtain appropriate ethical clearance from the institutional review board.
Title Page	☐ Full names of the authors directly affiliated with the work (First name and Last name), highest educational attainment ☐ Name and location of 1 institutional affiliation per author ☐ If presented in a scientific forum or conference, provide a footnote should be provided indicating the name, location and date of presentation
Abstract	☐ Provide an abstract conforming with the format ☐ Structured for Original Articles: Objective/s, Methodology, Results, Conclusion ☐ Unstructured for Case Reports and Feature Articles
Keywords	☐ Provide 3-5 keywords (listed in MeSH)
Content	☐ Provide text/content in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion) ☐ Make sure all abbreviations are 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 ☐ Make sure all measurements and weights are in SI units ☐ If appropriate, provide information on institutional review board/ethics review committee approval ☐ 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
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To: **The Editor-in-Chief**
Journal of the ASEAN Federation of Endocrine Societies (JAFES)

Subject: **SUBMISSION OF MANUSCRIPT FOR PUBLICATION**

We intend to publish the manuscript/, entitled “_____,” under the Section [*Original Article, Review Article, Feature Article, Case Report, Case Series, Interhospital Grand Rounds, Brief Communications, Letter-to-the-Editor, Special Announcements*] in the Journal of the ASEAN Federation of Endocrine Societies.

LIST OF AUTHORS

Complete Name	Position/ Designation	Institutional Affiliation	Role in writing the manuscript	Email address	ORCID iD

On behalf of all the authors, I shall act as the corresponding author with the journal from this point onward.

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For case reports/series, patient consent forms have been secured for the publication of information.

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COMPLETE TITLE OF MANUSCRIPT

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Methodology Development or design of methodology; creation of models										
Software Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components										
Validation Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs										
Formal analysis Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data										
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Resources Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools										
Data Curation Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse										
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