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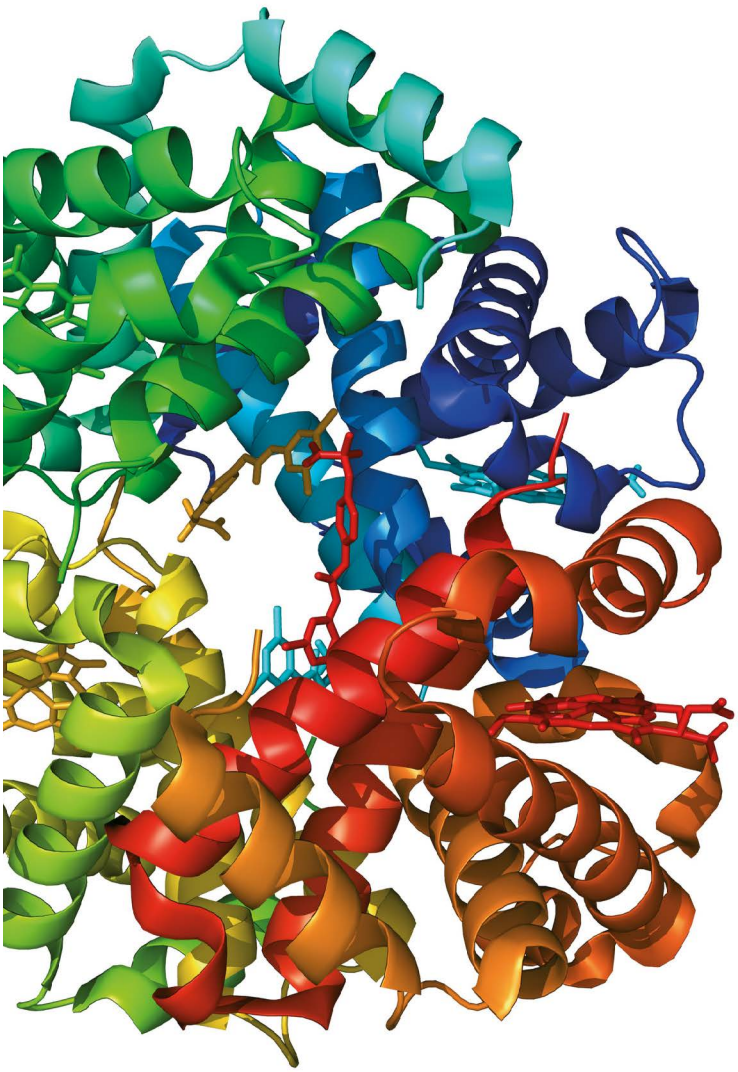

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Contents

REVIEW ARTICLES

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EDITORIAL
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'Clinical Diabetology': Highlights of 2024 and Thank You to Our Reviewers

Greetings from the Editorial Board of 'Clinical Diabetology'!

The year 2024 was the third for 'Clinical Diabetology' (CD) under the Editor-in-Chief, Dr. Viral N. Shah and his Editorial team. In a way, it is our duty to share some of our recent achievements and insights with readers of the Journal. We continue to see an increase in submissions to 'Clinical Diabetology' from around the world. Compared to 2024, both the number of submissions as well as acceptances to CD have grown by 20%, while the rejection rate has been stable at around 40%. Despite this increment, the Editors were able to keep the average 'submission to early publication' time below 100 days and our goal is to reduce time from 'acceptance to early publication' (Fig. 1).

The numbers of both downloads and views of articles published in CD are growing. Table 1 highlights the top three most downloaded research articles in the year 2024. Along with these trends, we have good reasons to expect growth of two crucial bibliometric parameters, i.e., Impact Factor by Clarivate Analytics and CiteScore by the Scopus database.

Additionally, at the end of 2024, CD joined ResearchGate, which we believe will enhance its visibility and circulation. Achieving this progress would not have been possible without contributions of expert reviewers

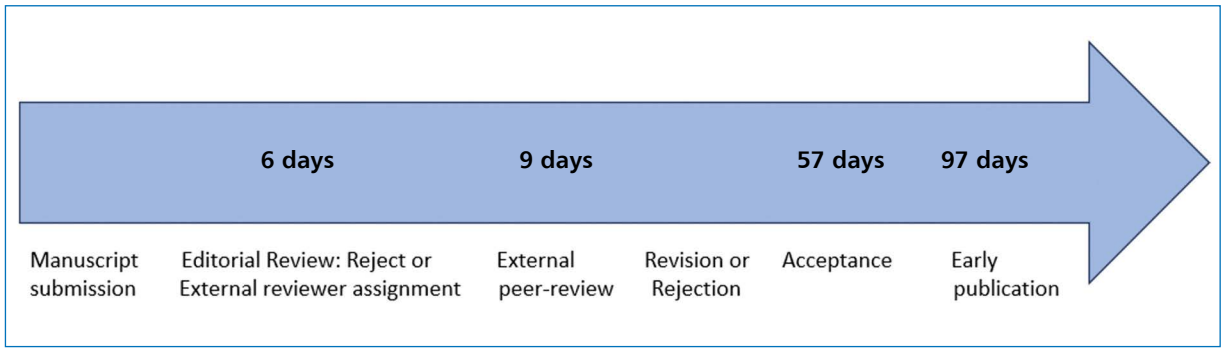

Figure 1. Average Time from Article Submission to Approval and Early Publication

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Table 1. Top Three Most Downloaded Articles Published in 2024 Issues (as of February 13th, 2025)

Issue	Title	First author	Number of views	Reference
2024;1	A Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context: Recommendations by Association of Clinical Endocrinologists Consensus Group	Erukulapati RS	842	[1]
2024;2	Self-Care Management and Glycemic Control Among Patients with Type 2 Diabetes in Bahrain: A Cross-Sectional Study	Al Ubaidi BAA	613	[2]
2024;1	Efficacy of Insulin Degludec/Insulin Aspart (IDegAsp) vs. Insulin Glargine (IGlarU300) in Insulin-Naïve Patients with Type 2 Diabetes: A Retrospective Study	Hasnani D	566	[3]

helping us select the best research articles. We would like to extend our thanks to all active reviewers but especially highlight the five experts who were most active in 2024:

— Edward Franek — Department of Internal Medicine, Endocrinology, and Diabetology, MSWiA, Warsaw, Poland
— Vinod Abichandani — MSc Endocrinology, University of South Wales, United Kingdom
— Vipul Chavda — Rudraksha Institute of Medical Sciences, Gujarat, India
— Dhruvi Hasnani — Department of Diabetology, Rudraksh Institute of Medical Sciences, Ahmedabad, Gujarat, India
— Kaumudi Chenamsetti — Diahappy Diabetes Reversal Clinic, Shyamal, Vastrapur Ahmedabad, India

We wish you all a very happy, healthy, and prosperous 2025! We invite you to join forces with us by submitting your research contributions, citing our scientific research articles and contributing as a reviewer.

Conflict of interest

Dr. Shah is the Editor-in-Chief for 'Clinical Diabetology'. Dr. Shah's institute has received research support from Dexcom, Zucara Therapeutics, Enable Bioscience, Eli Lilly, Cystic Fibrosis Foundation, Breakthrough T1D, and NIH. Dr. Shah reports receiving personal fees from Sanofi, Eli Lilly, NovoNordisk, Dexcom, Ascensia Diabetes Care, Insulet, Tandem Diabetes Care, Biomea Fusion, Sequel Med Tech, Genomelink, and Lumosfit for consulting, advising, or speaking, outside of this work.

Dr. Stolarczyk is a consultant advisor to Via Medica, publisher of scientific journals, including 'Clinical Diabetology'.

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Centre For Diabetes Care, Greater Noida, India

Rethinking Metabolic Health — Integrating Physical Activity and Body Composition in Diabetes Prevention and Management

The increasingly high global disease burden of type 2 diabetes (T2D) and insulin resistance (IR) compels the creation of effective strategies for prevention and management. The two studies of this issue of 'Clinical Diabetology' add thoughtful insights to the ongoing debate. Dubaj et al. [1] examine the contribution of daily step count to diabetes prevention and control, and Gołacki et al. [2] investigate the utility of bioimpedance body composition analysis in evaluating insulin resistance in women with overweight and obesity. Collectively, these articles present a strong case for a more subtle and personalized approach to metabolic health.

Small steps, big impact: physical activity and diabetes prevention

Dubaj et al. [1] describe a systematic review that shows how small daily step increases can provide significant metabolic health benefits. The research dispels the common 10,000-step daily recommendation, instead finding that an optimum of between 4500 and 9000 steps per day is needed for better glucose metabolism and T2D risk reduction. Notably, their research indicates that as few as 4000 steps a day provide tangible health benefits, highlighting the importance of setting realistic and achievable activity levels.

The molecular processes underlying these advantages are well established: enhanced insulin sensitivity, improved GLUT4 translocation, and improved lipid metabolism all serve to enhance glycemic control. Moreover, the review identifies that the mortality benefits of walking plateau after 9000 steps, further solidifying the principle that more is not always better. Clinically, this data supports a strategy of a gradual, incremental increase in daily physical activity over strict compliance with an arbitrary cutoff.

Beyond BMI: a new perspective on body composition and insulin resistance

Concurrently, Gołacki et al. [2] tackle a long-standing shortcoming in metabolic studies: the use of BMI and waist circumference (WC) as surrogates for metabolic risk. Their research assesses the utility of visceral fat rating (VFR) derived from bioimpedance body composition analysis in the prediction of insulin resistance. Although conventional markers like BMI and WC are still useful, they cannot distinguish between subcutaneous and visceral fat, the former of which is less linked to metabolic dysfunction.

The results of the study suggest that VFR can be used as a secondary biomarker for insulin resistance, especially in obese women. While bioimpedance is a cheap and non-invasive device, the study also recognizes the necessity for additional validation prior to its use in clinical settings. This study is especially well-timed, considering the increasing awareness of metabolic-associated steatotic liver disease (MASLD, previously NAFLD), a condition strongly associated

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with visceral fat deposition and insulin resistance. An improved method of body composition measurement may improve early detection and directed intervention.

Towards a more comprehensive approach to metabolic health

Taken together, these findings support the use of personalized, evidence-based methods in the management of metabolic health. Dubaj et al. offer an understandable and usable guide to physical activity enhancement, and Gołacki et al. point toward the importance of more nuanced measures of obesity. The combination of both methods — promoting sustainable movement objectives with more detailed measures of metabolic risk — has the potential to enhance diabetes prevention and treatment.

Future studies need to further tailor these strategies by examining how step count interventions may be tailored to metabolic risk profiles and whether or not bioimpedance assessments can be made more standardizable for wider clinical application. Furthermore, longitudinal trials are required to determine the long-term effects of these interventions on diabetes progression and complications.

Conclusions

The research published in this volume of 'Clinical Diabetology' joins a developing set of literature recommending a move from one-size-fits-all suggestions for the prevention and management of diabetes. Stimulating step-by-step increases in daily physical activity and using more accurate body composition measures might provide the kind of patient-specific strategies that interventions would need to effectively address. As our definition of metabolic health continues to expand, so must our clinical practices, so that interventions are not only effective but also sustainable in everyday practice.

Conflict of interest

The author declare no conflict of interest.

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RESEARCH PAPER
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Jakub Gołacki[1], Katarzyna Witczak[2], Kamil Górecki[2], Aneta Szafraniec-Porada[1], Jakub Wronecki[1], Dominik Porada[1], Beata Matyjaszek-Matuszek[1]

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Bioimpedance Body Composition Analysis in Estimating Insulin Resistance in Women with Overweight and Obesity (LUCAS 1.1): A Retrospective Analysis

ABSTRACT

Objective: Insulin resistance (IR) is a disruption in glucose homeostasis characterized by decreased tissue sensitivity to insulin. One of the main causes of IR is considered to be obesity, a significant problem in contemporary medicine. It can be diagnosed using easily measurable parameters such as body mass index (BMI), waist circumference (WC), or waist-to-hip ratio (WHR). In this study, we aimed to compare the effectiveness of conventional obesity markers with parameters obtained from bioimpedance body composition analysis in assessing the severity of insulin resistance in individuals with overweight and obesity

Materials and methods: A retrospective analysis of 702 patients, including 557 women (79%) with overweight and obesity, was conducted, focusing on metrics like BMI, WC, visceral fat rating (VFR), and indirect indicators of insulin resistance: Quantitative Insulin Sensitivity Check Index (QUICKI), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and triglyceride to high-density lipoprotein ratio (TG/HDL ratio).

Results: Due to significant differences in body composition, men and women were analyzed separately. Because of the high number of male patients with insulin resistance, only the female group was analyzed. Both BMI and WC had a greater AUC than VFR. Analyzing the Youden graph, a cutoff point value for VFR, suggested to be 16% body fat (PBF), showed limited predictive value.

Conclusions: The VFR could serve as a valuable additional biomarker in assessing insulin resistance in female patients with obesity. (Clin Diabetol 2025; 14, 1: 5–11)

Keywords: obesity; visceral fat rating; insulin resistance; bioimpedance; body composition

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Introduction

Obesity has become an increasingly significant health problem worldwide. According to the World Health Organization (WHO), in 2016 1.9 billion adults aged 18 years and older were overweight, with 650 million of them classified as persons with obesity [1]. The statistics mentioned above clearly indicate the need to raise public awareness about obesity, its consequences,

early detection, and the search for newer therapeutic methods. One method for detecting and monitoring this condition is utilization of the body mass index (BMI) indicator. Calculating this indicator requires easily measurable parameters: height in centimeters and weight in kilograms. Unfortunately, it does not take into account the distribution of body fat, which can lead to inaccurate results. Subcutaneous fat tissue, despite representing the highest percentage of mass and surface area of all fat tissue in the body, is not as metabolically active as visceral fat tissue. Excessive accumulation of visceral fat is associated with numerous cardiometabolic complications. Therefore, it is crucial to use methods in measurements that allow for differentiation between them [2, 3].

The amount of visceral fat tissue can be estimated using densitometry (DXA), computed tomography (CT), or magnetic resonance imaging (MRI). However, these methods are expensive, less accessible, or require radiation exposure, prohibiting their wide in clinical practice [4]. Due to the significant diagnostic and prognostic benefits of assessing visceral fat tissue, it is necessary to find another indicator that is easily accessible, cost-effective, and does not expose the patient to additional radiation. Promisingly, the use of the bioimpedance method appears to be suitable for this purpose [5]. This method is based on measuring the body's electrical response after introducing a low-level alternating current, allowing for the estimation of body composition [5]. Visceral obesity leads to insulin resistance (IR), characterized by decreased sensitivity of cells to insulin despite its elevated levels in the bloodstream [6]. The Lublin Comorbidity of Adiposity Study (LUCAS) is a project initiated by the Department of Endocrinology, Diabetology, and Metabolic Diseases at the Medical University of Lublin. Its aim is to determine the correlations between anthropometric parameters and various metabolic disorders as well as other consequences of obesity in a large population sample. The aim of this study, which is a part of this project, was to investigate the correlation between visceral obesity measured using bioimpedance and elevated IR indices.

Materials and methods

Study design and patients

This cross-sectional study was carried out at the Department of Endocrinology, Diabetology, and Metabolic Diseases at Independent Public Clinical Hospital No. 4 in Lublin, Poland. The study involved 702 patients with overweight or obesity, with an average age of 44.1 ± 13.8 years, including 557 women (79%). A retrospective analysis of data from medical records was conducted, with a particular focus on anthropometric data, such as age, gender, BMI, waist circumference (WC), waist to height ratio (WHtR), results of body composition analysis using the bioimpedance method (percent body fat (PBF), visceral fat rating (VFR)], and indirect indicators of insulin resistance: Quantitative Insulin Sensitivity Check Index (QUICKI), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and triglyceride to high-density lipoprotein ratio (TG/HDL ratio). This article is a part of the LUCAS series, with the main question being asked: is the visceral fat rating better than body mass index in predicting insulin resistance in patients with overweight and obesity?

Body composition measurement

Body weight was measured with an accuracy of 0.1 kg, along with body composition, using direct electrical bioimpedance. A Tanita Corporation Body Composition Analyzer DC-430MA device was used for this purpose. The device uses 4 integrated electrodes within the platform. This method is based on the introduction of low-level alternating current into the body at 2 frequencies: 6.25 kHz and 50 kHz. As a result of this measurement, the following data can be obtained: body weight in kg ± 0.1 kg, BMI, PBF (with an accuracy of ± 0.1%), and VFR.

Indices

One of the indicators used to assess abdominal obesity is waist circumference (WC). To measure it correctly, it is recommended that a measuring tape be placed at the midpoint between the hip bone and the lower margin of the last rib. The measurement should be taken with the patient standing, after soft expiration, with both feet touching the ground and arms hanging freely. The measuring tape should be positioned perpendicular to the body's long axis, horizontally to the floor, with appropriate tension, but without exerting pressure on the abdominal wall [7].

In the study, commonly used indices were utilized, such as HOMA-IR, QUICKI, and the TG/HDL ratio. HOMA-IR is a widely used index for detecting and assessing central insulin resistance dynamics, calculated by multiplying fasting blood glucose levels (mmol/L) by fasting insulin levels (μU/mL), and then dividing the result by 22.5 [8, 9]. QUICKI is calculated using the following formula: $QUICKI = 1/[\log(I) + \log(G_0)]$, where I_0 represents fasting insulin (μU/mL) and G_0 is fasting glucose (mg/dL) [9]. The triglyceride to HDL cholesterol ratio is a commonly used indicator for assessing cardiovascular risk and inflammatory status in the body. Calculating this ratio requires determining the lipid profile of the patient and calculating the TG/HDL ratio.

Table 1. Baseline Characteristics of the Patients

Variable	Female	Male	P-value
Age [years]	43.71 ± 13.63	45.52 ± 14.29	0.160647
Body weight [kg]	99.33 ± 17.75	119.38 ± 22.78	0.000000
BMI [kg/m^2]	36.66 ± 5.95	37.68 ± 6.58	0.000000
Waist circumference [cm]	109.51 ± 12.85	124.25 ± 15.22	0.000000
Visceral fat rating	10.71 ± 3.41	19.1 ± 5.27	0.000012
Percent body fat [%]	42.5 ± 5.58	36.3 ± 18.81	0.077400
Systolic blood pressure [mmHg]	132.39 ± 16.33	138.64 ± 14.41	0.002340
Diastolic blood pressure [mmHg]	86.68 ± 10.46	87.7 ± 9.34	0.434855
HOMA-IR index	3.46 ± 2.24	4.69 ± 2.82	0.000002
QUICKI index	0.33 ± 0.03	0.31 ± 0.03	0.000002
TG/HDL ratio	2.69 ± 1.65	4.54 ± 5.93	0.000000

BMI — body mass index; HOMA-IR — Homeostatic Model Assessment of Insulin Resistance; QUICKI — Quantitative Insulin Sensitivity Check Index; TG/HDL — triglyceride to high-density lipoprotein ratio

Ethics approval

This study did not require approval from the Ethics Committee because it was based solely on anonymized and non-identifiable data routinely gathered at our department.

Statistical analysis

Statistical analysis was performed using Statistica software, applying receiver operating characteristic (ROC) curve analysis to assess the diagnostic performance of different anthropometric and body composition indicators (BMI, WC, PBF, VFR) in predicting insulin resistance. For this purpose, 3 insulin resistance indices were used: HOMA-IR, QUICKI, and the TG/HDL ratio.

We utilized the Youden index and tangential method to determine the optimal cutoff points for each indicator. The area under the curve (AUC) was calculated to compare the effectiveness of these indicators in identifying insulin resistance across different patient groups (separated by gender), providing a measure of overall diagnostic accuracy. A higher AUC indicates a better discriminatory ability of the test or indicator in question. The Youden index was specifically used to identify the optimal cutoff value for visceral fat rating (VFR) in diagnosing insulin resistance. The Youden index is calculated using the following formula: J = Sensitivity (S) + Specificity (T) – 1, where sensitivity represents the ability of the test to correctly identify patients with insulin resistance (true positives), and specificity represents its ability to correctly identify patients without insulin resistance (true negatives). The Youden index ranges from 0 to 1, with values closer to 1 indicating a more effective test. The point at which the Youden index is maximized is considered the optimal cutoff, as it balances sensitivity and specificity.

In our analysis, we used the Youden index to find the most appropriate cutoff for VFR, which maximized the ability of VFR to differentiate between patients with and without insulin resistance. The index allows us to pinpoint the VFR value where the test's diagnostic performance is highest.

Results

In the analyzed group, women constituted a larger proportion (557, 79.34%) compared to men (145, 20.66%). Due to significant differences in average body composition, the groups were analyzed separately. Regarding sex, age, body weight, BMI, and WC, males exhibited a higher average body weight of 119.38 kg and WC of 124.25 cm. Females displayed lower average values in body weight (99.33 kg) and WC (109.51 cm). There were no significant differences observed in age and BMI between the genders.

Focusing on VFR and PBF, the mean VFR was significantly higher in men (19.1) compared to women (10.71), with a p-value approaching zero. Women had higher average PBF (42.50%). In terms of blood pressure, men showed elevated systolic blood pressure (mean: 138.64 mmHg), whereas women had an average systolic blood pressure of 132.39 mmHg. There were no significant differences in diastolic blood pressure.

Lastly, metabolic indicators revealed more pronounced dysfunction in men, evidenced by a higher average HOMA-IR of 4.69 and a TG/HDL ratio of 4.54. Women showed a more favorable profile, with an average HOMA-IR of 3.46 and a TG/HDL ratio of 2.69. Differences in QUICKI were also significant, indicating lower insulin sensitivity in men (mean QUICKI: 0.31) than in women (mean QUICKI: 0.33), with a p-value less than 0.00001. The results are gathered in Table 1.

Table 2. Percentage of Patients with Insulin Resistance

Variable	Female	Male
HOMA-IR > 2.5	59.01%	80.95%
QUICK-I > 0.34	70.56%	88.57%
TG/HDL > 2	58.98%	81.25%

HOMA-IR — Homeostatic Model Assessment of Insulin Resistance; QUICKI — Quantitative Insulin Sensitivity Check Index; TG/HDL — triglyceride to high-density lipoprotein ratio

Additionally, there was a higher percentage of insulin resistance in the population of males regarding all 3 insulin sensitivity indices, as shown in Table 2 (the difference between sexes was statistically significant, with $p < 0.001$).

Similar ROC curves were observed for BMI, WC, and VFR when using commonly accepted cutoff points for HOMA-IR (2.5), QUICKI (0.34), and TG/HDL ratio (2). Because of important statistical differences between genders regarding most of the analyzed statistics, they were calculated separately. In both genders, the highest AUC was observed regarding BMI, and WC regarding both HOMA-IR and QUICKI. The AUC for VFR was lower than both BMI and WC, and the difference was statistically significant ($p < 0.001$). The results are gathered in Table 3.

When analyzing VFR in the population, there were no males below rating 11. Additionally, because of the large percentage of male patients with insulin resistance in the studied group, only females were analyzed. The proposed cutoff value for VFR in the studied population, based on the Youden index, was 16, with a possible secondary value of 14, which had better sensitivity and reduced specificity (Fig. 1).

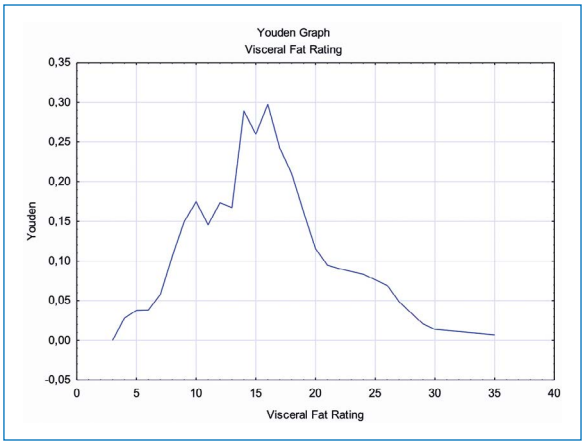

Figure 1. Youden Graph for Visceral Fat Rating (VFR) Predicting Insulin Resistance in Women

Discussion

In our study, patients with obesity underwent analysis using bioimpedance, and their results were compared with commonly used indicators in obesity diagnosis to assess the severity of IR.

In this study, we tried to determine whether the VFR is a valuable tool in predicting IR in comparison to traditional metrics like BMI and WC. Although the Youden index for VFR at a cutoff point of 16 was below 0.3, this should not immediately discount its clinical value. The VFR provides unique insights into visceral adiposity, a key factor in metabolic dysfunction and IR, which BMI and WC might not fully capture. Visceral fat is closely linked to metabolic risk, and the fact that VFR directly measures this parameter adds value, particularly in the context of obesity, where subcutaneous and visceral fat often present different metabolic risks. The relatively low Youden index suggests some limitations to the overall sensitivity and specificity of VFR for diagnosing insulin resistance compared to other measures, but this does not negate its utility. For example, VFR may offer additional value when used in conjunction with other indicators.

Table 3. AUC between Methods Detecting Obesity in Relation to Insulin Resistance Indices

	Male			Female		
	HOMA-IR	QUICK-I	TG/HDL	HOMA-IR	QUICK-I	TG/HDL
BMI	0.819	0.808	0.611	0.663	0.663	0.596
WC	0.871	0.879	0.644	0.65	0.657	0.596
VFR	0.674	0.7	0.647	0.562	0.572	0.598
PBF	0.684	0.679	0.597	0.552	0.588	0.592
Body weight	0.796	0.858	0.573	0.631	0.63	0.594

AUC — area under curve; BMI — body mass index; HOMA-IR — Homeostatic Model Assessment of Insulin Resistance; QUICKI — Quantitative Insulin Sensitivity Check Index; PBF — percentage body fat; TG/HDL — triglyceride to high-density lipoprotein ratio; VFR — visceral fat ratio; WC — waist circumference

While BMI and WC are well-established predictors of IR with higher AUC values, they do not specifically reflect visceral fat, which plays a critical role in the pathophysiology of IR and cardiovascular disease. Moreover, in clinical practice, the combination of VFR with BMI or WC could potentially enhance diagnostic accuracy, especially in patients with obesity, where the distinction between visceral and subcutaneous fat is crucial. Given that VFR was developed to assess visceral fat, its use alongside other indicators might improve the early detection of insulin resistance in certain populations, particularly those with abdominal obesity.

Using BMI as a widely accepted indicator in obesity diagnosis has many limitations. Cutoff points for this indicator do not account for differences in fat tissue distribution between genders or ethnic origins [10]. Another reason to seek alternative diagnostic methods is the inability to differentiate between total mass and muscle mass, rendering BMI unreliable, especially among athletes. It is also crucial to use a method capable of determining the amount of fat tissue in the body; however, the quantity of fat tissue alone is not a useful indicator due to numerous limitations. Samuel Klein et al. demonstrated in their study that patients undergoing liposuction, despite reducing the percentage of body fat tissue, do not experience improvements in obesity-related metabolic disorders, nor does their risk of coronary heart disease decrease, because only the amount of subcutaneous fat tissue is reduced [11].

In one cross-sectional study involving 418,343 workers in Spain, the glucose triglyceride index (TyG Index) was utilized and compared with BMI, WHtR, and WC. Statistical analysis showed that WC plays a key role in early detection of metabolic syndrome and identification of insulin resistance [12]. However, other researchers suggest that the correlation between TyG and BMI more accurately detects insulin resistance than the previously mentioned indicator [13]. WC is also significant among individuals with normal BMI because the TG concentration and WC were found to have the greatest diagnostic value in detecting insulin resistance in participants without obesity [14]. Additionally, increased TG and WC values affect the impairment of pancreatic beta cell function [14]. WC is not an ideal indicator, however, because it does not account for height — its diagnostic utility is limited among tall and short individuals [13, 15]. Considering this, a new method has been proposed based on the ratio of waist circumference to patient height, allowing for standardization and objectivity with respect to height. One of the advantages of WHtR is better prediction of dyslipidemia, hypertension, and metabolic syndrome compared to WC or BMI [16]. Additionally, both WHtR and WC show better detection of insulin resistance than newly emerged obesity indicators such as body adiposity index (BAI) or body roundness index (BRI) [17]. Jamar et al. demonstrated in their studies that among the mentioned indices, WHtR has the highest predictive value [18].

The reason we seek a better, more accurate indicator is the need to differentiate between types of adipose tissue and establish norms based on gender, age, and ethnic origin. Visceral fat tissue, besides its storage function, also acts as an active endocrine organ, producing and secreting numerous adipokines and cytokines. They play a crucial role in regulating cellular responses to insulin and controlling inflammatory processes. Disturbance in the balance of these substances in favor of resistin leads to decreased insulin sensitivity and increased production of pro-inflammatory cytokines. This association affects lipoprotein lipase (LPL), responsible for lipid metabolism, leading to their excessive accumulation. This effect manifests as atherogenic dyslipidemia, characterized by elevated levels of triglycerides and low-density lipoproteins (LDL), and decreased levels of HDL, resulting from increased free fatty acid (FFA) levels [19–21].

There is increasing discussion about metabolic-associated steatotic liver disease (MASLD) (formerly known as nonalcoholic fatty liver disease, NAFLD) associated with metabolic dysfunction and insulin resistance – a state in which the release of FFAs from adipocytes increases, making them less responsive to insulin. Excess FFA is deposited as fat in the visceral area, contributing to the development of MASLD. MASLD occurs when at least 5% of hepatocytes undergo steatosis, and one of the consequences is insulin resistance [22, 23].

Several authors have suggested a positive correlation between IR and VFR in the past. Researchers suggest that regardless of gender, individuals with insulin resistance exhibit higher parameters assessing visceral fat amount compared to those without insulin resistance, indicating a positive correlation between these two indicators [21, 24]. Similar results were also obtained in a group of patients with polycystic ovary syndrome, showing a strong correlation with the presence of visceral fat tissue and the occurrence of insulin resistance in patients [25]. Zhang et al. demonstrated a positive correlation between insulin resistance and fat tissue in various body parts in their meta-analysis, with the strongest correlation observed for visceral fat tissue [26].

The examples above illustrate how much information about health status can be provided by knowledge of visceral fat tissue quantity. Therefore, finding an

indicator that enables easy, widely accessible, and non-invasive measurement of visceral fat tissue is recommended. Among the indicators considered in the study, promising results were obtained using the bioimpedance method. This method has many advantages — it is inexpensive, simple to conduct, and relatively safe, though individuals with implanted pacemakers or metal implants, pregnant women, and patients with electrolyte disturbances should not undergo the examination. It does not expose the patient to additional radiation like CT and DXA scans, or the costs associated with MRI. Despite its many advantages, bioimpedance is not without flaws. In patients with electrolyte disturbances, very high BMI, or obesity, there are limitations in using this method due to the lack of measurement repeatability. Taking into account the above reasons, bioimpedance has great potential as an indicator for detecting insulin resistance; however, standardization of this method is needed to enable comparison of results obtained in different locations and greater measurement repeatability.

The male population in our study presented a higher percentage of patients with insulin resistance compared to the female group, which is why statistical differences were notable between the genders. The differences in results between the genders can be explained by several factors. Premenopausal women tend to accumulate subcutaneous fat in the buttock and thigh areas, known as gynoid obesity. In contrast, men tend to accumulate visceral fat in the abdominal region, known as android obesity [27]. Abdominal visceral fat is strongly associated with insulin resistance, unlike subcutaneous fat [27]. Another reason is that men are diagnosed later and are less willing to undergo obesity treatment compared to women [28]. These 2 factors result in a more advanced stage of the disease among men, leading to higher mortality and a lower percentage of successfully treated patients [28].

Despite these observations, men were excluded from further analysis primarily due to the significant imbalance in sample sizes. Men made up only 21% of the cohort. This distinction limits the statistical power and reliability of conclusions drawn for the male subgroup. Furthermore, the pronounced differences in visceral fat accumulation between men and women meant that analyzing the groups together would risk confusing the results, given that visceral fat has a clear impact on insulin resistance.

Conclusions

In conclusion, our findings revealed that VFR may serve as a valuable additional biomarker in assessing insulin resistance in female patients with obesity. However, further research in this area is recommended, focusing on a larger patient group with particular emphasis on the male gender.

Limitations

We conducted a retrospective study that was susceptible to selection bias. Additionally, limitations include a relatively small sample size, comprised entirely of white patients from Poland, predominantly from the Lublin Region. Body composition analysis using bioimpedance was performed using a two-electrode analyzer, and relied on the VFR index, which currently lacks full medical validation. The insulin resistance indices are estimations because the metabolic clamp method was not employed.

Article information

Authors' contributions

Conceptualization, J.G.; validation, D.P., A.Sz.-P.; formal analysis, J.W.; investigation, J.G., K.W., K.G.; writing — original draft preparation, K.W., K.G.; writing — review and editing, J.G., K.W., K.G.; visualization, J.W.; supervision, B.M.-M. All authors reviewed and edited the manuscript and approved for the submission.

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Conflict of interest

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Management Perspectives in Hyperglycemia in Type 1 Diabetes During Pregnancy: Insights from Indian Healthcare Providers

ABSTRACT

Objective: This study aims to explore the perspectives, practices, and challenges faced by healthcare professionals (HCPs) in India in managing type 1 diabetes (T1D) during pregnancy, focusing on preconception care, glucose control, and adherence to clinical guidelines.

Materials and methods: To collect anonymous data, a Google form was circulated among health care professionals managing diabetes, from December 2023 to February 2024. A handful of questions were enlisted regarding the nature of care and treatment provided by the HCP during the pregnancy in T1D, and the results were analyzed accordingly.

Results: A total of 543 HCPs, comprising of diabetologist, primary care physicians, gynecologists, and endocrinologists, filled out the questionnaire. Among all HCPs, diabetologists (33.03%) comprised the largest group. The responses underscore the importance of tight glucose control before pregnancy, with the majority recommending a glycated hemoglobin (HbA1c) range of < 6.5% to minimize risks during pregnancy. The dataset reflects adherence to various guidelines, including the Research Society for the Study of Diabetes in India (RSSDI) 31.55%, the International Society for Pediatric and Adolescent Diabetes (ISPAD) 33.95%, and the American Diabetes Association (ADA) 34.50%, indicating a diverse yet standardized approach to managing T1D in pregnancy. A significant majority offer preconception counselling services, underlining the critical role of early intervention and planning in the management of T1D pregnancies.

Conclusions: The dataset highlights the importance of preconception counselling, patient education, and personalized care for pregnant woman with T1D. Promoting adherence to unified guidelines can help reduce care disparities and ensure better outcomes. (Clin Diabetol 2025; 14, 1: 12–17)

Keywords: T1D, diabetes in pregnancy, Indian healthcare, glycemic control

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Introduction

Globally, the prevalence of type 1 diabetes (T1D) is estimated at 9.5 million cases as of 2021, with incidence rates varying significantly across regions. While precise data are limited in India, studies suggest a prevalence of approximately 0.3 per 1000 population, translating to over 800,000 individuals living with T1D [1]. India is also known as the diabetes capital of the world, with the highest rate of diabetes cases worldwide. 31.7 million people in India were estimated to have diabetes in 2000; by 2030, that number is expected to increase to 79.4 million [2]. Among the different forms of diabetes, T1D poses a substantial clinical problem. The autoimmune reaction that causes T1D leads to the destruction of the pancreatic -cells responsible for making insulin; hence, achieving euglycemia requires lifelong insulin replacement treatment. Globally, T1D usually manifests at an earlier age, and it affects women with T1D more severely when they are fertile. Every year, T1D complicates between 0.2% and 0.5% of births in the US [3].

T1D poses significant risks during pregnancy, requiring specialized care to optimize both maternal and fetal outcomes. Women with T1D face increased risks of serious pregnancy complications like pre-eclampsia, a serious pregnancy complication characterized by high blood pressure and signs of damage to other organ systems; higher glucose levels also lead to excessive fetal growth (macrosomia), increasing the chances of cesarean delivery or birth trauma, which can result in preterm delivery. Women with T1D are also at risk of stillbirth, congenital abnormalities, and neonatal morbidity [4, 5]. Out of the 131.4 million live births among women aged 20 to 49 years worldwide, 21.3 million (16.2%) are affected by hyperglycemia during pregnancy, and 6.2% of these people have a history of diabetes, including T1D [1].

Pregnancy-related T1D management requires particular care to optimize outcomes for both the mother and the fetus. Effective management requires multidisciplinary care, which includes personalized insulin therapy, continuous glucose monitoring, and preconception counselling. Achieving optimal glycemic control is essential to significantly reduce the probability of adverse outcomes. It has been shown that lowering the HbA1c level before conception lowers the chance of congenital malformations and other complications [6, 7].

There are many different ways to manage T1D during pregnancy due to India's diverse healthcare system and easy access to specialized care. Although endocrinologists, diabetologists, and gynecologists treat most T1D pregnancies in urban regions, primary care physician often manage these patients. The lack of uniform reference systems and multidisciplinary teams places the responsibility for patient care on individual clinicians, leading to a variety of practices and outcomes [8].

Strict glycemic management during pregnancy has become easier to maintain thanks to technological advancements like insulin pumps and continuous glucose monitoring (CGMs). Together with comprehensive patient education and support, these strategies are critical for treating the problems associated with gestational T1D [9]. However, there are disparities in care that are exacerbated by the uneven availability of this technology across India.

The survey seeks to address gaps in the consistency of care provided by different health care professionals (HCP), highlighting disparities that could be reduced through standardized practices to improve outcomes in women and their newborns.

Materials and methods

Study design and population

The online observational survey was conducted from December 2023 to February 2024 and included diabetologists (33%), endocrinologists (28%), primary care physicians (29%), and gynecologists (10%).

Questionnaire development

The survey was developed by collective input from the authors, and the questionnaires were evaluated by senior team members. The questions focused on several key areas, such as preconception care, glycemic management, follow-up practices, adherence to guidelines, patient education, and challenges and barriers. These questions were developed based on existing guidelines from the International Society for Pediatric and Adolescent Diabetes (ISPAD), the American Diabetes Association (ADA), and the Research Society for the Study of Diabetes in India (RSSDI), to ensure the relevance and accuracy of the data collected. The closed-ended questionnaire had multiple-choice and yes/no questions. For example, one question asked about the preconception HbA1c of pregnant women with T1D and provided options of < 6.6%, 6.6–7.5%, or 7.6–8.5%. Another question asked whether the HCPs provided preconception counselling to T1D females at their center. This ensured that the questionnaire covered the most relevant and pressing issues in managing T1D during pregnancy.

Data collection and analysis

The survey was distributed digitally through professional networks, email lists, and social media platforms specifically aimed at healthcare professionals responsible for diabetes management in India. The Google Forms platform provided convenient accessibility and

Table 1. Responses Recorded from the Healthcare Providers on the Management of T1D with Pregnancy

Questionnaire	Percentage (%)
HbA1c (before pregnancy)	
< 6.6	50
6.6–7.5	30
7.5–8.5	20
Guideline followed	
ADA	34.5
ISPAD	33.9
RSSDI	31.5
Preconception counselling	
Yes	80
No	20
Counselling provided by	
Endocrinologists, gynecologists, and diabetologists	40.1
Self	40.2
Primary care physicians	19.3
Appointment scheduled on	
Phone	59.7
Social media	40.2
Follow-up	
Weekly	29.8
Fortnight	30
Monthly	40
Diet plan given	
Yes	59.9
No	40
Carb counting session	
Yes	70
No	30
Prescribed with	
Any form of exercise	25
Healthy eating	24.7
Yoga	25.4
Regular check-ups	24.7

ADA — American Diabetes Association; HbA1c — glycated hemoglobin; ISPAD — International Society for Pediatric and Adolescent Diabetes; RSSDI — Research Society for the Study of Diabetes in India; T1D — type 1 diabetes

facilitated the collection of responses while maintaining anonymity. The participants were provided with information regarding the objective of the study and were guaranteed confidentiality. Completion of the survey implied consent.

The data collected from Google Forms was transferred to Microsoft Excel for the purpose of data cleansing and first analysis. Descriptive statistics were employed to provide a summary of the responses, which included frequency distributions and percentages for categorical variables.

Ethical considerations

The survey was done following ethical guidelines for research involving human participants. While official ethical approval was not necessary because of the anonymous and voluntary nature of the survey, participants were informed about the study's goals, and their agreement was indicated by their decision to participate. No personally identifiable information was gathered.

Limitations

The study's utilization of self-reported data may introduce bias because participants' responses could be impacted by their personal viewpoints and experiences. Furthermore, the convenience sampling strategy may not accurately depict the overall population of HCP managing T1D during pregnancy in India. The sample size, although substantial, may not fully represent rural healthcare providers where access to advanced technologies might be limited.

Results

A total of 543 HCPs participated in the survey, offering valuable insights into the management of T1D during pregnancy. The baseline characteristics reveal that most of the respondents were diabetologists, followed by primary care physicians and gynecologists, each with varying levels of experience (Tab. 1). The dataset reflects a broad range of specialties involved in T1D care, including a significant representation from diabetologists, highlighting their expertise in diabetes management. Primary care physicians also play a critical role, focusing on general health, while gynecologists emphasize their involvement in managing T1D during pregnancy, specifically addressing pregnancy and childbirth concerns. Collaborative efforts between primary care physician and diabetologists were also evident in providing comprehensive care for these patients.

The dataset showcases a wide range of experience levels, with practitioners spanning from 0–3 years to more than 30 years of practice. This diverse experience base ensures a well-rounded perspective on treatment approaches, with a slight emphasis on more experienced practitioners, indicating a depth of knowledge essential for managing the complexities of T1D in pregnancy. Regarding pre-pregnancy care, most of the respondents recommended an HbA1c level of < 6.5% prior to pregnancy, underscoring the critical need for tight glucose control to minimize risks and improve pregnancy outcomes.

In terms of clinical practices, respondents adhered to a variety of guidelines, such as RSSDI, ISPAD, and ADA, reflecting a standardized approach to managing T1D during pregnancy, with an even distribution of adherence to these professional standards. A significant majority of the respondents provided preconception counselling, emphasizing the importance of early intervention and careful planning before pregnancy. The survey also highlighted that medical professionals were the primary providers of this counselling, reinforcing their direct involvement in preparing patients for pregnancy.

The modes of appointment scheduling varied, incorporating both traditional and digital channels, reflecting the growing trend of integrating technology into healthcare practices. Follow-up frequencies ranged from weekly to monthly, indicating tailored approaches to monitoring patients based on individual needs. This variety also underscores the need for regular monitoring throughout pregnancy to manage T1D effectively.

Education about carb ratios and correction factors was prevalent, with most practitioners offering this as part of their patient care, which reflects the importance of patient self-management. Furthermore, individualized diet plans were commonly provided, underscoring the personalized approach to nutritional management for T1D patients during pregnancy. A wide range of lifestyle changes, such as pregnancy yoga, exercise, healthy eating, and regular check-ups, were recommended, demonstrating a holistic approach to supporting the health of pregnant individuals with T1D.

In summary, the survey sheds light on the diverse practices and preferences of clinicians treating T1D during pregnancy, highlighting the importance of a multidisciplinary approach that involves endocrinology, internal medicine, and gynecology. The findings suggest that managing T1D in pregnancy can be done in a thorough, individualized manner, with a strong focus on education, preconception counselling, and personalized treatment plans. Additionally, the use of technology in scheduling appointments reflects modern patient engagement practices, further enhancing the quality of care.

Discussion

The dataset provides a complete perspective on the medical specializations that are engaged in the management of T1D during pregnancy. The prevalence of diabetologists in the dataset highlights their crucial role in delivering specialist care for T1D, especially during the critical period of pregnancy. The inclusion of primary care physicians and gynecologists signifies a comprehensive approach to healthcare, guaranteeing that all facets of the patient's welfare are attended to. The cooperative partnership between primary care physicians and diabetologists demonstrates a shift towards interdisciplinary treatment, which is crucial for effective management of intricate cases of T1D during pregnancy [10, 11].

The survey results indicate that a higher proportion of females diagnosed with T1D receive treatment from diabetologists and primary care physicians, ranking second in terms of medical care providers. This study survey was conducted by metropolitan primary care physicians with extensive knowledge of the most recent guidelines due to their strong connections. However, it is important to note that the situation may vary in rural areas. The study revealed that over 70% of the HCPs had less than 20 years of experience, with a higher participation rate from younger, technologically adept professionals. The data about years of practice indicate a wide variety of experience among the practitioners, with a substantial number of individuals having more than 10 years of experience. This suggests that experienced professionals have a considerable impact in this field.

More than 50% of HCPs selected an HbA1C target of less than 6.5% for preconception [12, 13]. This indicates that a significant number of participating clinicians possess up-to-date knowledge. The dataset suggests that patients with T1D can expect to receive care from a well-rounded team of healthcare providers, with a collaborative approach to holistic care. This variety in specialties and levels of experience is likely to enhance the overall management of T1D during pregnancy, making it more comprehensive and effective.

The survey emphasizes the need for preconception counselling and demonstrates a proactive approach to managing T1D, where taking action early on is crucial [14]. The allocation of counselling duties demonstrates an equitable strategy, with a virtually equal proportion of primary care physicians engaging in self-counselling and seeking guidance from their colleagues, highlighting the significance of individualized care.

Appointment scheduling modes exhibit a combination of conventional and digital approaches, with phone calls being the most common, although a significant proportion also employ social media. This demonstrates the adjustment of healthcare services to contemporary communication methods. The diverse frequencies of follow-up indicate that the care provided is tailored to the individual needs of each patient, with check-ins occurring on a weekly to monthly basis.

Emphasizing the importance of patient education is crucial for successful self-management of T1D, particularly when teaching about carb ratios and correction variables. The inclination towards expert nutritional guidance is reinforced by the fact that the majority of HCPs offer tailored diet plans.

Ultimately, the suggested lifestyle modifications, including engaging in pregnancy yoga, maintaining a balanced diet, and attending frequent check-ups, propose a comprehensive strategy for treating T1D during pregnancy. The holistic approach that encompasses all facets of a patient's life, with the goal of achieving the best possible health results, is seen in the allocation of reactions to different types of exercises and lifestyle modifications.

The study has several strengths, including a large sample size of 543 HCPs, ensuring broad representation and reliable findings. The inclusion of diverse participants, such as diabetologists, endocrinologists, primary care physicians, and gynecologists, provides a comprehensive view of T1D management during pregnancy. The study also focuses on key aspects of care, such as preconception counselling, glucose control, and patient education, while integrating modern practices like digital scheduling. It highlights varying adherence to global clinical guidelines, emphasizing the need for standardized practices. Additionally, the study advocates for a holistic, patient-centered approach, incorporating lifestyle modifications.

However, there are some weaknesses. The reliance on self-reported data may introduce biases, and the sampling method, based on digital distribution, could over represent urban healthcare providers, limiting the inclusion of rural perspectives. The survey's digital nature also means it may not fully capture the challenges faced in rural areas with limited access to technology. Furthermore, the study has certain limitations and does not explore into specific challenges that HCPs face, such as resource constraints or patient adherence issues. The cross-sectional design limits the ability to track trends or causal relationships, and there are no direct data on patient outcomes.

In conclusion, when managing T1D during pregnancy, a multidisciplinary, collaborative approach is essential for improving outcomes. Strengthening preconception counselling, promoting tight glycemic control, and increasing access to technology, especially in rural areas, can significantly enhance care. Standardizing care practices and continuing patient education will help bridge gaps in treatment and ensure more consistent, effective management across diverse healthcare settings.

Article information

Data availability statement

The data associated with this paper are available on special requests.

Author contribution

HS, MG conceptualized the research idea and prepared the Google Forms. All co-authors contributed to data collection. The original draft was written by HS, MG, MS, and RG. AD and MS contributed to the data analysis. The draft was edited by MS and HS. All senior co-authors, BS, AS, and RS reviewed the work.

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Glycemic Variability as an Independent Predictor of 30-Day Mortality in Type 2 Diabetes Individuals with Sepsis in the Intensive Care Unit

ABSTRACT

Objective: Diabetes individuals are more likely to develop dysglycemia in 72 hours after intensive care admission and are associated with mortality. This retrospective study aimed to determine the role of glycemic variability (GV) in mortality in individuals with type 2 diabetes (T2D) with sepsis in the intensive care unit (ICU).

Materials and methods: Adult individuals diagnosed with sepsis or septic shock and T2D who were admitted to the ICU between January 2022 and June 2024 were include in the study. The GV parameters of mean amplitude of glucose excursion (MAGE) and the glucose coefficient of variation (GluCV) were used to determined survival at 30 days and length of stay (LoS). Acute Physiology and Chronic Health Evaluation-IV (APACHE-IV) and the Sequential Organ Failure Assessment (SOFA) score were used for comparison with the GV parameters for the survival outcome.

Results: A total 233 individuals were included for final analysis, divided into high GV (39.48%) and low GV (60.52%) based on a cut-off MAGE of 65 mg/dL. The low-GV group had a significantly lower mortality rate (1.4% vs. 97.8%, p = 0.000). The was no significant difference in LoS using MAGE (p = 0.14), but the difference became significant using GluCV < 25% (p = 0.029). Multivariate analysis with linear logistic regression showed that APACHE-IV, SOFA, hypoglycemic episode, MAGE, and GluCV were independently associated with survival at 30 days. Survival analysis showed a significant difference in the estimated survival time for patients with low MAGE (29.65 vs. 4.24 days, p = 0.000).

Conclusions: High glycemic variability was observed in 39% of individuals; it was associated with higher mortality in diabetic individuals with sepsis and was independently associated with high 30-day mortality. (Clin Diabetol 2025; 14, 1: 18–25)

Keywords: diabetes mellitus, sepsis, glycemic variability, APACHE-IV, SOFA

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Introduction

Sepsis is prevalent among critically ill individuals and results from a dysregulated immune response to infections and organ damage. This encompasses exaggerated

inflammatory, immunosuppressive, vascular leakage, and coagulative processes [1, 2]. Moreover, the incidence of sepsis remains high in high-risk individuals, such as those with diabetes mellitus (DM), cancer, the elderly, and the immunocompromised [1]. The prevalence of sepsis using the Sepsis-3 criteria is 22.4%, and it contributes to 11 million deaths annually or 20% of global deaths. The mortality remains high at 30–45% with more than one-third of individuals dying within 90 days, especially in low- and middle-income countries [2–4]. Respiratory, intra-abdominal, and urinary infections with gram-negative bacteria predominate in the etiology of sepsis [4].

Glucometabolic disorders are highly prevalent in critically ill individuals and adversely affect their prognosis. The activation of stress induces hyperglycemia and increases glycemic variability (GV). Although acute GV is closely associated with endothelial cell damage and leads to endothelial dysfunction [5], Magee et al. found that early fluctuation of blood glucose increased 30-day mortality and all-cause hospital mortality in sepsis individuals [6]. Lu et al. also stated that GV level during intensive care unit (ICU) hospitalization is relevant to septic prognosis [5]. However, there has been no standard consensus on a standard definition of glycemic variability until now. Available metrics of GV, such as coefficient variation (CV), mean amplitude of glucose excursion (MAGE), and glycemic lability index (GLI), are associated with increased mortality in sepsis, and the lower variability has a protective effect on sepsis [7, 8]. The exact targets for these parameters need to be established.

Individuals with diabetes are more likely to develop dysglycemia in 72 hours after intensive care admission. The event of hypoglycemia may be exaggerated in individuals with diabetes and is closely associated with worse outcomes and mortality [9, 10]. Moreover, the practical implication of MAGE and CV are still limited in sepsis patients in the ICU setting and need to be clarified. Therefore, we conducted a retrospective study to determine the role of glycemic variability (GV) in mortality in type 2 diabetes (T2D) individuals with sepsis in the ICU setting. We hypothesized that higher GV adversely affects the outcome in individuals with diabetes and sepsis.

Materials and methods

Subjects

Adult individuals diagnosed with sepsis or septic shock and T2D, admitted to the ICU between January 2022 and June 2024, were screened for eligibility according to the following criteria: 1) age 18–80 years; 2) quick sequential organ failure assessment (qSOFA) score ≥ 2 points within 24 h of admission; 3) history of diabetes treatment, and 4) minimum routine BG monitoring every 8 h in the ICU. The exclusion criteria were as follows: 1) discharge or death within 2 days of admission; 2) fewer than 3 records of BG per day in the ICU; 3) on high-dose corticosteroid therapy (dexamethasone > 6 mg daily or equivalent); and 4) concurrent major operative procedure, hemorrhagic stroke, tumors, pregnancy, blood diseases, and active bleeding.

Study design

This was a retrospective, exploratory study based on a review of the medical records of adult intensive care individuals at a secondary hospital (Sumber Waras Hospital, affiliated with the Faculty of Medicine, Tarumanagara University, Jakarta, Indonesia). This ICU has 7 critical beds. Individuals admitted to the ICU were treated based on the national intensive glucose regulation protocol, in which insulin is used for glucose control to maintain targets of 80–180 mg/dL (4.4–10 mmol/L). The initial dose of rapid-acting insulin drip was 0.5–1 U/h. The blood glucose (BG) target was 140–180 mg/dL with a decrement of 60 mg/dL per hour. If BG < 100 mg/dL, the insulin drip is stopped. The insulin dose reduces by 50% per hour and increases by 25% per hour if BG 100–140 mg/dL and > 180 mg/dL, respectively.

In the event of hypoglycemia, 50 mL of 25% dextrose solution (DS) was injected, followed by a 10% DS intravenous drip, and the BG was re-tested after one hour.

Data collection

Diabetes was diagnosed according to American Diabetes Association (ADA) 2023 [11]. Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction was defined as an increase in the quick Sequential (sepsis-related) Organ Failure Assessment (qSOFA) score by ≥ 2 points. Septic shock is a type of sepsis characterized by profound circulatory, cellular, and metabolic abnormalities associated with a greater risk of mortality than sepsis alone [12]. We quantify the sepsis-related critical score: APACHE-IV score (with online calculator: https://intensivecarenetwork.com/Calculators/Files/Apache4.html) and SOFA score.

The minimum routine BG level was measured applied every 8 h, depending on the individual's condition. All patients underwent 3 or more measurements on recording days. We used 2 parameters to assess glucose variation: mean amplitude of glucose excursion (MAGE) and glucose coefficient of variation (GluCV). Briefly, MAGE is a mean blood glucose value exceeding the standard deviation from the 24-h mean blood glucose level, whereas GluCv is the percentage ratio of

the standard deviation (SD) to the mean glucose level. According to scientific literature, the value of MAGE in patients without DM is nearly 30–40 mg/dL and nearly 60–70 mg/dL for cardiovascular events [13, 14]. In the studies from Furushima et al. [13] and Asakasa et al. [14], they found that MAGE > 65 mg/dL caused a significantly higher rate of cardiovascular events and mortality in ICU settings. The MAGE cut-off applied in this study was 65 mg/dL, based on the studies above. For the GluCV, Chao et al. [15] used a cut-off of 30% in their study and found that diabetic individuals with CV > 30% had worse outcomes which were independently associated with mortality. We decided to classify them into 3 groups: < 25%, 25–50%, and > 50%, to minimize the bias and increase the sensitivity [15].

Statistical analysis

The primary outcome was 30-day survival and length of stay (LoS) in low and high glucose variations based on MAGE and GluCV values. The secondary outcomes were 1) the significance of MAGE and GluCV in relation to 30-day mortality, 2) the sensitivity and specificity of MAGE and GluCV to predict 30-day mortality.

The minimum sample size calculated using G*Power software (power 0.80, alpha 0.05) for correlation analysis between the 2 groups was 201 participants.

Differences between the 2 groups were analyzed using Student's t test or the Mann-Whitney U test. The chi-squared test or Fisher's exact test was used for categorical variables. The correlation between MAGE and GluCV was analyzed using Pearson correlation. Kaplan-Meier analysis was used to test the association between 30-day mortality and acute GV using the cut-off MAGE and gluCV percentage. Variables were considered to be included in the multivariate analysis if the univariate p value was < 0.20. A linear regression model was constructed to identify independent variables that predicted 30-day mortality. The sensitivity and specificity of MAGE and GluCV for predicting mortality were analyzed using receiver operating characteristic (ROC) curves. Statistical significance was set at a two-sided p-value of < 0.05. All data were analyzed using SPSS software version 26.0 (SPSS Inc., Chicago, IL, USA).

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of the Sumber Waras Research Ethics Committee (approval No. 23/ /RSSW/KoM.EP/EC/V/2024)

Results

A total of 301 consecutive individuals were admitted to the medical ICU due to sepsis and T2D between January 2022 and June 2024; of these, 68 were excluded because lack of BG measurement, concurrent major operative procedure, and diagnosis of diabetic ketoacidosis/hyperosmolar hyperglycemia syndrome. The remaining 233 individuals were eligible for analysis and divided into high GV (n = 92, 39.48%) and low GV (n = 141, 60.52%) based on MAGE 65 mg/dL as a cut-off point. The Supplementary Figure 1 illustrates the subject flow in the study.

Table 1 summarizes the demographics, comorbidities, sepsis-related data, glycemic data, insulin prescriptions, and outcomes. The mean age was 60.49 ± 12.04 years, and 47.21% of subjects were female. The most common underlying comorbidity was cerebrovascular disease (50.21%), followed by congestive heart failure (36.91%). Septic shock was diagnosed in 34.76% of individuals, with a mean SOFA score of 10.43 ± 6.10. The mean MAGE and GluCV values were 58.18 ± ± 20.50 mg/dL and 28.04 ± 18.23%, respectively. The low-GV group had fewer comorbidities (1.62 vs. 1.98), a lower rate of septic shock (53.27% vs. 22.70%), lower APACHE-IV score (48.11 vs. 182.01), lower SOFA score (6.19 vs. 16.95), lower rate of mechanical ventilation (31.91% vs. 83.69%), and fewer hypoglycemic episodes (0.10 vs. 2.69). A full comparison of each variable in the 2 groups (low and high MAGE) is presented in Table 1.

The low-GV group showed significantly lower mortality rate [1.4% vs. 97.8%, p = 0.000, odds ratio (OR) = 68.49 (17.27–271.25)] compare to high GV. The GluCV < 25% showed a significantly lower mortality rate rather than 25–50% and > 50% groupw (0.8% vs. 83.6% vs. 100%, p = 0.000). There was no significant difference in ICU LoS using MAGE (p = 0.14), but it became significant using GluCV. A GluCV < 25% show significantly shorter LoS in ICU (p = 0.029). MAGE and GluCV also showed strong correlation (r = 0.930), where 92.1% low GV group had GluCV < 25%. A full description and analysis are presented in Table 2 and Figure 1.

Multivariate analysis with linear logistic regression was performed with variables that had a p-value < 0.20 (Suppl. Tab. 1). The APACHE-IV score (p = 0.001), SOFA score (0.000), number of hypoglycemic episodes (p = 0.000), MAGE (p = 0.000), and GluCV (p = 0.001) were significant independently associated with 30-day survival.

The mean estimated survival time of the low-MAGE group using Kaplan-Meier survival analysis in the 30-day observation was longer than in the high-MAGE group (29.65 vs. 4.24 days, respectively, p = 0.000). When using GluCV as a classifier, GluCV < 25% showed the longest survival time (29.79 vs. 8.37 vs. 3.16 days,

Table 1. Baseline Characteristics

	Low glucose variability (MAGE ≤ 65 mg/dL) (n = 141)	High glucose variability (MAGE > 65 mg/dL) (n = 92)	P-value
Age [years]	59.5 ± 12.0	61.9 ± 11.9	0.151
Female (%)	66 (46.8)	44 (47.8)	0.980
Comorbidities			
Cerebrovascular disease (%)	64 (45.4)	53 (57.6)	0.004*
Congestive heart failure (%)	34 (24.1)	52 (56.5)	0.003*
Kidney disease (%)	32 (22.7)	38 (41.3)	0.108
Myocardial infarct (%)	18 (12.8)	36 (39.1)	0.002*
Lung disease (%)	20 (14.2)	16 (17.4)	0.251
Hematological disease (%)	22 (15.6)	11 (12.0)	0.002*
Liver disease (%)	1 (0.7)	3 (3.3)	0.374
Malnutrition (%)	0 (0)	4 (4.33)	0.119
Individual comorbidity number (n)	1.6 ± 1.0	2.0 ± 1.0	0.009
Sepsis-related data			
Sepsis (%)	109 (77.3)	43 (46.7)	< 0.001*
Septic Shock (%)	32 (22.7)	49 (53.3)	< 0.001*
APACHE-IV Score	48.1 ± 31.6	182.0 ± 43.9	< 0.001**
SOFA Score	6.2 ± 2.7	17.0 ± 3.6	< 0.001**
Mechanical ventilation (%)	45 (31.9)	77 (83.7)	< 0.001*
Glycemic parameter			
Mean glucose at day-1 [mg/dL]	172.9 ± 12.5	147.5 ± 67.0	< 0.001**
Mean glucose during observation [mg/dL]	170.4 ± 9.3	154.0 ± 58.9	< 0.001**
MAGE [mg/dL]	24.1 ± 11.3	110.0 ± 35.4	< 0.001**
GluCV category			
Mean percentage (%)	14.4 ± 6.6	48.7 ± 7.4	< 0.001**
< 25% (n)	128 (90.8)	2 (2.2)	
25–50% (n)	13 (9.2)	40 (43.5)	
> 50% (n)	0 (0)	30 (32.6)	
Total hypoglycemic episodes (n)	0.1 ± 0.4	2.7 ± 0.9	< 0.001**
Outcome			
ICU LoS (days)	3.5 ± 2.0	3.9 ± 2.3	0.140
Mortality at D-30 (%)	3 (2.1)	90 (97.8)	< 0.001**

*p-value < 0.05 comparison using chi-square test; **p-value < 0.05 comparison using independent t-test

APACHE-IV — Acute Physiology and Chronic Health Evaluation-IV; GluCV — glucose coefficient of variation; ICU — intensive care unit; LoS — length of stay; MAGE — mean amplitude glucose excursion; SOFA — Sequential Organ Failure Assessment

p = 0.000) compared to GluCV 25–50% and > 50% (Fig. 2). MAGE and GluCV showed excellent sensitivity and specificity for predicting 30-day survival for sepsis individuals with T2D. The area under the curve (AUC) in the ROC analysis was 0.998 and 0.992 for MAGE and GluCV, respectively. The Supplementary Figure 2 shows the ROC curve.

Discussion

This study explored the association between GV and short-term mortality in T2D individuals with sepsis in an ICU setting. Based on the investigation of 233 medical records and 2559 glucose measurements, GV was prevalent in sepsis and T2D individuals. We found that 39% of individuals had high GV, reflected by MAGE > 65 mg/dL and GluCV > 25%. High MAGE and GluCV > 25% were independent variables for mortality in 30-day observation. The low-GV group also had a lower rate of critical related parameters, including the APACHE-IV and SOFA scores.

Glycemic variability, defined as the fluctuation of blood glucose levels that occurs throughout the day, includes hypoglycemic episodes and postprandial hyperglycemia [16]. Variability in blood glucose levels is

Table 2. Association between MAGE and GluCV with Survival and ICU LoS

	Mortality [n (%)]		ICU LoS (days)	
MAGE				
Low (≤ 65 mg/dL)	2 (1.4%)	p = 0.000*, OR = 68.5 (17.3-271.3)	3.5 ± 2.0	p = 0.140
High (> 65 mg/dL)	91 (97.8%)		3.9 ± 2.3	
GluCV				
< 25%	1 (0.8%)		3.5 ± 0.3	
25–50%	61 (83.6%)	p = 0.000*	3.2 ± 0.1	p = 0.029**
> 50%	31 (100%)		4.2 ± 0.1	

*p-value < 0.05 comparison using chi-square test; ** p-value < 0.05 comparison using independent t-test
GluCV — glucose coefficient of variation; ICU — intensive care unit; LoS — length of stay; MAGE — mean amplitude glucose excursion

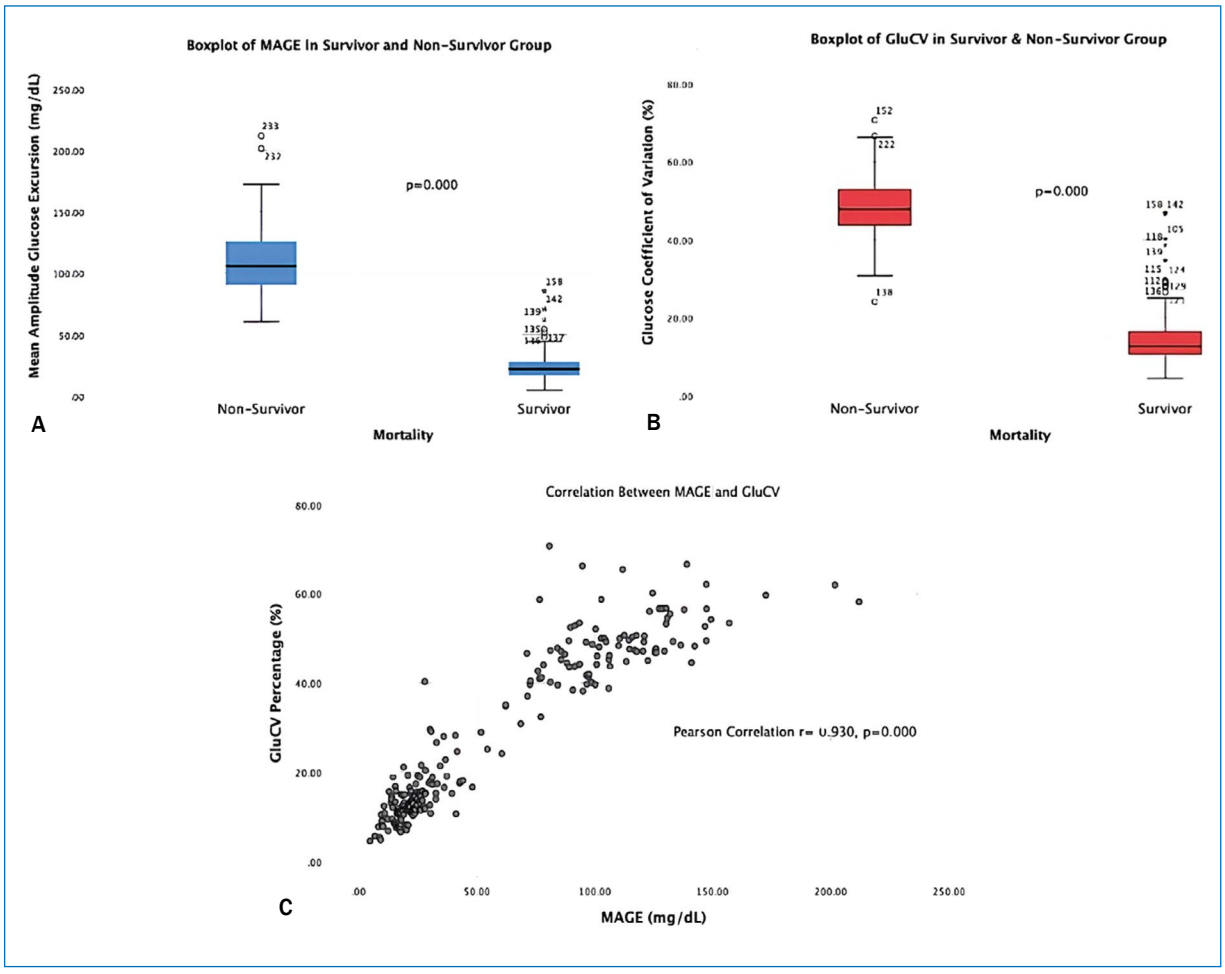

Figure 1. Chi-square analysis showing significantly lower rate of mortality in low GV using (**A**) MAGE and (**B**) GluCV. (**C**) Pearson correlation test showing strong and significant correlation between MAGE and GluCV score
GluCV — glucose coefficient of variation; MAGE — mean amplitude glucose excursion

independently associated with short-term mortality in individuals with sepsis. One strength of our study is that all enrolled individuals received intensive glucose monitoring (at least 3 times/day), which enabled us to investigate the prevalence of high GV and its association with 30-day mortality. In line with our findings, a retrospective study from Silveira et al. from 6730 glycemia measurements in the ICU showed a higher standard deviation of mean glycemia and MAGE associated with mortality in the ICU [17]. A study from

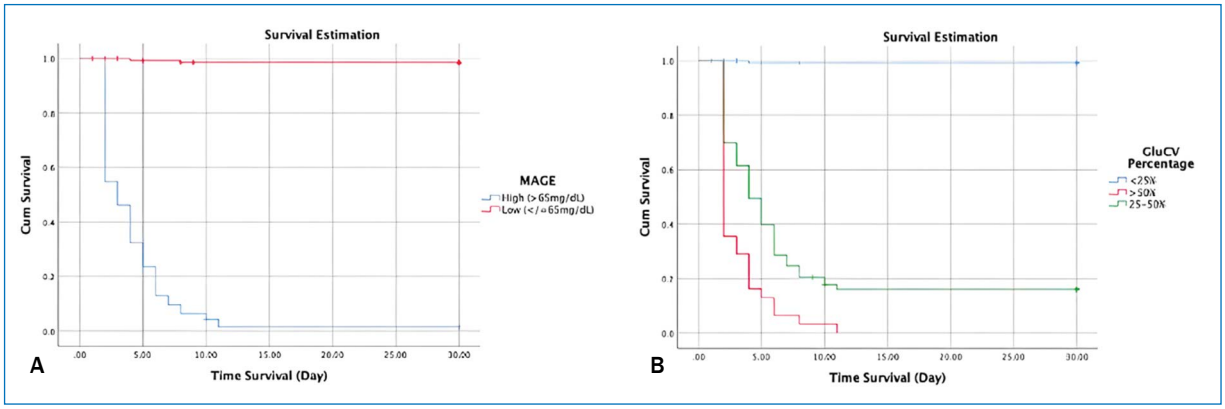

Figure 2. Kaplan-Meier survival analysis showing mean estimate survival time in low MAGE was 29.65 (29.16–30.13) days, and in high MAGE it was 4.24 (3.42–5.06) days. (**A**) The difference was 19.45 (17.78–21.12) days, SE = 0.85, p = 0.000. The mean estimate survival time in GluCV < 25% was 29.79 (29.39–30.20) days, GluCV 25–50% was 8.37 (6.13–10.61) days, and GluCV > 50% was 3.16 (2.42–3.91) days. (**B**) The difference was 19.45 (17.78–21.12), SE 0.85, p = 0.000
GluCV — glucose coefficient of variation; MAGE — mean amplitude glucose excursion; SE — standard error

Liu et al. found that T2D sepsis individuals with moderate maintenance blood glucose for 72 hours achieved better outcomes, including 90-day mortality [7]. In addition, a prospective study by Furushima et al. from 48 critically ill individuals with sepsis also found that higher MAGE (> 65 mg/dL) was independently inversely correlated with 90-day survival in the ICU [8].

There are several mechanism adverse effects of GV in sepsis individuals, including excessive protein glycation end products (AGE) and activation of oxidative stress, which cause endothelial dysfunction. GV induces overproduction of superoxide by the mitochondrial electron-transfer chain and causes a cascade of deleterious effect such as enhanced polyol activity, activation protein kinase C (PKC), nuclear factor-kß, and hexosamine pathway flux. Through these pathways, the increase of intracellular reactive oxygen species (ROS) causes vascular endothelial dysfunction by decreasing the of activity nitrite oxide synthase and activation of adhesion molecules [18, 19]. An observational study from Rodrigues et al. with 90 T1D individuals in the ICU showed that glycemic fluctuation correlated with oxidative stress and erythrocyte membrane stability parameters by interference with lipid peroxidation and cell membrane behavior [20].

We found a significant association between GV and increased incidence of hypoglycemia. Hypoglycemia induces the release of inflammatory cytokines and increases platelet and neutrophil activation and adrenaline secretion, which contribute to arrhythmia events and cardiovascular risk [21, 22]. In line with our study, we found that the high-GV group had more episodes of hypoglycemia, especially on the first day of admission, and hypoglycemia itself became an independent variable for mortality.

Our findings found that GluCV < 25% had better outcome for 30-day survival compared to GluCV 25–50% and > 50%. A study by Lanspa on 6106 critical ill individuals showed that GluCV was associated with mortality for the entire cohort, with OR1.25 for every 10% increase (p < 0.001) [23]. In the present study, GluCV > 25% had very strong association with mortality and excellent sensitivity to predict 30-day survival [0.992 (0.983–1.000), p = 0.000]. A recent study also showed that lower GV was associated with lower microvascular complications and decreased occurrence of hypoglycemia [16, 24]. Unlike glycated hemoglobin (HbA1c), GV can estimated hypoglycemic episode up to 40–50% in the future, and it is an independent predictor of hypoglycemia [25].

Our multivariate analysis showed that high MAGE and GluCV > 25% were significantly associated with short-term mortality, the same as with validated critically ill parameters, such as APACHE-IV and SOFA. The GluCV < 25% group also had shorter duration of ICU LoS significantly. This is in line with a retrospective study by Guo et al. on a total 6777 individuals, in which they found that the hazard ratio (HR) of CV > 25% was 1.37 (1.21–1.56), p < 0.001, after adjustment for SOFA score and multiple comorbidities [26]. A meta-analysis from Brett et al. from 41 studies (162,259 individuals) also showed a consistent association between increased measure of glycemic variability and higher short-term mortality in individuals with critical illness [24]. A study from Asakasa et al. suggested that large glycemic excursion parameter (MAGE, CV) was closely linked with

vascular endothelial dysfunction and deterioration of vascular endothelium. They found that MAGE was associated with higher risk of cardiovascular events and was a risk factor for coronary stenosis [14].

In consideration of easier measurement and modality, GV itself could become a good prognostic marker to predict the mortality and length of hospital stay in T2D individuals with sepsis. Furthermore, monitoring GV fluctuations could provide early clues for anticipating potential deterioration and aiding therapeutic adjustment [27].

There are several limitations to this study. First, it was a retrospective study in a single-center, which limited the robustness. Second, we excluded 30 subjects who died after < 24 h in the ICU, and this group may have greater fluctuations in BG levels. Third, despite highlighting the role of GV in T2D individuals with sepsis, the study only used periodic blood glucose monitoring (every 8 hours), not continuous glucose monitoring (CGM), which could offer more precise data on glucose fluctuations. Fourth, the generalizability of the findings should be applied with caution because of the high frequency of comorbidities that may influence BG fluctuations. Finally, we did not consider a variety of treatments that may influence BG.

Despite these limitations, the present study highlights the critical role of intensive GV monitoring in diabetic individuals with sepsis, which is feasible and can be incorporated into standard ICU procedures. CGM technology provides enhanced capabilities for closely tracking and identifying rapid fluctuations in BG levels. The reported CGM measurements significantly correlated with oxidative stress and endothelial dysfunction markers (urinary 8-iso-prostaglandin F2a, Gensini score, reactive hyperemia index) [14]. CGM has been associated with better control of short-term fluctuations in BG levels, reduced HbA1c values, reduced risk of severe hyperglycemia, and improved glycemic control [27]. Further studies are needed to investigate the optimal control strategy for individuals with high BG fluctuation with CGM.

Conclusions

High glycemic variability was observed in 39% of individuals; it was associated with higher mortality in diabetic individuals with sepsis, and was independently associated with high 30-day mortality. These findings emphasize the critical importance of early monitoring and detection of blood glucose fluctuations, especially to prevent large excursions and hypoglycemia episodes. Additional studies are required to explore the mechanism underlying GV and to optimize glucose control.

Article information

Supplementary material

Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/102762.

Data availability

Original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethical approval

The present study protocol was reviewed and approved by the Institutional Review Board of the Sumber Waras Research Ethics Committee (approval No. 23/ /RSSW/KoM.EP/EC/V/2024). Written informed consent was not applicable due to the retrospective design of the study from medical records.

Authors' contributions

Conception or design: BG, J, RS, SS, LD; acquisition, analysis, or interpretation of data: BG, J; drafting the work or revising: BG, J, RS; final approval of the manuscript: J, RS, SS, LD.

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Conflict of interest

The authors declare no conflict of interest.

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Fasting Serum Irisin is Low in Gestational Diabetes but Significantly Correlates with Glucose Level after Oral Challenge with Glucose

ABSTRACT

Objective: To ascertain the role of serum irisin in pregnant women with gestational diabetes mellitus (GDM) and to compare it with a control group.

Materials and methods: Pregnant women, irrespective of their gestational age, were recruited according to World Health Organization (WHO) 2013 criteria [GDM; n = 50, age: 28 (25.0, 32.0) years; body mass index (BMI): 27.01 kg/m^2, median and normal glucose tolerance (NGT); n = 50, age: 27.0 (22.0, 29.0) years, median] and were studied for fasting irisin along with insulin indices. Glucose was measured by glucose oxidase method, irisin by sandwich enzyme-linked immunosorbent assay (ELISA), and insulin by chemiluminescent immunoassay, whereas insulin indices were calculated using the homeostatic model assessment (HOMA) model.

Results: Serum irisin levels (pg/mL) were lower in GDM than NGT [7.14 (1.13, 15.93) vs. 8.61 (2.88, 34.33), p = 0.055]. Comparison of irisin levels between GDM and NGT mothers showed no significant differences (p = 0.132, p = 0.243, p = 0.194, respectively, for the first, second, and third trimesters). The fasting glucose-insulin ratio (FGIR) was statistically similar between the study groups. Irisin significantly and positively correlated with both one- [r = 0.399, p = 0.004] and 2-hour oral glucose tolerance test (OGTT) [r = 0.474, p = 0.001] in GDM mothers whereas it was significantly and inversely correlated with BMI [r = –0.281, p = 0.048] in NGT mothers. Irisin found to be an independent predictor of GDM by multivariate logistic regression (OR = 1.05; p = 0.012).

Conclusions: This study demonstrated that serum irisin is lower in GDM than NGT, but it is not statistically different. However, it is an independent predictor of GDM. (Clin Diabetol 2025; 14, 1: 26–31)

Keywords: irisin, insulin indices, GDM, HOMA-IR

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Introduction

Hyperglycemia in pregnancy is a major public health problem, and its prevalence is increasing globally [1]. The offspring of mothers with gestational diabetes mellitus (GDM) are not only at risk of perinatal complications but also have a substantial risk of developing metabolic complications like obesity, type 2 diabetes

(T2D), hypertension, and cardiovascular diseases in the future [2]. Women with a history of GDM appear to have a nearly 10-fold higher risk of developing T2D than those with a normoglycemic pregnancy [3]. However, the pathogenesis of GDM is yet to be fully understood. Based on this, the isolation of irisin, an exercise-inducible secreted novel myokine, was found in the year 2012, which improves glucose tolerance and increases energy expenditure in mice [4].

Irisin has been identified as an exercise-mediated, hormone-like polypeptide that is presumably secreted after cleavage of the extracellular portion of the fibronectin type III domain containing 5 (FDNC5) in response to activation of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) [4]. Irisin increases peripheral glucose uptake and decreases hepatic gluconeogenesis, respectively; consequently, the net effect is an increase in insulin sensitivity [4]. Limited studies have been performed to assess irisin in GDM, with contradictory results. One study found serum irisin levels to be higher in pregnancy [5] whereas 3 studies [6–8] found lower concentrations. Irisin, shows promise as a biomarker in GDM due to its role in glucose metabolism and insulin sensitivity. Monitoring irisin levels early in pregnancy could help predict GDM risk, allowing for early intervention. While more studies are needed, irisin shows potential as a complementary marker to traditional GDM screening methods.

Homeostasis model assessment of insulin resistance (HOMA-IR) is a mathematical model used to estimate insulin resistance by analyzing fasting plasma glucose and insulin levels, providing insights into glucose homeostasis. One study also found a positive association between circulating irisin and insulin [9]. In contrast, other studies reported that serum irisin level was negatively correlated with HOMA-IR [7, 8].

The present study aimed to assess circulating irisin levels in pregnant women with GDM to assess if they significantly vary from normal glucose tolerance (NGT) in Bangladeshi women, which has not been evaluated earlier, and explore its potential role as a biomarker for predicting GDM. The relationship of irisin with HOMA indices (HOMA-IR, HOMA-B, HOMA-%S) both in GDM and NGT was also observed.

Materials and methods

Study design and study participants

This cross-sectional study was conducted in the GDM Clinic of the Department of Endocrinology, BSMMU from July 2020 to October 2021. After obtaining approval from the Institutional Review Board (IRB), 100 pregnant women, irrespective of gestational age, with singleton pregnancy, were consecutively recruited as GDM (n = 50) or NGT (n = 50) after 3-sample 75-gm OGTT according to World Health Organization (WHO) 2013 criteria [10]. An overnight fasting venous blood sample was obtained from all participants to assess irisin and insulin levels on the day of OGTT screening. Overt diabetes or diabetes in pregnancy (DIP) were excluded from the study. With informed written consent, socio-demographic information and anthropometric measurements were noted in data record forms.

Ethical approval

Before starting the research work the Institutional review board (IRB) of BSMMU approved the study protocol (No. BSMMU/2021/514; date: 19.01.2021).

Data collection and analytic methods

Fasting serum was stored at -70°C until irisin assay. Quantitative determination of irisin in serum was done by 2-site sandwich enzyme-linked immunosorbent assay (ELISA) technique using the Elabscience® Human Irisin ELISA Kit (E-EL-H6 120) assay. Reference ranges for irisin were 0.0–1000 pg/mL. Intra-assay precision was CV < 10% for irisin, with the expected mean value in healthy subjects being 125 pg/mL. Plasma glucose was measured by the hexokinase method using the Dimension EXL 200 Integrated Chemistry System (Siemens, Germany) in the Biochemistry laboratory, BSMMU on the day of sample collection. Insulin was assayed using chemiluminescent immunoassay, and insulin indices (HOMA-IR and HOMA-B) were calculated using the HOMA model.

Statistical methods

Data were analyzed using SPSS version 26. Quantitative data with normal distribution were expressed as mean (± SD), and with skewed distribution as median and interquartile range [interquartile range (IQR); 25th–75th percentile], whereas qualitative data were shown as frequencies or percentages. Comparison between the 2 groups was done by Student's unpaired t-test, the Mann-Whitney U test, and the chi-square test, as applicable. For more than 2 groups, the Kruskal-Wallis H test was applied for quantitative data with skewed distribution. Correlations were determined by Spearman's correlation test. Regression analysis was done to adjust the effects of the covariates. A p-value < 0.05 was considered statistically significant.

Results

This study aimed to see irisin levels and their association with insulin indices in GDM (n = 50) and NGT

Table 1. Characteristics of the Study Population

Variables	GDM (n = 50)	NGT (n = 50)	P-value
Age [years]	28.00 (25.00–32.00)	26 (22.00–29.00)	0.014
BMI at diagnosis [kg/m^2]	26.74 (24.30–28.48)	26.56 (23.82–29.31)	0.807
Gestational [age, weeks]	21 (12–28)	27 (24–32)	< 0.001
SBP [mmHg]	110 (100–115)	110 (100.00–117.50)	0.881
DBP [mmHg]	70 (70–80)	70 (65.00–72.50)	0.745
Occupation			
Service	13 (25.5)	9 (17.0)	0.341
Housewife	38 (74.5)	44 (83.0)	
Family H/O DM, n (%)			
Yes	24 (47.1)	21 (39.6)	0.553
No	27 (51)	32 (60.4)	
H/O GDM, n (%)			
Yes	6 (11.8)	0 (0)	0.012
No	45 (88.2)	53 (100)	

Within parenthesis are interquartile range and percentages over column total; quantitative data comparison between groups was done by Student's t-test and the Mann-Whitney U test, as appropriate; for qualitative data, comparison between groups done by chi-square test
BMI — body mass index; DBP — diastolic blood pressure; DM — diabetes mellitus; GDM — gestational diabetes mellitus; NGT — normal glucose tolerance; SBP — systolic blood pressure

(n = 50), and to compare these between the 2 groups. It also explored the context of demographic and clinical variables with irisin in GDM and NGT.

Table 1 demonstrates the demographic characteristics and clinical variables of the study subjects. Both the study groups were statistically similar in BMI, BP, occupation, and family history of DM (p = NS) except age. Mothers with GDM were significantly older than the NGT mothers (GDM vs. control; age: 28.0 (25.0, 32.0) vs. 27.0 (22.0, 29.0) years, p = 0.014). However, a previous history of GDM was significantly more frequent among mothers with NGT than in GDM (12% vs. 0.0%, p = 0.027), and gestational age was higher in NGT than in GDM (p < 0.001).

Figure 1 depicts low serum irisin levels (pg/mL) in GDM mothers, but statistically similar with mothers with NGT [7.14 (1.13, 15.93) vs. 8.61 (2.88, 34.33), p = NS].

The fasting insulin and fasting glucose-insulin ratio (FGIR) were statistically similar between the study groups [NS for both] (Tab. 2). Irisin significantly and positively correlated with both one-hour (r = 0.399, p = 0.004) and 2-hour OGTT glucose (r = 0.474, p = 0.001) in GDM mothers; whereas, it was significantly but negatively correlated with BMI (r = –0.281, p = 0.048) in NGT mothers (Tab. 2).

Multivariate logistic regression analysis was done to find independent predictors of GDM; age, gestational age, and irisin had significant predictive associations with development of GDM (Tab. 3).

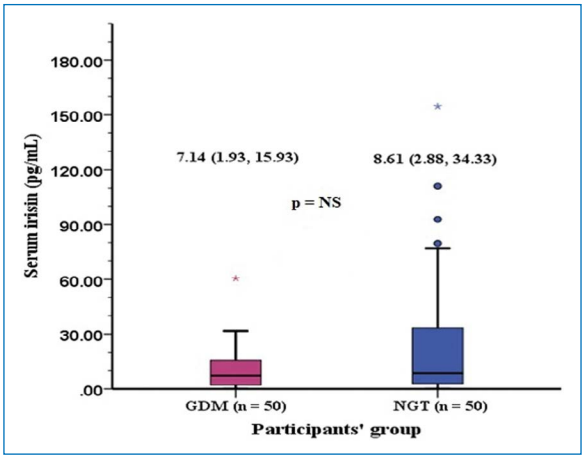

Figure 1. Serum Irisin Level in the Study Groups (N = 100)
Serum irisin levels (pg/mL) were statistically similar in GDM and in NGT [7.14 (1.13, 15.93) vs. 8.61 (2.88, 34.33), p = 0.055]; GDM — gestational diabetes mellitus; NGT — normal glucose tolerance

Receiver operator (ROC) curves were used to assess the sensitivity and specificity of serum irisin in determining GDM patients. The area under the curve (AUC) value was 0.611 (95% CI 0.501–0.722) and was not statistically significant.

Discussion

The present study aimed to assess circulating irisin levels in pregnant women with GDM and to ascertain

Table 2. Correlation between Irisin Levels and Anthropometric and Biochemical Parameters in Patients with GDM and NGT

Determinants of 'r'	GDM		NGT	
	r	p	r	p
Age [years]	0.241	0.092	–0.029	0.842
BMI [kg/m2]	–0.196	0.172	–0.281	0.048
SBP [mmHg]	0.254	0.075	–0.056	0.700
DBP [mmHg]	0.274	0.055	–0.091	0.530
Fasting plasma glucose [mmol/L]	0.062	0.669	0.024	0.867
1-h OGTT glucose [mmol/L]	0.399	0.004	–0.049	0.735
2-h OGTT glucose [mmol/L]	0.474	0.001	–0.119	0.411
Fasting insulin [μIU/mL]	0.108	0.457	0.163	0.257
HOMA-IR	0.169	0.242	0.174	0.228
HOMA1-%B	0.016	0.910	0.130	0.368

Spearman's correlation test was performed; data were expressed as median followed by interquartile range in parentheses; p-values were calculated by the Mann-Whitney U test model assessment of insulin sensitivity
BMI — body mass index; GDM — gestational diabetes mellitus; HOMA-B — homeostasis model assessment of β-cell function; HOMA-IR — homeostasis model assessment of insulin resistance; NGT — normal glucose tolerance.

Table 3. Multivariate Logistic Regression for Independent Predictors of GDM

Independent variables	GDM	
	p-value	OR (95% CI)
Age [years]	0.012	0.84 (0.73–0.96)
BMI [kg/m2]	0.084	1.14 (0.98–1.33)
Gravida	0.274	1.92 (0.60–6.23)
Gestational [age, weeks]	0.001	1.14 (1.05–1.23)
Family history of diabetes	0.501	0.71 (0.26–1.93)
Irisin [pg/mL]	0.012	1.05 (1.01–1.08)
Fasting insulin [μIU/mL]	0.202	0.92 (0.79–1.05)

BMI — body mass index; CI — confidence interval; GDM — gestational diabetes mellitus; OR — odds ratio

whether there were any differences in irisin levels between GDM and NGT. Early diagnosis and effective treatment of gestational diabetes are beneficial in minimizing bad maternal and fetal outcomes, as well as in protecting mothers and infants from long-term repercussions of the condition. Because of the significant effects of irisin on the metabolism, numerous studies have been undertaken to ascertain the relationship between irisin and pregnancy, anticipating use of irisin levels as a novel marker to predict GDM.

In this study, the mean age of the GDM mothers was 28 years (range: 25–32 years), and it was significantly higher than that of the NGT mothers. Hence, it is evident that pregnant mothers with an age greater than 25 years are at risk for GDM, which is also a concern in terms of irisin levels.

The results of the current investigation revealed that serum irisin levels were considerably lower in patients with GDM than in healthy pregnant women in the control group, but this was not statistically significant. Similarly to our study, Zahra et al. [7], Ebert et al. [9], and Yuksel et al. [11] also found that there was no significant difference between serum irisin levels in healthy and GDM mothers. However, in their study, a direct relationship between serum irisin and fasting insulin levels was observed, but we did not find any correlation between them.

Low blood levels of irisin are closely related to BMI and fat mass although its effect on energy metabolism is debatable. Stengel et al. [12] reported positive correlation between circulating irisin levels and BMI in people without diabetes. In our study, irisin did not correlate with BMI in GDM, which was consistent with the findings of some studies [7, 13] but contradictory to reports from other studies that demonstrated a positive correlation [14]. In contrast, irisin showed a negative correlation with BMI in NGT mothers. A study reported that circulating irisin correlated negatively with BMI and body weight in non-diabetic, non-pregnant adults [15]. One explanation for this discrepancy could be that gestational rather than pre-gestational BMI was measured. BMI is a measure of generalized obesity and not a true measure of adiposity because it does not take into account abdominal obesity.

The outcome of other investigations on irisin and glucose homeostasis in pregnancy have been met with much disagreement. Piya et al. [14] confirmed that in pregnant women serum irisin was positively

correlated with fasting blood glucose, insulin, and HOMA-IR. Contrary to this, irisin levels are negatively associated with HOMA-IR in some studies [16]. These seemingly contradictory results may be explained by differences in gestational age at the time of sample, parity, variations in physical activity, and even diet (rich in vegetable protein and saturated fatty acid) [17, 18].

Additionally, we observed that serum irisin correlated significantly and positively with both one-hour and 2-hour glucose levels in GDM mothers, which is not consistent with the result found by other researchers [13, 19]. Choi et al. [13] also found that 2-h plasma glucose was an independent negative predictor of irisin concentration in patients with newly diagnosed T2D. However, in our study multivariate logistic regression analysis revealed that along with age and gestational age, irisin could independently predict the development of GDM. All these discrepancies may result from differences in the clinical characteristics of the study subject and various diagnostic criteria.

Receiver operator (ROC) curves were used to assess the sensitivity and specificity of serum irisin in determining GDM patients. ROC curve analysis showed that irisin is not a useful predictor of GDM in our population. However, ROC-AUC analysis in other studies showed that serum irisin had sensitivity of 90.0% and specificity of 84.0% in determining GDM women, which also showed that the AUC was 0.93 (95% CI 0.883–0.977).

The major limitation of this study is its cross-sectional nature limited to a small sample. Irisin was not measured in all 3 trimesters of pregnancy in the same sample, and pre-pregnancy BMI was not included. If we could incorporate pre-pregnancy BMI and reflect on how irisin levels change throughout different trimesters of pregnancy, it would provide us with a more robust description of the relationship between irisin and GDM. Perhaps, more precise findings can be depicted from a multi-centered, large-scale, prospective cohort study on pregnant women from the early stage of pregnancy.

Conclusions

The current investigation revealed that serum irisin levels were considerably lower in patients with GDM than in healthy pregnant women, but this was not statistically significant. Serum irisin correlated significantly and positively with both one-hour and 2-hour glucose levels in GDM mothers, which is a potential area of future research. A longitudinal design would provide more comprehensive insights into the temporal dynamics of irisin in GDM.

Article information

Data availability

A data file can be made available upon request.

Ethics statement

Before carrying out the research work, permission from the Institutional Review Board was obtained.

Authors' contributions

MA Hasanat conceived the concept of the study. Farhana Sayeed obtained funding. Tania-Tofail wrote the first draft of the study. Mohana CA and Sharmin-Jahan helped with patient recruitment. Tania-Tofail analyzed the data. All authors reviewed and edited the manuscript and approved it for submission.

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Conflicts of interests

The authors declare no conflict of interest.

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The Concentration of Triglycerides is Significantly Associated with the Prevalence of Coronary Artery Disease in Pancreas Recipients with Type 1 Diabetes: A Cross-Sectional Study

ABSTRACT

Objective: Coronary artery disease (CAD) and its complications significantly affect the post-transplant prognosis in pancreas recipients. This study aimed to evaluate the associations between CAD and its major risk factors (RFs) and to identify the strongest modifiable predictor of CAD in potential pancreas recipients with type 1 diabetes (T1D).

Materials and methods: This is a prospective, cross-sectional study. Patients with T1D qualified for simultaneous pancreas-kidney transplantation or pancreas transplantation alone were enrolled. The diagnosis of CAD was based on invasive coronary angiography. The major cardiovascular RFs included in the analyses were hypertension, lipid profile, obesity, and smoking.

Results: The study population included 113 patients with a median age of 40 (35–46) years. The median duration of T1D was 26 years (23–32), and 61.9% of participants (n = 70) were on hemodialysis. CAD was found in 31 (27.4%) participants. Multivariate logistic regression analysis demonstrated that age (OR 1.159; 95% CI: 1.062–1.265, p = 0.001), the concentration of triglycerides (TG) (OR 4.534; 95% CI: 1.803–11.403, p = 0.001), and hemodialysis (OR 4.027; 95% CI: 1.13–14.358, p = 0.032) were independently associated with the prevalence of CAD in this cohort. Finally, the concentration of TG was the only modifiable RF that was independently associated with the prevalence of CAD.

Conclusions: Fasting TG levels were positively associated with the prevalence of CAD in potential pancreas recipients with T1D. The concentration of TG has the potential to serve as a modifiable RF or at least as an important biomarker in this group and should be included in the cardiological pre-transplant assessment. (Clin Diabetol 2025; 14, 1: 32–39)

Keywords: type 1 diabetes, triglycerides, pancreas transplantation, pancreas-kidney transplantation, coronary artery disease, risk factors

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Introduction

Pancreas transplantation is a well-established treatment method for selected patients with type 1 diabetes (T1D) [1]. The most common transplant methods are simultaneous pancreas-kidney transplantation (SPKT) and pancreas transplantation alone (PTA). Patients with severe diabetic nephropathy are qualified for SPKT, while patients with preserved kidney function are qualified for PTA. Both treatment options improve patients' prognoses, eliminate the need for exogenous insulin administration, and improve diabetes-related complications [2, 3].

Advances in surgical techniques and immunosuppressive protocols have contributed to excellent patient survival; however, cardio-cerebrovascular events remain one of the main reasons for death in the first year after transplantation [4]. Therefore, a precise cardiac evaluation of pancreas recipients is crucial to reduce peri-transplant complications. Considering the relatively long waiting time for the organ, the preoperative assessment should include both the patient's current cardiological status and the risk of developing coronary artery disease (CAD) in the next few years. The accelerated progression of atherosclerosis in T1D patients is mainly due to hyperglycemia and glycemic variability, but other cardiovascular risk factors (RFs) are also of great importance [5–7]. Hence, it is necessary to identify the factors that play the most significant role. This knowledge could be used to modify cardiovascular risk, thereby slowing the progression of atherosclerosis and decreasing perioperative risk.

Therefore, this study aimed to evaluate the prevalence of major cardiovascular RFs and to identify the most significant modifiable predictor of CAD in potential pancreas recipients with T1D.

Materials and methods

Study design and subjects

This prospective cross-sectional study population included pancreas transplant candidates with T1D who were referred for cardiological pre-transplant assessment and included both patients eligible for SPKT and PTA. Patients were prospectively enrolled from August 2018 to November 2023. The exclusion criteria for study participants were type 2 diabetes, severe valvular heart disease, heart failure, history of coronary heart disease or stroke, and changes in lipid-lowering and/or antihypertensive therapy within 3 months before the study entry.

Data collection

The following demographic and medical data were collected: age, sex, type of planned transplantation procedure, age at onset and duration of T1D, renal replacement therapy, and major risk factors for CAD (hypertension, smoking habit, dyslipidemia, obesity). Hypertension was defined as systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) > 90 mmHg and/or if a patient was on antihypertensive therapy before admission. Dyslipidemia was defined when TC > 4.9 mmol/L and/or TG > 1.7 mmol/L or if a patient was on lipid-lowering therapy [8]. Smoking was defined as active smoking in the last 5 years. All patients were rated for hypotensive and lipid-lowering therapy.

Height (m) and weight (kg) were measured with light clothes and without shoes. People on dialysis were weighed on a non-dialysis day. BMI was calculated as weight divided by height squared. Obesity was defined as a BMI $\geq$ 30 kg/m^2.

SBP and DBP were measured on 3 consecutive days between 8 and 9 a.m. using an automatic oscillometric blood pressure monitor. Measurements were taken in a seated position after 10 min of rest, and each measurement was repeated 3 times. The mean value of SBP and DBP was calculated as an average of 3 measurements over 3 days.

A commercially available analyzer (Beckman Coulter Inc., Brea, CA, USA) was used to measure the concentrations of HbA1C, serum creatinine, total cholesterol (TC), high-density lipoprotein (HDL), and triglycerides (TG) from fasting blood samples. The concentration of low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald formula: LDL-C = TC – HDL-C – TG/2.2 (mmol/L) [9]. Non-high-density lipoprotein-cholesterol (n-HDL-C) was calculated as n-HDL-C = TC – HDL-C.

The diagnosis of CAD was based on noninvasive and invasive tests. Patients with severe chronic kidney disease (eGFR < 30 mL/min/1.73 m^2) and long T1D duration ($\geq$ 20 years) were directly subjected to invasive coronary angiography. The other patients were referred for noninvasive tests, including an exercise stress test on a treadmill or a pharmacological stress test using dipyridamole 99 mTc-sestamibi single-photon emission computed tomography (SPECT) for patients with physical limitations. Patients with positive or inconclusive results of noninvasive tests were uniformly subjected to invasive coronary angiography. Invasive coronary angiography was performed with a Philips Allura Xper DF20 X-ray system using standard diagnostic catheters. Vascular access through the radial artery was used. CAD was defined as obstructive coronary disease based on the detection of at least one stenosis > 50% in at least one of the major coronary arteries.

Table 1. Baseline Characteristics of the Study Population Stratified by CAD

	Total (n = 113)	CAD (n = 31)	No CAD (n = 82)	P-value
Age [years]	40 (35–46)	44 (38–51)	38.5 (34–44)	0.005
Sex (male)	49 (43.3%)	17 (54.8%)	32 (39%)	0.1
Age of diagnosis of T1D [years]	13 (8–17)	14 (9–20)	12 (8–16)	0.2
Duration of T1D [years]	26 (23–32)	27 (24–35)	25 (22–31)	0.07
Hemodialysis	70 (61.9%)	26 (83.9%)	44 (53.7%)	0.004
Duration of hemodialysis [months]	18 (9–28)	22.5 (11–28)	14 (8–27)	0.25
BMI [kg/m^2]	22.95 (20.8–25.4)	23.6 (20.6–26.7)	22.8 (20.8–24.7)	0.4
HbA1c [%]	7.66 (6.95–8.42)	7.79 (7.2–8.64)	7.47 (6.82–8.4)	0.2

Categorical variables are presented as numbers and percentages (%), and continuous variables are presented as median with interquartile range (IQR)
BMI — body mass index; CAD — coronary artery disease; HbA1c — glycated hemoglobin; T1D — type 1

Statistical analysis

Continuous data were presented as median with interquartile range (IQR) and categorical variables as numbers and percentages of distribution. The normality of the data distribution was tested using the Shapiro-Wilk test. The participants were categorized into 2 groups by CAD diagnosis. For parameters not having normal distributions, statistical analyses were based on non-parametric tests. The Mann-Whitney U test was used to compare continuous variables between 2 groups, and Fisher's exact test or the chi-squared test was used to examine the significance of differences between categorical variables.

Multivariate logistic regression analysis was used to test the combined relationship between the prevalence of CAD and cardiovascular RFs. The multivariable logistic regression model included all modified RFs that were significant in the univariate analysis and potential confounding factors. The multivariate model used the backward stepwise elimination method, starting with a model including all the variables. The results were presented as odds ratio (OR) with a 95% confidence interval (CI).

Statistical analyses were performed using Statistica version 13.3 (TIBCO Software Inc., California, USA). For all statistical analyses, a p-value < 0.05 was considered significant.

Results

Participants' characteristics

The study population included 113 patients, of whom 29 patients (25.7%) were qualified for PTA and 84 patients (74.3%) for SPKT. The median age of the population was 40 (35–46) years, and 64 patients (56.7%) were female. The median duration time of T1D was 26 (23–32) years, and most of the study group (n = 93; 82.3%) were participants with long-standing diabetes (over 20 years). Above two-thirds of patients (n = 70; 61.9%) were on hemodialysis.

Invasive coronary angiography was performed in 107 patients (94.7%). The other patients (n = 6; 5.3%) had negative results of stress tests and were excluded from invasive assessment. Finally, CAD was found in 31 participants (27.4% of the entire cohort). The baseline characteristics of the enrolled patients stratified by CAD are illustrated in Table 1. In general, patients with CAD were older [44 years (38–51) vs. 38.5 years (34–44), p = 0.005] than patients without CAD, and the majority were on hemodialysis [26 (83.9%) vs. 44 (53.7%), p = 0.004]. The duration of renal replacement therapy and diabetes-specific RFs (age of diagnosis, duration of T1D, level of HbA1c) did not have any significant associations with the prevalence of CAD.

Assessment of cardiovascular RFs

The prevalence of traditional cardiovascular RFs was very high. Most participants (n = 81; 71.7%) had 2 to 3 major RFs (Tab. 2). However, there was no significant association between the number of RFs and the prevalence of CAD. As shown in Table 3, hypertension and dyslipidemia were the most common RFs in the study group (n = 96; 85% and n = 80; 70.8%, respectively). Active smoking was declared by 31 participants (27.4%) with a median of 13 pack-years (6–18.3) of smoking exposure. Obesity was the least common RF in the study group.

Table 2. The Association Between the Number of Major Modifiable Cardiovascular RFs and the Prevalence of CAD

Number of RFs	Total (n = 113)	CAD (n = 31)	No CAD (n = 82)	P-value
0	2 (1.77%)	0	2 (2.4%)	0.6
1	10 (8.85%)	2 (6.45%)	8 (9.76%)	
2	43 (38.05%)	10 (32.26%)	33 (40.2%)	
3	38 (33.62%)	12 (38.7%)	26 (31.7%)	
4	20 (17.7%)	7 (22.6%)	13 (15.85%)	

Major cardiovascular risk factors included: hypertension, dyslipidemia, smoking, and obesity; categorical variables are presented as numbers and percentages (%)
CAD — coronary artery disease; RFs — risk factors

Table 3. Characteristics of the Major Modifiable Cardiovascular RFs

	Total (n = 113)	CAD (n = 31)	No CAD (n = 82)	P-value
Hypertension	96 (85%)	30 (96.8%)	66 (80.5%)	0.04
ACEi/ARBs	55 (48.7%)	23 (74.2%)	32 (39.0%)	0.001
Calcium channel blockers	70 (61.9%)	21 (67.7%)	49 (59.8%)	0.5
Beta-blockers	61 (54.0%)	22 (71.0%)	39 (47.6%)	0.03
Diuretics	57 (50.4%)	18 (58.1%)	39 (47.6%)	0.4
Alpha-blockers	20 (17.7%)	6 (19.3%)	14 (17.1%)	0.8
Centrally acting agents	6 (5.3%)	2 (6.45%)	4 (4.9%)	0.7
SBP [mmHg]	132 (122–146)	144 (129–158)	130.5 (122–138)	0.0002
DBP [mmHg]	77 (71–84)	80 (72–88)	76 (71–83)	0.04
Dyslipidemia	80 (70.8%)	25 (80.65%)	55 (67.1%)	0.2
Statin users	49 (43.36%)	17 (54.8%)	28 (34.1%)	0.05
Statin dose [mg]	20 (10–40)	20 (10–20)	20 (20–40)	0.06
TC [mmol/L]	4.7 (3.8–5.6)	5 (3.5–5.7)	4.7 (3.9–5.6)	0.97
LDL-C [mmol/L]	2.5 (2–3.1)	2.7 (1.8–3.2)	2.5 (2.1–3.1)	0.75
HDL-C [mmol/L]	1.4 (1.2–1.8)	1.3 (1.2–1.4)	1.5 (1.3–1.9)	0.01
non-HDL-C [mmol/L]	3.1 (2.5–3.8)	3.1 (2.5–3.7)	3.2 (2.3–4.1)	0.7
TG [mmol/L]	1.3 (1–1.8)	1.8 (1.4–2.1)	1.2 (1–1.7)	0.00003
Obesity	6 (5.3%)	3 (9.7%)	3 (3.7%)	0.3
Current smoking	31 (27.4%)	11 (35.5%)	20 (24.4%)	0.2
Smoking exposure [pack-years]	13 (6–18.3)	13 (5–20)	12.75 (7–17.5)	0.94

Categorical variables are presented as numbers and percentages (%), and continuous variables are presented as median with interquartile range (IQR)
ACEi — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; CAD — coronary artery disease; DBP — diastolic blood pressure; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; RFs — risk factors; SBP — systolic blood pressure; TC — total cholesterol; TG — triglycerides

Associations between CAD and RFs

Associations between the prevalence of CAD and cardiovascular RFs of interest are shown in Table 3. There were no significant between-group differences in the prevalence of hypertension, dyslipidemia, smoking, or obesity. However, significant differences were found in specific lipid parameters and blood pressure values. Both SBP and DBP were significantly higher in patients with CAD than in patients without CAD (144 mmHg [129–158] vs. 130.5 mmHg [122–138], p = 0.0002, and 80 mmHg [72–88] vs. 76 mmHg [71–83], p = 0.04, respectively). The concentration of TG was significantly higher (1.8 mmol/L [1.4–2.1] vs. 1.2 mmol/L [1–1.7], p = 0.00003), while HDL-C was significantly lower (1.3 mmol/L [1.2–1.4] vs.1.5 mmol/L [1.3–1.9], p = 0.01) in patients with CAD than in the other participants. There were no significant differences in other lipid parameters (TC, LDL-C, non-HDL) between patients with and without CAD.

Table 4. Logistic Regression Analyses of Cardiovascular RFs Associated with CAD

Univariate logistic regression analysis			
Variable	**OR**	**95% CI**	**P-value**
Sex (male)	0.576	0.179–1.849	0.35
Age [years]	1.135	1.040–1.240	0.005
Smoking	0.668	0.203–2.198	0.5
Triglycerides [mmol/L]	4.127	1.831–9.299	0.001
Systolic blood pressure [mmHg]	1.058	1.027–1.09	0.0002
Diastolic blood pressure [mmHg]	1.057	1.008–1.107	0.021
Hemodialysis	4.491	1.57–12.846	0.005
Statins using	1.053	0.346–3.209	0.92
Multivariate logistic regression analysis			
Age [years]	1.159	1.062–1.265	0.001
Triglycerides [mmol/L]	4.534	1.803–11.403	0.001
Hemodialysis	4.027	1.13–14.358	0.032

The multivariate logistic regression analysis model included all modified RFs that were significantly different in the univariate analysis (TG, SBP, DBP) and potential confounding factors (sex, age, smoking, hemodialysis, HDL-C, statins using)
CAD — coronary artery disease; CI — confidence interval; OR — odds ratio; RFs — risk factors

Associations of various cardiovascular RFs for CAD are presented in Table 4. In the univariate logistic regression analysis, age (OR 1.135; 95% CI: 1.040–1.240, p = 0.005), the concentration of TG (OR 4.127; 95% CI: 1.831–9.299, p = 0.001), SBP (OR 1.058; 95% CI: 1.027–1.09, p = 0.0002), and DBP (OR 1.057; 95% CI: 1.008–1.107, p = 0.021), and hemodialysis (OR 4.491; 95% CI: 1.57–12.846, p = 0.005) were significantly associated with CAD.

The multivariate analysis model included all modified RFs that were significantly different in the univariate analysis (TG, SBP, DBP) and potential confounding factors (sex, age, smoking, hemodialysis, HDL-C, statin use). The multivariate analysis demonstrated that age (OR 1.159; 95% CI: 1.062–1.265, p = 0.001), the concentration of TG (OR 4.534; 95% CI: 1.803–11.403, p = 0.001), and hemodialysis (OR 4.027; 95% CI: 1.13–14.358, p = 0.032) were independently associated with the prevalence of CAD in the presented cohort. Finally, the concentration of TG was the only modifiable RF independently associated with the prevalence of CAD in the entire cohort.

Discussion

The study included potential pancreas recipients referred to our center for cardiological pre-transplant assessment. The vast majority were patients with long-standing diabetes and many complications, including hemodialysis.

Multivariate analysis demonstrated that age, hemodialysis, and TG levels were independently associated with the prevalence of CAD in potential pancreas recipients with T1D. Higher values of these parameters were significant predictors of CAD, suggesting that older patients, those undergoing hemodialysis, and those with higher TG levels have a higher risk of CAD.

The most impressive result of this study is that the concentration of TG was the only modifiable RF independently associated with the prevalence of CAD. When the concentration of TG increased by 1 mg/dL, the odds of having CAD increased 4.5-fold.

Our study results demonstrated the high prevalence of CAD in pancreas recipients. Obstructive CAD was revealed in 27.4% of participants. Data from other researchers have shown very divergent results, and the incidence of CAD ranged from 19 to 71.7%, depending on the study population and the criteria for CAD diagnosis [10–12]. The high prevalence of CAD in pancreas transplant recipients justifies the multifactorial approach to identifying and controlling the most important modifiable cardiovascular RFs.

Additionally, we demonstrated that hemodialysis was independently associated with the prevalence of CAD in the presented cohort. HD increased the odds of having CAD 4.03-fold. In this regard, our results are in line with the results from other researchers suggesting a link between diabetic nephropathy and CAD in T1D patients. According to Tuomilehto et al. [13], the presence of nephropathy in T1D patients increased the relative risk for cardiovascular disease 10.3-fold. Giménez-Pérez et al. [14] demonstrated that decreased GFR and elevated albumin/creatinine ratio were both strongly associated with a first cardiovascular event in T1D patients and should be considered when estimat-

ing CV in primary prevention measures. The results from Harjutsalo et al. [15] also suggest that a higher degree of kidney disease increased the risk of CAD in T1D patients. Moreover, Oliveira et al. [16] assessed CAD in 20 hemodialyzed T1D patients using quantitative invasive coronary angiography and intravascular ultrasound. They found 29 lesions in 15 patients, of which 50% were significant (≥ 70% stenosis), even though the patients were asymptomatic. Additionally, subclinical CAD was present in all coronary arteries. Furthermore, according to Kim et al. [17], patients subjected to SPK were at higher risk of CAD among all pancreas recipients. After multivariable adjustment, the odds of any cardiovascular complication in the SPK group were significantly higher than in patients subjected to solitary pancreas transplantation (OR 1.48, 95% CI 1.21 to 1.80, p = 0.01). Moreover, there was a robust association between diabetic nephropathy and dyslipidemia [18]. Their findings may partly explain the results we observed.

The key finding of the present study is the high prevalence of traditional cardiovascular RFs (hypertension, dyslipidemia, smoking, obesity) and the lack of any significant associations between them and the prevalence of CAD. However, significant between-group differences were found in specific blood pressure values and lipid parameters. Both SBP and DBP were significantly higher in patients with CAD than in patients without CAD. The concentration of TG was also significantly higher in patients with CAD. It can, therefore, be assumed that the degree of control of a given risk factor is more important than the fact of having it. The achievement of therapeutic goals in cardiovascular RFs is probably crucial in decreasing the risk of CAD.

In the present study, the concentration of TG was significantly and independently associated with the prevalence of CAD. In observational studies, a higher concentration of TG was also significantly associated with the increased risk of CAD in the general population [19, 20]. Moreover, researchers from the PROVE IT-TIMI 22 trial demonstrated that higher concentrations of TG were associated with atherosclerotic cardiovascular disease independently of LDL-C levels [21]. The authors of the aforementioned research suggested that achieving low TG should be an additional consideration beyond low LDL-C in patients after ACS. In contrast to these results, several trials failed to prove that lowering the concentration of TG decreased the risk for CAD [22]. Presumably, for this reason, guidelines for many years ignored elevated TG, focusing on lowering LDL-C to reduce the risk of atherosclerosis. The therapy to lower TG levels might only be considered in high-risk patients when TGs are more than 2.3 mmol/L [23]. For some time, researchers have noticed that in statin-treated patients, the risk of cardiovascular events increased with a higher concentration of TG, even when LDL-C was at the target level [24, 25]. That is in line with results from Hero et al. [26], who demonstrated in 30,778 people with T1D that LDL-C was not a good predictor of cardiovascular disease. New insights suggest that elevated TG-rich lipoproteins are associated with the residual risk of atherosclerotic cardiovascular disease [27, 28]. Furthermore, there is evidence from genetic studies demonstrating that elevated TG-rich lipoproteins are causally associated with atherosclerotic cardiovascular disease [29, 30]. A cause-and-effect relationship between elevated triglyceride-rich lipoproteins and atherosclerosis was independent of low HDL cholesterol levels. Recent research based on Mendelian randomization studies also supports a causal relationship between plasma TG levels and atherosclerotic cardiovascular disease, including CAD (OR 1.33, 95% CI 1.24–1.43, p = 2.47 × 10^−13) [31]. The strong association between TG and CAD we observed was consistent with prior studies in T1D patients [6, 32, 33]. There are many potential mechanisms to explain the relationship between CAD and TG. The degradation products of TG-rich lipoproteins elicited cytotoxicity and apoptosis in human macrophages and endothelial cells, leading to an atherosclerotic process [34]. Furthermore, they increased the expression of macrophage inflammatory proteins, adhesion molecules, and coagulation factors (e.g., tumor necrosis factor-α, interleukin-1β, monocyte chemotactic protein-1, intercellular adhesion molecule-1) that lead to atherosclerosis [35, 36]. Finally, there is evidence from the Mendelian randomization approach on the causal relationship between elevated triglyceride-rich lipoproteins and low-grade inflammation [37]. It is worth noting that Tolonen et al. [38] observed that the association between CAD and TG was particularly observed at a lower concentration of TG. According to these authors, the TG cutoff point for predicting the occurrence of CAD in T1D was 0.94 mmol/L. The increasing importance of the link between TG and CAD was also seen by the authors of the latest guidelines, who suggested moderately increased fasting TG levels (more than > 1.7 mmol/L) as an indication for treatment, which should aim for TG levels less than 1.1 mmol/L [8]

Taken together, our findings strongly support intensive TG control in T1D patients qualified for pancreas transplantation. Current recommendations should be reconsidered to capture and minimize the residual cardiovascular risk in potential pancreas recipients with T1D.

Limitations

Our study has some limitations. The 2 main limitations are due to the application of a cross-sectional approach. First, the risk factors were measured only once, so the observed associations represented only a single-point estimate. Second, the results did not allow for establishing a causal relationship, which makes it impossible to say whether the high level of TG is a cause, an effect, or a marker of CAD. The third limitation is the small size of the group, which is due to the small number of patients referred for pancreas transplantation in Poland. Another limitation is the use of statins and antihypertensive drugs, which may have confounded the presented relationships. Nonetheless, the great value of our study is that the presented results reflect daily medical practice, and therefore the conclusions could be adopted for routine pre-transplant management.

Conclusions

Fasting TG levels were positively associated with the prevalence of CAD in potential pancreas recipients with T1D. The concentration of TG has the potential to serve as an important modifiable RF or at least as an important biomarker in this group and should be included in the cardiological pre-transplant assessment. Further research is needed to understand the mechanisms of the relationship between TG and CAD and develop more effective prevention and treatment methods.

Article information

Data availability statement

Raw data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request, in accordance with the policy of the authors' institutions.

Ethics statement

The study was conducted according to the Declaration of Helsinki. The study protocol was approved by the local Bioethics Committee at the Medical University of Warsaw, Poland (no. KB/115/2018). All the patients enrolled signed an informed consent form to participate in the study.

Author contributions

Małgorzata Buksińska-Lisik: conceptualization, methodology, acquisition of data, analysis and interpretation of data, investigation, project administration, writing — original draft preparation, review, and editing. Przemysław Kwasiborski: analysis and interpretation of data, writing — original draft preparation. Paweł Skrzypek: acquisition of data. Artur Mamcarz: critical revision of the manuscript for important intellectual content. Wojciech Lisik: acquisition of data, critical revision of the manuscript for important intellectual content. All authors approved the final version of the submitted manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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In-Hospital Hyperglycemia and Sliding Scale Insulin Regimen as Risk Factors for Critical Illness and Mortality in Patients with COVID-19 and Type 2 Diabetes

ABSTRACT

Objective: Diabetes mellitus (DM) and in-hospital hyperglycemia are independent risk factors for severe pneumonia and mortality in patients with coronavirus disease 2019 (COVID-19). We aimed to identify the prevalence of critical COVID-19 disease and mortality in hospitalized patients with DM and COVID-19 infection and associated risk factors before the introduction of COVID-19 vaccines.

Materials and methods: All hospitalized patients ≥ 18 years old with DM and COVID-19 during 2020 were included. We compared clinical findings and outcomes between survivors and non-survivors. The main risk factors associated with mortality and critical COVID-19 were determined.

Results: Among 248 patients, 59.3% were discharged and 40.7% died. Their mean age was 60 ± 12.9 years, and 58.1% were male. Critical COVID-19 was associated with age ≥ 60 years (OR 3.13, p = 0.003), hypoxemia on admission (OR 4.86, p ≤ 0.001), inpatient hyperglycemia (OR 6.15, p = 0.001), and sliding scale insulin (OR 2.70, p = 0.010). Increased mortality was associated with age ≥ 60 years (OR 2.29, p = 0.028), cancer (OR 7.77, p = 0.023), hypoxemia (OR 3.42, p = 0.004) hypotension on admission (OR 10.21, p = 0.044), leukocytosis (OR 2.42, p = 0.048), anemia (OR 3.07, p = 0.013), thrombocytopenia (OR 4.66, p = 0.006), inpatient hyperglycemia (OR 4.44, p = 0.007), and sliding scale insulin (OR 3.24, p = 0.003). The basal bolus

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regimen was protective mortality (OR 0.17, p = 0.003). Conclusions: COVID-19 was associated with a mortality of 40.7% in hospitalized patients with DM. Inpatient hyperglycemia and sliding scale insulin increased the risk of critical COVID-19 and mortality, while the implementation of a basal plus insulin regimen (basal insulin + sliding scale prandial insulin) protected against mortality. Defining strategies for in-hospital glucose control should be a priority. (Clin Diabetol 2025; 14, 1: 40–49)

Keywords: type 2 diabetes, COVID-19, mortality

Introduction

Since the outbreak of the coronavirus-19 (COVID-19) infection in December 2019, more than 350 million people worldwide have been infected and more than 5 million have died as of this writing. Before the application of vaccines against COVID-19 in Mexico, the median age of COVID-19 infection was 44 years [interquartile range (IQR) 33–56], affecting both men and women equally; approximately a quarter of patients required hospitalization, and overall reported mortality was about 10% [1]. The clinical presentation ranged from mild symptoms to severe pneumonia, sepsis, acute kidney injury, acute respiratory distress syndrome, respiratory failure, and multiple organ dysfunction. Mortality due to COVID-19 pneumonia has been related to male gender, older age (> 60 years), and comorbidities such as diabetes mellitus (DM), obesity, hypertension, respiratory disease, cancer, and cardiovascular disease [2–6].

Among patients with COVID-19 infection, DM is an independent risk factor for severe pneumonia, hospitalization, admission to an intensive care unit, and intubation [7–8]. Prior to vaccination, in patients with DM and COVID-19, the incidence rate of death was as high as 1153 cases per 100,000 person-days, compared to 292 cases per 100,000 persons-days in those without DM [1]. Older age, male gender, lower socioeconomic status, poorer glycemic control, previous cardiovascular disease, smoking status, and the presence of comorbidities are some of the factors that have been recognized as predictors of poor outcome [9]. The need to carry out studies to ascertain the relationship between patients with COVID-19 and diabetes was established. However, most of the studies have been carried out with a population that does not include patients of Hispanic origin; hence, little is known about the predictors of mortality and severe disease in this group of patients.

The present study was conducted with the aim of identifying the prevalence of hospital mortality in Hispanic patients with DM and COVID-19 pneumonia. The main factors associated with hospital mortality and critical disease were also identified.

Materials and methods

Hospital-based cohort study

An analytical, retrospective, cohort study was carried out in High Specialty Medical Unit (UMAE) No. 25 of the Mexican Institute of Social Security (IMSS) in Monterrey, Nuevo León, Mexico during the period from March to December 2020. Additionally, patients from 6 IMSS second-level hospitals and one third-level private hospital, all with similar low and medium socioeconomic and cultural status, were included. The study was carried out in accordance with the ethical standards established by the general health law and was approved by the local research and ethics committee in health research of the IMSS.

Study population

All patients aged 18 years and older with DM and a confirmed diagnosis of COVID-19-associated pneumonia who required hospitalization were included. Patients with viral pneumonia due to agents other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (respiratory syncytial virus, parainfluenza, influenza A, influenza B), glycated hemoglobin (HbA1c) < 6.5% at admission without a history of diabetes, and those with incomplete medical records were excluded. Regarding diabetes, age at diagnosis, disease duration, comorbidities, treatment, and presence of chronic complications were assessed. The clinical and biochemical outcome of hospital-acquired pneumonia was reviewed, including the presence and remission of symptoms, oxygen requirement, admission to the intensive care unit, biochemical parameters, treatment for diabetes, mechanical ventilation requirement, and reason for discharge.

DM was defined in patients who had a history documented medication usage or HbA1c at admission ≥ 6.5%. Diabetic kidney disease was defined in patients with a history of GFR ≤ 60 mL/min/1.73 m^2 during the 3 months prior to hospitalization. The diagnosis of diabetic neuropathy was defined according to what was documented in the medical file or use of treatment. History of acute myocardial infarction, unstable angina, cerebral vascular event, peripheral vascular disease, and amputations were defined as macrovascular complications.

The diagnosis of pneumonia due to SARS-CoV-2 was made by means of a pharyngeal exudate sample,

which was analyzed by reverse transcriptase polymerase chain reaction test. COVID-19 infection was categorized as mild, severe, or critical. Critically ill patients were defined as those with acute respiratory distress syndrome, septic shock, cardiac dysfunction, and/or exacerbation of cardiac, hepatic, renal, central nervous system, or thrombotic disease. Acute kidney injury was documented when there was an increase in serum creatinine concentration of ≥ 0.3 mg/dL during 48 h or an increase of ≥ 1.5 times in the last 7 days, or diuresis < 0.5 mL/kg/h for 6 hours.

The criteria considered for hospital discharge were absence of fever for at least 3 days, radiological improvement, and remission of respiratory symptoms [10].

Outcomes

Patients were classified into 2 groups according to the reason for discharge: group 1 (survivors) were patients who were discharged or transferred to another hospital, and group 2 (non survivors) included patients who died during hospitalization. The primary outcome was to determine the prevalence of in-hospital mortality and critical COVID disease. Demographic, clinical, and biochemical differences were considered as secondary outcomes.

Statistical analysis

Analysis was performed using SPSS version 22.0. Data were assessed for parametric and nonparametric distribution by the Kolmogorov-Smirnov test. Quantitative data with a normal distribution were presented as mean (SD) and those with a non-normal distribution were presented as median IQR. Qualitative variables are presented as frequency and percentage. Student's t-test or the Mann-Whitney U test was used for continuous variables. To evaluate differences in categorical variables we used the chi-square test or the Fisher´s exact test. Adjusted logistic regression analysis was performed to determine the main risk factors associated with mortality and critical illness. Odds ratios and 95% confidence intervals were calculated. A value of $p < 0.05$ was considered significant.

Results

A total of 248 patients were included, of whom 147 (59.3%) were discharged and 101 (40.7%) died. Table 1 shows the demographic characteristics and evolution of DM. The mean age was 60 (± 12.9) years, and 144 patients (58.1%) were male. Household managers/ /homemakers and retired patients comprised the majority of our study population (67/119 patients [56.3%]). 86.2% (n = 212/246) of patients were at home prior to admission and 13.8% (n = 34/246) were transferred from another hospital. Regarding the reason for admission, 102 patients (41.1%) were hospitalized with a confirmed diagnosis of COVID-19 pneumonia, 130 (52.4%) as a suspected case, and 16 (6.5%) were admitted for other reasons. The use of oral antidiabetics was the most common treatment modality (63.7%). Regarding complications associated with DM, macrovascular disease was identified in 16.1%, diabetic kidney disease in 15.7%, neuropathy in 6.5%, and retinopathy in 3.2%, with no differences between the 2 groups. More than half of the patients used antihypertensive treatment (56.9%), 12.9% statins, and 6.5% acetylsalicylic acid. Mortality increased with age, especially in those over 60 years of age, longer duration of DM, and use of antihypertensive treatment. Obesity was found in 40.0% and hypertension in 65.7%, without finding significant differences between the 2 groups. Chronic kidney disease and cancer were identified as more prevalent in patients with fatal outcomes, while dyslipidemia was more frequent in those who survived.

Table 2 shows the clinical and biochemical characteristics at hospital admission. In the non-survivor group, lower blood pressure and oxygen saturation were identified, as well as a higher proportion of patients with fever, dyspnea, and headache. Among the radiographic findings, bilateral infiltrate was the most prevalent, i.e., in 63.2% of the patients. Furthermore, differences in leukocytosis, lymphocytosis, neutrophilia, anemia, and thrombocytopenia were detected, in addition to a lower glomerular filtration rate and higher levels of C-reactive protein and D-dimer in non-survivors.

Regarding the clinical evolution during hospitalization (Tab. 3), 34.7% of the patients were classified as mild disease, 24.6% as moderate, and 40.7% in critical condition, with critical disease being most prevalent in non-survivors. The median hospital stay was 8 days (IQR 4–12): 8 days (IQR 5–13) in patients who survived and 7 days (IQR 3–10) in non-survivors ($p = 0.03$). 47.5% of the patients who were non-survivors were on invasive mechanical ventilation, compared to 4.5% of those who survived. The mean glucose during hospitalization was 10.1 mmol/L, IQR 7.66-14.49 mmol/L (182 mg/dl, IQR 138–261 mg/dL). A higher prevalence of hospital hyperglycemia was found in the group of non-survivors (67.7% vs 48.4%, $p=0.02$). A sliding scale insulin scheme was used in about half of the patients. Regarding the rest of the treatment, the use of basal insulin with special interest in basal plus insulin regimen (basal insulin + sliding scale prandial insulin) was more prevalent in survivors, while continuous insulin infusion was more common in non-survivors. 65.6% of patients required glucocorticoids

Table 1. Demographic Characteristics

	Total	Survivors	Non-survivors	P-value
N [%]	248	147 (59.3)	101 (40.7)	
Age [years], X [SD]	60.1 (12.9)	56.9 (12.5)	64.7 (12.1)	< 0.001
Age, n [%]				< 0.001
18–39 [years]	15 (6.0)	13 (8.8)	2 (2.0)	
40–79 [years]	217 (87.5)	130 (88.5)	87 (86.1)	
≥ 80 [years]	16 (6.5)	4 (2.7)	12 (11.9)	
Male gender, n [%]	144 (58.1)	91 (61.9)	53 (52.5)	0.14
Smoking, n [%]	23/192 (12.0)	14/118 (11.9)	9/74 (12.2)	0.95
Occupation, n [%]				0.04
Home/retired	67/119 (56.3)	30/65 (46.2)	37/54 (68.5)	
Employee	30/119 (25.2)	20/65 (30.8)	10/54 (18.5)	
Health	15/119 (12.6)	12/65 (18.5)	3/54 (5.6)	
Others	7/119 (5.8)	3/65 (4.6)	4/54 (7.4)	
Age at diagnosis of diabetes [years], X [SD]	49.6 (12.7)	47.9 (12.5)	52.4 (12.7)	0.06
Duration of diabetes [years], med [IQR]	10 (4–15)	8.5 (2–13)	10 (5–15)	0.02
Duration of diabetes, n [%]				0.18
< 5 [years]	40/139 (28.2)	30/86 (34.9)	10/53 (18.9)	
5–10 [years]	25/139 (17.3)	15/86 (17.4)	9/53 (17.0)	
> 10 [years]	75/139 (53.9)	41/86 (47.6)	34/53 (64.2)	
Home diabetes medication regimen				
Oral antidiabetics, n [%]	128 (63.7)	75 (65.2)	53 (61.6)	0.60
Insulin, n [%]	76 (37.8)	45 (39.1)	31 (36.0)	0.65
No treatment, n [%]	27 (13.4)	15 (13.0)	12 (14.0)	0.85
Diabetes associated complications				
Macrovascular, n [%]	40 (16.1)	20 (13.6)	20 (19.8)	0.19
Diabetic kidney disease, [%]	39 (15.7)	20 (19.8)	19 (12.9)	0.14
Neuropathy, n [%]	16 (6.5)	10 (6.8)	6 (5.9)	0.78
Retinopathy, n [%]	8 (3.2)	5 (3.4)	3 (3.0)	0.94
Other comorbidities				
Obesity, n [%]	66/165 (40.0)	36/101 (35.6)	30/64 (46.9)	0.15
Hypertension, n [%]	163 (65.7)	92 (62.6)	71 (70.3)	0.21
Dyslipidemia, n [%]	34 (13.7)	26 (17.7)	8 (7.9)	0.03
End stage renal disease, n [%]	29 (11.7)	12 (8.2)	17 (16.8)	0.03
Cancer, n [%]	14 (5.6)	3 (2.0)	11 (10.9)	**0.01**
Other treatments				
Any treatment for hypertension, n [%]	141 (56.9)	74 (50.3)	67 (66.3)	**0.01**
ACE inhibitors or MRAs [%]	119 (48.0)	65 (44.2)	54 (53.5)	0.15
Statins, n [%]	32 (12.9)	24 (16.3)	8 (7.9)	0.05
Acetylsalicylic acid, n [%]	16 (6.5)	8 (5.4)	8 (7.9)	0.43

In addition to these data, the following were evaluated: origin at the time of hospitalization and case definition at admission
ACE — angiotensin-converting enzyme; IQR — interquartile range; MRAs — mineralocorticoid receptor antagonists; SD — standard deviation

during hospitalization, and this requirement was more prevalent in the non-survivor group. The patients who died presented greater complications compared to the survivors in terms of admission to intensive care (23.8% vs. 11.6%, p = 0.01), acute respiratory distress syndrome (71.3% vs. 8.8%, p < 0.001), acute kidney injury (27.7% vs. 7.5%, p < 0.001), hemodynamic shock (19.8% vs. 1.4%, p < 0.001), sepsis (18.8% vs. 4.1%, p < 0.001), metabolic acidosis (11.9% vs. 2.0%, p = 0.01), disseminated intravascular coagulation (7.9% vs. 0.7%, p = 0.01), and multiple organ failure (15.8% vs. 0%, p < 0.001).

Table 2. Clinical and Biochemical Characteristics at Hospital Admission

	Total	Survivors	Non-survivors	P-value
N (%)	248	147 (59.3)	101 (40.7)	
Time from onset of symptoms to hospitalization (days)	7 (3–10)	7 (3–9)	7 (3–10)	0.76
Signs and anthropometry at admission				
Body mass index [kg/m2]	31.1 (7.2)	31.2 (7.2)	30.9 (7.5)	0.88
Respiratory rate [bpm]	22 (20–25)	22 (20–25)	22 (19–25)	0.87
Heart rate [bpm]	90 (80–103)	89 (80–100)	90 (80–105)	0.33
Temperature [°C]	36.8 (36.3–37.3)	36.7 (36.1–37.2)	36.8 (36.4–37.5)	0.45
Systolic pressure [mmHg]	126 (110–138)	130 (115–140)	120 (107–137)	0.02
Diastolic pressure [mmHg]	75 (67–81)	79 (70–82)	70 (36–80)	0.001
Oxygen saturation [%]	89 (83–94)	91 (86–95)	86 (76–92)	< 0.001
Symptoms, n [%]				
Dyspnea	190 (76.6)	105 (71.4)	85 (84.2)	0.02
Fever	162 (65.3)	87 (59.2)	75 (74.3)	0.01
Cough	152 (61.3)	88 (59.9)	64 (63.4)	0.58
Myalgias and arthralgias	108 (43.5)	67 (45.6)	41 (40.6)	0.44
Fatigue	88 (35.5)	53 (36.1)	35 (34.7)	0.82
Headache	82 (33.1)	56 (38.1)	26 (25.7)	0.04
Radiographic findings, n [%]				0.33
Bilateral infiltrate	115/182 (63.2)	72/112 (64.3)	43/70 (61.4)	
Ground glass opacities	49/182 (26.9)	29/112 (25.9)	20/70 (28.6)	
One-sided consolidation	13/182 (7.1)	6/112 (5.4)	7/70 (10.0)	
Biochemical findings				
Leukocyte count [K/uL]	9.8 (7.2–13.6)	9.0 (7.1–12.7)	10.9 (8.0–14.6)	0.03
Lymphocyte count [K/uL]	1.1 (0.7–1.6)	1.2 (0.8–1.7)	0.9 (0.7–0.9)	0.05
Neutrophils [K/uL]	8.3 (5.2–11.9)	7.1 (4.9–10.2)	9.6 (5.8–13.0)	0.01
Hemoglobin [g/dL]	13.2 (11.2–14.7)	13.7 (12.0–14.8)	12.1 (10.2–14.3)	0.001
Platelet count [K/uL]	238 (166–318)	255 (187–335)	195 (140–287)	0.001
Albumin [g/dL]	3.3 (2.8–3.6)	3.4 (2.9–3.7)	3.1 (2.7–3.6)	0.07
Glucose [mmol/L]	10.7 (7.3–15.9)	10.7 (7.7–15.7)	10.2 (7.0–16.8)	0.68
Creatinine [mg/dL]	0.83 (0.64–1.50)	0.80 (0.67–1.10)	0.90 (0.60–1.70)	0.13
Glomerular filtration rate [ml/min]	91 (45–107)	94 (54–110)	75 (32–102)	0.005
D-Dimer [ng/mL]	638 (395–1144)	601 (396–932)	950 (368–1766)	0.08
C-reactive protein [mg/L]	70 (15–127)	42 (11–87)	109 (41–191)	0.009

Continuous variables are expressed as median and interquartile range

Table 4 shows the main risk factors associated with mortality and critical illness. The results were adjusted by age, gender, and duration of DM. Among the general characteristics, age ≥ 60 years was significantly associated with critical illness and mortality while cancer was associated with higher mortality risk. Regarding the clinical presentation of COVID-19: hypoxemia, oxygen requirement at hospital admission and thrombocytopenia were all associated with severe illness and mortality. Hypotension, leukocytosis, and anemia were only associated with higher mortality risk. We found no association between the duration of DM, the presence of DM-related complications, or diabetes treatment prior admission with the risk of critical illness or fatal outcome. The persistence of hospital hyperglycemia significantly increased the risk of critical illness and mortality. In addition, sliding scale insulin during hospitalization increased both critical illness and mortality while the use of basal plus insulin scheme (basal insulin + sliding scale prandial insulin) reduced the risk of both critical illness and mortality.

Table 3. Clinical Course During Hospitalization

	Total	Survivors	Non-survivors	P-value
N [%]	248	147 (59.3)	101 (40.7)	
COVID-19 severity, n [%]				**< 0.001**
Mild	86 (34.7)	77 (52.4)	9 (8.9)	
Severe	61 (24.6)	52 (35.4)	9 (8.9)	
Critical	101 (40.7)	18 (12.2)	83 (82.2)	
Hospital stay, median [IQR] (days)	8 (4–12)	8 (5–13)	7 (3–10)	0.03
Maximum oxygen requirement, n (%)				<0.001
Noninvasive mechanical ventilation	5/231 (2.2)	2/132 (1.5)	3/99 (3.0)	
Invasive mechanical ventilation	53/231 (22.9)	6/132 (4.5)	47/99 (47.5)	
Average glucose during hospitalization [mg/dL], median [IQR]	182 (138–261)	176 (122–250)	202 (157–289)	0.02
Hospital hyperglycemia [> 180 mg/dL], n [%]	90/160 (56.3)	46/95 (48.4)	44/65 (67.7)	0.02
Treatment, n [%]				
Glucocorticoids	148/229 (64.6)	79/133 (59.4)	69/96 (71.9)	0.05
Statins	38/226 (16.8)	23/128 (18.0)	15/98 (15.3)	0.59
Plasmapheresis	14/248 (5.6)	7/147 (4.8)	7/101 (6.9)	0.47
Dialysis / hemodialysis	6/236 (2.5)	3/136 (2.2)	3/100 (3.0)	0.70
Treatment of hyperglycemia, n [%]				
Sliding scale insulin	119/239 (49.8)	64/140 (45.7)	55/99 (55.6)	0.09
Basal plus (Basal + sliding scale insulin)	46/239 (19.2)	37/140 (26.4)	9/99 (9.1)	0.01
Basal bolus (Basal + fixed prandial insulin)	37/239 (15.5)	21/140 (15.0)	16/99 (16.2)	0.73
Continuous insulin infusion	11/239 (4.6)	1/140 (0.7)	10/99 (10.1)	0.01
No treatment	26/239 (10.9)	17/140 (12.1)	9/99 (9.1)	0.50
Complications during hospitalization, n [%]				
Admission to intensive care	41/248 (16.5)	17/147 (11.6)	24/101 (23.8)	0.01
Acute respiratory distress syndrome	85/248 (34.3)	13/147 (8.8)	72/101 (71.3)	< 0.001
Acute kidney injury	39/248 (15.7)	11/147 (7.5)	28/101 (27.7)	< 0.001
Diabetic ketoacidosis	13/248 (5.2)	5/147 (3.4)	8/101 (7.9)	0.12
Hemodynamic shock	22/248 (8.9)	2/147 (1.4)	20/101 (19.8)	< 0.001
Sepsis	25/248 (10.1)	6/147 (4.1)	19/101 (18.8)	< 0.001
Metabolic acidosis	15/248 (6.0)	3/147 (2.0)	12/101 (11.9)	0.01
Disseminated intravascular coagulation	9/248 (3.6)	1/147 (0.7)	8/101 (7.9)	0.01
Multiple organ failure	16/248 (6.5)	–	16/101 (15.8)	< 0.001

COVID-19 — coronavirus-disease-2019; IQR — interquartile range

Discussion

We found a mortality rate of 40.7% in Hispanic patients with DM hospitalized with COVID-19 pneumonia in the period prior vaccination. Our main findings included the following: 1) Inpatient hyperglycemia was associated with a 4-fold increase of mortality and 6-fold increase of critical COVID-19 infection. 2) The use of sliding scale insulin further increased the risk of critical disease and death while the implementation of a basal plus insulin (basal insulin + sliding scale prandial insulin) regimen protected against fatal outcome. 3) The DM profile prior to hospitalization did not influence the outcome during hospitalization. 4) We did not find a higher prevalence of fatal outcome associated with hypertension, obesity, or cardiovascular disease.

Hyperglycemia at admission is an independent predictor of poor prognosis with a longer hospital stay and a 4-fold increase in mortality [7–11]. In patients with DM, an increased acute-to-chronic glycemic ratio [12] and poor glycemic control (blood glucose > 10 mmol/L or 180 mg/dL) have shown to be associated with increased risk of hospital mortality, intensive care unit admission, and mechanical ventilation. Conversely, patients with DM and optimal glycemic control (blood glucose 3.89–10 mmol/L or 70–180 mg/dL and HbA1c 6.6–8.2% prior to and during hospitalization)

Table 4. Risk Factors Associated with Critical COVID or Fatal Outcome (Logistic Regression Analysis)

Risk factor	Critical COVID			Risk factor	Fatal outcome		
	OR	IC 95%	P-value		OR	IC 95%	P-value
Age ≥ 60 [years]	3.13	1.49–6.58	0.003	Age ≥ 60 [years]	2.30	1.09–2.39	0.03
Oxygen requirement on admission	8.16	1.75–38.08	0.008	Cancer	7.77	1.34–45.19	0.02
Hypoxemia on admission [≤ 90%]	4.87	2.14–11.52	<0.001	Hypoxemia on admission [≤ 90%]	3.42	1.49–7.89	0.004
Thrombocytopenia [< 150 K/UL]	3.13	1.07–9.16	0.03	Hypotension on admission [≤ 90 mmHg]	10.22	1.070–97.598	0.04
Inpatient hyperglycemia (> 10 mmol/L)	6.15	2.07–18.24	0.001	Leukocytosis [≥ 10 K/UL]	2.42	1.01–5.80	0.05
Sliding scale insulin	2.70	1.27–5.72	0.01	Thrombocytopenia [< 150 K/UL]	4.66	1.56–13.99	0.006
				Anemia [< 12 g/dL]	3.07	1.262–7.482	0.01
				Inpatient hyperglycemia (> 10 mmol/L)	4.44	1.50–13.19	0.007
				Sliding scale insulin	3.24	1.49–7.02	0.003
				Basal + sliding scale insulin	0.17	0.05–0.55	0.003

The logistic regression analysis model was performed to evaluate the risk factors for mortality and critical COVID. Mortality adjusted to age ranges, gender and time of evolution of diabetes. In addition to these variables, the following were analyzed: Female gender, smoking, hypertension, obesity, cardiovascular disease, end stage renal disease, hypotension on admission [≤ 90 mmHg], anemia [< 12 g/dL], glomerular filtration rate [≤ 60 mL/min], diabetes duration, insulin treatment, oral antidiabetics, macrovascular complications, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic ketoacidosis on admission, ACE inhibitors or MRAs, acetylsalicylic acid, statins, glucose at admission ≥ 10 mmol/L, and continuous insulin infusion. These variables were not shown to be risk factors for mortality or severe disease

have significant reductions in inflammatory markers, severity of complications, and mortality risk compared to those with glucose levels >10 mmol/L (180 mg/dL) [8–13]. In our patients, persistent hyperglycemia during the hospital stay was more prevalent in those who died compared to those who survived (67.7% vs. 48.4%, p = 0.016), with a mean glucose level of 11.21 mmol/L, IQR 8.71–16.04 mmol/L (202 mg/dL, IQR 157–289 mg/dL) compared to 9.77 mmol/L, IQR 6.77–13.88 mmol/L (176 mg/dL, IQR 122–250 mg/dL) (p = 0.018). Furthermore, inpatient hyperglycemia increased the risk of both critical illness and mortality with an odds ratio (OR) of 6.15 (confidence interval [CI] 95% 2.07–18.24, p = 0.007) and 4.44 (CI 95% 1.50–13.19, p = 0.007), respectively.

The mechanisms that associate DM and adverse outcomes of COVID-19 include the following: 1) chronic inflammation, dysregulated immune function, and hypercoagulable state related to COVID-19 and DM [7]; 2) attenuation of the synthesis of pro-inflammatory cytokines and a drastic reduction in regulatory T-cell levels in the presence of hyperglycemia and insulinopenia [14–15]; 3) pulmonary dysfunction [8]; 4) possible increase of the viral replication rate and direct structural changes in the lung [16]; 5) secretion of hormones such as catecholamines and glucocorticoids, present in the state of acute infection [17]; and 6) increased levels and activity of angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP-4) enzyme in patients with diabetes, which has also been identified as the cellular receptor that mediates the entry of SARS-COV2 into cells and subsequently leads to viral replication [7]. In our patients, some of these mechanisms were shown by the high prevalence of acute respiratory distress syndrome, acute kidney injury, hemodynamic shock, sepsis, metabolic acidosis, disseminated intravascular coagulation and multiple organ failure in non-survivors compared to survivors.

Patients with COVID-19 and DM have 40–50% increased risk of 28-day mortality compared to patients without DM [1–9]. According to McGurnaghan et al., longer duration of DM, more previous hospitalizations for hyperglycemia, diabetic ketoacidosis, lower estimated glomerular filtration rate, having retinopathy and the more diabetes drug subclasses were all associated with fatal or critical COVID-19 disease among patients with DM [9]. Holman conducted a large cross-sectional study and reported that previous cardiovascular disease is a risk factor for mortality [18]. Previous meta-analyses have also reported that older age, male sex [19–21],

current smoking [20] and obesity [22–23] confer highest COVID-19 in-hospital mortality. We found no association between mortality and the above-mentioned factors in our population.

Diabetes management during COVID-19 infection is crucial for the prevention of adverse outcomes. Among all the diabetes medications, metformin and DPP-4 inhibitors are the ones most studied that might contribute to mitigating the progression to severe COVID-19 complications. In experimental studies, metformin reduces the SARS-CoV-2 viral recognition by the ACE2 receptor [24]. Metformin has also been proven to reduce pro-inflammatory cytokines and contribute to a lower coagulation risk [7]. In patients with COVID-19 and DM, the use of metformin prior to and during the infection has been associated with reduced inflammation and reduced risk of early death [25–28]. The use of DPP-4 inhibitors has been related with a reduction of cytokine production, a decrease in platelet aggregation, and a reduction of the COVID-19 virus entry and replication within the respiratory tract [7]. A meta-analysis based on retrospective observational studies provided inconclusive results on the association between the use of DPP-4 inhibitors and outcomes of COVID-19 and concluded a neutral effect [29]. In a randomized clinical trial of hospitalized adult patients with DM and COVID-19, the use of linagliptin did not alter the clinical outcome compared with standard care [30]. Regarding the use of other diabetes medications, there are proven anti-inflammatory and anti-thrombotic benefits with the use of glucagon-like peptide-1 agonists (GLP-1a), sodium-glucose-linked transporter-2 inhibitors (SGLT2i), and thiazolidinediones [7]. The use of oral DM treatments was the most common treatment modality (63.7%) in our patients. Because this was a population that received care in a public hospital in Mexico, most of the patients who used oral treatments were on metformin or sulfonylureas, with very few patients using iDPP4, SGLT2i, or GLP-1a, so it was not possible to analyze whether there were differences in mortality or complications by evaluating each of the treatments individually.

The Standards of Medical Care in Diabetes recommend insulin as the preferred treatment for hospital hyperglycemia [31]. These recommendations are justified by the benefits of insulin beyond glycemic control: while it decreases plasma glucose with no adverse effects other than hypoglycemia, it also has crucial anabolic activity by stimulating protein synthesis, inhibiting intracellular triglyceride lipolysis, preventing diabetic ketoacidosis, limiting the lipotoxic effects of free fatty acids, and may also have a regulatory influence in the inflammatory response to infections [13–32]. Sardu et al. showed that insulin infusion-mediated optimal blood glucose control improves prognosis for hospitalized patients with COVID-19 and hyperglycemia [13]. Insulin can also be a marker for advanced DM and more severe disease. Riahi et al. showed that patients who were on insulin at home and were hospitalized with COVID-19 had increased rates of death, as well as peak in-hospital insulin requirements [33]. A meta-analysis that included observational studies that evaluated the use of insulin in patients with COVID-19 infection concluded that insulin treatment was associated with a more than twofold risk of mortality; however, there was substantial heterogeneity among studies, and they did not discriminate between prior use and inpatient use of insulin [32]. In our results, we found that prior insulin use was similar among both groups. On the other hand, the use of only sliding scale insulin without basal insulin during hospitalization was associated with both higher mortality (OR 2.70, CI 95% 1.27–5.72, $p = 0.01$) and critical COVID-19 infection (OR 3.24, CI 95% 1.49–7.02, $p = 0.003$) wile a basal plus insulin scheme (basal insulin + sliding scale prandial insulin) was related with an improved outcome.

Statins are frequently prescribed in patients with diabetes due to their cardioprotective effect. In patients with COVID-19, statin therapy is associated with a 35% decrease in the adjusted risk of COVID-19 related mortality. Some explanations of this benefit are their anti-oxidative, anti-inflammatory, anti-arrhythmic, anti-thrombotic properties as well as beneficial effects on endothelial dysfunction with a potential protective effect against fatal respiratory, cardiovascular, and thromboembolic complications in patients with COVID-19 [34]. In our patients, despite dyslipidemia being more prevalent in those who survived as well as the use of statins, we did not find a significant association with increased mortality or critical COVID.

As a retrospective study we must consider some limitations in the interpretation of our results: 1) It was not possible to collect the information regarding clinical history and DM profile in all our patients, including glycemic control prior to hospitalization, which could explain their lack of association with mortality and severe disease. 2) The inclusion of the patients was carried out consecutively, so it was not possible to match the patients; however, the estimation of risk factors was made adjusted to age, gender, and time of evolution of diabetes. 3) Our results reflect the rate of mortality and critical illness in patients with type 2 diabetes before the existence of vaccines for COVID-19, so they could differ from the population that is currently vaccinated. On the other hand, we confirmed that the persistence of hospital hyperglycemia and the insulin regimen

used during hospitalization are independent factors that influence mortality and critical illness, similarly to what happens with patients with diabetes who are hospitalized for other diseases.

Conclusions

In this study we observed a mortality rate of 40.7% in Hispanic patients with DM hospitalized with COVID-19 pneumonia prior to vaccination. Our baseline finding of advanced age as a mortality risk factor is in line with previous evidence in the literature. Our study also found that mortality increases in those with longer duration of DM and in those who use antihypertensive treatment. Patients with hypoxemia, oxygen requirement at hospital admission and thrombocytopenia were associated with severe illness and mortality.

Inpatient hyperglycemia significantly increased the risk of critical illness and mortality. The use of sliding scale insulin without basal insulin also increased the risk of critical illness and death, while the implementation of a basal plus insulin scheme (basal insulin + sliding scale prandial insulin) protected against fatal outcome. According to these results, defining strategies for in-hospital glucose control should be a priority for health.

Article information

Author contribution

D.L.Q.F. conceptualized the study, researched the data, wrote the manuscript, and reviewed/edited the manuscript. G.G.M. conceptualized the study and researched the data. I.A.M.D conceptualized the study and researched the data. D.S.G. researched the data. C.A.O.V researched the data. F.J.G.M. conceptualized the study and researched the data. R.O.M.C conceptualized the study and researched the data. J.J.C.D conceptualized the study and researched the data. R.F.G.B. conceptualized the study and researched the data. P.P.S. wrote the manuscript and reviewed/edited the manuscript. C.C.C. wrote the manuscript and reviewed/edited the manuscript. M.A.S.M. researched the data. S.G.C.H. researched the data. A.L.S.N. researched the data. E.S.C. researched the data.

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Conflict of interest

The authors declare no conflict interests.

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A Call for a Modern Satyagraha Against Metabolic Syndrome

ABSTRACT

Objective: In 1923, while India was engaged in the Flag Satyagraha movement for independence, the medical community witnessed the discovery of insulin and the early recognition of metabolic syndrome (MetS) by Swedish physician Eskil Kylin. This article draws parallels between the historical Satyagraha movement and the current fight against MetS, advocating for a comprehensive and integrated approach to managing this syndrome. We explore the multifaceted role of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in managing MetS, emphasizing their cardioprotective and renoprotective benefits.

Materials and methods: A detailed review of existing literature on MetS, its definitions, prevalence, and management strategies was conducted. The therapeutic potential of SGLT2i was examined through a meta-analysis of randomized controlled trials (RCTs) to assess their impact on key components of MetS, including fasting plasma glucose, waist circumference (WC), blood pressure, body weight, and uric acid levels.

Results and conclusions: SGLT2is, including empagliflozin, dapagliflozin, and canagliflozin, demonstrated significant efficacy in improving several components of MetS. Notably, these agents reduced fasting plasma glucose by up to 30.02 mg/dL and WC by 1.28 cm, while also providing modest reductions in systolic blood pressure and body weight. Additionally, SGLT2is were associated with significant reductions in uric acid levels, contributing to their renoprotective effects. Despite the minimal impact on high-density lipoprotein (HDL) cholesterol levels, SGLT2is showed broad cardiometabolic benefits, including anti-inflammatory effects and modulation of sympathetic nervous system activity. Public health initiatives must also prioritize lifestyle modifications and early detection to curb the rising prevalence of this condition. (Clin Diabetol 2025; 14, 1: 50–55)

Keywords: metabolic syndrome, SGLT2 inhibitors, cardioprotection, renoprotection, public health, diabetes, cardiovascular disease, hypertension, insulin resistance

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Introduction

In 1923, India saw a powerful movement of nonviolent resistance known as the Flag Satyagraha, led by Ballav Bhai Patel in Nagpur — a significant moment in

Table 1. Definitions of Metabolic Syndrome

Organization	Year	Mandatory criterion	Additional criteria	Diagnosis
WHO [4]	1998	Insulin resistance	Waist-hip ratio [> 0.90 (M), > 0.85 (F)], BMI > 30 kg/m^2, TG ≥ 150 mg/dL, HDL < 35 mg/dL (M), < 39 mg/dL (F), BP ≥ 140/90 mmHg, microalbuminuria	Insulin resistance + ≥ 2 other criteria
EGIR [5]	1999	Hyperinsulinemia (plasma insulin > 75th percentile)	WC ≥ 94 cm (M), ≥ 80 cm (F), TG ≥ 177 mg/dL, HDL < 39 mg/dL, BP ≥ 140/90 mmHg	Hyperinsulinemia + ≥ 2 other criteria
AACE [6]	2003	None	BP ≥140/90 mmHg, fasting glucose 110–125 mg/dL, TG ≥ 150 mg/dL, family history of diabetes, hypertension, or CVD, sedentary lifestyle	≥ 2 criteria plus family history or sedentary lifestyle
IDF [7]	2005	Central obesity [WC ≥ 94 cm (M), ≥80 cm (F)]	Fasting glucose ≥100 mg/dL, TG ≥ 150 mg/dL, HDL < 40 mg/dL (M), <50 mg/dL (F), BP ≥ 130/85 mmHg	Central obesity + ≥ 2 other criteria
NCEP ATP III [8]	2000, revised 2005	None	WC > 40 inches (M), > 35 inches (F), fasting glucose ≥ 100 mg/dL, HDL < 40 mg/dL (M), < 50 mg/dL (F), BP ≥ 130/85 mmHg	≥ 3 criteria

AACE — American Association of Clinical Endocrinologists; BMI — body mass index; BP — blood pressure; CVD — cardiovascular disease; EGIR — European Group for the Study of Insulin Resistance; F — female; HDL — high-density lipoprotein; IDF — International Diabetes Federation; M — male; NCEP ATP III — National Cholesterol Education Program Adult Treatment Panel III; TG — triglycerides; WC — waist circumference; WHO — World Health Organization

the nation's struggle for independence [1]. In the same year, medical science celebrated a milestone with the awarding of the Nobel Prize for the discovery of insulin, forever transforming the management of diabetes [2]. However, a lesser-known yet profoundly important development from 1923 also merits attention: the identification of metabolic syndrome (MetS) by Swedish physician Eskil Kylin, who described a pathological triad of hypertension, hyperglycemia, and hyperuricemia [3]. This syndrome, first observed over a century ago, continues to pose a significant threat to global health, and its growing prevalence demands a robust response.

As we reflect on the enduring spirit of resistance embodied by the Satyagraha movement, it is time to channel that same energy into combating MetS, which has emerged as a silent epidemic. Just as the Satyagraha sought to dismantle colonial oppression, our modern "Satyagraha" must be directed against the interlinked pathologies that constitute MetS, which collectively increase the risk of cardiovascular diseases (CVD), diabetes, and other life-threatening conditions.

The challenge of metabolic syndrome

MetS is a constellation of interrelated risk factors that includes central obesity, insulin resistance, dyslipidemia, hypertension, and hyperuricemia. These factors collectively elevate the risk of developing CVD and type 2 diabetes (T2D), making MetS a significant public health concern. The World Health Organization (WHO) first conceptualized MetS in 1998, emphasizing insulin resistance as a mandatory criterion alongside obesity, dyslipidemia, and hypertension [4]. Subsequent definitions by the European Group for the Study of Insulin Resistance (EGIR) in 1999 [5], the American Association of Clinical Endocrinologists (AACE) in 2003 [6], the International Diabetes Federation (IDF) in 2005 [7], and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) in 2000 [8], have further refined the diagnostic criteria, each adding nuances based on regional and clinical perspectives. Despite the variations in definitions, the prevalence of MetS is consistently high, particularly in urban populations and among women. Studies in India suggest that the age-adjusted prevalence of MetS is approximately 25%, with higher rates in women compared to men [9]. This high prevalence, coupled with the syndrome's role as a precursor to several chronic conditions, underscores the need for heightened awareness and more effective screening and management strategies. The clustering of risk factors, particularly in populations like the Indian Armed Forces, where fitness levels are typically high, highlights the insidious nature of MetS and the importance of early intervention [10]. In addition, recent research highlights that anthropometric measures, such as waist, hip, and mid-thigh circumferences, can serve as easy and inexpensive markers for predicting T2D, even in resource-constrained settings, thereby reinforcing the importance of early detection and intervention in populations at risk [11].

Table 1 summarizes the various definitions of MetS, highlighting the differences in mandatory and additional criteria across the major health organizations.

Recent studies underscore the importance of a comprehensive approach to the management of MetS, which should address not only hyperglycemia but also other components like hyperuricemia and hypertension. Among the therapeutic strategies that have shown promise is the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i). These agents, initially developed for the management of T2D, have demonstrated pleiotropic benefits that extend beyond glycemic control.

SGLT2 inhibitors: a comprehensive approach to metabolic syndrome

SGLT2i have increasingly been recognized for their multifaceted role in managing MetS, a condition characterized by a cluster of interrelated risk factors, including insulin resistance, central obesity, dyslipidemia, hypertension, and hyperuricemia. In a comprehensive meta-analysis [12] involving 26,427 patients, SGLT2i demonstrated significant efficacy in improving several key components of MetS. Specifically, SGLT2i, including dapagliflozin and empagliflozin, were associated with a mean reduction in fasting plasma glucose (FPG) of up to 30.02 mg/dL at higher doses (10 mg), while lower doses (2.5 mg) showed a minimal impact on FPG. Furthermore, these agents reduced WC by an average of 1.28 cm, highlighting their beneficial effects on central obesity, a core feature of MetS [12].

In addition to glycemic control, SGLT2i have shown a modest yet meaningful impact on systolic blood pressure (SBP), with reductions averaging 1.37 mmHg. Notably, dapagliflozin exhibited a more pronounced effect on SBP compared to empagliflozin, possibly due to differences in the number of randomized controlled trials (RCTs) analyzed and the baseline characteristics of the study populations. Although the reduction in diastolic blood pressure (DBP) was not statistically significant, the overall cardiometabolic profile of patients treated with SGLT2i improved significantly [12].

SGLT2i also exert beneficial effects on body weight (BW) and uric acid (UA) levels, both of which are crucial in the management of MetS. The use of SGLT2i resulted in an average weight loss of 1.79 kg, which is particularly important given the role of obesity in the pathogenesis of MetS. Additionally, these inhibitors significantly reduced UA levels by 1.03 mg/dL, with dapagliflozin showing a more substantial effect compared to empagliflozin [12]. This reduction in UA is clinically relevant, given the strong association between hyperuricemia and both MetS and CVD.

Despite these promising outcomes, the effect of SGLT2i on high-density lipoprotein (HDL) cholesterol was not significant, as indicated by a non-significant change in HDL levels across the analyzed studies [12]. This finding contrasts with the improvements observed in other MetS components and may reflect the heterogeneity in the study designs, patient populations, and treatment durations included in the analysis.

The mechanisms by which SGLT2i improve MetS components are multifactorial and include enhanced glucosuria, osmotic diuresis, natriuresis, and modulation of key metabolic pathways. These effects contribute to improvements in insulin sensitivity, blood pressure regulation, and lipid metabolism, making SGLT2i a valuable tool in the integrated management of MetS [13]. Furthermore, the upregulation of glucose transporter 9, which facilitates UA excretion in the kidneys, and the modulation of genes involved in lipid metabolism, such as peroxisome proliferator-activated receptor alpha (PPAR-) and adenosine monophosphate-activated protein kinase (AMPK), further underscore the broad cardiometabolic benefits of these agents [14, 15].

SGLT2i offer a comprehensive approach to managing MetS by targeting multiple risk factors simultaneously. While the improvements in individual MetS components may be modest, the cumulative benefits, particularly in reducing cardiovascular risk and improving overall metabolic health, position SGLT2i as a cornerstone in the treatment of MetS. Further research, particularly in the form of long-term RCTs, is warranted to fully elucidate the potential of SGLT2i in comparison to existing therapeutic strategies and lifestyle interventions.

A call for action: a modern Satyagraha

The parallels between the historical Satyagraha movement and the modern fight against MetS are compelling. Just as the Satyagraha movement was grounded in the principles of truth and nonviolent resistance, the contemporary battle against MetS must be rooted in scientific evidence and a commitment to holistic, patient-centered care. This new "Satyagraha" calls for healthcare providers to adopt an integrated approach that addresses the multifactorial nature of MetS.

Furthermore, this movement should extend beyond the clinic and into the community. Public health initiatives that promote lifestyle modifications — such as healthy diets, regular physical activity, and weight management — are essential in preventing the onset of MetS. Additionally, increasing public awareness about the condition and its long-term risks is crucial for early intervention and effective management.

MetS, once a debated concept, is now universally acknowledged as a critical public health issue both globally and in India. MetS is characterized by a cluster of risk factors, including central obesity, insulin resist-

Table 2. Recommendations for Physical Activity to Prevent and Manage Metabolic Syndrome [16–18]

Exercise type	Minimum recommendation	Optimal recommendation
Endurance exercises	150 min/week of moderate-intensity aerobic activity (e.g., 30 min/day, 5 days/week) or 75 min/week of vigorous-intensity activity	300 min/week of moderate-intensity aerobic activity (e.g., 60 min/day, 5 days/week) or 150 min/week of vigorous-intensity activity
Muscle-strengthening	Exercises involving major muscle groups on 2–3 days per week	Exercises involving major muscle groups on 2–3 days per week
Flexibility exercises	Gentle stretching (including yoga) for 5–10 min before and after exercise sessions	Gentle stretching (including yoga) for 5–10 min before and after exercise sessions
Lifestyle modifications	Incorporate physical activity into daily routines, such as using stairs, walking, cycling, and standing during phone calls	Maintain an active lifestyle with a conscious effort to reduce sedentary habits and integrate more physical movement into daily activities

Table 3. Dietary Guidelines for the Prevention and Control of Metabolic Syndrome [17, 19–21]

Nutritional element	Guideline
Total fats	Less than 30% of daily calories, preferably under 20%
Saturated fats	Less than 10% of daily calories, preferably under 7%
Trans-fatty acids	Should be eliminated from the diet
Polyunsaturated/monounsaturated fats	Polyunsaturated fats up to 10% of calories, monounsaturated fats 10–15%
Refined sugars	Less than 10% of daily caloric intake
Salt	Less than 5 grams per day
Dietary cholesterol	Less than 300 mg per day
Dietary recommendations	Emphasize whole grains, legumes, fruits, vegetables, and low-fat dairy products. Minimize gravied, fried, creamed, and sugared foods

ance, dyslipidemia, hypertension, and hyperuricemia, all of which significantly elevate the risk of CVD and T2D. Given the widespread prevalence and serious health implications of MetS, it should be a primary focus for public health policymakers and healthcare professionals.

Preventing and managing MetS effectively requires two core strategies: encouraging regular physical activity and maintaining a healthy diet. Public health guidelines emphasize the necessity of these lifestyle modifications. Physical activity recommendations, outlined in Table 2, suggest a minimum of 150 minutes per week of moderate-intensity aerobic exercise, such as brisk walking, or 75 minutes of vigorous-intensity activity. For those seeking optimal health benefits, increasing this to 300 minutes per week of moderate exercise or 150 minutes of vigorous exercise is advisable. Additionally, muscle-strengthening exercises should be incorporated into routines 2 to 3 times a week, focusing on major muscle groups. Flexibility exercises, including yoga, should also be practiced regularly to improve overall physical health [16–18].

Equally important is dietary management, as detailed in Table 3. The guidelines recommend a balanced diet where total fat intake is limited to less than 30% of daily calories, with an emphasis on polyunsaturated and monounsaturated fats. Saturated fats should constitute less than 10% (preferably under 7%) of total calories, and trans-fatty acids should be eliminated entirely. Refined sugars should make up less than 10% of caloric intake, and daily salt consumption should be restricted to under 5 grams. A diet rich in whole grains, legumes, fruits, vegetables, and low-fat dairy products is strongly advised, while foods high in cholesterol and unhealthy fats should be minimized [17, 19–21].

Public health initiatives should extend beyond individual counseling and include community-wide efforts to promote an active lifestyle and healthy eating habits. Encouraging simple lifestyle changes, such as using stairs instead of elevators, opting for walking or cycling instead of driving, and standing while on the phone, can significantly aid in the prevention of MetS.

Early detection of MetS is also crucial. Regular screening for central obesity, particularly through WC measurements by healthcare workers, provides an effective and straightforward method for identifying individuals at risk.

Table 4. Beneficial Effects of SGLT2 Inhibitors on Cardiometabolic Health [15, 22]

Cardiometabolic aspect	Impact of SGLT2 inhibitors
Blood pressure	Reduction in systolic BP (approx. -1.37 mmHg)
	Greater reduction observed with dapagliflozin vs. empagliflozin
Glycemic control	Reduction in fasting plasma glucose (up to -30.02 mg/dL)
	HbA1c reduction (-0.68%)
Weight management	Average weight reduction (-1.79 kg)
Lipid profile	Minimal impact on HDL; however, improvements in triglycerides in animal models
Renal protection	Reduction in uric acid levels (-1.03 mg/dL)
	Renoprotective effects, including reduced albuminuria
Anti-inflammatory effects	Reduction in inflammatory markers (e.g., IL-1β, IL-6)
Sympathetic nervous system	Modulation of SNS activity, reducing blood pressure and enhancing metabolic control

BP — blood pressure; IL — interleukin, HbA1c — glycated hemoglobin; HDL — high-density lipoprotein; SGLT2i — sodium-glucose cotransporter-2 inhibitors; SNS — sympathetic nervous system

Furthermore, there is a pressing need for targeted research into the etiology, epidemiology, and management of MetS, especially within the Indian context. Developing culturally tailored, evidence-based definitions and cut-off values for key parameters such as WC, waist-hip ratio, and fasting plasma glucose is essential for more accurate diagnosis and treatment of MetS in the Indian population. By prioritizing these public health measures and supporting them with focused research, we can substantially reduce the burden of MetS and its related health complications.

This structured approach, integrating both physical activity and dietary modifications, provides a comprehensive framework for the prevention and management of MetS, addressing both individual and community health needs.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as a cornerstone in the battle against MetS, offering a comprehensive approach that addresses multiple aspects of this syndrome. SGLT2is, such as empagliflozin, dapagliflozin, and canagliflozin, have shown considerable promise in improving glycemic control, reducing body weight, lowering blood pressure, and decreasing uric acid levels. Beyond their glucose-lowering effects, these agents confer significant cardioprotective and renoprotective benefits, making them a powerful tool in the integrated management of MetS.

Table 4 summarizes the cardiometabolic benefits of SGLT2i, emphasizing their broad impact on various aspects of MetS and highlighting their role as a comprehensive treatment strategy.

The mechanisms by which SGLT2i exert their benefits are multifaceted. These agents reduce blood glucose levels by inhibiting glucose reabsorption in the renal proximal tubule, leading to glucosuria. This effect is independent of insulin and provides glycemic control even in patients with insulin resistance. Additionally, SGLT2is promote osmotic diuresis and natriuresis, contributing to reductions in plasma volume, blood pressure, and arterial stiffness. These effects not only improve metabolic parameters but also mitigate the risk of heart failure and other cardiovascular events [22].

Recent studies have also highlighted the anti-inflammatory properties of SGLT2is, which play a crucial role in reducing atherosclerosis and endothelial dysfunction — key drivers of CVD in MetS patients. By downregulating markers of inflammation, such as IL-1β, IL-6, and TNF-α, and improving lipid profiles, SGLT2is help to stabilize plaques and reduce the risk of adverse cardiovascular outcomes [23].

SGLT2is have been shown to modulate sympathetic nervous system (SNS) activity, which is often upregulated in patients with MetS and contributes to hypertension and insulin resistance. By reducing SNS activation, SGLT2is not only lower blood pressure but also enhance metabolic control, offering a dual benefit in managing both hypertension and insulin resistance [22, 24].

The comprehensive benefits of SGLT2is extend beyond the individual components of MetS, providing a holistic approach to managing this complex syndrome. As healthcare providers, it is imperative to embrace these therapeutic advancements and integrate them into our treatment strategies. Public health initiatives must also prioritize lifestyle modifications, such as promoting physical activity and healthy dietary habits, to prevent the onset of MetS. Early detection and intervention, particularly in high-risk populations, are crucial for curbing the global burden of this condition.

In conclusion, just as the Flag Satyagraha played a pivotal role in India's fight for independence, a modern Satyagraha against MetS can be instrumental in combating the escalating prevalence of this condition. By leveraging the full therapeutic potential of SGLT2i and fostering a culture of prevention and early intervention, we can make significant strides in improving public health outcomes and reducing the burden of chronic diseases associated with MetS.

Article information

Author contributions

SSS: study design, literature search, intellectual content, manuscript preparation and review

AT: study design, literature search, intellectual content, manuscript preparation and review

SM: study design, literature search, intellectual content, manuscript preparation and review BS: intellectual content, manuscript preparation and review

JP: intellectual content, manuscript review

SRJ: intellectual content, manuscript review, study supervision

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Small Steps, Big Changes: The Impact of Daily Step Counts on Diabetes Prevention and Management — A Systematic Review

ABSTRACT

Objective: Physical activity is one of the primary components of non-pharmacological therapy for impaired glucose metabolism. The following study aimed to investigate the impact of daily step counts on the prevention and management of type 2 diabetes (T2D).

Materials and methods: A systematic review of 15 publications available from scientific databases (PubMed, Medline, Google Scholar, WOS) spanning the period 2014–2024 was conducted.

Results: Daily physical activity, which can be measured indirectly by the daily step count, has been shown to reduce overall morbidity and mortality from T2D. Optimal effects on glucose metabolism are seen with a daily step count ranging from 4500 to 9000 per day. Going beyond this range is not associated with a direct health benefit for T2D prevention and management.

Conclusions: Advising patients with glucose metabolism disorders, such as T2D, to take at least 10,000 steps per day is not recommended due to the lack of metabolic benefits and potential discouragement of setting too high of a goal. Recommending at least 4500 steps per day appears to be more appropriate. (Clin Diabetol 2025; 14, 1: 56–64)

Keywords: steps per day, diabetes, physical activity, treatment; monitoring, prevention

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Introduction

Diabetes mellitus is one of the most prevalent chronic diseases worldwide, with an increasing incidence. The IDF (International Diabetes Federation) estimates that there are currently 537 million people aged 20–79 years with diabetes globally, regardless of etiology. This number is projected to reach 643 million in 2030, and by 2045 it could be as high as 783 million. It also poses an extremely difficult challenge for modern medicine, not only because of its prevalence in the population but also because of the number of deaths caused by it and the huge economic costs associated with the disease. In 2021, diabetes accounted for approximately 6.7 million deaths annually, and its financial burden is estimated at $966 trillion [1].

Pharmacological treatment of this disease is based on insulin therapy as well as non-insulin drugs. It has been suggested that a daily walking habit combined

with the use of an oral hypoglycemic drug helps achieve better control of type 2 diabetes (T2D) [2]. Non-pharmacologic management of all patients with diabetes includes ongoing education and adequate personalized nutritional management, regular physical activity, avoidance of stimulants (e.g., smoking cessation), psychological support, proper sleep hygiene, and maintenance of normal weight or reduction of excessive weight [3].

Physical activity, which is associated with a better quality of life, can reduce morbidity and mortality from many chronic diseases, including diabetes [4]. The steps count taken per day is a simple measure of physical activity. Monitoring daily steps is now easier than ever because applications, smartwatches, wristbands, etc. are becoming increasingly available and popular [5]. For all patient groups, doing a certain amount of physical activity is better than none [4].

The main aim of this paper was to explore the relationship between taking a certain number of steps daily and the prevention and effectiveness of diabetes treatment.

Materials and methods

A systematic review of publications in the PubMed, Medline, Web of Science, and Google Scholar databases was conducted using the keywords "diabetes" and "daily step count". Initially, 450 articles were obtained. Then the time criterion was set to the period 2014–2024. One article from 2012 [6] was included due to its high value of content. As a result of eliminating duplicate articles and setting the time criterion, 134 papers were obtained. Then only full-text papers were included — 98 of them were received. Then, the authors analyzed the titles and abstracts of all papers and selected 17 articles for inclusion in the final analysis.

The impact of physical activity on the course of glucose metabolism disorders from a molecular perspective

During any physical activity, there is an increased uptake of glucose into active skeletal muscle cells through insulin-independent pathways [7]. Regular physical activity improves systemic and hepatic insulin sensitivity, counteracting the progression of insulin resistance in T2D. Physical activity has also been shown to improve the secretory functioning of pancreatic β-cells and impact the functioning of the intestinal microflora [7, 8]. The process of glucose uptake from the extracellular fluid into the skeletal muscle cell is mediated by 2 families of proteins found in the cell membrane: solute carriers family 2 (SLC2), which includes 14 glucose transporters (GLUT1-14), and solute carriers family 5 (SLC5), which includes 6 sodium-dependent glucose cotransporters (SGLT1-6). The GLUT4 isoform is most abundant in skeletal muscle cells, where it moves from intracellular vesicles to the cell surface when exposed to physical activity, playing a significant role in glucose transport into muscle. It is worth noting here that in diabetes, there is an impairment of insulin-stimulated GLUT4 translocation to the cell surface, while exercise-induced translocation remains intact [9]. In the cell, glucose becomes phosphorylated by hexokinase, forming glucose-6-phosphate. According to some studies, aerobic training increases hexokinase activity [9]. Glucose is stored in the cell as glycogen. It is known that aerobic activity increases the level and rate of expression of glycogen in the cell (walking up stairs can intensify glycogen synthesis in the muscles by up to 2 times). The process of glycolysis in the cell takes place after fructose-6-phosphate is converted to fructose-1,6-bisphosphate by the enzyme phosphofructokinase (PFK). Studies have shown a more than twofold increase in PFK activity in association with aerobic training. Therefore, it can be concluded that regular physical activity induces a beneficial effect on systemic glucose homeostasis in every aspect occurring at the molecular level [9].

Muscle cells receive fatty acids through chylomicrons, the number of which remain unchanged, even with chronic training. Instead, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels decrease, while high-density lipoprotein cholesterol (HDL-C) concentrations increase. It is worth noting that lipids could be the substrate in short-interval light- to moderate-intensity exercise [10]. Triacylglycerol lipase of fatty acids is characterized by increased activity during training compared to resting [11]. All these processes prove that physical exercise in any form has health-promoting effects in the context of molecular mechanisms. A summary of the molecular mechanisms of the effects of physical activity on carbohydrate and lipid metabolism is shown in Figure 1.

Daily step count and its health effects

When giving recommendations to patients on the appropriate amount of physical activity, doctors often face the problem of defining the appropriate length or intensity. In 2004, Tudor-Locke and Bassett proposed a classification of physical activity according to the daily step count [12].

Daily step count vs. overall mortality

It is widely believed that a daily step count appropriate for good health is 10,000, but there is only limited scientific evidence to support this thesis. Moreover,

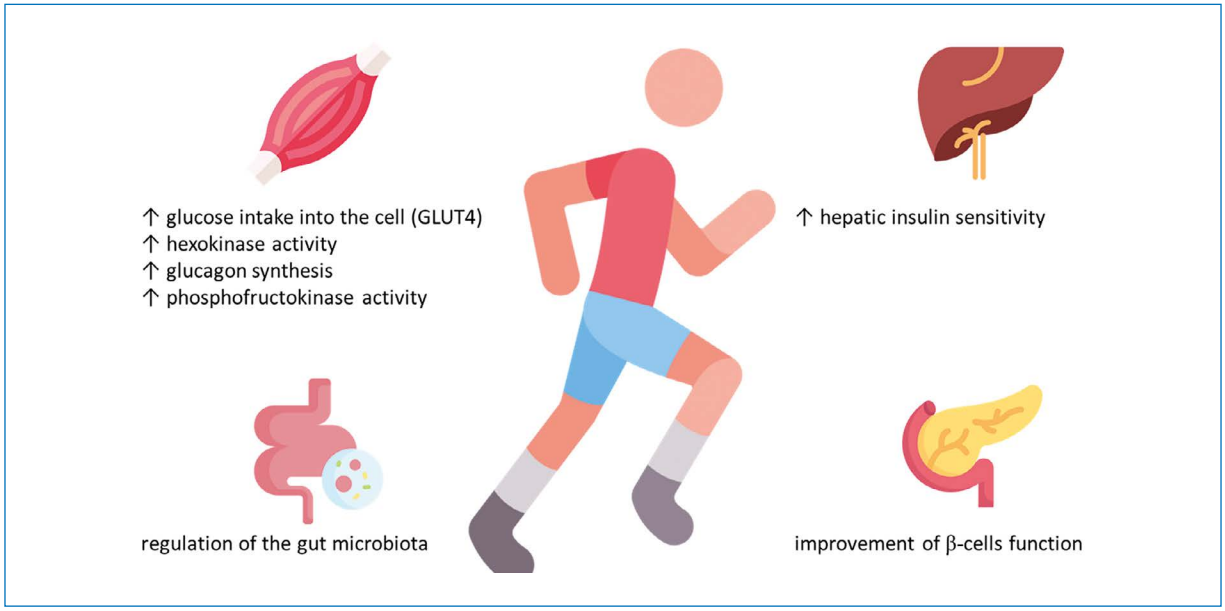

Figure 1. Molecular Mechanism of the Effect of Physical Activity on Carbohydrate and Lipid Metabolism [7–11]

recommending this scale of activity to a patient may discourage people from following it, intensifying a sedentary lifestyle. Saint-Maurice, in a study in a group of 4840 people, observed that a higher daily number of steps was associated with a reduction in overall mortality. According to them, walking 8000 steps per day significantly reduced all-cause mortality compared to 4000 steps per day (HR = 0.49; 95% CI = 0.44–0.55), similarly for 12,000 steps per day (HR = 0.35; 95% CI = 0.28–0.45). Interestingly, mortality was not affected by walking intensity [13]. Similar conclusions were made by Paluch et al. in their meta-analysis of 15 studies (n = 47,471). They divided the subjects into 4 groups, depending on the median daily number of steps, respectively: 3553, 5801, 7842, and 10,901. The HR for mortality compared to group one was, respectively: HR = 0.60; 95% CI = 0.51–0.71 for group two; HR = 0.55; 95% CI = 0.49–0.62 for group three; and HR = 0.47; 95% CI = 0.39–0.57 for group four [14]. This means that taking up physical activity reduces mortality from any cause; however, there is no definitive ratio between these phenomena. In a meta-analysis, Stens et al. (n = 111,309) found that taking 2517 steps per day reduces the risk of death from any cause (HR = 0.92; 95% CI = 0.84–0.999). This relationship was observed up to 8763 steps (HR = 0.40; 95% CI = 0.38–0.43). Above this value, a significant decrease in mortality was no longer observed, so 8800 steps per day was defined as the health optimum [15]. Moreover, Sheng et al. (n = 132,674) indicated that a 1000-step increment is associated with an 11% reduction in mortality (RR = 0.87; 95% CI = 0.84–0.91). In another subgroup of this study (n = 130,209), the authors observed that taking 6893 steps per day versus 4228 steps was associated with a 21.6% lower risk of death from any cause, and taking 9188 steps per day was associated with a 36.65% lower risk (RR = 0.31, 95% CI = 0.23–0.42) [16]. A Polish meta-analysis by Banach et al. (n = 226,889) found that increasing the number of steps by 1000 per day was associated with a reduced risk of death from any cause by 15% (HR = 0.85; 95% CI = 0.81–0.91). In addition, daily step numbers of 5537, 7370, and 11,529, were associated with 48, 55, and 67% lower mortality rates, respectively, compared with 3867 steps [17]. Jayedi et al. in their meta-analysis indicated that each additional 1000 steps were associated with lower mortality (HR = 0.88; 95% CI = 0.83–0.93), as was a total of 10,000 steps (HR = 0.44; 95% CI = 0.31–0.63) [18]. A similar number of steps was indicated by Del Pozo Cruz et al. (n = 78,500). According to them, it was associated with lower overall mortality [mean rate of change (MRC) = = –0.08; 95% CI = –0.11, –0.06] [19]. Ahmadi et al. (n = 72,174) defined the minimum daily step count as 4000–4500, and the best in reducing the risk of mortality from any cause as 9000–10,500 (HR = 0.61; 95% CI = 0.53–0.71 for high sedentary time and HR = 0.69; 95% CI = 0.52–0.92 for low sedentary time) [20]. The results of the above studies suggest that there is no single and universal answer to the question of the optimal daily number of steps. Based on these studies, even at just 4000 steps per day, there may be health

benefits, and increasing this number by 1000 steps is associated with a significantly lower risk of death from any cause. The mortality benefit is proportional to the increase in steps up to 8000–9000 per day.

Interestingly, measuring the number of steps using a wrist pedometer can be characterized by an overestimation of the number of steps, falsifying the results. On the other hand, using a much more precise accelerometer requires a minimum speed of 67 m/min for the measurement to be reliable [16]. In addition, it is indicated that an accelerometer placed near the waist performs better than one on the wrist [21]. This shows that the accuracy of measurements is also affected by the selection of the right device.

Daily steps and progression and treatment outcomes of diabetes

Impact on anthropometric measurements

Majoo et al. conducted a study in a group of 190 people with an average duration of diabetes of 10 years. The average number of steps in this group was 5338, which was characterized as low physical activity. Increasing the number of steps by a standard deviation value (SD = 2609) was associated with a significant reduction in BMI by 1.6 kg/m^2 (95% CI = –2.4, –0.8), waist circumference by 4.6 cm (95% CI = –6.4, –2.8), and waist–hip ratio (WHR) by 0.01 (95% CI = –0.02, –0.00). In addition, increasing the number of steps by the SD value resulted in a decrease in HbA1c by 0.21% (95% CI = –0.41, –0.02), but when adjusted for BMI, WC, or WHR the change was not significant [6]. Herzig et al. (n = 78) noted that taking at least 6520 steps per day or walking for 90 minutes at a speed of 2–3 km/h resulted in a statistically significant reduction in low-density lipoprotein (LDL) levels by 0.7 mmol/L (95% CI = 0.1–1.2) and visceral fat area by 16 cm^2 (95% CI = 7–25) in a 3-month follow-up. In contrast, they found no significant relationship between the daily number of steps and glucose and insulin levels at fasting and 2 h after main meals, or the HOMA-IR index [22]. Improving these indices as components of the metabolic syndrome would enable better control of diabetes. On the other hand, Nakanishi et al. (n = 236), in a 12-month follow-up, noted that patients taking at least 7500 steps per day were significantly more likely to reduce BMI (HR = 4.54; 95% CI = 1.48–13.920) and visceral fat volume (HR = 6.96; 95% CI = 1.98–24.45), independently of sedentary time and waist circumference at high ST segment on electrocardiography (ECG) (HR = 5.27; 95% CI = 1.69–16.47) [23]. Thus, they indicated that physical activity is an important component of diabetes treatment. Ferrari et al. in a study in Latin American countries (n = 2524) observed a weak negative correlation between daily step count and BMI ($r = –0.17$; $p < 0.05$) and waist circumference ($r = –0.16$; $p < 0.05$) [24]. The above data suggest that taking an adequate number of steps (6500–8000) is associated with beneficial effects on metabolic and anthropometric parameters, particularly BMI and adipose tissue volume.

Impact on the risk of developing type 2 diabetes and carbohydrate metabolism

Kraus et al. (n = 7118) divided their study group into 4 cohorts according to average number of steps: 1831, 4652, 7096, and 11,240. The authors observed that increasing the daily number of steps by 2000 to 10,000 steps resulted in a 5.5% significantly lower risk of developing diabetes (HR = 0.95; 95% CI = = 0.92–0.97). The aforementioned number of steps corresponds to about 20 minutes of walking at a moderate pace [25]. Cuthbertson et al. in a study in a group of 6634 U.S. residents of Hispanic origin observed that each 1000-step increase was associated with a 2% decrease in the risk of developing diabetes (HR = = 0.98; 95% CI = 0.95–1.0). Moreover, in adults with pre-diabetes, taking 10,000 steps resulted in a 26% lower risk of developing diabetes compared to 3400 steps (HR = 0.74; 95% CI = 0.58–0.95) [26]. The lower risk of diabetes in this case was mainly related to the reduction of obesity as one of the main factors in the development of this disease, as well as improvements in muscle glucose transport and metabolism [26, 27]. Ballin et al. in a study in a group of 3055 seniors in their 70s observed that a reduction in diabetes risk is most strongly associated with 4500 steps per day, decreasing slightly at 6000 steps, and stabilizing at 8000 steps a day. Those with ≥ 4500 steps per day had a 59% lower risk of developing diabetes than those with a lower step count (HR = 0.41; 95% CI = 0.25–0.66). The authors identified physical activity as a factor that reduces insulin resistance by affecting muscle glucose metabolism and reducing the visceral adipose tissue [28]. Other conclusions were reached by Perry et al. (n = 5677). They noted that any increase in daily steps is reflected in a reduction in diabetes risk. With an increase from 6000 to 10,700, the risk decreased by 44% (95% CI = =15–63%). At an activity of 4301 (10th percentile) the predicted cumulative incidence of the disease was 2.3% (95% CI = 1.4–3.3%), and at 13,245 steps (90th percentile) it was already 0.8% (95% CI = 0.3–1.3%) over 5 years. This represents as much as a 3-fold decrease. Moreover, the result was not influenced by BMI, length of time spent sedentary, or age and gender [29]. Master et al. (n = 6042) observed a decrease in the risk of

diabetes with an increase in the number of steps up to about 9000, while after that it remained constant. Moreover, increasing the number of steps resulted in a 36-50% decrease in BMI [30].

Siddiqui et al. (n = 95) observed that an increase in the average daily number of steps from 4610 to 7245 in the study group resulted in a statistically significant decrease in HbA1c of 1.04% over 3 months. In the control group, taking an average of up to 3431 steps per day, an increase in HbA1c of 0.86% was observed. In contrast, there was no significant change in BMI values in either group. The authors concluded that taking at least 7000 steps per day has a positive effect on glycemic levels in the diabetic patient population [31]. Wang et al. (n = 9509) observed that taking at least 5000 steps per day reduces average weekly glucose levels by about 13 mg/d (95% CI = –22.6; –3.14). An extra day of taking > 8000 steps reduces average weekly glucose levels by 0.47 mg/d (95% CI = –0.77; –0.16) [32]. Similar conclusions were made by Dhali et al. in their review. They noted that increased physical activity resulted in a decrease in fasting glucose levels by 12.37 mg/d, (95% CI = –20.06, –4.68) and HbA1c by 0.35% (95% CI = –0.70, –0.01) [33]. Kerr et al. in a study of 121 Hispanic patients noted that increased step count was associated with decreased HbA1c levels in those < 50 years of age (r = –0.47; p < 0.005) and in those who were overweight (r = –0.429; p = 0.005) [34]. Fayehun et al. in a Nigerian study in a group of 121 diabetic patients noted that a difference of 2913 steps between the study and control groups was associated with a 0.74% lower HbA1c level (95% CI = –1.32%, –0.02%), which indicated a significant improvement in control of carbohydrate balance [35]. The results from the above studies show a significant relationship between daily step count (preferably in the range of 4500–8000) and parameters of carbohydrate metabolism in patients with T2D.

Impact on systemic complications of type 2 diabetes

Researchers agree that physical activity, especially walking, is fundamental to diabetes treatment [36, 37]. It is also one of the effective methods of preventing systemic complications of T2D [36–38].

Macroangiopathy

Yu et al. (n = 1415) analyzed the effect of the step count on the course of diabetes and its associated complications. An increased daily number of steps was associated with reduced subclinical myocardial injury (lower troponin T [β = –0.207; r = 0.14; p < 0.001]) [39]. Zucatti et al. (n = 151) observed that taking > > 4873 steps per day was correlated with lower systolic blood pressure (SBP) values (β = 6.40; 95% CI = = 0.31–12.46; p = 0.040), 24-hour SBP (β = 5.32; 95% CI = 0.89–9.74; p = 0.019), daytime SBP (β = 6.29; 95% CI = 1.90–10.69; p = 0.005), and mean daily BP (β = 3.24; 95% CI = 0.20–6.28; p = 0.037) [40]. Moreover, Yates et al. in a randomized trial (n = 9306) observed that an increase in daily step count by 2000 was associated with a decrease in the risk of a cardiovascular event by 10% (HR = 0.90, 95% CI = 0.84–0.96), and by 8% (HR = 0.92; 95% CI = 0.86–0.99) after one year [41]. Dasgupta et al. (n = 230) noted that an increase of 1000 steps/day was significantly associated with a decrease in carotid-femoral pulse wave velocity (cfPWV) of 0.13 m/s (95% CI = –0.2, –0.02). CfPWV is the gold standard for measuring vessel wall stiffness and overall vascular health [42].

Microangiopathy

Yu et al. (n = 1415) showed that higher daily step count was associated with significantly better renal function and reduced microalbuminuria (lower urine albumin/creatinine ratio [β = –0.0268; r = 0.087; p < 0.001], and higher glomerular filtration rate [β = 0.709; r = 0.16; p < 0.001]) [40]. These data are confirmed by a meta-analysis by Cai et al. The authors, while not indicating the exact number of steps, note the positive effect of physical activity on renal function in patients with diabetes. They observed increases in the glomerular filtration rate [standardized mean difference (SMD) = 0.01, 95% CI = 0.02–0.17] and decreases in the urinary albumin creatinine ratio (SMD = −0.53, 95% CI = −0.72, −0.34), rate of microalbuminuria (OR = 0.61, 95% CI = 0.46–0.81), rate of acute kidney injury (OR = 0.02, 95% CI = 0.01–0.04), and rate of renal failure (OR = 0.71, 95% CI = 0.52–0.97) [43]. Unfortunately, patients with diabetic chronic kidney disease take significantly fewer steps per day than patients without diabetes (3580 vs. 5628, p = 0.008) [44]. Many studies have also reported on the effectiveness of aerobic exercise and physical activity in preventing and inhibiting the progression of microvascular complications of T2D: diabetic foot, diabetic neuropathy, or diabetic retinopathy [45–52]. However, these studies do not indicate the exact cutoff points for the daily number of steps. The results of the presented studies lead to the conclusion that aerobic activity, including walking and Nordic walking, are essential elements in the prevention and treatment of diabetes in the context of its complications.

The above data from the literature review are presented in Table 1. The effect of the optimal number of steps on the development and control of diabetes is shown in Figure 2.

Table 1. The Effect of Daily Step Counts on the Development and Control of Diabetes

Research	Country	Study group	Device used to measure steps	Mean number of steps (SD)	Significant increase in the number of steps	Effect of increasing the number of steps
Manjoo et al. 2012 [6]	Canada	n = 190	Pedometer	5338 (2609)	2609	↓ WHR, ↓ BMI, ↓ waist circumference, ↓ HbA1c
Herzig et al. 2014 [22]	Finland	n = 78	Accelerometer	5870 (3277)	> 6520	↓ LDL, ↓ visceral fat
Nakanishi et al. 2021 [23]	Japan	n = 236	Pedometer	6666 (2981)	7500	↓ BMI, ↓ visceral fat, ↓ waist circumference
Ferrari et al. 2021 [24]	Chile, Argentina, Brazil, Colombia, Costa Rica, Venezuela, Peru, Ecuador	n = 2524	Accelerometer	10,699 (5148)	1000	↓ BMI, ↓ waist circumference
Kraus et al. 2018 [25]	USA	n = 7118	Pedometer	1831 (1151) 4652 (659) 7096 (800) 11,240 (2344)	2000, up to 10,000	↓ the risk of developing diabetes
Cuthbertson et al. 2022 [26]	USA	n = 6634	Accelerometer	8164	1000	↓ the risk of developing diabetes
Ballin et al. 2020 [28]	Sweden	n = 3055	Accelerometer	7193 (3072)	> 4500	↓ the risk of developing diabetes
Perry et al. 2023 [29]	USA	n = 5677	Accelerometer	7924	All	↓ the risk of developing diabetes
Master et al. 2022 [30]	USA	n = 6042	Accelerometer	7731	1000	↓ the risk of developing diabetes, ↓ BMI
Siddiqui et al. 2018 [31]	South Africa	n = 95	Pedometer	4610 (1702) 7245 (1419)	2635 > 7000	↓ HbA1c
Wang et al. 2022 [32]	USA	n = 9509	Pedometer	4833 (3266)	≥ 5000	↓ glucose
Kerr et al. 2024 [34]	USA	n = 121	accelerometer	7751.9 (3255.9)	1000	↓ HbA1c
Fayehun et al. 2018 [35]	Nigeria	n = 46	Pedometer	6507 (1716)	2913	↓ HbA1c
Yu et al. 2023 [39]	China	n = 1415	Pedometer	6370 (4431)	1000	↓ TnT, ↓ UACR
Zucatti et al. 2017 [40]	Brazil	n = 151	Pedometer	6391 (3357)	> 4873	↓ office SBP, ↓ 24 h SBP, ↓ daytime SBP, ↓ mean BP
Yates et al. 2014 [41]	The USA	n = 9306	Pedometer	—	> 2000	↓ risk of cardiovascular event
Dasgupta et al. 2017 [42]	Canada	n = 230	Pedometer, accelerometer	5010 (2800)	> 1000	↓ cfPWV

BMI — body mass index; BP — blood pressure; cfPWV — carotid-femoral pulse wave velocity; HbA1c — glycated hemoglobin; LDL — low-density lipoprotein; n — number; SBP — systolic blood pressure; SD — standard deviation; TnT — troponin T; UACR — urine albumin–creatinine ratio; USA — United States of America; WHR — waist–hip ratio

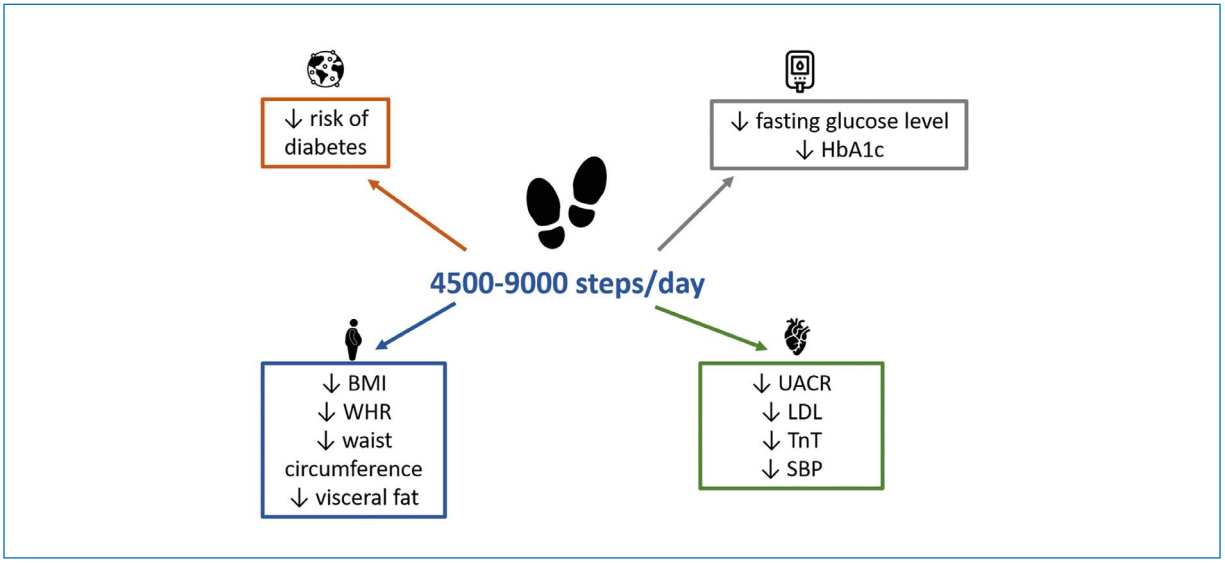

Figure 2. Impact of the Recommended Daily Number of Steps on the Development and Course of Diabetes and their Factors [6, 23–43]

BMI — body mass index; HbA1c — glycated hemoglobin; LDL — low-density lipoprotein; SBP — systolic blood pressure; TnT — troponin T; UACR — urine albumin-creatinine ratio; WHR — waist–hip ratio

Conclusions

The daily number of steps affects both mortality from any cause and the risk of developing and controlling the course of T2D. Any physical activity has positive health effects, but the most beneficial effects for are observed in the range of 4500–9000 steps per day. Advising patients to take 10,000 or more steps per day may negatively affect their motivation to engage in activity, while not significantly improving the risk or course of T2D.

Article information

Author contribution

Conceptualization: MD, DP; methodology: MD, KB, MC, MR, DP; software: MD; data collection: MD, KB, MC, MR, writing — original draft preparation: MD, KB, MC, MR; writing — review and editing: MD, KB, MC, MR, DP; supervision: MD, DP. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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