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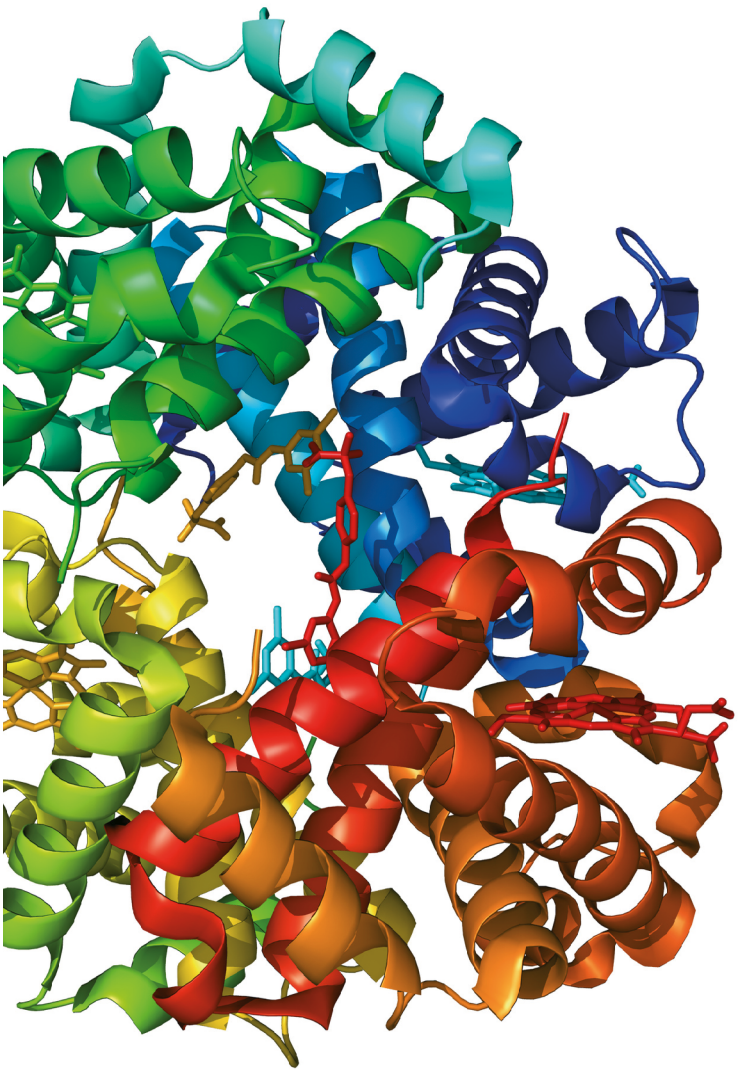

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CLINICAL DIABETOLOGY

2024, Vol. 13, No. 3

Contents

EDITORIAL

Will Continuous Glucose Monitoring Metrics Replace Hemoglobin A1c in Assessing the Risk of Retinopathy (and Other Complications) in Patients with Type 2 Diabetes?
Magdalena Walicka, Edward Franek ____ 129

REVIEW ARTICLE

Time in Range: Unveiling the Correlation with Diabetic Retinopathy in Type 2 Diabetes: A Systematic Review and Meta-Analysis
Kevin Gracia Pratama, Maria Angelia, Yufilia Suci Amelia, Norman Sukmadi ____ 132

ORIGINAL ARTICLES

Effectiveness and Safety of Add-on Once-Daily Liraglutide (1.2 mg) in Type 2 Diabetes Patients with Obesity: Data from a Real-World Cohort of Iraqi Patients
Haider Ayad Alidrisi, Sameh Abed Odhaib, Hussein Ali Nwayyir, Ammar Mohammed Saeed Almomin ____ 140

A Randomized Trial of Carbohydrate Preloading in Patients with Type 2 Diabetes Undergoing General Anesthesia
Silvy Anna Varughese, Dhivya D., Sandhya K. ____ 148

Effects of Sitagliptin versus Empagliflozin on the Stress Hyperglycemic Ratio in People with Type 2 Diabetes: An Open-Label, Randomized Controlled Trial
Marwan S. Al-Nimer, Ismail Ibrahim Latif, Thaqeef Murtada Jawad ____ 156

World Health Organization 5 (WHO-5) Well-Being Index and Problem Areas in Diabetes 5 Scale (PAID-5): A Cross-Sectional Study in Screening Tools for Depression and Anxiety Patients with Type 1 and Type 2 Diabetes in Kerala, India
Juliet George, Kalpana Randhawa ____ 164

Adverse Drugs Reaction and Prescribing Pattern of Antidiabetic Medications in Type 2 Diabetes Patients: An Observational Ambispective Study
Sani Prajapati, Jalpa Suthar, Dhruvi Hasnani, Vipul Chavda ____ 170

Relative Handgrip Strength Positively Correlates with Low-Density Lipoprotein Cholesterol Level in Patients with Type 2 Diabetes: A Cross-Sectional Study
Shuichi Okada, Yasuyo Nakajima, Koji Kikkawa, Atsushi Isoda, Hiroto Hoshi, Junichi Okada, Kazuya Okada, Tsugumichi Saito, Eijiro Yamada, Tetsuro Andou, Kihachi Ohshima ____ 180

LETTERS

Specific Considerations in the Interpretation of the Relationship between Relative Handgrip Strength and Lipid Profile in Type 2 Diabetes
Marwan S. Al-Nimer ____ 185

Letter to the Editor
Shuichi Okada ____ 187

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EDITORIAL
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Will Continuous Glucose Monitoring Metrics Replace Hemoglobin A1c in Assessing the Risk of Retinopathy (and Other Complications) in Patients with Type 2 Diabetes?

Time in range (TIR) is an important contemporary diabetes measurement derived from continuous glucose monitoring (CGM) data [1]. International consensus recognizes TIR as a measure of glycemic control that provides more useful information than hemoglobin A1c (HbA1c) alone [2].

In this issue of "Clinical Diabetology", Pratama et al. presented a systematic review and meta-analysis exploring the link between time in range and diabetic retinopathy (DR). The authors showed that lower TIR is significantly associated with DR [3]. Similar correlations are well known for hemoglobin A1c — higher HbA1c indicates poor metabolic control of diabetes and higher risk of DR [4–6]. The question arises which of these two measures better assesses the risk of retinopathy (but also other diabetes complications) in patients with type 2 diabetes.

Rapidly evolving CGM technology allows for a very deep insight into glycemia. The traditional gold standard for evaluating glycemic control is hemoglobin A1c. Continuous glucose monitoring, however, offers insights that HbA1c cannot provide. HbA1c evaluates static glucose exposure and does not account for intraday glycemic fluctuations that can lead to acute events such as hypoglycemia or postprandial hyperglycemia, both of which are associated with diabetic complications [7–10]. CGM tracks glucose levels consistently, detects fluctuations in blood glucose (glycemic variability), monitors how quickly glucose levels change, assess time spent in hyper- or hypoglycemia and provides a better understanding of an individual's unique glycemic profiles. Continuous glucose monitoring additionally overcomes the problems inherent in HbA1c, such as interference with this metric by anemia, hemoglobinopathies, pregnancy, chronic kidney disease, liver disease.

So far HbA1c has been the sole method systematically studied to assess the risk of diabetes-related complications [11], however, more and more data are available indicating TIR as a metric for correlation with micro- and macrovascular complications [12–19]. Nevertheless, it should be noted that there are no established ranges for TIR that specifically reduce diabetes complications [20]. Most adults with type 1 or type 2 diabetes are recommended to spend at least 70% of the day (around 17 hours) in the target glycemic range of 70 to 180 mg/dL, which corresponds to the approved

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hemoglobin A1c target of approximately 7% [2] and may constitute a threshold value for increased complications' risk. This is, however, not yet confirmed in any prospective outcome study.

There are only very limited data comparing TIR and HbA1c in predicting complications in diabetes. In a cross-sectional analysis of 161 patients with type 1 diabetes, both TIR and HbA1c were associated with adverse consequences of the disease. The authors concluded that TIR may be a better predictor than HbA1c for any complication and microvascular complications, while HbA1c may be a better predictor of macrovascular complications [21]. TIR has been shown to have an inversely linear relationship with HbA1c [22, 23]. However, recently published study by Eliasson et al. [24], besides a strong association between glycated hemoglobin and TIR, describes the relationship between HbA1c and other CGM metrics, such as time above range (TAR) and CGM mean glucose.

A question arises: which CGM parameter would be the best predictor of diabetic complications? As of now, there is no evidence-based answer to this question. One might consider that if prolonged hyperglycemia in patients with poor metabolic control is the primary cause of chronic complications in diabetes, higher TAR appears to be a more natural predictor of them than TIR. Additionally, high TIR can result not only from low TAR but also from extended time below range (TBR). Therefore, any predictions based on TIR should be adjusted considering TBR. This latter parameter needs also to be considered in predicting retinopathy. There is a substantial body of evidence, although mainly from preclinical studies, linking this complication of diabetes to hypoglycemia [25–27].

Further research is needed to address the above-mentioned question and to respond to another one: Is HbA1c measurement necessary in patients using CGM? It appears that it is not, as CGM metrics may perform equally well in assessing blood glucose control and the risk of complications. Additionally, HbA1c can be calculated from blood glucose values. It seems therefore quite possible that in the future, at least in patients using CGM and glucose meters, we will use only a calculated HbA1c value, as at present we use only a GFR value calculated from creatinine concentration.

Understanding of how TIR, TAR and TBR relate to HbA1c is important and discussion on this issue is still ongoing. There is a need to perform large-scale studies to establish clear associations between CGM parameters and HBA1c as well as to compare their usefulness as predictors of the risk of complications in patients with diabetes. For now, available data suggest that monitoring CGM metrics could be a reliable way to assess glucose exposure, potentially reducing the need for HbA1c testing in clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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Time in Range: Unveiling the Correlation with Diabetic Retinopathy in Type 2 Diabetes: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: Research has established an association between glycemic control and retinopathy progression; however, the use of continuous glucose monitoring (CGM) and diabetic retinopathy (DR) progression remains less explored. Our study aims to explore the link between time in range (TIR) and DR and its clinical implications.

Materials and methods: Following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guideline, we conducted a systematic review by searching databases such as PubMed, EBSCO, and ProQuest, supplemented by manual exploration. Studies reporting TIR or other CGM-derived metrics in association with DR were included. The quality of each study was evaluated using the Newcastle-Ottawa Scale (NOS). Review Manager 5.4 software, was used to performed a meta-analysis with random-effects model.

Results: The meta-analysis of five studies indicated significant associations between CGM-derived metrics and diabetic retinopathy. TIR exhibited a mean difference of –6.44 (95% CI: –8.10, –4.78, $p < 0.001$), standard deviation (SD) showed a mean difference of 0.20 (95% CI: 0.16, 0.24, $p < 0.001$), mean amplitude of glycemic excursion (MAGE) displayed a mean difference of 0.45 (95% CI: 0.31, 0.58, $p < 0.001$), and coefficient of variation (CV) demonstrated a mean difference of –0.99 (95% CI: 0.43, 1.55, $p = 0.0006$). Stratification by TIR percentage (< 70% vs. ≥ 70%) revealed an odds ratio of 2.06 (95% CI: 0.85, 4.97, $p = 0.11$) for diabetic retinopathy risk, although statistically insignificant.

Conclusions: Lower TIR is significantly associated with DR in T2D patients. Furthermore, higher SD, MAGE, and CV were linked to the presence of DR. (Clin Diabetol 2024; 13, 3: 132–139)

PROSPERO Registration: CDR42023452999

Keywords: diabetic retinopathy, type 2 diabetes, continuous glucose monitoring

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Introduction

Effective management of type 2 diabetes (T2D) revolves around glycemic control, with hemoglobin A1c (HbA1c) being a central parameter [1]. HbA1c offers a retrospective overview of blood glucose levels spanning several months, providing valuable insights into long-term glycemic regulation [2]. However, its usage is limited by factors such as age, hemolytic anemia,

or conditions that affect the interaction between red blood cells and glucose-bound hemoglobin [2]. Additionally, HbA1c has more limitations such as capturing the fluctuations and patterns of glycemic variability, which lead to differences between mean glucose levels and HbA1c readings [2, 3]. Among the microvascular complications associated with T2D, diabetic retinopathy (DR) is a concern, affecting approximately one-third of T2D patients [4, 5]. It is considered a leading etiology contributing to global blindness [6]. Research showed the prevalence of DR reaching 22.27%, highlighting the crucial need for timely recognition and intervention to reduce any complications [7].

Continuous glucose monitoring (CGM) emerges as a promising new technology in management in T2D [8]. CGM offers a real-time variability of glycemic patterns, offering valuable insight into an individual's glucose levels. In 14 days, CGM provides time in range (TIR), the percentage of time glucose concentrations remain within the range of 70 to 180 mg/dL [8]. Unlike HbA1c, CGM could capture the fluctuations and patterns in glucose levels, providing a more comprehensive picture of an individual's glycemic profile [8, 9]. Furthermore, nocturnal, or asymptomatic hypoglycemia, can be mitigated or minimized. This results is an enhancement of the quality of life for patients with T2D [10]. Additionally, metrics such as mean amplitude of glycemic excursion (MAGE), coefficient of variation (CV), and standard deviation (SD) provide a further understanding of glucose variability and consistency [11]. Research indicates that CGM correlates with HbA1c, thus establishing both approaches as reliable means for monitoring glycemic control. However, CGM has the advantage of detecting hypoglycemia, a capability lacking in HbA1c measurements [12].

Research has established an association between glycemic control and retinopathy progression. A study revealed a 64% increase in the hazard ratio for retinopathy progression with every 10% decrease in TIR [13]. Based on these results, we carried out a systematic review and meta-analysis to highlight the association between TIR and other CGM-derived metrics and DR. Furthermore, we will explore the practical implications for clinical strategies.

Materials and methods

This systematic review was carried out according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [14] and registered in PROSPERO (CDR42023452999).

Subjects

In devising search strategies to identify pertinent studies regarding the association between TIR and DR, we employed medical subject headings (MeSH) and unstructured text expressions. Our thorough search encompassed multiple databases, including PubMed, EBSCO, and ProQuest. For comprehensiveness, we manually reviewed the references of included studies and relevant reviews. Additionally, we searched Google Scholar to uncover any potentially overlooked literature. This exploration involved synonyms and variations of the terms 'time in range', 'continuous glucose monitoring', and 'diabetic retinopathy', restricted to the period from 2013 to 2023 (Suppl. File 1). We excluded studies that reported TIR but did not use CGM in their measurement or studies that reported TIR in type 1 diabetes. Moreover, we confined our investigation to articles published exclusively in English and Indonesian languages.

Research studies could be considered for inclusion if they met the following criteria.

- Designs: randomized controlled trial (RCT), prospective and retrospective studies, case-control, or nested-case control studies, and cross-sectional studies. Case series and case reports are excluded from the analysis.
- Population: T2D patients using CGM
- Intervention/Exposure: DR
- Control/Comparison: Non-DR
- Outcome: TIR and other CGM-derived metrics

Study design

Our study adopted a systematic review and meta-analysis approach to investigate the relationship between TIR in T2D patients and the presence of DR.

Data collection

We employed the Zotero reference manager to manage the identified studies. Initially, a deduplication procedure was done, followed by the evaluation of study titles and abstracts to determine eligibility. This evaluation was conducted independently by two co-authors (KGP and MA). If studies were deemed potentially relevant during this preliminary assessment, a comprehensive full-text review was undertaken. In instances of disagreement during the selection or quality assessment phases, these matters were deliberated with two other co-authors (YSA and NS) to reach a consensus. Relevant data was extracted to perform a qualitative synthesis. The extracted data encompassed details such as author, year of publication, geographical

locations, study designs, inclusion, and exclusion criteria, CGM model, CGM-derived metric (TIR in particular), diagnosis and classification of DR, the incidence of diabetic retinopathy and related key findings.

Outcome

The main outcome of the study was association between DR and CGM-derived metric, including TIR.

Risk of bias

The quality of each study was evaluated using the Newcastle-Ottawa Scale (NOS) [15]. It consists of three main components: Selection, Comparability, and Outcome. Each component is assessed based on predetermined criteria, with higher scores indicating better quality. Selection evaluates representativeness and appropriate selection criteria, Comparability assesses control of confounding factors, and Outcome examines outcome definition and ascertainment methods. Scores between 0–3 suggest significant limitations, 4–6 indicate moderate quality with some limitations, while scores of 7–9 represent good quality and minimal bias.

Statistical analysis

Our approach will involve a comprehensive qualitative synthesis, entailing the integration of data from both the textual content and tables of the studies encompassed. This synthesis is aimed at providing a concise recapitulation and explication of the attributes and discoveries of these studies, alongside delving into the interrelations among them. In cases where the studies demonstrate satisfactory uniformity in terms of design and comparator, we will undertake meta-analyses utilizing the random effects model. The assessment of the overall impact will involve the analysis of the mean difference, along with a 95% confidence interval (CI). For the evaluation of statistical heterogeneity, the I^2 statistic will be employed. The data will be consolidated and computed employing the statistical tool Review Manager (version 5.4, Cochrane Collaboration, Copenhagen Denmark).

Results

Study characteristics

A total of 582 studies were identified through a combination of three databases and manual searching, as depicted in Figure 1. Following a screening process, we ultimately incorporated five studies that investigated the relationship between TIR and various other CGM-derived metrics with DR [16–20]. These studies consisted of a combination of three cross-sectional and two prospective-cohort designs. Geographically, the distribution involved two studies conducted in Japan and three studies conducted in China. The cumulative participant count across all the studies included 7328 individuals, showcasing a diverse demographic range within the context of T2D. In terms of CGM utilization, Medtronic Inc. was highlighted in three studies, while the FreeStyle Libre Pro (Abbott Japan) and iPro 2 (Medtronic Inc.) CGMs were each employed in one study. A spectrum of CGM metrics was gathered throughout these investigations, with consistent measurements of TIR, SD, CV, and MAGE across multiple studies. The assessment of DR was conducted by experienced ophthalmologists in four studies, while non-mydriatic fundus photography was utilized in two studies to ascertain the presence and severity of DR. Furthermore, certain studies categorized DR into subtypes. All the included studies consistently show the connection between CGM metrics and diabetic retinopathy even when adjusting for risk factors and varying patient populations. For a comprehensive overview of study characteristics, refer to Table 1.Top of Form

Meta-analysis of CGM-derived metrics and diabetic retinopathy

The meta-analysis encompassed four CGM-derived metrics: TIR, CV, MAGE and SD. Three studies were employed to compare the TIR percentage between DR and Non-DR. The analysis revealed a mean difference of –6.44 (95% CI: –8.10, –4.78, $p < 0.001$) with moderate heterogeneity ($I^2 = 37\%$). This suggests a significant association between lower TIR and DR (Fig. 2). The analysis of SD, involving four studies, demonstrated a mean difference of 0.20 (95% CI: 0.16, 0.24, $p < 0.001$) with no heterogeneity ($I^2 = 0\%$), indicating a relationship between higher SD and DR (Suppl. File 2). Similarly, the MAGE analysis from three studies indicated a mean difference of 0.45 (95% CI: 0.31, 0.58, $p < 0.001$) with no heterogeneity ($I^2 = 0\%$), emphasizing that higher MAGE is associated with DR (Suppl. File 3). Additionally, the CV percentage analysis from three studies revealed a mean difference of 0.99 (95% CI: 0.43, 1.55, $p = 0.0006$) with substantial heterogeneity ($I^2 = 58\%$), highlighting the link between CV percentage and DR (Suppl. File 4). Furthermore, stratification based on TIR percentage was performed in two studies, with participants categorized as TIR < 70% and TIR ≥ 70% in accordance with American Diabetes Association (ADA) recommendations [21]. While not statistically significant, TIR< 70% exhibited an odds ratio of 2.06 (95% CI: 0.85, 4.97, $p = 0.11$) for the risk of DR (Suppl. File 5). These findings, with corresponding figures, collectively emphasize the significant associations between CGM-derived metrics and the presence of diabetic retinopathy.

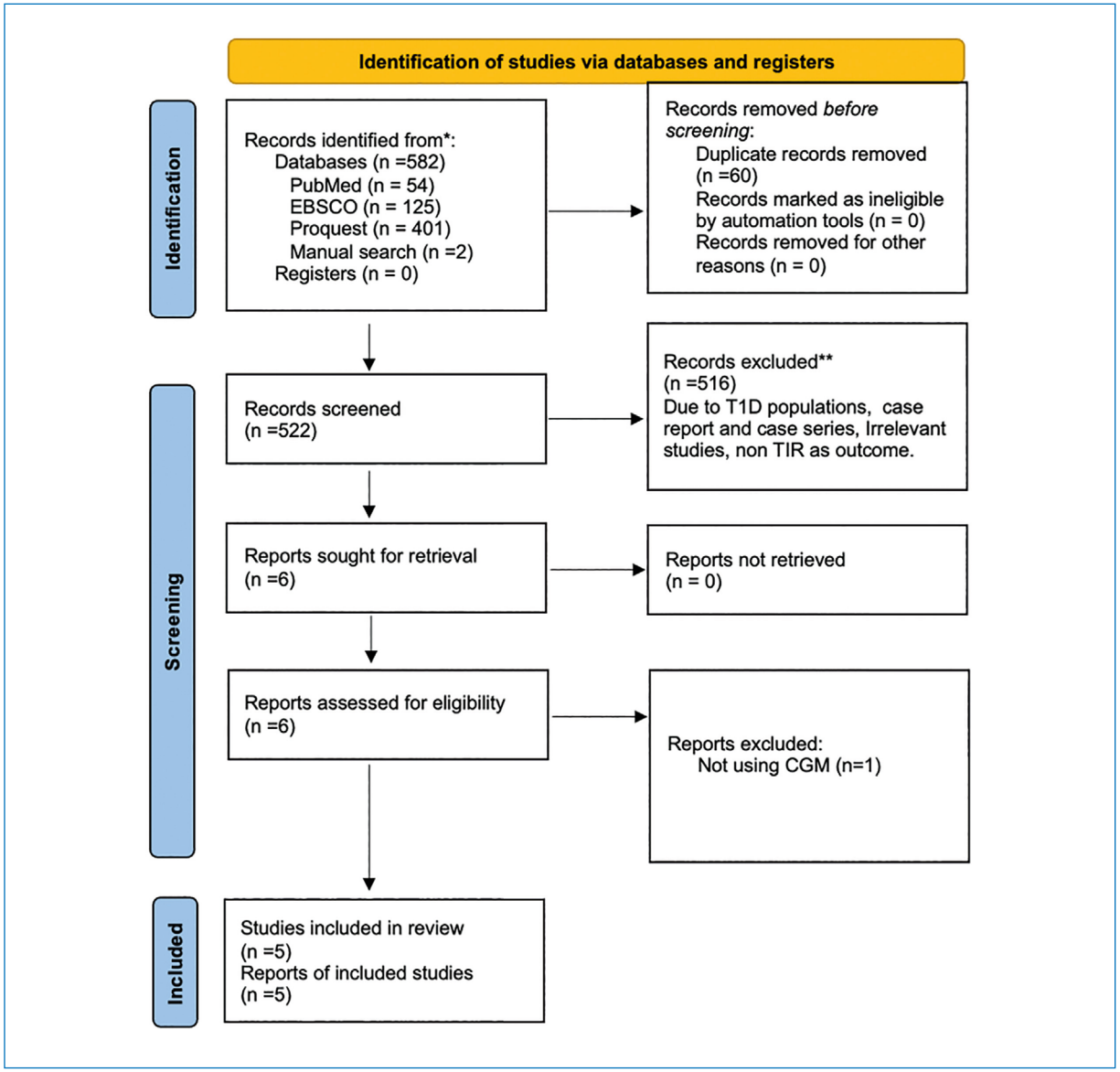

Figure 1. PRISMA Flow Diagram 2020
CGM — continuous glucose monitoring; T1D — type 1 diabetes; TIR — time in range

Risk of bias

Risks of bias were assessed using Newcastle-Ottawa Scale (Suppl. File 6). All of the study are considered good quality.

Discussion

HbA1c offers a basic view of average glucose levels over a few months but lacks insight into daily fluctuations and hypoglycemia [22, 23]. HbA1c mainly reflects high blood sugar and doesn't consider glycemic variability or daily pattern [12]. It can also vary due to conditions like anemia or kidney diseases, even when these conditions are not present, it can give a wide range of mean glucose value [13, 22].

In contrast, CGM metrics, like TIR, offer real-time insights into glycemic control [23]. CGM tracks time spent in target glucose ranges, identifying trends toward high or low blood sugar. [8] This technology catches quick changes in daily glucose levels, enabling prompt therapy adjustments [8]. It is important to note that CGM values can differ from lab-based measurements like HbA1c and mean plasma glucose [24].

Critical CGM metrics include TIR, time below range (TBR), and time above range (TAR), with the goal being to increase TIR while decreasing TBR [8]. This study also considered metrics like MAGE, CV and SD to assess daily glucose variability. Studies have demonstrated the usefulness of these metrics in assessing glucose

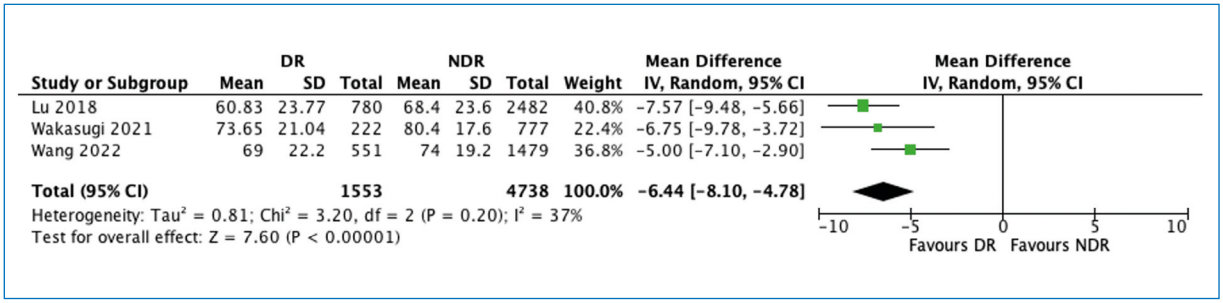

Figure 2. TIR and Diabetic Retinopathy
CI — confidence interval; DR — diabetic retinopathy; NDR — non-diabetic retinopathy; SD — standard deviation; TIR — time in range

variability and its link to microvascular complications in T2D [25, 26].

It has been widely recognized that persistently high levels of blood sugar play a significant role in causing severe complications and mortality in diabetes [27]. Numerous metabolic processes have been implicated in the vascular damage resulting from elevated blood sugar, including the polyol pathway, the accumulation of advanced glycation end products, activation of the protein kinase C pathway, and engagement of the hexosamine pathway [17]. However, presently, the fluctuation of daily blood glucose levels has emerged as a notable contributor to the development of micro- and macrovascular complications in diabetes [27]. Rapid fluctuations in blood sugar levels can lead to increased oxidative stress, inflammation, compromised endothelial function, and changes in gene expression [26].

A Cochrane review reveals that elevated HbA1c levels independently raise the risk of proliferative diabetic retinopathy (PDR) in T2D. Similarly, advanced retinopathy stages are linked to increased PDR risk [28]. Notably, two cohort studies emphasize the role of glycemic control assessed by HbA1c in diabetic retinopathy development and progression [29, 30]. A study by Tsujimoto et al. [31] revealed that after 4 years, individuals with good glycemic control experienced significantly lower incidence of vision-threatening retinopathy than those with poor control. However, there are participants with good glycemic control that also develop DR. Exploring the risk of DR in individuals with similar HbA1c levels but differing glycemic variation profiles, as assessed by CGM presents intriguing ideas for future research.

This study demonstrated that lower TIR and higher MAGE, CV SD significantly associated with DR. The association between TIR and DR in our study consistent with clinical trials reporting that glycemic control prevents or delays the development and progression of DR and development of microalbuminuria [13]. Moreover, current evidence demonstrated the associations between TIR and diabetes-related complications, such as DR, albuminuria, cardiovascular autonomic neuropathy, and peripheral neuropathy [23, 32, 33].

Several limitations should be considered in interpreting our findings. The relatively small number of available studies might impact the strength of our meta-analysis results. The prevalence of cross-sectional studies makes it challenging to establish cause-and--effect relationships and understand the underlying mechanisms. Additionally, the regional focus of the studies in Asia limits the generalization of our conclusions to broader populations.

The use of different CGM models across studies introduces potential heterogeneity in data interpretation. CGM devices from different manufacturers may vary in accuracy, calibration requirements, and data interpretation algorithms, influencing the consistency of CGM-derived metrics across studies. Variability in sensor placement, calibration techniques, and patient adherence further adds to the diversity in CGM data. Moreover, variations in CGM data reporting could affect the consistency of our findings.

Despite these limitations, our study has practical implications and suggests directions for future research. Our results can aid in identifying individuals at a higher risk of DR, enabling timely interventions. Notably, the variability in glycemic profiles among patients with similar HbA1c levels emphasizes the need for tailored approaches in managing DR and related complications.

To enhance our understanding, future studies could explore longer follow-up durations and employ prospective designs to uncover causal relationships between specific glycemic patterns and DR onset or progression. Intervention studies focusing on improving TIR through targeted therapeutic interventions, such as medication adjustments, lifestyle modifications, or

Table 1. Characteristics of Studies

Author (year)	Country	Design	N	CGM Duration	Study Population	CGM Brand	CGM Metrics Reported	DR diagnosis	Classification of DR	Key Findings
Hayashi [16] (2023)	Japan	Cross-sectional	107	48 hours	T2D undergoing maintenance HD	System Gold (Medtronic Minimed, Northridge, CA) in 40 people, and Medtronic iPro2® CGM (Medtronic Minimed) in 67 people	TIR, mean glucose, CV, SD, GMI	Preproliferative or proliferative retinopathy diagnosed by experienced ophthalmologists within 6 months of CGM attachment	Not specified	Higher TIR resulted in lower rate of DR
Wang [17] (2022)	China	Cross-sectional	2.030	7 days	18–80 years old T2DM patients with complete CGM dat	iPro 2; Medtronic Inc, Northridge, CA, USA)	TIR, AUC_{IR}, SD, CV, GMI	Screening involved the use of non-mydriatic fundus photography. In cases where the outcomes were unclear, an experienced ophthalmologist would examine further	Not Specified	For every 10% decrease in TIR, the risk of DR increases by 8% (95% CI 1.03–1.14). With every 10% reduction in AUC_{IR}, there was a corresponding 7% increase in risk (95% CI 1.02–1.13).
Wakasugi [18] (2021)	Japan	Prospective-Cohort study	999	14 days	30–80 years old T2DM patients, receiving treatment with no treatment changes for 6 months	The FreeStyle Libre Pro (Abbott Japan, Tokyo, Japan) CGM (FLP-CGM) device	TIR, Mean glucose, SD, CV, MAGE, LBGI, HBGI, MODD	The presence and severity of DR were determined by trained ophthalmologists.	SDR, PPDR, PDR	CGM-derived metrics concerning both daily and inter-day fluctuations in glucose levels are notably linked to the severity of DR This association remains significant even after accounting for diverse risk factors.
Lu [19] (2018)	China	Cross-sectional	3.262	72 hours	≥ 18 years old, T2DM, stable glucose-lowering regimen over previous 3 months	Medtronic Inc, Northridge CA	TIR, SD, CV, MAGE	Fundus photography using digital nonmydriatic camera	Mild NPDR, Moderate NPDR, VTDR	TIR assesed by CGM is significantly associated with DR.
Lu [20] (2019)	China	Prospective-Cohort study	2927	72 hours	All patients were taking a stable antidiabetic regimen for the previous 3 months. Diabetes was diagnosed according to the 1999 WHO	Medtronic Inc. (Northridge, CA, USA)	SD, CV, MAGE	DR was diagnosed by an ophthalmologist blinded according to International Classification of DR using fundus photography with a digital non-mydriatic camera. (Proposed International Clinical Diabtetic Retinopathy and Diabetic Macular Edema disease severity scales)	Not Specified	CGM-derived metrics are significantly associated with DR

AUC_{IR} — area under curve in range; CGM — continuous glucose monitoring; CV — coefficient of variability; DR — diabetic retinopathy; HBGI — high blood glucose index; GMI — glucose management indicator; LBGI — low blood glucose index; MAGE — mean amplitude of glucose excursion; MODD — mean of daily differences; NDPR — non-proliferative diabetic retinopathy; PDR — proliferative diabetic retinopathy; PPDR — preproliferative diabetic retinopathy; SD — standard deviation; SDR — simple diabetic retinopathy; T2M — type 2 diabetes; TIR — time in range; VTDR — vision-threatening diabetic retinopathy.

personalized treatment plans, could help explain the direct impact of glycemic variability on DR outcomes. By monitoring changes in TIR alongside traditional markers like HbA1c, these studies can assess the efficacy of interventions in optimizing glycemic control and reducing the risk of DR development or progression. These insights can guide clinical strategies towards personalized medicine and precision healthcare, where treatment decisions are tailored to individual patient characteristics and metabolic profiles.

Conclusions

In conclusion, our study revealed that lower TIR is significantly associated with DR in T2D patients. Additionally, higher SD, MAGE, and CV were linked to the presence of DR. These findings emphasize the potential utility of these CGM-derived metrics in assessing and managing the risk of DR in individuals with T2D.

Article information

Supplementary materials

The Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/99931.

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Conflict of interest

The authors declare no conflict of interest.

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Effectiveness and Safety of Add-on Once-Daily Liraglutide (1.2 mg) in Type 2 Diabetes Patients with Obesity: Data from a Real-World Cohort of Iraqi Patients

ABSTRACT

Objective: This study aimed to evaluate real-world effectiveness and safety of once-daily liraglutide (1.2 mg) as an add-on to oral antidiabetic drugs (OADs) and/or insulin, in type 2 diabetes (T2D) patients with obesity in Iraq.

Materials and methods: A total of 55 T2D patients with obesity (mean ± SD age: 46.5 ± 8.7 years, 60% were females) initiating once-daily liraglutide (1.2 mg) as an add-on to OADs and/or insulin were included in this prospective cohort study. Change in body weight and serum HbA1c levels, and the insulin and sulfonylurea (SU) requirement were recorded during 24-week liraglutide therapy.

Results: Liraglutide yielded significant reduction in HbA1c values (from 10.7 ± 2.0% at baseline to 8.7 ± ± 2.4 % and 8.1 ± 1.6 % at weeks 12 and 24, respectively, p < 0.001 for each) and body weight (from 112.0 ± 19.6 kg at baseline to 109 ± 19.1 kg, 102 ± ± 16.9 kg and 97.0 ± 15.8 kg at weeks 4, 12 and 24, respectively, p < 0.001 for each). SU was stopped in 9/17 (52.9%) patients, and insulin therapy was discontinued in 15/44 (34%) patients after liraglutide treatment, and either with discontinuation or switch to basal insulin, 22/34 (64.7%) patients were no longer requiring prandial insulin (premixed and basal/bolus). No unexpected safety or tolerability issues occurred.

Conclusions: In conclusion, our findings support the consideration of liraglutide as a favorable intensifying therapy in T2D patients with obesity and metformin failure, given that it enables a sustained HbA1c and body weight reduction even at 1.2 mg once-daily dose, alongside the potential benefits in reducing SU and insulin requirements with no serious side effects. (Clin Diabetol 2024; 13, 3: 140–147)

Keywords: type 2 diabetes, obesity, liraglutide 1.2 mg daily dose, efficacy, real-world, Iraq

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Introduction

Obesity is a strong risk factor and a frequent comorbidity of type 2 diabetes (T2D), with presence of overweight or obesity in up to 85.2% of T2D patients at the time of diagnosis [1, 2]. Both obesity and T2D are associated with high susceptibility to diseases as-

sociated with increased risk of premature mortality, and thus weight reduction has clinically meaningful implications in T2D [2–4].

Also, the avoidance of hypoglycemia and weight gain are amongst the key considerations in selecting the appropriate individualized treatment intensification following failure of first line therapy [5, 6]. Liraglutide (Victoza®), once-daily glucagon-like peptide-1 (GLP-1) analog used at doses 1.2 to 3.0 mg, is considered a preferable noninsulin injectable agent following metformin, given its potential to enable optimal care via patient-oriented treatment goals (i.e., lower risk of weight gain, hypoglycemia and cardiovascular complications) beyond the improved glycated hemoglobin (HbA1c) values [5–8].

Observational real-world studies are considered to be of utmost importance to ascertain the long-term impacts of liraglutide in diverse patient populations and clinical settings and to explore the factors having a high impact on liraglutide-mediated effects [9, 10]. The real-world data on the effect of liraglutide in obese people with T2D as well as in those using injectable therapy are scarce in Iraq.

Therefore, this study aimed to evaluate the effectiveness (HbA1c and weight reduction) and safety of once-daily liraglutide (1.2 mg; less expensive dose), as an add-on to OADs and/or insulin, in a real-world cohort of Iraqi T2D patients with obesity. The additional objectives were to determine the baseline patient/clinical characteristics with a potential for better liraglutide effectiveness, and to evaluate the changes in insulin and SU requirement during the liraglutide treatment.

Materials and methods

Study population

A total of 55 T2D patients with obesity (mean ± SD age: 46.5 ± 8.7 years, 60% were females) initiating liraglutide as an add-on to OADs and/or insulin were included in this prospective cohort study conducted at two tertiary care specialized diabetes centers in Iraq. Adult patients (16–65 years of age) with T2D who failed to achieve glycemic control (HbA1c > 7%) and weight reduction (body mass index [BMI] ≥ 30 kg/m^2) on OADs and/or insulin and gave consent to initiate liraglutide and pay for it were included in the study. Previous history of bariatric surgery or intervention, previous weight-loss treatment, personal and/or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 and pregnancy were the exclusion criteria of the study.

Verbal consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Faiha Specialized Diabetes Endocrine and Metabolism Center (FDEMC) Research (date of approval: 1/05/2021; protocol no: 66/31/21).

Assessments

Data on patient demographics, duration of diabetes, ongoing anti-diabetic treatment (OADs, insulin) and cardiovascular disease history were recorded at baseline. Data on body weight (kg) and serum HbA1c (%) levels were recorded at baseline and during 24-week liraglutide therapy (at weeks 4,12 and 24 for the body weight, and at weeks 12 and 24 for the HbA1c). Changes in the insulin and SU requirements depending on the self-monitoring blood glucose (SBGM) recordings were evaluated during 4th, 12th and 24th weeks of liraglutide therapy. Treatment-related adverse events were recorded at 1st, 4th, 12th and 24th weeks of liraglutide therapy. The changes in HbA1c and body weight under 24-week liraglutide therapy was also evaluated in subgroups of age (< 50 years vs. ≥ 50 years), gender (male vs. female), diabetes duration (< 5 years vs. ≥ 5 years) and concomitant insulin treatment (yes vs. no).

Liraglutide treatment

Patients received once-daily subcutaneous liraglutide (Victoza®) therapy at a starting dose of 0.6 mg/day for one week, which was then titrated up to 1.2 mg/day for 24 weeks.

SMBG recordings

Each patient was instructed to do a 4–6-point SMBG before and after each meal at home through the period of the study. The SMBG data on fasting blood glucose (FBG), pre-meal blood glucose (BG), and 2-hour postprandial blood glucose (PPG) were evaluated at 1st, 4th, 12th and 24th weeks of therapy.

Modification of anti-diabetes treatments

All patients received 2 g metformin per day in addition to standard life-style interventions (diet and exercise). For other OADs and insulin therapy, treatment modifications were based on FBG, 2h PPG or pre-meal BG levels obtained through analysis of SMBG data.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Change over time was analyzed with dependent group t test or Wilcoxon test depending on the distribution pattern of continuous variables.

Repeated-measures analysis of variance (ANOVA) with a Greenhouse-Geisser correction and post hoc test with Bonferroni correction were used to compare the mean reductions in HbA1c and body weight at the points of evaluations after liraglutide initiation. Data were expressed as mean ± standard deviation (SD) and percent (%) where appropriate. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics and anti-diabetic treatments

Mean ± SD age was 46.5 ± 8.7 years, and females comprised 60.0% of the study population. Mean ± SD duration of diabetes was 6.3 ± 3.4 years (≥ 5 years in 67.3%). Mean ± SD body weight, BMI and HbA1c values at baseline were 112.0 ± 19.6 kg, 41.2 ± 7.4 kg/m^2 and 10.7 ± 2.0%, respectively (Tab. 1).

Prior to add-on liraglutide therapy, 80% of patients were receiving insulin (premixed insulin in 36.4%) and 78.2% were on metformin therapy. SU, DPP4i and pioglitazone were the other antidiabetic treatments in 30.9%, 21.8% and 9.1% of patients, respectively (Tab. 1).

Table 1. Baseline Characteristics and Anti-Diabetic Treatments

Patient demographics	
Age [year], mean ± SD	46.5 ± 8.7
Gender (F), n (%)	33 (60.0)
Duration of diabetes [year], mean ± SD	6.3 ± 3.4
≥ 5 years of duration, n (%)	37 (67.3)
Cardiovascular disease history, n (%)	8 (14.5)
Baseline measurements, mean ± SD	
Weight [kg]	112.0 ± 19.6
BMI [kg/m2]	41.2 ± 7.4
HbA1c [%]	10.7 ± 2.0
Anti-diabetic treatments, n (%)	
OADs	
Metformin	43 (78.2)
SU	17 (30.9)
DPP4i	12 (21.8)
Pioglitazone	5 (9.1)
Insulin	44 (80.0)
Basal insulin	10 (18.2)
Premixed insulin	20 (36.4)
Basal/bolus insulin	14 (25.4)

BMI — body mass index; DPP4i — dipeptidyl peptidase-4 inhibitor; HbA1c — glycated hemoglobin; OADs — oral antidiabetics; SU — sulfonylurea

HbA1c reduction after add-on liraglutide therapy

When compared to baseline HbA1c values (10.7 ± ± 2.0%), 12th week (8.7 ± 2.4 %, $p < 0.001$) and 24th week (8.1 ± 1.6 %, $p < 0.001$) assessments revealed significant improvement in HbA1c levels. There was also significant reduction in HBA1c values from the 12th week to 24th week of therapy ($p = 0.007$) (Fig. 1).

At weeks 12 and 24, the absolute changes from the baseline HbA1c were –1.9 ± 1.5% and –2.6 ± 1.5%, while the percent changes from baseline were 18.9 ± ± 12.5% and 23.3 ± 11.0%, respectively.

Weight reduction after add-on liraglutide therapy

When compared to baseline values (112.0 ± ± 19.6 kg), body weight was significantly reduced at 4th week (109 ± 19.1 kg, $p < 0.001$), 12th week (102 ± ± 16.9 kg, $p < 0.001$) and 24th week (97.0 ± 15.8 kg, $p < 0.001$) of therapy. There was also significant reduction in body weight throughout the follow up visits ($p < 0.001$ for each) (Fig. 1).

At weeks 4, 12 and 24, the absolute changes from the baseline weight were –3.0 ± 2.5 kg, –9.7 ± 7.3 kg, and –14.5 ± 9.7 kg, while the percent changes from baseline were 2.7 ± 1.9%, 8.4 ± 4.9%, and 12.5 ± ± 6.7%, respectively.

HbA1c and body weight reduction in subgroups

The significant reduction in HbA1c and body weight values were consistent throughout the follow up visits, regardless of the age, gender, diabetes duration, and concomitant insulin therapy ($p < 0.001$ for each) (Tab. 2).

Nonetheless, mean ± SD HbA1c reduction at 12th week was greater in patients with shorter (< 5 years) vs. longer (≥ 5 years) disease duration (2.7 ± 2.0 vs. 1.6 ± 1.0%, $p = 0.01$), and in non-insulin-treated vs. insulin-treated patients (2.6 ± 1.7 vs. 1.4 ± 0.9%, $p = 0.04$). Also, mean ± SD body weight reduction at 12th week was greater in patients <50 years of age vs. those ≥ 50 years of age (10.0 ± 7.9 vs. 9.2 ± 6.0 kg, $p = 0.03$), in males vs. females (11.7 ± 9.5 vs. 8.3 ± ± 5.0 kg, $p = 0.01$), and in non-insulin-treated patients vs. insulin-treated patients (11.9 ± 9.8 vs. 7.7 ± 2.8 kg, $p = 0.03$) (Tab. 2).

Changes in the insulin and SU requirement

At 12 weeks of liraglutide treatment, SU was stopped in 9 (52.9%) out of 17 SU-treated patients and basal insulin was stopped in 7 (70.0%) of 10 patients on basal insulin therapy. Of 20 patients on premixed

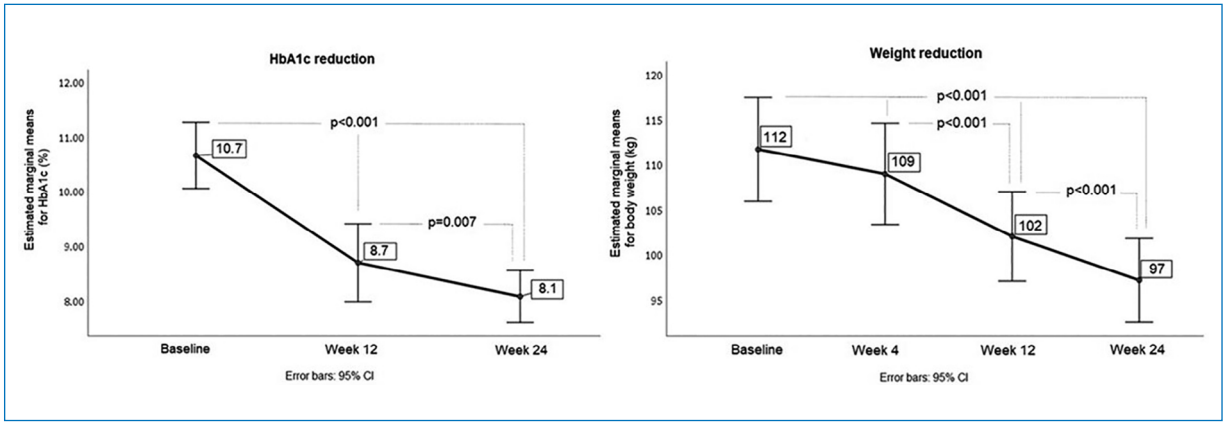

Figure 1. HbA1c reduction at Week 12 and Week 24 of Therapy and Weight Reduction at Week 4, Week 12 and Week 24 of Therapy
CI — confidence interval; HbA1c — glycated hemoglobin

Table 2. HbA1c and Body Weight Reduction in Subgroups of Age, Gender, Disease Duration and Insulin Therapy

Subgroups		Reduction in HbA1c [%], mean ± SD			
		12 weeks	24 weeks	p-value	
				Intra-group	Inter-group
Age	< 50 years	1.8 ± 1.6	2.6 ± 1.6	< 0.001	0.06
	≥ 50 years	2.2 ± 1.2	2.4 ± 1.0	< 0.001	
Gender	Male	2.1 ± 1.8	3.4 ± 1.5	< 0.001	0.05
	Female	1.8 ± 1.2	2.0 ± 1.1	< 0.001	
Diabetes duration	< 5 years	2.7 ± 2.0	2.4 ± 1.7	< 0.001	0.01
	≥ 5 years	1.6 ± 1.0	2.6 ± 1.4	< 0.001	
Insulin therapy	Yes	1.4 ± 0.9	2.5 ± 1.4	< 0.001	0.04
	No	2.6 ± 1.7	2.5 ± 1.6	< 0.001	

Subgroups		Reduction in body weight [kg], mean ± SD				
		Week 4	Week 12	Week 24	p-value	
					Intra-group	Inter-group
Age	< 50 years	2.9 ± 2.2	10.0 ± 7.9	15.8 ± 10.5	< 0.001	0.03
	≥ 50 years	3.3 ± 3.1	9.2 ± 6.0	11.5 ± 6.8	< 0.001	
Gender	Male	2.9 ± 2.1	11.7 ± 9.5	19.9 ± 11.7	< 0.001	0.01
	Female	3.1 ± 2.7	8.3 ± 5.0	10.0 ± 5.9	< 0.001	
Diabetes duration	< 5 years	4.5 ± 3.3	12.4 ± 11.1	16.1 ± 13.4	0.001	0.2
	≥ 5 years	2.3 ± 1.6	8.4 ± 3.9	13.8 ± 7.5	< 0.001	
Insulin therapy[a]	Yes	1.7 ± 1.1	7.7 ± 2.8	12.7 ± 5.9	< 0.001	0.03
	No	4.4 ± 2.8	11.9 ± 9.8	16.8 ± 12.8	< 0.001	

[a]Those continued insulin after 12 weeks of liraglutide initiation, whether on the same or a reduced dosage regimen

HbA1c — glycated hemoglobin; SD — standard deviation

insulin, 6 (30.0%) patients stopped insulin and further 6 (30.0%) were switched to basal insulin. Of 14 patients on basal/bolus insulin, 2 (14.3%) stopped insulin and 8 (57.1%) were switched to basal insulin. Overall, insulin therapy was discontinued in 15/44 (34%) patients after liraglutide treatment, and either with discontinuation or switch to basal insulin, 22/34 (64.7%) patients were no longer requiring prandial insulin (premixed and basal/bolus) (Fig. 2).

Treatment-related adverse events

The most frequently reported adverse events were nausea [by 36 (65.5%) and 19 (34.5%) patients at weeks 1 and 4, respectively] and vomiting [by 14

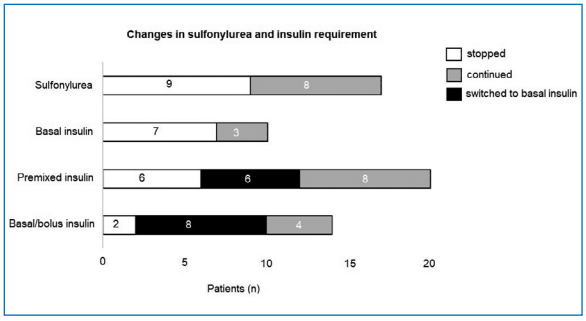

Figure 2. Changes in the Insulin and Sulfonylurea Requirement with Liraglutide Treatment

(25.5%) and 4 (7.3%) patients at weeks 1 and 4, respectively], which were gradually decreased towards the 4th week of therapy, and reported by none of the patients at 12th and 24th weeks. Hypoglycemia (SMBG < 70 mg/dL with or without symptoms) was reported by 2 (3.6%) and 6 (10.9%) insulin-treated patients at weeks 1 and 4, respectively, while no hypoglycemic events occurred at 12th and 24th weeks of therapy. No serious side effects were reported like acute pancreatitis or cholelithiasis.

Discussion

The present real-world cohort of T2D patients with obesity (mean age: 46.5 years, 60.0% were females, 67.3% with > 5 years of diabetes duration, 78.2% on metformin and 80.0% on insulin) indicated that the use of liraglutide in routine clinical practice, even at the lowest effective once-daily dose of 1.2 mg, successfully promoted the reduction of HbA1c values and significant weight loss, which was maintained throughout the study. The decrease in SU and insulin need was remarkable, which were no longer required by 52.9% and 34.0% of patients after 12th week of liraglutide therapy, respectively. Notably, liraglutide abolished the prandial insulin (premixed and basal/bolus) need in 64.7% patients through discontinuation or switch to basal insulin.

Similarly, in another study among Iraqi T2D patients with obesity (mean age: 48 years, 51.9% were males, diabetes duration < 5 years in 51.9%), a 1.2 mg daily dose of liraglutide as an add-on to OADs was reported to be associated with weight loss by 8.0% (–9.1 kg on average) and HbA1c reduction by 20% (–2.0% on average) at the end of 12th week [11]. Also, the higher liraglutide doses (1.8 mg/day) were associated with greater reduction in HbA1c (by 26.5%, –2.6% on average) levels, whereas no further reduction in body weight was noted with increasing the dosage from 1.2 to 1.8 mg/day (by 11.9%, –13.6 kg on average) [11].

In a prospective observational study in an Arab population of T2D patients (mean age 50.4 years, 71% were females, 56.3% were on insulin-based regimen, 90.1% were on metformin), 1.2 to 1.8 mg once-daily dose of liraglutide revealed a reduction in HbA1c from 8.3% to 7.7% at the 3rd month and to 7.6% at the 6th month, along with weight reduction of –2.01 ± 0.3 kg and –2.5 ± 0.6 kg, respectively [12].

In a real-world Portuguese cohort of T2D patients with obesity (median age: 59 years, 60.7% were females, 98.4% were under anti-diabetic), liraglutide effectively reduced HbA1c levels from 8.3% to 7.5%, while a weight reduction of at least 3% was noted in 44.0%, 47.6%, and 54.4% of patients at 6, 12, and 24 months, respectively [9].

In another real-world study of T2D patients with obesity in Saudi Arabia (mean age: 54.9 years, 60.3% were females, concomitant insulin in 77.3%, metformin in 80.2%), liraglutide was associated with significantly reduced HbA1c (–0.9% on average) and weight loss (–2.3 kg on average) [13]. Also, the covariates (age, gender, insulin use) had no significant impact on HbA1c and weight, while higher baseline HbA1c (> 9%) and weight (>100 kg) were associated with greater improvements [13].

In a systematic review of 106 studies on the effectiveness of liraglutide in the real-world setting of T2D, the mean HbA1c change from baseline was reported range from –0.6% to –2.26%, while the mean weight from baseline ranged from –1.3 kg to –8.65 kg [14].

The LEAD trial program revealed 1.2–1.6% reduction in HbA1c and 1.8 to 3.2 kg reduction in body weight at liraglutide doses of 1.2–1.8 mg [15]. In the SUSTAIN 10 trial, once-daily 30-week liraglutide (1.2 mg) in patients with T2D uncontrolled by 1–3 OADs was reported to reduce mean HbA1c (baseline 8.2%) by 1.0% and mean body weight (baseline 96.9 kg) by 1.9 kg [16].

In a meta-analysis of 9 RCTs including 2981 patients receiving liraglutide as an add-on to metformin, the authors reported significant reduction in HbA1c values at 1.8 mg/day (by –0.47%) and 1.2 mg/day (by –0.35%) doses of liraglutide [17].

Accordingly, despite use of lowest effective dose, the HbA1c reduction and weight loss obtained via liraglutide treatment in our patients seem to be higher than those reported by other liraglutide studies in T2D patients including clinical trials [15–17] as well as most real-world studies [9, 12–14]. This may relate to the fact that the insulin and SU treatments were no longer required by a considerable proportion of our patients after the 12-week of liraglutide therapy, both of which

are known to be associated with weight gain (4 kg with insulin and 2 kg with SUs) [18].

In the present study, more advantageous groups in terms of better liraglutide effectiveness were those with < 5 years of diabetes duration and insulin-naïve status for a greater HbA1c reduction, and those with < 50 years of age, male gender and insulin-naïve status for a greater weight loss. Similarly, a higher baseline HbA1c, longer duration of T2D, and concomitant insulin and longer duration of insulin treatment have been shown to counter the glycemic effects of liraglutide, while weight reduction was correlated positively with a higher baseline weight and a longer duration of liraglutide treatment, and negatively with the prior insulin treatment [10].

The LEAD series of studies revealed inconsistent data on the correlates of weight loss caused by liraglutide treatment, which was found to be dose-dependent in LEAD-2 and LEAD-4, to be closely related to nausea and not dose-dependent in LEAD-3, and to be independent of gastrointestinal adverse reactions in LEAD-5, although a few patients with sustained nausea seemed to lose more weight [19–21].

In our cohort, insulin therapy was stopped by one third of liraglutide-treated patients, and either via discontinuation or switch to basal insulin, two third of patients were no longer requiring prandial insulin (premixed and basal/bolus). In this regard, the decrease in insulin need in our patients seems to be consistent with the post-prandial effects of GLP-1 RAs (through decelerating gastric emptying, stimulating insulin, or suppressing glucagon secretion), which enables to achieve the target ranges for fasting, post-prandial, and overall (HbA1c) glycemic control [22, 23].

Notably, basal insulin when combined with liraglutide is considered to result in clinically significant weight loss relative to treatment with insulin alone, which is the rationale behind the fixed-ratio combination of insulin degludec/liraglutide (IDegLira) studies [24–26].

The SCALE Diabetes trial in 846 T2D patients with overweight or obesity from 9 countries compared the 56-week use of once-daily 3.0 mg liraglutide (n = 423), 1.8 mg liraglutide (n = 211) and placebo (n = 212) as an add-on therapy to 0–3 OADs (metformin, thiazolidinedione, SU) [7]. The significantly higher weight loss was noted with 3.0 mg liraglutide (6.0%, 6.4 kg) than with 1.8 mg liraglutide (4.7%, 5.0 kg) or placebo (2.0%, 2.2 kg) [7]. The SCALE Insulin trial which included T2D patients with overweight or obesity treated with basal insulin and ≤ 2 OADs, revealed that at 56 weeks, liraglutide 3.0 mg (n = 198) was associated with a mean weight change of –5.8% (versus –1.5% with placebo) and a ≥ 5% weight loss in 51.8% of patients (vs. 24.0% with placebo), in addition to less need for insulin and significantly greater reductions in mean HbA1c despite lower basal insulin requirements [25]. These glycemic improvements are considered likely the result of the preferential effects of liraglutide on post-prandial (rather than pre-prandial) glucose combined with the significantly greater weight loss versus placebo [25]. Notably, the weight loss findings in the SCALE Insulin trial are in line with those observed in the previously described SCALE Diabetes trial in which insulin-treated individuals were excluded [7, 25].

In our cohort, despite presence of younger patients but higher baseline body weight as compared to the SCALE Insulin trial, once-daily liraglutide (1.2 mg) achieved 12.5% weight loss after 24 weeks. Besides, younger age was found to be associated with better liraglutide-mediated weight reduction, which seems notable given that younger age groups of diabetes patients are considered to have a lower adherence to a diabetes care plan and lifestyle changes due to the active occupational and social life in this age group [11]. In fact, patient adherence is considered the key factor determining the treatment effectiveness, specifically, in the real-world studies [24], while being accustomed to treatment with injectable insulins is considered likely to have a positive influence on treatment adherence to liraglutide in insulin-treated patients [25].

Hence, the association of younger age particularly with the improved weight loss outcome in our patients may indicate the likelihood of obesity rather than the early-stage diabetes to be considered bothersome and a major complaint by younger patients, leading to the adoption of a better self-care practice towards improved adherence to lifestyle interventions.

Nonetheless, whether the weight loss observed in our study is the result of the direct (via feelings of hunger and satiety and delayed gastric emptying) or indirect (reduced insulin and SU requirements) action of liraglutide requires further investigation, in addition to potential role of improved patient adherence [25].

Hence, our findings support the use of liraglutide for treatment intensification in T2D patients with obesity, even before insulin treatment, as a preferred noninsulin injectable agent providing effective HbA1c reduction and the additional benefit of weight loss and no intrinsic risk of hypoglycemic episodes [5, 6, 8, 11]. Similarly, the LIRA PRIME study in the primary care setting suggested that treatment intensification with liraglutide as add on therapy to metformin OADs is a feasible and effective strategy in patients with metformin-failure, given that liraglutide was associated with similar rates of hypoglycemia but a greater

HbA1c and body weight reductions versus a pooled OAD group (SGLT 2i, DPP 4i, and SUs) [27].

Notably, liraglutide is suggested to show higher efficacy when used as an add-on to metformin alone than when used as an add-on to insulin secretagogues, particularly in reducing cardiovascular risk in T2D patients [28]. In fact, use of liraglutide as add-on treatment (versus switching to liraglutide), and using liraglutide 1.2 mg (versus the highest dose of 1.8 mg) were considered amongst the positive predictors of achieving an HbA1c reduction of ≥ 1%, together with higher baseline HbA1c, shorter diabetes duration (versus > 5 years) and prior metformin monotherapy [29].

Safety data in our patients support the consistently reported favorable tolerability profile of liraglutide in T2D patients, including relatively frequent (but moderate and transient) gastrointestinal adverse events (i.e., nausea and vomiting and diarrhea) during first weeks of therapy, while the major hypoglycemic episodes are also considered to be uncommon, possibly due to liraglutide's glucose-dependent mechanism of action [9, 13–15, 19, 21, 27, 30].

The major strength of our study seems to be the detailed analysis of the effectiveness of the lowest effective dose of liraglutide, with consideration of potential confounders and the changes in insulin and SU requirement, in a real-world cohort of Iraqi T2D outpatients with obesity. However, there are also a few limitations that should be considered, such as the small sample size and the potential presence of selection bias and uncontrolled variables due to observational non-controlled and non-randomized design, as well as the lack of data on certain patient-reported outcome measures related to quality of life or treatment satisfaction.

Conclusions

In conclusion, our findings revealed that once-daily liraglutide (1.2 mg) as an add-on to OAD and/or insulin therapy significantly improved HbA1c levels and enabled weight loss, along with a favorable safety profile and decreased insulin and SU need, among Iraqi T2D patients with obesity. The HbA1c reduction and weight loss were both maintained throughout the 24-week treatment period and more pronounced in non-insulin treated patients, while the liraglutide therapy also reduced the need for SUs and insulin. Accordingly, our findings support the consideration of liraglutide as a favorable intensifying therapy in T2D patients with obesity and metformin failure, given that it enables a sustained HbA1c and body weight reduction even at 1.2 mg once-daily dose, alongside the potential benefits in reducing SU and insulin requirements with no serious side effects.

Article information

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics statement

This study was approved by the Faiha Specialized Diabetes Endocrine and Metabolism Center (FDEMC) Research (date of approval: 1/05/2021; protocol no: 66/31/21).

Author contributions

Haider Ayad Alidrisi: conceptualization, methodology, data curation, formal analysis, investigation, project administration, writing — original draft preparation. Sameh Abed Odhaib: conceptualization, methodology, data curation, formal analysis, investigation, project administration, writing — original draft preparation. Hussein Ali Nwayyir: project administration, writing — original draft preparation, writing — review and editing, supervision. Ammar Mohammed Saeed Almomin: project administration, writing — original draft preparation, writing — review and editing, supervision.

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Conflict of interest

The authors declare no conflict of interest.

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A Randomized Trial of Carbohydrate Preloading in Patients with Type 2 Diabetes Undergoing General Anesthesia

ABSTRACT

Objective: The objective of the study was to determine the efficacy and safety of preoperative carbohydrate (CHO) loading among patients with type 2 diabetes (T2D) undergoing low to intermediate risk surgery.

Materials and methods: A randomized controlled trial was conducted among 50 T2D patients on oral hypoglycemic drugs selected based on the American Society of Anesthesiologists (ASA) grade 2, posted for low to intermediate risk surgeries. Twenty-five participants were randomly allocated to group A (carbohydrate group) and group B (placebo group). Patient well-being in terms of visual analog scale (VAS) scores for hunger, thirst, and postoperative vomiting was assessed. Mean plasma glucose was the primary outcome, gastric volume and pH and VAS scores were secondary outcomes.

Results: Clinical variables such as age, gender, body mass index (BMI), fasting plasma glucose (FPG), random plasma glucose (RPG), glycated hemoglobin (HbA1c), surgical duration, fluids, and opioids administered were comparable between both groups ($p > 0.05$).The mean plasma glucose levels in the postoperative period at 0 hour in group A and group B was 19.32 mg/dL and 30.13 mg/dL respectively and the difference was statistically significant ($p = 0.008$). At 10 hours post-surgery, the mean plasma glucose of group A (20.04 mg/dL) was significantly lower than group B (28.5 mg/dL) ($p = 0.035$). Secondary outcomes in both groups did not show any significant difference ($p > 0.05$).

Conclusions: The improved glycemic control and insulin resistance was observed in the carbohydrate loading group, with no adverse effects, resulting in improved outcomes among patients with T2D undergoing surgery. (Clin Diabetol 2024; 13, 3: 148–155)

Keywords: carbohydrate loading, diabetes, gastric fluid volume, insulin resistance

Introduction

The advent of a starvation period prior to general anesthesia for any elective surgery to avoid chances of regurgitation and/or aspiration has been so deeply engrained into anesthetic practice that it took years to rethink the approach in any way. Due to this, patients have been benefited from significant advances over the past 25 years [1]. The enhanced recovery after surgery (ERAS) is a multidisciplinary, multimodal project which aimed to aid patient recovery post-surgery during the perioperative period with reduction of overall complication occurrences by about 50% when ERAS protocols

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were implemented when compared to the traditional patient management techniques. ERAS protocols involve the concept of preoperative carbohydrate loading which lowers tissue glycosylation and insulin resistance (IR) and enhances postoperative glucose management as well as accelerates recovery post-surgery leading to reduced hospital stay [2].

Diabetes is a potentially devastating disease that is becoming more and more common in low and middle income nations like India. According to projections, by the year 2025, the population of patients with diabetes in India will increase to 69.9 million cases as a great majority of them remain unidentified [3]. In normal individuals, increased tissue resistance to insulin is seen after surgery, along with decreased secretion of anabolic hormones and increased secretion of catabolic hormones like cortisol. These pathophysiological reactions help to explain why even a patient without diabetes might experience perioperative hyperglycemia. This effect will be even more pronounced in patients with diabetes. Based on a study conducted by Albrecht et al., 2019 [4], one out of the 20 study patients with diabetes developed intraoperative hypoglycemia. Due to the lack of symptoms, this complication — along with hyperglycemia — is quite concerning for patients undergoing general anesthesia or for drowsy patients in the recovery area. Two of the major concerns that have led to the exclusion of study participants with diabetes in any research examining patients who received carbohydrate loaded drinks are namely the theoretical increased risk of aspiration due to gastroparesis and an increased risk of pre-operative hyperglycemia leading to deleterious effects including impaired wound healing which could lead to infection [5–7].

The ERAS programs encourage the preoperative consumption of carbohydrate-rich beverages. Given the conflicting data regarding the advent of carbohydrate loading among all patients and the uncertainty surrounding its safety in patients with diabetes, some have urged for a moratorium while more study is conducted [8]. Based on previous studies, we hypothesize that preoperative carbohydrate loading can improve insulin resistance without much interference in glycemic control in the immediate postoperative period. Our study aimed to investigate the effects of preoperative oral carbohydrate administration among perioperative glycemic controls, gastric fluid volume and pH, preoperative discomfort, and postoperative vomiting in American Society of Anesthesiology classification physical status II (ASA 2) patients undergoing elective surgery under general anesthesia. We proposed the following objectives: The primary objective was to ascertain glycemic control based on plasma glucose levels of type 2 diabetes (T2D) patients. The secondary objective was to assess the safety of carbohydrate preloading by measuring gastric fluid volume and pH. Finally, the overall patient well-being by visual analog scale scores for hunger and thirst, and incidence of postoperative vomiting.

Materials and methods

Study design

This was a prospective randomized triple blinded study conducted among T2D patients at a tertiary care multi-specialty hospital located in Coimbatore. The study was conducted after obtaining clearance from the Institutional Human Ethics Committee with project no 21/367. It was also registered with the clinical trials registry of India with reference number CTRI/2023/05/052860.

Study population

Patients with T2D, well controlled on oral hypoglycemic drugs, planned for low to intermediate risk surgeries under general anesthesia and posted first on the list at 8 AM were involved in the study. Patients who were allergic to maltodextrins, pregnant, had a body mass index (BMI) > 40, suffering from any pre-existing condition which can affect gastric motility, or posted for emergency surgeries were excluded from participation in the study.

Procedure

The study participants were allotted to their respective groups: group A which received carbohydrate loaded 50 g sachet in 400 mL water, 47.5 g carbohydrate 190 kcal/kilojoules plus other minerals, and group B which received placebo which was 400 mL of flavored water, three hours before surgery. After obtaining informed consent from the participants, the selected patients were randomized at the first point of contact in outpatient settings by means of computer-generated random numbers and were allotted to one of two groups using sequential sealed envelopes. The sealed envelopes were handed to the dietary department which prepared the drinks accordingly. Neither the attendee handing over the drink, nor the patient was aware of the constituents of the drink. Furthermore, the staff in the ward and operation theatre recording the visual analog scores (VAS) and plasma glucose levels were also not informed about the randomization, thereby making it a triple-blinded study. The investigators were informed of the allocation only after the complete follow-up of the patient was completed. The patients were allowed to take their usual meals until up to 10 PM and were given the carbohydrate or placebo

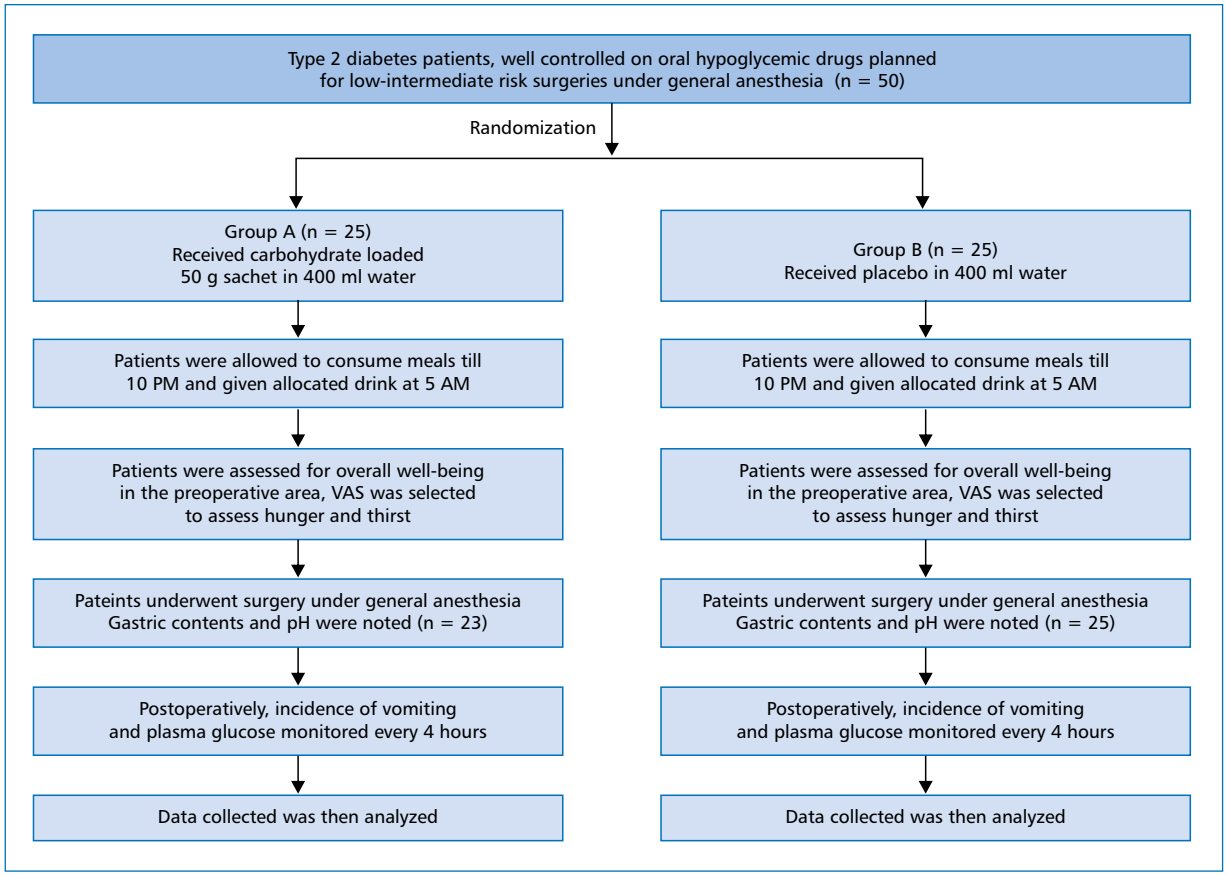

Figure 1. Flow Diagram of the Methodology

drink at 5 AM. All patients were premedicated with tablet Pantoprazole 40 mg and tablet Metoclopramide 10 mg on the morning of surgery. Morning samples for fasting plasma glucose (FPG) and insulin were recorded at 5 AM followed by the post-carbohydrate drink among the intervention group C. Patients were assessed for overall well-being in the preoperative area, VAS was selected to assess hunger and thirst. All patients were administered general anesthesia and glucose levels were noted at the time of induction. Patients were premedicated with Fentanyl 2 mcg/kg and induction of anesthesia was done with Propofol titrated to loss of verbal response. After securing the airway, a nasogastric tube was inserted to measure the gastric contents and the pH of gastric contents was noted. Total opioids administered during the surgery were then recorded, injection ondansetron was administered on completion of the surgery. Hourly monitoring of plasma glucose was done in the intraoperative period and ringer lactate used for maintenance. Steroids were not administered during the surgery. In the postoperative period, any incidence of vomiting was noted in the recovery room where the patient was observed for a minimum of 4 hours and fourth hourly plasma glucose monitoring was done. The next reading for random plasma glucose (RPG) was taken at 3 PM, which is, ten hours after the carbohydrate load. Any plasma glucose value above 200 mg/dL and insulin requirement for correction was noted. The entire methodology was been depicted in a flow diagram (Fig. 1).

A total of fifty patients were enrolled for the study with twenty-five patients allocated into each group with data collected from May 2023 to June 2023. Two patients in group A were not included in the analysis stage because their plasma glucose value on the morning of the surgery was more than 200 mg/dL. Hence, we analyzed 23 patients in group A and 25 patients in group B. There were no cancellations or postponement of surgery in either of the groups. The two patients with morning plasma glucose level more than 200 also underwent surgery on the same day after optimization of glucose level.

Glucose levels were tested for using the Cobas Integra 400 plus which had a precision of 1.61 and HbA1c was tested using Tosoh G8 which a precision of 0.68.

Statistical analysis

Sample size estimation

Sample size estimation was done based on the results of a study conducted by Faria et al. [9], using a confidence interval of 95% and the power of the study 80%. As we have evaluated mean plasma glucose in intraoperative and post-operative period as our primary outcomes, the mean plasma glucose measured at the time of induction of anesthesia, were used to calculate the sample size:

Mean blood glucose (mg/dL) 70 ± 8 (carbohydrate loading group) and 82 ± 17 (control group)

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

$$(Z_{1-\frac{\alpha}{2}} + Z_{1-\frac{\beta}{2}})2 = 7.84$$

μ_d (mean difference) = 82–70) = 12, standard deviation (SD) = 8.17

The calculated sample size approximated to 19 in each group. To account for attrition and drop out, we considered a sample size of 25 participants per group.

The data obtained during the course of the study was analyzed using Statistical Package for the Social Sciences (SPSS) v20. Analysis was conducted using chi-square test and Student's t-test to check for any significant difference with regard to the glycemic control between the two groups. Qualitative variables such as sex, ASA classification and gradings, incidence of aspiration and vomiting and VAS were compared using chi-square test. Quantitative variables such as weight, age, height, duration of surgery, glucose levels, gastric volume, and pH between the groups were compared by means of Student's t-test. Categorical variables were represented by frequency tables and continuous variables were represented as mean ± standard deviation. Categorical data like gender distribution was compared using chi-square test. Continuous data was tested using independent sample t-test for normally distributed and Man-Whitney U-test for non-normally distributed data. Shapiro Wilk test used to test the normality. A p-value less than 0.05 was considered statistically significant at 95% confidence level.

Results

Demographic details

The present study included fifty patients with two groups including twenty-five patients each. Supplementary Table 1 shows that the study included mainly participants who had to undergo laparoscopic cholecystectomy (9 each in both groups). The baseline characteristics such as mean age of the study participants were 59.08 ± 10.25 years in group A and 58.7 ± ± 8.29 years in group B, and this difference was not statistically significant (p = 0.888). The gender distribution showed that the number of male and female participants was not significantly different (p = 0.563). Furthermore, clinical variables such as the reported BMI, FPG, RPG and HbA1c, duration of surgery, intraoperative fluids, and intraoperative opioids administered were also comparable between both groups (p > 0.05) (Tab. 1).

Table 1. The Baseline Characteristics of Participants

		Group A	Group B	p-value
Age [years]		59.08 (10.25)	58.7(8.29)	0.888
Sex CS	Female	15	11	0.563
BMI		27 (4.92)	26.09 (3.72)	0.475
Preoperative FPG [mg/dL]		130.64 ± 46.61	153 ± 38.95	0.101
RBG [mg/dL]		160.71 ± 49.22	190 ± 50.99	0.072
HBA1c M [mmol/mol]		21.50	24.71	0.395
Duration of surgery M [minutes]		25.18	23.76	0.713
Intraoperative fluids M [minutes]		23.18	25.93	0.491
Intraoperative opioids administered M [minutes]		25.88	23	0.363

CS indicates testing done using chi square test; M indicates Mann-Whitney U-test results expressed in mean rank; the rest were tested using Student's t-test, expressed as mean ± SD

BMI — body mass index; FPG — fasting blood glucose; HbA1c — glycated hemoglobin; RBG — random blood glucose

Table 2. Intraoperative and Postoperative Glycemic Outcomes, Visual Analog Scores and Gastric Volume, pH of Study Participants

Variables		Group A		Group B		Mean adjusted difference of two groups (95% CI)
Primary outcomes		Mean ± SD	Mean rank	Mean ± SD	Mean rank	
FPG [mg/dL]		125.68 ± 28.41		142.26 ± 27.83		16.58 (0.219, 32.94)
Intraoperative hour 1 M [mg/dL]		139.46 ± 29.44	26.04	144.48 ± 26.127	22.04	4.00 (–11.36, 21.40)
Intraoperative hour 2 [mg/dL]		150.53 ± 37.34		173.17 ± 50.72		22.46 (–1.89, 46.81)
Intraoperative hour 3 M [mg/dL]		150.53 ± 37.34	16.13	173.17 ± 50.72	12.3	3.83 (–12.50, 57.52)
Intraoperative hour 4 [mg/dL]		148.36 ± 33.97		160.83 ± 21.648		–22.52 (–55.69, 10.64)
Postoperative hour 0 M [mg/dL]		146.56 ± 35.44	30.13	167.74 ± 32.6	19.32	10.81 (7.00, 39.00)
Postoperative hour 4 M [mg/dL]		148.36 ± 33.97	28.26	160.83 ± 21.648	21.04	7.22 (–3.97, 28.90)
10th hour M [mg/dL]		146.24 ± 34.07	28.5	158.27 ± 18.67	20.04	8.46 (2.00, 33.00)
Insulin consumption M	Intraoperative	8.41		8.41		–0.29 (–4.26, 4.48)
	Postoperative	6.17		6.83		–0.66 (–2.75, 2.09)
Secondary outcomes						
Gastric volume M [mL]		10.15±6.88	23.37	11.67±5.57	25.54	–0.71 (–4.73, 3.30)
Gastric pH M		6.69±1.18	13.28	7.33±1	10.27	0.64 (–0.34, 1.62)
VAS (hunger) M		26.04	21.87	21.87	26.04	–0.48 (–1.34, 0.39)
VAS (thirst) M		24.96	23	23	24.96	–0.09 (–0.93, 0.74)

M indicates Mann-Whitney U-test results expressed in mean rank; the rest were tested using Student's t-test, expressed as mean ± SD

FPG — fasting blood glucose; SD — standard deviation; VAS — visual analog score

Mean plasma glucose levels

The mean FPG of the participants on the day of procedure was 125.68 ± 28.41 mg/dL in group A which was significantly lower than group B (142.26 ± 27.83 mg/dL) and (p = 0.047). The plasma glucose levels at 0 hours in group A was 146.56 ± 35.44 mg/dL which was significantly reduced when compared to group B (167.74 ± ± 32.6 mg/dL), and this difference was statistically significant (p = 0.008). The levels at 10 hours postoperative was also significantly different, with group A glucose levels being 146.24 ± 34.07 in group A and 158.27 ± ± 18.67 in group B (p = 0.035). Insulin consumption was compared in intraoperative and postoperative periods and was similar between both groups (Tab. 2).

Gastric findings and VAS scores of participants

None of the patients in both groups had any incidence of aspiration. The median gastric volume in group A was 10.15 ± 6.88 mL and 11.67 ± 5.57 mL in group B, the gastric pH in group A was 6.69 ± 1.18 and 7.33 ± 1 in group B, and these variables did not show any statistically significant difference between both groups (p = 0.558 and p = 0.262). The median VAS score for hunger and thirst between both groups was statistically not significant (p > 0.05) (Tab. 2).

With regard to confounding characteristics: Among the included samples, the common co morbidities noted were hypertension (11), anemia (2), coronary artery disease (6), hypothyroidism (3), seizure disorder (1), smoker (1), old cerebral vascular accident (1) in placebo group. Hypertension (11), anemia (2), coronary artery disease (4), hypothyroidism (4), seizure disorder (1), smoker (1), old cerebral vascular accident (2), heart failure with preserved ejection fraction (2) Down syndrome (1) in post carbohydrate loaded drink group.

The amount of insulin administered in the two groups has been mentioned in Table 2 and the two groups were comparable in the regard ($p > 0.05$).

We do not have data of exact medications used in the preoperative period but all the patients were only on oral hypoglycemic agents, morning medications were omitted for all the patients, preoperative blood glucose profiles were comparable in both the groups (Tab. 2) and all surgeries were posted as first case at 8 AM.

Discussion

This randomized controlled trial was conducted to demonstrate the efficacy as well as safety of carbohydrate preloading in patients with T2D undergoing general anesthesia. Implementing carbohydrate preloading protocols in patients with T2D can help optimize glycemic control without compromising patient safety and improve surgical outcomes. Further research, including larger-scale studies, is warranted to establish standardized guidelines for carbohydrate preloading among patients with T2D undergoing general anesthesia.

The baseline investigations of the present study show that the two groups of participants were comparable with regard to demographic variables such as age and sex, clinical and operative variables such as BMI, duration of surgery, intraoperative fluids and intraoperative opioids administered as well as glucose level variables such like preoperative FPG, RPG and HBA1c levels, making them ideal for comparison.

The FPG of the participants on the day of surgery was lower in the carbohydrate group A when compared to the control group, with this difference being statistically significant ($p=0.047$) despite obtaining comparable baseline HbA1c levels in both the groups.

The plasma glucose levels in both groups at 0 hour and 10 hours was significantly much higher in the placebo group when compared to the carbohydrate group, with p-values of 0.008 and 0.035 respectively. Laffin et al., 2018 [10] in their study among patients with diabetes, did not report any increase in the mean preoperative plasma glucose levels within the group getting preoperative carbohydrate drink. The preoperative plasma glucose value of patients compliant to the post carbohydrate drink was found to be non-inferior to the values in non-compliant subjects (p for non-inferiority < 0.01), among both groups who received evening and morning preloading and morning preloading alone. This result points to the longer-term effects of preoperative carbohydrate loading with regard to patients with T2D.

There are currently two possible explanations for the exact mechanism of insulin release after stress: on the one hand, increased catecholamine, growth hormone, glucocorticoid, and tumor necrosis factor release in response to surgical trauma causing an increase in liver glycogen release and IR; on the other hand, glucocorticoids and epinephrine reduce glucose uptake in peripheral tissues, while cytokines such as interleukin-1 and tumor necrosis factor inhibit insulin signal transmission. Reduced glucose absorption and IR are caused by the absence of the insulin signal receptor and glucose transporter 4 [11]. However, the intra operative and postoperative insulin consumption was similar in both groups with regard to the present study. A systematic review by Ge et al., 2020 reported that of the studies that were part of the review, a study conducted by Breuer et al., 2006 did not find any significant difference between the comparison and control groups with regard to insulin resistance ($p > 0.05$) [12, 13]. A study conducted by Lu et al., 2015 [14] also reported that postoperative insulin resistance index was significantly lower in the comparison group ($p < 0.05$).

None of the patients in both groups had any incidence of aspiration. The median gastric volume and pH values did not show a statistically significant difference between both groups ($p = 0.558$ and $p = 0.262$). Results of a previously conducted study showed that with regard to conditions such as intraoperative hypertension ($p = 0.031$) and postoperative nausea and vomiting ($p = 0.034$), the carbohydrate group showed significantly lower incidences when compared to the control group [15]. These findings are similar to the study by Gustafsson et al., 2008 [16] who assessed gastric emptying by co-administration of paracetamol and did not find delayed gastric emptying after intake of a 12.5% CHO-rich drink for preoperative use among patients with well-controlled T2D compared with healthy control subjects. If anything, a slightly increased gastric emptying rate was found in patients with T2D. The residual gastric volume 2 hours after intake of the drink was similar in healthy subjects compared to patients with T2D.

The median VAS score for hunger and thirst between both groups was also found to be statistically

not significant ($p > 0.05$). These results contrasted those reported in a study by Li et al., 2022 [15] wherein VAS scores of preoperative feelings of thirst, hunger, and fatigue, as well as postoperative feeling of thirst, hunger, and fatigue (all $p < 0.05$), were significantly lower in the carbohydrate group when compared with the control group. A study conducted by Hausel et al., 2001 [17] using VAS for a larger sample size of ASA I/II patients undergoing abdominal surgery found no difference in thirst after the morning carbohydrate drink and placebo. However in the study by Faria et al., 2009 [9] the patients' given carbohydrates reported significantly lower rate of hunger and anxiety. Some patients had reported lesser postoperative nausea and vomiting with carbohydrate loading [9]. These results help in affirming the improved comfort of the patients with administration of preoperative carbohydrates. The effects of glucose ingestion two to three hours prior to surgery on insulin resistance in patients with diabetes have been inconsistently reported; however, the data that is currently available indicates a tendency to improve insulin resistance and prevent postoperative hyperglycemia following surgery [12]. The variation in results could also be caused due to patients being given a carbohydrate loading the night before the surgery too which was not done in our study. However, we do not consider it essential as the patient is allowed their usual dinner. This randomized controlled study provides an effective insight into the safety and efficacy of preoperative carbohydrate loading, perioperative glycemic control, and insulin requirements.

While the study showed promising results, some limitations which are to be acknowledged include the appropriate sample size warranting larger multicenter trials for further validation. The study did not involve patients with type 1 diabetes and patients with T2D who were insulin-dependent as results may vary among different diabetes subtypes. However, the study is a triple blinded study which makes it free of bias and did not have any dropouts which makes up the advantages of the study. Future studies could explore the differential effects of carbohydrate preloading based on diabetes type and severity.

Conclusions

The results of the study help provide improved evidence to recommend carbohydrate preloading as part of ERAS protocols to be extended to well-controlled T2D patients. The benefits of improved insulin resistance and glycemic control, reduced preoperative discomfort, and reduced nausea/vomiting, can also be extended to this subset of patients without any increased risk of aspiration.

Article information

Ethics statement

The study was conducted after obtaining clearance from the Institutional Human Ethics Committee with project no 21/367.

Supplementary materials

The Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/99377.

Data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

Author contributions

Silvy Anna Varughese: conceptualization, methodology, software.

Silvia Anna Varughese, Dhivya D., Sandhya K.: data curation, writing, original draft preparation.

Silvy Anna Varughese, Dhivya D.: visualization, investigation.

Silvy Anna Varughese: project administration.

Silvy Anna Varughese, Dhivya D.: supervision.

Silvy Anna Varughese: formal analysis, software, validation.

Silvy Anna Varughese, Dhivya D., Sandhya K.: writing, reviewing and editing.

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Conflict of interest

The authors declare no conflict of interest.

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Effects of Sitagliptin versus Empagliflozin on the Stress Hyperglycemic Ratio in People with Type 2 Diabetes: An Open-Label, Randomized Controlled Trial

ABSTRACT

Objective: Stress hyperglycemia (SH) is simply assessed by calculating the stress hyperglycemia ratio (SHR). This study aimed to calculate the SHR in type 2 diabetes (T2D) patients receiving oral diabetes medications that worked through two different mechanisms.

Materials and methods: This open-label randomized clinical trial was conducted in the College of Medicine, University of Diyala, Baqubah, Iraq, from January 1, 2022, to December 31, 2022. Patients with T2D without a previous history of surgical procedures and with no acute or chronic infections were randomly assigned to receive sitagliptin/metformin 50/500 mg or empagliflozin/metformin 10/500 mg orally once daily. Patients were randomized in-hospital, and treated for up to 10 weeks. The primary outcome of this open-label clinical trial was SH, defined as the estimated plasma glucose, and SHR values. The secondary outcome included hematological indices and C-reactive protein (CRP).

Results: Eighty patients with T2D were enrolled in the study and divided into two groups. Group I (n = 40) received sitagliptin/metformin, and Group II (n = 40) received empagliflozin/metformin. The baseline data showed non-significant difference between the two groups in the SH and SHR. The median values of SHR decreased by 9.2% (0.925 vs. 0.840, p = 0.047) in Group I compared with an 8.7% decrease (0.940 vs. 0.858, p = 0.113) in Group II patients. The median values of CRP were non-significantly decreased in Group I (6.0 vs. 5.3 mg/dL, p = 0.507) and remained unchanged in Group II (3.4 vs. 3.4 mg/dL, p = 0.769).

Conclusions: Sitagliptin has a better effect against stress hyperglycemia ratio than empagliflozin. (Clin Diabetol 2024; 13, 3: 156–163)

This study was registered on ClinicalTrial.gov (NCT 05822674)

Keywords: type 2 diabetes, stress hyperglycemia, sitagliptin, empagliflozin

Introduction

Stress hyperglycemia (SH) is an increase in circulating glucose levels in biological fluids as a physiological response to stress in patients with established or newly diagnosed diabetes, or a pathological condition associated with in-hospital-related hyperglyce-

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mia [1–3]. It is also known as transient hyperglycemia during the course of diabetes, and it is thought to be a predictor of increased morbidity and mortality [4]. Stress hyperglycemia has been found to be a short- and long-term prognostic marker for complicated or associated diabetes mellitus. In a cohort study that included 3636 patients admitted to the intensive care unit, it was found that the stress hyperglycemia ratio (SHR) is associated with mortality in patients with critical illnesses, and a higher mortality rate was observed in non-diabetic patients [5]. In another study, the cutoff point of SHR for poor prognosis in patients with acute coronary syndrome, who were followed up for two years, was 0.78 [6]. In a retrospective study that included 599 patients with acute heart failure, the risk of mortality was associated with a low SHR of 0.88 in diabetes, while such an association was not observed in non-diabetes [7]. Therefore, the SHR was linked with a poor prognosis in patients who were critically ill, irrespective of whether they were subjected to the stress of the surgical procedures. In in-hospital patients with diabetes and heart failure, both low and high ratios of SHR were associated with unfavorable outcome events [8]. Glycated hemoglobin (HbA1c) is a measure of average blood glucose levels over the last 2–3 months and is not affected by transient hyperglycemia [9, 10]. The SHR is a proposed measure of SH that can be calculated by dividing the blood glucose on admission (current) (mmol/L) by the HbA1c value [11]. Others calculated the SHR by dividing the admission (current) blood glucose level by the estimated average glucose level over the preceding 2–3 months, according to the following formula: ([1.59 × HbA1c current value] – 2.59) [12, 13]. Through their pleiotropic effects, some oral hypoglycemic agents improve SH. When compared to non-SGLTi (sodium glucose transporter inhibitor) users, patients with diabetes who used SGLTi and had an acute myocardial infarction had less prevalent SH, a smaller infarct size, and evidence of a low inflammatory response [14]. Empagliflozin has been approved for the treatment of diabetes and symptomatic heart failure with preserved and reduced ejection fraction, and it significantly reduces the mortality rate in hospitalized chronic heart failure patients [15]. Empagliflozin provides a good prognosis for diabetes treatment outcomes, which is due to improvement in related risk factors for cardiovascular events [16]. In addition, it showed an anti-inflammatory effect that is mediated by attenuating the formation of inflammatory cytokines [16]. Another double-blind randomized clinical trial reported that pre-operative sitagliptin (a dipeptidyl peptidase-4 inhibitor) did not prevent SH in patients with diabetes undergoing general surgery [17]. Another study found that sitagliptin did not prevent acute hyperglycemia in patients without diabetes undergoing coronary artery bypass graft surgery [18].

The rationale for this study is that oral hypoglycemic agents may potentially overcome the stress-induced hyperglycemia to a certain extent. The aim of this observational clinical study was to assess SHR in type 2 diabetes (T2D) patients without other serious diseases who used fixed dose combinations of sitagliptin/metformin compared with those who used empagliflozin/metformin.

Materials and methods

Study design

This open-labeled randomized clinical trial included consecutive patients between January 1 and December 31, 2022 from the consultant clinics at the diabetes center and the public clinic database.

Study participants

The patients who were treated with oral antidiabetics (either sitagliptin/metformin or empagliflozin/metformin) were allocated randomly between two treatment groups using 1:1 allocation system (Fig. 1).

The inclusion criteria for the patients included: (i) patients aged 35 to 70 years; (ii) patients with the duration of diabetes of 1–8 years; (iii) patients treated with oral hypoglycemic agents in form of a combination of sitagliptin/metformin or empagliflozin/metformin. Exclusion criteria included: (i) serious illnesses or surgical interventions within 3 months; (ii) anemia; (iii) patients with chronic inflammatory or autoimmune diseases; (iv) treatment with corticosteroids or non-steroidal anti-inflammatory drugs; (v) pregnancy and nursing mothers. Ultimately, 80 participants with T2D were enrolled. Then, patients were divided according to their pharmacotherapy based on the use of oral hypoglycemic agents into Group I (n = 40): patients treated with sitagliptin/metformin (50 mg/500 mg) and Group II (n = 40): patients who were treated with empagliflozin/metformin (10 mg/500 mg). The duration of each treatment was 10 weeks.

Ethical approval

This study was approved by the Medical Ethics Committee of the College of Medicine at the University of Diyala in Iraq (No. MSM735, date 01-03-2023) and registered on ClinicalTrial.gov (NCT 05822674). Given the patient follow-up nature of this study, informed consent from each patient was obtained. The study protocol was conducted according to the ethical guidelines of the Declaration of Helsinki.

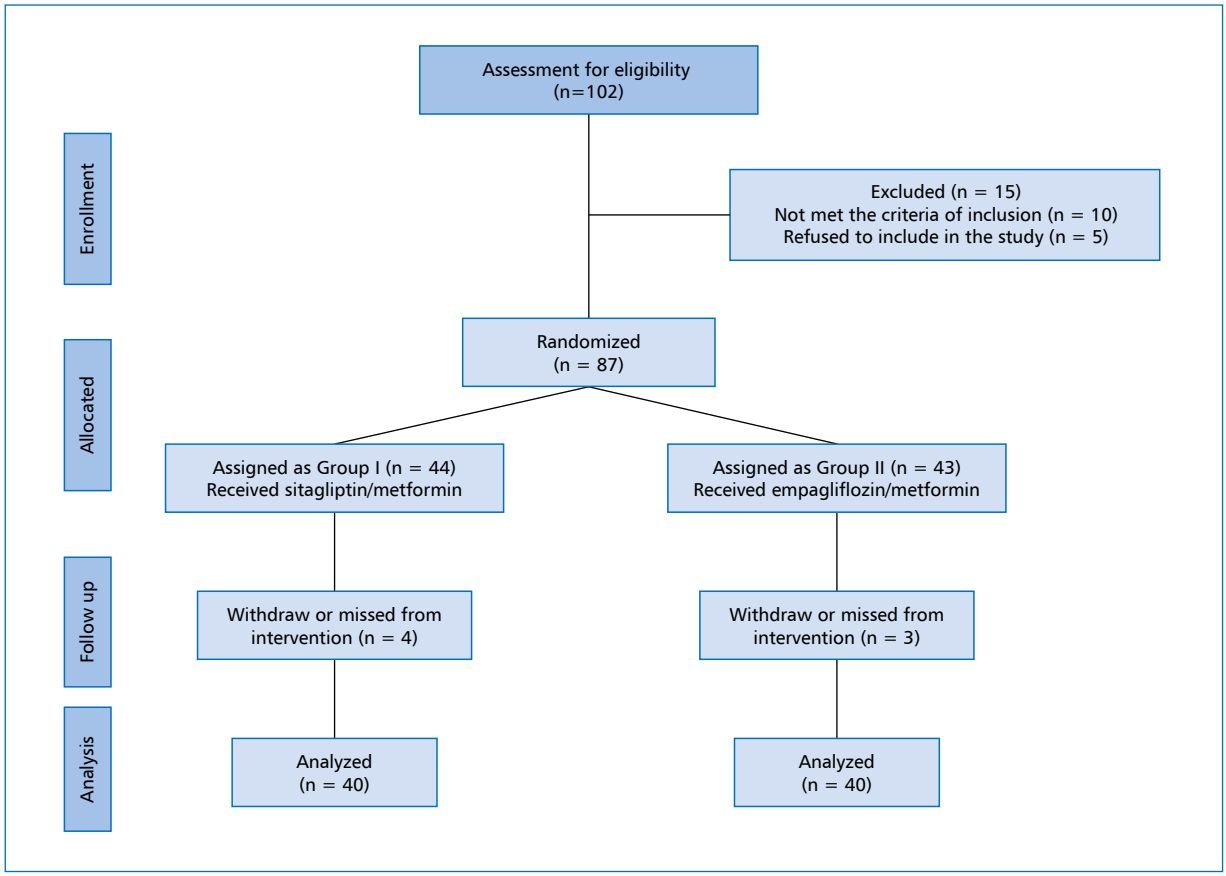

Figure 1. Flowchart of the Participants Included in the Study

Data collection

The medical records of patients attending the clinics were reviewed. Patient characteristic including age, gender, duration of diabetes, history of surgical interventions, and hospital admissions were collected. Laboratory tests [fasting plasma glucose levels (FPG), HbA1c%, hemoglobin (Hb), mean corpuscular volume of red blood cell (MCV), and C-reactive protein (CRP) were carried out at the time of attending the clinics. The laboratory data were collected at the initiation of pharmacotherapy and at the end of 10 weeks of treatment.

Assessment of stress hyperglycemia

Blood samples were drawn in the morning after an overnight fast (at least 8 h) to measure fasting plasma glucose (FPG), HbA1c%, and hematological indices (Hb and MCV). Each blood sample was divided into two portions; the first portion was drawn into an EDTA-test tube, and the second portion was drawn into a plain test tube. Then the samples were centrifuged at 3000 rpm for 15 minutes. The Cobas C311 analyzer (Roche, Germany) was used for the determination of FPG, HbA1c%, and CRP coefficients of variation ranged between 1.8 and 2.3%). The hematological indices were determined by an automatic Coulter analyzer. SHR was calculated according to the following formula: current FPG (measured during a clinic visit) / FBS estimated, the estimated FPG was calculated by sing the formula: 28.7 × current HbA1c % (measured during a clinic visit) minus 46.7 [13, 19].

Statistical analysis

The results are presented as number, percentage, median, interquartile range, and 95% confidence interval (CI). The sample size for the participants was estimated using the GPower software version 3.1 (software developed by Heinrich-Heine-Universität Düsseldorf, Germany, which is free to download for both Windows and Mac OS X platforms), with power (1-error) set at 0.80 and error (α) set at 0.05. The principle of this program is to obtain the sample size, the critical t-value, and the actual power by selecting the appropriate statistical text and the types of power analysis, then feeding the input parameters, which included two tails, alpha error (0.05), and the power (1-beta power of 0.8). The sample size was computed and found to

be 40 participants for each group. The analysis of the data using Shapiro Wilk test showed that the data were not normally distributed. The results were analyzed by Mann Whitney U-test for the effects of each drug on the variables and comparison between two groups, and Chi-squared test for categorical data. Pearson's (rho) correlation between SHR and CRP was computed to show the association between SHR and the inflammatory biomarker. All statistical analysis and boxplot graphs were carried out using SPSS version 24 (IBM Corp., Chicago, USA). A p-value of less than 0.05 is considered significant.

Results

Table 1 shows a non-significant difference in the baseline characteristics, including age, sex, and glycemic indices, between Groups I and II. A significantly higher median value of MCV was observed in Group I, while the Hb and CRP levels were not significantly different between Groups I and II. Table 2 shows sitagliptin/metformin treatment significantly reduced the glycemic indices measured on visiting (current), and attended 22.7% (FPG) and 14.6% (HbA1c%) after ten weeks of treatment. The estimated FPG was significantly decreased by 17.9%, which is less than the reduction in this percentage of median value on visiting (current). The median value of SHR was significantly decreased by 9.2% (Tab. 2 and Fig. 2). These changes were accompanied by a significant ($p = 0.006$) decrease in the Hb level (6%), and non-significantly reduction in the MCV (0.7%) and CRP (11.7%) median values. Comparable effects were observed in Group II as FPG and HbA1c % were decreased by 40.7% and 26.1%, respectively (Tab. 2). The estimated FPG was significantly decreased by 31.7%, which is higher than the corresponding value in Group I. The changes in the SHR were non-significant (decrease by 7.4%) (Tab. 2 and Fig. 2). The median values of Hb, MCV, and CRP were non-significantly changed. The baseline (current values) correlation between SHR and CRP values was non-significant ($r = 0.099$, df: 78, $p = 0.382$). The number of participants with a SHR value more than one, and treated with empagliflozin-metformin (Group II), was significantly decreased from 16 to 7 patients ($p = 0.026$), but those treated with sitagliptin-metformin (Group I) were not significantly decreased from 12 to 8 patients ($p = 0.301$).

Discussion

The results of this study show that oral hypoglycemic drugs have variable effects on the estimated FPG and SHR by reducing the magnitude or the number of the participants who had an SHR value of more than one, in absence stress by the evidence of a non-significant correlation between SHR and CRP. There is no significant difference in the baseline characteristics between Groups I and II except for the MCV, which is within the normal range. Sitagliptin significantly reduced the current FPG values and estimated (stress) median values by 22.7% and 17.9%, respectively, indicating that sitagliptin is effective in reducing stress hyperglycemia. This effect supported a previous study, which showed that sitagliptin supplementation to burned patients significantly attenuated the stress hyperglycemia and reduced the insulin requirements [20]. On the other hand, sitagliptin does not prevent stress hyperglycemia in patients without diabetes who were subjected to open cardiac surgery as it did not reduce

Table 1. The Characteristics Baseline Data of the Participants

Characteristics	Group I (n = 40)	Group II (n = 40)	p-value
Age [year]	47.5 (42.3–53.8)	46.0 (39–52)	0.090
Sex (female:male)	30:10	22:18	0.060
Duration of diabetes [year]	4.0 (2.0–5.0)	3.0 (2.0–4.0)	0.453
Fasting plasma glucose [mg/dL]	185.0 (162.5–238.0)	216.0 (177.0–302.0)	0.235
HbA1c%	8.9 (8.4–10.0)	9.2 (8.4–10.3)	0.855
Hemoglobin [g/dL]	13.4 (12.6–15.2)	14.2 (12.7–15.1)	0.331
Mean corpuscular volume [fL]	88.2 (84.6–90.8)	84.9 (79.6–87.9)	0.006
C-reactive protein [mg/L]	6.0 (1.9–11.3)	3.4 (2.1–8.6)	0.167

The results are expressed as number and median (25th–75th percentiles); p-value was calculated by non-parametric (Mann-Whitney U) test and Chi-square test; Group I: sitagliptin/metformin-treated group, and Group II: empagliflozin/metformin-treated group

HbA1c — glycated hemoglobin

Table 2. Comparison between the Effects of Sitagliptin/Metformin and Empagliflozin/Metformin on the Glycemic, Hematological, and Inflammatory Indice

Variables	Group I (n = 40)					Group II (n = 40)				
	Before treatment		After treatment		p-value	Before treatment		After treatment		p-value
	Median (interquartile range)	95% CI	Median (interquartile range)	95% CI		Median (interquartile range)	95% CI	Median (interquartile range)	95% CI	
Stress hyperglycemia ratio	0.925 (0.17)	0.866–1.018	0.840 (0.15)	0.836–0.939	0.047	0.940 (0.41)	0.939–1.139	0.870 (0.15)	0.858–0.997	0.113
Estimated FPG (mg/dL)	208.7 (44.5)	208.1–227.3	171.4 (27.3)	166.3–168.9	<0.001	217.3 (53.8)	207.9–228.4	148.5 (35.9)	148.9–164.1	< 0.001
Current FPG (mg/dL)	185.0 (75)	183.7–231	143.0 (43.8)	142.1–172.9	<0.001	216.0 (125.0)	204–244.6	128.0 (38.5)	131.1–160.8	< 0.001
Current HbA1c %	8.9 (1.6)	8.9–9.5	7.6 (0.95)	7.4–8.1	<0.001	9.2 (1.9)	8.9–9.6	6.8 (1.3)	6.8–7.3	< 0.001
Hemoglobin (g/dL)	13.4 (2.6)	13.2–14.2	12.6 (2.5)	12.2–13.3	0.006	14.2 (2.4)	13.3–14.5	13.7 (1.5)	12.9–13.9	0.142
Mean corpuscular volume (fL)	88.2 (6.1)	85.0–89.0	87.6 (4.4)	84.1–88.2	0.389	84.9 (8.3)	78.7–85.0	81.8 (16.0)	75.9–82.5	0.184
C-reactive protein (mg/L)	6.0 (9.5)	6.2–11.9	5.3 (5.3)	5.1–8.2	0.507	3.4 (6.5)	4.2–8.1	3.4 (6.0)	3.8–7.5	0.769

The results are presented as a median (interquartile range), and 95% confidence interval (CI); p-values were calculated by non-parametric (Mann-Whitney U) test;
Group I: sitagliptin/metformin-treated group, and Group II: empagliflozin/metformin-treated group

FPG — fasting plasma glucose; HbA1c — glycated hemoglobin

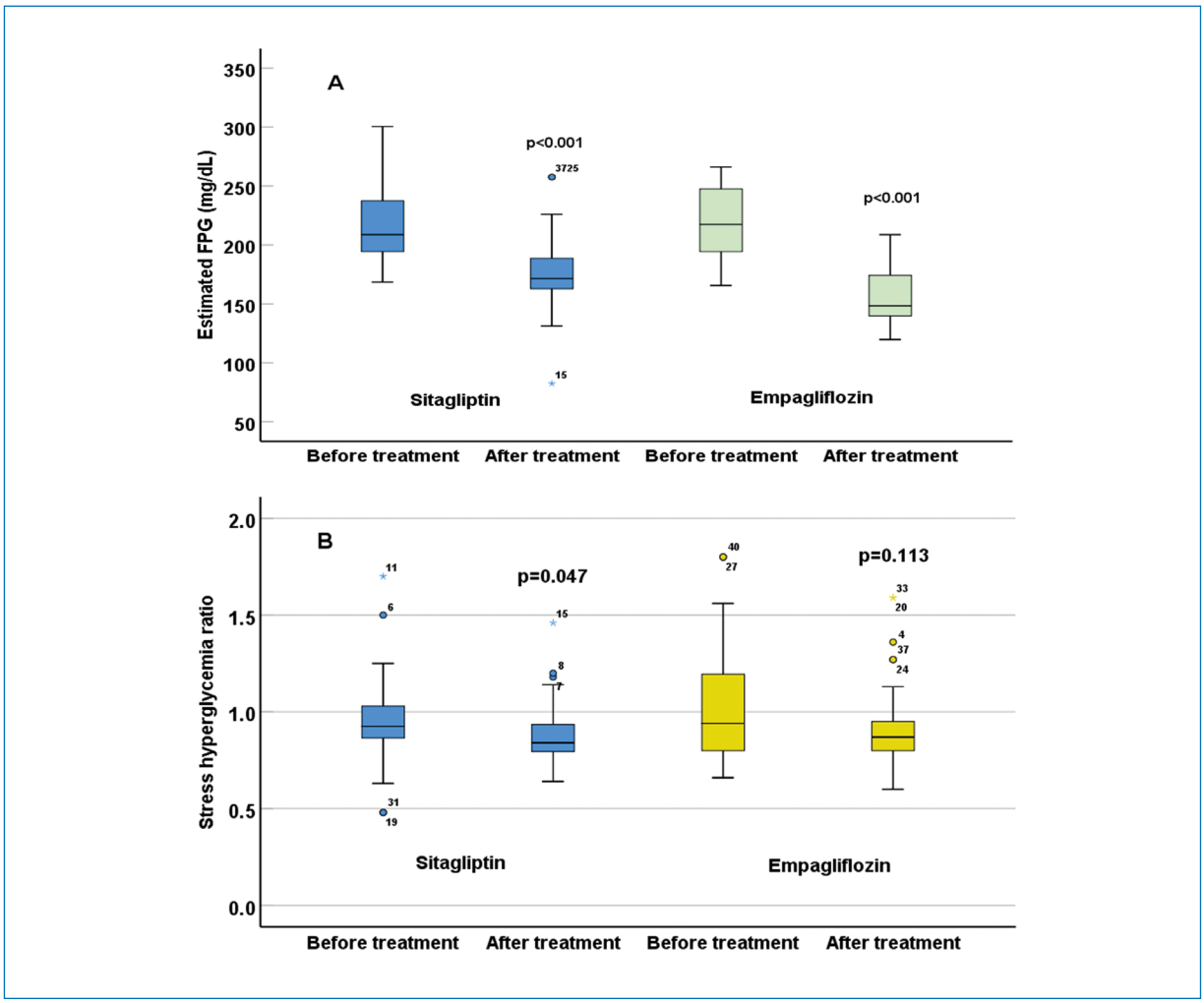

Figure 2. Effects of Sitagliptin and Empagliflozin **A.** on the Estimated (Stress) Fasting Plasma Glucose (FPG) Level and **B.** on the Stress Hyperglycemia Ratio
p-values compared with the corresponding before-treatment level of each intervention

the frequency of stress hyperglycemia [18]. Therefore, sitagliptin could be useful to combat stress hyperglycemia in the presence of inflammation, as sitagliptin has anti-inflammatory property [21]. In this study, sitagliptin reduced CRP levels from a median value of 6 mg/L to 5.3 mg/L, which supports previous studies that sitagliptin suppressed diabetes-related inflammation [22]. These observations explained the results of our study which found that sitagliptin significantly decreased the SHR value but not the frequency of participants with SHR value of > 1 as a marker of stress hyperglycemia. Hemoglobin level was significantly decreased in sitagliptin-metformin group from a median value of 13.4 g/dL to 12.6 g/dL. This effect may be due a rare side effect of sitagliptin, which can cause red blood cell hemolysis, or metformin, which rarely causes megaloblastic anemia due to vitamin B12 deficiency [23, 24]. Empagliflozin-metformin significantly reduced the FPG (current and estimated values), and glycated hemoglobin, but it did not significantly reduce the median SHR value. It significantly decreased the frequency of participants who had an SHR value of > 1. These results confirmed a previous experimental study, which showed that empagliflozin reduced stress-induced hyperglycemia in certain number of mice, and it cannot protect the brain from the effect of hyperglycemia on memory [25]. In another experimental animal study, empagliflozin attenuated the late sequalae of acute hyperglycemia associated with acute myocardial infarction by reducing the cardiac tissue fibrosis [26]. Non-significant effects of empagliflozin on the red blood cell indices confirmed a previous study, which showed that empagliflozin has positive effect on hemoglobin by reducing the new-onset anemia, and its pleotropic effects are not affected by the presence of anemia [27]. Empagliflozin in a dose higher than that

used in this study (25 mg vs. 10 mg, daily) suppresses the inflammatory biomarkers, which explained our results that empagliflozin had no significant effect on the median value of CRP [28]. This study indicates that the pleiotropic effects of sitagliptin and empagliflozin have a role in decreasing the SHR value. Among these pleiotropic effects are cardioprotection with empagliflozin and the anti-inflammatory effect with sitagliptin [29, 30]. Patients with diabetes are at risk for developing acute coronary syndrome, heart failure, autonomic cardiac neuropathy, etc., which are categorized as life-threatening conditions [31]. Therefore, the determination of the SHR value as a prognostic biomarker will be helpful in those patients who were treated with empagliflozin. On the other hand, the comorbidities of diabetes indicate that inflammation is a predisposing etiopathological factor, as with diabetic foot, peripheral neuropathies, etc. [32]. The determination of SHR could be useful in the assessment of sitagliptin in these pathological conditions. Therefore, the application of SHR is not solely related to the stress that results from surgical interventions or septicemia, but it can be extended to the assessment of diabetic co-morbidities as well as the pleiotropic effects of oral antidiabetic agents. The strength of this study is the demonstration of a significant effects of oral hypoglycemic agents on SHR, that characterized by a reduction in the SHR level (to less than 1) and the frequency of patients with SHR of > 1. Another important point is that determining the SHR value helps the clinician in controlling diabetes. Limitations of the study include small sample size and inclusion of only two red blood cell indices. Further investigation into the application of SHR as a predictive biomarker in empagliflozin-treated chronic heart failure with or without diabetes could be a valuable strategy because cardiovascular events are potentially critical illnesses associated with the risk of poor outcome.

Conclusions

Both sitagliptin and empagliflozin reduced the magnitude of the median value of SHR from 0.925 to 0.840 (9.2%) with sitagliptin treatment, and the frequency of patients with SHR > 1 from 16 to 7 patients (43.8%) with empagliflozin treatment. Sitagliptin significantly suppressed the inflammatory marker and reduced the hemoglobin levels. Therefore, SHR value could help the clinicians to monitor diabetes control. This study leads us to identify the SHR cutoff value as a short- and long-term prognostic biomarker in the management of hospitalized patients with diabetes and concomitant cardiovascular diseases or neuropathies, as these comorbidities are associated with inflammation and poor prognosis.

Article information

Data availability statement

The data is available upon request with permission from the corresponding author.

Ethics statement

This study was approved by the Medical Ethics Committee of the College of Medicine at the University of Diyala in Iraq (No. MSM735, date 01-03-2023) and registered on ClinicalTrial.gov (NCT 05822674). Given the patient follow-up principle of this study, informed consent from each patient was obtained. The study protocol was conducted according to the ethical guidelines of the Declaration of Helsinki.

Authors contribution

MSAl-N conceived and designed the study, collected the data, performed the statistical analysis, and wrote the first draft. IIL: collecting and interpreting the data. TNJ: collecting, performing the statistical analysis, and interpreting the data. All authors reviewed and edited the manuscript and approved the submission.

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Conflict of interest

The authors declare no conflicts of interest.

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World Health Organization 5 (WHO-5) Well-Being Index and Problem Areas in Diabetes 5 Scale (PAID-5): A Cross-Sectional Study in Screening Tools for Depression and Anxiety Patients with Type 1 and Type 2 Diabetes in Kerala, India

ABSTRACT

Objective: This cross-sectional study aimed to explore the multifaceted interplay of screening tools for the mental health of patients with type 1 (T1D) and type 2 (T2D) diabetes in Kerala, India, with a focus on depression and anxiety.

Materials and methods: Data were collected from 384 patients with diabetes in Kerala, between August and October 2023. The Krejcie and Morgan Method was employed for sample selection, ensuring a confidence level of 99.0% and a margin error of 3.5%. Participants, aged 35 years and above, with T1D or T2D and proficiency in Malayalam, were included. Demographic and clinical factors, World Health Organization 5 Well-Being (WHO-5), and Problem Areas in Diabetes 5 (PAID-5) data were gathered through structured interviews. Statistical analyses included mean, 95% confidence interval, independent sample test, chi-square test, and receiver operating characteristic (ROC) curve analysis.

Results: The study revealed a high prevalence of depression (74%) and anxiety (82%) among patients with diabetes in Kerala. T2D participants exhibited significantly higher rates of depression and anxiety. Poor glycemic control, longer disease duration, lower socioeconomic status, comorbid conditions, and a lack of strong social support were identified as significant predictors of psychological distress. ROC analysis demonstrated the predictive capacity of the WHO-5 [area under the curve (AUC) 0.745 and PAID-5 index (AUC 0.822) for depression and anxiety, respectively].

Conclusions: Tailored interventions addressing glycemic control, disease management, and psychosocial support are crucial for reducing the burden of depression and anxiety. Health education programs targeting vulnerable subgroups and routine screening for mental health issues in diabetes care are recommended to improve patient outcomes in Kerala. (Clin Diabetol 2024; 13, 3: 164–169)

Keywords: depression and anxiety, patients with diabetes, WHO-5 Well-Being Index, PAID-5 index, physical and mental health

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Introduction

Depression and anxiety are prevalent mental health disorders that often co-occur with chronic medical conditions, such as diabetes. This co-occurrence can significantly impact the overall well-being and management of diabetes. India is currently facing a substantial diabetes epidemic [1]. The country has witnessed dramatic growth in the number of people diagnosed with diabetes, with millions affected by the disease [2]. The factors contributing to this surge include genetic predisposition, urbanization, dietary changes, sedentary lifestyles, and an aging population [3]. Given that diabetes is most prevalent in the Indian state of Kerala, it is imperative to investigate the variables influencing depression and anxiety in people with diabetes [4]. This study aims to explore and understand the multifaceted interplay of screening tools for the mental health of patients with diabetes in Kerala.

In this study, researchers aim to examine the well-being and emotional status of patients with diabetes in Kerala by administering the World Health Organization 5 Well-Being Index (WHO-5), a well-known and verified tool for evaluating a person's subjective well-being and emotional condition [5, 6]. Five straightforward questions are used in the WHO-5 to gauge an individual's general state of well-being and mood during the previous 2 weeks. By doing this, they can learn more about the frequency and intensity of anxiety and depression in this population and pinpoint possible causes of these mental health problems. The research further includes the Problem Areas in Diabetes (PAID-5) questionnaire, which serves several important purposes in the context of diabetes management and healthcare [7]. The PAID-5 questionnaire is a concise and validated tool used to assess the emotional and psychological challenges specific to diabetes management. Through the utilization of tools like the PAID-5 questionnaire, healthcare providers and researchers can pinpoint areas of concern, implement targeted interventions, and ultimately enhance the quality of care for individuals living with diabetes.

The combination of the WHO-5 and PAID-5 index questionnaires is a powerful approach to assessing the emotional well-being of individuals with diabetes. It ensures a more detailed and nuanced understanding of emotional challenges and can inform more targeted interventions and support strategies to improve the overall quality of life for patients with diabetes [8]. This study aims to explore and understand the multifaceted interplay of screening tools for the mental health of patients with diabetes in Kerala. All these factors can contribute to the development of depression and anxiety in individuals managing the chronic burden of diabetes.

Materials and methods

In this cross-sectional study, data were collected from 384 patients with diabetes, who also suffered from depression and anxiety, in Kerala, India, between August and October 2023. Participants with T1D and T2D have chronic conditions characterized by high blood sugar, marked by elevated hemoglobin A1C, and glucose tolerance test levels. The samples of 384 cases were selected using the Krejcie and Morgan method, with a confidence level of 99.0% and a margin error of 3.5%. To be eligible for this study, the respondents should have either T1D or T2D, be over 35 years of age, and be able to read, speak, and write in Malayalam. Ethical approval to conduct the present study was granted by the Ethics Committee of the Department of Psychology at Suresh Gyan Vihar University, Jaipur, India, with an approval letter bearing the reference number (IEC/DPSY/2023/DRKR/2-002). All patients were fully informed about the purpose of the study and the confidentiality of the data. Before data collection, each subject provided written informed consent. The questionnaire included demographic/clinical factors, WHO-5, and PAID-5.

Quantitative data such as age, body mass index (BMI), sex, family type, marital status, employment, history of depression, hypertension, alcohol consumption, smoking habits, and comorbidity were expressed as the mean and 95% confidence intervals. After the data were tested for normality of distribution, the statistical test was allotted. The independent sample test and chi-square test were used to compare the groups of T1D and T2D patients.

The receiver operating characteristic (ROC) curve is a valuable tool for assessing the diagnostic performance of psychological assessment instruments in identifying conditions such as depression and anxiety. In this study, we used the WHO-5 and the PAID-5 index to evaluate their ability to discriminate between individuals with and without depression and anxiety. ROC curve analysis was employed to determine the diagnostic accuracy of these indices. Plotting the test's sensitivity (power) against the relative false-positive rate (1-specificity) as the model's cutoff level is changed is a widely used technique to measure a test's predictive capacity [9]. Using Egger's approach and the algorithm recommended by Delong et al., we compared the areas under the ROC curves [10]. For this analysis, statistical significance was determined as $p < 0.05$. Data were analyzed using the dedicated software program SPSS 26.0 (IBM Corporation).

Exclusion criteria

Exclusion criteria were implemented in the WHO-5 and PAID-5 index cross-sectional study conducted in Kerala, India, to refine the participant pool and ensure the study's specificity. Individuals below the age of 35 years were excluded to concentrate on the impact of diabetes within the later stages of adulthood. Proficiency in Malayalam, the primary language of the region, was essential for accurate communication during data collection. Unwillingness to provide informed consent resulted in exclusion, upholding ethical standards and ensuring voluntary participation. Exclusion criteria that were also considered as medical conditions affecting cognitive function were severe psychiatric disorders beyond depression and anxiety, incomplete or inaccurate survey responses, and pregnancy in females, which could introduce confounding factors.

Results

The comparison of demographic and clinical parameters between participants with T1D and T2D revealed several noteworthy findings (Tab. 1). Firstly, there were no significant differences observed in age or BMI between the 2 groups, indicating that age and

Table 1. Demographic and Clinical Parameters in Participants with T1D and T2D

Mean ± SD or n (%)

Variables	T1D	T2D	p-value
Age	50.7 ± 11.3	48.9 ± 11.0	0.555
BMI	26.6 ± 5.0	26.7 ± 4.6	0.304
Sex			0.923
Male	56 (50.9)	138 (50.4)	
Female	54 (49.1)	136 (49.6)	
Family type			0.874
Joint	38 (34.5)	97 (35.4)	
Nuclear	72 (65.5)	177 (64.6)	
Marital status			0.644
Married	102 (92.7)	250 (91.2)	
Unmarried	6 (5.5)	14 (5.1)	
Separated/divorced	2 (1.8)	10 (3.6)	
Employment			0.405
Employed	83 (75.5)	218 (79.6)	
Unemployed	18 (16.4)	43 (15.7)	
Retired	9 (8.2)	13 (4.7)	
Duration of diabetes	12.8 ± 2.8	12.4 ± 2.8	0.711
Family history of depression	84 (76.4)	204 (74.5)	0.006**
Hypertension	79 (71.8)	176 (64.2)	0.015*
Alcohol	36 (32.7)	106 (38.7)	0.024*
Smoking	36 (32.7)	91 (33.2)	0.027*
Regular blood glucose checks	110 (100.0)	274 (100.0)	—
Diabetes complications			0.000**
Eye disease	66 (60.0)	150 (54.7)	
Kidney disease	60 (54.5)	159 (58.0)	
Heart disease	77 (70.0)	200 (73.0)	
Stroke	15 (13.6)	44 (16.1)	
Paresthesia	97 (88.2)	240 (87.6)	
Diabetes medications			0.728
Pills	46 (41.8)	115 (42.0)	
Insulin	12 (10.9)	23 (8.4)	
Both	52 (47.3)	136 (49.6)	

*is significant at the 0.05 level; **is significant at the 0.01 level
BMI — body mass index; SD — standard deviation; T1D — type 1 diabetes; T2D — type 2 diabetes

Table 2. ROC Curve Analysis for WHO-5 Well-Being Index and PAID-5 Index of Depression and Anxiety

Variables	AUC	SE	p-value	95% CI		Sensitivity	Specificity
				Lower bound	Upper bound		
WHO-5 Well-Being Index	0.745	0.051	0.000*	0.644	0.845	0.640	0.740
PAID-5 Index	0.822	0.044	0.000*	0.736	0.907	0.740	0.820

*is significant at the 0.01 level
AUC — area under the curve; PAID-5 — Problem Areas in Diabetes 5 scale; ROC — receiver operating characteristic; SE — standard error; WHO-5 — World Health Organization 5 Well-Being Index

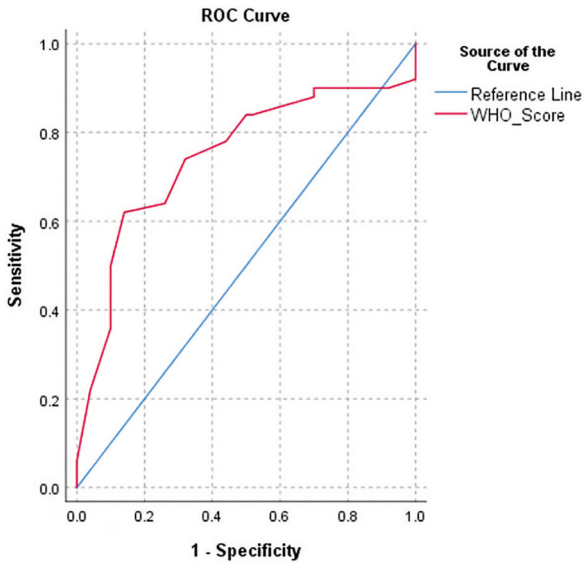

Figure 1. Receiver Operating Characteristic Curve of Depression and World Health Organization 5 Well-Being Index (WHO-5) in Patients with Diabetes

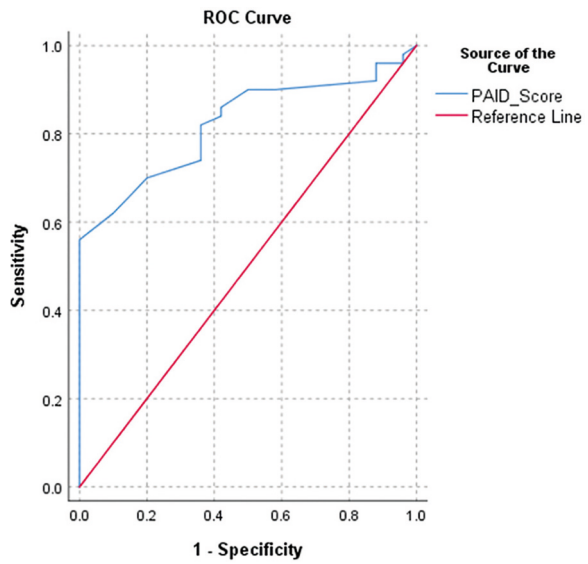

Figure 2. Receiver Operating Characteristic Curve of Anxiety and Problem Areas in Diabetes (PAID-5) Index Score in Patients with Diabetes

BMI are not distinguishing factors between T1D and T2D in this study population. Similarly, there were no significant disparities in sex distribution, family type, marital status, or employment status between individuals with T1D and T2D. The duration of diabetes revealed no significant difference between the 2 groups, as indicated by the p-value of 0.711. Both groups exhibited similar mean durations of diabetes, with T1D showing an average duration of 12.8 years (± 2.8) and T2D with 12.4 years (± 2.8). However, it is notable that participants with T1D showed a higher prevalence of family history of depression compared to those with T2D, suggesting a potential link between T1D and familial predisposition to depression. Moreover, while both groups exhibited high adherence to regular blood sugar checks, there were differences in the prevalence of certain comorbidities and lifestyle factors. Notably, individuals with T1D showed higher rates of hypertension, while those with T2D had higher rates of alcohol consumption and smoking. Additionally, participants with T1D demonstrated a higher prevalence of various diabetes complications such as eye disease, kidney disease, heart disease, stroke, and numbness disease compared to those with T2D, suggesting potentially different disease trajectories and complications associated with each diabetes type. However, there were no significant differences in the diabetes medications received between the 2 groups.

When the WHO-5 was used as a predictor of depression in diabetes patients, ROC curve analysis showed an AUC of 0.745 ($p < 0.001$) (Tab. 2 and Fig. 1). Depression was predicted with 64.0% sensitivity and 74.0% specificity when the WHO-5 score was greater than 2.4. Similarly to ROC analysis, we discovered that the ideal cutoff value of 2.0 for the PAID-5 index had 74.0% sensitivity and 82.0% specificity (AUC 0.822, $p < 0.001$) for anxiety prediction in diabetes patients (Fig. 2).

Discussion

This PAID-5 and WHO-5 study examined the variables related to anxiety and depression in Indian patients with diabetes living in Kerala. We discovered that 74% of the participants screened positive for depression and 82% matched the criteria for anxiety when it came to the factors affecting depression and anxiety. The study's findings about anxiety and depression were in line with those found in earlier research, which estimated their incidence to be between 18% and 30% [11]. Furthermore, patients with T2D had significantly higher WHO-5 and PAID-5 ratings for depression and anxiety than did patients with T1D. According to earlier research, diabetes may be associated with higher levels of anxiety and depression [12, 13]. Additionally, across all populations, people with T1D are found to experience higher rates of depression and anxiety than those with T2D. Patients diagnosed with T2D may develop lifelong insulin dependency, hypoglycemia episodes connected to insulin, diabetes management-related family disputes, and comorbidities, all of which suggest a higher likelihood of early development of diabetes signs.

The study discovered that among Kerala's patients with diabetes, anxiety and depression were highly prevalent. The WHO-5 scores were significantly lower in those with depression, indicating reduced psychological well-being. The PAID-5 scores were higher among those with anxiety, demonstrating a strong association with diabetes-related distress. Several factors emerged as significant predictors: First, among patients with diabetes, poor glycemic control was substantially linked to anxiety and depression. Higher HbA1c levels were linked to increased psychological distress. Second, patients living with diabetes for a longer period were more likely to experience anxiety and depression, probably as a result of the difficulties in managing the condition in the long term. Third, lower socioeconomic status, limited access to healthcare, and educational disparities were correlated with higher depression and anxiety rates. Fourth, patients with diabetes were more likely to experience anxiety and despair if they also had comorbid conditions such as neuropathy, heart disease, stroke, kidney disease, or eye illness. Finally, a lack of strong social support systems was associated with higher psychological distress.

These findings underscore the importance of addressing both physical and mental health aspects of diabetes care. Improving glycemic control, enhancing disease management strategies, and providing psychosocial support are essential steps in reducing the burden of depression and anxiety in this population [14, 15]. The study also highlights the need for tailored interventions to target vulnerable subgroups, such as those with low socioeconomic status or longer disease duration. Health education and awareness programs should be designed to address these disparities and encourage patients to seek early psychological support when needed [16].

Furthermore, healthcare professionals in Kerala should recognize the strong connection between diabetes-related distress and mental health, integrating routine screening for depression and anxiety into diabetes care. Collaborative care models that involve mental health professionals may also be beneficial for improving patient outcomes.

Conclusions

The study, using the WHO-5 and PAID-5, sheds light on the screening results for depression and anxiety among Indian patients in Kerala with diabetes. It highlights the urgency of addressing psychological well-being as an integral part of diabetes management. Kerala's diabetes population could have improved quality of life if healthcare providers apply comprehensive care plans and interventions that address the highlighted issues.

Article information

Data availability

The datasets generated during and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

The authors, Juliet George and Kalpana Randhawa, contributed collaboratively to the conception, design, data collection, and analysis of the study. Additionally, both authors played integral roles in drafting and revising the manuscript, ensuring the accuracy and integrity of the intellectual content.

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None.

Conflict of interest

The authors declare no conflict of interest.

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Adverse Drugs Reaction and Prescribing Pattern of Antidiabetic Medications in Type 2 Diabetes Patients: An Observational Ambispective Study

ABSTRACT

Objective: Type 2 diabetes (T2D) is a global health concern and multiple medications are used for its treatment. Adverse drug reactions (ADR) pose a concern for patient health and treatment compliance. This study aimed to evaluate ADR in T2D patients receiving antidiabetic medications and to analyze the prescribing patterns.

Materials and methods: An observational ambispective study was conducted in a six-month period, enrolling 615 T2D patients. Collected data included patient demographics, comorbidities, disease duration, body mass index, prescribed medications, and ADRs. The causal relationship between ADR and drug was assessed as per WHO-Uppsala Monitoring Centre (WHO--UMC) criteria. Data was descriptively summarized using Microsoft Excel 365 software.

Results: In 615 patients, 220 experienced at least one ADR. Out of 220, percentage of ADR occurrence among female (37.6%) was higher than male (34.4%) patients. The most commonly prescribed drugs were biguanides, followed by dipeptidyl peptidase-4 inhibitors and thiazolidinediones. ADRs were higher in patients prescribed metformin followed by pioglitazone, glimepiride, sitagliptin and dapagliflozin. Thirty-two types of ADRs (424 incidents) were recorded, with gastrointestinal disturbances as most prevalent followed by weakness and tiredness. All reported ADRs were categorized as "Possible" according to WHO UMC causality categories.

Conclusions: The study emphasizes the notable occurrence of ADRs in T2D patients and highlights the need for vigilant monitoring. Although ADRs were mild to moderate in nature, optimal treatment strategies for T2D management will benefit from multicenter studies establishing a comprehensive ADR database. (Clin Diabetol 2024; 13, 3: 170–179)

Keywords: type 2 diabetes (T2D), antidiabetic medications, adverse drugs reaction, prescribing pattern

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Introduction

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose, progressively leading to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. The most common is type 2 diabetes (T2D), usually in adults, which occurs when the production of insulin by the pancreas and/or the sensitivity of tissues to insulin is reduced (insulin resistance), leading to chronically elevated blood glucose levels [1, 2]. The countries with the largest numbers of adults with diabetes aged 20–79 years in 2021 were China, India and Pakistan. They are anticipated to remain so in 2045. India is one of the top 5 countries in the South East Asian (SEA) region with an age-standardized diabetes prevalence of 9.6% in 2021 whereas Mauritius in the SEA region had the highest prevalence rate (22.6%), followed by Bangladesh (14.2%), Sri Lanka (11.3%), and Bhutan (10.4%) [3].

The class of medications for treatment of T2D available in India are biguanides, sulfonylureas (SU), dipeptidyl peptidase-4 inhibitors (DPP4i), thiazolidinedione (TZD), sodium glucose co-transport 2 inhibitors (SGLT2i), alpha-glucosidase inhibitors (αGI), non-sulphonyl urea secretagogues, insulin and glucagon-like peptide-1 receptor agonists (GLP1RA) [4]. Drugs continue to be the most common interventions used to achieve glycemic control, but drugs themselves have their adverse effect and can adversely impact mental and social health [5]. According to World Health Organization (WHO), an adverse drug reaction (ADR) is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function" [6]. ADR is one of the leading causes of morbidity and mortality worldwide [7]. The consequences of ADRs burden the healthcare system with increased cost of therapy and prolongation of hospitalization. In developing countries, the cost of adverse reactions in the general population is very high and under-recognized. It is, therefore, imperative to evaluate the safety of medicines by specialized methods like Pharmacovigilance [8–11].

The detection of ADRs has become significant because of introduction of large number of drugs in the last two decades [12]. ADR may occur daily in hospitals and adversely affect patients' life, often causing considerable morbidity and mortality [13, 14]. Attention should be given to identifying the patient populations at risk, the drugs most commonly responsible and the causes of ADRs. Increased supply of drugs in the market and an upward trend in polypharmacy are contributing factors to the prevalence of ADRs worldwide [15]. ADRs may result in a loss of patient confidence, leading to negative emotions toward the treatment recommended by their physician and may result in the patient choosing self-treatment options, which may consequently precipitate additional ADRs [16, 17].

Getting more information on prescribed drugs and their side effects will be beneficial to the healthcare professional as well as to the patients [18]. Hence the present study was planned to evaluate the ADRs and prescribing patterns of the drugs.

Materials and methods

Study design

An observational ambispective study was conducted on 615 patients with T2D to assess ADR and prescribing pattern of antidiabetic drugs.

Study population/study participants

The study was conducted on out-patients of Rudraksha Institute of Medical Sciences (RIMS Healthcare), Ghodasar and Rudraksha Hospital, Bareja in Ahmedabad, Gujarat, India for a period of 6 months (March 2022 to May 2022 and March 2023 to May 2023). T2D patients with or without associated conditions, aged 18 years or above, of both sexes, taking antidiabetic medications were included in the study, except for pregnant women, patients with associated malignant condition and acute communicable diseases.

Ethical approval

Approval of Institutional Ethics Committee (IEC) "Rudraksha Hospital Ethics Committee" was obtained before initiation of the study. Patients were explained the procedure of the study and requested to provide signed Informed Consent Forms (ICFs) to Investigators before enrolment for the study.

Data collection/variables

All relevant details such as age, sex, height, weight, body mass index (BMI), duration of disease, diagnosis, comorbidities, and prescribed medicines were recorded. Patients were followed up and ADRs were recorded. The causal relationship between ADR and drug was assessed by the investigators as per WHO-UMC criteria.

Statistical analysis

Collected data were descriptively summarized using Microsoft Excel 365 software. As the experiment was exploratory in nature, there were no specific hypotheses planned to be tested and no claims were made regarding treatment usage.

Results

A total of 615 T2D patients on antidiabetic medications were enrolled in the study, of which 266 (43.3%) were female, and 349 (56.8%) were male. Among 220 patients, who had ADR, 100 (45.5%) were female, and 120 (54.6%) were male. Percentage of ADR occurrence among female patients was 37.6%, and among male, it was 34.4% (Tab. 1).

The average age of the patients enrolled in the study was 52.14 years, ranging from 23 to 78 years. Out of 615 patients, 235 (38.2%) were 51–60 years old, 163 (26.5%) were 41–50, 116 (18.9%) were 61–70, 81 (13.2%) were 31–40, 9 (1.5%) were 21–30, and 11 (1.8%) were over 70 years old. In 220 patients with ADR, 87 (39.6%) were 51–60 years old, 62 (28.2%) were 41–50, 32 (14.6%) were 61–70, 28 (12.7%) were 31–40, 8 (3.6%) were 21–30 and 3 (1.4%) were over 70 years. ADR occurrence was observed as 37.0% (51–60), 38.0% (41–50), 27.6% (61–70), 34.6% (31–40), 88.9% (21–30), 27.3% (above 70 years) in patients of various age groups (Tab. 1).

The average duration of T2D was 7.31 years ranging from newly diagnosed to 33 years. Out of 615 patients, in 304 (49.4%) patients the disease duration was 0–5 years, in 193 (31.4%) patients 6–10 years, in 65 (10.6%) patients 11–15 years, in 37 (6.0%) patients 16–20 years and in 16 (2.6%) patients more than 20 years. In 220 patients with ADR, in 108 (49.1%) patients the disease duration was 0–5 years, in 66 (30.0%) patients 6–10 years, in 32 (14.6%) patients 11–15 years, in 9 (4.1%) patients 16–20 years and in 5 (2.3%) patients more than 20 years. ADR occurrence was observed as 35.5% (0–5 years), 34.2% (6–10 years), 49.2% (11–15 years), 24.3% (16–20 years) and 31.25% (above 20 years) in patients with various duration of disease for T2D (Tab. 1).

The average BMI of the patients was 28.1 kg/m^2 enrolled in the study ranging from 16.6 to 54.5 kg/m^2. As per obesity classification according to WHO, out of 615

Table 1. Demographic Distribution of Patients with T2D and ADR

Groups	No. of patients	No. of patients with ADRs	Percentage of ADRs n = 220	Percentage of ADRs occurrence
Sex distribution				
Female	266	100	45.5%	37.6%
Male	349	120	54.6%	34.4%
Age distribution [years]				
51–60	235	87	39.6%	37.0%
41–50	163	62	28.2%	38.0%
61–70	116	32	14.6%	27.6%
31–40	81	28	12.7%	34.6%
21–30	9	8	3.7%	88.9%
Above 70	11	3	1.4%	27.3%
Duration of disease distribution [years]				
0–5	304	108	49.1%	35.5%
6–10	193	66	30.0%	34.2%
11–15	65	32	14.6%	49.2%
16–20	37	9	4.1%	24.3%
Above 20	16	5	2.3%	31.3%
BMI distribution (kg/m^2)				
Overweight: 25–29.9	264	99	45.0%	37.5%
Obese: > 30	181	68	30.9%	37.6%
Normal: 18.5–24.9	162	48	21.8%	29.7%
Underweight: < 18.5	8	5	2.2%	62.5%
Comorbidities distribution				
Only T2D	210	68	30.9%	32.4%
T2D + 1	214	87	39.6%	40.7%
T2D + 2	135	43	19.6%	31.9%
T2D + 3 and more	56	22	10.0%	39.3%

ADR — adverse drug reaction; BMI — body mass index; T2D — type 2 diabetes

patients, 264 (42.9%) were overweight — 25 kg/m^2 to 29.9 kg/m^2, 181 (29.4%) were obese — more than 30 kg/m^2, 162 (26.3%) had a normal body weight — 18.5 kg/m^2 to 24.9 kg/m^2 and 8 (1.3%) were underweight — less than 18.5 kg/m^2. In 220 patients with ADR, 99 (45.0%) were overweight, 68 (30.9%) were obese, 48 (21.8%) had a normal body weight and 5 (2.3%) were underweight, based on BMI categories. ADR occurrence was observed as 37.5% (overweight), 37.6% (obese), 29.6% (normal), 62.5% (underweight) in patients of various BMI range.

Out of 615 patients, no comorbidity was reported in 210 (34.2%), at least one comorbidity in 214 (34.8%), two comorbidities were reported in 135 (22.0%) and three or more comorbidities in 56 (9.1%) patients. Among 220 patients who had ADR, 68 (30.9%) patients did not have any comorbidity, 87 (39.6%) had at least one, 43 (19.6%) had two and 22 (10.0%) had three or more comorbidities. ADR occurrence was observed as 32.4% (no comorbidity), 40.7% (1 comorbidity), 31.9% (2 comorbidities) and 39.3% (3 or more comorbidities) (Tab. 1).

In 615 patients, oral antidiabetic drugs were prescribed to 527 (85.7%), oral and injectables to 86 (14.0%) and only injectables to 2 (0.3%) patients. Out of 527 patients who were on oral antidiabetic drugs, 186 (35.3%) reported ADR and out of 86 who were on oral and injectable drugs, 32 (37.2%) reported ADR. Two patients who were on only injectable drugs, both reported ADR.

Commonly prescribed fixed-dose combinations (FDCs) contain biguanide, SU and TZD in 336 (54.6%) patients followed by biguanide, αGI and SU in 261 (42.4%), biguanide and DPP4i in 208 (33.8%), biguanide, DPP4i and SGLT2i in 171 (27.8%), biguanide and SGLT2i in 95 (15.5%), biguanide and TZD in 93 (15.1%), DPP4i and SGLT2i in 75 (12.2%) and biguanide and SU in 51 (8.3%). In 220 patients, who had ADR, biguanide, SU and TZD was given to 118 (19.2%) patients followed by biguanide, αGI and SU in 100 (16.3%), biguanide and DPP4i in 80 (13.0%), biguanide, DPP4i and SGLT2i in 69 (11.2%), biguanide and SGLT2i in 28 (4.6%), biguanide and TZD in 38 (6.2%), DPP4i and SGLT2i in 22 (3.6%) and biguanide and SU in 14 (2.3%) (Tab. 2).

A total of 9 classes of drugs were prescribed to 615 patients, as biguanide in 607 (98.7%), DPP4i in 494 (80.3%), TZD in 448 (72.9%), SU in 437 (71.1%),

Table 2. Prescribing Pattern of Antidiabetic Medications Including FDCs Formulations and Number of Patients with ADR

Prescribed formulations	No. of patients	No. of patients with ADRs	Percentage of ADR (n = 615)	Percentage of ADR (n = 220)
Biguanide + SU + TZD	**336**	**118**	**19.2%**	**53.7%**
Metformin + Glimepiride + Pioglitazone	318	112	18.2%	50.9%
Metformin + Gliclazide + Pioglitazone	18	6	1.0%	2.7%
Biguanide + αGI + SU	**261**	**100**	**16.3%**	**45.5%**
Metformin + Voglibose + Glimepiride	249	96	15.6%	43.6%
Metformin + Voglibose + Gliclazide	12	4	0.7%	1.8%
Biguanide + DPP4i	**208**	**80**	**13.0%**	**36.4%**
Metformin + Sitagliptin	93	35	5.7%	15.9%
Metformin + Vildagliptin	76	29	4.7%	13.9%
Metformin + Teneligliptin	38	15	2.4%	6.8%
Metformin + Linagliptin	1	1	0.2%	0.5%
Biguanide + DPP4i + SGLT2i	**171**	**69**	**11.2%**	**31.4%**
Metformin + Sitagliptin + Dapagliflozin	147	61	9.9%	27.7%
Metformin + Vildagliptin + Dapagliflozin	22	7	1.1%	3.1%
Metformin + Vildagliptin + Remogliflozin etabonate	2	1	0.2%	0.5%
Insulin	**96**	**38**	**6.2%**	**17.3%**
Insulin Glargine	54	24	3.9%	10.9%
Insulin degludec + Insulin aspart	19	5	0.8%	2.3%
Insulin degludec	8	3	0.5%	1.4%
Insulin aspart	7	3	0.5%	1.4%

Human insulin	3	1	0.2%	0.5%
Insulin isophane + Human insulin	2	1	0.2%	0.5%
Insulin glulisine	1	1	0.2%	0.5%
Insulin aspart + Insulin aspart protamine	1	0	0	0
Insulin detemir	1	0	0	0
Biguanide + SGLT2i	**95**	**28**	**4.6%**	**12.7%**
Metformin + Dapagliflozin	72	20	3.3%	9.1%
Metformin + Empagliflozin	23	8	1.3%	3.6%
Biguanide + TZD	**93**	**38**	**6.2%**	**17.3%**
Metformin + Pioglitazone	93	38	6.2%	17.3%
DPP4i + SGLT2i	**75**	**22**	**3.6%**	**10.0%**
Sitagliptin + Dapagliflozin	31	9	1.5%	4.1%
Linagliptin + Empagliflozin	19	8	1.3%	3.6%
Vildagliptin + Dapagliflozin	17	5	0.8%	2.3%
Vildagliptin + Remogliflozin Etabonate	8	0	0	0
Biguanide + SU	**51**	**14**	**2.3%**	**6.4%**
Metformin + Glimepiride	35	8	1.3%	3.4%
Metformin + Gliclazide	9	4	0.7%	1.8%
Metformin + Glipizide	7	2	0.3%	0.9%
Biguanide + αGI	**37**	**16**	**2.6%**	**7.3%**
Metformin + Acarbose	33	14	2.3%	6.4%
Metformin + Voglibose	4	2	0.3%	0.9%
Biguanide	**35**	**17**	**2.8%**	**7.7%**
Metformin	35	17	2.8%	7.7%
DPP4i	**21**	**7**	**1.1%**	**3.2%**
Vildagliptin	14	4	0.7%	1.8%
Teneligliptin	6	2	0.3%	0.9%
Linagliptin	1	1	0.2%	0.5%
GLP1RA	**20**	**6**	**1.0%**	**2.7%**
Semaglutide	18	6	1.0%	2.7%
Liraglutide	2	0	0	0
Biguanide + DPP4i + TZD	**19**	**3**	**0.5%**	**1.4%**
Metformin + Sitagliptin + Pioglitazone	19	3	0.5%	1.4%
SGLT2i	**16**	**11**	**1.8%**	**5.0%**
Dapagliflozin	8	5	0.8%	2.3%
Empagliflozin	7	5	0.8%	2.3%
Canagliflozin	1	1	0.2%	0.5%
Meglitinides + αGI	**6**	**5**	**0.8%**	**2.3%**
Repaglinide + Voglibose	6	5	0.8%	2.3%
αGI	**6**	**0**	**0**	**0**
Acarbose	5	0	0	0
Voglibose	1	0	0	0
SU	**3**	**3**	**0.5%**	**1.4%**
Glimepiride	3	3	0.5%	1.4%
TZD	**1**	**1**	**0.2%**	**0.5%**
Pioglitazone	1	1	0.2%	0.5%

αGI — alpha-glucosidase inhibitors; ADR — adverse drug reaction; DPP4i — dipeptidyl peptidase-4 inhibitors; FDC — fixed-dose combination; GLP1RA — glucagon-like peptide-1 receptor agonists; SGLT2i — sodium glucose co-transport 2 inhibitors; SU — sulfonylureas; TZD — thiazolidinedione

SGLT2i in 357 (58.1%), αGI in 309 (50.2%), insulin in 110 (17.9%), GLP1RA in 20 (3.3%) and meglitinides in 6 (1.0%). In 220 patients with ADR, biguanide was prescribed to 215 (35.0%), DPP4i to 181(29.5%), TZD to 160 (26.0%), SU to 155 (25.2%), SGLT2i to 130 (21.1%), αGI to 121 (19.7%), insulin to 42 (6.8%), GLP1RA to 6 (1.0%) and meglitinides to 5 (0.8%). ADR occurrence was observed as 35.4% (biguanide), 36.6% (DPP4i), 35.7% (TZD), 35.5% (SU), 36.4% (SGLT2i), 39.2% (αGI), 38.2% (insulin), 30.0% (GLP1RA) and 83.3% (meglitinides).

A total of 32 types of ADRs (424 incidents) were reported in 220 out of total 615 enrolled patients. Most commonly ADR reported were GI disturbances (80), followed by weakness (66), tiredness (38), hypoglycemic events (29), headache (28), sleep disturbance (24), burning and painful urination (20), restlessness and uneasiness (16), decreased appetite (15), body ache (14), pedal edema (9), etc. A total 23 antidiabetic medications from 9 classes of drugs were given to patients. Biguanide had the highest number of ADR events (414) followed by DPP4i (351), SU (306), TZD (299), αGI (244), SGLT2i (235), insulin (88), GLP1RA (12) and meglitinides (6) (Tab. 3).

None of the ADR was fatal or required hospitalization. No ADR was categorized as "Certain" or "Probable" as all the patients were on more than one drugs. Hence, all the reported ADRs were categorized as "Possible" as per WHO UMC causality categories. Reported ADRs were mild (78.77%) to moderate (21.23%) in nature. No severe ADR was reported in the study.

Discussion

The study indicates that the percentage (35.8%) of ADRs is substantial and emphasizes the importance of monitoring ADRs in T2D patients. It also highlights the need for healthcare providers to be cautious about potential adverse effects.

Although ADRs were reported in both male and female patients, it has been observed that ADR occurrence was slightly higher in female patients (37.6%) compared to male patients (34.4%). In a study conducted in Korea, antidiabetic agent-associated AEs were more frequently reported by women than men [19]. In studies conducted in Bhopal, Kerala and Odisha in India, predominance of adverse effects in female patients with diabetes was reported [20–22]. Further studies and research may be required to examine the causes behind these gender differences.

The majority of T2D patients were from age group 51–60 years, followed by 41–50. Most ADRs occurred among patients 51–60 years (39.6%), 41–50 years (28.2%), and 61–70 years old (14.6%). In a study conducted in Karnataka (India), it was found that the majority of the ADRs occurred in the age group of 40–80 years of patients on antidiabetic medications [23]. The limited number of patients (1.5%) in the 21–30 age group highlights the need for further studies focusing on this demographic.

Most patients (49.4%) have been diagnosed with T2D within the past 5 years. This group has the highest number of patients with ADRs. Percentage of ADR occurrence for disease duration group of 11–15 years is the highest (49.2%). Further research and a more comprehensive study may be required to identify specific factors contributing to ADRs in different disease duration groups.

The majority of patients fall into the overweight category followed by obese. Patients classified as overweight reported the highest proportion of ADRs (45.0%), followed by patients with obesity (30.9%), with normal weight (21.8%), and underweight (2.3%). A meta-analysis of observational studies indicated that obesity is moderately associated with T2D [24].

In patients with T2D, comorbidities are common [25, 26];. 65.9% patients had at least one or more comorbidities. The data indicates that patients with comorbidities had a higher incidence of ADRs.

Mostly oral antidiabetic drugs were prescribed to the patients (85.7%). ADRs are higher in this patient group since this patient group had highest number of patients and oral antidiabetic drugs are known to have various ADRs.

Prescribing FDCs are most common for T2D patients [27, 28]. The most frequently prescribed FDC includes biguanide, SU, and TZD, with 54.6% of patients followed by biguanide, αGI and SU (42.4%). The highest ADRs (19.2%) in FDC of biguanide, SU, and TZD may be due to the combined effect of individual drugs.

The data shows that wide range of antidiabetic drugs were prescribed to T2D patients, with the most commonly biguanide (98.7%) followed by DPP4i (80.3%), TZD (72.9%), SU (71.1%), SGLT2i (58.1%), αGI (50.2%), insulin (17.9%). Other classes, including GLP1RA and meglitinides, have a lower prescription rate.

The systematic review of various publications suggests that FDCs of various oral hypoglycemic agents (OHAs) are beneficial to T2D patients to achieve their target glycemic levels by effectively controlling hyperglycemia. Most widely used component of FDCs is metformin with other OHAs such as glimepiride, pioglitazone, rosiglitazone, acarbose, and sitagliptin [29].

The study reveals that 32 types of ADRs were recorded, with a cumulative total of 424 incidents.

Table 3. Class and Name of the Drugs vs. ADR Events

Class and name of the drugs	No. of ADR events
Biguanide	414
Metformin: GI disturbances (76), Weakness (65), Tiredness (38), Hypoglycemic events (28), Headache (28), Sleep disturbance (23), Burning and painful urination (20), Restlessness and uneasiness (16), Decreased appetite (14), Body ache (14), Pedal edema (8), Weight gain (8), Increased appetite (8), Dizziness (7), Blurred vision (7), Back pain (7), Joint pain (6), Itching (6), Chest pain (5), Throat pain (4), Itching and redness over penile foreskin (3), Urinary incontinence (3), Eructation (3), Itching at vaginal region (3), Chills (3), Cough (2), Breathlessness (2), Swelling on face (2), Excess thirst (2), Vulvar rashes (1), Rash (1), Muscle pain (1)	414
Dipeptidyl peptidase-4 inhibitors	351
Sitagliptin: GI disturbances (36), Weakness (35), Tiredness (21), Hypoglycemic events (20), Headache (14), Sleep disturbance (12), Restlessness and uneasiness (11), Burning and painful urination (7), Decreased appetite (7), Body ache (5), Pedal edema (5), Weight gain (4), Increased appetite (4), Joint pain (4), Itching (4), Dizziness (3), Blurred vision (3), Throat pain (3), Back pain (2), Chest pain (2), Cough (2), Eructation (2), Chills (2), Breathlessness (2),Swelling on face (2), Urinary incontinence (1),Excess thirst (1), Vulvar rashes (1)	215
Vildagliptin: GI disturbances (16), Weakness (15), Tiredness (7), Sleep disturbance (5), Headache (4), Weight gain (4), Restlessness and uneasiness (3), Body ache (3), Hypoglycemic events (2), Burning and painful urination (2), Decreased appetite (2), Pedal edema (2), Increased appetite (2), Blurred vision (2), Chest pain (2), Itching and redness over penile foreskin (2), Itching at vaginal region (2), Joint pain (1), Itching (1), Throat pain (1), Urinary incontinence (1), Eructation (1), Excess thirst (1)	81
Teneligliptin: GI disturbances (7), Weakness (5), Headache (5), Burning and painful urination (4), Body ache (4), Decreased appetite (3), Back pain (3), Tiredness (2), Sleep disturbance (2), Hypoglycemic events (1), Restlessness and uneasiness (1), Increased appetite (1), Dizziness (1), Chest pain (1), Itching and redness over penile foreskin (1), Urinary incontinence (1)	42
Linagliptin: Hypoglycemic events (4), GI disturbances (3), Burning and painful urination (3), Weakness (2), Sleep disturbance (1)	13
Sulfonylureas	306
Glimepiride: GI disturbances (52), Weakness (45), Tiredness (22), Headache (19), Hypoglycemic events (18), Sleep disturbance (18), Burning and painful urination (13), Restlessness and uneasiness (10), Decreased appetite (10), Body ache (9), Increased appetite (6), Dizziness (5), Back pain (5), Itching (5), Weight gain (4), Blurred vision (4), Pedal edema (3), Joint pain (3), Chest pain (3), Throat pain (3), Itching and redness over penile foreskin (3), Urinary incontinence (3), Itching at vaginal region (3),Chills (3), Cough (2), Eructation (2), Swelling on face (2), Excess thirst (2), Breathlessness (1), Muscle pain (1)	279
Gliclazide: Weakness (3), Hypoglycemic events (3), GI disturbances (2), Tiredness (2), Burning and painful urination (2), Pedal edema (2), Headache (1), Sleep disturbance (1), Restlessness and uneasiness (1), Weight gain (1), Increased appetite (1), Dizziness (1), Vulvar rashes (1)	21
Glipizide: Burning and painful urination (2), Tiredness (1), Hypoglycemic events (1), Restlessness and uneasiness (1), Itching (1)	6
Thiazolidinedione	299
Pioglitazone: GI disturbances (50), Weakness (50), Tiredness (30), Hypoglycemic events (20), Sleep disturbance (20), Headache (19), Burning and painful urination (15), Body ache (11), Restlessness and uneasiness (9), Decreased appetite (7), Weight gain (6), Dizziness (6), Back pain (6), Pedal edema (5), Itching (5), Increased appetite (4), Blurred vision (4), Joint pain (4), Chest pain (3), Throat pain (3), Urinary incontinence (3), Eructation (3), Chills (3), Itching and redness over penile foreskin (2), Itching at vaginal region (2),Swelling on face (2), Excess thirst (2), Cough (1), Breathlessness (1), Vulvar rashes (1), Rash (1), Muscle pain (1)	299
Alpha-glucosidase inhibitors	244
Voglibose: GI disturbances (46), Weakness (32), Hypoglycemic events (17), Headache (16), Tiredness (12), Sleep disturbance (11), Burning and painful urination (10), Decreased appetite (9), Restlessness and uneasiness (6), Body ache (6), Increased appetite (5), Weight gain (4), Dizziness (4), Blurred vision (4), Back pain (4), Itching (4), Pedal edema (3), Joint pain (3), Itching and redness over penile foreskin (3), Itching at vaginal region (3), Chest pain (2), Throat pain (2),Cough (2), Urinary incontinence (2), Eructation (2), Swelling on face (2), Chills (1), Breathlessness (1)	216

Acarbose: GI disturbances (5), Weakness (4), Tiredness (3), Sleep disturbance (3), Hypoglycemic events (2), Headache (1), Burning and painful urination (1), Restlessness and uneasiness (1), Decreased appetite (1), Weight gain (1), Increased appetite (1), Dizziness (1), Blurred vision (1), Throat pain (1), Chills (1), Excess thirst (1)	28
Sodium glucose co-transport 2 inhibitors	235
Dapagliflozin: GI disturbances (39), Weakness (33), Tiredness (19), Hypoglycemic events (13), Headache (13), Restlessness and uneasiness (10), Sleep disturbance (9), Decreased appetite (6), Body ache (5), Increased appetite (5), Pedal edema (4), Dizziness (4), Itching (4), Burning and painful urination (3), Weight gain (3), Blurred vision (3), Joint pain (3), Chest pain (3), Throat pain (3), Chills (3),Eructation (2), Breathlessness (2), Excess thirst (2), Back pain (1), Cough (1), Urinary incontinence (1), Itching at vaginal region (1), Swelling on face (1), Vulvar rashes (1), Muscle pain (1)	198
Empagliflozin: Sleep disturbance (6), Burning and painful urination (6), GI disturbances (5), Weakness (5), Hypoglycemic events (3), Headache (2), Blurred vision (2), Decreased appetite (1), Pedal edema (1), Increased appetite (1), Dizziness (1), Joint pain (1), Rash (1)	35
Remogliflozin etabonate: GI disturbances (1)	1
Canagliflozin: Chills (1)	1
Insulin	88
Insulin glargine: GI disturbances (8), Weakness (8), Burning and painful urination (5), Hypoglycemic events (3), Sleep disturbance (3), Tiredness (2), Decreased appetite (2), Body ache (2), Pedal edema (2), Weight gain (2), Increased appetite (2), Throat pain (2), Cough (2), Urinary incontinence (2), Headache (1), Restlessness and uneasiness (1), Back pain (1), Itching (1), Itching at vaginal region (1), Breathlessness (1)	51
Insulin aspart: Weakness (3), Increased appetite (3), GI disturbances (2), Tiredness (2), Weight gain (2), Blurred vision (2), Hypoglycemic events (1), Sleep disturbance (1), Pedal edema (1), Itching at vaginal region (1)	18
Insulin degludec: GI disturbances (3), Weakness (3), Tiredness (2), Sleep disturbance (2), Blurred vision (2), Weight gain (1), Increased appetite (1), Itching at vaginal region (1)	15
Insulin isophane + Human insulin: Weakness (1), Tiredness (1), Muscle pain (1)	3
Insulin glulisine: Hypoglycemic events (1)	1
GLP1RA	12
Semaglutide: GI disturbances(8), Tiredness(1), Headache(1), Decreased appetite(1), Joint pain(1)	12
Liraglutide	0
Meglitinides	6
Repaglinide: GI disturbances(3), Hypoglycemic events(2), Weakness(1)	6

ADR — adverse drug reaction; GI disturbances — gastrointestinal disturbances; GLP-1 — glucagon-like peptide-1 receptor agonists

Gastrointestinal disturbance (GI), weakness and tiredness were common ADRs across various drug classes, followed by hypoglycemic events, headache, sleep disturbances, burning and painful urination, restlessness and uneasiness, Decreased appetite, body ache and pedal edema. GI disturbances is the most commonly reported ADR followed by weakness and tiredness across various classes of antidiabetic drugs. Hypoglycemic events are frequent with several classes of drugs, including SU, DPP4i, SGLT2i and biguanides, αGIs and TZD when used in combination with one or more drugs. Managing blood glucose levels is the primary goal of T2D management, but severe hypoglycemia can be dangerous, so close monitoring is necessary. Sleep disturbances, headache, weight gain, pedal edema, burning and painful urination are reported with multiple drug classes, such as biguanides, TZD, SU, DPP4i, and SGLT2i, αGI when used in combination with one or more drugs. No pancreatic related ADR was reported in this study. Treatment adherence and daily life can be affected by these ADRs. Few drugs have limited ADR data, as they were less commonly prescribed. For example, meglitinides and GLP1RA have relatively fewer ADR reports. In a study conducted in 220 T2D patients in New Delhi, it was found that most commonly observed ADRs were related to endocrine and gastrointestinal system [30].

The assessment to categorize all ADRs as "Possible" because of the complexity of managing T2D. Patients

in the study were on multiple antidiabetic drugs, which can make it difficult to conclusively attribute specific ADR to a single drug. The "Possible" classification indicates that while there may be a reasonable link between the ADRs and the drugs, causality cannot be established with certainty. The study results indicate that patients generally experience mild to moderate ADRs from antidiabetic medications.

Study limitations

The study was conducted at two hospitals which may limit the generalizability of the findings to a broader population. The study had a relatively short duration of 6 months for data collection, which might not capture long-term trends or variations in antidiabetic drug prescribing patterns and ADRs. Multicentric trials and larger sample size could provide more robust insights into the prevalence and patterns of ADRs in T2D patients. Addressing these limitations in future research can enhance the robustness and applicability of findings in similar studies.

Conclusions

The present study provided data on prescription pattern, the prevalence (35.8%) of ADRs and their distribution among different groups with respect to genders, age, BMI, duration of disease, comorbidities and prescribed FDCs. The study indicated that percentage of ADR occurrence among female (37.6%) was higher than male patients (34.4%). Metformin (215, 35.0%) exhibited the highest ADRs, followed by pioglitazone (160, 26.0%), glimepiride (142, 23.0%), sitagliptin (108, 17.6%), and dapagliflozin (107, 17.4%), voglibose (106, 17.2%) and vildagliptin (46, 7.5%). Gastrointestinal disturbances (80, 36.4%) emerged as the most prevalent ADR trailed by weakness (66, 30.0%) and tiredness (38, 17.3%). FDC of biguanide, SU, and TZD (336, 54.6%) was prescribed most frequently followed by biguanide, SU and αGI (261, 42.4%). Although ADRs are not life-threatening, they can cause discomforts in many patients. Hence, healthcare providers should remain vigilant in observing and attending ADRs.

Article information

Ethics statement

Approval of Institutional Ethics Committee (IEC) "Rudraksha Hospital Ethics Committee" was obtained before initiation of the study.

Authors contribution

Conception and design of study: Dr Jalpa Suthar, Sani Prajapati, Acquisition of data: Sani Prajapati, Dr. Dhruvi Hasnani, Dr. Vipul Chavda, Analysis, or interpretation of data: Sani Prajapati, Dr Jalpa Suthar, Dr. Dhruvi Hasnani, Dr. Vipul Chavda, Drafting the work and revising it critically for important intellectual content and Final approval of the version to be published: Sani Prajapati, Dr Jalpa Suthar, Dr. Dhruvi Hasnani, Dr. Vipul Chavda.

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Conflict of interest

The authors declare no conflict of interest.

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Relative Handgrip Strength Positively Correlates with Low-Density Lipoprotein Cholesterol Level in Patients with Type 2 Diabetes: A Cross-Sectional Study

ABSTRACT

Objective: The aim of this clinical study was to discover a new factor affecting muscle strength and quality in patients with type 2 diabetes (T2D).

Materials and methods: The relationship between muscle strength and quality and low-density lipoprotein cholesterol (LDL-C), random triglyceride (TG), and high-density lipoprotein cholesterol (HGL-C) levels were studied. Relative handgrip strength (RHGS) was used to evaluate muscular strength and quality. RHGS was calculated by dividing the absolute handgrip strength by body mass index (BMI). Using the stepwise method, multiple regression analysis was conducted and the linear correlation between variables was calculated by estimating Pearson correlation coefficient.

Results: This study enrolled 68 patients with T2D. The majority of the participants were men, accounting for 71.5%. The median values of the measured parameters were as follows: age 67 years, physical activity level 10.1 METs/h/week, estimated glomerular filtration rate 57.0 mL/min/1.73 m^2, systolic blood pressure 123.5 mmHg, diastolic blood pressure 69.0 mmHg, body weight 64.1 kg, body mass index 24.35 kg/m^2, HbA1c level 7.4%, random TG level 139 mg/dL, HDL-C level 52.5 mg/dL, and T2D duration 16.0 years. RHGS was 1.47 ± 0.40 kg/BMI. RHGS was associated with LDL-C (r = 0.349) but was not correlated with random TG and HDL-C (r = 0.124 and r = 0.088, respectively).

Conclusions: Patients with T2D with better muscle strength and quality demonstrated an increased LDL-C level. In patients with T2D, LDL-C may be a factor affecting muscle strength and quality. (Clin Diabetol 2024; 13, 3: 180–184)

Keywords: relative handgrip strength, low-density lipoprotein cholesterol, type 2 diabetes

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Introduction

Type 2 diabetes (T2D) is a progressive disease characterized by insulin resistance and continuous loss of endogenous insulin secretion [1]. Furthermore, T2D is associated with sarcopenia, which results in the loss of whole-body homeostasis and decline in physical function [2]. Sarcopenia-derived muscle weakness is consistently associated with deterioration of glucose metabolism in patients with diabetes, even among well-nourished subjects [3, 4]. Relative handgrip strength (RHGS) has been proposed as a diagnostic tool for assessing muscular strength and quality, including in overweight individuals [5]. In this clinical study, the relationship between muscle strength and quality and low-density lipoprotein cholesterol (LDL-C), random triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels was studied in patients with T2D to search for a new factor affecting RHGS in patients with T2D as the relationship between RHGS and LDL-C in patients with T2D is inconclusive.

Materials and methods

Participants

Our study protocol was reviewed and approved by the Institutional Review Board of Hoshi-iin as 3–1 (March 31, 2021). Written informed consent was obtained from each participant.

We excluded participants who had been diagnosed with type 1 diabetes (n = 1). Also, patients with orthopedic diseases such as chronic rheumatoid arthritis or cerebrovascular diseases with paralysis were excluded (n = 1 and n = 2, respectively).

Patients consistently visited the hospital for follow-up examinations once a month. Using the same random blood samples as previously reported, the patients' lipid profiles, plasma glucose levels, and glycated hemoglobin (HbA1c) levels were measured [6]. When patients visited the hospital, a registered nurse and registered dietician advised on the necessary dietary and lifestyle modifications.

Definition of T2D

Diabetes is defined as a fasting plasma glucose of 126 mg/dL or greater and/or a 2-h glucose level of 200 mg/dL or greater during a 75-g OGTT [7]. Anti-glutamic acid decarboxylase antibody was negative and insulin secretion was not depleted in all participants.

Handgrip strength and RHGS measurement

Using a digital grip strength dynamometer (Model T.K.K 5401; Takei Scientific Instruments Co., Tokyo, Japan, measurement range: 5.0–100.0 kg), handgrip strength was measured in each hand three times [8]. The participants were instructed to hold the dynamometer with the second proximal interphalangeal joint of the hand flexed at 90° to the handle and squeeze the handle as hard as they could in the standing position (elbow extension status). The participants rested for at least 30 s after each measurement. The maximum value of the three measurements was used [9].

RHGS was used for assessing muscular strength and quality. RHGS was calculated by dividing the absolute handgrip strength by body mass index (BMI) [10].

Statistical analysis

All statistical data were analyzed using the SPSS software (version 10.0, SPSS Inc., Chicago, IL, USA). All numerical values are expressed as mean ± standard deviation. Using the stepwise method, multiple regression analysis was conducted with a software program. We calculated Pearson correlation coefficient to estimate the linear correlation between variables.

Results

Participant characteristics

This study enrolled 68 patients with T2D who visited our hospital in April 2022. Patient characteristics are shown in Table 1. The majority of the participants were men, accounting for 71.5%. The median values of the measured parameters were as follows: age 67 (range 24–94) years, body weight 64.1 (range 45.7–136.2) kg, BMI 24.35 (range 17.9– 42.2) kg/m^2, HbA1c level 7.4% (range 5.8–12.8), random TG level 139 (range 53–493) mg/dL, HDL-C level 52.5 (range 36–119) mg/dL, LDL-C level 104.8 (range 30–174) mg/dL.

Proportion of patients prescribed with antidiabetic, antihypertensive, and antihyperlipidemic medications

The proportion of patients prescribed antidiabetic medications are shown in Table 2. The proportion of prescribed antidiabetic medications was as follows: sodium-glucose cotransporter 2 inhibitors, biguanides, insulin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, α- glucosidase inhibitors, GLP-1 receptor analogs, and glinides were prescribed in 40.5%, 43.2%, 54.1%, 2.7%, 37.8%, 29.7%, 27.0%, and 48.6% of patients, respectively, while no thiazolidinedione was prescribed.

Antihypertensive and antihyperlipidemic drugs were prescribed in 72.2% and 61.1% of patients, respectively.

Analysis of multiple comparisons for factors affecting RHGS

RHGS was 1.47 ± 0.40 kg/BMI. Stepwise multiple regression analysis demonstrated that the LDL-C was

Table 1. Characteristics of the Study Participants

	Median value	Range
Age [years]	67	24–94
Physical activity level [METs/h/week]	10.1	3.0–20.8
Estimated glomerular filtration rate [mL/min/1.73 m^2]	57.0	33.0–93.0
Systolic blood pressure [mmHg]	123.5	93–191
Diastolic blood pressure [mmHg]	69.0	47–101
Body weight [kg]	64.1	45.7–136.2
Body mass index [kg/m^2]	24.35	17.9– 42.2
Glycated hemoglobin (HbA1c) [%]	7.4	5.8–12.8
Random triglyceride (TG) [mg/dL]	139	53–493
High density lipoprotein cholesterol (HDL-C) [mg/dL]	52.5	36–119
Low density lipoprotein cholesterol (LDL-C) [mg/dL]	104.8	30–174
Duration of type 2 diabetes (T2D) [years]	16.0	4–45

Table 2. Proportion of Patients Prescribed Antidiabetic Medications

Sodium glucose cotransporter inhibitors (%)	40.5
Biguanides (%)	43.2
Insulin (%)	54.1
Sulfonylureas (%)	2.7
Dipeptidyl peptidase-4 inhibitors (%)	37.8
α-glucosidase inhibitors (%)	29.7
Glucagon-like peptide 1 analogs (%)	27.0
Glinides (%)	48.6
Thiazolidinedione (%)	0

a significant determinant of RHGS and not TG and HDL-C ($r = 0.349$, $p < 0.001$, $r = 0.130$, $p =$ not significant, $r = 0.084$, $p =$ not significant, respectively). Thus, RHGS correlated with the LDL-C level and the result was shown in Figure 1.

Discussion

Recently, handgrip strength (HGS) has emerged as a substitute for muscle strength measurement owing to its convenience and economic advantages. Hence, various organizations defining sarcopenia accepted HGS as one of the most reliable tools to establish a diagnosis of sarcopenia [11–13]. However, the cutoff values of HGS defining low muscle strength differed among different studies. A review paper on sarcopenia indicated that muscle strength measured by HGS should be stratified by BMI [14]. With this data, several studies have revealed that the relative HGS adjusted for BMI (RHGS) instead of absolute HGS are inversely related to numerous age-related diseases, such as metabolic syndrome, diabetes mellitus, cardiovascular disease, and chronic kidney disease [15, 16]. In recent nationwide population-based studies, RHGS demonstrated a stronger correlation with cardiovascular biomarkers than absolute HGS and dominant HGS [17, 18]. Higher RHGS was considerably associated with a lower systolic blood pressure, TG, plasma insulin and glucose, and HDL-C levels [17].

However, any correlation between RHGS and random TG and HDL-C level was not observed in our study. Thus, our results are different from previous paper reporting that the HDL-C and TG levels were determinant factors for RHGS in the participants from the National Health and Nutrition Examination Survey [17]. Conversely, limited literature exists regarding whether RHGS correlates with the LDL-C level.

Interestingly, our study demonstrated that a positive correlation between RHGS and LDL-C level exists. However, in another previous paper, RHGS was negatively associated with LDL-C level in middle-aged and elderly community-dwelling women [10]. Compared to our results, these discrepancies may be secondary to the differently selected participants. We examined patients with T2D alone and the majority of the participants were men, accounting for 71.5%. On the other hand, the previous studies analyzed participants from National Health and Nutrition Examination Survey and middle-aged women. Also, the sample size was different from our study.

Our study has few limitations that merit consideration. First, the omission of comprehensive covariate adjustment in our analysis, including variables such as age, gender, duration of diabetes, and BMI, restricts our ability to fully account for potential confounding effects. Second, the cross-sectional design prohibits the establishment of causal relationships. Third, the analysis of nominal variables, such as gender, using traditional correlation methods presents challenges due to linearity assumptions, and while biserial cor-

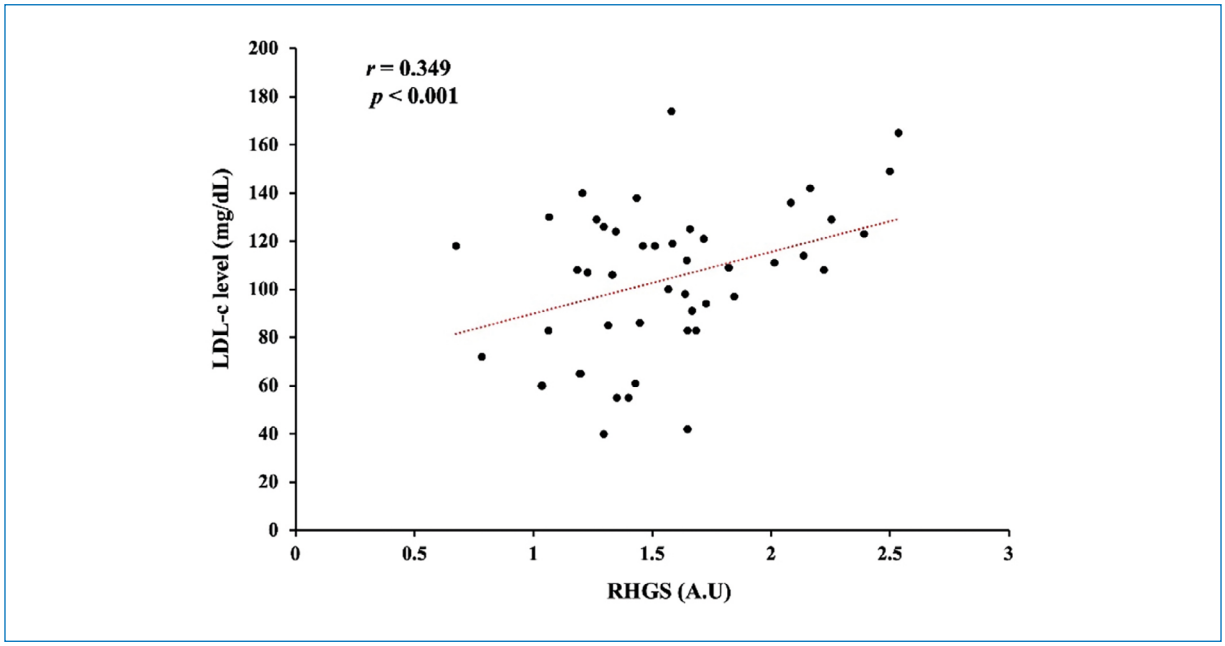

Figure 1. Regression Coefficients between the Relative Handgrip Strength (RHGS) and Low-Density Lipoprotein Cholesterol (LDL-C) Level

Regression coefficients of the univariate linear regression analysis between the RHGS and LDL-C level showed a positive correlation (r = 0.349, p < 0.001). The y- and x-axes reflect the LDL-C level and RHGS, respectively.

A.U. — arbitrary unit; LDL-C: low-density lipoprotein cholesterol; RHGS — relative handgrip strength

relation would be ideal, software constraints limited its implementation. Fourth, while our study focuses on the Japanese population, variations in socioeconomic status, cultural diversity, and healthcare access may limit the generalizability of our findings across all segments of the population. Finally, the sample size was relatively small (n = 68) and the majority of the participants were men (71.5%). Therefore, this study may be exploratory in nature without adequate power. These limitations underscore the need for cautious interpretation and highlight avenues for future research with more comprehensive datasets and study designs.

Despite these limitations, this study can suggest the following clinical implications. In the secondary prevention program of cardiovascular disease in patients with T2D, the target range of LDL-C level is below 70 mg/dL [19]. Based on our result, an extremely lower LDL-C level may cause a reduced RHGS leading to an increased risk of sarcopenia. Furthermore, as an adverse effect of cholesterol-lowering statin, an increased risk of T2D is well recognized. This adverse effect may be secondary to a reduced RHGS by cholesterol-lowering statin. When clinicians reduce the LDL-C level using a cholesterol-lowering drug, they are required to monitor the RHGS including the lipid profile to detect the early sign of sarcopenia in patients with T2D. As an extremely low LDL-C may cause a reduced RHGS leading to an increased risk of sarcopenia, clinicians are required to monitor RHGS stringently.

Article information

Data availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Ethics statement

This study complies with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki. The subjects have signed written consent for the publication. This study protocol was reviewed and approved by the review boards of Hoshi-iin as 3-1 (March 31, 2021).

Author contributions

Shuichi Okada, Tsugumichi Saito, Tetsuro Andou, and Kihachi Ohshima designed the clinical study. Shuichi Okada and Hiroto Hoshi performed the clinical study. Kikkawa Koji, Atsushi Isoda, Junichi Okada, Kazuya Okada, Eijiro Yamada, and Shuichi Okada collected data and attended every meeting to discuss this

project. Junichi Okada, Yasuyo Nakajima, and Shuichi Okada prepared the manuscript. Shuichi Okada and Yasuyo Nakajima performed statistical analysis.

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Conflict of interest

The authors declare no conflict of interest.

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COMMENT
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Specific Considerations in the Interpretation of the Relationship between Relative Handgrip Strength and Lipid Profile in Type 2 Diabetes

I read with great interest an elegant research paper ("Relative Handgrip Strength Positively Correlates with Low-Density Lipoprotein Cholesterol in Patients with Type 2 Diabetes: A Cross-Sectional Study") by Okada et al. that was published online on April 23, 2024 [1]. The authors reported a significant positive correlation between the serum levels of low-density lipoprotein cholesterol (LDL-C) and relative handgrip strength (RHGS). In this study, there are many points that strengthen it.

The authors attributed the muscle weakness to the sarcopenia that is commonly reported in T2D, while using lipid-lowering agents, particularly statins, can cause muscle weakness, thereby reducing the RHGS. In the Okada et al.'s study, 61.1% of the patients were currently using lipid lowering agents.

The authors measured the RHGS in both hands, but they did not specify that the RHGS of the left hand is less than that of the right hand. Furthermore, females showed a lower RHGS compared with males.

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The significant level of the positive correlation between LDL-C and RHGS is < 0.001, while the correct value is 0.0035, i.e., < 0.01. This finding is contrary to other studies that found an inverse association with LDL-C [2, 3]. The interpretation of this discrepancy is related to the normal levels of LDL-C as the median value was 104.8 mg/dL, which is related to the adverse effects of lipid lowering agents (e.g., using statins); and those who are not using statins, may have a higher LDL-C level and RHGS [4]. Moreover, a significant inverse correlation between triglyceride level and RHGS was reported in many studies, while the Okada study reported a non-significantly positive correlation ($r = 0.130$).

The authors expressed the RHGS per body mass index, but they did not adjust or normalize the values of the RHGS according to the body mass index, as such an adjustment would show the difference between males and females [4].

In Table 1, the authors mentioned the physical activity of the patients, but there is no evidence about their nutritional status, which is an important determinant of handgrip strength [5].

I would like to thank the authors for their study rationale, as it highlights important issues about the relationship between the RHGS and dyslipidemia that necessitate further research to settle their associations.

Conflict of interest

The author declare no conflict of interest.

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Dear Editor,

We thank Dr. Al-Nimer for his comments on issues related to our work [1]. In our study, after measuring the grip strength of both hands, the relative hand grip strength (RHGS) was calculated using the grip strength of the one with the larger measured value. It should be added that all participants in this study were right-handed. In addition, 71.5% of the population used in this study was male, and we mentioned that the results were obtained in such a population. We also confirmed that gender was not a factor affecting RHGS in our study. The differences between the previous report and the results of this study were discussed in the discussion section, but the points made by Dr. Al-Nimer may be worth considering. Although nutritional status may be a factor affecting the results of this study, prealbumin levels were measured to determine nutritional status and confirmed that there were no problems in the participants. Once again, I would like to thank Dr. Al-Nimer for critical comments.

Sincerely yours,
Shuichi Okada

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