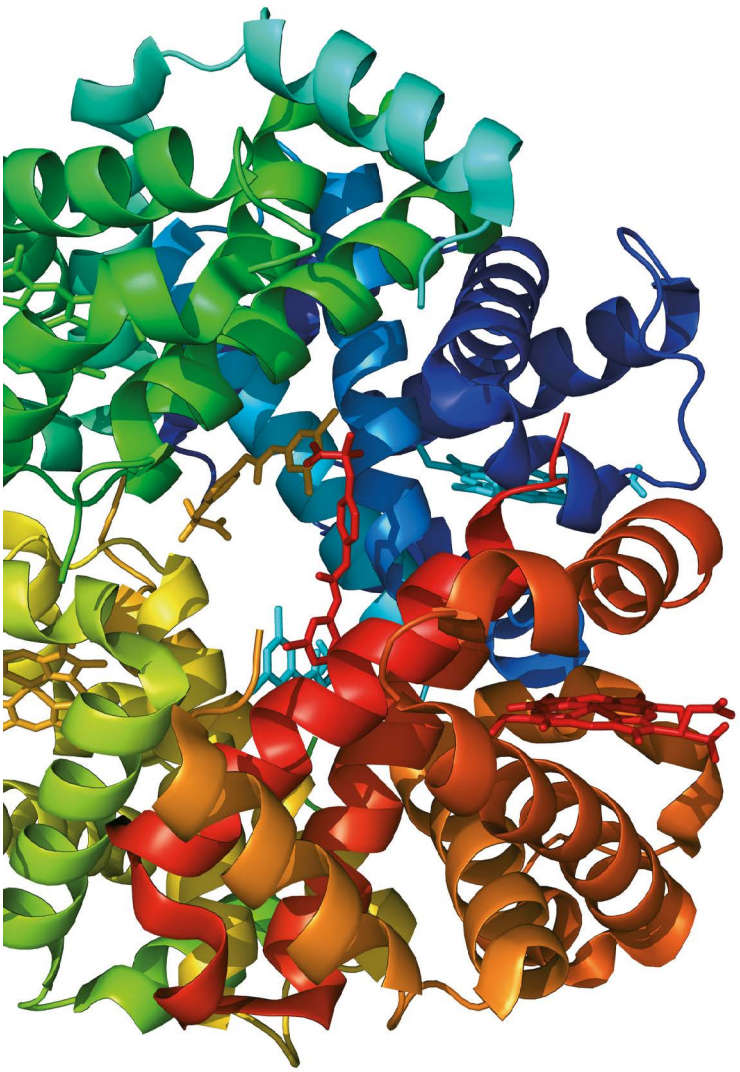
Clinical Diabetology 2023, Vol. 13, No. 6, 319–396

# CLINICAL DIABETOLOGY

2024, Vol. 13, No. 6

e-ISSN 2450–8187 ISSN 2450–7458





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**Clinical Diabetology** (ISSN 2450–7458, e-ISSN 2450–8187) is published six times a year by VM Media Group sp. z o.o.
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23-0638.004.001

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Indexed in base of CAS, Index Copernicus (ICV 2023 = 162.00), Ulrich's Periodicals Directory, in base of Polish Ministry of Education and Science (100) and Cite Score (0.90). Current Impact Factor of "Clinical Diabetology" (2023) is 0.7.

The journal "Clinical Diabetology" is financed under Contract No. 790/P-DUNdem/2019 by the funds of the Minister of Polish Ministry of Education and Science for the science promotion activities.



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**2024, Vol. 13, No. 6**

## Contents

ISSN 2450–7458
e-ISSN 2450–8187

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# Reality of Real-World Experience with Oral Semaglutide in Type 2 Diabetes

Oral semaglutide is the first oral glucagon-like-peptide-1 receptor agonist (GLP-1RA) approved for the treatment of type 2 diabetes (T2D) since the United States Food Drug Administration (US-FDA) approval in 2019, based on extensive phase 3 randomized Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) clinical developmental program. Indeed, in people with T2D, oral semaglutide 14 mg has not shown only superior efficacy (HbA1c and weight reduction) against placebo but also demonstrated a significant superiority against other active comparators, including sitagliptin 100 mg (PIONEER-3, PIONEER-7), empagliflozin 25 mg (PIONEER-2), injectable liraglutide 1.8 mg once daily (PIONEER-4), and injectable dulaglutide 0.75 mg once weekly (PIONEER-10) [1]. Following the approval of oral semaglutide worldwide, including in India in 2022, many real-world studies have been conducted and published to date.

In this issue of "Clinical Diabetology", Ray and Colleagues [2] present an 18-month follow-up of a real-world retrospective survey conducted with oral semaglutide as adjunctive therapy in T2D from three centers in India based on electronic health/medical records (EHR/EMR). This study of 60 Indian patients of T2D (mean 5.8-year duration) with a mean baseline HbA1c of 8.7% and body weight of 82.3 kg showed a significant reduction in HbA1c (Δ –1.9 to –1.6% at 6 and 18 months, respectively) and body weight (Δ –6.0 to –4.7 kg at 6 and 18 months, respectively) with oral semaglutide 3–14 mg once daily over 6 to 18 months duration, while some plateau effect observed between 12 and 18 months. This reduction in HbA1c appears to be more prominent even though more than 50% were on a submaximal dose of 7 mg oral semaglutide, likely due to tolerance issues. However, two other recent retrospective studies [3, 4] done with oral semaglutide on Indian patients with T2D had both convergent and divergent results compared with this study. For example, a retrospective EHR-based Semaglutide OraL In Indian T2D (SOLID) patients study [3] conducted with oral semaglutide in 209 patients from eight centers in India showed a significant reduction in HbA1c (Δ –2.0%) and body weight (Δ –5.3 kg) at 3 months, with a mean baseline HbA1c of 9.2% and body weight of 92 kg. Even in the SOLID study, HbA1c reduction appears very prominent despite less than 45% of patients being on the maximal approved dose of 14 mg oral semaglutide primarily due to tolerability issues. However, the duration of T2D was unknown in the SOLID study. Other single-center retrospective EMR survey of 6 months consisting of 46 Indian patients with T2D (median base-

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Clinical Diabetology 2024, 13; 6: 319–322
DOI: 10.5603/cd.103963
Received: 1.12.2024 Accepted: 2.12.2024
Early publication date: 13.12.2024

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**Table 1. Baseline Characteristics and Key Results from Six PIONEER REAL Studies of Mean/Median 38 Weeks Duration**

| Trial Eponyms | N (FAS) | Duration of T2D, Yrs (mean) | Male (%) | Age, Yrs (mean) | Weight, kg (mean) | BMI, kg/m$^2$ (mean) | HbA1c, % (mean) | HbA1c change at EOS, % | Weight change at EOS, kg | HbA1c < 7% at EOS, % | Composite of ≥ 1% HbA1c reduction and ≥ 5% weight loss, % | Dose of oral SEMA at EOS, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PIONEER REAL, Canada [6] | 182 | 8.1 | 64.3 | 58.6 | 93.7 | 32.5 | 8 | –1.1 | –7.2 | 53.7 | 31.6 | 3 mg: 11.7<br>7 mg: 32.8<br>14 mg: 55.5 |
| PIONEER REAL, Switzerland [7] | 185 | 6.4 | 63.7 | 62 | 95.6 | 33.2 | 7.7 | –0.9 | –4.7 | 64.2 | 28.3 | 3 mg: 7.0<br>7 mg: 26.8<br>14 mg: 66.2 |
| PIONEER REAL, UK [8] | 333 | 7.4 | 61.3 | 58.5 | 102.8 | 35.5 | 8.6 | –1.1 | –4.8 | 46.3 | 27.1 | 3 mg: 5.3<br>7 mg: 21.6<br>14 mg: 73.1 |
| PIONEER REAL, Netherlands [9] | 187 | 8.7 | 54 | 58.8 | 103.1 | 35.1 | 8.6 | –1.2 | –5.8 | 47.5 | 35.5 | 3 mg: 4.1<br>7 mg: 42.2<br>14 mg: 53.7 |
| PIONEER REAL, Sweden [10] | 187 | 6.8 | 64.7 | 62.5 | 96.9 | 32.4 | 7.7 | –0.9 | –4.6 | 64.6 | 22.9 | 3 mg: 6.4<br>7 mg: 39.7<br>14 mg: 53.2 |
| PIONEER REAL, Japan [11] | 624 | 10.7 | 56.9 | 64.1 | 72.4 | 27.5 | 7.7 | –0.7 | –2.8 | 55.3 | 16.5 | 3 mg: 26.6<br>7 mg: 61.8<br>14 mg: 11.2 |

BMI — body mass index; EOS — end of study; FAS — full analysis set; HbA1c — glycated hemoglobin; SEMA — semaglutide; T2D — type 2 diabetes; Yrs — years

line HbA1c of 8% and mean body weight of 81.8 kg) receiving oral semaglutide showed a significant HbA1c (Δ –0.7%) and body weight (Δ –2.7 kg) reduction, even though 43% were receiving 14 mg of oral semaglutide [4]. However, the duration of T2D is also unknown in this study. Interestingly, most of the other retrospective EHR/EMR surveys from the USA, Spain, Japan, Italy, and Croatia showed an HbA1c reduction from –0.3 to –1.4%, while body weight reduction varied from –1.4 to –5.9 kg [5]. Only the United Kingdom (UK) retrospective study showed an HbA1c and body weight reduction of –1.8% and -9.0 kg with a mean baseline HbA1c and body weight of 9.3% and 110 kg, respectively [5]. Notwithstanding, these varying degrees of HbA1c and body weight reduction are partly related to differences in baseline characteristics and partly to the associated bias inherent with retrospective studies. This requires a high-quality, well-planned, prospective, control-armed, real-world study.

To this end, thirteen Phase 4 prospective real-world studies, PIONEER REAL, were initiated and completed [5]. However, full data from only six PIONEER REAL studies are currently available [6–11]. The baseline characteristics and key findings from these six PIONEER REAL studies are summarized in Table 1. The PIONEER REAL INDIA is the fourteenth prospective study initiated in 2022 and is currently underway [5]. Overall, there was an average –1.0% reduction in HbA1c and –5 kg weight loss across five PIONEER REAL, where the majority (> 50%) tolerated the 14 mg dose of oral semaglutide [6–10]. In PIONEER REAL Japan, there was –0.7% HbA1c and –3 kg weight reduction, with the majority on a 7 mg dose of oral semaglutide [11]. Notably, adding oral semaglutide to pre-existing pharmacotherapy allowed nearly 55% of patients with T2D to achieve the target HbA1c of < 7%, while more than one-fourth of the proportion had a composite reduction of HbA1c of ≥ 1% and weight loss of ≥ 5%. Figure 1 captures the impact of oral semaglutide on HbA1c and body weight, while Figure 2 summarizes its effect on the composite of both HbA1c and body weight lowering and the proportion of patients achieving the target of HbA1c of < 7% across six PIONEER REAL studies [6–11]. Indeed, a pooled analysis of seven PIONEER REAL studies (including those of unpublished results from PIONEER REAL Italy and Denmark but excluding PIONNER Japan) showed a mean HbA1c reduction of –1% and –5 kg weight loss with oral semaglutide in T2D in addition with other pharmacotherapies [12]. Nevertheless, the absence of a control arm remains

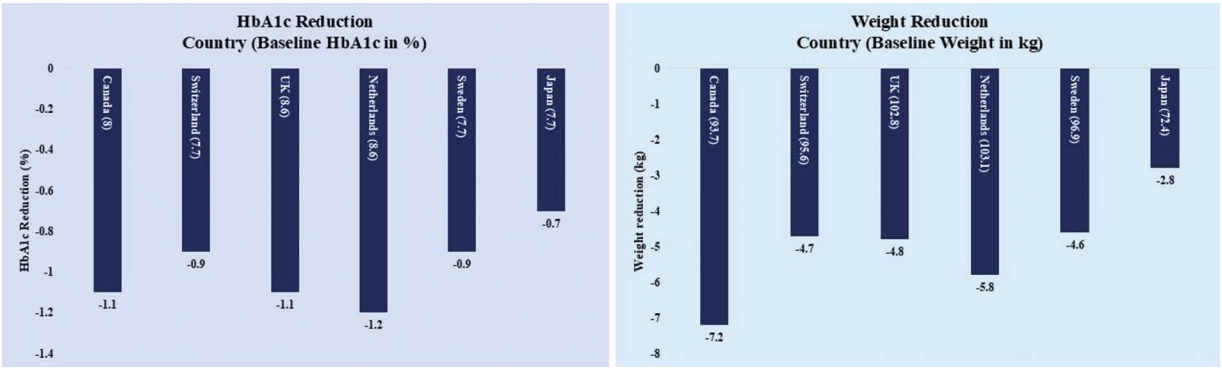


**Figure 1.** PIONEER REAL: Real-World-Evidence with Oral Semaglutide on HbA1c and Weight
HbA1c — glycated hemoglobin

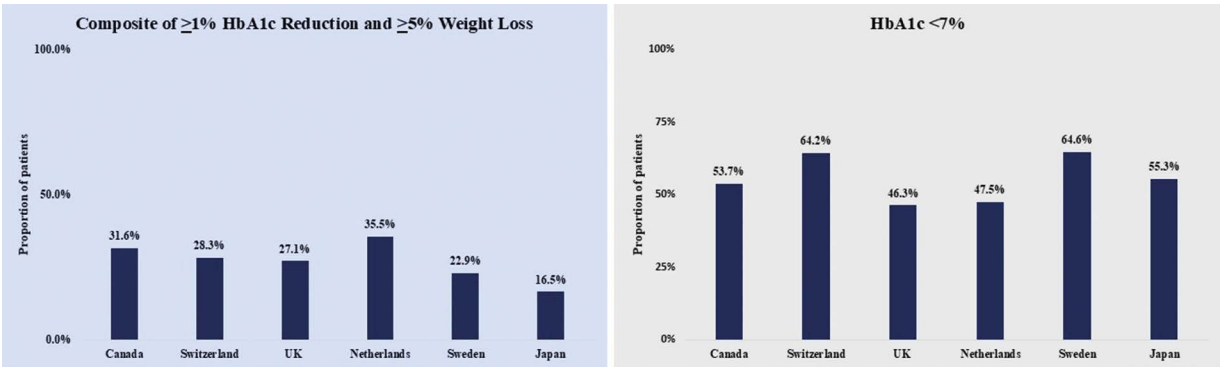


**Figure 2.** PIONEER REAL: Real-World-Evidence with Oral Semaglutide on Composite of HbA1c plus Weight and HbA1c Target < 7%
HbA1c — glycated hemoglobin

the main limitation of all PIONEER REAL studies. Additionally, most retrospective studies have limited data on safety issues.

Summarily, the HbA1c and body weight-lowering ability of oral semaglutide, as demonstrated in Phase 4 real-world studies, complement the findings from eight global and 2 Japanese PIONEER programs. The 14% relative risk reduction in the composite of major adverse cardiovascular outcome data as reported in top-line results [13] of SOUL (Semaglutide cardiOvascular oUtcomes trial) will be an additional milestone for oral semaglutide, even though the non-inferiority PIONEER 6 trial did show a non-significant positive trend on cardiovascular endpoints including mortality outcomes. Full results of SOUL and a deep dive into cardiovascular (primary) and renal outcomes (secondary) are eagerly awaited in the first quarter of 2025.

## Article information

### Author's contribution

AKS conceptualized and searched the literature; AKS and RS did the statistical interpretation; AS wrote the first draft; AKS, AS, RS, and JS edited the final draft. All authors agreed mutually to submit for publication.

### Funding

No funding.

### Conflict of interest

The authors declare no conflict of interest.

### REFERENCES

1. Singh AK, Singh R, Misra A. Oral semaglutide in type 2 diabetes mellitus: Comprehensive review, critical appraisal and clinical consideration of its use in India. Diabetes Metab Syndr. 2022;

16(3): 102436, doi: 10.1016/j.dsx.2022.102436, indexed in Pubmed: 35245858.
2. Ray S, Ray A, Goutam S, et al. Efficacy and Safety of Oral Semaglutide in Managing Type 2 Diabetes in India: A Real-World Study. Clin Diabetol. 2024; 13(6): 323–330, doi: 10.5603/cd.102374.
3. Bhattacharyya S, Saboo B, Mohit M, et al. Insights into the Early Use of Oral Semaglutide in Routine Indian Clinical Practice. International Journal of Diabetes and Technology. 2022; 1(4): 127–132, doi: 10.4103/ijdt.ijdt_15_23.
4. Kesavadev J, Ashik A, Yasmin S, et al. Effectiveness of Oral Semaglutide in Weight Loss and Glycemic Control among Type 2 Diabetes Population: A Real-world Longitudinal Study. International Journal of Diabetes and Technology. 2024; 2(3): 79–84, doi: 10.4103/ijdt.ijdt_33_23.
5. Singh AK, Singh R, Singh A, et al. Efficacy and safety of oral semaglutide in type 2 diabetes: A systematic review of real-world evidence. Diabetes Metab Syndr. 2024; 18(5): 103024, doi: 10.1016/j.dsx.2024.103024, indexed in Pubmed: 38718449.
6. Jain AB, Reichert SM, Amadid H, et al. Use of once-daily oral semaglutide and associated clinical outcomes among adults with type 2 diabetes in routine clinical practice in Canada: A multicentre, prospective real-world study (PIONEER REAL Canada). Diabetes Obes Metab. 2024; 26(5): 1799–1807, doi: 10.1111/dom.15493, indexed in Pubmed: 38468125.
7. Kick A, M'Rabet-Bensalah K, Acquistapace F, et al. Real-World Use of Oral Semaglutide in Adults with Type 2 Diabetes: The PIONEER REAL Switzerland Multicentre, Prospective, Observational Study. Diabetes Ther. 2024; 15(3): 623–637, doi: 10.1007/s13300-023-01525-y, indexed in Pubmed: 38240875.
8. Saravanan P, Bell H, Braae UC, et al. PIONEER REAL UK: A Multi-Centre, Prospective, Real-World Study of Once-Daily Oral Semaglutide Use in Adults with Type 2 Diabetes. Adv Ther. 2024; 41(11): 4266–4281, doi: 10.1007/s12325-024-02973-z, indexed in Pubmed: 39316289.
9. van Houtum W, Schrömbges P, Amadid H, et al. Real-World Use of Oral Semaglutide in Adults with Type 2 Diabetes in the PIONEER REAL Netherlands Multicentre, Prospective, Observational Study. Diabetes Ther. 2024; 15(8): 1749–1768, doi: 10.1007/s13300-024-01588-5, indexed in Pubmed: 38861137.
10. Catrina SB, Amadid H, Braae UC, et al. PIONEER REAL Sweden: A Multicentre, Prospective, Real-World Observational Study of Oral Semaglutide Use in Adults with Type 2 Diabetes in Swedish Clinical Practice. Diabetes Ther. 2024; 15(9): 2079–2095, doi: 10.1007/s13300-024-01614-6, indexed in Pubmed: 39052163.
11. Yabe D, Hamamoto Y, Kawanami D, et al. PIONEER REAL Japan: Primary results from a multicenter, prospective, real-world study of oral semaglutide in adults with type 2 diabetes in Japanese clinical practice. J Diabetes Investig. 2024; 15(11): 1566–1577, doi: 10.1111/jdi.14291, indexed in Pubmed: 39172634.
12. Rudofsky G, Amadid H, Braae UC, et al. Oral Semaglutide Use in Type 2 Diabetes: A Pooled Analysis of Clinical and Patient-Reported Outcomes from Seven PIONEER REAL Prospective Real-World Studies. Diabetes Ther. 2024 [Epub ahead of print], doi: 10.1007/s13300-024-01668-6, indexed in Pubmed: 39535683.
13. Topline: Oral Semaglutide Cuts Cardiovascular Events in T2D. https://www.medscape.com/viewarticle/topline-oral-semaglutide-cuts-cardiovascular-events-t2d-2024a1000jaa?form=fpf (30.11.2024).

VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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# Efficacy and Safety of Oral Semaglutide in Managing Type 2 Diabetes in India: A Real-World Study

## ABSTRACT

**Objective: To examine the effectiveness, safety, and tolerability of oral semaglutide, the only tablet that delivers glucagon-like peptide-1 (GLP-1) receptor agonists (RA) orally, in a real-world setting, for Indian patients with type 2 diabetes (T2D).**

**Materials and methods: Medical data were included for patients with uncontrolled T2D. Glycated hemoglobin (HbA1c) in the laboratory was the main outcome measure. Hypoglycemia, weight, and fasting plasma glucose (FPG) were used as secondary metrics. Results: The weight reduction was significant during the first 6 months, then it was in a plateau phase, and again it went up from 12 months until the end of the study period. The mean FPG dropped from 156.4 mg/dL to 103.8 mg/dL, and the mean postprandial blood glucose (PPPG) changed from 248.9 mg/dL to 169.8 mg/dL over the treatment period. Similarly, the HbA1c level changed from 8.6% to 7.0%. A small percentage of patients had hypoglycemia: 0.5% of patients at T6, 1.1% at T12, and 1.4% reported having a moderate episode (54–70 mg/dL); one incident of severe hypoglycemia was observed at T12.**

**Conclusions: For people with T2D, oral semaglutide therapy significantly reduced blood sugar levels and helped them lose weight. (Clin Diabetol 2024; 13, 6: 323–330)**

**Keywords: GLP-1 RA, oral semaglutide, type 2 diabetes, real world**

## Introduction

Diabetes mellitus is a very common disorder affecting more than 70 million people in India [1]. Most of these belong to the type 2 diabetes (T2D) category, which is considered a lifestyle disease. Moreover, India has the highest number of people with diabetes still undiagnosed, and by 2045 the number of diabetics is expected to reach 134.3 million (103.4–165.2) [2]. The steady migration of people from rural to urban areas, the economic boom, and corresponding changes in lifestyle all affect the level of diabetes [3]. While managing Indian patients with diabetes, it is imperative to recognize that, due to associated obesity and inadequate lifestyle modifications, metformin and lifestyle management alone may not be enough in the initial

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Clinical Diabetology 2024, 13; 6: 323–330
DOI: 10.5603/cd.102374
Received: 1.09.2024 Accepted: 3.10.2024
Early publication date: 19.11.2024

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management of some patients. While choosing oral antidiabetic agents (ADAs), apart of the risk of hypoglycemia, it is important to also look into their impact on weight, renal safety, cardiac safety, and possible beta cell prevention. Awareness of the disease and its aggressive management are considered the cornerstone to control the disease in India.

During previous decades, management was primarily "beta cell" centric with the use of sulfonylureas and insulin. With the advent of newer therapies and a greater understanding of T2D, it has come to our understanding that it is important to address as many pathophysiological defects as possible to achieve better glycemic control. Glucagon-like peptide 1 (GLP-1) receptor agonists (RA) stimulate glucose-dependent insulin release from the beta cell. They also slow down gastric emptying, reduce appetite, improve satiety, and reduce glucagon levels. In animal models, GLP-1RAs have resulted in proliferation and regeneration of beta cells. The mechanism of action of GLP-1RAs is complex and involves multiple systems and pathways. The pathological approach to treatment favors the use of GLP-1RAs because they address several defects of T2D.

The first palatable GLP-1RA is semaglutide, which depends on cutting-edge pharmaceutical technology to guarantee absorption and efficacy upon ingestion: sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) is mixed with semaglutide to enhance absorption and shield the peptide from stomach enzyme degradation [4]. The oral formulation of GLP-1RAs has the advantage of greater patient acceptability and convenience than injectable GLP-1RAs [5].

In several clinical trials, despite receiving glucose-lowering medication, study participants' glucose control was suboptimal (mean baseline HbA1c 8.0–8.4%, 64–68 mmol/mol). Semaglutide substantially reduced HbA1c in a dose-dependent manner compared to all other comparators, including other GLP-1 analogues [6–10]. The highest HbA1c decrease was seen after 16–30 weeks, and semaglutide helped more patients reach HbA1c < 7% (53 mmol/mol) than placebo or other comparators. However, there have only been a small number of published studies on the practical application of this medication [11, 12]. As a result, the effects of this medication in routine clinical practice — both when oral semaglutide is added to other medications and when patients switch to it from glucose-lowering agents — remain to be fully established. As is well known, real-world research enables evaluation of the generalizability of experimental study findings to larger patient populations under standard clinical practice [13]. Thus, the current study's goal was to evaluate its efficacy and tolerability in the context of T2D treatment as an adjunctive therapy.

## Materials and methods

### Study procedure

This research was retrospective and observational. Through the use of electronic medical data, adult Indian patients (over the age of 18 years) with T2D who were receiving oral semaglutide and being monitored at the outpatient Diabetes Clinic were identified between January 2023 and August 2024. The concepts of T2D care and treatment advised by national Indian Council of Medical Research (ICMR) guideline, Research Society for the Study of Diabetes in India — Endocrine Society of India (RSSDI-ESI) clinical practice recommendations for the management of T2D [14, 15], and worldwide recommendations served as the foundation for the prescription of oral semaglutide. For this audit, a pre-made structured proforma was utilized to gather data from the participating doctors regarding the effectiveness of oral semaglutide when used in conjunction with other antidiabetic medications.

### Primary and secondary endpoints

The change in mean HbA1c levels from baseline to 6 months was the primary endpoint. The following were continuous secondary endpoints: changes in mean fasting plasma glucose (FPG) levels and weight/ /body mass index from baseline to T6, T12, and T18 months; changes in mean HbA1c levels from baseline to T6, T12, and T18 months.

Categorical secondary endpoints were changes in serum urea and serum creatinine from baseline to T6, T12, and T18 months, patients discontinuing semaglutide, and reasons for discontinuation.

### Therapy selection

The maintenance dose of semaglutide and any subsequently adjusted dosage were decided by the treating physician. The dose of oral semaglutide is as follows: a starting dose of 3 mg in empty stomach with 120 mL of water, then no food for the next 30 minutes. If the patient tolerated the 3 mg dose, we increased the dose to 7 mg after one month, and to 14 mg after another month. The therapy selection was based on the judgment of the physicians in charge and the agreement of the subject. No monitoring or diagnostic treatments beyond standard clinical practice were performed on the patients. A case-by-case determination of the maintenance semaglutide dosage was made after a 12-week semaglutide treatment, considering both the drug's cost and clinical response. Baseline was defined as the appointment (T0) at which the

patient was initially prescribed semaglutide; follow-up appointments were scheduled 6, 12, and 18 months after baseline. When semaglutide was started, each person received counselling on regular exercise and diet. One National Accreditation Board for Testing and Calibration Laboratories (NABL)-accredited lab was used for all pathology and biochemistry laboratory tests, and it was attached to each participating clinic. A self-monitoring blood glucose gadget was used at home to measure blood glucose on a regular basis. Hypoglycemia was defined as a blood sugar level of less than 70 mg/dL.

### Patient data collection

The participating doctors' pre-existing hospital records provided the data, and an audit of the data was carried out to assess real-world efficacy in the past. Electronic health records were used to gather data, which was then compiled in a Microsoft Excel sheet. Demographic details, the length of the disease, the medication (withdrawn and/or associated, if any), the last oral semaglutide dose, the length of follow-up (from the start of the medication until the last visit), HbA1c, body weight, serum urea and creatinine levels, the frequency and reason for stopping the drug, and the frequency and kind of adverse events were all included.

### Inclusion and exclusion criteria

Men and women over the age of 18 years, a diagnosis of T2D as defined by the American Diabetes Association (ADA) for at least 3 months, a minimum of 3 months of stable antihyperglycemic therapy using insulin or oral hypoglycemic agents (OHA), a prescription for oral semaglutide based on standard clinical practice, and signed informed consent were the requirements for inclusion.

The following conditions were excluded: other kinds of diabetes, any condition preventing the patient from understanding informed consent, and the patient's past or present involvement in interventional clinical trials.

### Ethical approval

The Declaration of Helsinki and the norms for good clinical practice were followed in the retrospective evaluation of the patient files. Because it was a clinical audit intended to record the clinical results of patients started on semaglutide within the parameters of its legal use for weight reduction, and all the treatments were standard care, it was exempted from the need for ethical clearance. Therefore, this trial did not receive ethical approval.

### Population size

Assuming a baseline standard deviation of HbA1c of 2.0% [larger than that reported in randomized clinical trials (RCTs)] due to the greater variability expected in an observational setting), and with a significance level (alpha error) of 0.05%, a minimum sample size of 80 subjects allowed detection with a statistical power of 80% and a minimum reduction of HbA1c of 0.6% at T6 (slightly lower than that obtained in RCTs but reflecting the greater variability of results derived from "real life" clinical experience, taking into account also the variability of associated therapies).

### Statistical analysis

Data analysis was done using Microsoft Excel and SPSS (v.20). For continuous variables, descriptive data were summarized as mean and standard deviation; for categorical variables, they were summarized as percentage. Mixed models for repeated data were used to evaluate changes in the continuous study outcomes. The estimated mean or estimated mean difference from T0, together with its 95% confidence interval (95% CI), was used to express the results. For pre-post comparisons within groups, the paired t-test that was generated from linear mixed models for repeated measures was used. The trend of changes in categorical study endpoints was evaluated using the chi-square test. A p-value of less than 0.05 was used to indicate statistical significance.

## Results

In our study, a total of 80 subjects were included. All the patients were on oral GLP-1 analogue. Out of these, the data of 20 patients were not included in efficacy analysis due to discontinuation for various reasons. For safety analysis and adherence all the patient data were included (Tab. 1). The participants' average age was 46.6 ± 8.1 years, with 70% of them being male. The mean duration of diabetes was 5.8 ± 3.9 years. At the time of semaglutide beginning (T0), the average weight was 82.27 ± 22.2 kg and the average HbA1c was 8.67 ± 1.3%. All patients received treatment with one or more OHAs, whereas 92.5% patients were on metformin and 22.5% had treatment with basal insulin plus OHAs. Approximately 65% of the individuals received treatment with antihypertensive and lipid-lowering medications, and around half (52.4%) of the subjects reported problems related to diabetes (Tab. 1). Dosages of oral semaglutide were adjusted by the attending physicians during treatment, resulting in 8 subjects treated with 3 mg/day, 33 with 7 mg/day, and 19 with 14 mg/day at 6 months. The highest dose of oral semaglutide was selected in sub-

**Table 1. Patients' Baseline Characteristics**

| Baseline criteria | Value (N = 80) |
|---|---|
| M:F (%) | 70:30 |
| Age [years] | 46.6 ± 8.1 |
| Height [cm] | 171.01 ± 8.4 |
| Weight [kg] | 82.27 ± 22.2 |
| Waist circumference [cm] | 94.68 ± 8.1 |
| Duration of diabetes [years] | 5.8 ± 3.9 |
| FPG [mg/dL] | 156.42 ± 21.6 |
| PPPG [mg/dL] | 248.95 ± 56.8 |
| HbA1c [%] | 8.67 ± 1.3 |
| SBP [mmHg] | 131.4 ± 13.6 |
| DBP [mmHg] | 79.4 ± 7.4 |
| Creatinine [mg/dL] | 0.844 ± 0.1 |
| Urea [mg/dl] | 31.6 ± 10.2 |
| LDL cholesterol [mg/dL] | 92.3 ± 28.2 |
| HDL cholesterol [mg/dL] | 46.2 ± 10.8 |
| Triglycerides [mg/dL] | 165.7 ± 90.4 |
| Heart rate [bpm] | 76.0 ± 10.9 |
| Presence of co-morbidities (%) | |
| Hypertension | 52 (65%) |
| Dyslipidemia | 41 (51%) |
| CV Events | 21 (26%) |
| Oral hypoglycemic agents before starting semaglutide (%) | |
| Sulfonylureas (%) | 14 (22.5%) |
| SGLT2-i (%) | 66 (82.5%) |
| Metformin (%) | 74 (92.5%) |
| Pioglitazone | 9 (11%) |
| DPP4i | 12 (15%) |
| Basal insulin (%) | 18 (22.5%) |
| Short-acting insulin (%) | 5 (6%) |

Data presented as mean ± SD or number (%)
CV — cardiovascular; DBP — diastolic blood pressure; F — female; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; HDL — high-density lipoprotein; LDL — low-density lipoprotein; PPPG — postprandial plasma glucose; SBP — systolic blood pressure; SD — standard deviation; SGLT2i — sodium-glucose cotransporter-2 inhibitors

jects with higher body weight and/or those treated with other GLP-1RAs.

The mean changes in body weight, FPG, and HbA1c at 6 and 12 months were clinically meaningful and statistically significant (Tab. 2).

The weight reduction was significant during the first 6 months, then it was in a plateau phase, and again it went up from 12 months until the end of the study period (Fig. 1A). There was no significant change in waist circumference (Fig. 1B)

There was a significant reduction in all blood glucose parameters. The mean FPG dropped from 156.4 mg/dL to 103.8 mg/dL (Fig. 1C), and the mean postprandial blood glucose (PPPG) changed from 248.9 mg/dL to 169.8 mg/dL over the treatment period (Fig. 1D). Similarly, the HbA1c level changed from 8.6% to 7.0% (Fig. 1E).

Analysis of variance (ANOVA) for HbA1c reduction throughout the treatment at T0, T6, T12, and T18 revealed an f-ratio value of 157.75878 with a p value of $< 0.0001$. The result is significant at $p < 0.05$.

Among the study participants, 74% continued their treatment. Out of the 26% patients who discontinued their treatment, in 14% this was due to adverse effects and in 12% it was due to the high cost of the therapy.

All the adverse effects noted in the study were non-serious in nature. The common adverse effects observed in the study were nausea (10 pts), vomiting (9 pts), belching (2 pts), and reflux (7 pts).

A small percentage of patients had hypoglycemia (0.5% of patients at T6, 1.1% at T12, and 1.4% at T18) reported having a moderate episode (54–70 mg/dL); one incident of severe hypoglycemia was observed at T12. During the 18-month period, no significant changes in concurrent glucose-lowering, antihypertensive, and lipid-lowering medications were seen.

## Discussion

We found that oral semaglutide was a safe and effective therapy for uncontrolled T2D, independent of the patient's background, in this real-world observational retrospective cohort trial conducted in India. The research also demonstrated the safety and tolerability of oral semaglutide because all the side effects were mild and did not cause the medication to cease working; moreover, at the conclusion of the trial, there was a decrease in the number of hypoglycemic episodes.

We found that our patient subpopulation with HbA1c ≥ 8% showed a similar decrease in HbA1c at 6 months (−1.8%) as that reported in the IGNITE (−1.4%), PIONEER REAL Canada (−1.1%), and Japanese population (−1.2%) studies, despite the challenge of comparing our results with those of available real-world studies due to the significant baseline differences [11, 16, 17].

This is the longest real-world oral semaglutide trial to date. Our study's follow-up period was longer than that of the IGNITE worldwide observational study (about 6 months) [11], but further observational research will be required to evaluate the oral long-term effects and persistence of semaglutide in relation to body weight and glycemic control. The pattern of the HbA1c and body weight curves over time, which tended to plateau between 6 and 9 months and then rise further after 12 months, provides further evidence of the significance of dosage optimization.

**Table 2. Changes in Estimated Mean Levels of Continuous Clinical Endpoints over Time**

| Change in | Visit | Estimated mean and 95% CI | Estimated mean difference from baseline and 95% CI | Within-group p-value |
|---|---|---|---|---|
| HbA1c [%] | T0 | 8.67 ± 1.3 | | |
| | T6 | 6.80 ± 1.2 (6.537; 7.063) | 1.87 ± 0.7 (1.717; 2.023) | < 0.0001 |
| | T12 | 6.85 ± 1.5 (6.521; 7.179) | 1.82 ± 0.6 (1.689; 1.951) | < 0.0001 |
| | T18 | 7.07 ± 1.1 (6.829; 7.311) | 1.6 ± 0.3 (1.534; 1.666) | < 0.0001 |
| FPG [mg/dL] | T0 | 156.42 ± 21.6 | | |
| | T6 | 91.64 ± 24.1 (86.359; 96.921) | 64.78 ± 12.1 (62.129; 67.431) | < 0.0001 |
| | T12 | 94.38 ± 23.2 (89.296; 99.464) | 62.04 ± 10.2 (59.805; 64.275) | < 0.0001 |
| | T18 | 103.8 ± 20.5 (99.308; 108.292) | 52.62 ± 9.4 (50.560; 54.680) | < 0.0001 |
| PPPG [mg/dL] | T0 | 248.95 ± 56.8 | | |
| | T6 | 156.46 ± 49.3 (145.657; 167.263) | 92.49 ± 24.7 (87.077; 97.903) | < 0.0001 |
| | T12 | 157.88 ± 51.6 (146.573; 169.187) | 91.07 ± 21.3 (86.403; 95.737) | < 0.0001 |
| | T18 | 168.86 ± 38.5 (160.423; 177.297) | 80.09 ± 18.6 (76.014; 84.166) | < 0.0001 |
| Body weight [kg] | T0 | 82.27 ± 22.2 | | |
| | T6 | 76.24 ± 20.3 (71.792; 80.688) | 6.03 ± 2.8 (5.416; 6.644) | < 0.0001 |
| | T12 | 76.12 ± 18.6 (72.044; 80.196) | 6.15 ± 2.4 (5.624; 6.676) | < 0.0001 |
| | T18 | 77.61 ± 15.2 (74.279 – 80.941) | 4.66 ± 1.7 (4.287; 5.033) | < 0.0001 |
| Waist circumference [cm] | T0 | 94.68 ± 8.1 | | |
| | T6 | 91.07 ± 7.3 (89.470; 92.670) | 3.61 ± 1.1 (3.369–3.851) | < 0.0001 |
| | T12 | 91 ± 6.4 (89.598; 92.402) | 3.68 ± 0.9 (3.483–3.877) | < 0.0001 |
| | T18 | 91.15 ± 5.8 (89.879; 92.421) | 3.53 ± 0.4 (3.442–3.618) | < 0.0001 |
| Serum urea | T0 | 31.6 ± 10.2 | | |
| | T6 | 30.8 ± 8.9 (28.850; 32.750) | 0.8 ± 0.1 (0.778–0.822) | 0.02 |
| | T12 | 29.7 ± 7.4 (28.078; 31.322) | 1.7 ± 0.8 (1.525; 1.875) | < 0.0001 |
| | T18 | 28.6 ± 6.2 (27.241; 29.959) | 3 ± 0.5 (2.890–3.110) | < 0.0001 |
| Serum creatinine | T0 | 0.844 ± 0.1 | | |
| | T6 | 0.813 ± 0.1 (0.791; 0.835) | 0.031 ± 0.03 (0.0244–0.0376) | 0.06 |
| | T12 | 0.792 ± 0.1 (0.770; 0.814) | 0.052 ± 0.02 (0.0476–0.0564) | 0.04 |
| | T18 | 0.782 ± 0.1 (0.760; 0.804) | 0.062 ± 0.01 (0.0598–0.0642) | 0.05 |

Data presented as mean ± SD or number (%)
CI — confidence interval; HbA1c — glycated hemoglobin; FPG — fasting plasma glucose; PPPG — postprandial plasma glucose

The effects of GLP-1RAs on body weight reduction are therapeutically significant, given the rising incidence of obesity. Patients in our sample lost around 6.03 kg (6.03 ± 2.8 kg) after 6 months and 6.15 kg (6.15 ± 2.4 kg) at 12 months, and the weight reduction remained stable even after 18 months. Therefore, this research can serve as a first step in proving that semaglutide is beneficial for people who want to reduce weight. A significant difference in body weight was also seen in earlier semaglutide experiments and in other investigations, in which people with T2D lost less weight than comparable individuals without the condition [18, 19]. One reason for this might be that people with T2D have a larger reduction in energy expenditure when compared to those without the condition. Additionally, losing weight improves glucose regulation, which lowers glycosuria. As a result, there is a positive calorie balance, which makes it harder to lose weight. Another cause is the use of other anti-diabetic drugs such glipizide and insulin, which are linked to weight gain.

Additionally, the study showed that significant improvements in HbA1c were seen in both GLP-1RA--naive and GLP-1RA-experienced people, as expected. Although the safety profile is consistent with previous GLP-1RA reports, the information that is now available indicates that semaglutide may be more efficacious than its equivalents [20]. What exactly is causing semaglutide to be more successful than other GLP-1RAs is yet unknown. However, it is possible that liraglutide and semaglutide vary in this regard, and the acyl moiety found in acylated medications such as semaglutide may facilitate penetration into different parts of the central

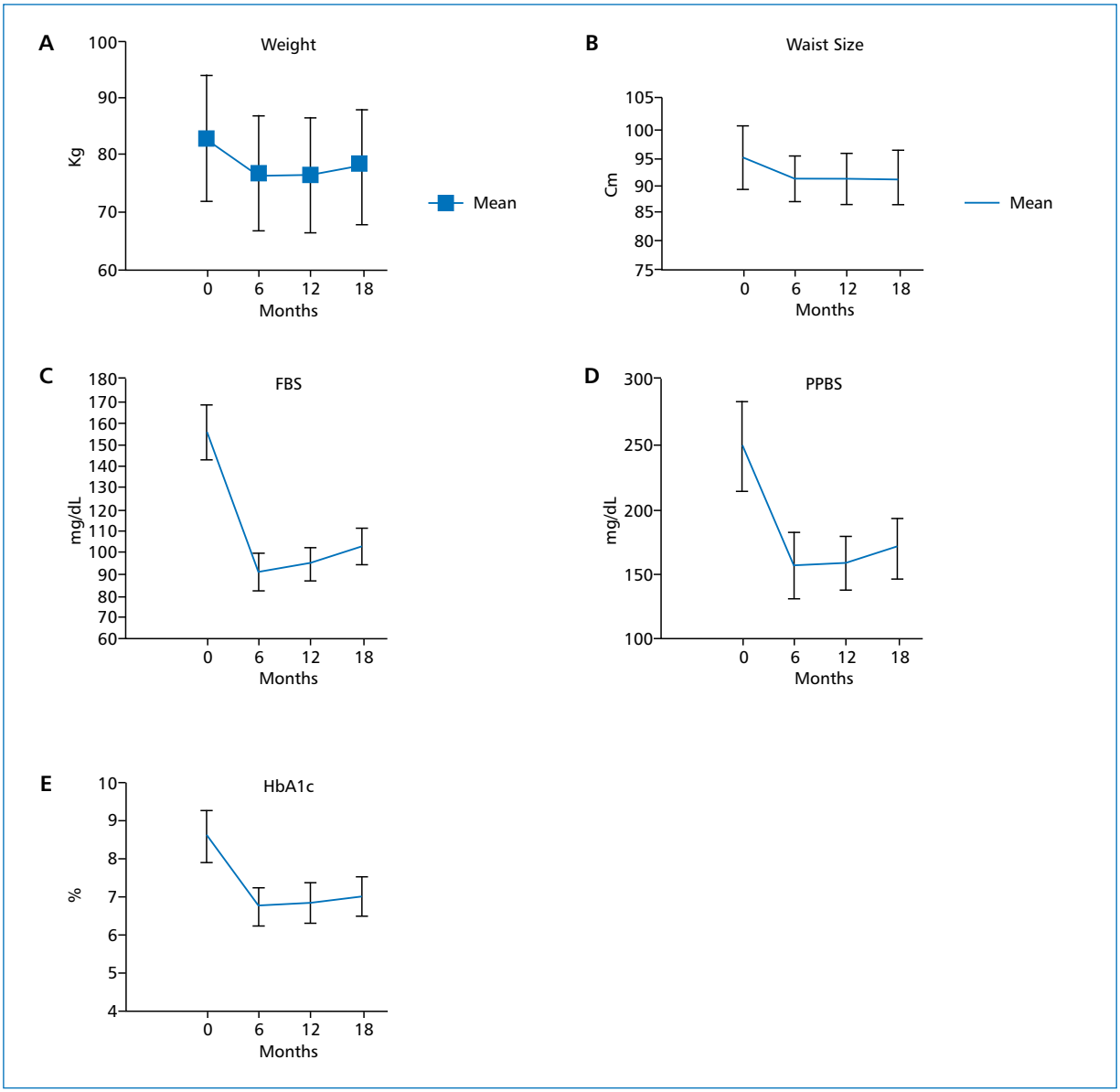


**Figure 1. A.** Weight change in overall population (N = 80); **B.** Change in waist circumference in overall population (N = 80); **C.** Change in fasting blood sugar (FBS) in overall population (N = 80); **D.** Change in postprandial blood sugar (PPBS) in overall population (N = 80) **E.** Change in glycated hemoglobin (HbA1c) in overall population (N = 80)

nervous system (CNS). Because of the way semaglutide is chemically structured, there is a theory that its effect on weight is mediated via CNS receptors that provide access to different parts of the nervous system [21].

GLP-1RAs, such as semaglutide, have been shown in cardiovascular (CV) outcome trials to lower CV risk and delay the deterioration of renal function. While improvements in glycemic management may play a role, these advantages are probably also mediated by additional effects, including decreased body weight, blood pressure, and albuminuria, enhanced endothelial function, and suppression of proinflammatory mediators [22]. In patients with diabetes kidney disease and moderate renal impairment (estimated glomerular filtration rate [eGFR]: 30–59 mL/min/1.73 $m^2$), the PIONEER-5 study demonstrated the safety and efficacy of oral semaglutide. Both the oral semaglutide and placebo groups' renal function did not change during the study period, but the oral semaglutide group's albumin-to-creatinine ratio dropped relative to the placebo group [23]. GLP1 can inhibit the expression of vascular cell adhesion molecule-1 and tumor necrosis factor-$\alpha$ in glomerular endothelial cells. GLP1 has been shown to increase nitric oxide synthesis, which may improve glomerular endothelial function [24]. The complete results of the FLOW study show that semaglutide sig-

nificantly lowers the risk of major renal disease events, major adverse cardiac events, and all-cause death in individuals with T2D and chronic kidney disease. It also slows down the decline of kidney function [25]. Furthermore, regardless of whether serum creatinine, cystatin C, or both were used to compute the eGFR, the effect of semaglutide was independent of changes in body weight [26, 27]. As a result, even in our trial, long-term use of oral semaglutide has a significant effect on the reduction of serum urea and creatinine.

Gastrointestinal events were the most common adverse events (AEs) with oral semaglutide that were recorded, and the ones that most commonly led to an early termination, as would be anticipated for a GLP-1RA and consistent with previous studies [28, 29]. However, most of these adverse events (AEs) happened early in the main phase, and no patient stopped because of an AE later in the durability phase. This suggests that discontinuations from oral semaglutide because of gastrointestinal AEs are more likely to happen early in treatment (during the initial dose-escalation phase) rather than with long-term use.

The study had merits and weaknesses. Our work is notable for being the first long-term observational retrospective research study in India to describe the effects of semaglutide in real-world settings. Extensive data on blood pressure, lipid profile, FPG, PPPG, side effects, and hypoglycemia further enhance its strength. However, there are many restrictions on the research. First, the absence of control groups makes it hard to separate the role that oral semaglutide played in lowering body weight and glycemic index from the role that lifestyle modifications may have played concurrently. Second, the data had to be forced into 6-month intervals to predict changes in body weight and HbA1c. This was because not every patient had the same observation duration and follow-up routine. Third, we had very little knowledge on the tolerability, adherence, or causes for stopping oral semaglutide, which left us with few options for enhancing persistence. Nevertheless, the retrospective design of the research and the lack of prearranged subgroup analysis according to age group, obesity, diabetes, or severity are drawbacks that make it impossible to draw firm conclusions about outcomes in these subgroups. More investigation is needed to determine the long-term efficacy and safety of semaglutide and implications on other endpoints (such the fatty liver index).

## Conclusions

To sum up, this research represents the biggest multicenter real-world investigation of uncontrolled T2D patients in India receiving oral semaglutide as part of standard clinical practice. In an unselected group, oral semaglutide was safe and effective; almost two-thirds achieved a HbA1c of less than 7%, and one-third reported weight reduction of more than 10%. There were no signs of a safety hazard. Considering the worldwide supply chain challenges associated with subcutaneous GLP-1 RAs, the results of this investigation may aid in supporting clinical judgment.

## Article information

### Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

### Author contributions

Saswati Ray: conceptualization, formal analysis, methodology, writing — original draft, data collection. Aparajita Ray: conceptualization, supervision, data collection, writing — review and editing. Siddhartha Goutam: investigation, resources, formal analysis, data collection. Asis Mitra: methodology, formal analysis, writing — review and editing.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### Acknowledgments

We gratefully appreciate all departmental staff of respective clinic for supporting us throughout the research and the study participants for their meticulous information. We are also thankful to Intigent Research for their help in medical writing and data analysis.

### Conflict of interests

The authors declare no conflict of interest.

## References

1. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021; 69(11): 2932–2938, doi: 10.4103/ijo.IJO_1627_21, indexed in Pubmed: 34708726.
2. Pradeepa R, Mohan V. Prevalence of type 2 diabetes and its complications in India and economic costs to the nation. Eur J Clin Nutr. 2017; 71(7): 816–824, doi: 10.1038/ejcn.2017.40, indexed in Pubmed: 28422124.
3. Kaveeshwar S, Cornvall J. The current state of diabetes mellitus in India. Australas Med J. 2014; 7(1): 45–48, doi: 10.4066/amj.2014.1979, indexed in Pubmed: 24567766.
4. Buckley S, Bækdal T, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018; 10(467), doi: 10.1126/scitranslmed.aar7047, indexed in Pubmed: 30429357.
5. Gallwitz B, Giorgino F. Clinical Perspectives on the Use of Subcutaneous and Oral Formulations of Semaglutide. Front Endocrinol (Lausanne). 2021; 12: 645507, doi: 10.3389/fendo.2021.645507, indexed in Pubmed: 34267725.

6. Lavernia F, Blonde L. Clinical review of the efficacy and safety of oral semaglutide in patients with type 2 diabetes compared with other oral antihyperglycemic agents and placebo. Postgrad Med. 2020; 132(sup2): 15–25, doi: 10.1080/00325481.2020.1798638 , indexed in Pubmed: 32815436.
7. Aroda V, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. Diabetes Care. 2019; 42(9): 1724–1732, doi: 10.2337/dc19-0749, indexed in Pubmed: 31186300.
8. Rodbard HW, Rosenstock J, Canani L, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care. 2019; 42(12): 2272–2281, doi: 10.2337/dc19-0883.
9. Pratley R, Aroda V, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018; 6(4): 275–286, doi: 10.1016/s2213-8587(18)30024-x, indexed in Pubmed: 29397376.
10. Guzauskas GF, Rind DM, Fazioli K, et al. Cost-effectiveness of oral semaglutide added to current antihyperglycemic treatment for type 2 diabetes. J Manag Care Spec Pharm. 2021; 27(4): 455–468, doi: 10.18553/jmcp.2021.27.4.455, indexed in Pubmed: 33769850.
11. Aroda VR, Faurby M, Lophaven S, et al. Insights into the early use of oral semaglutide in routine clinical practice: The IGNITE study. Diabetes Obes Metab. 2021; 23(9): 2177–2182, doi: 10.1111/dom.14453, indexed in Pubmed: 34060209.
12. Yanai H, Hakoshima M, Adachi H, et al. Editorial Office, Editorial Office, Editorial Office, Editorial Office, Editorial Office. A Significant Effect of Oral Semaglutide on Cardiovascular Risk Factors in Patients With Type 2 Diabetes. Cardiol Res. 2022; 13(5): 303–308, doi: 10.14740/cr1441, indexed in Pubmed: 36405226.
13. Blonde L, Khunti K, Harris S, et al. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. Adv Ther. 2018; 35(11): 1763–1774, doi: 10.1007/s12325-018-0805-y, indexed in Pubmed: 30357570.
14. Anjana R, Unnikrishnan R, Deepa M, et al. Achievement of guideline recommended diabetes treatment targets and health habits in people with self-reported diabetes in India (ICMR-INDIAB-13): a national cross-sectional study. Lancet Diabetes Endocrinol. 2022; 10(6): 430–441, doi: 10.1016/s2213-8587(22)00072-9, indexed in Pubmed: 35461575.
15. Chawla R, Madhu SV, Makkar BM, et al. RSSDI-ESI Consensus Group. RSSDI-ESI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2020. Indian J Endocrinol Metab. 2020; 24(1): 1–122, doi: 10.4103/ijem.IJEM_225_20, indexed in Pubmed: 32699774.
16. Yamada H, Yoshida M, Funazaki S, et al. Retrospective Analysis of the Effectiveness of Oral Semaglutide in Type 2 Diabetes Mellitus and Its Effect on Cardiometabolic Parameters in Japanese Clinical Settings. J Cardiovasc Dev Dis. 2023; 10(4): 176, doi: 10.3390/jcdd10040176, indexed in Pubmed: 37103055.
17. Reichert S, Amadid H, Braae U, et al. Clinical outcomes associated with the use of oral semaglutide in an adult population with type 2 diabetes in Canada: a prospective real-world study (PIONEER REAL Canada). Canadian Journal of Diabetes. 2023; 47(7): S96–S97, doi: 10.1016/j.jcjd.2023.10.189.
18. Wing R, Marcus M, Epstein L, et al. Type II Diabetic Subjects Lose Less Weight Than Their Overweight Nondiabetic Spouses. Diabetes Care. 1987; 10(5): 563–566, doi: 10.2337/diacare.10.5.563, indexed in Pubmed: 3677974.
19. Evert AB, Franz MJ. Why Weight Loss Maintenance Is Difficult. Diabetes Spectr. 2017; 30(3): 153–156, doi: 10.2337/ds017-0025, indexed in Pubmed: 28848306.
20. Holst JJ, Madsbad S. Semaglutide seems to be more effective the other GLP-1Ras. Ann Transl Med. 2017; 5(24): 505, doi: 10.21037/atm.2017.11.10, indexed in Pubmed: 29299466.
21. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest. 2014; 124(10): 4473–4488, doi: 10.1172/JCI75276, indexed in Pubmed: 25202980.
22. Muskiet MHA, Tonneijck L, Smits M, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol. 2017; 13(10): 605–628, doi: 10.1038/nrneph.2017.123, indexed in Pubmed: 28869249.
23. Mosenzon O, Blicher TM, Rosenlund S, et al. PIONEER 5 Investigators. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019; 7(7): 515–527, doi: 10.1016/S2213-8587(19)30192-5, indexed in Pubmed: 31189517.
24. Mima A, Qi W, King GL. Implications of Treatment That Target Protective Mechanisms Against Diabetic Nephropathy. Semin Nephrol. 2012; 32(5): 471–478, doi: 10.1016/j.semnephrol.2012.07.010, indexed in Pubmed: 23062988.
25. Perkovic V, Tuttle KR, Rossing P, et al. FLOW Trial Committees and Investigators. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med. 2024; 391(2): 109–121, doi: 10.1056/NEJMoa2403347, indexed in Pubmed: 38785209.
26. Tuttle KR, Lakshmanan MC, Rayner B, et al. Body weight and eGFR during dulaglutide treatment in type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7). Diabetes Obes Metabol. 2019; 21(6): 1493–1497, doi: 10.1111/dom.13668, indexed in Pubmed: 30762290.
27. Heerspink HJL, Sattar N, Pavo I, et al. Effects of Tirzepatide Versus Insulin Glargine on Cystatin C-Based Kidney Function: A SURPASS-4 Post Hoc Analysis. Diabetes Care. 2022; 46(8): 1501–1506, doi: 10.2337/dc23-0261, indexed in Pubmed: 37267479.
28. Sun F, Chai S, Yu K, et al. Gastrointestinal Adverse Events of Glucagon-Like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis. Diabetes Technol Ther. 2015; 17(1): 35–42, doi: 10.1089/dia.2014.0188, indexed in Pubmed: 25375397.
29. Htike ZZ, Zaccardi F, Papamargaritis D, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. Diabetes Obesi Metab. 2017; 19(4): 524–536, doi: 10.1111/dom.12849, indexed in Pubmed: 27981757.

VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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# Relations between Intensity of Symptoms of Eating Disorders and Glycated Hemoglobin, Number of Complications, Mood, and Problems with Type 2 Diabetes in a One-Year Follow-Up Study

## ABSTRACT

**Objective: Assessment of the relations between intensity of symptoms of eating disorders with psychological factors, glycated hemoglobin (HbA1c) levels, and number of complications in type 2 diabetes (T2D).**

**Materials and methods: Sixty-eight (68) individuals aged 38 to 71 years (M = 61.1; SD = 8.2) took part in the baseline of prospective and 36 (52.9%) in follow-up after one year. They completed the Eating Attitude Test (EAT-26), Questionnaire for Binge Eating Screening (QBES), Brief Self-Rating Scale of Depression and Anxiety (BS-RSDA), and Problem Areas in Diabetes Questionnaire (PAID).**

**Results: At baseline, 12 individuals (18.5%) met the screening criteria of eating disorders and 29 (42.6%) met the screening criteria of binge eating disorder. The level of HbA1c among persons with symptoms of eating disorders was significantly higher than in the group without these symptoms. The intensity of binge eating at baseline was significantly correlated with intensity of depressive symptoms after 6 months (r = 0.34) and 12 months (r = 0.52), anxiety symptoms after 6 months (r = 0.42) and 12 months (r = 0.49), and problems with diabetes after 6 months (r = 0.5). Intensity of bulimia and food preoccupation symptoms at baseline was correlated after 6 months with intensity of anxiety symptoms (r = 0.35) and problems with diabetes (r = 0.52) and HbA1c level (r = –0.42), and after 12 months with intensity of symptoms of anxiety (r = 0.56), depression (r = 0.35), and problems with diabetes (r = 0.39).**

**Conclusions: The intensity of eating disorder symptoms had moderate correlations with the level of depressive and anxiety symptoms and intensity of diabetes-related problems. Due the small and non-representative sample size, these findings should be confirmed in a future high-quality study. (Clin Diabetol 2024; 13, 6: 331–340)**

**Keywords: eating disorders, diabetes, HbA1c, depression, anxiety**

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Clinical Diabetology 2024, 13; 6: 331–340
DOI: 10.5603/cd.100257
Received: 7.05.2024 Accepted: 19.08.2024
Early publication date: 30.09.2024

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## Introduction

Epidemiological data indicate that there were 536.6 million individuals with diabetes in 2021, and it is expected that a total of 783.2 million will be affected by diabetes in 2045 [1]. Diabetes frequently leads to serious and often life-threatening and lethal complications, including cardiovascular complications, such as heart attack and stroke, neuropathy (nerve damage), nephropathy (kidney damage), and retinopathy (eye damage). Management of diabetes requires the daily monitoring of blood glucose levels and modification of one's lifestyle, mainly in maintaining a healthy diet and doing regular physical exercise. Ultimately, adhering to these requirements constitutes a problem for many people with diabetes. Psychological factors also play an important role in this process, and the current guidelines for diabetes treatment, i.e. the American Diabetes Association [2], International Diabetes Federation [3], and Poland Diabetes Association [4], recommend inclusion of the psychological aspects of diabetes in diagnosis, treatment, and management.

The largest international study to date that focused on gaining a comprehensive understanding of the situation of individuals with diabetes confirmed that the psychological difficulties they encounter constitute an important and widespread phenomenon in the course of the disease [5]. The study in question did not include the individuals' eating attitudes or eating disorders, which are also listed in the guidelines as an area requiring routine assessment.

Eating disorders in diabetes remain an underinvestigated topic, particularly in comparison with comprehensive studies on depression in diabetes. The vast majority of studies on relationships between eating disorders and diabetes have focused on individuals with type 1 diabetes (T1D), especially on adolescents and women aged 15-35 years [6–9]. Relatively little research has been conducted on the population of individuals with type 2 diabetes (T2D). This is mainly because T1D occurs mainly in persons under 30 years of age, and most frequently in children and adolescents, i.e., in groups where eating disorders are also generally more frequent [7].

Data on the co-occurrence of eating disorders, abnormal eating attitudes, and T2D are rather limited. An analysis of the literature shows that the prevalence of eating disorders and abnormal eating attitudes differs depending on the characteristics of the subjects in question (outpatients vs. inpatients), the method that is used for diagnosis (self-descriptive questionnaires vs. diagnostic interviews), and on the subject matter of the measurement (eating disorders according to diagnostic criteria vs. their subclinical forms). Nevertheless, available studies indicate a significant co-occurrence of eating disorders and abnormal eating attitudes with T2D [8, 10–13]. Binge eating disorder (BED) is the most prevalent eating disorder among individuals with T2D, and it is mainly related to overweight and obesity in this group of individuals [8, 14]. Binge eating differs from bulimia mainly by the lack of compensatory behaviors (e.g., self-induced vomiting, using laxatives, and excessive exercising). A literature review identified 9 studies on the prevalence of binge eating disorder among persons with T2D in the range between 1.2% and 8% [13]. The prevalence was lower in studies when the diagnosis was made during a clinical examination than when self-rating questionnaires were used. Some studies indicated a higher level of glycated hemoglobin (HbA1c) among patients with BED than among those without BED [15, 16], but the results of most research studies indicate no differences in HbA1c between the above-mentioned groups [8, 17–19]. Persons with T2D and comorbid BED had a higher prevalence of depressive disorders and a higher intensity of depressive symptoms than persons without it [8, 18]. Only a few studies indicated positive correlations between intensity of symptoms of eating disorders as measured by the Eating Attitudes Test (EAT-26) and intensity of depressive symptoms as measured by the Beck Depression Inventory [8, 18].

One available prospective study on people with T2D indicated that having satisfactory follow-up HbA1c levels (< 7%) after one year was correlated with baseline variables such as HbA1c, insulin use, and eating behavior [20]. The authors concluded that clinical variables are more important than psychopathological variables for the achievement of therapeutic goals.

The first objective of this study was to conduct a cross-sectional and prospective study assessment of differences in intensity of depressive and anxiety symptoms, intensity of problem areas in diabetes, HbA1c levels, and the number of complications among subjects who met the criteria for eating disorders according to EAT-26 and QBES and among those who did not. The second objective was to conduct a cross-sectional and prospective study assessment of the relationship between intensity of symptoms of eating disorders and intensity of depressive and anxiety symptoms, intensity of problem areas in diabetes, HbA1c level, and the number of complications.

## Materials and methods

### Subjects

The study involved individuals with T2D who had been diagnosed in the last 12 months and who were at the point of treatment intensification, i.e., the introduc-

tion of insulin hypoglycemic drugs or insulin analogs to their treatment regimen.

### Study design

The study was prospective and consisted of 3 phases: the first phase took place within one month after change of treatment, the second phase followed after 6 months, and the third phase took place 12 months after the start of the study. At each phase, participants completed a set of questionnaires and their HbA1c level was tested. Sixty-eight respondents took part in the first phase, 44 respondents (64.7%) in the second phase, and 36 respondents (52.9%) in the third phase. The study was approved by an Ethics Committee, and all participants signed an informed consent participation form.

### Data collection

The Eating Attitudes Test (EAT-26) was used to assess symptoms of eating disorders [21, 22]. EAT-26 is a popular tool that is used worldwide to screen for self-assessment of eating disorders, and it has proven psychometric properties [22, 23]. EAT-26 consists of 26 items that cover 3 subscales to assess symptoms in 3 areas, i.e., dieting, bulimia and food preoccupation, and oral control. The test may be used for screening diagnosis of eating disorders that requires verification in a clinical examination.

The occurrence of binge eating was assessed using the Questionnaire for Binge Eating Screening (QBES) [24]. It consists of 4 closed YES/NO questions. According to the QBES authors, a positive answer to at least one question indicates that symptoms of binge eating may be present. Sensitivity and specificity of the QBES was assessed among Polish women with polycystic ovary syndrome (PCOS). A positive answer to at least one question had a sensitivity of 88% and a specificity of 67% in detecting BED.

The Problem Areas in Diabetes Questionnaire (PAID) was used to assess the intensity of diabetes-related problem areas [25]. This questionnaire has proven psychometric properties and is widely used throughout the world to assess the intensity of problem areas associated with diabetes, both for individuals with T1D and for those with T2D [25–28]. It consists of 4 subscales that describe the intensity of problems related to negative emotions, treatment, food, and lack of social support. PAID's reliability and accuracy are high in the Dutch version, although the original English version does not differentiate these subscales. An analysis of the Polish version does not allow the subscales to be distinguished, although the whole scale is reliable and accurate

The intensity of depressive and anxiety symptoms was assessed using the Brief Self-Rating Scale of Depression and Anxiety (BS-RSDA) [29], which is a part of the Psychodiabetic Kit [30]. The questionnaire consists of 2 subscales. Its psychometric properties have been tested on a population of individuals with diabetes, and it has standards developed for this population.

For this study, questionnaires were constructed to collect both demographic and medical data, such as information regarding complications of diabetes and past episodes of severe hypoglycemia. The questionnaires were filled out by either doctors or researchers during each measurement.

The level of HbA1c was measured to assess glycemic control.

### Statistical analysis

The differences in the measured variables between the first, second, and third measurements were calculated using ANOVA variance analysis with repeated measurement. For statistically significant contrasts, Duncan's post-hoc tests were calculated. Comparison of psychological and clinical characteristics between groups with and without eating disorders was calculated with the Mann-Whitney U-test. Relationships between intensity of eating disorders and other psychological and clinical factors in cross-sectional and prospective study were calculated with the Pearson correlation coefficient.

## Results

Sixty-eight subjects aged 38 to 71 years (M = 61.1; SD = 8.2) were qualified for the study, of whom 45.6% were men (N = 31) and 54.4% were women (N = 36). The period from diagnosis of T2D was 2 to 30 years (M = 10.4; SD = 6.3), and the mean HbA1c was 9.15%. Of all the subjects, 39 (60%) had secondary education, 17 (26.2%) had a university degree, and 9 (13.8%) had an elementary education. Fifty (75.8%) respondents lived in a large city (> 100,000), 10 (15.2%) lived in a small city (< 100,000), and 6 (9.1%) lived in a rural area.

Out of 68 respondents, 12 (18.5%) met the EAT-26 screening criteria for eating disorders, and 29 (42.6%) met the binge eating disorder screening criteria. Both diagnoses were more frequent in women, but this relationship was not statistically significant.

Table 1 shows the values of the measured variables in 3 measurements. It was found that the mean score on the EAT-26 Bulimia scale increased significantly during the study. The third measurement value was significantly higher than the first and second measurement values, which did not differ significantly. The level of

**Table 1. Baseline, 6-Month, and 12 -Month Follow-Up Results**

| | | Baseline I | 6 months II | 12 months III | ANOVA test statistics with repeated measurements |
|---|---|---|---|---|---|
| QBES | Mean | 1.60 | 1.57 | 1.31 | F (2; 70) = 1.460 |
| | N | 68 | 44 | 36 | p=0.239 |
| | SD | 1.43 | 1.39 | 1.47 | |
| EAT-26 Dieting scale | Mean | 10.15 | 10.59 | 9.00 | F (2; 58) = 0.416 |
| | N | 65 | 41 | 35 | p = 0.662 |
| | SD | 6.03 | 6.76 | 5.21 | |
| EAT-26 Bulimia and Food Preoccupation scale | Mean | 1.09 | 1.20 | 2.11 | F (2; 60) = 4.696 |
| | N | 65 | 41 | 35 | p = 0.013* |
| | SD | 2.19 | 1.65 | 2.48 | |
| EAT-26 Oral Control scale | Mean | 2.75 | 2.83 | 2.80 | F (2; 60) = 1.510 |
| | N | 65 | 42 | 35 | p = 0.229 |
| | SD | 3.03 | 3.04 | 3.47 | |
| EAT-26 Total score | Mean | 14.00 | 14.70 | 13.91 | F (2; 58) = 1.678 |
| | N | 65 | 40 | 35 | p = 0.196 |
| | SD | 8.94 | 10.00 | 8.63 | |
| BS-RSDA Depression scale | Mean | 11.71 | 8.95 | 9.50 | F (2; 70) = 0.178 |
| | N | 68 | 44 | 36 | p = 0.387 |
| | SD | 10.66 | 8.06 | 8.02 | |
| BS-RSDA Anxiety scale | Mean | 10.62 | 7.91 | 9.56 | F (2; 70) = 1.099 |
| | N | 68 | 44 | 36 | p = 0.339 |
| | SD | 11.00 | 6.87 | 8.42 | |
| PAID Total score | Mean | 26.84 | 26.93 | 27.36 | F (2; 70) = 2.858 |
| | N | 68 | 44 | 36 | p = 0.064 |
| | SD | 22.70 | 21.88 | 22.11 | |
| HbA1c | Mean | 9.15 | 7.74 | 7.97 | F (2; 60) = 16.407 |
| | N | 62 | 35 | 34 | p < 0.01* |
| | SD | 1.98 | 1.09 | 1.53 | |
| Number of complications | Mean | 0.60 | 0.70 | 0.89 | F (2;70) = 8.448 |
| | N | 67 | 43 | 36 | p < 0.01* |
| | SD | 0,74 | 0,80 | 0,95 | |

BED — binge eating disorder; BS-RSDA — Brief Self-Rating Scale of Depression and Anxiety; EAT-26 — Eating Attitude Test; HbA1c — glycated hemoglobin; QBES — Questionnaire for Binge Eating Screening; PAID — Problem Areas in Diabetes Questionnaire; SD — standard deviation

HbA1c decreased, which was significantly higher in the first measurement than in the second and third measurements (although there was no difference between the second and third measurements). The number of complications increased, and it was significantly higher in the third measurement than in the first, and significantly higher than in the second measurement. No significant changes in intensity of the other variables were observed.

Based on existing sten standards for persons with diabetes [29, 30], the intensity of depressive symptoms in the 3 measurements was average, and although it decreased slightly over the course of the study, the change was not statistically significant. The intensity of anxiety symptoms was average in the first and third measurements and low in the second. However, these differences were not statistically significant. Similarly, the level of diabetes-related problems measured with

**Table 2. Comparison of Psychological and Clinical Characteristics between Groups with and without Eating Disorders According to EAT-26**

| | Baseline measurement | | | | | | U Mann-Whitney test | |
|---|---|---|---|---|---|---|---|---|
| | Absence of eating disorders according to EAT-26 | | | Presence of eating disorders according to EAT-26 | | | | |
| | M | n | SD | M | n | SD | Z | p |
| BS-RSDA Depression scale | 10.23 | 53 | 8.85 | 17.58 | 12 | 16.09 | –1.314 | 0.189 |
| BS-RSDA Anxiety scale | 8.94 | 53 | 8.85 | 14.17 | 12 | 15.33 | –0.806 | 0.420 |
| PAID Total score | 24.29 | 53 | 21.78 | 36.15 | 12 | 24.28 | –1.540 | 0.124 |
| Height | 165.5 | 48 | 8.70 | 165.25 | 12 | 13.32 | –0.590 | 0.611 |
| Age | 62.38 | 52 | 7.48 | 56.17 | 12 | 10.55 | –2.025 | 0.043 |
| Weight | 86.33 | 48 | 20.58 | 97.15 | 12 | 23.00 | –1.387 | 0.166 |
| BMI | 31.12 | 48 | 6.87 | 35.60 | 12 | 7.55 | –1.904 | 0.057 |
| Years of diabetes | 11.17 | 52 | 6.62 | 8.79 | 12 | 4.26 | –0.932 | 0.351 |
| HbA1C | 8.93 | 49 | 1.97 | 10.45 | 11 | 1.50 | –2.459 | 0.014 |
| Number of complications | 0.56 | 52 | 0.70 | 0.92 | 12 | 0.90 | –1.371 | 0.170 |

BED — binge eating disorder; BS-RSDA — Brief Self-Rating Scale of Depression and Anxiety; EAT-26 — Eating Attitude Test; HbA1c — glycated hemoglobin; QBES — Questionnaire for Binge Eating Screening; PAID — Problem Areas in Diabetes Questionnaire; SD — standard deviation

the PAID, which remained low, did not change significantly.

## Cross-sectional and prospective study comparison of psychological and clinical characteristics between groups

Table 2 shows the differences between the group of subjects with the EAT-26 diagnosis of eating disorders and the group without this diagnosis, in the first phase of the study (baseline measurement).

Individuals who met the EAT-26 criteria for eating disorders were younger and had a higher HbA1c level than those who did not meet the criteria. There were no other statistically significant differences between these groups. However, according to the adopted sten standards,[29,30] the intensity of depressive symptoms in patients with diagnosed eating disorders was high, and it was average in individuals without such a diagnosis.

Among those who were diagnosed with binge eating disorder according to the QBES, the intensity of depressive symptoms was high (M = 14.72), and the intensity of depressive symptoms was average in those without the diagnosis (M = 9.46); this difference was statistically significant (p = 0.037). No significant differences were observed among the sizes of the other variables.

After 6 months and after 12 months, there were no significant differences between groups with eating disorders according to EAT-26 and binge eating disorder according to QBES, and groups without such diagnosis in relation to HbA1c levels, number of complications, intensity of depressive and anxiety symptoms, and intensity of problem areas in diabetes. The exception was a higher intensity of depressive and anxiety symptoms in the binge eating group after 12 months.

## Correlations between symptoms of eating disorders and binge eating and psychological and clinical characteristics in a cross-sectional study

The cross-sectional study assessed the relationship between intensity of binge eating and eating disorder symptoms and HbA1c levels, number of complications, intensity of depressive and anxiety symptoms, and intensity of problems in diabetes. Table 3 presents the results of the correlation matrix. The QBES result showed moderate positive correlations with all psychological factors at levels ranging from r = 0.345 to r = 0.408, which indicates a significant, moderate relationship between intensity of binge eating and intensity of depressive symptoms, and anxiety and negative emotions associated with various aspects of diabetes. The Bulimia and Food Preoccupation scale showed positive weak and moderate correlations with psychological factors at r = 0.258 to r = 0.472. The absence of any correlation between the EAT-26 Oral Control scale and psychological factors and clinical status is noteworthy. There were also no correlations between QBES, EAT-26, and its scales with clinical characteristics.

**Table 3. Correlations of Intensity of Symptoms of Eating Disorders and Binge Eating with Psychological and Clinical Characteristics in the Cross-Sectional Study**

| ` | | BS-RSDA Depression scale | BS-RSDA Anxiety scale | PAID | Age | HbA1c | Number of complications |
|---|---|---|---|---|---|---|---|
| QBES | r | .345** | .380** | .408** | –0.020 | 0.111 | –0.096 |
| | p | 0.004 | 0.001 | 0.001 | 0.873 | 0.393 | 0.439 |
| EAT-26 Dieting scale | r | 0.225 | .275* | .334** | –.278* | 0.121 | 0.139 |
| | p | 0.072 | 0.027 | 0.006 | 0.026 | 0.357 | 0.274 |
| EAT-26 Bulimia and Food Preoccupation scale | r | .258* | .410** | .472** | –0.116 | 0.088 | 0.113 |
| | p | 0.038 | 0.001 | 0.000 | 0.360 | 0.502 | 0.375 |
| EAT-26 Oral Control scale | r | –0.139 | –0.046 | 0.075 | –0.142 | –0.111 | 0.120 |
| | p | 0.269 | 0.714 | 0.552 | 0.263 | 0.399 | 0.344 |
| EAT-26 total score | r | 0.170 | .273* | .362** | –.261* | 0.063 | 0.151 |
| | p | 0.176 | 0.028 | 0.003 | 0.037 | 0.631 | 0.232 |

BED — binge eating disorder; BS-RSDA — Brief Self-Rating Scale of Depression and Anxiety; EAT-26 — Eating Attitude Test; HbA1c — glycated hemoglobin; QBES — Questionnaire for Binge Eating Screening; PAID — Problem Areas in Diabetes Questionnaire; SD — standard deviation

### Relationship between intensity of symptoms of eating disorders and binge eating and psychological characteristics and clinical condition in a prospective perspective

The prospective study assessed the relationship between intensity of symptoms of eating disorders and binge eating at the beginning of the study and the patients' psychological characteristics and clinical condition after 6 months and 12 months. The results are presented in Table 4.

There were numerous interactions between the results of the QBES scale, EAT-26 Bulimia and Food Preoccupation scale, and overall EAT-26 score with the intensity of symptoms of depression, anxiety, and negative emotions associated with different areas of diabetes, both after 6 months and after 12 months. In most cases, the strength of the relationship not only persisted but also increased. There was a small but significant inverse correlation between the Bulimia and Food Preoccupation scale at the baseline and the HbA1c level after 6 months. This correlation might be connected with the beneficial effect of food preoccupation, which is measured by this scale, on the course and control of diabetes when insulin treatment is included

## Discussion

According to our knowledge, this is the first prospective study on the relationships between symptoms of eating disorders and BED and the clinical and psychological characteristics of the course of T2D. The negative, moderate correlation between the level of HbA1c and scores on the Bulimia and Food Preoccupation scale of the EAT-26 is a paradoxical finding. An analysis of the content of items included in this subscale indicates that they describe paying attention to one's diet and to the way of eating, both of which are helpful in diabetes. Because of this, applying EAT-26 among patients with diabetes should be done with consideration. Such sentences as "I give too much time and thought to food," "I find myself preoccupied with food," and "I feel that food controls my life," according to EAT-26, indicates an intensity of symptoms, but these can also reflect one's natural and positive focus on food as required to manage diabetes. This finding implies that a diagnosis of eating disorders among people with diabetes requires a careful assessment of the symptoms of one's preoccupation with food, and the self-rating scales should not include items that are open to doubt. The lack of other significant correlations between the level of HbA1c, number of complications, and other psychological factors suggests that they have no clinically significant meaning in comparison with the impact of implementing insulin or its analogs.

The EAT-26 results suggesting eating disorders in 18.5% of the respondents is one of the most important findings in the baseline studies. This result is similar to results presented by other researchers. In a study by Nicolau [8], eating disorders according to EAT-26 and QEWP-R were diagnosed in 14% and 16% of respondents, respectively. The fact that a higher percentage of respondents met the criteria for an eating disorder in our study may have resulted from

**Table 4. Correlations between Intensity of Symptoms of Eating Disorders and Binge Eating at the Beginning of the Study and Psychological Characteristics and Clinical Condition after 6 Months and after 12 Months**

| | | | QBES | EAT-26 Dieting scale | EAT-26 Bulimia and Food Preoccupation scale | EAT-26 Oral Control total | EAT-26 Total score |
|---|---|---|---|---|---|---|---|
| After 6 months | BS-RSDA Depression scale | r | .346* | 0.037 | 0.263 | –0.069 | 0.055 |
| | | p | 0.022 | 0.816 | 0.092 | 0.663 | 0.730 |
| | BS-RSDA Anxiety scale | r | .423** | 0.144 | .355* | 0.041 | 0.194 |
| | | p | 0.004 | 0.362 | 0.021 | 0.798 | 0.219 |
| | PAID | r | .502** | 0.280 | .525** | 0.082 | .352* |
| | | p | 0.001 | 0.073 | 0.000 | 0.606 | 0.022 |
| | HbA1c | r | –0.099 | 0.024 | –.420* | –0.111 | –0.086 |
| | | p | 0.571 | 0.897 | 0.015 | 0.538 | 0.634 |
| | Number of new complications | r | 0.023 | –0.230 | –0.175 | –0.274 | –0.278 |
| | | p | 0.884 | 0.148 | 0.273 | 0.083 | 0.078 |
| | Number of complications | r | –0.076 | –0.042 | 0.109 | 0.046 | –0.003 |
| | | p | 0.628 | 0.795 | 0.496 | 0.776 | 0.985 |
| After 12 months | BS-RSDA Depression scale | r | .526** | –0.009 | .357* | –0.156 | 0.025 |
| | | p | 0.001 | 0.958 | 0.038 | 0.378 | 0.889 |
| | BS-RSDA Anxiety scale | r | .494** | 0.216 | .563** | 0.138 | 0.310 |
| | | p | 0.002 | 0.220 | 0.001 | 0.437 | 0.074 |
| | PAID | r | 0.318 | 0.259 | .394* | .376* | .389* |
| | | p | 0.058 | 0.139 | 0.021 | 0.028 | 0.023 |
| | HbA1c | r | –0.096 | –0.068 | –0.151 | –0.006 | –0.104 |
| | | p | 0.588 | 0.711 | 0.410 | 0.975 | 0.570 |
| | Number of new complications | r | –0.035 | –0.245 | –0.128 | –0.067 | –0.237 |
| | | p | 0.841 | 0.163 | 0.469 | 0.705 | 0.177 |
| | Number of complications | r | 0.015 | –0.086 | 0.097 | –0.093 | –0.066 |
| | | p | 0.930 | 0.629 | 0.584 | 0.601 | 0.709 |

BED — binge eating disorder; BS-RSDA — Brief Self-Rating Scale of Depression and Anxiety; EAT-26 — Eating Attitude Test; HbA1c — glycated hemoglobin; QBES — Questionnaire for Binge Eating Screening; PAID — Problem Areas in Diabetes Questionnaire; SD — standard deviation

a different, higher cut-off point in the EAT-26 test than the one Nicolau applied, thus resulting in a lower percentage of positive diagnoses. Furthermore, in our study, the subjects differed from Nicolau's subjects in a higher mean HbA1c level and were at the point of having a change introduced to their treatment for this very reason. Considering some of the literature data indicating higher HbA1c levels in patients with binge eating disorder and the results of our study on higher HbA1c levels in patients with eating disorders, we may hypothesize that patients who do not achieve satisfactory glycemic control are more likely to have symptoms of eating disorders — further research is needed to verify this hypothesis.

In our study, 42% of individuals met the QBES binge eating screening criteria. According to a literature review, the prevalence of BED in persons with T2D ranges from 1.2% to 8% [18]. In a study of 82 patients not included in the above review, 34.1% were diagnosed with BED [16]. In a study by Nicolau [8], the prevalence of BED was 12.2% in a large study group of 320 patients. The much higher percentage of diagnosis of this disorder in our study may have resulted from both the tool that was used and from the screening diagnosis. However, given the available data on its high sensitivity and specificity, it is more likely that samples of patients who need treatment intensification include a larger number of persons with binge eating symptoms, which may then be the reason for problems with glycemia control.

Changes found in the subsequent phases of our study are particularly noteworthy. The Bulimia and Food Preoccupation scale score increased significantly. This may have been due to the implementation of insulin treatment and the need for the subjects to pay more attention to the food they ate. The HbA1c level

decreased significantly from 9.15% in the first measurement to 7.74% in the second measurement, which may be interpreted as the result of successful treatment intensification via inclusion of insulin. The mean number of complications increased from 0.6 in the first measurement to 0.7 in the second measurement, and to 0.89 in the third measurement. This is consistent with the results of studies indicating that the age of the patients and disease duration are factors that increase the risk of late complications, and current and short-term HbA1c levels do not lead to rapid changes in the development of complications [30, 31].

Individuals who were diagnosed with eating disorders according to EAT-26 at the point of a change in their treatment had significantly higher HbA1c levels than those who did not meet the criteria for such a diagnosis (M = 10.4 vs. M = 8.9; p = 0.014). This is a very important result, as the HbA1c level accurately reflects the quality of metabolic control in people with diabetes, and the available literature has found few psychological variables that may be related to it. Most of the studies cited in this paper which focused on persons with T2D confirmed no differences between individuals with and without eating disorders or abnormal eating attitudes in terms of HbA1c levels or their correlation with HbA1c levels. The results here are unique in the context of other studies and need to be verified in studies on larger, more representative groups of individuals with diabetes. We can hypothesize that the prevalence of eating disorders differs between patients with respect to HbA1c levels, but only in the group of patients with worse hemoglobin control and already elevated levels. Further research is necessary to fully investigate the dependencies described here.

Persons who were diagnosed with binge eating via a screening questionnaire were different from those who were not diagnosed in that manner, and a higher intensity of depressive symptoms measured with the BS-RSDA questionnaire was observed in those subjects (M = 14. 72 vs. M = 9.46; p = 0.037). In the study by Nicolau [8], individuals diagnosed with BED were significantly more likely to meet the Beck Depression Questionnaire depression screening criteria than those not diagnosed with the BED (p = 0.0021). Çelik et al. also described a significantly higher intensity of depressive symptoms in patients with BED as compared to patients without BED [18].

In a cross-sectional study, positive correlations were found between intensity of eating disorders, intensity of depressive and anxiety symptoms, and intensity of diabetes-related distress (including problems with treatment, food, social support, and negative emotions). Available studies have shown positive correlations between intensity of eating disorders and intensity of depressive symptoms [8, 18].

In this prospective study, several positive correlations were found between intensity of symptoms of eating disorders and binge eating and the subjects' psychological characteristics in subsequent measurements. As regards the symptoms, the relationship with the largest number of variables describing the subjects' mental state was exacerbated by the bulimia and food preoccupation scale of EAT-26 and scores of QBES. The higher the patient's intensity of particular traits at the beginning of the study, the more severe the symptoms of anxiety and diabetes-related problems after 6 months. One year later, the patients had more severe symptoms of depression, anxiety, and diabetes-related problems. Similarly, the intensity of binge eating at the beginning of the study was positively correlated with the intensity of depression symptoms, anxiety symptoms, and diabetes-related problems with the intensity of depression symptoms and anxiety symptoms after 6 months and then after one year.

According to our knowledge, this is the first study to analyze the relationship between the measured factors and different EAT-26 subscales, whereas in the other cited studies only general EAT-26 results were used. The practical conclusion from an assessment of EAT-26 subscale relationships is that the symptoms of bulimia and food preoccupation are significantly related to the intensity of depression and anxiety symptoms and problems in individuals with T2D. Oral control and dieting were found to have no significant relationship.

Notably, apart from the inverse correlation of bulimia intensity with HbA1c levels after one year, there were no symptoms of eating disorders correlated with HbA1c levels and number of complications in the cross-sectional or prospective study. The results obtained here are similar to those of a prospective study that was conducted by other researchers [20]. Apparently, the widely examined psychopathology, including depressive symptoms, that was observed at the beginning of the study created no differentiation between the 2 groups in the follow-up study. The results of the "food-related behavior" scale were only marginally different for individuals from those who achieved their intended therapeutic goal. The correlations between psychological variables (symptoms of eating disorders) and HbA1c levels, as well as the number of complications, transpired to be insignificant. This can be explained, among other things, by the small sample size, especially in prospective measurements. Another explanation is the hypothesis that individuals with diabetes can use insulin to correct high blood sugar levels resulting from behaviors such as binge eating. This leads to a lack

of association between these variables and medical indicators.

Based on the results obtained here, we suggest that clinical variables such as duration of diabetes, insulin use, and baseline HbA1c level are more important than mental variables to achieve optimal HbA1c levels. In the study presented herein, only the results of the "Bulimia and Food Preoccupation" scale proved to be important, albeit in a counterproductive manner, probably because behaviors assessed by the food preoccupation questions were beneficial to those individuals with diabetes who had to maintain an optimal diet. The "Bulimia and Food Preoccupation" scale includes items such as: "Find myself preoccupied with food," "Feel that food controls my life," and "Give too much time and thought to food." In the case of individuals not being treated for diabetes, these may reflect significant, maladaptive preoccupation with food, possibly indicative of eating disorders. However, management of diabetes requires patients to pay considerable attention to their eating habits. Preoccupation with food may represent an adaptive approach in coping with diabetes and controlling the disease. Patients who pay a lot of attention to what they eat may thus better control their HbA1c levels. Therefore, scores on the "Bulimia and Food Preoccupation" scale at the beginning of the study may negatively correlate with HbA1c levels after 6 months.

This is an important finding because it shows that scores on a scale measuring psychopathology may be elevated due to adaptive attitudes and behaviors in this group of patients. Therefore, we suggest some consideration in interpreting the results of scales measuring eating disorder symptoms in diabetes patients.

The presented results have some significant limitations, mainly due to the small sample size, the lack of randomization in the study group, and the use of screening tools for diagnosis. These results should be considered as preliminary, due to the high drop-out rate in follow-up examinations. It is noteworthy that participation in prospective studies is difficult and demanding for participants. Replication in a randomized study with a large enough sample and a reliable diagnosis of eating disorders according to current diagnostic criteria is needed.

## Conclusions

The cross-sectional data analysis indicates that throughout the course of the study there were considerable moderate correlations between intensity of symptoms of eating disorders and binge eating vs. symptoms of anxiety, depression, and intensity of diabetes-related problems that underwent no significant changes. At the baseline, the level of HbA1c among persons with symptoms of eating disorders was significantly higher than in the group without these symptoms. Successful treatment of symptoms of eating disorders could contribute to improvement of emotional state and disease management in people with T2D. The small and non-representative sample size means that these findings should be confirmed in a future study with a representative and larger group of participants.

The results of the Eating Attitude Test in individuals with diabetes should be interpreted with consideration of the potentially beneficial role of a person's attitude of focusing on food and their way of eating when coping with diabetes.

## Article information

### Ethical approval and consent to participate

The study was approved by an Ethics Committee of Medical University of Warsaw, and all participants signed an informed consent participation form.

### Authors' contributions

Marcin Obrębski, Joanna Ostasz-Ważny, and Andrzej Kokoszka contributed to the study design. Edward Franek and Magdalena Walicka helped with patient recruitment and acquisition of data. All the authors contributed to data analysis and interpretation, discussion of the results, revision of the article, and approval of the final version of the manuscript for submission.

### Funding

This study was part of a project "Impact of psychological factors on treatment of type 2 diabetes" funded by the Medical University of Warsaw.

### Conflict of interest

The authors declare no conflict of interest.

### REFERENCES

1. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022; 183: 109119, doi: 10.1016/j.diabres.2021.109119, indexed in Pubmed: 34879977.
2. American Diabetes Association. Summary of Revisions: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021; 44(Suppl 1): S4–S6, doi: 10.2337/dc21-Srev, indexed in Pubmed: 33298411.
3. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. International Diabetes Federation, Brussels 2019.
4. Araszkiewicz A, Bandurska-Stankiewicz E, Borys S, et al. 2021 Guidelines on the management of patients with diabetes. A position of Diabetes Poland. Clinical Diabetology. 2021; 10(1): 1–113, doi: 10.5603/dk.2021.0001.
5. Nicolucci A, Kovacs Burns K, Holt RIG, et al. DAWN2 Study Group. Diabetes Attitudes, Wishes and Needs second study (DAWN2™): cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes. Diabet Med. 2013; 30(7): 767–777, doi: 10.1111/dme.12245, indexed in Pubmed: 23711019.

6. Colton P, Rodin G, Bergenstal R, et al. Eating Disorders and Diabetes: Introduction and Overview. Diabetes Spectrum. 2009; 22(3): 138–142, doi: 10.2337/diaspect.22.3.138.
7. Young-Hyman D, Davis C. Disordered Eating Behavior in Individuals With Diabetes. Diabetes Care. 2010; 33(3): 683–689, doi: 10.2337/dc08-1077.
8. Nicolau J, Simó R, Sanchís P, et al. Eating disorders are frequent among type 2 diabetic patients and are associated with worse metabolic and psychological outcomes: results from a cross-sectional study in primary and secondary care settings. Acta Diabetol. 2015; 52(6): 1037–1044, doi: 10.1007/s00592-015-0742-z, indexed in Pubmed: 25841588.
9. de Groot M, Golden SH, Wagner J. Psychological conditions in adults with diabetes. Am Psychol. 2016; 71(7): 552–562, doi: 10.1037/a0040408, indexed in Pubmed: 27690484.
10. Herpertz S, Albus C, Wagener R, et al. Comorbidity of diabetes and eating disorders. Does diabetes control reflect disturbed eating behavior? Diabetes Care. 1998; 21(7): 1110–1116, doi: 10.2337/diacare.21.7.1110, indexed in Pubmed: 9653604.
11. Johnson JG, Spitzer RL, Williams JB. Health problems, impairment and illnesses associated with bulimia nervosa and binge eating disorder among primary care and obstetric gynaecology patients. Psychol Med. 2001; 31(8): 1455–1466, doi: 10.1017/s0033291701004640, indexed in Pubmed: 11722160.
12. Papelbaum M, Appolinário JC, Moreira Rd, et al. Prevalence of eating disorders and psychiatric comorbidity in a clinical sample of type 2 diabetes mellitus patients. Braz J Psychiatry. 2005; 27(2): 135–138, doi: 10.1590/s1516-44462005000200012, indexed in Pubmed: 15962139.
13. Abbott S, Dindol N, Tahrani AA, et al. Binge eating disorder and night eating syndrome in adults with type 2 diabetes: a systematic review. J Eat Disord. 2018; 6: 36, doi: 10.1186/s40337-018-0223-1, indexed in Pubmed: 30410761.
14. Herpertz S, Albus C, Lichtblau K, et al. Relationship of weight and eating disorders in type 2 diabetic patients: a multicenter study. Int J Eat Disord. 2000; 28(1): 68–77, doi: 10.1002/(sici)1098-108x(200007)28:1<68::aid-eat8>3.0.co;2-r, indexed in Pubmed: 10800015.
15. Meneghini LF, Spadola J, Florez H. Prevalence and associations of binge eating disorder in a multiethnic population with type 2 diabetes. Diabetes Care. 2006; 29(12): 2760, doi: 10.2337/dc06-1364, indexed in Pubmed: 17130226.
16. Canan F, Gungor A, Onder E, et al. The association of binge eating disorder with glycemic control in patients with type 2 diabetes. Turk J Endocrinol Metab. 2011; 15(2): 26–27.
17. Crow S, Kendall D, Praus B, et al. Binge eating and other psychopathology in patients with type II diabetes mellitus. Int J Eat Disord. 2001; 30(2): 222–226, doi: 10.1002/eat.1077, indexed in Pubmed: 11449458.
18. Çelik S, Kayar Y, Önem Akçakaya R, et al. Correlation of binge eating disorder with level of depression and glycemic control in type 2 diabetes mellitus patients. Gen Hosp Psychiatry. 2015; 37(2): 116–119, doi: 10.1016/j.genhosppsych.2014.11.012, indexed in Pubmed: 25670634.
19. Herbozo S, Flynn PM, Stevens SD, et al. Dietary Adherence, Glycemic Control, and Psychological Factors Associated with Binge Eating Among Indigenous and Non-Indigenous Chileans with Type 2 Diabetes. Int J Behav Med. 2015; 22(6): 792–798, doi: 10.1007/s12529-015-9478-y, indexed in Pubmed: 25786595.
20. Rotella F, Cresci B, Monami M, et al. Are psychopathological features relevant predictors of glucose control in patients with type 2 diabetes? A prospective study. Acta Diabetol. 2012; 49 Suppl 1: S179–S184, doi: 10.1007/s00592-012-0403-4, indexed in Pubmed: 22644473.
21. Garner DM, Garfinkel PE. The Eating Attitudes Test: an index of the symptoms of anorexia nervosa. Psychol Med. 1979; 9(2): 273–279, doi: 10.1017/s0033291700030762, indexed in Pubmed: 472072.
22. Garner DM, Olmsted MP, Bohr Y, et al. The eating attitudes test: psychometric features and clinical correlates. Psychol Med. 1982; 12(4): 871–878, doi: 10.1017/s0033291700049163, indexed in Pubmed: 6961471.
23. Mintz LB, O'Halloran MS. The Eating Attitudes Test: validation with DSM-IV eating disorder criteria. J Pers Assess. 2000; 74(3): 489–503, doi: 10.1207/S15327752JPA7403_11, indexed in Pubmed: 10900574.
24. Tomalski R, Żak-Gołąb A, Zahorska-Markiewicz B. Czy rezygnacja z terapii odchudzającej wiąże się z występowaniem żarłocznego jedzenia? [Is there a relationship between binge eating and termination of body weight loos therapy?]. Endokrynologia, Otyłość i Zaburzenia Przemiany Materii. 2008; 4(2): 53–57.
25. Polonsky WH, Anderson BJ, Lohrer PA, et al. Assessment of diabetes-related distress. Diabetes Care. 1995; 18(6): 754–760, doi: 10.2337/diacare.18.6.754, indexed in Pubmed: 7555499.
26. Glasgow RE. Behavioral and psychosocial measures for diabetes care: what isimportant to assess. Diabetes Spectr. 1997; 10(1): 12–17.
27. Welch GW, Jacobson AM, Polonsky WH. The Problem Areas in Diabetes Scale. An evaluation of its clinical utility. Diabetes Care. 1997; 20(5): 760–766, doi: 10.2337/diacare.20.5.760, indexed in Pubmed: 9135939.
28. Snoek FJ, Pouwer F, Welch GW, et al. Diabetes-related emotional distress in Dutch and U.S. diabetic patients: cross-cultural validity of the problem areas in diabetes scale. Diabetes Care. 2000; 23(9): 1305–1309, doi: 10.2337/diacare.23.9.1305, indexed in Pubmed: 10977023.
29. Kokoszka A. Krótka Skala Samooceny Depresji i Lęku: opis konstrukcji oraz właściwości psychometryczne dla osób z cukrzycą [Brief Self-Rating Scale of Depression and Anxiety: description of the scale construction and psychometric properties for persons with diabetes]. Przewodnik Lekarza. 2008; 6: 74–81.
30. Kokoszka A, Jodko-Modlińska A, Obrębski M, Ostasz-Ważny J, Radzio R. Psychodiabetic Kit and its application in clinical practice and research. In: Masuo K. ed. Type 2 Diabetes. IntechOpen, London 2013: 507–531.
31. Wändell PE. Risk factors for microvascular and macrovascular complications in men and women with type 2 diabetes. Scand J Prim Health Care. 1999; 17(2): 116–121, doi: 10.1080/028134399750002755, indexed in Pubmed: 10439496.
32. Litwak L, Goh SY, Hussein Z, et al. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study. Diabetol Metab Syndr. 2013; 5(1): 57, doi: 10.1186/1758-5996-5-57, indexed in Pubmed: 24228724.

VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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# Effect of Single, Accumulated, and Conventional Walking on Glucose Level, Aerobic Capacity, Fatigue, and Quality of Life in Type 2 Diabetes: A Randomized Trial

## ABSTRACT

**Objective: This study evaluated the effectiveness of different walking protocols on various physiological and psychological factors in type 2 diabetes (T2D).**

**Materials and methods: In this randomized study, 45 individuals with T2D, aged 55–65 years, with diabetes duration between 1 and 10 years were recruited. They were randomly assigned to 1 of 3 groups: single walking (SW), accumulated walking (AW), or conventional walking (CW). The primary outcome measure was fasting blood glucose (FBG) while secondary outcomes assessed were 6-minute walk distance (6MWD), fatigue, and quality of life (QoL). Intervention was given for 6 weeks. Intra-group changes were analyzed using the Wilcoxon signed rank test, while inter-group differences were evaluated with the Kruskal-Wallis test.**

**Results: 42 participants completed the study. The baseline data showed non-significant difference across the groups for age and duration of diabetes. FBG showed a minor reduction in the SW (12%) and AW (15.5%) groups, while it increased in the CW group (2.5%). The 6MWD improved significantly in the SW (21.3%, p = 0.003) and AW (21%, p = 0.008) groups, but decreased in the CW (9.5%) group. Fatigue decreased in the SW (4.5%, p = 0.027) and AW (4.8%, p = 0.003) groups, while it slightly increased in the CW (0.5%) group. QoL improved in the SW (2.3%, p = 0.016) and AW (4.3%, p = 0.008) groups but decreased in the CW (1.78%) group. Post-hoc analysis showed significant differences in 6MWD (p = 0.010) and QoL (p = 0.008) between the AW and CW groups.**

**Conclusions: SW and AW showed similar effects on glucose levels, aerobic capacity, fatigue, and QoL. However, AW is more effective than CW in enhancing aerobic capacity and QoL.**

**Clinical trial registration number: CTRI/2022/08/044936**

**(Clin Diabetol 2024; 13, 6: 341–348)**

**Keywords: type 2 diabetes, fasting blood glucose, aerobic capacity, walking**

## Introduction

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by hyperglycemia due to insulin resistance. It is linked with insulin secretory deficits due to genetics, inflammation, and metabolic stress. It makes up 90% of all diabetes cases and is a worldwide epidemic. Approximately 77 million individuals in India had diabetes in 2019, and by 2045 it is projected to

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Clinical Diabetology 2024, 13; 6: 341–348
DOI: 10.5603/cd.102291
Received: 27.08.2024 Accepted: 10.10.2024
Early publication date: 21.11.2024

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reach over 134 million. As it is a long-term disorder, it can lead to adverse complications, which are associated with increased expenditure on the family, community, and healthcare system [1–3].

Exercise is an essential part of T2D management because it helps optimize glycemic levels, improve insulin sensitivity, and positively impacts cardiovascular health. Unfortunately, most of these individuals are physically inactive and have reduced aerobic capacity. Inadequate glycemic control (GC) can cause uncontrolled diabetes and its associated consequences, which can significantly lower quality of life (QoL), shorten life expectancy, and raise healthcare costs [4, 5].

Fatigue has been reported as a frequent symptom in those with T2D, resulting in poor self-reported health. It may reduce an individual's capacity to perform daily activities necessary for optimal GC (e.g., glucose monitoring, preparing a healthy meal, and regular physical activity). Despite this, it is often unnoticed during healthcare visits because acute issues take priority. T2D is a psychologically demanding chronic condition because it affects many aspects of QoL. Episodes of hypoglycemia, changes in lifestyle, and concerns of long-term effects may all affect QoL [6–9].

Walking is an easy, convenient, and cost-effective means to adopt a physically active lifestyle. It is the most preferred form of leisure-time exercise, and because it involves the use of large skeletal muscles, it contributes to peripheral glucose uptake and improves glucose homeostasis [10, 11]. T2D is associated with obesity, fatigue, and certain health conditions such as hip and knee osteoarthritis, which limit engagement in extended, continuous bouts of exercise. Hardman noted in a systematic review on the benefits of exercise fractionation that multiple short sessions of exercise are just as effective as longer continuous sessions. The former may be both practical and effective. However, the advantages of such modifications remain unclear [12, 13]. So, this study aims to assess the effects of different walking exercises on glucose level, aerobic capacity, fatigue, and QoL in persons with T2D.

## Materials and methods

### Subjects

Individuals with T2D, aged 55 to 65 years, were recruited from settings such as residential societies and physiotherapy outpatient departments. This was done with the help of in-person outreach, informational flyers, and referrals from healthcare providers. Participants with duration of diabetes between 1 and 10 years, with fair glycemic control (HbA1c < 7%, or fasting blood glucose (FBG) level 70–130 mm/dL, or postprandial blood glucose level <180 mm/dL) and on an oral hypoglycemics regimen were included. Exclusion criteria included one or more positive marks on the Physical Activity Readiness Questionnaire (PAR-Q), history of stroke, cancer, acute illness, lower limb pain, complications (a general sensory, motor, and vascular examination was done to rule out complications), or those participating in regular exercise (minimum 20 minutes on 3 or more days per week). Participants were randomly assigned to one of three groups: single walking, accumulated walking, or conventional walking.

### Study design

This was a randomized, single-blinded, parallel-group, active-controlled study. Group allocation was done using sealed, opaque envelopes and computer-generated randomization (www.random.org), as illustrated in Figure 1. Participants remained unaware of their assigned groups. Group allocation was blinded to the participants.

### Data collection

The outcome measures were assessed at baseline and after 6 weeks of intervention.

Primary outcome measure for glucose level was FBG level, which was measured using a glucometer (Accu Chek Instant S, Roche Diabetes Care GmbH, Mannheim, Germany) after 8 hours of overnight fasting. It has acceptable accuracy [14].

Secondary outcomes included aerobic capacity, fatigue, and QoL. Six-minute walk test (6MWT) was performed using the American Thoracic Society guidelines, and the six-minute walk distance (6MWD) in meters was calculated to measure the aerobic capacity [15].

Multidimensional Fatigue Inventory 20 (MFI-20) was used to evaluate fatigue. It is a 20-item, self-reported questionnaire that assesses 5 dimensions of fatigue including general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. It uses a 5-point Likert scale with scores ranging from 20 to 100. Higher scores indicate a higher burden of fatigue. It has a reliability of 0.84 with acceptable validity [16].

The appraisal of diabetes scale (ADS) was used to assess QOL. This is a 7-item, self-reported questionnaire that evaluates an individual's appraisal of their diabetes. It uses a 5-point Likert scale with scores ranging from 0 to 35. The lower the score, the better the QoL. It has a reliability of 0.73 [17].

### Intervention

#### Single walking (SW) exercise group

Participants started the exercise with a 3-minute warm-up, walking at a leisurely pace. This was followed by 30 minutes of brisk walking at a moderate intensity,

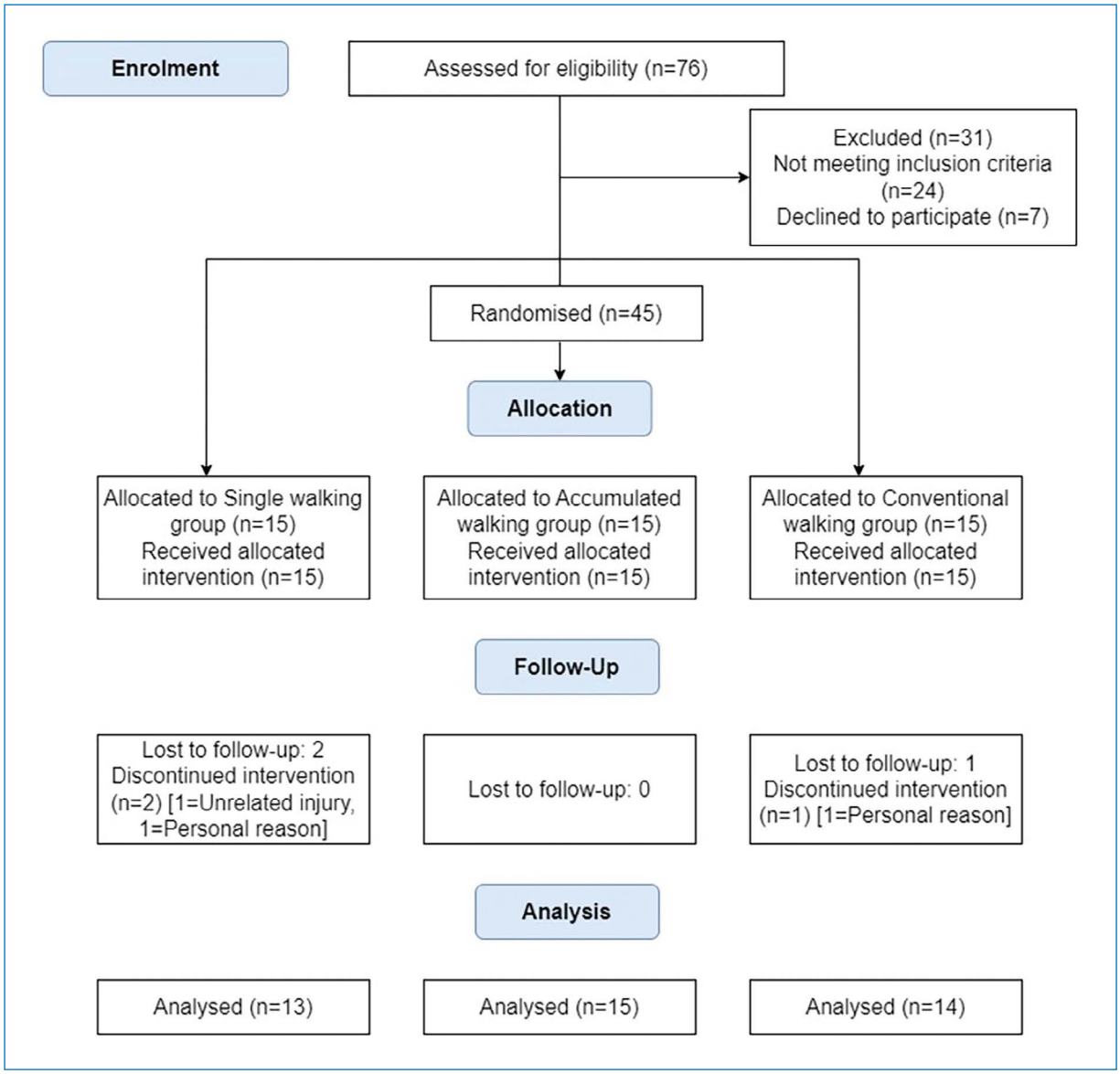


**Figure 1.** CONSORT Flow Diagram

i.e., rate of perceived exertion (RPE) of 5 to 6 [13]. They were advised to walk at a pace at which breathing was slightly hard but still allowed for conversation without gasping (talk test) [18]. After this, participants performed a cool-down with another 3 minutes of leisurely walking. This routine was performed on 3 alternate days per week for 6 weeks. One session each week was supervised, while the remaining sessions were done at home. Participants were asked to log their activities on an exercise chart with weekly follow-ups via phone calls or text messages.

### Accumulated walking (AW) exercise group

Participants started the exercise with a one-minute warm-up, walking at a leisurely pace. This was followed by 10 minutes of brisk walking at a moderate intensity, i.e., RPE of 5 to 6 [13]. They were advised to walk at a pace at which breathing was slightly hard but still allowed for conversation without gasping (talk test) [18]. After this, participants performed a cool-down with another minute of leisurely walking. This routine was performed thrice a day (with an interval of 4 to 5 hours between each exercise bout) on 3 alternate days per week for 6 weeks. One session each week was supervised, while the remaining sessions were done at home. Participants were asked to log their activities on an exercise chart with weekly follow-ups via phone calls or text messages.

### Conventional walking (CW) exercise group

Participants in the control group were instructed to walk for 30 minutes per day on 3 alternate days each

**Table 1. Demographic Data of All Participants**

| | SW group | AW Group | CW Group | F | p-value |
|---|---|---|---|---|---|
| Gender: | | | | | |
| Male | 6 (40%) | 10 (66.6%) | 7 (46.6%) | — | — |
| Female [N (%)] | 9 (60%) | 5 (33.3%) | 8 (53.3%) | | |
| Age [years] (Mean ± SD) | 60.3 ± 2.6 | 59.6 ± 3.5 | 58.5 ± 4.3 | 0.965 | 0.389 |
| Duration of diabetes [years] (Mean ± SD) | 5.5 ± 2.7 | 5.1 ± 3.3 | 6.5 ± 2.2 | 1.170 | 0.320 |

Values are N (%) or mean ± SD; F and p-values were derived from one-way ANOVA

AW — accumulated walking; CW — conventional walking; SD — standard deviation; SW — single walking

**Table 2. Intra-Group Analysis**

| Group | Outcome measure | Baseline | Post 6 weeks | p-value |
|---|---|---|---|---|
| Single | MFI-20 score | 50.8 ± 16.9 | 46.3 ± 17.0 | 0.027 |
| | ADS score | 24.3 ± 6.7 | 22 ± 5.4 | 0.016 |
| | FBG [mm/dL] | 97.9 ± 18.1 | 85.9 ± 14.4 | 0.004 |
| | 6MWD [m] | 396.7 ± 49.0 | 418.0 ± 43.0 | 0.033 |
| Accumulated | MFI-20 score | 41.7 ± 15.5 | 36.8 ± 14.6 | 0.003 |
| | ADS score | 25.2 ± 7.9 | 20.9 ± 6.6 | 0.008 |
| | FBG [mm/dL] | 107.6 ± 14.1 | 91.9 ± 15.3 | 0.001 |
| | 6MWD [m] | 384.1 ± 33.1 | 405.1 ± 35.9 | 0.008 |
| Conventional | MFI-20 score | 40.6 ± 13.0 | 41.1 ± 13.5 | 0.801 |
| | ADS score | 20.3 ± 6.8 | 22.1 ± 8.5 | 0.094 |
| | FBG [mm/dL] | 109.0 ± 17.7 | 106.5 ± 18.8 | 0.594 |
| | 6MWD [m] | 382.2 ± 56.2 | 372.6 ± 66.5 | 0.198 |

Values are mean ± SD; p-value was set at 0.05

6MWD — six-minute-walk-distance; ADS — appraisal of diabetes scale; FBG — fasting blood glucose; MFI-20 — Multidimensional Fatigue Inventory-20; SD — standard deviation

week for 6 weeks [13]. All sessions were home-based, and participants were asked to log their activities on an exercise chart. Weekly follow-ups were conducted via phone calls or text messages to ensure a compliance rate of at least 70%.

Participants who were considered dropouts were the ones who chose to withdraw due to personal reasons and sustained an injury that necessitated discontinuation of exercise until recovery.

## Statistical analysis

The results are presented as numbers, percentages, and mean ± standard deviation (SD). Sample size was calculated using the formula $[2 \times SD^2 \times (1.96 + 0.84)]/d^2$. SD and d (mean difference) values were based on previous studies [19]. The sample size was found to be 45, i.e., 15 for each group. Intra-group analysis was done using the Wilcoxon Signed Rank test, and intergroup analysis was done using the Kruskal-Wallis test. Post hoc analysis was done for group-wise comparison. The statistical significance was set at $p \leq 0.05$ and the confidence interval at 95%. Data analysis was done using Statistical Package for the Social Sciences (SPSS) version 26.

## Results

Of 45 participants, 42 (93.33%) were followed up in the study. Loss to follow-up was 6.67%. Figure 1 shows the number of participants at each stage according to the CONSORT diagram. Table 1 shows the baseline demographic characteristics of all participants with T2D comparable across the study groups.

## Glucose level

FBG significantly reduced in the SW (12%) and AW (15.5%) groups while the decrease in the CW group (2.5%) was non-significant. Inter-group analysis was non-significant (Tab. 2 and 3).

## Aerobic capacity

Significant improvements in 6MWD were seen in the SW (21.3%) and AW (21.05%) groups while it de-

**Table 3. Inter-Group and Post Hoc Analysis**

| Outcome measure | Group | Mean ± SD | p-value | Pair wise groups | p-value |
|---|---|---|---|---|---|
| MFI-20 score | Single | 4.5 ± 5.9 | 0.039 | Single — Accumulated | 1.000 |
| | Accumulated | 4.8 ± 5.3 | | Single — Conventional | 0.065 |
| | Conventional | –0.5 ± 6.2 | | Accumulated — Conventional | 0.109 |
| ADS score | Single | 2.3 ± 3.7 | 0.008 | Accumulated — Single | 1.000 |
| | Accumulated | 4.3 ± 5.9 | | Accumulated — Conventional | 0.008 |
| | Conventional | –1.7 ± 3.3 | | Single — Conventional | 0.107 |
| FBG [mm/dL] | Single | 12 ± 10.7 | 0.389 | — | — |
| | Accumulated | 15.6 ± 13.5 | | | |
| | Conventional | –2.5 ± 25.9 | | | |
| 6MWD [m] | Single | 21.3 ± 27.7 | 0.008 | Conventional — Single | 0.054 |
| | Accumulated | 21.0 ± 26.6 | | Conventional — Accumulated | 0.010 |
| | Conventional | –9.5 ± 23.2 | | Single — Accumulated | 1.000 |

Values are mean ± SD; p-value was set at 0.05

6MWD — 6-minute-walk-distance; ADS — appraisal of diabetes scale; FBG — fasting blood glucose; MFI-20 — Multidimensional Fatigue Inventory-20; SD — standard deviation

creased in the CW group (9.57%). Inter-group analysis was significant (p = 0.008). Post hoc analysis showed that the change in aerobic capacity between the AW and CW groups was significant (p = 0.010) (Tab. 2 and 3).

### Fatigue

This lowered significantly in the SW (4.53%) and AW (4.86%) groups while the CW group (0.5%) showed a non-significant increment. Inter-group analysis was significant (p = 0.039); however, post-hoc analysis was insignificant (Tab. 2 and 3).

### Quality of Life

QoL improved significantly in the SW (2.38%) and AW (4.33%) groups while it decreased in the CW (1.78%) group. Inter-group analysis was significant (p=0.001). Post hoc analysis was significant between the AW and CW groups (p = 0.008) (Tab. 2 and 3).

## Discussion

We observed a significant decrease in glucose levels in both intervention groups (SW and AW) as compared to the control group (CW) along with a greater reduction in the AW group. Similar results were demonstrated in the study done by Eriksen et al. [20] in 2007, in which improvements in FBG in adults with T2D after engagement in multiple-bout, moderate-intensity aerobic exercise for 5 weeks were seen. This finding is consistent with 2 previous studies which showed reduced postprandial glycemia with post-meal walking bouts compared with one-time daily exercise in T2D [21, 22]. This could be due to higher energy expenditure during multiple bouts of exercise than during a single bout of exercise, because of an acute rise in exercise-induced metabolic rate caused by excess post-exercise oxygen consumption, which improves glucose homeostasis [23].

As demonstrated by Eriksen et al. [20] in 2007, cardiorespiratory fitness had similar increases with both single and multiple sessions of exercise training done for 5 weeks. Similar findings have been reported in a previous review that compared the effectiveness of accumulating exercise in multiple bouts of at least 10 minutes throughout a day with exercise completed in a single bout in inactive healthy individuals [24]. Aerobic exercise involves repetitive contractile activity of muscles, which is known to stimulate an increase in mitochondrial size, number, and mitochondrial enzymes, thus improving the aerobic capacity, which could explain the results of this study [25].

In comparison to the control group, participants in both intervention groups saw equal and favorable changes in fatigue. According to a study by Abd El Kader et al. [19] in 2015, aerobic exercise performed for 12 weeks improved fatigue symptoms in obese people with T2D. Short and long bouts of low-impact aerobic exercise have a similar influence on fatigue in sedentary women with fibromyalgia, according to the results of another study by Schachter et al. in 2003 [12]. Fatigue in T2D can occur due to endocrine-related causes such as poor glucose control or inflammatory markers, as well as lifestyle factors like inactivity. Due to inactivity, these individuals are frequently overweight

or obese, which raises the level of pro-inflammatory cytokines and causes fatigue. This inflammatory marker production is inhibited by aerobic exercise [19, 26–28]. Furthermore, research by Park et al. [29] in 2015 asserted that only in patients with elevated HbA1c levels does fatigue have a direct correlation to glucose control. Fatigue is mostly influenced by the presence of diabetic symptoms and distress with adequate glycemic control.

Individuals with T2D have a lower QoL than those without the disease due to a variety of causes such as the accompanying complications and psychological issues including anxiety and depression, which influence psychosocial life and functioning and thus lower QoL. Comorbidities and different treatment regimen demands also have an impact on QoL. It declines with increasing age, disease duration, poor metabolic management, combination treatment with oral hypoglycemics and insulin, sedentary lifestyle, in women, and the presence of comorbidities [30]. Incentives such as regular phone follow-ups, supervised training sessions, self-monitoring of exercises, and group sessions boost participant motivation and adherence, promote a positive mindset, and encourage increased physical activity, hence enhancing QoL. Aerobic exercise improves QOL by increasing physical activity and altering body composition while maintaining glycemic control, blood pressure, and insulin resistance [31]. Previous research by Esha et al. [32] in 2019, Guglani et al. [9] in 2014, Praet et al. [33] in 2008, and Aylin et al. [34] in 2009 that found that walking-based training increased QOL in T2D, confirming the findings of this study.

As a result of having more individuals with hypertension (Group SW = 4, Group AW = 2) and female participants (Group SW = 9, Group AW = 5) than Group AW, Group SW experienced lower increases in QoL (Tab. 1).

Even though the current study's results show a positive effect of exercise on fasting blood glucose level, Morton et al. [35] in 2010 claimed that a 7-week walking exercise program improved cardiorespiratory fitness but had no effect on blood glucose levels. The perceived intensity of the exercise protocol in the study was light whereas in this study it was of moderate intensity.

Most individuals with T2D do not achieve the recommended amount of physical activity per day. In catering to the needs of this large number of individuals, a better understanding of the kind of exercise program that they can effectively benefit from is necessary. Although there are pharmacological regimens to manage diabetes and its symptoms, those alone cannot effectively address the various aspects of the condition. In the current study, an accumulated walking exercise protocol was proven to be more practical and effective in optimizing aerobic fitness and QoL.

The strengths of this study include emphasis on efficacy and the use of a cost-effective exercise regimen. Low discontinuation rates indicate that the exercise program was well tolerated. The study also had some limitations. There was no long-term follow-up to understand the durability of the treatment effect. Due to certain constraints, only urban populations with access to personal electronic gadgets were included. Also, factors like stress, daily activity levels, sleep quality, obesity, and dietary intake were not considered during the treatment process to see if they influenced the outcomes.

## Conclusions

There is no difference between single and accumulated walking exercises on glucose level, aerobic capacity, fatigue, and QoL in those with T2D. However, as compared to the control group, accumulated walking is preferable in improving aerobic capacity and QoL.

Future studies on long-term follow-up can be done to determine the effectiveness of the walking intervention. The effect of exercises along with other factors can also be evaluated to understand the role of both.

## Article information

### Data availability statement

The original contributions presented in this study are detailed within the article, and any additional inquiries can be directed to the corresponding author.

### Ethics statement

This study was approved by Institutional Ethics Committee (under the number IEC — SIOR/Agenda 070 on 08/07/2022) and was registered with the Clinical Trials Registry – India (https://ctri.nic.in/Clinicaltrials/login.php) with identifier CTRI/2022/08/044936. Written informed consent was obtained from all the participants prior to commencement of the study, and the data were used solely for research and educational purposes. The study was conducted in accordance with the guidelines of the Helsinki Declaration 2013 prior to its start.

### Author contributions

SGM: conceived and designed the study, acquired the data, performed the statistical analysis, and prepared the first draft of the manuscript. SM: contributed to the concepts, design, and manuscript editing and review. APS: contributed to the concepts and design,

interpretation of data, and reviewed the manuscript. All contributors reviewed, edited, and approved the final submission of the manuscript.

## Funding

The authors did not receive any external source of funding for this study.

## Acknowledgments

The authors extend their gratitude to all the participants for their support and cooperation in taking part in this study. We also wish to express our sincere thanks to Dr. Farheen Patel and Dr. Shivani Chutke for their valuable inputs and guidance.

## Conflict of interest

The authors declare no conflict of interest.

## REFERENCES

1. Goyal R. Type 2 diabetes. U.S. National Library of Medicine; 2023. https://www.ncbi.nlm.nih.gov/books/NBK513253/ (22.04.2024).
2. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care. 2023; 46(Suppl 1): S19–S40, doi: 10.2337/dc23-S002, indexed in Pubmed: 36507649.
3. Pradeepa R, Mohan V, et al. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021; 69(11): 2932–2938, doi: 10.4103/ijo.IJO_1627_21, indexed in Pubmed: 34708726.
4. Poitras VJ, Hudson RW, Tschakovsky ME. Exercise intolerance in Type 2 diabetes: is there a cardiovascular contribution? J Appl Physiol (1985). 2018; 124(5): 1117–1139, doi: 10.1152/japplphysiol.00070.2017, indexed in Pubmed: 29420147.
5. Bin Rakhis SA, AlDuwayhis NM, Aleid N, et al. Glycemic Control for Type 2 Diabetes Mellitus Patients: A Systematic Review. Cureus. 2022; 14(6): e26180, doi: 10.7759/cureus.26180, indexed in Pubmed: 35891859.
6. Alghadir A, Gabr S, Anwer S, et al. Fatigue and oxidative stress response to physical activity in type 2 diabetic patients. International Journal of Diabetes in Developing Countries. 2015; 36(1): 59–64, doi: 10.1007/s13410-015-0420-2.
7. Ba J, Chen Y, Liu D. Fatigue in Adults with Type 2 Diabetes: A Systematic Review and Meta-analysis. West J Nurs Res. 2021; 43(2): 172–181, doi: 10.1177/0193945920938636, indexed in Pubmed: 32627705.
8. Drivsholm T, de Fine Olivarius N, Nielsen ABS, et al. Symptoms, signs and complications in newly diagnosed type 2 diabetic patients, and their relationship to glycaemia, blood pressure and weight. Diabetologia. 2005; 48(2): 210–214, doi: 10.1007/s00125-004-1625-y, indexed in Pubmed: 15650820.
9. Guglani R, Shenoy S, Sandhu JS. Effect of progressive pedometer based walking intervention on quality of life and general well being among patients with type 2 diabetes. J Diabetes Metab Disord. 2014; 13(1): 110, doi: 10.1186/s40200-014-0110-5, indexed in Pubmed: 25493265.
10. Fayehun AF, Olowookere OO, Ogunbode AM, et al. Walking prescription of 10 000 steps per day in patients with type 2 diabetes mellitus: a randomised trial in Nigerian general practice. Br J Gen Pract. 2018; 68(667): e139–e145, doi: 10.3399/bjgp18X694613, indexed in Pubmed: 29335328.
11. Belli T, Ribeiro LF, Ackermann MA, et al. Effects of 12-week overground walking training at ventilatory threshold velocity in type 2 diabetic women. Diabetes Res Clin Pract. 2011; 93(3): 337–343, doi: 10.1016/j.diabres.2011.05.007, indexed in Pubmed: 21636159.
12. Schachter CL, Busch AJ, Peloso PM, et al. Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: a randomized controlled trial. Phys Ther. 2003; 83(4): 340–358, indexed in Pubmed: 12665405.
13. Kanaley JA, Colberg SR, Corcoran MH, et al. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. Med Sci Sports Exerc. 2022; 54(2): 353–368, doi: 10.1249/MSS.0000000000002800, indexed in Pubmed: 35029593.
14. Kermani SK, Khatony A, Jalali R, et al. Accuracy and Precision of Measured Blood Sugar Values by Three Glucometers Compared to the Standard Technique. J Clin Diagn Res. 2017; 11(4): OC05–OC08, doi: 10.7860/JCDR/2017/23926.9613, indexed in Pubmed: 28571181.
15. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166(1): 111–117, doi: 10.1164/ajrccm.166.1.at1102, indexed in Pubmed: 12091180.
16. Smets EM, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995; 39(3): 315–325, doi: 10.1016/0022-3999(94)00125-o, indexed in Pubmed: 7636775.
17. Carey MP, Jorgensen RS, Weinstock RS, et al. Reliability and validity of the appraisal of diabetes scale. J Behav Med. 1991; 14(1): 43–51, doi: 10.1007/BF00844767, indexed in Pubmed: 2038044.
18. Centers for Disease Control and Prevention | CDC [Internet]. Measuring Physical Activity Intensity | Physical Activity; 2020. https://www.cdc.gov/physicalactivity/basics/measuring/index.html (26.04.2022).
19. Abd El-Kader SM, Al-Jiffri OH, Al-Shreef FM. Aerobic exercises alleviate symptoms of fatigue related to inflammatory cytokines in obese patients with type 2 diabetes. Afr Health Sci. 2015; 15(4): 1142–1148, doi: 10.4314/ahs.v15i4.13, indexed in Pubmed: 26958015.
20. Eriksen L, Dahl-Petersen I, Haugaard SB, et al. Comparison of the effect of multiple short-duration with single long-duration exercise sessions on glucose homeostasis in type 2 diabetes mellitus. Diabetologia. 2007; 50(11): 2245–2253, doi: 10.1007/s00125-007-0783-0, indexed in Pubmed: 17763840.
21. Reynolds AN, Mann JI, Williams S, et al. Advice to walk after meals is more effective for lowering postprandial glycaemia in type 2 diabetes mellitus than advice that does not specify timing: a randomised crossover study. Diabetologia. 2016; 59(12): 2572–2578, doi: 10.1007/s00125-016-4085-2, indexed in Pubmed: 27747394.
22. Pahra D, Sharma N, Ghai S, et al. Impact of post-meal and one-time daily exercise in patient with type 2 diabetes mellitus: a randomized crossover study. Diabetol Metab Syndr. 2017; 9: 64, doi: 10.1186/s13098-017-0263-8, indexed in Pubmed: 28883892.
23. Zhang X, Zheng C, Ho RST, et al. The Effects of Accumulated Versus Continuous Exercise on Postprandial Glycemia, Insulin, and Triglycerides in Adults with or Without Diabetes: A Systematic Review and Meta-Analysis. Sports Med Open. 2022; 8(1): 14, doi: 10.1186/s40798-021-00401-y, indexed in Pubmed: 35072806.
24. Shambrook P, Kingsley MI, Taylor NF, et al. Accumulated or continuous exercise for glycaemic regulation and control: a systematic review with meta-analysis. BMJ Open Sport Exerc Med. 2018; 4(1): e000470–907, doi: 10.1136/bmjsem-2018-000470, indexed in Pubmed: 30774976.
25. Kenney WL, Wilmore JH, Costill DL. Physiology of sport and exercise. 8th ed. Human Kinetics, Champaign, IL 2021.
26. Singh R, Teel C, Sabus C, et al. Fatigue in Type 2 Diabetes: Impact on Quality of Life and Predictors. PLoS One. 2016; 11(11):

e0165652, doi: 10.1371/journal.pone.0165652, indexed in Pubmed: 27824886.
27. Kalra S, Sahay R. Diabetes Fatigue Syndrome. Diabetes Ther. 2018; 9(4): 1421–1429, doi: 10.1007/s13300-018-0453-x, indexed in Pubmed: 29869049.
28. Bi Y, Zhang Lu, Li X, et al. Contributing factors of fatigue in patients with type 2 diabetes: A systematic review. Psychoneuroendocrinology. 2021; 130: 105280, doi: 10.1016/j.psyneuen.2021.105280, indexed in Pubmed: 34049018.
29. Park H, Park C, Quinn L, et al. Glucose control and fatigue in type 2 diabetes: the mediating roles of diabetes symptoms and distress. J Adv Nurs. 2015; 71(7): 1650–1660, doi: 10.1111/jan.12632, indexed in Pubmed: 25690988.
30. Aarthy R, Mikocka-Walus A, Pradeepa R, et al. Quality of Life and Diabetes in India: A Scoping Review. Indian J Endocrinol Metab. 2021; 25(5): 365–380, doi: 10.4103/ijem.ijem_336_21, indexed in Pubmed: 35300441.
31. Cai H, Li G, Zhang P, et al. Effect of exercise on the quality of life in type 2 diabetes mellitus: a systematic review. Qual Life Res. 2017; 26(3): 515–530, doi: 10.1007/s11136-016-1481-5, indexed in Pubmed: 27990609.
32. Esha K, Prajakta S, Ashok S, et al. Effect of alternate walking and yoga on blood sugar levels in type 2 diabetes. Indian Journal of Physiology and Pharmacology. 2019; 63(1): 16–20.
33. Praet SFE, van Rooij ESJ, Wijtvliet A, et al. Brisk walking compared with an individualised medical fitness programme for patients with type 2 diabetes: a randomised controlled trial. Diabetologia. 2008; 51(5): 736–746, doi: 10.1007/s00125-008-0950-y, indexed in Pubmed: 18297259.
34. Aylin K, Arzu D, Sabri S, et al. The effect of combined resistance and home-based walking exercise in type 2 diabetes patients. Int J Diabetes Dev Ctries. 2009; 29(4): 159–165, doi: 10.4103/0973-3930.57347, indexed in Pubmed: 20336198.
35. Morton RD, West DJ, Stephens JW, et al. Heart rate prescribed walking training improves cardiorespiratory fitness but not glycaemic control in people with type 2 diabetes. J Sports Sci. 2010; 28(1): 93–99, doi: 10.1080/02640410903365685, indexed in Pubmed: 20391086.

VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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# Heme Oxygenase-1 as Crucial Biomarker for Detecting Oxidative Stress and Some Parameters in a Sample of Obese Patients with and without Diabetes

## ABSTRACT

**Objective: Obesity is a significant contributor to various metabolic disorders, including type 2 diabetes (T2D), resulting in heightened oxidative stress. This study aims to examine the levels of heme oxygenase-1 (HO-1), their correlation with high-density lipoprotein (HDL) concentration, and their influence on the onset of T2D in obese individuals with diabetes.**

**Materials and methods: The study comprised 150 samples categorized into 3 groups, with each group further subdivided into 2 subgroups: males and females aged 30 to 65 years. Samples were collected at AL-Kindy Teaching Hospital. All sample variables for fasting subjects in every group were assessed. The colorimetric approach was employed for biochemical assays, encompassing fasting blood sugar (FBS) and lipid profiles. Insulin, HO-1, and dipeptidyl peptidase-4 (DPP-4) levels were also quantified using ELISA. Subsequently, we employed statistical analysis to elucidate the results.**

**Results: Compared to the obesity group, the HO-1 and HDL concentrations were higher in T2D with obesity [(18.0 ± 0.40), (39.86 ± 1.26) vs. (10.41 ± 0.74), (36.27 ± 0.85), with (ng/mL), (mg/dL), respectively]. The T2D with obesity group also showed higher insulin resistance compared to the obesity and control groups [(4.19 ± 0.874) vs. (1.21 ± 0.39), (0.74 ± 0.142)]. The diabetes with obesity male group had elevated HO-1 concentrations compared with the obesity male group, a result that also applied to females.**

**Conclusions: The T2D with obesity group had higher concentrations of the HO-1 enzyme than the obesity group. We found a positive association between higher HDL concentrations and increased enzyme concentrations in the T2D with obesity group. This enzyme may serve as a biomarker to predict the development of diabetes or the onset of other metabolic diseases. (Clin Diabetol 2024; 13, 6: 349–357)**

**Keywords: obesity, type 2 diabetes, heme oxygenase-1, dipeptidyl peptidase-4, oxidative stress**

## Introduction

It is well-acknowledged that obesity is a serious public health issue. Obesity raises the risk of heart disease, metabolic disorders, and some kinds of cancer. Obesity can harm pancreatic islet cells through chronic inflammation, in addition to causing metabolic abnormalities like insulin resistance (IR) and hyperglycemia [1]. Body mass index (BMI), defined as body mass divided by the square of body height and expressed in kilograms per square meter (kg/m$^2$), is used to deter-

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Clinical Diabetology 2024, 13; 6: 349–357
DOI: 10.5603/cd.101994
Received: 8.08.2024 Accepted: 29.10.2024
Early publication date: 16.12.2024

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mine obesity. It is divided into the following groups: (18.5–24.9) normal weight, (25–29.9) overweight, (30–34.9) obesity grade 1, (35–39.9) obesity grade 2, and ≥ 40 extremely severe obesity [2].

Diabetes is a metabolic disease characterized by impaired insulin action, insufficient insulin secretion, or both. It impairs protein, fat, and carbohydrate metabolism [3]. Higher concentrations of hormones, pro-inflammatory cytokines, glycerol, and non-esterified fatty acids are released by obese patients, which may contribute to the development of insulin resistance released by adipose tissue [4]. Insulin is a polypeptide hormone primarily secreted by β cells in the pancreas, namely in islets of Langerhans. To control blood glucose levels, the hormone works in tandem with glucagon; glucagon has catabolic effects, whereas insulin acts through anabolic pathways [5].

One of the numerous hereditary and environmental risk factors linked to obesity and type 2 diabetes (T2D) is oxidative stress. The body's ability to detoxify and generate reactive oxygen species (ROS) can be out of balance, leading to oxidative stress. Because obesity can cause oxidative stress and inflammation through a variety of cellular and metabolic pathways, there is a close relationship between obesity and oxidative stress [6]. Insulin signaling pathways and pancreatic beta cells are negatively impacted by oxidative stress in T2D, accelerating the disease's progression [7].

Heme oxygenase-1 (HO-1) is thought to be the only enzyme that enables cells to break down heme, a molecule that is a component of hemoglobin and other hemoproteins [8]. HO activity produces biliverdin (BV), ferrous iron (Fe2+), and carbon monoxide (CO), which can be made by cleaving heme. Biliverdin reductase (BVR) converts BV to bilirubin (BR) [9]. According to earlier research, by releasing these numerous molecules with anti-inflammatory and antioxidant qualities, HO-1 shields different tissues and organs from oxidative stress and heightened inflammatory reactions [10]. In humans, the absence of HO-1, also referred to as heat shock protein 32 (Hsp32), is linked to anemia among abnormalities in coagulation, early death, growth retardation, and increased iron deposition [8].

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that controls the metabolism of glucose, raising blood sugar levels in people with diabetes through the degradation of incretin hormones, including gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1). Upon consumption, various hormones generated from the stomach are produced [11, 12]. This study seeks to ascertain the concentration of the HO-1 enzyme, its correlation with high-density lipoproteins (HDL), and its impact on the progression of diabetes in obese individuals with T2D.

## Materials and methods

### Collecting, selecting, and analyzing samples

Samples were collected from AL-Kindy Teaching Hospital, and the study was carried out at the College of Science for Women, University of Baghdad, from September 2023 to December 2023. The study included 150 individuals with an age range of 30–65 years. The samples were divided as follows: The first group included 50 samples represented by the control group (healthy individuals) — 25 samples were taken from females and 25 from males. The second group included 50 samples represented by diabetes mellitus (DM) with obesity — 24 samples taken from males, and 26 samples taken from females. The third group included 50 samples, represented by the obesity group — 25 samples taken from females and 25 from males. Following a fasting period of 8 to 12 hours, a 7-mL blood sample was obtained from each participant. The samples were subsequently divided into 4 sections for necessary analyses, which encompassed quantifying the enzyme levels of HO-1, DPP-4, and insulin via ELISA (Cloud-Clone Corp.), as well as conducting additional biochemical assessments, including fasting blood glucose and lipid profile evaluations using linear reagents (S.L.U.). Furthermore, the following formula was employed to ascertain insulin resistance: The Homeostasis Model Assessment of Insulin Resistance (HOMA IR) was calculated as glucose multiplied by insulin divided by 405 (with glucose measured in mg/dL). Additionally, the BMI was determined using the formula: weight divided by height squared, and the waist-to-hip ratio (WHR) was assessed with a tape measure.

### Exclusion criteria

This study excluded the following individuals: thyroid patients and those with kidney disease, individuals suffering from heart disease, pregnant women, and patients using insulin injections to treat diabetes and diabetic complications.

### Statistical analysis

All statistical analyses were conducted using version 26.0 of the SPSS program. Pairwise post hoc comparisons were employed among many groups, alongside variance analysis (ANOVA), ROC curve analysis, and the correlation coefficient (r) between parameters. The data was exhibited using a normal distribution represented as mean ± standard error (SE). A p-value

**Table 1. Mean ± SE between patient and control groups with all parameters**

| Groups<br>Parameters | Control group<br>(N = 50) | Diabetes mellitus with obesity group<br>(N = 50) | Obesity group<br>(N = 50) | P-value |
|---|---|---|---|---|
| Age [year] | 38.30 ± 1.25 [a] | 51.96 ± 1.15 [c] | 44.20 ± 1.43 [b] | 0.001** |
| BMI [kg/m$^2$] | 23.35 ± 0.28 [a] | 33.52 ± 0.41 [b] | 34.49 ± 0.615 [b] | 0.001** |
| W/H ratio | 0.96 ± 0.031 [a] | 1.00 ± 0.014 [a] | 0.95 ± 0.018 [a] | 0.310 |
| FBS [mg/dL] | 96.87 ± 1.01 [a] | 194.24 ± 10.54 [b] | 100.74 ± 1.18 [a] | 0.001** |
| Insulin [μlU /mL] | 3.05 ± 0.584 [a] | 8.06 ± 1.39 [b] | 4.80 ± 1.54 [ab] | 0.018* |
| HOMA IR | 0.74 ± 0.142 [a] | 4.19 ± 0.874 [b] | 1.21 ± 0.39 [a] | 0.001** |
| TC [mg/dL] | 174.54 ± 2.75 [a] | 189.26 ± 7.68 [a] | 179.24 ± 3.83 [a] | 0.128 |
| TG [mg/dL] | 128.28 ± 3.72 [a] | 216.56 ± 19.82 [b] | 136.56 ± 6.06 [a] | 0.001** |
| HDL-C [mg/dL] | 42.42 ± 0.542 [b] | 39.86 ± 1.26 [b] | 36.27 ± 0.85 [a] | 0.001** |
| LDL-C [mg/dL] | 106.46 ± 2.70 [a] | 109.26 ± 7.0 [a] | 115.66 ± 3.34 [a] | 0.376 |
| VLDL-C [mg/dL] | 25.66 ± 0.74 [a] | 45.45 ± 4.39 [b] | 27.31 ± 1.21 [a] | 0.001** |
| HO-1 [ng/mL] | 15.20 ± 0.43 [b] | 18.0 ± 0.40 [c] | 10.41 ± 0.74 [a] | 0.001** |
| DPP-4 [ng/mL] | 15.55 ± 0.83 [b] | 7.71 ± 0.28 [a] | 6.48 ± 0.27 [a] | 0.001** |

**Significant difference between means using ANOVA -test at 0.01 level

BMI — body mass index; DPP-4 — dipeptidyl peptidase-4; FBS — fasting blood sugar; HDL-C — high-density lipoprotein cholesterol; HO-1 — heme oxygenase-1; HOMA IR — Homeostasis Model Assessment of Insulin Resistance; LDL-C — low-density lipoprotein cholesterol; SE — standard error; TC — total cholesterol; TG — triglycerides; VLDL-C — very low-density lipoprotein cholesterol; WHR — waist-to-hip ratio

≤ 0.05 indicated a significant difference, considered a statistical signal.

## Results

The results of age, BMI, fasting blood sugar (FBS), insulin, HOMA IR, triglycerides (TG), HDL cholesterol, very low-density lipoprotein cholesterol (VLDL-C), HO-1, and DPP-4 were significant ($p \leq 0.05$) between groups. The age showed a mean ± SE of 51.96 ± 1.15 years for DM with obesity and 44.20 ± 1.43 years for obesity, a high value compared with the control group, at 38.30 ± 1.25 years. The patient group showed a high BMI mean value for DM with obesity compared with the control group. As in Table 1, for FBS and HOMA IR for DM with obesity compared with obesity and control groups [(194.24 ± 10.54 mg/dL), (4.19 ± 0.874 mg/dL) vs. (100.74 ± 1.18 mg/dL) (1.21 ± 0.39 mg/dL), (96.87 ± ± 1.01 mg/dL) (0.74 ± 0.142 mg/dL)]. The statistical function showed a significant difference in the probability value of insulin in the DM with obesity group compared to the control group.

The results showed that there was a statistically significant increase in the p-value in triglycerides, HDL cholesterol, and (VLDL-C); the mean value ± SE increased significantly between groups, but there was no significant difference for total cholesterol and low-density lipoproteins (LDL). As in Table 1, the patients' group showed a mean value of triglycerides ± SE of 216.56 ± 19.82 mg/dL for DM with obesity, a high value compared to 136.56 ± 6.06 mg/dL for obesity, and the control group at 128.28 ± 3.72 mg/dL. While the HDL value was lower in obesity (36.27 ± 0.85 mg/dL) compared to DM with obesity (39.86 ± 1.26 mg/dL) and the control group (42.42 ± 0.542 mg/dL), the mean value of VLDL increased for DM with obesity compared to the obesity group and the control group. The mean value between groups increased significantly in HO-1 and DPP-4.

The patient groups showed an increase in the mean heme oxygenase-1 value ± SE (18.0 ± 0.40 ng/mL) for DM with obesity and a low value (10.41 ± 0.74 ng/dL) for obesity compared with the control group (15.20 ± ± 0.43 ng/dL). The mean value ± SE of DPP-4 decreased for (6.48 ± 0.27 ng/mL) obesity and (7.71 ± ± 0.28 ng/mL) DM with obesity compared to the control group (15.55 ± 0.83 ng/mL), as indicated in Table 1.

Table 2 shows the correlation of different parameter levels with HO-1 in groups. The results showed a positive correlation between HO-1 and BMI, insulin, and HOMA IR in the control group, DM and obesity, and a significantly positive correlation with HDL in DM with obesity. At the same time, there was a negative significant correlation in the control group and the obesity group, while a significant positive and strong correlation was seen between HO-1 and DPP-4 in DM with obesity.

**Table 2. Correlations between HO-1 and all parameters**

| | | Heme oxygenase-1 [ng/mL] | | |
|---|---|---|---|---|
| | | Control group (N = 50) | Diabetes mellitus with obesity group (N = 50) | Obesity group (N = 50) |
| Age [years] | r | 0.057 | –0.063 | –0.083 |
| | P | 0.692 | 0.666 | 0.567 |
| BMI [kg/m$^2$] | r | 0.298* | 0.462** | 0.115 |
| | P | 0.035 | 0.001 | 0.426 |
| WHR | r | 0.236 | –0.073 | 0.030 |
| | P | 0.099 | 0.615 | 0.837 |
| FBS [mg/dL] | r | 0.007 | 0.229 | 0.110 |
| | P | 0.963 | 0.109 | 0.449 |
| TC [mg/dL] | r | 0.200 | –0.005 | –0.005 |
| | P | 0.164 | 0.971 | 0.973 |
| TG [mg/dL] | r | 0.079 | –0.124 | 0.113 |
| | P | 0.584 | 0.389 | 0.434 |
| HDL-C [mg/dL] | r | –0.302* | 0.289* | –0.300* |
| | P | 0.033 | 0.041 | 0.034 |
| LDL-C [mg/dL] | r | 0.204 | –0.075 | 0.030 |
| | P | 0.155 | 0.607 | 0.837 |
| VLDL-C [mg/dL] | r | 0.001 | –0.160 | 0.113 |
| | P | 0.995 | 0.267 | 0.434 |
| Insulin [$\mu$IU /mL] | r | 0.319* | 0.497** | –0.027 |
| | P | 0.024 | 0.000 | 0.852 |
| HOMA IR | r | 0.314* | 0.456** | –0.036 |
| | P | 0.026 | 0.001 | 0.806 |
| DPP-4 [mg/dL] | r | –0.161 | 0.315* | 0.281* |
| | P | 0.265 | 0.026 | 0.048 |

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level

BMI — body mass index; DPP-4 — dipeptidyl peptidase-4; FBS — fasting blood sugar; HDL-C — high-density lipoprotein cholesterol; HO-1 — heme oxygenase-1; HOMA IR — Homeostasis Model Assessment of Insulin Resistance; LDL-C — low-density lipoprotein cholesterol; SE — standard error; TC — total cholesterol; TG — triglycerides; VLDL-C — very low-density lipoprotein cholesterol; WHR — waist-to-hip ratio

Alongside our study, which comprised a cohort of patients and healthy controls, a cross-sectional analysis was performed, including male and female patients. The male group with DM and obesity had a mean age ± SE of 53.16 ± 1.78 years, significantly higher than the obesity-only male group, at 43.20 ± 2.09 years, as depicted in Table 3. The average BMI values of the DM with obesity group comprising fat males and obese females exhibited a statistically significant difference. Obesity females exhibited a higher BMI than DM with obesity males, measuring 35.67 ± 0.85 vs. 32.32 ± ± 0.31 kg/m$^2$. The WHR in DM with obesity males was greater than that in obesity females. Results for FBS, insulin, and HOMA IR between male and female patients indicate that the mean ± SE of FBS in DM with obesity males was higher than that in obesity females. Additionally, the mean ± SE for DM and obesity females was greater than that for obesity females. Insulin and insulin resistance (HOMA IR) exhibited elevated mean ± SE values in DM with obesity females compared to their male counterparts, namely 10.42 ± 2.49 $\mu$IU/mL, 5.09 ± 1.50 $\mu$IU/mL vs. 1.75 ± 0.51 $\mu$IU/mL, 0.43 ± ± 0.12 $\mu$IU/mL, respectively.

The mean value ± SE increased significantly ($p \leq 0.05$) between groups concerning triglycerides, HDL, and VLDL, while no group showed a significant value ($p > 0.05$) for LDL and total cholesterol between groups. When comparing males and females in the patient group. The mean triglyceride values ± SE were highest in DM with obesity males compared to obesity males and obesity females. The values were 226.45 ± ± 33.24 mg/dL, 141.84 ± 9.63 mg/dL, and 131.28 ± ± 7.42 mg/dL, respectively. The mean HDL ± SE for females suffering from DM with obesity revealed a high value in comparison with DM with obesity males and obesity female groups (43.34 ± 1.87 vs. 36.08 ± 1.33, 36.54 ± 0.96 mg/dL). The DM with obesity male group showed a high mean value ± SE for VLDL compared with

**Table 3. Mean ± SE between males and females in patient groups with all parameters**

| Groups<br>Parameters | Diabetes mellitus with obesity male group (N = 24) | Diabetes mellitus with obesity female group (N = 26) | Obesity female group (N = 25) | Obesity male group (N = 25) | P-value |
|---|---|---|---|---|---|
| Age [year] | 53.16 ± 1.78 $^{c}$ | 50.84 ± 1.48 $^{bc}$ | 45.20 ± 1.98 $^{ab}$ | 43.20 ± 2.09 $^{a}$ | 0.001** |
| BMI [kg/m$^2$] | 32.32 ± 0.31 $^{a}$ | 34.62 ± 0.66 $^{ab}$ | 35.67 ± 0.85 $^{b}$ | 33.31 ± 0.83 $^{ab}$ | 0.007** |
| WHR | 1.03 ± 0.02 $^{b}$ | 0.97 ± 0.01 $^{ab}$ | 0.90 ± 0.009 $^{a}$ | 1.0 ± 0.03 $^{b}$ | 0.001** |
| FBS [mg/dL] | 202.16 ± 18.65 $^{b}$ | 186.92 ± 10.89 | 100.31 ± 1.66 $^{a}$ | 101.17 ± 1.72 a | 0.001** |
| Insulin [$\mu$IU /mL] | 5.51 ± 0.90 $^{ab}$ | 10.42 ± 2.49 $^{b}$ | 7.85 ± 2.95 $^{ab}$ | 1.75 ± 0.51 a | 0.023* |
| HOMA IR | 3.21 ± 0.80 $^{ab}$ | 5.09 ± 1.50 $^{b}$ | 1.97 ± 0.75 $^{ab}$ | 0.43 ± 0.12 a | 0.006** |
| TC [mg/dL] | 182.5 ± 9.92 $^{a}$ | 195.5 ± 11.64 $^{a}$ | 179.80 ± 5.86 $^{a}$ | 178.68 ± 5.06 $^{a}$ | 0.480 |
| TG [mg/dL] | 226.45 ± 33.24 $^{b}$ | 207.42 ± 23.13 $^{ab}$ | 131.28 ± 7.42 $^{a}$ | 141.84 ± 9.63 $^{a}$ | 0.003** |
| HDL-C [mg/dL] | 36.08 ± 1.33 $^{a}$ | 43.34 ± 1.87 $^{b}$ | 36.54 ± 0.96 $^{a}$ | 36.0 ± 1.42 $^{a}$ | 0.001** |
| LDL-C [mg/dL] | 104.29 ± 8.85 $^{a}$ | 113.84 ± 10.79 $^{a}$ | 117.0 ± 5.11 $^{a}$ | 114.31 ± 4.40 $^{a}$ | 0.689 |
| VLDL-C [mg/dL] | 46.19 ± 6.84 $^{c}$ | 44.76 ± 5.73 $^{bc}$ | 26.25 ± 1.48 $^{a}$ | 28.36 ± 1.92 $^{ab}$ | 0.002** |
| HO-1 [ng/mL] | 16.90 ± 0.62 $^{b}$ | 19.0 ± 0.46 $^{b}$ | 11.53 ± 0.84 $^{a}$ | 9.29 ± 1.19 $^{a}$ | 0.001** |
| DPP-4 [ng/mL] | 7.10 ± 0.38 $^{ab}$ | 8.26 ± 0.40 $^{b}$ | 6.53 ± 0.34 $^{a}$ | 6.43 ± 0.44 $^{a}$ | 0.004** |

**Significant difference between means using ANOVA -test at 0.01 level

BMI — body mass index; DPP-4 — dipeptidyl peptidase-4; FBS — fasting blood sugar; HDL-C — high-density lipoprotein cholesterol; HO-1 — heme oxygenase-1; HOMA IR — Homeostasis Model Assessment of Insulin Resistance; LDL-C — low-density lipoprotein cholesterol; SE — standard error; TC — total cholesterol; TG — triglycerides; VLDL-C — very low-density lipoprotein cholesterol; WHR — waist-to-hip ratio

**Table 4. ROC curve analysis of HO-1 between obesity and diabetes mellitus with obesity groups**

| Area under the curve | | | | | |
|---|---|---|---|---|---|
| Test result variable(s) | Area | Std. error[a] | Asymptotic Sig.[b] | Asymptotic 95% confidence interval | |
| | | | | Lower bound | Upper bound |
| Heme oxygenase-1 (ng/mL) | .886 | .036 | .000 | .816 | .956 |

HO-1 — heme oxygenase-1

[a]Under the nonparametric assumption; [b]Null hypothesis: true area = 0.5

the obesity male group. A high value for DM with obesity females was seen compared with the obesity male group.

Table 3 shows that the mean ± SE values of DM with obesity males, which is high compared with obesity males (16.90 ± 0.62 vs. 9.29 ± 1.19 ng/mL), and the mean for DM with obesity females is high compared to obesity females (19.0 ± 0.46 vs. 11.53 ± 0.84 ng/mL). The mean value increased for DPP-4 in DM with obesity females compared with obesity females and males (8.26 ± 0.40 vs. 6.53 ± 0.34 and 6.43 ± 0.44 ng/mL).

Table 4 presents the findings of the ROC analysis using the following parameters between the groups of obesity and DM with obesity. The area under the ROC curve (AUC) for OH-1 demonstrated good diagnostic accuracy with a value of 0.886. The cut-off value for OH-1 (16.30) and the sensitivity and specificity of HO-1 (0.70 and 0.16, respectively) are shown in Figure 1.

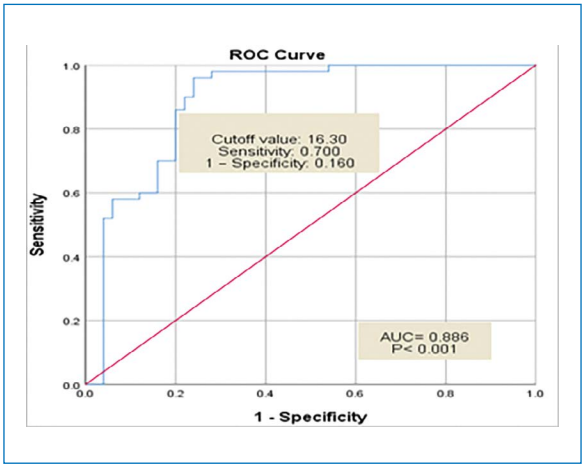


**Figure 1.** ROC curve analysis of HO-1 for obesity and diabetes mellitus with obesity group
AUC — area under the curve; HO-1 — heme oxygenase-1

## Discussion

Table 1 displays the results, revealing a statistically significant difference in BMI between the control and patient groups. The correlation between a higher body mass index and an increased risk of T2D is evident [13]. Obese patients who accumulate significant amounts of body fat have a higher likelihood of developing T2D because obesity influences both insulin action and B-cell function. This finding aligns with the research conducted by Klein et al. [14]. Research indicates that males exhibit a higher susceptibility to T2D compared to females, with diagnoses occurring at lower BMI levels in males than in females. The current study indicates, as illustrated in Table 3, that males with DM and obesity exhibit a lower BMI than females. Furthermore, it has been noted that men typically exhibit a greater tendency to accumulate weight in the abdominal area, whereas women are more inclined to store weight in the hips and thighs. There is a correlation between abdominal fat and an elevated risk of developing diabetes. The findings align with the research presented in study [15]. Furthermore, individuals with a high BMI exhibit a greater propensity for developing T2D, with women showing a higher likelihood than men. The results are consistent with the findings of previous research [16]. Furthermore, males exhibiting a higher waist-to-hip ratio demonstrate a greater vulnerability to insulin resistance and various metabolic irregularities compared to females. The results of our analysis corresponded with those of a previous study [17]. Our study's results indicate a statistically significant difference between the patient group and the healthy group, highlighting a notable association between the increasing risk of developing diabetes and advancing age. The probability of an individual developing heart disease generally increases as they age [18].

The results presented in Table 1 indicate that the average values of FBS, INS, and HOMA-IR show a significant upward trend in the DM with obesity group compared to both the control group and the obesity group ($p \leq 0.05$). The findings align with the research conducted by Abed et al. [19]. Obesity represents a significant risk factor for diabetes, closely linked to the phenomenon of insulin resistance. The adipose tissue in obese individuals secretes elevated levels of hormones, pro-inflammatory cytokines, glycerol, and non-esterified fatty acids, potentially playing a role in the onset of insulin resistance. Additionally, oxidative stress and lipodystrophy impact insulin resistance, as demonstrated in the research conducted by Wondmkun et al. [20]. Table 3 presents results showing that females experienced a greater increase in HOMA IR value compared to males. The study's findings are consistent with earlier research [21]. Although various research findings contradict our own, which indicate that men are more prone to developing obesity, insulin resistance, and hyperglycemia in response to nutritional challenges, it is evident that women exhibit distinct energy partitioning patterns in comparison to men. Fat and carbohydrates serve as fuel sources, facilitating energy storage in subcutaneous adipose tissues while safeguarding against visceral and ectopic fat accumulation. Women exhibit a greater insulin sensitivity than men do [22].

A previous study showed that DM with obesity has higher triglyceride levels than those with obesity, as indicated in a study conducted by Aljabri et al. [23], which was consistent with our current study, as displayed in Table 1. Individuals suffering from DM with obesity have higher levels of triglyceride deposition in non-adipose tissue. A decrease in HDL cholesterol was observed. Fat accumulation in the visceral and abdominal subcutaneous depots is strongly associated with the risk of metabolic and cardiovascular issues. The results are consistent with the study by Khalid Jaid et al. [24]. Advanced end products of inflammation, oxidative stress, and hyperglycemia induce dysregulation of HDL cholesterol in diabetes. This elevates the risk of cardiovascular disease. Our findings align with those of Abed et al. [25]. Table 3 indicates that triglyceride levels were elevated in obese males with DM compared to obese females, although HDL levels were greater in obese females than in males. Consequently, the findings of our research align with those of a prior study [23]. A greater amount of HDL further substantiates the advantageous benefits of estrogen.

The present research revealed that serum HO-1 concentrations were markedly elevated in individuals with DM accompanied by obesity compared to the control group. The findings of our research align with those presented by Bao et al. [26], which indicated a heightened level of HO-1 in the plasma of individuals diagnosed with T2D. The observed increase is thought to correlate with heightened oxidative stress in these individuals, stemming from the generation of significant quantities of free radicals capable of inflicting cellular damage. The elevation of the HO-1 enzyme is viewed as a component of the body's protective mechanism against oxidative stress and is crucial in mitigating disease complications.

Individuals with T2D and obesity demonstrate elevated HO-1 activity, which correlates with increased levels of plasma glucose, iron, and thiobarbituric acid reactive substances (TBARS), suggesting a potential rise in stress levels [27, 28]. Obese patients exhib-

ited reduced levels of HO-1 when compared to the healthy group. The increase in ROS production leads to a reduction in HO-1 levels. This increases the likelihood of developing metabolic syndrome associated with obesity [29]. In this study, it was observed that diabetic males with obesity exhibited elevated levels of the enzyme HO-1 compared to their non-diabetic obese counterparts, and a similar pattern was noted among females. HO-1 serves as the body's primary line of defense against oxidative stress. This enzyme plays a crucial role in the regulation of adipogenesis, a process that is significant in the development of obesity and contributes to the reduction of oxidative stress. Our findings indicate a correlation between obesity and metabolic syndrome in obese females and the presence of inflammation, which subsequently elevates reactive oxygen species (ROS) levels. The oxidant assault increases isoprostane levels and leads to the oxidation of HDL (Ox-HDL) [15]. Table 2 illustrates a correlation between HO-1 enzyme concentration and HDL levels in the context of DM accompanied by obesity. Men experiencing metabolic syndrome and aging demonstrate elevated rates of morbidity and mortality. Lower levels of stress proteins, particularly intracellular HO-1, contribute to their increased susceptibility to illness [30]. Numerous studies utilizing animal models and data from individuals with insufficient HO-1 indicate its significant role in various clinical scenarios characterized by elevated inflammation and oxidative stress levels. Pharmacological therapy aimed at stimulating HO-1 production represents a novel and promising strategy for the management of inflammatory diseases [16].

Research suggests that DM accompanied by obesity may have elevated DPP-4 levels. Elevated DPP-4 levels may diminish the efficacy of incretins, resulting in reduced insulin secretion and glucose intolerance [31]. This contrasts with our findings: Vildagliptin, an oral medication for T2D, reduced DPP-4 levels. These pharmaceuticals are referred to as DPP-4 inhibitors, functioning by inhibiting the enzyme DPP-4 from degrading incretin hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Consequently, these drugs elevate GIP and GLP-1 levels, enhancing glucose control by augmenting insulin secretion and diminishing glucagon secretion [32]. Studies have shown that DPP-4 inhibitors protect cells against several diabetes-related problems affecting the kidneys, liver, heart, retina, and neurons [33]. In comparison to obese females and obese males, the cohort of DM with obese females had a higher mean value of DPP-4. The conclusions of the investigation correspond with those of a prior study [34].

Table 4 indicates that the ROC analysis of HO-1 produced favorable outcomes. This suggests that this enzyme could serve as a biomarker for predicting the progression of diabetes or the emergence of other metabolic disorders.

## Conclusions

DM associated with obesity demonstrated a higher concentration of the HO-1 enzyme in comparison to the obesity group alone. Male subjects with DM and obesity exhibited higher levels of the HO-1 enzyme compared to their male counterparts who had obesity without diabetes. Obese females with DM exhibited higher enzyme concentrations compared to their non-diabetic counterparts. This increase can be linked to the enzyme's antioxidant and anti-inflammatory properties, which potentially reduces the risk of T2D and other metabolic disorders. A positive correlation was identified with HDL, indicating that higher HDL levels were associated with increased enzyme concentrations in individuals with DM in the obese group. This enzyme could serve as a potential indicator for predicting the advancement of diabetes or the onset of various metabolic disorders.

## Article information

### Data availability statement

All research data are accessible on reasonable inquiry.

### Ethics statement

The Declaration of Helsinki's ethical guidelines guided the research. We conducted the procedure after obtaining the patients' verbal and analytical consent prior to sample collection. The research protocol, subject information, and permission form underwent assessment and approval by the local Ethical Committee at the University of Baghdad.

### Author contributions

Mays Mohammed Abdullah was responsible for collecting samples, conducting analysis, interpreting data, writing the manuscript, and proofreading it. Fayhaa Muqdad Khaleel conceived the idea, supervised the research, and read the manuscript.

### Funding

There is no financial support or sponsorship from any institute.

## Acknowledgments

The authors acknowledge with sincere gratitude all staff of "AL-Kindy Teaching Hospital" for their help in obtaining samples for the current study.

## Conflict of interest

The authors declare no conflict of interest.

## REFERENCES

1. Abdulrahman M, Elbakry S, Samy N, et al. Pregnancy outcome in a cohort of Egyptian women with rheumatoid arthritis. The Egyptian Rheumatologist. 2020; 42(2): 83–87, doi: 10.1016/j.ejr.2019.11.001.
2. Mohammed AH, Nadr JH. Early complications associated with obesity following coronary artery bypass graft surgery. J Fac Med Baghdad. 2021; 63(4): 158–162, doi: 10.32007/jfacmedbagdad.6341877.
3. Zaid A, Al-Yassin HD. Correlation of Serum levels of Chromium, Copper, and Manganese with the Glucose levels in Type 2 Diabetes Mellitus in Iraq. Journal of the Faculty of Medicine Baghdad. 2024; 65(4), doi: 10.32007/jfacmedbagdad.2126.
4. Wondmkun YT. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes Metab Syndr Obes. 2020; 13: 3611–3616, doi: 10.2147/DMSO.S275898, indexed in Pubmed: 33116712.
5. Rahman MdS, Hossain KS, Das S, et al. Role of Insulin in Health and Disease: An Update. Int J Mol Sci. 2021; 22(12), doi: 10.3390/ijms22126403, indexed in Pubmed: 34203830.
6. Wang L, Tang J, Wang L, et al. Oxidative stress in oocyte aging and female reproduction. J Cell Physiol. 2021; 236(12): 7966–7983, doi: 10.1002/jcp.30468, indexed in Pubmed: 34121193.
7. Yaribeygi H, Sathyapalan T, Atkin SL, et al. Molecular Mechanisms Linking Oxidative Stress and Diabetes Mellitus. Oxid Med Cell Longev. 2020; 2020: 8609213, doi: 10.1155/2020/8609213, indexed in Pubmed: 32215179.
8. Wegiel B, Nemeth Z, Correa-Costa M, et al. Heme oxygenase-1: a metabolic nike. Antioxid Redox Signal. 2014; 20(11): 1709–1722, doi: 10.1089/ars.2013.5667, indexed in Pubmed: 24180257.
9. Mohammed NA, Khaleel FM. Studying the Role of Heme Oxygenase-1 in Obese Patients. Baghdad Science Journal. 2024; 21(7): 8406, doi: 10.21123/bsj.2023.8406.
10. Yachie A. Heme Oxygenase-1 Deficiency and Oxidative Stress: A Review of 9 Independent Human Cases and Animal Models. Int J Mol Sci. 2021; 22(4), doi: 10.3390/ijms22041514, indexed in Pubmed: 33546372.
11. Shao DW, Zhao LJ, Sun JF. Synthesis and clinical application of representative small-molecule dipeptidyl Peptidase-4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus (T2DM). Eur J Med Chem. 2024; 272: 116464, doi: 10.1016/j.ejmech.2024.116464, indexed in Pubmed: 38704940.
12. Huang J, Liu X, Wei Y, et al. Emerging Role of Dipeptidyl Peptidase-4 in Autoimmune Disease. Front Immunol. 2022; 13: 830863, doi: 10.3389/fimmu.2022.830863, indexed in Pubmed: 35309368.
13. Jaid H, Khaleel F, Salman I, et al. Estimation of Apelin Levels in Iraqi Patients with Type II Diabetic Peripheral Neuropathy. Baghdad Science Journal. 2023; 20(5): 1684, doi: 10.21123/bsj.2023.7566.
14. Klein S, Gastaldelli A, Yki-Järvinen H, et al. Why does obesity cause diabetes? Cell Metab. 2022; 34(1): 11–20, doi: 10.1016/j.cmet.2021.12.012, indexed in Pubmed: 34986330.
15. Roche MM, Wang PP. Factors associated with a diabetes diagnosis and late diabetes diagnosis for males and females. J Clin Transl Endocrinol. 2014; 1(3): 77–84, doi: 10.1016/j.jcte.2014.07.002, indexed in Pubmed: 29159087.
16. Censin JC, Peters SAE, Bovijn J, et al. Causal relationships between obesity and the leading causes of death in women and men. PLoS Genet. 2019; 15(10): e1008405, doi: 10.1371/journal.pgen.1008405, indexed in Pubmed: 31647808.
17. Mirzaei M, Khajeh M. Comparison of anthropometric indices (body mass index, waist circumference, waist to hip ratio and waist to height ratio) in predicting risk of type II diabetes in the population of Yazd, Iran. Diabetes Metab Syndr. 2018; 12(5): 677–682, doi: 10.1016/j.dsx.2018.04.026, indexed in Pubmed: 29680518.
18. Otto T, Diesing J, Borchert J, et al. Age-dependent prevalence of type 2 diabetes, cardiovascular risk profiles and use of diabetes drugs in Germany using health claims data. Diabetes Obes Metab. 2023; 25(3): 767–775, doi: 10.1111/dom.14924, indexed in Pubmed: 36457132.
19. Abed BA, Farhan LO, Dawood AS. Relationship between serum Nesfatin-1, Adiponectin, Resistin Concentration, and Obesity with Type 2 Diabetes Mellitus. Baghdad Science Journal. 2024; 21(1): 117–123, doi: 10.21123/bsj.2023.8119.
20. Wondmkun YT. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes Metab Syndr Obes. 2020; 13: 3611–3616, doi: 10.2147/DMSO.S275898, indexed in Pubmed: 33116712.
21. Yang Y, Zhang Y, Wang J, et al. Sex Differences in the Association of HOMA-IR Index and BDNF in Han Chinese Patients With Chronic Schizophrenia. Front Psychiatry. 2021; 12: 656230, doi: 10.3389/fpsyt.2021.656230, indexed in Pubmed: 34234699.
22. Tramunt B, Smati S, Grandgeorge N, et al. Sex differences in metabolic regulation and diabetes susceptibility. Diabetologia. 2020; 63(3): 453–461, doi: 10.1007/s00125-019-05040-3, indexed in Pubmed: 31754750.
23. Aljabri K, Bokhari S, Akl A. The relation between overweight, obesity and plasma lipids in Saudi adults with type 2 diabetes. Journal of Health Specialties. 2016; 4(2): 140, doi: 10.4103/1658-600x.179817.
24. Jaid HK, Khaleel FM, Salman IN, et al. Evaluation of Insulin Resistance and Glutathione-S-transferase in Iraqi Patients with Type 2 Diabetes Mellitus and Diabetic Peripheral Neuropathy. Ibn AL-Haitham Journal For Pure and Applied Sciences. 2022; 35(4): 194–205, doi: 10.30526/35.4.2916.
25. Abed BA, Hamid GS. Evaluation of Lipocalin-2 and Vaspin Levels in In Iraqi Women with Type 2 Diabetes Mellitus. Iraqi J Sci. 2022; 63(11): 4650–4658, doi: 10.24996/ijs.2022.63.11.3.
26. Bao W, Song F, Li X, et al. Plasma heme oxygenase-1 concentration is elevated in individuals with type 2 diabetes mellitus. PLoS One. 2010; 5(8): e12371, doi: 10.1371/journal.pone.0012371, indexed in Pubmed: 20811623.
27. Andrews M, Leiva E, Arredondo-Olguín M. Short repeats in the heme oxygenase 1 gene promoter is associated with increased levels of inflammation, ferritin and higher risk of type-2 diabetes mellitus. J Trace Elem Med Biol. 2016; 37: 25–30, doi: 10.1016/j.jtemb.2016.06.001, indexed in Pubmed: 27473828.
28. Song F, Li X, Zhang M, et al. Association between heme oxygenase-1 gene promoter polymorphisms and type 2 diabetes in a Chinese population. Am J Epidemiol. 2009; 170(6): 747–756, doi: 10.1093/aje/kwp196, indexed in Pubmed: 19696228.
29. McClung JA, Levy L, Garcia V, et al. Heme-oxygenase and lipid mediators in obesity and associated cardiometabolic diseases: Therapeutic implications. Pharmacol Ther. 2022; 231: 107975, doi: 10.1016/j.pharmthera.2021.107975, indexed in Pubmed: 34499923.
30. Chekol GZ, Mengistu D, Tadesse AW. Is the Duration of Diabetes Diseases Positively Associated With Knowledge About Diabetic Complications? Knowledge of Diabetes Mellitus Complications and Associated Factors Among Type-2 Diabetic Patients in Public Hospitals of Addis Ababa, 2020. Front Public Health. 2021; 9: 812586, doi: 10.3389/fpubh.2021.812586, indexed in Pubmed: 35265583.

31. Sarkar J, Nargis T, Tantia Om, et al. Increased Plasma Dipeptidyl Peptidase-4 (DPP4) Activity Is an Obesity-Independent Parameter for Glycemic Deregulation in Type 2 Diabetes Patients. Front Endocrinol (Lausanne). 2019; 10: 505, doi: 10.3389/fendo.2019.00505, indexed in Pubmed: 31402899.
32. Deacon CF. Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. Front Endocrinol (Lausanne). 2019; 10: 80, doi: 10.3389/fendo.2019.00080, indexed in Pubmed: 30828317.
33. Bae EJu. DPP-4 inhibitors in diabetic complications: role of DPP-4 beyond glucose control. Arch Pharm Res. 2016; 39(8): 1114–1128, doi: 10.1007/s12272-016-0813-x, indexed in Pubmed: 27502601.
34. Tahara N, Yamagishi Si, Takeuchi M, et al. Serum levels of advanced glycation end products (AGEs) are independently correlated with circulating levels of dipeptidyl peptidase-4 (DPP-4) in humans. Clin Biochem. 2013; 46(4-5): 300–303, doi: 10.1016/j.clinbiochem.2012.11.023, indexed in Pubmed: 23219738.

VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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# Study of the Relationship between the Condition of Periodontal Tissues and Bone Mineral Density in People with Newly Diagnosed Type 2 Diabetes

## ABSTRACT

**Objective: The aim of the study was to assess the relationship between the condition of periodontal tissues and reduced bone mineral density (BMD) in patients with newly diagnosed type 2 diabetes (T2D).**

**Materials and methods: A group of 108 patients with newly diagnosed T2D, up to 3 months after diagnosis, were included in the study. Smoking patients were excluded from the study. The patients underwent a periodontal examination, a blood test, and densitometry on the same day. The results were then subjected to statistical analysis by the PQStat v. 1.6.8. program using the Spearman test, as well as multivariate analysis by logistic regression. The threshold of significance was $p < 0.05$.**

**Results: A group of 103 patients with newly diagnosed T2D were qualified for the study, including 38 women (36.9%) and 65 men (63.1%). The mean age of the patients was 56.5 years (SD = 13.0 years). In the group of women, the relationship between bone density and clinical attachment loss (CAL) was statistically significant also after taking age into account. The correlation between CAL and femoral neck density was so strong that, when taking it into account, age did not show a statistically significant relationship. The density of the femoral neck showed a strong relationship with the number of missing teeth, completely dominating the importance of age.**

**Conclusions: It was shown that the degree of periodontal disease in the group of women with newly diagnosed T2D was affected by reduced BMD, regardless of age. (Clin Diabetol 2024; 13, 6: 358–365)**

**Keywords: periodontitis, bone mineral density, newly diagnosed type 2 diabetes**

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Clinical Diabetology 2024, 13; 6: 358–365
DOI: 10.5603/cd.99682
Received: 6.03.2024 Accepted: 3.10.2024
Early publication date: 18.11.2024

## Introduction

Due to bone loss in both periodontitis and osteoporosis, it was considered highly likely that systemic bone loss could contribute to periodontal tissue destruction. In a meta-analysis of studies on the relationship between periodontal disease and osteoporosis, it was shown that patients suffering from osteoporosis are significantly exposed to periodontitis (the risk of periodontitis increased by 70%), and this risk is higher in women [1]. The patho-

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genesis of this relationship is believed to be a decrease in jaw bone density [2], which is the result of systemic, simultaneous bone resorption, due to inflammatory mediators (IL-1, TNF-α, RANKL), stimulating osteoclastogenesis, genetic conditions, and susceptibility to bone resorption associated with inflammation [3]. However, the exact pathomechanism has not been proven. The correlation between type 2 diabetes (T2D) and osteoporosis has been a subject of research for many years. People with T2D have increased risk of bone fractures compared to people without diabetes. This higher risk of fractures may occur with normal or even increased bone mineral density (BMD) because of poorer bone quality in patients with T2D [4, 5]. The pathophysiological mechanisms underlying increased risk of osteoporotic fractures in the population of patients with T2D are complex. The main ones include chronic hyperglycemia and accumulation of collagen glycation end products (AGEs), insulin resistance, bone marrow adiposity, numerous cytokines, adipokines, oxidative stress, and reduced concentration of hydrogen sulfide [6, 7]. Disease duration, glycemic control, and the presence of chronic complications (retinopathy, nephropathy, macroangiopathy) are predictors of osteoporotic fractures. Antidiabetic drugs are also of significance for bone tissue metabolism [4].

The primary outcome of this study was to analyze the relationship between periodontal disease severity, as represented by clinical attachment loss (CAL), and neck-femur BMD, including patients' age and gender as potential confounders.

The secondary outcomes included the relationship between other indices of periodontal state [plaque index (PI), bleeding index (BI), pocket depth (PD), number of deep pockets with bleeding, and tooth loss as a general indication of poor oral health] and 3 indices describing BMD: neck-femur BMD, femur total BMD, and L1–L4 BMD, as well as biochemical parameters related to the BMD [calcium (Ca), phosphorus (P), parathyroid hormone (PTH), and vitamin D3 levels].

## Materials and methods

### Subjects

The study group consisted of patients hospitalized at the Department of Internal Medicine, Endocrinology, and Diabetology of the Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw and patients of the Diabetes Clinic of this hospital. The maximum time since diagnosis of T2D was 3 months. A group of 103 patients with newly diagnosed T2D was qualified for the study, including 38 women (36.9%) and 65 men (63.1%). The mean age of the patients was 56.5 years (SD = 13.0 years). Smoking patients were excluded from the study. The mean body mass index (BMI) was 29.1 kg/m$^2$ (SD = 4.3). The percentage of overweight (BMI 25.0–29.99 kg/m$^2$) and obese (BMI ≥ 30 kg/m$^2$) patients was 43% and 40.5%, respectively, among newly diagnosed ones. All tests were carried out in accordance with the provisions of the Helsinki Declaration of 1973 (updated in 2002). A positive opinion was obtained from the Ethics and Supervision Committee for Research on Humans and Animals of the Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw (10/2012). All patients were presented with a study information form, and their written consent for the study was obtained.

### Study design

The patients underwent a detailed periodontal examination. It was performed in artificial light, using a dental mirror and a Hu-Friedy PCP-15 UNC probe, calibrated every 1 mm, each time with force not exceeding 0.25 N (25 g). The patients also underwent a blood test and densitometry on the same day.

### Data collection

The following parameters were rated in periodontal examination: number of teeth, presence or absence of plaque on 4 tooth surfaces - mesial, distal, buccal, and palatal, simplified PI according to O' Leary [8] was calculated, presence or absence of bleeding during probing at 4 points around the tooth — mesially, centrally, and distally from the buccal side and centrally from the oral cavity, and then the bleeding rate was calculated — bleeding on probing (BOP) (%), according to Ainamo and Bay [9], PD at 6 points around the tooth — mesially, centrally, distally from the buccal side and mesially, centrally, and distally from the oral cavity. Pocket depth was defined as the distance from the bottom of the pocket, assessed by probing, to the gingival margin. The location of the connective tissue attachment — CAL at 6 points around teeth — 3 measurement points on the buccal surface (mesial, central, distal) and similarly 3 points on the palatal/lingual surface (mesial, central, distal). Measurement of connective tissue attachment was defined as the distance from the bottom of the pocket, assessed by probing, to the cementoenamel junction [10].

In the general blood test, basic morphological and biochemical parameters were determined, as well as the level of glycemia (mg/dL) and concentration of glycated hemoglobin (HbA1c). The following values were considered the norm: fasting glucose < 100 mg/dL; HbA1c ≤ 6.5%. Additionally, the following were determined: the level of acute phase protein — C-reactive protein (normal 0–5 mg/L); Ca (norm 2.1–2.6 mmol/L); P (normal 0.8–1.4 mmol/L); PTH (normal 10–60 pg/mL); and vitamin D3 (norm 31–50 ng/mL).

In densitometric examination, the following parameters of measurable BMD were determined: neck-femur

**Table 1. Comparison of Age, BMI, and Laboratory Parameters Depending on Gender (Mann-Whitney Test) and Age (Spearman Test)**

| | Total (n = 103) | Men (n = 65) | Women (n = 38) |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | Mean ± SD |
| Age | 56.5 ± 13.0 | 56.6 ± 12.6 | 56.4 ± 13.8 |
| BMI | 29.1 ± 4.3 | 28.3 ± 3.9 | 30.7 ± 4.7 |
| WBC | 6.9 ± 1.7 | 7.1 ± 1.7 | 6.5 ± 1.6 |
| Fasting blood glucose | 163.7 ± 85.8 ** | 177.1.2 ± 94.0* | 142.6 ± 67.0 |
| HbA1c | 8.3 ± 2.6 ** | 8.6 ± 2.5 * | 7.7 ± 2.7 |
| Cholesterol | 187.2 ± 57.5 ** | 185.9 ± 63.7 | 189.2 ± 46.2 |
| HDL | 47.0 ± 15.4 ** | 44.3 ± 13.3* | 51.5 ± 17.5 |
| LDL | 106.4 ± 50.3** | 105.9 ± 56.7 | 107.2 ± 38.4 |
| Triglycerides | 187.0 ± 218.8** | 203.1 ± 256.1 | 160.4 ± 136.1 |
| Ca | 2.3 ± 0.2 | 2.3 ± 0.2 | 2.4 ± 0.1 |
| P | 3.4 ± 0.6 ** | 3.3 ± 0.6 | 3.6 ± 0.5* |
| PTH | 38.0 ± 21.9 | 35.6 ± 18.9 | 41.8 ± 25.8 |
| Vit. D3 | 14.4 ± 7.0 | 14.3 ± 6.9 | 14.5 ± 7.4 |
| CRP | 9.6 ± 19.5 | 6.9 ± 12.5 | 15.4 ± 29.1 |
| ALT | 46.6 ± 50.0** | 52.4 ± 60.7 | 36.8 ± 20.3 |
| AST | 37.1 ± 41.6 | 41.8 ± 51.1 | 29.3 ± 13.0 |
| Neck-Femur BMD | 0.99 ± 0.14** | 1.01 ± 0.13 | 0.96 ± 0.14 |
| Femur total BMD | 1.08 ± 0.15** | 1.12 ± 0.13 | 1.02 ± 0.15* |
| L1–L4 BMD | 1.21 ± 0.18 | 1.24 ± 0.17 | 1.15 ± 0.18* |

*p-value < 0.05 comparison depending on gender (Mann-Whitney test); **p-value < 0.05 comparison depending on age (Spearman test) — relationships were statistically inverse with the exception of the HDL parameter
ALT — alanine transaminase; AST — aspartate transaminase; BMD — bone mineral density; BMI — body mass index; Ca — calcium; CRP — C-reactive protein; HbA1c — glycated hemoglobin; HDL — high-density lipoprotein; LDL — low-density lipoprotein; P — phosphorus; PTH — parathyroid hormone; SD — standard deviation; WBC — white blood cells

BMD — mineral density of the femur neck, femur total BMD — femur mineral density, and L1–L4 BMD — bone mineral density of lumbar spine.

## Statistical analysis

The results obtained from the periodontal examination, blood test, and densitometric examination were then subjected to statistical analysis by PQStat v. 1.6.8. software using the Mann-Whitney U test, Spearman test, and multivariate analysis by logistic regression. The threshold of significance was $p < 0.05$. The minimum sample size calculated using G*Power software (power 0.80, alpha 0.05) for correlation analysis was 67 participants.

## Results

The study group was characterized by an unsatisfactory condition of periodontal tissues, in particular the large number of lost teeth (median of 9 lost teeth), number of pockets ≥ 4 and ≥ 4 with associated bleeding (median of 10 and 4 pockets per person, respectively), as well as CAL (median 3 mm) and BOP (average 27.1%). These parameters mostly correlated significantly with the age of patients in the study group but did not differ depending on gender. In the study group, women had significantly higher BMI, high-density lipoproteins (HDL), and values of P concentration. The level of phosphorus also decreased with the age of patients. Men, however, had higher glycemia and HbA1c levels (Tab. 1).

Mineral density of the femoral neck, femur, and lumbar spine (L1–L4) decreased with age. In addition, the densities of the femur and lumbar spine (L1–L4) were significantly lower in women than in men (Tab. 1).

An inverse correlation was found between bone density and clinical attachment loss and the number of lost teeth (for neck-femur BMD also with median PD) (Tab. 2).

All these parameters are age-dependent; therefore, multi-factor models have been developed that also take age into account. Due to the differences in the results of the densitometric examination between men and women, the analysis was carried out separately for each sex (Tab. 2–4).

After adjusting for age, bone density was not independently correlated with loss of attachment position in the male group.

**Table 2. Correlation of Periodontal Parameters with Biochemical and Densitometric Parameters (Spearman Correlation Analysis)**

| | Ca | P | PTH | Vit. D3 | Neck-Femur BMD | Femur total BMD | L1–L4 BMD |
|---|---|---|---|---|---|---|---|
| Number of missing teeth | r = –0.05 | r = –0.07 | r = –0.16 | r = 0 | r = –0.39* | r = –0.27* | r = –0.10 |
| PI | r = –0.03 | r = –0.08 | r = –0.11 | r = 0.11 | r = –0.07 | r = –0.02 | r = –0.03 |
| BI | r = –0.05 | r = –0.17* | r = –0.10 | r = 0 | r = –0.14 | r = 0 | r = –0.08 |
| PD mean | r = –0.04 | r = –0.07 | r = –0.09 | r = –0.03 | r = –0.15 | r = –0.08 | r = –0.13 |
| PD median | r = –0.07 | r = –0.02 | r = –0.15 | r = –0.01 | r = –0.24 * | r = –0.18 | r = –0.19 |
| PD ≥ 4 mm (number) | r = 0.03 | r = –0.08 | r = 0.10 | r = –0.08 | r = 0 | r = 0.06 | r = –0.01 |
| PD ≥ 4 mm (%) | r = –0.02 | r = –0.09 | r = 0 | r = –0.07 | r = –0.18 | r = –0.10 | r = –0.08 |
| PD ≥ 4 mm + BOP (number) | r = 0 | r = –0.10 | r = 0.03 | r = –0.03 | r = 0.01 | r = 0.11 | r = 0.02 |
| PD ≥ 4 mm + BOP (%) | r = –0.04 | r = –0.11 | r = –0.03 | r = –0.03 | r = –0.10 | r = 0 | r = –0.02 |
| CAL mean | r = –0.03 | r = –0.10 | r = –0.14 | r = 0.02 | r = –0.44* | r = –0.29* | r = –0.25* |
| CAL median | r = –0.05 | r = –0.08 | r = –0.15 | r = 0.07 | r = –0.43* | r = –0.32* | r = –0.31* |

*p value < 0.05; Spearman correlation analysis
BI — bleeding index; BOP — bleeding on probing; BMD — bone mineral density; CAL — clinical attachment loss; PD — pocket depth; PI — plaque index; PTH — parathyroid hormone

**Table 3. Analysis of the Relationship between Median CAL, Age, and Bone Mineral Density Using Linear Regression, and between the Number of Missing Teeth, Age, and Bone Mineral Density Using Linear Regression in the Group of Women**

| **Women** | | | | | |
|---|---|---|---|---|---|
| **Missing teeth** | | | **Median CAL** | | |
| **P-value for the model: < 0.0001** | | | **P-value for the model: 0.0001** | | |
| **$R^2$ = 0.56** | | | **$R^2$ = 0.46** | | |
| | **Standardized coefficient β** | **P-value** | | **Standardized coefficient β** | **P-value** |
| Intercept | | 0.003 | Intercept | | 0.0588 |
| Age | 0.2 | 0.1893 | Age | 0.31 | 0.0651 |
| Neck-Femur BMD | –0.62 | 0.0002 | Neck–Femur BMD | –0.45 | 0.0085 |
| P-value for the model: < 0.0001 | | | P-value for the model: 0.0003 | | |
| $R^2$ = 0.48 | | | $R^2$ = 0.42 | | |
| | **Standardized coefficient β** | **P-value** | | **Standardized coefficient β** | **P-value** |
| Intercept | | 0.0427 | Intercept | | 0.2012 |
| Age | 0.37 | 0.0156 | Age | 0.43 | 0.0074 |
| Femur total BMD | –0.46 | 0.0032 | Femur total BMD | –0.34 | 0.0313 |
| P-value for the model: < 0,0001 | | | P-value for the model: 0.0009 | | |
| $R^2$ = 0,50 | | | $R^2$ = 0.36 | | |
| | **Standardized coefficient β** | **P–value** | | **Standardized coefficient β** | **P-value** |
| Intercept | | 0.053 | Intercept | | 0.8566 |
| Age | 0.51 | 0.0004 | Age | 0.56 | 0.0005 |
| L1–L4 BMD | –0.46 | 0.0011 | L1–L4 BMD | –0.19 | 0.1872 |

BMD — bone mineral density; CAL — clinical attachment loss

In the group of women, however, the relationship between bone density and attachment loss remained statistically significant also after taking age into account. The correlation with the density of femoral neck was so strong that when age was taken into account, it did not show a statistically significant relationship (Tab. 3).

Similarly, the number of lost teeth in men did not depend on bone density, but only on age (Tab. 4).

In the group of women, the results were not so clear. The density of the femoral neck showed a strong relationship with the number of lost teeth, completely dominating the importance of age. Examination of the proximal femur as a whole correlated with the number

**Table 4. Analysis of the Relationship between the Number of Missing Teeth, Age, and Bone Mineral Density Using the Linear Regression Method, and between Median CAL, Age, and Bone Mineral Density Using Linear Regression in the Group of Men**

| **Men** | | | | |
|---|---|---|---|---|
| **Missing teeth** | | | **Median CAL** | |
| **P-value for the model: 0.0002** | | | | |
| **$R^2$ = 0.30** | | | | |
| | **Standardized coefficient β** | **P-value** | **Standardized coefficient β** | **P-value** |
| Intercept | | 0.4116 | | 0.4116 |
| Age | 0.54 | 0.0002 | 0.54 | 0.0002 |
| Neck-Femur BMD | –0.02 | 0.9008 | –0.02 | 0.9008 |
| P-value for the model: 0.0002 | | | | |
| $R^2$ = 0.30 | | | | |
| | **Standardized coefficient β** | **P-value** | **Standardized coefficient β** | **P-value** |
| Intercept | | 0.2629 | | 0.2629 |
| Age | 0.55 | < 0.0001 | 0.55 | < 0.0001 |
| Femur total BMD | 0.02 | 0.9022 | 0.02 | 0.9022 |
| P-value for the model: < 0.0001 | | | | |
| $R^2$ = 0.33 | | | | |
| | **Standardized coefficient β** | **P-value** | **Standardized coefficient β** | **P-value** |
| Intercept | | 0.9156 | | 0.9156 |
| Age | 0.52 | < 0.0001 | 0.52 | < 0.0001 |
| L1–L4 BMD | –0.19 | 0.1229 | –0.19 | 0.1229 |

BMD — bone mineral density; CAL — clinical attachment loss

of missing teeth, with age also being a significant risk factor. The result of the bone density test in the lumbar spine did not significantly modify the relationship between the number of lost teeth and age (Tab. 3).

There was no relationship between BMD and selected biochemical parameters related to bone tissue, as well as glucose and HbA1c levels (Tab. 1).

Among the biochemical parameters, a statistically significant correlation was observed only for the bleeding index and phosphorus — higher values of the bleeding index were accompanied by lower levels of phosphorus in the patients' blood (Tab. 1).

## Discussion

The relationship between BMD reduction and periodontal tissue condition, and between bone density and diabetes, has been extensively reported [2–6]. However, there are few studies describing reduced bone density in patients with T2D and periodontitis. Numerous studies [11–15] show a positive correlation between systemic BMD and oral bone loss. Given these results, this study hypothesizes that decreased systemic BMD associated with osteopenia or osteoporosis may affect alveolar bone microarchitecture, possibly affecting the rate of periodontal tissue destruction in periodontitis.

Studies examining the relationship between BMD and periodontitis have used different sites to assess systemic mineral density, namely the metacarpals [16], femoral neck [17, 18], and lumbar spine [19]. Iki E et al. [20] reported faster loss of BMD in lumbar spine compared to BMD in femoral neck in 4550 Japanese women. Sigh et al. [21] chose the lumbar spine as the preferred site for BMD measurement because the lumbar spine is mainly composed of trabecular bone. They believe that examination of the lumbar spine may be the most sensitive indicator of systemic deterioration of bone microarchitecture in osteoporosis.

In our study, results of BMD from the femoral neck, proximal femur, and lumbar spine (L1–L4 ) were used. It was observed that the mineral density of the femoral neck, femur, and lumbar spine decreased significantly with the age of the patients. In addition, the mineral density of femur and lumbar spine showed significantly lower values in women.

The number of lost teeth in the study group demonstrated significant inverse correlation with the mineral density of both the femoral neck and the

bone itself. On the other hand, clinical attachment loss showed a significant inverse correlation with bone density at all sites examined. Both tooth loss and clinical attachment loss are manifestations of periodontal disease progression, and progressive bone loss is critical in both cases. Age is a non-modifiable risk factor for both periodontitis and osteoporosis [22], and bone loss accelerates in women with onset of menopause [23]. In our own study, information about menopause was not included in anamnesis; however, the average age of the woman was 56.4 ± 13.8 years, which may indicate a postmenopausal period. The age parameter was included in multivariate analyses. It was shown that loss of connective tissue attachment was affected by reduced bone mineral density, regardless of age. In the case of the number of lost teeth, the strongest correlation that was independent of age was noted for density of the femoral neck. For the proximal femur as a whole, age was a significant risk factor, while the lumbar spine mineral density score did not significantly modify the relationship between the number of lost teeth and age.

Tak et al. [24], in a study on the Korean population, observed an inverse correlation between mineral density of the lumbar spine and CAL in a group of women, but they did not report a similar relationship in the case of the femoral neck or the number of lost teeth in relation to BMD. The number of missing teeth, however, was correlated with the mineral density of the lumbar spine in men. Singh et al. studied women aged 46–54 years in the early postmenopausal period [21]. They conducted an analysis dividing the patients into 3 groups — normopenic, osteopenic, and osteoporotic. They showed an inverse correlation between mineral density and average CAL and average PD, and statistically significant differences between the groups. Regarding the number of missing teeth, the correlation with bone mineral density was not statistically significant.

Iwasaki et al. [25], examining the mineral density of the proximal femur and lumbar spine, also showed that the group of women with osteopenia/osteoporosis were more exposed to higher values of loss of connective tissue attachment; however, the number of lost teeth was not mentioned. Different results were obtained by Moeintaghavi et al. [26]; they did not observe a difference in either the number of lost teeth or loss of connective tissue attachment between the groups differing in mineral density, as in the previously mentioned publications. In our study, osteoporosis was diagnosed in one woman based on L1–L4 T-score. However, the normopenic and osteopenic groups were not homogeneous in terms of size, which prevented a thorough analysis between the groups.

Regarding the number of lost teeth, Grocholewicz et al. [27] described a positive correlation with reduced mineral density, while Drozdowska et al. [28] observed a decrease in bone mineral density in edentulous women compared to women with partially missing teeth.

Similar results to our own observations regarding CAL and BMD of the femoral neck were published by Gondim et al. [29]. However, a significant correlation was observed only in the group of women with CAL > 5 mm, but the correlation with BMD was significant. Perhaps an additional factor influencing this correlation in our study was newly diagnosed diabetes.

In these scientific reports, the glycemic status of patients was not taken into account, or patients with diabetes were excluded from the study.

Although our study did not show a statistically significant relationship between parameters of mineral density and the level of HbA1c, a possible impact of glycemic disorders on bone tissue metabolism and indirectly on the condition of periodontal tissues should not be overlooked. Diabetes has a significant impact on intensification of osteoclastogenesis and increased apoptosis of osteoblasts. Interestingly, the effect of diabetes on bone loss is likely related to the effect of diabetes on both innate and adaptive immune responses [30]. There are also reports of normal or even increased BMD density in patients with T2D. However, bone microarchitecture is remodeled in this case, which in turn leads to increased predisposition to fractures in this group of patients [4, 5].

One of the few studies taking into account the impact of T2D on BMD density reduction and periodontitis was published by Ateeq et al. [31].

They studied BMD in patients with T2D with chronic periodontitis and in patients with T2D who were periodontally healthy, as well as in non-diabetic patients with periodontitis and in healthy patients. Importantly, the study excluded women in early menopause and those taking hormone replacement therapy.

The mean BMD density was lowest in the group of patients with T2D and periodontitis in comparison to those with diabetes and periodontitis only. However, there was no correlation between BMD and HbA1c in any of the groups of diabetic patients. The effect of diabetes on the condition of periodontal tissues and BMD density was concluded, emphasizing aggravation of this condition in patients with periodontitis. However, the cause of the relationship between a decrease in BMD and T2D and periodontitis has not been determined. The authors suggest that additional risk factors, such as BMI and other comorbidities, as well as duration of T2D, may play a role.

## Conclusions

In summary, low BMD may be associated with T2D and periodontitis. Early diagnosis of reduced BMD can significantly affect the condition of periodontal tissues. Therefore, it is advisable to refer patients with reduced BMD for a dental and periodontal examination. Similarly, patients with T2D should be assessed for osteoporosis risk to reduce the risk of bone loss and fractures.

## Article information

### Availability of data and materials

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

### Ethical approval and consent to participate

A positive opinion was obtained from the Ethics and Supervision Committee for Research on Humans and Animals of the Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw (10/2012). The patients gave their written informed consent to participate in this study.

### Author contributions

Conception and design of the study: Górska R., Franek E.

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Drafting the manuscript: Wyszyńska-Pomian M.

### Funding

This publication was prepared without any external source of funding.

### Competing interests

The authors declare no conflict of interest.

### REFERENCES

1. Xu S, Zhang G, Guo JF, et al. Associations between osteoporosis and risk of periodontitis: A pooled analysis of observational studies. Oral Dis. 2021; 27(2): 357–369, doi: 10.1111/odi.13531, indexed in Pubmed: 32615008.
2. Takaishi Y, Okamoto Y, Ikeo T, et al. Correlations between periodontitis and loss of mandibular bone in relation to systemic bone changes in postmenopausal Japanese women. Osteoporos Int. 2005; 16(12): 1875–1882, doi: 10.1007/s00198-005-1955-8, indexed in Pubmed: 16027956.
3. Lerner UH, Lerner UH. Bone remodeling in post-menopausal osteoporosis. J Dent Res. 2006; 85(7): 584–595, doi: 10.1177/154405910608500703, indexed in Pubmed: 16798857.
4. Eller-Vainicher C, Cairoli E, Grassi G, et al. Pathophysiology and Management of Type 2 Diabetes Mellitus Bone Fragility. J Diabetes Res. 2020; 2020: 7608964, doi: 10.1155/2020/7608964, indexed in Pubmed: 32566682.
5. Yamamoto M, Yamaguchi T, Yamauchi M, et al. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications. J Bone Miner Res. 2009; 24(4): 702–709, doi: 10.1359/jbmr.081207, indexed in Pubmed: 19049338.
6. Napoli N, Chandran M, Pierroz DD, et al. IOF Bone and Diabetes Working Group. Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol. 2017; 13(4): 208–219, doi: 10.1038/nrendo.2016.153, indexed in Pubmed: 27658727.
7. Bełtowski J, Wójcicka G, Jamroz-Wiśniewska A. Hydrogen sulfide in the regulation of insulin secretion and insulin sensitivity: Implications for the pathogenesis and treatment of diabetes mellitus. Biochem Pharmacol. 2018; 149: 60–76, doi: 10.1016/j.bcp.2018.01.004, indexed in Pubmed: 29307653.
8. O'Leary TJ, Drake RB, Naylor JE. The plaque control record. J Periodontol. 1972; 43(1): 38, doi: 10.1902/jop.1972.43.1.38, indexed in Pubmed: 4500182.
9. Ainamo J, Bay I. Problems and proposals for recording gingivitis and plaque. Int Dent J. 1975; 25(4): 229–235, indexed in Pubmed: 1058834.
10. Page RC, Eke PI, Page RC, et al. Case Definitions for Use in Population-Based Surveillance of Periodontitis. J Periodontol. 2007; 78(7 Suppl): 1387–1399, doi: 10.1902/jop.2007.060264, indexed in Pubmed: 29539084.
11. Kribbs PJ, Smith DE, Chesnut CH. Oral findings in osteoporosis. Part II: Relationship between residual ridge and alveolar bone resorption and generalized skeletal osteopenia. J Prosthet Dent. 1983; 50(5): 719–724, doi: 10.1016/0022-3913(83)90215-9, indexed in Pubmed: 6358473.
12. Payne JB, Reinhardt RA, Nummikoski PV, et al. Longitudinal alveolar bone loss in postmenopausal osteoporotic/osteopenic women. Osteoporos Int. 1999; 10(1): 34–40, doi: 10.1007/s001980050191, indexed in Pubmed: 10501777.
13. Wactawski-Wende J, Grossi SG, Trevisan M, et al. The role of osteopenia in oral bone loss and periodontal disease. J Periodontol. 1996; 67(10 Suppl): 1076–1084, doi: 10.1902/jop.1996.67.10s.1076, indexed in Pubmed: 8910826.
14. Geurs NC, Lewis CE, Jeffcoat MK. Osteoporosis and periodontal disease progression. Periodontol 2000. 2003; 32: 105–110, doi: 10.1046/j.0906-6713.2003.03208.x, indexed in Pubmed: 12756036.
15. Yoshihara A, Seida Y, Hanada N, et al. A longitudinal study of the relationship between periodontal disease and bone mineral density in community-dwelling older adults. J Clin Periodontol. 2004; 31(8): 680–684, doi: 10.1111/j.1600-051X.2004.00548.x, indexed in Pubmed: 15257747.
16. Inagaki K, Kurosu Y, Kamiya T, et al. Low metacarpal bone density, tooth loss, and periodontal disease in Japanese women. J Dent Res. 2001; 80(9): 1818–1822, doi: 10.1177/00220345010800090901, indexed in Pubmed: 11926240.
17. Weyant RJ, Pearlstein ME, Churak AP, et al. The association between osteopenia and periodontal attachment loss in older women. J Periodontol. 1999; 70(9): 982–991, doi: 10.1902/jop.1999.70.9.982, indexed in Pubmed: 10505800.
18. Lundström A, Jendle J, Stenström B, et al. Periodontal conditions in 70-year-old women with osteoporosis. Swed Dent J. 2001; 25(3): 89–96, indexed in Pubmed: 11813450.
19. Taguchi A, Suei Y, Ohtsuka M, et al. Relationship between bone mineral density and tooth loss in elderly Japanese women. Menopause. 2005; 12(2): 144–148, doi: 10.1097/00042192-200512020-00007, indexed in Pubmed: 15772560.
20. Iki M, Kagamimori S, Kagawa Y, et al. Bone mineral density of the spine, hip and distal forearm in representative samples of the Japanese female population: Japanese Population-Based Osteoporosis (JPOS) Study. Osteoporos Int. 2001; 12(7): 529–537, doi: 10.1007/s001980170073, indexed in Pubmed: 11527049.
21. Singh A, Sharma RK, Siwach RC, et al. Association of bone mineral density with periodontal status in postmenopausal women. J Investig Clin Dent. 2014; 5(4): 275–282, doi: 10.1111/jicd.12047, indexed in Pubmed: 23766246.

22. Kellie SE, Brody JA. Sex-specific and race-specific hip fracture rates. Am J Public Health. 1990; 80(3): 326–328, doi: 10.2105/ajph.80.3.326, indexed in Pubmed: 2305917.
23. Vico L, Prallet B, Chappard D, et al. Contributions of chronological age, age at menarche and menopause and of anthropometric parameters to axial and peripheral bone densities. Osteoporos Int. 1992; 2(3): 153–158, doi: 10.1007/BF01623823, indexed in Pubmed: 1627903.
24. Tak I, Shin M, Kweon S, et al. The association between periodontal disease, tooth loss and bone mineral density in a Korean population. J Clin Periodontol. 2014; 41(12): 1139–1144, doi: 10.1111/jcpe.12309, indexed in Pubmed: 25207848.
25. Iwasaki M, Taylor GW, Nakamura K, et al. Association between low bone mineral density and clinical attachment loss in Japanese postmenopausal females. J Periodontol. 2013; 84(12): 1708–1716, doi: 10.1902/jop.2013.120613, indexed in Pubmed: 23451986.
26. Moeintaghavi A, Pourjavad M, Dadgar S, et al. Evaluation of the association between periodontal parameters, osteoporosis and osteopenia in post menopausal women. J Dent (Tehran). 2013; 10(5): 443–448, indexed in Pubmed: 24910652.
27. Grocholewicz K, Bohatyrewicz A. Oral health and bone mineral density in postmenopausal women. Arch Oral Biol. 2012; 57(3): 245–251, doi: 10.1016/j.archoralbio.2011.09.001, indexed in Pubmed: 22153129.
28. Drozdzowska B, Pluskiewicz W, Michno M. Tooth count in elderly women in relation to their skeletal status. Maturitas. 2006; 55(2): 126–131, doi: 10.1016/j.maturitas.2005.10.011, indexed in Pubmed: 16822625.
29. Gondim V, Aun J, Fukuda CT, et al. Severe loss of clinical attachment level: an independent association with low hip bone mineral density in postmenopausal females. J Periodontol. 2013; 84(3): 352–359, doi: 10.1902/jop.2012.120090, indexed in Pubmed: 22548585.
30. Wu YY, Xiao E, Graves DT. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci. 2015; 7(2): 63–72, doi: 10.1038/ijos.2015.2, indexed in Pubmed: 25857702.
31. Ateeq H, Zia A, Husain Q, et al. Comparative assessment of bone mineral density levels in type 2 diabetic subjects with or without chronic periodontitis: A cross-sectional study. J Adv Periodontol Implant Dent. 2021; 13(1): 28–34, doi: 10.34172/japid.2021.008, indexed in Pubmed: 35919913.

VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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# The Relationship between Retinal and Ganglion Layer Thickness and Perfusion in Patients with Type 2 Diabetes: A Cross-Sectional Study in Indonesia

## ABSTRACT

**Objective: To assess the differences and the relationship between retinal nerve fiber layer (RNFL) thickness, ganglion cell-internal plexiform layer (GCIPL) thickness, capillary perfusion density, and flux index in patients with type 2 diabetes (T2D) with and without diabetic retinopathy (DR).**

**Materials and methods: This cross-sectional analytic study with consecutive sampling, which divided individuals into healthy, people with T2D without DR (no DR), and people with T2D with DR (DR) groups. The subjects were patients with T2D aged 40–75 years with or without DR. The collected data included age, gender, glycated hemoglobin test result (HbA1c), duration of diabetes, intraocular pressure (IOP), RNFL thickness, GCIPL thickness, peripapillary perfusion density, and peripapillary flux index.**

**Results: This study included 137 eyes from 83 people with T2D. There were significant differences in minimum GCIPL thickness (p = 0.0001), peripapillary perfusion (p = 0.003), and peripapillary flux (p = 0.001) between the 3 groups, but no significant difference in RNFL thickness between the 3 groups (p = 0.222). There were significant positive correlations between RNFL thickness and peripapillary perfusion (p = 0.002, r = 0.264), RNFL thickness and peripapillary flux (p = 0.0001, r = 0.320), GCIPL thickness and peripapillary perfusion (p = 0.003, r = 0.256), as well as GCIPL thickness and peripapillary flux (p = 0.002, r = 0.268).**

**Conclusions: There were relationships between RNFL thickness and peripapillary retinal perfusion, RNFL thickness and peripapillary flux, GCIPL thickness and peripapillary perfusion, and GCIPL thickness and peripapillary flux, in patients with T2D with and without DR. (Clin Diabetol 2024; 13, 6: 366–372)**

**Keywords: diabetes mellitus, diabetic retinopathy, RNFL, GCIPL, papillary perfusion density**

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Clinical Diabetology 2024, 13; 6: 366–372
DOI: 10.5603/cd.101840
Received: 30.07.2024 Accepted: 6.11.2024

## Introduction

Diabetic retinopathy (DR) is the most common ocular complication of diabetes mellitus (DM). The global

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prevalence is 34.6% or about 93 million people, and it is estimated to double by 2025. It is als estimated that around 10.2% of cases are visual-threatening diabetic retinopathy (VTDR), which can cause blindness. Diabetic retinopathy is the leading cause of blindness in productive age. According to data from the International Diabetes Federation (IDF), the prevalence of diabetes in Indonesia in 2021 was about 10.8%. A population-based cross-sectional study reported that the prevalence of DR among Indonesian adults with type 2 diabetes (T2D) was 43.1% while VTDR affected 26.3% of the population. About one in four adults with T2D had VTDR, and about one in twelve with VTDR was bilaterally blind [1–4].

Indonesia ranked fifth in the world for the number of adults with diabetes, reporting 19.5 million cases in 2021 from a total adult population of 179 million. This number is expected to increase to 28.6 million by 2045. A study by Jang et al. in South Korea found that around one-third of patients with T2D were unaware of their condition, and 10% had already developed DR [1, 5].

Microvascular disorders of the eye form the basis of the pathogenesis of DR, but there is also evidence to suggest that retinal neurodegeneration has occurred before clinically detectable microvascular damage is present. Retinal neuron cell apoptosis and peripapillary nerve layer thinning also play a role in the pathogenesis of DR. The microcirculation, radial peripapillary capillaries, and optic disc regions play a role in providing some nutrition to the retinal nerve fiber layer (RNFL) originating from the adjacent peripapillary retinal arteries. Microvascular dysfunction in this area may affect RNFL or ganglion cell-internal plexiform layer (GCIPL) function [3, 6].

Microvascular changes in the optic disc area could serve as early markers for DR, and they can be identified using non-invasive diagnostic tests such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). There is still limited research investigating this issue, particularly in Indonesia [7]. This study aims to compare and find correlation between RNFL, GCIPL, and peripapillary retinal perfusion in healthy people, people with T2D without DR, and people with T2D with DR. Given the high prevalence of diabetes and DR in Indonesia, this could lead to improved early diagnostic strategies for patients at risk of DR, offering valuable data for public health strategies.

## Materials and methods

### Study design

This is a cross-sectional study in healthy people, people with T2D without DR, and people with T2D with DR.

### Subjects

The inclusion criteria in this study were patients with T2D, with and without DR, with an age range from 40 to 75 years, and healthy people without diabetes with matched characteristics. Exclusion criteria were history of ocular trauma, history of ocular surgery, optic nerve abnormalities, optic nerve atrophy, glaucoma, and retinal vein or artery occlusion, as well as patients with refractive errors more than or equal to S-6.00 diopters (high myopia).

### Ethical approval

This study received ethical clearance from the Ethics Committee of the Faculty of Medicine Universitas Padjadjaran, and it was carried out based on the ethical principles of the Declaration of Helsinki. The study was conducted at the National Eye Center, Cicendo Eye Hospital, Bandung from February to April 2020.

### Data collection

Subjects were divided into 3 groups, namely, a control group consisting of healthy individuals, people with T2D without DR (No DR), and people with T2D with DR (DR). All subjects were examined using OCT (Carl Zeiss CIRRUS HD OCT) and OCTA (Carls Zeiss CIRRUS OCT Angiography) to measure the RNFL thickness, GCIPL thickness, capillary perfusion density, and flux index. The RNFL thickness measurement was carried out using an OCT optical disc cube 200 × 200 scan program with a signal strength of at least 6/10. Measurement of GCIPL thickness was carried out using the OCT program ganglion cell analysis macular cube 200 × 200. Capillary perfusion density and flux index were measured using OCTA by measuring the percentage of areas that have perfused blood vessels and capillary perfusion as seen from the brightness (intensity) of the flow signal with the optic nerve head program angiography at 4.5 × 4.5 mm.

### Statistical analysis

Statistical analysis for numerical variables using one-way ANOVA test with the Kruskal-Wallis alternative test. Categorical data were obtained out by using the chi-square test. Furthermore, correlation tests were carried out to determine the correlation between each variable if the data has normal distribution followed by Pearson's correlation statistical test, while for abnormal data Spearman's test was used. The strength of the correlation was based on the criteria of Guillford (1956), as follows: 0.00 to < 0.2 very weak; 0.2 to < 0.4 weak; 0.4–0.7 moderate; 0.7 to < 0.9 strong; and 0.9–1.0 very strong, with a significance criterion of

**Table 1. Comparison of the Characteristics of Patients in the Three Groups**

| Variable | Group | | | P-value |
|---|---|---|---|---|
| | Control N = 22 | No DR N = 22 | DR N = 39 | |
| **Age [years]** | | | | 0.181 |
| Mean ± SD | 50.64 ± 6.477 | 53.09 ± 5.309 | 53.38 ± 5.764 | |
| **Gender** | | | | 0.185 |
| Male | 8(36.4%) | 4(18.2%) | 16(41.0%) | |
| Female | 14(63.6%) | 18(81.8%) | 23(59.0%) | |
| **HbA1c [%]** | | | | 0.0001* |
| Mean ± SD | 5.50 ± 0.463 | 9.05 ± 1.909 | 9.374 ± 2.082 | |
| **DM duration [years]** | | | | |
| Mean ± SD | — | 4.51 ± 3.225 | 8.32 ± 5.898 | 0.030* |
| **IOP (N = 137 eyes) [mmHg]** | N = 39 | N = 42 | N = 56 | 0.481 |
| Mean ± SD | 15.92 ± 2.507 | 16.21 ± 2.754 | 15.46 ± 3.751 | |

For numerical data, the p value is tested by one-way ANOVA test if the data are normally distributed or the Kruskal-Wallis test if the data are not normally distributed. For categorical data, the p value was tested with the chi-square test. The significance is based on the value of $p < 0.05$. * indicates the p-value $< 0.05$

DM — diabetes mellitus; HbA1c — glycated hemoglobin; IOP — intra-ocular pressure; SD — standard deviation

$p < 0.05$. The data were processed using SPSS version 24.0 for Windows.

## Results

The subjects in this study comprised 83 people (137 eyes), who were divided into 3 groups: a control group consisting of 22 healthy people (39 eyes), people with T2D without DR comprising 22 people (42 eyes), and people of T2D with DR comproising 39 people (56 eyes). The mean age in this study was 51.32 ± 5.764 (41–64) years with 28 males (33.7%) and 55 females (66.3%). Table 1 shows the characteristics of the subjects in the 3 groups.

Table 2 shows papillary perfusion and papillary flux in the 3 groups. There was a significant difference of papillary perfusion between the 3 groups both overall and assessed per quadrant except for the temporal quadrant. Moreover, there was a significant difference of papillary flux between the 3 groups in all quadrants.

Table 3 shows the comparison of RNFL thickness and GCIPL thickness in the 3 groups. In this study, the thickness of the RNFL did not show a significant difference in general, but there was a tendency for GCIPL thickness thinning, and a significant difference can be seen in the ratio of the minimum GCIPL thickness.

Table 4 shows the correlation between papillary flux with RNFL thickness and GCIPL thickness. There was a significant positive correlation between RNFL thickness and average papillary perfusion density and flux ($p = 0.002$ and $p = 0.0001$, respectively), although the correlation strength was weak ($r = 0.264$ and $r = 0.320$, respectively). There was also a significant positive correlation between papillary perfusion density and papillary flux with GCIPL thickness ($p = 0.003$ and $p = 0.002$, respectively), even though the correlation strength was weak ($r = 0.256$ and $r = 0.268$, respectively).

## Discussion

Diabetes mellitus is a complex metabolic disease that affects the microvascular system, including the eyes. Diabetic retinopathy is the leading cause of blindness in patients with diabetes mellitus (DM) and is the leading cause of visual impairment in working-age adults. Indonesia has a specific range for productive age, which is 18 to 55 years. The prevalence of DM increases with age; this is related to a decrease in pancreatic function with increasing age. Type 2 (adult-onset) or noninsulin-dependent diabetes mellitus is characterized by insulin resistance accompanied by insulin deficiency or impaired insulin secretion [8–10].

In Indonesia, individuals with T2D are in the age range of 55–64 years (6.3%), 65–74 years (6.03%), then 45–54 years (3.9%) with a higher rate in women (1.8%) than men (1.2%). More people with T2D live in urban areas (1.9%) than in rural areas (1.0%). Mihardja et al. [9] stated that in 2007 4.6% of the population had DM, 10.4% were 45–55 years old, and 5% were 35–44 years old. The prevalence of T2D increases with age and is higher in high socioeconomic groups. Diabetes mellitus affects women 1.6 times (95% CI 1.4–1.7) more than men.

**Table 2. Overview and Comparison of Peripapillary Perfusion Density and Peripapillary Retinal Flux Index**

| Variable | Group | | | P-value |
|---|---|---|---|---|
| | Control N = 39 | No DR N = 42 | DR N = 56 | |
| **Superior perfusion** | | | | **0.002*** |
| Mean ± SD | 43.09 ± 2.298 | 42.29 ± 3.523 | 41.25 ± 2.922 | |
| **Inferior perfusion** | | | | **0.001*** |
| Mean ± SD | 44.00 ± 1.761 | 42.29 ± 2.802 | 42.05 ± 3.554 | |
| **Temporal perfusion** | | | | **0.715** |
| Mean ± SD | 46.03 ± 2.115 | 46.68 ± 2.582 | 44.95 ± 8.055 | |
| **Nasal perfusion** | | | | **0.032*** |
| Mean ± SD | 42.10 ± 1.934 | 42.96 ± 3.494 | 42.20 ± 2.941 | |
| **Total perfusion** | | | | **0.003*** |
| Mean ± SD | 44.01 ± 1.201 | 43.55 ± 2.355 | 43.03 ± 2.123 | |
| **Superior flux** | | | | **0.003*** |
| Mean ± SD | 0.403 ± 0.033 | 0.383 ± 0.035 | 0.385 ± 0.041 | |
| **Inferior flux** | | | | **0.040*** |
| Mean ± SD | 0.409 ± 0.024 | 0.392 ± 0.035 | 0.394 ± 0.037 | |
| **Temporal flux** | | | | **0.001*** |
| Mean ± SD | 0.437 ± 0.038 | 0.401 ± 0.053 | 0.403 ± 0.053 | |
| **Nasal flux** | | | | **0.013*** |
| Mean ± SD | 0.393 ± 0.036 | 0.370 ± 0.040 | 0.371 ± 0.045 | |
| **Total flux** | | | | **0.001*** |
| Mean ± SD | 0.423 ± 0.029 | 0.390 ± 0.036 | 0.389 ± 0.041 | |

For numerical data, the p value is tested by one-way ANOVA if the data are normally distributed, or with the Kruskal-Wallis test if the data are not normally distributed; for categorical data, the p value was tested with the chi-square test. The significance is based on the value of $p < 0.05$. *indicates the p-value < 0.05

DR — diabetic retinopathy; SD — standard deviation

There was no significant difference in IOP between the 3 groups, this is so that the results are not influenced by vascular resistance that can occur due to IOP. Autoregulation of arteriolar and capillary vascular resistance serves to compensate for changes in IOP. Arterioles are also responsible for regulating blood flow in response to neural activity – retinal arterioles dilate to increase neuronal activity locally so that working neurons get adequate blood supply. The average glycated hemoglobin (HbA1c) test result in the no DR group was 9.05 ± 1.909 and in the DR group it was 9.374 ± 2.082, which indicates that glycemia is still not well controlled. HbA1c can only describe glycemic values in the last 3 months and cannot show fluctuations in glycemia, so HbA1c is not a perfect parameter to determine good metabolic control [11, 12].

Peripapillary neurovascular coupling (connection between vascular and neuronal) may reflect early changes in the progression of vascular disease. Axons from all ganglion cells pass through the RNFL and converge to the optic disc. Microvascular dysfunction in these areas may affect RNFL or ganglion cell function. Decreased vascular density may reflect microvascular disorders. The results of this study showed a decrease in total flux index ($p = 0.001$) and a decrease in total perfusion density ($p = 0.003$).

The study of Vujosevic et al. [13] stated that there was no difference in perfusion density (total area filled with blood vessels) between the control group, T2D without DR, and mild DR, but there was a difference in vascular density (capillary blood vessels only, not including large vessels). The study of Rodrigues et al. [14] stated there was a decrease in peripapillary perfusion density in all groups with diabetic eyes in multivariate analysis when compared to the control group (no DR = 2.95, $p < 0.001$; mild non-proliferative DR [NPDR] = 1.76, $p = 0.017$; and moderate NPDR = 2.82, $p < 0.001$). According to the study of Cao et al. [15], there was a decrease in vascular density in the peripapillary and within the disc, which was significantly lower in diabetic patients without DR compared to controls, and a decrease in vascular density was evident in 8 peripapillary sectors in diabetic eyes (all $p < 0.05$). Cao et al. [15] also mention higher axon density in the superior

**Table 3.** Overview and Comparison of Peripapillary RNFL and GCIPL Thickness

| Variable | Groups | | | P-value |
|---|---|---|---|---|
| | Control N = 39 | No. DR N = 42 | DR N = 56 | |
| RNFL total | | | | 0.222 |
| Mean ± SD | 97.87 ± 8.189 | 98.40 ± 12.031 | 103.46 ± 18.191 | |
| GCIPL average thickness | | | | 0.076 |
| Mean ± SD | 83.74 ± 3.878 | 83.10 ± 9.929 | 77.21 ± 18.019 | |
| GCIPL minimum thickness | | | | 0.0001* |
| Mean ± SD | 81.38 ± 4.482 | 77.98 ± 12.765 | 61.00 ± 24.336 | |

For numerical data, the p value is tested by one-way ANOVA if the data are normally distributed or the Kruskal-Wallis test if the data are not normally distributed. For categorical data, the p value was tested with the Chi Square test. The significance is based on the value of $p < 0.05$. * indicates the p-value < 0.05

GCIPL — ganglion cell-inner plexiform layer; RNFL — retinal nerve fiber layer; SD — standard deviation

**Table 4. Correlation between Papillary Perfusion Density and Papillary Flux with RNFL Thickness and GCIPL Thickness**

| Variable | Correlation | R | P-value |
|---|---|---|---|
| Correlation between AVG RNFL thickness and AVG papillary perfusion density | *Spearman* | 0.264 | 0.002* |
| Correlation between AVG RNFL thickness and AVG papillary flux | *Spearman* | 0.320 | 0.0001* |
| Correlation between AVG GCIPL thickness and AVG papillary perfusion density | *Spearman* | 0.256 | 0.003* |
| Correlation between MIN GCIPL thickness and AVG papillary perfusion density | *Spearman* | 0.323 | 0.0001* |
| Correlation between AVG GCIPL thickness and AVG papillary flux | *Spearman* | 0.268 | 0.002* |
| Correlation between MIN GCIPL thickness and AVG papillary flux | *Spearman* | 0.330 | 0.0001* |

*indicates the p-value < 0.05

AVG — average; GCIPL — ganglion cell-inner plexiform layer; MIN — minimum; r — correlation coefficient; RNFL — retinal nerve fiber layer

and inferior regions making the superior and inferior quadrants more susceptible to ischemia. The significant decrease in density in the superior ($p = 0.002$) and inferior ($p = 0.001$) quadrant perfusion in this study may be due to the higher axon density in both making them more susceptible to ischemia [16].

Decreased blood flow in patients with T2D occurs due to changes in capillary structure including basement membrane thickening, pericyte apoptosis, and endothelium dysfunction, which can reduce blood flow and block capillaries. Retinal vascular endothelial cells are damaged by releasing endothelial nitric oxide synthase, which affects retinal vascular autoregulation. There is also an increase in plasma viscosity, platelet aggregation, and decreased red blood cell deformability, leading to impaired retinal and optic nerve head perfusion [10, 11, 15, 17].

Lott et al. [18] stated that patients with type 2 diabetes had impaired vasodilation and vasoconstriction responses, which may be due to impaired nitric oxide (vasoregulatory factor) in diabetes. Flicker-induced vasodilation is impaired, and hyperoxia-induced vasoconstriction occurs. To maintain a constant oxygen level, the velocity of blood flow is decreased by increasing the partial pressure of arterial oxygen (hyperoxia). Pechauer et al. [19] said that there was a greater percentage decrease in flux index compared to vascular density after hyperoxia. The population variation is smaller in the flux index compared to vascular density, so the flux index is more sensitive in detecting the hyperoxia response. In this study, the flux index decreased in all quadrants, and perfusion density also decreased in all quadrants except the temporal quadrant [11, 18–21].

In this study, there was no significant difference in the total thickness of the RNFL in the 3 groups. The results of this study are in accordance with Li et al. [22], in whose study there was no difference in peripapillary RNFL thickness between the T2D group without DR and the control group, in contrast to the study of Rodrigues et al. [14], where there was a depletion of RNFL in the diabetic eye group (T2D without DR, mild NPDR, moderate NPDR) compared to controls. The absence of significant RNFL depletion and temporal quadrant RNFL thickening in this study may be due to glial cell

swelling, which is part of the neuroinflammatory process that occurs early in diabetes, so RNFL depletion does not occur due to neural cell swelling. Muller cells, which are highly susceptible to hyperglycemia, can also undergo hypertrophy because of inflammation (gliosis), which can affect the thickness of the retinal nerve layer. Thickening of the RNFL can also be caused by damage to the inner blood retinal barrier leading to edema [12–14, 22].

In this study, there was a significant depletion of GCIPL minimum ($p = 0.0001$) in the control group (81.38 ± 4.482), the no DR group (77.98 ± 12.765), and the DR group (61.00 ± 24.336). These results are in line with the study of van Dijk et al. [23] who showed that there was depletion of the ganglion cell layer (GCL) in the pericentral area in diabetic patients with minimal DR compared to the control group [23].

The results of this study showed a weak positive correlation of average papillary perfusion density and flux with average RNFL thickness. This indicates that in patients with T2D without DR, perfusion density and radial peripapillary capillary flux index decrease with RNFL thickness, and vice versa. The results of this study are consistent with that of Shin et al. [10], who reported that there is a correlation between perfusion density and vascular density with the average thickness of GCL and RNFL in the DM group without retinopathy and NPDR. In contrast to the study of Liu et al. [17], there was a significant positive correlation between vascular density and RNFL thickness in the mild NPDR group, but no significant relationship in the group without diabetic retinopathy. This may be due to the shorter duration of DM without retinopathy in Liu et al.'s study, which took place over 3 years. The study by Mase et al. [24] conducted on healthy people showed that there was a correlation between RNFL thickness and vascular density. These results indicate that the radial peripapillary capillaries are responsible for providing nutrition to the peripapillary RNFL. In healthy individuals, the radial peripapillary capillaries are the most important structures in maintaining the integrity of the nerve fiber layer. The combination of high metabolic demand and low vascular supply resulting from diabetes may decrease the neural ability of the retinal layer to adapt to metabolic stress [10, 12, 15, 17, 24].

In this study, there was a significant positive correlation between papillary perfusion and GCIPL thickness ($p = 0.003$), although the correlation strength was weak ($r = 0.256$). The study by Kim et al. [25] described strong positive correlations between loss of macular GCIPL and vessel density from baseline to 24 months ($r = 0.817$, $p < 0.001$). Multivariable regression analysis showed that thinner baseline macular GCIPL and greater loss of macular GCIPL thickness ($B = 0.658$, $p < 0.001$) were significantly associated with change of vessel density. The study of Serrato-Martin et al. [26] found a weak positive correlation of complete and deep papillary perfusion with inferior and inferotemporal retinal ganglion thickness.

We also found a significant positive correlation between papillary flux and GCIPL thickness ($p = 0.002$), although the correlation level was weak ($r = 0.268$). There has been no previous research that examines this finding.

Currently there is limited research on the significance of peripapillary flux in pre-diabetic retinopathy, although early retinal changes may occur before DR becomes clinically apparent. Additionally, there are limited studies looking at the association of peripapillary density and peripapillary flux with GCIPL; most of them are associated with RNFL. This study focuses on peripapillary flux and its correlation with GCIPL thickness in patients with T2D in Indonesia, utilizing non-invasive techniques like OCT and OCTA, which provide valuable and accessible diagnostics for retinal assessments. However, the cross-sectional design of this study limits the ability to draw causal conclusions, and it restricts insights into longitudinal changes in retinal thickness and perfusion. The absence of a control group for pre-diabetic retinopathy also limits the understanding of these markers at the earliest stages of disease progression. Further longitudinal studies with a broader participant base, including those at pre-diabetic stages, are recommended to explore how early changes in retinal thickness and perfusion metrics could improve early detection and intervention strategies for DR.

The findings of this study indicate significant relationships between RNFL thickness, GCIPL thickness, and peripapillary perfusion and flux. Peripapillary vascular and neuronal (neurovascular coupling) relationships may represent early markers of microvascular dysfunction in DR, suggesting that monitoring of RNFL and GCIPL thickness and perfusion density with non-invasive diagnostic tools such as OCT and OCTA could support early identification of patients at risk for DR progression.

## Article information

### Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

### Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the

protocol by the local Ethics Committee of Universitas Padjadjaran, Bandung, Indonesia. (https://kep.unpad.ac.id). Approval number: 0320010094. Informed consent to participate the study was obtained from the patient.

## Author contributions

RMR, SD: conceptualization and original draft writing; AP, BA, ASK: review and editing.

## Acknowledgements

The authors would like to thank Iffa Nadifa for helping with the manuscript preparation.

## Funding

Not applicable.

## Conflict of interest

The authors declare no conflict of interest.

## REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas [Internet]. 10th ed. Brussels: International Diabetes Federation; 2021. www.diabetesatlas.org (29.07.2024).
2. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. Clin Exp Ophthalmol. 2016; 44(4): 260–277, doi: 10.1111/ceo.12696, indexed in Pubmed: 26716602.
3. Gardner TW, Davila JR. The neurovascular unit and the pathophysiologic basis of diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2017; 255(1): 1–6, doi: 10.1007/s00417-016-3548-y, indexed in Pubmed: 27832340.
4. Sasongko MB, Widyaputri F, Agni AN, et al. Prevalence of Diabetic Retinopathy and Blindness in Indonesian Adults With Type 2 Diabetes. Am J Ophthalmol. 2017; 181: 79–87, doi: 10.1016/j.ajo.2017.06.019, indexed in Pubmed: 28669781.
5. Jang HNa, Moon MK, Koo BoK. Prevalence of Diabetic Retinopathy in Undiagnosed Diabetic Patients: A Nationwide Population-Based Study. Diabetes Metab J. 2022; 46(4): 620–629, doi: 10.4093/dmj.2021.0099, indexed in Pubmed: 35193173.
6. Lechner J, O'Leary OE, Stitt AW. The pathology associated with diabetic retinopathy. Vision Res. 2017; 139: 7–14, doi: 10.1016/j.visres.2017.04.003, indexed in Pubmed: 28412095.
7. Huang J, Zheng B, Lu Y, et al. Quantification of Microvascular Density of the Optic Nerve Head in Diabetic Retinopathy Using Optical Coherence Tomographic Angiography. J Ophthalmol. 2020; 2020: 5014035, doi: 10.1155/2020/5014035, indexed in Pubmed: 32411429.
8. Wong T, Sun J, Kawasaki R, et al. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. Ophthalmology. 2018; 125(10): 1608–1622, doi: 10.1016/j.ophtha.2018.04.007, indexed in Pubmed: 29776671.
9. Mihardja L, Soetrisno U, Soegondo S. Prevalence and clinical profile of diabetes mellitus in productive aged urban Indonesians. J Diabetes Investig. 2014; 5(5): 507–512, doi: 10.1111/jdi.12177, indexed in Pubmed: 25411617.
10. Shin YI, Nam KiY, Lee SE, et al. Peripapillary microvasculature in patients with diabetes mellitus: An optical coherence tomography angiography study. Sci Rep. 2019; 9(1): 15814, doi: 10.1038/s41598-019-52354-8, indexed in Pubmed: 31676848.
11. Moran EP, Wang Z, Chen J, et al. Neurovascular cross talk in diabetic retinopathy: Pathophysiological roles and therapeutic implications. Am J Physiol Heart Circ Physiol. 2016; 311(3): H738–H749, doi: 10.1152/ajpheart.00005.2016, indexed in Pubmed: 27473938.
12. Araszkiewicz A, Zozulinska-Ziolkiewicz D. Retinal Neurodegeneration in the Course of Diabetes-Pathogenesis and Clinical Perspective. Curr Neuropharmacol. 2016; 14(8): 805–809, doi: 10.2174/1570159x14666160225154536, indexed in Pubmed: 26915422.
13. Vujosevic S, Muraca A, Gatti V, et al. Peripapillary Microvascular and Neural Changes in Diabetes Mellitus: An OCT-Angiography Study. Invest Ophthalmol Vis Sci. 2018; 59(12): 5074–5081, doi: 10.1167/iovs.18-24891, indexed in Pubmed: 30357402.
14. Rodrigues TM, Marques JP, Soares M, et al. Peripapillary neurovascular coupling in the early stages of diabetic retinopathy. Retina. 2019; 39(12): 2292–2302, doi: 10.1097/IAE.0000000000002328, indexed in Pubmed: 30260919.
15. Cao D, Yang D, Yu H, et al. Optic nerve head perfusion changes preceding peripapillary retinal nerve fibre layer thinning in preclinical diabetic retinopathy. Clin Exp Ophthalmol. 2019; 47(2): 219–225, doi: 10.1111/ceo.13390, indexed in Pubmed: 30203562.
16. Victor AA. Optic Nerve Changes in Diabetic Retinopathy. In: Ferreri FM. ed. Optic Nerve. IntechOpen, [Internet] 2019.
17. Liu L, Wang Y, Liu HX, et al. Peripapillary Region Perfusion and Retinal Nerve Fiber Layer Thickness Abnormalities in Diabetic Retinopathy Assessed by OCT Angiography. Transl Vis Sci Technol. 2019; 8(4): 14, doi: 10.1167/tvst.8.4.14, indexed in Pubmed: 31388466.
18. Lott MEJ, Slocomb JE, Shivkumar V, et al. Comparison of retinal vasodilator and constrictor responses in type 2 diabetes. Acta Ophthalmol. 2012; 90(6): e434–e441, doi: 10.1111/j.1755-3768.2012.02445.x, indexed in Pubmed: 22682034.
19. Pechauer AD, Jia Y, Liu L, et al. Optical Coherence Tomography Angiography of Peripapillary Retinal Blood Flow Response to Hyperoxia. Invest Ophthalmol Vis Sci. 2015; 56(5): 3287–3291, doi: 10.1167/iovs.15-16655, indexed in Pubmed: 26024111.
20. Yu J, Gu R, Zong Y, et al. Relationship Between Retinal Perfusion and Retinal Thickness in Healthy Subjects: An Optical Coherence Tomography Angiography Study. Invest Ophthalmol Vis Sci. 2016; 57(9): OCT204–OCT210, doi: 10.1167/iovs.15-18630, indexed in Pubmed: 27409474.
21. Barber AJ. Diabetic retinopathy: recent advances towards understanding neurodegeneration and vision loss. Sci China Life Sci. 2015; 58(6): 541–549, doi: 10.1007/s11427-015-4856-x, indexed in Pubmed: 25951929.
22. Li Z, Wen X, Zeng P, et al. Do microvascular changes occur preceding neural impairment in early-stage diabetic retinopathy? Evidence based on the optic nerve head using optical coherence tomography angiography. Acta Diabetol. 2019; 56(5): 531–539, doi: 10.1007/s00592-019-01288-8, indexed in Pubmed: 30656435.
23. van Dijk HW, Verbraak FD, Kok PHB, et al. Decreased retinal ganglion cell layer thickness in patients with type 1 diabetes. Invest Ophthalmol Vis Sci. 2010; 51(7): 3660–3665, doi: 10.1167/iovs.09-5041, indexed in Pubmed: 20130282.
24. Mase T, Ishibazawa A, Nagaoka T, et al. Radial Peripapillary Capillary Network Visualized Using Wide-Field Montage Optical Coherence Tomography Angiography. Invest Ophthalmol Vis Sci. 2016; 57(9): OCT504–OCT510, doi: 10.1167/iovs.15-18877, indexed in Pubmed: 27454659.
25. Kim K, Kim E, Kim D, et al. Progressive retinal neurodegeneration and microvascular change in diabetic retinopathy: longitudinal study using OCT angiography. Acta Diabetologica. 2019; 56(12): 1275–1282, doi: 10.1007/s00592-019-01395-6.
26. Serrato-Martín G, Razo-Blanco-Hernández D, Somilleda-Ventura S, et al. Correlation between perfusion density and ganglion cell layer thickness in non-diabetic subjects and diabetic patients without retinopathy. Revista Mexicana de Oftalmología (English Edition). 2021; 95(3): 92–97, doi: 10.24875/rmoe.m21000164.

VIA MEDICA
REVIEW ARTICLE
ISSN 2450–7458
e-ISSN 2450–8187

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# The Impact of War and Conflict on People Living with Diabetes: A Scoping Review

## ABSTRACT

**Objective: There is substantial literature detailing the interaction between war and conflict on overall human health. However, there is limited understanding of the impact of war and conflict on people living with diabetes. This scoping review describes the impact of short- and long-term effects of exposure to war and conflict settings on people living with diabetes.**

**Materials and methods: The scoping review was conducted between May and August of 2023, using articles published in the PubMed Central and Google Scholar databases. Articles published from 1950 to 2023 with the following key terms "diabetes", "type 1 diabetes", "type 2 diabetes", "war", "armed conflict", "organized violence", and "refugees" were reviewed.**

**Results: A total of 151,347 articles were reviewed. After applying review criteria, 21 applicable articles were included in this scoping review. Three themes emerged from this review:**

**1) People living with diabetes in conflict zones are subject to elevated blood glucose and hemoglobin A1C (HbA1c) levels, which can lead to severe long-term complications.**

**2) The stress of war and conflict negatively impacts diabetes self-management and quality of life.**

**3) Healthcare access, including services and medication, is severely disrupted for people living with diabetes in these tumultuous environments.**

**Conclusions: The findings underscore the profound and direct impacts of war and conflict on people living with diabetes, highlighting the disparities in care and the urgent need for further research to identify factors that exacerbate these challenges and strategies to mitigate them. (Clin Diabetol 2024; 13, 6: 373–385)**

**Keywords: type 1 diabetes, type 2 diabetes, war, conflict, refugees**

**OSF Registration Title and Number: The Impact of War and Conflict on People Living with Diabetes; osf-registrations-jrf5m-v1URL: https://doi.org/10.17605/OSF.IO/JRF5M**

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Clinical Diabetology 2024, 13; 6: 373–385
DOI: 10.5603/cd.100617
Received: 8.05.2024 Accepted: 3.09.2024
Early publication date: 21.11.2024

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## Introduction

War is defined as violent conflict between nations or states, whereas conflict is defined as a competitive or opposing action of incompatibilities [1]. As of 2023, 32 countries are currently involved in conflict, varying in severity and accounting for tens of thousands of casualties since 2022 [1]. An astonishing 117.2 million individuals were displaced or stateless in 2023 as a result of war and conflict [2].

War not only devastates human lives but also imposes a heavy toll on the global economy and healthcare systems. As of 2021, the global economic impact of violence including armed conflict, displaced persons, interpersonal war, and large militaries was estimated to be 14.4 trillion dollars [3].

The literature extensively documents the multifaceted short- and long-term impacts of war and conflict on human health [4]. In the short term, individuals often face stress, limited access to proper nutrition, and the distressing separation from family and community. This separation can adversely affect diabetes management, potentially leading to increased instances of hyperglycemia and hypoglycemia. Furthermore, inadequate nutrition can cause frequent hyperglycemia in the short term and may escalate to severe complications like vision loss or nerve damage over time [5].

The equally severe long-term effects include mental health disorders, displacement from homes, and disruptions to essential health and social services, all of which have been linked to negative outcomes [6]. Housing insecurity has been shown to influence diabetes management and care leading to lasting complications [7]. Additionally, the psychological impacts of violence are profound, prompting heightened rates of anxiety, depression, and post-traumatic stress disorder (PTSD) [8].

People living with diabetes are tasked with the ongoing management of a chronic illness, a state that is heavily reliant on regular access to medication and a stable environment to manage their condition daily [5]. The constant vigilance required for diabetes management, including monitoring and blood glucose management, is often complicated by the stress of high-conflict environments [8]. Securing medications, and accessing consistent healthcare become formidable tasks in these regions, potentially leading to detrimental impacts on the management of diabetes.

The purpose of this scoping review is to discuss the short- and long-term effects (such as effects on glycemic targets impacts on diabetes management, and access to medical services and medications) of exposure to war and conflict settings on people living with diabetes. With the number of ongoing conflicts around the world continuing to expand, the need for this review is as crucial as ever.

**Table 1. Inclusive Search Criteria**

| Search | Search criteria |
|---|---|
| **Search Period: May 22nd — July 6th, 2023** | |
| 1 | Type 1 diabetes and war |
| 2 | Type 2 diabetes and war |
| 3 | Diabetes and War |
| 4 | Type 1 OR type 2 diabetes and armed conflict |
| 5 | Diabetes and armed conflict |
| 6 | Type 1 OR type 2 diabetes and organized violence |
| 7 | Diabetes and organized violence |
| **Second Search Period: July 28th — August 11th, 2023** | |
| 1 | Diabetes and refugees |

## Materials and methods

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) — Scoping Reviews guidelines following Arksey and O'Malley's methodologic framework [9].

### Scoping review question

What are the effects of living in areas exposed to war and conflict on people living with diabetes?

### Protocol and eligibility criteria

The scoping review search terms included "type 1 diabetes" OR "type 2 diabetes" OR "diabetes", as well as "war" OR "conflict" OR "combat" OR "organized violence" OR "armed conflict" in the PubMed Central and Google Scholar databases (Tab. 1).

Human randomized controlled trials, non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies, case reports, cross-sectional, mixed methods, and case series published between 1950 and 2023 in English language were eligible for inclusion. Studies that referenced people living with diabetes exposed to some form of war, organized violence, or armed conflict on a larger scale were included. The following were excluded from this review: animal studies, studies not in English, and those that were outside of the established time frame. Studies that only had included an abstract or were systematic or scoping reviews were excluded. Studies that did not reference diabetes specifically or directly or focused on the incidence of diabetes rather than the impact on people already living with diabetes were excluded. Studies where the context of "conflict" was related to diabetes-related conflict or other smaller-scale conflict were excluded (Fig. 1).

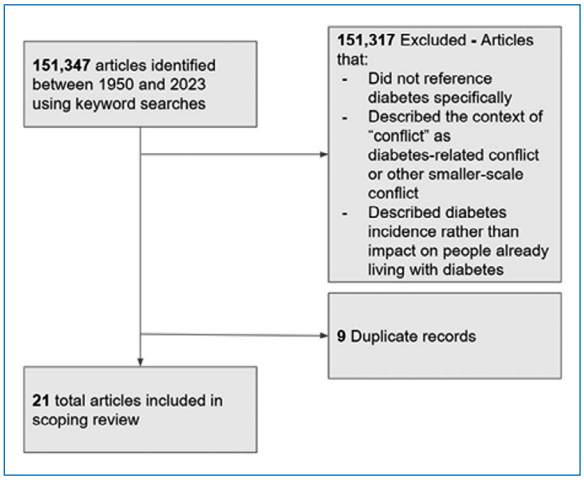


**Figure 1.** Scoping Review Flow Diagram

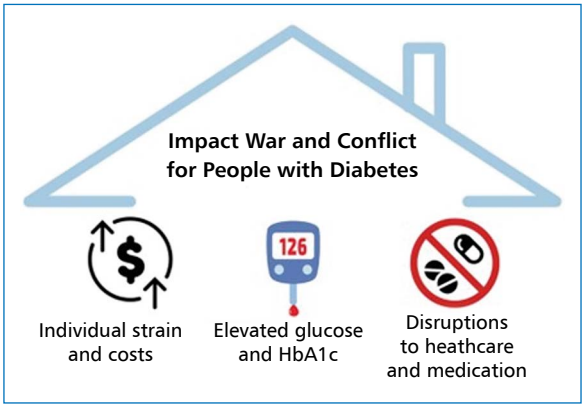


**Figure 2.** The Impact of War and Conflict on People with Diabetes

The first (EO) and third (HH) authors independently reviewed the titles and abstracts from 2 databases during an initial search conducted from May 22 to July 6, 2023. With input from a senior author (OE), all authors resolved any disagreements via consensus discussion. The initial PubMed search yielded 1358 results, specifically 691 when searching "war" and "diabetes", 155 when searching "war" and "type 2 diabetes", 36 when searching "war" and "type 1 diabetes", 338 when searching "armed conflict" and "diabetes", and 138 after searching "organized violence" and "diabetes". After title reviews, removing duplicate articles and applying the above-mentioned exclusion criteria and screening the abstracts, 24 moved onto the next phase. The initial Google Scholar search yielded 130,100 results, specifically 33,800 when searching "war" and "diabetes", 28,000 when searching "war" and "type 2 diabetes", 28,000 when searching "war" and "type 1 diabetes", 18,100 when searching "armed conflict" and "diabetes", and 21,400 after searching "organized violence" and "diabetes". After title reviews, removing duplicates, and applying the above-mentioned exclusion criteria and screening the abstracts, 18 moved onto the next phase, and the remaining articles were examined by the first and third authors. The first and third authors examined 42 remaining articles from the above two searches, reading the abstracts in depth and examining methodologies in a more detailed way, resulting in 11 studies included in this review.

An additional search was conducted from July 28 to August 11, 2023. The first 3 authors prompted an additional search to include refugees and diabetes in their search terms, after this topic had come up in their first search on multiple occasions. This second PubMed search yielded 325 results when searching "refugee" and "diabetes". The second Google Scholar search yielded 19,600 when searching "refugee" and "diabetes". Similar exclusion criteria were applied for this search. After examining these articles, and applying inclusion and exclusion criteria, the number of eligible articles was reduced to 22. Following in-depth abstract and methodology review, 10 additional articles were included in the review (Fig. 1).

## Results

A total of 21 studies were reviewed in this scoping review. Of the reviewed studies, the largest percentage of studies (27%) utilized a qualitative study design followed by mixed-methods (18%), cross-sectional (18%), retroactive case-control (10%), time series (9%), secondary data analysis (9%), and case series (9%). Table 2 includes the list of all relevant studies.

During the second search, 10 new studies were added to the scoping review. Of these reviewed studies, 40% were cross-sectional and 30% were retrospective design, while surveys, qualitative studies, and cluster design were each 10%.

Overall, 3 major themes emerged from this review (Fig. 2): 1) People living with diabetes in war and conflict settings experience increased or prolonged glucose levels above range, which can lead to long-term complications; 2) People living with diabetes in war and conflict settings are exposed to stressors and other factors that negatively impact diabetes self-management and quality of life; and 3) People living with diabetes in war and conflict settings experience significant disruptions in healthcare access such as services and medication.

**Table 2. Scoping Review Study Characteristics**

| Authors last name, year of publication | Type of study | Sample size | Exposure | Outcome | Main findings |
|---|---|---|---|---|---|
| **Diabetes outcomes** | | | | | |
| Al-Sharafi, 2017 [10] | Cross-sectional | 430 people with T2D | War | HbA1c levels | People with diabetes experienced an elevated mean HbA1c during war, with an increase from 7.7 (61 mmol/mol) (SD 1.9) before the war to 9.4 (80 mmol/mol) (SD 2.4) (p value: < 0.001) during the war compared to those with no diabetes diagnosis or those with low risk |
| Kohrt, 2022 [11] | Case series | Data from 108 individuals including 85 Somali Ethiopians who self-reported a T2D diagnosis and 23 additional persons who are adult siblings of the individuals with diabetes | Repeated conflicts, displacements, disasters; droughts | T2D rates; HbA1c; obesity | Investigators sampled various biometrics during a spike in political violence in Ethiopia, and found that individuals without diabetes had a lower mean HbA1c compared to those with diabetes (6.06 vs. 8.8) |
| Roglic, 1993 [12] | Mixed methods | 35 people with T2D | War-related protracted stress | HbA1c levels | Findings noted a slight increase (9.13 to 9.53) in HbA1c among individuals with T2D exposed to war for 3 months; however, this change in HbA1c was not significant |
| Yitshak-Sade, 2020 [13] | Time series | 408,706 glucose tests of 37,214 subjects | Living near MO | | Exposure to stressful circumstances related to MO, particularly living near one, was associated with increased fasting glucose levels, with an increased effect on individuals living with diabetes. Glucose levels were 1.29% higher (95% CI 0.63%; 1.96%) during MO among people without diabetes, and 3.35% higher (95% CI 1.23%; 5.52%) during MO among people with diabetes who were treated with glucose-lowering medications |
| Hammad, 2022 [14] | Retrospective cross-sectional study | 418 patients with diabetes | Living in refugee camp, smoking status, insulin use, TyG index | HbA1c | Data was collected from 1577 Syrian refugees living with diabetes, and only 6% were found to have controlled diabetes, which was defined as participants having an HbA1c% of less than 7. Most refugees (94%) had uncontrolled HbA1c, with the potential to lead to long term complications |
| **Self-management of diabetes and quality of life** | | | | | |
| Elliot, 2018 [15] | Cross-sectional | 292 people with diabetes | Refugee status | DSMES score which reflects the level of knowledge and understanding of diabetes self-management | The mean DSMES score was 6/10. Researchers assessing diabetes self-management, education, and support (DSMES) among adult Syrian refugees seeking care for diabetes at a medical humanitarian organization found that individuals diagnosed during the conflict were significantly more likely to have lower DSMES score compared to those who were previously diagnosed after controlling for confounders in multivariable regression modeling |

| Authors last name, year of publication | Type of study | Sample size | Exposure | Outcome | Main findings |
|---|---|---|---|---|---|
| Maar, 2011 [16] | Qualitative | 13 focus groups with 76 participants consisting of sessions with health care providers, elders, and community members with diabetes | Structural violence | Self-management behaviors | Several participants explained that some aboriginal patients face cultural barriers communicating with some of the non-aboriginal health care providers. They discussed that some patients have good management knowledge but still experience overwhelming barriers, such as current or past, unresolved physical or sexual abuse issues, or violence or addictions within their families |
| Eljedi, 2006 [17] | Cross-sectional | 197 people with diabetes | Refugee | Health related quality of life | All domains were strongly reduced in diabetic patients as compared to controls, with stronger effects in physical health (36.7 vs. 75.9 points of the 0–100 score) and psychological domains (34.8 vs. 70.0), and weaker effects in social relationships (52.4 vs. 71.4) and environment domains (23.4 vs. 36.2) |
| **Access to healthcare and medication usage** | | | | | |
| Saleh, 2021 [18] | Secondary data analysis | 10,082 Syrian refugees | Refugee status and other predictors including age, gender, smoking status, alcohol intake, physical inactivity and location of diagnosis | Prevalence of diabetes | While access to medications was high, interval medication interruptions occurred due to financial barriers and lacking knowledge of where to buy medications. Additionally, females who were diagnosed with diabetes before being displaced were more likely to take medications (87.5%) compared to those who were diagnosed after displacement (63%) |
| Ratnayake, 2020 [19] | Cross-sectional | 1022 randomly sampled households, 2798 adults aged 18 years or older | Armed conflict-related stress | Glucose level (mg/dL) | Among Syrian refugee populations living with diabetes, 26.8% of individuals 18 years and older had missed a medication dose in the past week and about 18% of individuals taking medication reported taking a smaller dose to prolong their supply. Of the refugee population living with diabetes, 49.1% sought care in the last month for diabetes. For those that did not receive care, the main reported barrier was costs, including transportation and lost time |
| Saleh, 2022 [20] | Cross-sectional | 1700 Lebanese and Syrian refugees with diabetes | Fragility settings (urbanized area of greater Beiruit vs. rural area of bequaa valley) | Comprehensiveness of service | Women were significantly less likely to be offered lifestyle counselling advice and referral to cardiologists (58.4% vs. 68.3% in Beqaa and 58.1% vs. 62% in Beirut) and ophthalmologists, compared with men. Across both settings, there was a significant trend for Lebanese people with diabetes to receive more services and more advice related to nutrition and diabetes management (89.8% vs. 85.2% and 62.4% vs. 55.5%, respectively) |

| Authors last name, year of publication | Type of study | Sample size | Exposure | Outcome | Main findings |
|---|---|---|---|---|---|
| Doocy, 2016 [21] | Cluster design with probability proportional to size sampling | 1363 cases of NCD<br>250 with diabetes | Post- conflict/refugees | Healthcare utilization | 84.7% had received care in Jordan upon fleeing their country, emphasizing the importance of continuing care for those with NCD, and demonstrating an increasing burden on the existing health care system |
| Malembaka, 2020 [22] | Cross-sectional | 1266 participants | Protracted socio-political instability and conflict | Prevalence of healthcare utilization | Researchers examined healthcare service utilization in conflict-recovering South Kivu province, eastern DR Congo; findings demonstrate that most people (82%), including those who self-identified as having diabetes, utilized healthcare services during times of conflict, suggesting that this greater need for services requires increased availability and quality of care |
| Khader, 2014 [23] | Retrospective cohort study | 119 people with diabetes | Refugees | Healthcare utilization/blood glucose level in mg/dL | In the first 3 years of follow-up among people living with diabetes among a cohort of Palestine refugees, the proportion of clinic attendees decreased from 72% to 64% and then to 61%; the proportion lost to-follow-up increased from 9% to 19% and then to 29%. Overtime refugees attended less visits |
| Rimawi, 2022 [24] | Retrospective matched cohort study | 30 people with DM | The implementation of the Health for Palestine (H4P) Community Health Worker Program in West Bank Camp refugee camps | HbA1c levels over time and systolic and diastolic blood pressure values over 9–12 months | Researchers found that refugees with access to CHW saw a greater decline (1.4 points) in their HbA1c values compared to those without access (95% CI = −0.66, −2.1; $p < .001$), suggesting that refugees without access to care may experience higher HbA1c values |
| Baxter, 2018 [25] | Qualitative | 15 adults who had fled Mosul and presented to Médecins Sans Frontières clinics in the Kurdistan region with HTN and/or diabetes | Armed conflict | Access to care | Participants reported consistent barriers to NCD care during the so-called Islamic State period, including drug shortages, insecurity, and inability to afford privately sold medication. Coping strategies included drug rationing. All interviewed patients in conflict-affected settings had completely or partially lost access to care when a city in Iraq was occupied by the Islamic State group, and 100% of respondents reported cost and availability of drugs to be barriers to access |
| Mansour, 2008 [26] | Mixed methods | The subjects analyzed in this study were adults (≥ 18 years old) with previously diagnosed diabetes (n = 3522) | Armed conflict | Mean HbA1c | Majority of Patient opinion for not achieving good glycemic control among 2688 patients with HbA1c ≥ 7% included no drug supply from primary health care center (PHC) or drug shortages (50.8%), drugs and or laboratory expenses (50.2%), and migration realted reasons (30%), while drugs and or laboratory expense were the cause in 50.2%, and related to migration was 30% |

| Authors last name, year of publication | Type of study | Sample size | Exposure | Outcome | Main findings |
|---|---|---|---|---|---|
| Jacklin, 2017 [27] | Qualitative | 32 participants in the study | Indigenous social determinants | Diabetic care | For several participants, diabetes care was mediated by traumatic historical relations between indigenous people in Canada and the government. The structural violence lens is useful in revealing and understanding barriers to diabetes care for indigenous people |
| Lyles, 2020 [28] | Household survey | 1,376 refugee and 686 host community households | Refugee situation | Care seeking and healthcare utilization | Among 136 diabetes index cases in refugee households, most received care for the condition in Lebanon (88.2%, CI: 81.8–92.6%). Of all Lebanese diabetes cases, 8.5% (CI: 4.9–14.3) of all cases stopped medication without physician instruction. Again, the most common reason for stopping medication without physician instruction was cost |
| Ofosu, 2022 [29] | Qualitative | 3 focus groups (2 groups of 8 and one of 13 participants) and 22 individual interviews (13 community members and 9 brokers) | The syndemic interactions of immigrant and refugee context. With diabetes and obesity. | The challenges faced by individuals in the vulnerable ethnocultural with newcomer communities living with diabetes and obesity | Lack of understanding of pre-migration factors, immigration route/status, and post-immigration stressors culminates in a gap in support for diabetes and obesity care. Consequently, care for people with diabetes and/or obesity from vulnerable immigrant and refugee situations should include a holistic approach |
| Aziz, 2020 [30] | Retrospective case-control | A total of 2317 people with diabetes visited the clinic regularly with 2722 diabetes-related foot symptoms. Study found 2006 lesions belonging to 1630 people with diabetes | War injuries in the diabetic foot | Occurrence of minor and major amputations | Findings demonstrate that that people with diabetes with foot complications are at higher risk of neglect during long term crisis in Syria, potentially resulting in infection (42% experienced infection) and an increased rate of amputations (38.5% for minor amputations and 8.44% for major amputations) |

BMI — body mass index; CHW — community health worker; DFU — diabetic foot ulcers; DM — diabetes mellitus; DSMES — diabetes self-management, education and support; FBG — fasting blood glucose; HbA1c — hemoglobin A1c; HTN — hypertension; MO — military operations; NCD — non-communicable diseases; PAD — peripheral occlusive artery disease; PHC — primary health care center; SEM — structural equation modeling; T2D — type 2 diabetes; TG — triglycerides

## Diabetes outcomes

Five studies described the impact that exposure to war and conflict can have on glycemic outcomes for individuals living with diabetes, particularly examining how exposure may affect an individual's fasting glucose levels and HbA1c before, during, and after a conflict event.

Three studies reviewed patients with type 2 diabetes (T2D) relating specifically to glycemic outcomes. Findings from one study demonstrated that people living with diabetes experienced an elevated mean HbA1c during war, with an increase from 7.7 (61 mmol/mol) (SD 1.9) before the war to 9.4 (80 mmol/mol) (SD 2.4) (p-value: $< 0.001$) during the war, compared to those with no diabetes diagnosis or those with low risk [10]. In another study, investigators sampled various biometrics during a spike in political violence in Ethiopia, and found that individuals without diabetes had a lower mean HbA1c compared to those with diabetes (6.06 vs. 8.8) [11]. One small study ($n = 35$) noted a slight increase (9.13 to 9.53) in HbA1c among individuals with T2D exposed to war for 3 months; however, this change in HbA1c was not significant [12].

One study [13] found exposure to stressful circumstances related to military operations (MO), particularly living in close proximity, to be associated with increased fasting glucose levels, with an increased effect on individuals living with diabetes. Glucose levels were 1.29% higher (95% CI 0.63%; 1.96%) during MO among people without diabetes, and 3.35% higher (95% CI: 1.23%; 5.52%) during MO among people living with diabetes who were treated with glucose-lowering medications. Additionally, when data was collected from 1577 Syrian refugees living with diabetes, only 6% were found to have controlled diabetes, which was defined as participants having an HbA1c% of less than 7. Most refugees (94%) had uncontrolled HbA1c, which has the potential to lead to long-term complications [14].

## Self-management of diabetes and quality of life

Three studies examined how exposure to the direct and indirect effects of war and conflict may lead to negative implications for diabetes self-management and care, leading to a diminished quality of life. Researchers assessing diabetes self-management, education, and support (DSMES) among adult Syrian refugees seeking care for diabetes at a medical humanitarian organization found that individuals diagnosed during the conflict were significantly more likely to have lower DSMES score compared to those who were previously diagnosed after controlling for confounders in multivariable regression modeling [15]. In a qualitative study, [16] aboriginal populations shared their perspective on barriers that negatively affect their self-management of diabetes as it related to structural violence including cultural safety, health literacy, colonialism, and multigenerational trauma. One physician noted that "[These patients] know what they need to do – but they cannot identify what stops them from acting — they know they must exercise, watch their diet, and take their medications, but sometimes perhaps due to their busy lifestyles, or problems in the extended family or preexisting social issues are blocking them so they cannot make (self-management) a priority." In a matched case-control study implementing health-related quality of life (HRQOL) analysis, researchers found that individuals living with diabetes in refugee camps scored significantly lower in all 4 domains of physical health (36.7 vs. 75.9), psychosocial (34.8 vs. 70.0), social relationships (52.4 vs. 71.4), and environmental (23.4 vs. 36.2) compared to those living without diabetes on a 100-point scale [17]. These results suggest that individuals with diabetes living in refugee camps experience a lower quality of life compared to those living without diabetes.

## Access to healthcare and medication usage

Studies also described, through various methods, the impact of war and conflict on healthcare services and medication access and usage. Five studies used cross-sectional and secondary data analysis methodologies to review the impact on healthcare access. The first study analyzed medication use among Syrian refugees in Lebanon for a variety of non-communicable diseases (NCD), including diabetes. Researchers found that while access to medications was high, interval medication interruptions occurred due to financial barriers and a lack of knowledge of where to buy medications. Additionally, females who were diagnosed with diabetes before being displaced were more likely to take medications (87.5%) compared to those who were diagnosed after displacement (63%) [18]. The second study found that among Syrian refugee populations living with diabetes, 26.8% of individuals 18 years old and above had missed a medication dose in the past week, and about 18% of individuals taking medication reported taking a smaller dose to prolong their supply. Of the refugee population living with diabetes, 49.1% sought care in the last month for diabetes. For those who did not receive care, the main reported barrier was cost, including transportation and lost time [19]. Another study highlighted the inequity in treatment for Syrian refugees, especially females and older adults when comparing Lebanese and Syrian refugees. Lebanese people living with diabetes had more access to educa-

tion, nutrition, and diabetes management compared to their counterparts, and they received significantly more advice on diabetes management compared with Syrians in a health service setting (85.2% vs. 55.5%) [20]. Finally, 2 studies described the need for continued care and effects on health care bandwidth among refugees. In a survey of Syrian refugees, 84.7% had received care in Jordan upon fleeing their country, emphasizing the importance of continuing care for those with NCD and demonstrating an increasing burden on the existing health care system [21]. Researchers examined healthcare service utilization in conflict-recovering South Kivu province, eastern DR Congo; findings demonstrated that most people (82%), including those who self-identified as having diabetes, utilized healthcare services during times of conflict, suggesting that this greater need for services requires increased availability and quality of care [22].

Two studies utilized a cohort design. One study showcased the decline in clinic visits among people living with diabetes in refugee camps in the first three years from 72% to 61% and an increase in loss to follow-up from 9% to 29% [23]. Another study emphasized the importance of community health workers (CHW). Using a matched retroactive cohort design, researchers found that refugees with access to CHW saw a greater decline (1.4 points) in their HbA1c values compared to those without access (95% CI −0.66, −2.1; $p < .001$), suggesting that refugees without access to care may experience higher HbA1c values [24].

Five studies utilized patient interviews to understand the impacts of war and conflict on healthcare and medication access. In one study, researchers interviewed patients with NCD, including diabetes, and examined their experience with drug shortages, insecurity, and inability to afford privately sold medications. All interviewed patients in conflict-affected settings had completely or partially lost access to care when a city in Iraq was occupied by the Islamic State group, and 100% of respondents reported cost and availability of drugs to be barriers to access [25]. One study assessed patient-reported barriers to glycemic control among adults (≥ 18 years old) with previously diagnosed diabetes in a clinic in the south of Iraq where war has caused damage to healthcare infrastructure. People living with diabetes declared that causes for poor glycemic control were most likely related to no drug supply or a shortage of drugs (50.8%), the cost of drugs (50.2%), and migration (30%) [26]. Another study examined patients in a very different context by interviewing indigenous people living with T2D in Canada on their healthcare experiences. Participants reflected on experiences in their past relating to residential schools and mentioned that memories can be easily triggered in clinical encounters when doctors are too authoritarian, making participants feel "tired of being told what to do." One participant related such experiences to what physicians sometimes label "noncompliance," noting that physicians often "can't figure out why [people living with diabetes] are doing a certain thing, or why they're not looking after their sugar properly." People living with diabetes revealed that their healthcare was impacted by the colonial legacy and related perpetuation of inequities in medical care and denial in services and treatment [27]. Researchers facilitated interviews in Syrian refugee households living in Lebanon to better understand care seeking behaviors and reasons for interruptions in care. Refugees living with diabetes were most likely to select facilities to seek care based on financial reasoning (78.4%, CI: 69.1–85.5%), whereas residents of Lebanon were most likely to select care based on the care quality and provider factors (50.8%, (CI: 42.1–59.4%). Additionally, 25% (CI: 9.5–51.3) of the population reported stopping medication for 2 weeks or more due to costs (76.5%, CI: 57.8–88.5) [28]. Another study highlighted that post-immigration stress, lack of social network, and cost can negatively impact diabetes outcomes and result in gaps of care or loss of follow-up. One individual stated "They tell me to buy diabetes supply… So I go to the pharmacy and they say it costs me about 90 bucks and bring like that. No coverage. I have to pay. But that time I don't got money in my pocket, so I say I have to wait until I get the pension coming." Barriers such as physician shortages, geographic isolation, appointment time allocation, and healthcare worker turnover or continuity of care impacted healthcare experience [29].

Finally, one study investigated the impact of war and conflict on refugees with diabetes with foot complications. The results of this study demonstrated that this population is at an increased risk of medical neglect during war and conflict, with 42% experiencing infection, 38.5% requiring a minor amputation, and 8.44% requiring a major amputation [30].

## Discussion

### Clinical and policy implications

This review provided a limited number of articles on this specific topic. Analytic methods varied, ranging from qualitative to cross-sectional methodologies. Several studies examined the impact of war and conflict and its effects on glycemic outcomes among those living with diabetes. Some studies found links to increased mean HbA1c during war, particularly among older adults, higher risk of long-term complications for those diagnosed during conflict, and unfavorable gly-

cemic outcomes for individuals living in refugee camps after having fled a war zone [11, 14, 15].

Additionally, a few studies examined the impact that stress related to structural violence may have on diabetes self-management. Exposure to this kind of stress was associated with increased fasting glucose levels and a decrease in self-management due to identified barriers such as cultural safety, health literacy, colonialism, and multigenerational trauma [13, 16, 17] .

Many studies described the impact of war and conflict on healthcare services and medication access including patterns of healthcare utilization during and following war or conflict, inequity in treatment for refugees, drug shortages, insecurity, and inability to afford privately sold medications, and loss of access to care as barriers in conflict settings [18, 20–25, 27–29].

Many of the articles focused on people with T2D. Additionally, many of the listed articles describe the immediate or short-term outcomes (during or up to 5 years post-conflict) of structured violence.

Related topics not explored in this manuscript include the impact of neighborhood-level violence or crime, mirroring similar results found in this study. Tung et al. [31] found that people living with diabetes exposed to community violence had a more difficult time managing chronic conditions. Additionally, Smalls et al. [32] demonstrated that social support and access to healthy foods were significantly associated with diabetes self-care compared with exposure to neighborhood violence, which was not.

Factors predisposing people living with diabetes to deteriorated access to care in conflict settings included mass displacement, medication storage constraints, and disrupted communication between patients and care teams. Healthcare workers are often re-positioned to focus on trauma events during high-conflict settings, and financial challenges and disrupted healthcare supply lines made it extremely difficult for patients to receive more routine care and life-saving supplies [33]. Lack of access to education, medication, and routine care are reported to lead to a higher prevalence of diabetes ketoacidosis (DKA) and lower diabetes compliance in rural and high-conflict settings [34].

Disruptions in food distribution, housing, routine medical care, medications and supplies, and psychosocial care make it nearly impossible for people living with diabetes to manage diabetes effectively [35]. Limited access to insulin in a high stress environment has been shown to cause an increase in HbA1c [10]. These negative impacts can be greatly felt by displaced individuals who are living in refugee camps experiencing even greater interruptions and barriers to care [17, 20, 21, 23, 24, 28].

Long-term solutions that may mitigate these adverse effects during or after exposure to war or conflict would be improved by policies addressing the root causes of war and conflict [35]. The healthcare sector has a role to play in advocating for peace, including "preventing or mitigating the outbreak, escalation, continuation, and recurrence of conflict and addressing its root causes and drivers, including health inequity" [36]. Advocacy efforts can support conditions for people living with diabetes exposed to conflict. Organizations such as the American Diabetes Association (ADA) advocate for access to affordable and evidence-based insulin preparations for all people living with diabetes [37]. Providers in Lebanon are calling on advocacy efforts for more affordable insulin delivering devices, particularly insulin pen injection devices, especially for individuals in humanitarian settings [38]. ADA in collaboration with organizations such as DEFA (Diabetes Education for All) and iADA (international Alliance for Diabetes Actions) put forth resources including insulin switching guides and healthcare professional and patient-facing capacity building and education focusing on conflict and low-income settings [39]. Nonprofit organizations are also aiding in providing diabetes care and supplies for those in areas of war and conflict [40]. These efforts can help to increase access to care in conflict-ridden and post-conflict environments.

While peace advocacy would be most impactful, addressing the direct, short-term impacts of war and conflict on people living with diabetes would support glycemic outcomes, management, and sustained access to healthcare. Having CHW present has been documented to show improvements in glycemic outcomes among people living with diabetes who are living in refugee conditions [24]. Additionally, the potential role of medical students to fill gaps in medical workforce shortages during humanitarian crises is currently being explored as an approach to further assist individuals during war and conflict scenarios [41]. Involvement in support groups to share on stress, diabetes-related complications, and lack of resources is beneficial for people living with diabetes to lessen the emotional and mental burden [42]. War and conflict can, understandably, minimize prioritization of healthcare and quality of life needs for people living with diabetes. In disruptive scenarios like war, the limited articles that met inclusion criteria for this review suggest a need for continuity of healthcare, reliable sources of medication, and customized support for people living with diabetes who have experienced this kind of stress.

### Future direction

The search terms of this paper were limited to "war" and "conflict" that were openly and clearly defined as such. Related but less explicit or colloquially defined as structural violence related to colonialism and structural racism against indigenous populations may illuminate similar impacts on people living with diabetes through stress, historical trauma, and impacts on social determinants of health. Future research should continue investigation of the impact of structural violence on these communities, as well as sharing of best practices to support optimal glycemic outcomes in indigenous populations. Additionally, limited evidence exists to show the intergenerational impact of colonialism and trauma on diabetes self-management.

Recent global developments significantly influence individuals living with diabetes, and ongoing research is deepening our understanding of how events like the COVID-19 pandemic, climate change, and war and conflict affect people living with diabetes. The need for immediate attention and support for advocacy efforts pushing policy changes addressing the cost and other barriers that are adversely affecting the needs of individuals living with diabetes in war and conflict settings is crucial.

### Strengths and limitations

Strengths of this study include the fact that the authors conducted a structured review process to identify current literature on this topic with a long study period. Limitations of this study include the small sample size of identified studies. Due to the lack of variety and quantity of different study methodologies, the quality of evidence could not be appraised. Only publications in English were considered; it is possible that studies on this topic may have been published in other languages.

## Conclusions

The effects of war and conflict on people living with diabetes are profound and multifaceted, directly influencing their glycemic control and other health outcomes, and indirectly affecting individuals through social determinants of health (SDOH), access to care, and availability of medications. There is a pressing need for more extensive research to fully comprehend the nuances of this relationship and to unravel the long-term consequences, both over individual lifespans and across generations, of war and conflict on the health and well-being of people living with diabetes.

## Article information

### Author contributions

O.E conceptualized the manuscript. E.O., H.H., and A.M. wrote the draft manuscript and performed the review. All authors critically reviewed and approved the final version. E.O is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

### Funding

This research was supported in part by The Leona M. and Harry B. Helmsley Charitable Trust.

### Acknowledgments

The authors appreciate Jesse Cases-Villablanca for contributing to an earlier draft of this manuscript.

### Conflict of interest

O.E is a member of the Medtronic and Sanofi Advisory Board and receives consultation and speaker fees from Medtronic Diabetes, Sanofi, and Vertex Pharmaceuticals. He is PI on research supported by Medtronic Diabetes, MannKind Pharmaceuticals, Dexcom, United States, Abbott, Vertex Pharmaceuticals, Janssen Pharmaceuticals, United States.

### REFERENCES

1. Wisevoter. Countries Currenlty at War 2023. https://wisevoter.com/country-rankings/countries-currently-at-war/#tracker_introduction (7.05.2024).
2. Global Appeal 2023 | Regional summary UNHCR 2022. https://reporting.unhcr.org/globalappeal/west-and-central-africa (7.05.2024).
3. How High is the Cost of War Around the World in 2019? Vision of Humanity 2023. https://www.visionofhumanity.org/how-does-war-and-violence-affect-an-economy/#:~:text=The%202021%20Economic%20Value%20of,estimated%20to%20be%20%2414.4%20trillion (7.05.2024).
4. Harada KH, Soleman SR, Ang JS, et al. Conflict-related environmental damages on health: lessons learned from the past wars and ongoing Russian invasion of Ukraine. Environ Health Prev Med. 2022; 27: 35, doi: 10.1265/ehpm.22-00122, indexed in Pubmed: 36058871.
5. Cheraghi F, Shamsaei F, Mortazavi SZ, et al. The Effect of Family-centered Care on Management of Blood Glucose Levels in Adolescents with Diabetes. Int J Community Based Nurs Midwifery. 2015; 3(3): 177–186, indexed in Pubmed: 26171406.
6. Devakumar D, Birch M, Osrin D, et al. The intergenerational effects of war on the health of children. BMC Med. 2014; 12: 57, doi: 10.1186/1741-7015-12-57, indexed in Pubmed: 24694212.
7. Mosley-Johnson E, Walker RJ, Thakkar M, et al. Relationship between housing insecurity, diabetes processes of care, and self-care behaviors. BMC Health Serv Res. 2022; 22(1): 61, doi: 10.1186/s12913-022-07468-7, indexed in Pubmed: 35022049.
8. Carpiniello B. The Mental Health Costs of Armed Conflicts-A Review of Systematic Reviews Conducted on Refugees, Asylum-Seekers and People Living in War Zones. Int J Environ Res Public

Health. 2023; 20(4), doi: 10.3390/ijerph20042840, indexed in Pubmed: 36833537.
9. Daudt HML, van Mossel C, Scott SJ. Enhancing the scoping study methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. BMC Med Res Methodol. 2013; 13: 48, doi: 10.1186/1471-2288-13-48, indexed in Pubmed: 23522333.
10. Sharafi BAl, Tahami B. The Effect of War on the Control of Diabetes in Patients with Type 2 Diabetes Mellitus in Yemen: A Cross-Sectional Study. Endocrinol Metab Syndr. 2017; 6(4): 1–5, doi: 10.4172/2161-1017.1000270.
11. Kohrt BA, Carruth L. Syndemic effects in complex humanitarian emergencies: A framework for understanding political violence and improving multi-morbidity health outcomes. Soc Sci Med. 2022; 295: 113378, doi: 10.1016/j.socscimed.2020.113378, indexed in Pubmed: 33051023.
12. Roglic G, Metelko Z. Effect of war on glycemic control in type II diabetic patients. Diabetes Care. 1993; 16(5): 806–808, doi: 10.2337/diacare.16.5.806, indexed in Pubmed: 8495623.
13. Yitshak-Sade M, Mendelson N, Novack V, et al. The association between an increase in glucose levels and armed conflict-related stress: A population-based study. Sci Rep. 2020; 10(1): 1710, doi: 10.1038/s41598-020-58679-z, indexed in Pubmed: 32015387.
14. Hammad AM, Al Qerem W, Alaqabani H, et al. Factors influencing hypertension and diabetes mellitus control among Syrian refugees in Zaatari refugee camp. Eur Rev Med Pharmacol Sci. 2022; 26(7): 2408–2414, doi: 10.26355/eurrev_202204_28474, indexed in Pubmed: 35442495.
15. Elliott JA, Das D, Cavailler P, et al. A cross-sectional assessment of diabetes self-management, education and support needs of Syrian refugee patients living with diabetes in Bekaa Valley Lebanon. Confl Health. 2018; 12: 40, doi: 10.1186/s13031-018-0174-9, indexed in Pubmed: 30214472.
16. Maar M, Manitowabi D, Gzik D, et al. Serious Complications for Patients, Care Providers and Policy Makers: Tackling the Structural Violence of First Nations People Living with Diabetes in Canada. International Indigenous Policy Journal. 2011; 2(1), doi: 10.18584/iipj.2011.2.1.6.
17. Eljedi A, Mikolajczyk RT, Kraemer A, et al. Health-related quality of life in diabetic patients and controls without diabetes in refugee camps in the Gaza strip: a cross-sectional study. BMC Public Health. 2006; 6: 268, doi: 10.1186/1471-2458-6-268, indexed in Pubmed: 17074088.
18. Saleh S, Abdouni L, Dimassi H, et al. Prevalence of non-communicable diseases and associated medication use among Syrian refugees in Lebanon: an analysis of country-wide data from the Sijilli electronic health records database. Confl Health. 2021; 15(1): 77, doi: 10.1186/s13031-021-00411-3, indexed in Pubmed: 34663406.
19. Ratnayake R, Rawashdeh F, AbuAlRub R, et al. Access to Care and Prevalence of Hypertension and Diabetes Among Syrian Refugees in Northern Jordan. JAMA Netw Open. 2020; 3(10): e2021678, doi: 10.1001/jamanetworkopen.2020.21678, indexed in Pubmed: 33052405.
20. Saleh S, Muhieddine D, Hamadeh RS, et al. Outpatient use patterns and experiences among diabetic and hypertensive patients in fragile settings: a cross-sectional study from Lebanon. BMJ Open. 2022; 12(5): e054564, doi: 10.1136/bmjopen-2021-054564, indexed in Pubmed: 35613758.
21. Doocy S, Lyles E, Akhu-Zaheya L, et al. Health Service Utilization among Syrian Refugees with Chronic Health Conditions in Jordan. PLoS One. 2016; 11(4): e0150088, doi: 10.1371/journal.pone.0150088, indexed in Pubmed: 27073930.
22. Malembaka EB, Karemere H, Bisimwa Balaluka G, et al. Are people most in need utilising health facilities in post-conflict settings? A cross-sectional study from South Kivu, eastern DR Congo. Glob Health Action. 2020; 13(1): 1740419, doi: 10.1080/16549716.2020.1740419, indexed in Pubmed: 32191159.
23. Khader A, Ballout G, Shahin Y, et al. Treatment outcomes in a cohort of Palestine refugees with diabetes mellitus followed through use of E-Health over 3 years in Jordan. Trop Med Int Health. 2014; 19(2): 219–223, doi: 10.1111/tmi.12241, indexed in Pubmed: 24341942.
24. Rimawi A, Shah A, Louis H, et al. Community Health Worker Program Outcomes for Diabetes and Hypertension Control in West Bank Refugee Camps: A Retrospective Matched Cohort Study. Glob Health Sci Pract. 2022; 10(5), doi: 10.9745/GHSP-D-22-00168, indexed in Pubmed: 36316145.
25. Baxter LM, Eldin MS, Al Mohammed A, et al. Access to care for non-communicable diseases in Mosul, Iraq between 2014 and 2017: a rapid qualitative study. Confl Health. 2018; 12: 48, doi: 10.1186/s13031-018-0183-8, indexed in Pubmed: 30619506.
26. Mansour AA. Patients' opinion on the barriers to diabetes control in areas of conflicts: The Iraqi example. Confl Health. 2008; 2: 7, doi: 10.1186/1752-1505-2-7, indexed in Pubmed: 18577229.
27. Jacklin KM, Henderson RI, Green ME, et al. Health care experiences of Indigenous people living with type 2 diabetes in Canada. CMAJ. 2017; 189(3): E106–E112, doi: 10.1503/cmaj.161098, indexed in Pubmed: 28246155.
28. Lyles E, Burnham G, Chlela L, et al. Lebanon Health Access Survey (LHAS) Study Team. Health service utilization and adherence to medication for hypertension and diabetes among Syrian refugees and affected host communities in Lebanon. J Diabetes Metab Disord. 2020; 19(2): 1245–1259, doi: 10.1007/s40200-020-00638-6, indexed in Pubmed: 32963978.
29. Ofosu NN, Luig T, Chiu Y, et al. Understanding the bigger picture: syndemic interactions of the immigrant and refugee context with the lived experience of diabetes and obesity. BMC Public Health. 2022; 22(1): 345, doi: 10.1186/s12889-021-12305-3, indexed in Pubmed: 35180854.
30. Aziz AR, Alsabek MB. Diabetic foot and disaster; risk factors for amputation during the Syrian crisis. J Diabetes Complications. 2020; 34(2): 107493, doi: 10.1016/j.jdiacomp.2019.107493, indexed in Pubmed: 31801697.
31. Tung EL, Johnson TA, O'Neal Y, et al. Experiences of Community Violence Among Adults with Chronic Conditions: Qualitative Findings from Chicago. J Gen Intern Med. 2018; 33(11): 1913–1920, doi: 10.1007/s11606-018-4607-3, indexed in Pubmed: 30076574.
32. Smalls BL, Gregory CM, Zoller JS, et al. Effect of neighborhood factors on diabetes self-care behaviors in adults with type 2 diabetes. Diabetes Res Clin Pract. 2014; 106(3): 435–442, doi: 10.1016/j.diabres.2014.09.029, indexed in Pubmed: 25451904.
33. Stacey M, Gifford R, Pye A. Diabetes care in times of armed conflict. British Journal of Diabetes. 2022; 22(1): 1–4, doi: 10.15277/bjd.2022.339.
34. Ahmed AM, Ahmed NH. Diabetes mellitus in Sudan: the size of the problem and the possibilities of efficient care. Practical Diabetes International. 2002; 18(9): 324–327, doi: 10.1002/pdi.292.
35. Alessi J, Yankiv M. War in Ukraine and barriers to diabetes care. Lancet. 2022; 399(10334): 1465–1466, doi: 10.1016/S0140-6736(22)00480-9, indexed in Pubmed: 35325602.
36. Khan W, Jama M, Pesigan A, et al. Health can contribute to peace in the Eastern Mediterranean Region-what should be done to make it happen? Lancet. 2023; 402(10413): 1601–1603, doi: 10.1016/S0140-6736(23)01795-6, indexed in Pubmed: 37689076.
37. American Diabetes Association Professional Practice Committee. 17. Diabetes Advocacy: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2022; 45(Suppl 1): S254–S255, doi: 10.2337/dc22-S017, indexed in Pubmed: 34964878.
38. New MSF report shows unacceptable global double standard in diabetes care, even though better treatments cost little to produce and could be much more affordable [press release]. Access Campaign 2024. https://www.msfaccess.org/new-msf-report-shows-unacceptable-global-double-standard-diabetes-care-even-though-better (7.05.2024).
39. Improving diabetes care in humanitarian settings International Alliance for Diabetes Action 2022. https://www.iadadiabetes.org/ (7.05.2024).

40. Ocheretenko V. Diabetes and War: The Critical Role of Diabetes Organizations during Humanitarian Emergencies Direct Relief 2022. https://www.directrelief.org/2022/07/diabetes-and-war-the-critical-role-of-diabetes-organizations-during-humanitarian-emergencies/ (7.05.2024).
41. Yoo JiW, Barmanray RD. The role of medical students in humanitarian responses to armed conflict. Lancet Diabetes Endocrinol. 2024; 12(2): 92–94, doi: 10.1016/S2213-8587(23)00366-2, indexed in Pubmed: 38184000.
42. Virmani A, Brink SJ, Middlehurst A, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Management of the child, adolescent, and young adult with diabetes in limited resource settings. Pediatr Diabetes. 2022; 23(8): 1529–1551, doi: 10.1111/pedi.13456, indexed in Pubmed: 36537524.

VIA MEDICA
REVIEW ARTICLE
ISSN 2450–7458
e-ISSN 2450–8187

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# Decoding the Genetic Blueprint: Advancing Personalized Medicine in Type 2 Diabetes through Pharmacogenomics

## ABSTRACT

**Objective: The escalation of type 2 diabetes (T2D) as a global health crisis necessitates a shift towards personalized medicine to optimize treatment efficacy and minimize adverse drug reactions (ADRs). This review article underscores the significant role of pharmacogenomics in refining T2D management. We explore the influence of genetic variations on the pharmacokinetics and pharmacodynamics of commonly used antidiabetic drugs, including metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and SGLT2 inhibitors.**

**Materials and methods: A systematic review of existing literature was carried out, concentrating on studies exploring personalized medicine in T2D through pharmacogenomics. The literature search encompassed databases such as Medline, Scopus, Web of Science (WOS), and PubMed. Key insights regarding the role of pharmacogenomics in managing T2D were compiled and analyzed.**

**Results and conclusions: The review highlights how genetic polymorphisms in drug transporters, metabolizing enzymes, and drug targets correlate with variations in drug response and tolerance. We advocate for preemptive genotyping and integration of genetic data into clinical decision-making, which could revolutionize patient care in T2D. The future of diabetes treatment lies in harnessing pharmacogenomic insights to tailor therapeutic regimens, thereby transitioning from a one-size-fits-all approach to a more nuanced, individualized treatment strategy. With advancements in genomic technologies and a reduction in genotyping costs, the implementation of genetic testing in routine clinical practice is becoming increasingly viable, signaling a new era in the personalized management of T2D.**
**(Clin Diabetol 2024; 13, 6: 386–396)**

**Keywords: type 2 diabetes, pharmacogenomics, personalized medicine, antidiabetic drugs, genotyping**

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Clinical Diabetology 2024, 13; 6: 386–396
DOI: 10.5603/cd.102035
Received: 11.08.2024 Accepted: 15.09.2024
Early publication date: 22.10.2024

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## Introduction

Type 2 diabetes (T2D) remains a global epidemic, characterized by significant variability in individual responses to pharmacotherapy, complicating effective management and control. With the increasing prevalence of T2D worldwide, there is a pressing need for personalized treatment strategies that not only enhance therapeutic efficacy but also minimize adverse effects. In this context, pharmacogenomics (PGx) — the study of how genes affect a person's response to drugs — emerges as a transformative approach to diabetes management. This review article delves into the potential of pharmacogenomics to tailor treatments based on genetic profiles, thus revolutionizing the paradigm of T2D management.

Pharmacogenomics combines the disciplines of pharmacology and genomics to predict how individuals might respond to specific drugs based on their genetic makeup. It holds the promise of optimizing drug therapy by customizing medications in a way that maximizes efficacy and minimizes risk, thereby embodying the principles of personalized medicine. By analyzing the interplay between genetic variants and drug responses, pharmacogenomics aims to identify the most suitable drug and dosage for each patient, reducing the trial-and-error approach that is often prevalent in diabetes treatment.

The field of pharmacogenomics distinguishes itself from pharmacogenetics, although the terms are often used interchangeably. Pharmacogenetics focuses on the influence of single gene variants on drug response, traditionally examining monogenic effects, where variations in one gene can significantly impact how a patient metabolizes or responds to a drug. Common examples include variations in genes encoding drug-metabolizing enzymes like the CYP450 family, which significantly influence the metabolism of various antidiabetic drugs[1].

Conversely, pharmacogenomics embraces a broader scope, examining the effects of multiple genes (polygenic influences) and how they interact with environmental and lifestyle factors to affect drug response. This comprehensive approach is particularly vital in T2D, where the disease mechanism and drug reactions are influenced by a complex network of genetic, environmental, and lifestyle factors. Pharmacogenomics, therefore, seeks to understand these complex interactions on a genome-wide scale using advanced technologies such as genome-wide association studies (GWAS) [1].

However, the application of pharmacogenomics in clinical practice faces significant challenges, including the need for large-scale studies to validate genetic markers of drug response and the integration of complex genetic data into practical treatment decisions. Moreover, the variability in drug response genes across different populations highlights the necessity for diverse and inclusive research that ensures the global applicability of pharmacogenomic discoveries.

This review aims to explore the current landscape of pharmacogenomics research in T2D, highlighting key genetic determinants of drug response, the integration of pharmacogenomic data into clinical practice, and future directions in this field. By advancing our understanding of genetic influences on drug efficacy and safety in T2D, pharmacogenomics not only promises to enhance individual patient care but also to facilitate broader advancements in the field of personalized medicine.

## Types of genetic variation influencing drug response

In the context of T2D treatment, the impact of genetic variation on drug response is a critical consideration for tailoring effective therapies. Genetic variations, or pharmacogenetic traits, influence drug efficacy and safety, dictating personalized treatment approaches. These variations can be broadly categorized based on their frequency in the population, the number of base pairs involved, their location within the gene, and the effects on the encoded protein. In a groundbreaking study involving approximately 150,000 individuals from 5 diverse ancestry groups, researchers have discovered 12 rare protein-truncating variants in the SLC30A8 gene, which is responsible for encoding the islet zinc transporter ZnT8. This gene was already known for a common variant that impacts T2D susceptibility and influences glucose and proinsulin levels. Notably, individuals carrying these truncating variants exhibited a significant 65% reduction in the risk of developing T2D, highlighting a novel protective genetic mechanism. Specifically, Icelandic carriers of a frameshift variant (p.Lys34Serfs*50) showed notably lower glucose levels, underscoring the potential of targeting ZnT8 for T2D prevention. This discovery provides robust human evidence that contradicts previous animal models, suggesting that inhibiting ZnT8 could be a viable therapeutic strategy for reducing T2D risk [2]. This insight not only advances our understanding of genetic influences on diabetes but also opens new avenues for therapeutic intervention. This section discusses how these genetic factors affect drug response and highlights the relevance of understanding these variations in the management of T2D.

## Frequency and commonality of pharmacogenetic variants

Pharmacogenetic variants differ greatly in their frequency within populations, which can significantly influence the selection pressure on these genes. For instance, variants involved in drug metabolism often have no noticeable impact until a drug is administered, leading to a lack of natural selection against potentially deleterious alleles. As a result, certain pharmacogenetic variants are remarkably common compared to those associated with severe genetic disorders. An example relevant to diabetes treatment is the variability in the CYP3A5 gene, where most individuals of European descent carry non-functional alleles, whereas many from African descent have one or more functional alleles. This difference can affect the metabolism of drugs commonly used in diabetes management, such as sulfonylureas, which are metabolized by CYP enzymes [1].

## Size and nature of genetic variations

Genetic variations influencing drug response include single-nucleotide variants (SNVs), which are alterations of a single base pair, and copy number variants (CNVs), which involve larger segments of DNA and can include whole genes. For example, the number of functional CYP2D6 enzyme variants a person has can vary widely, influenced by over 100 possible SNVs and CNVs that might delete or duplicate the gene. Such variability can affect the metabolism of many drugs used in diabetes care, altering their effectiveness and risk of adverse effects [1].

## Impact on protein function and expression

Variations can also directly alter the amino acid sequence of proteins, potentially leading to gains or losses of function. For instance, the UGT1A1*28 variant, which features an additional TA repeat in the promoter region, is associated with reduced expression of the enzyme in the liver [3]. This variant not only influences drug metabolism but is also linked to Gilbert's syndrome, a condition that may complicate drug therapy in diabetes due to elevated bilirubin levels. Understanding these genetic variations is crucial for anticipating drug responses in diabetic patients.

## Pharmacogenomic haplotypes and their clinical implications

The complexity of pharmacogenomic effects is often encapsulated in haplotypes — a series of linked genetic variants that tend to be inherited together. Haplotypes can be more predictive of drug response than individual SNVs due to the combined effects of multiple linked variants. The "star allele" nomenclature is used to describe these haplotypes concisely, with "1" typically indicating a functional allele. For example, the CYP3A51 allele indicates normal enzyme activity, crucial for the metabolism of certain diabetes medications, while CYP3A5*3, common in Europeans, indicates a loss of function, which can alter drug processing and efficacy [4].

## Implications for diabetes management

The identification and characterization of these genetic variants through association studies and genome-wide association studies (GWAS) provide critical insights into patient-specific drug metabolism profiles. However, these studies must be followed by functional characterizations to confirm the causative links between genetic variants and drug responses [1, 4]. Moreover, the variations in linkage disequilibrium patterns across populations highlight the need for population-specific studies to ensure the generalizability of pharmacogenomic applications in diabetes treatment.

By integrating pharmacogenomic data into the clinical management of diabetes, healthcare providers can better predict patient responses to various therapeutic agents, optimizing treatment plans to achieve better glycemic control while minimizing adverse effects. This approach not only enhances individual patient care but also moves the field toward a more nuanced and effective management strategy for T2D.

## The role of pharmacogenes in drug response

Pharmacogenes play a pivotal role in the body's response to medications by determining drug effects and concentrations. These genes encode for enzymes, transporters, and drug targets that are integral to pharmacokinetics — the movement of drugs through the body — and pharmacodynamics, which concerns the effects drugs have on the body. For instance, variations in the CYP2C9 gene affect the metabolism of Warfarin, a widely used anticoagulant, which can lead to differences in drug efficacy and safety profiles among individuals. Likewise, genetic differences in SLCO1B1 can alter the transport and hence the impact of simvastatin, which is used to control hyperlipidemia. These pharmacogenomic variations also extend to the drug targets themselves, such as VKORC1 with warfarin, where genetic differences can influence the drug's anticoagulant effect. The intricacies of these interactions become even more pronounced when considering adverse drug reactions, which can be categorized as immune-mediated or non-immune. For example, genetic variants in HLA-B5701 are associated with hy-

persensitivity to abacavir, while variants in HLA-B5801 are linked to severe skin reactions with allopurinol [5]. Such knowledge is instrumental in anticipating individual responses to pharmacotherapy, emphasizing the need for genetic screening prior to prescribing certain medications.

## Genetic variability and drug metabolism

The genetic blueprint of an individual significantly influences their capacity to metabolize drugs. This process is highly heritable, and certain genetic phenotypes are associated with varying degrees of metabolism efficiency, categorized as poor, intermediate, or normal metabolizers. A classic example is the CYP2C19 gene, where different haplotypes, referred to as "star alleles," can profoundly affect the enzyme's functionality. The CYP2C191 allele is associated with normal function, whereas the CYP2C192 and 3 alleles result in no enzyme activity. Conversely, the CYP2C1917 allele leads to increased enzyme expression and potentially ultra-rapid drug metabolism. These genetic variations can have significant implications for the efficacy and safety of drugs metabolized by CYP2C19, such as certain anticonvulsants and antiplatelet agents [1]. Large-scale studies, including twin studies, have underlined the genetic underpinnings of these metabolic traits, which has substantial ramifications for personalized medicine, especially in the context of diabetes, where pharmacotherapy is a cornerstone of disease management.

## A framework for evaluating PGx in type 2 diabetes

To harness the full potential of pharmacogenomics in the context of T2D, a structured approach to evaluate its impact on drug therapy is essential. The provided framework delineates the variation in pharmacokinetic and pharmacodynamic responses, as well as genetic predisposition to diabetes itself. For example, the genetic makeup affecting drug transport and metabolism can lead to variations in treatment efficacy, such as the intolerance seen in some patients to metformin, a first-line T2D medication. Similarly, the genetic factors contributing to the disease's etiology, such as those influencing the risk of developing diabetes, have been linked to disparate pharmacogenomic effects in monogenic versus polygenic forms of diabetes. Large PGx effects are observed in monogenic diabetes due to the direct association with single-gene defects, while smaller PGx effects are seen with polygenic T2D. Additionally, the genetic determinants of drug targets and downstream action can inform the selection of therapies, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, where moderate PGx effects are possible [6]. This framework underscores the complexity of evaluating PGx in T2D and the necessity for a comprehensive understanding of genetic influences to optimize pharmacotherapy for individual patients.

Together, these insights underscore the intricate connections between genetic variation and drug response in T2D management. They provide a blueprint for integrating pharmacogenomic data into clinical practice, paving the way for more personalized, effective, and safe treatment strategies.

## Genetic variability and its impact on metformin efficacy in type 2 diabetes

Metformin operates through complex pharmacokinetic processes influenced significantly by genetic polymorphisms in transporter genes. The absorption and distribution of metformin are mediated by various organic cation transporters (OCTs) and multidrug and toxin extrusion proteins (MATEs), which are encoded by the SLC22 and SLC47 gene families, respectively [7]. Notably, the SLC22A1 gene, encoding OCT1, plays a pivotal role in metformin's hepatic uptake, with polymorphisms such as rs622342 significantly affecting therapeutic efficacy in different ethnic groups. For instance, this polymorphism has been associated with varied responses in South Indian and Chinese patients with T2D, indicating a differential impact on metformin's glucose-lowering effect [8, 9].

Furthermore, the impact of genetic variations extends to other transporter genes like SLC22A2 and SLC22A3, which encode OCT2 and OCT3, respectively. These transporters facilitate the renal and hepatic uptake of metformin. Studies have shown that polymorphisms in these genes can alter the pharmacokinetics of metformin, influencing its clearance from the bloodstream and consequently its efficacy in lowering blood glucose levels. For example, the SLC22A2 808G>T variant has been observed to enhance the glucose-lowering efficiency of metformin in Chinese patients by delaying its renal transport [10].

Moreover, the SLC47A1 and SLC47A2 genes, encoding MATE1 and MATE2, are crucial for the excretion of metformin into urine and bile. Polymorphisms in these genes, such as SLC47A1 rs2289669, have been linked to significant differences in metformin response, with some variants associated with improved glycemic control through delayed renal elimination or increased basal glucagon-like peptide-1 (GLP-1) levels [11, 12]. Understanding these genetic influences is essential for tailoring metformin therapy to individual patients, potentially enhancing therapeutic outcomes and minimizing side effects.

**Table 1. The Impact of Genetic Polymorphisms on Metformin Pharmacokinetics and Therapeutic Response**

| Gene | Protein | Function in Metformin transport | Polymorphism | Impact on metformin response | Notable ethnic variation |
|---|---|---|---|---|---|
| SLC22A1 | OCT1 | Hepatic uptake of metformin | rs622342 | Affects therapeutic efficacy; linked to varied glucose-lowering effects | Significant in South Indian, Chinese |
| SLC22A2 | OCT2 | Renal uptake of metformin | 808G>T | Enhances glucose-lowering efficiency by delaying renal transport | Notable in Chinese |
| SLC22A3 | OCT3 | Uptake in intestine and liver | Various | Influence on therapeutic efficacy varies with specific polymorphisms | Varies by ethnicity |
| SLC47A1 | MATE1 | Excretion into urine and bile | rs2289669 | May improve glycemic control through delayed renal elimination | Varied responses in different populations |
| SLC47A2 | MATE2 | Renal excretion of metformin | Various | Linked to changes in HbA1c levels and treatment failure rates | Significant in diverse populations |
| SLC29A4 | PMAT | Intestinal absorption of metformin | Various | Associated with gastrointestinal intolerance and renal clearance | Significant in Korean |

Table 1 provides an overview of how different polymorphisms in key transporter genes can influence the effectiveness of metformin in managing T2D across various ethnic groups, highlighting the importance of personalized medicine.

## Genetic influences on sulfonylurea efficacy and metabolism in type 2 diabetes management

Sulfonylureas are a critical class of medications used in the management of T2D by enhancing insulin secretion. This class of drugs operates by targeting and closing the ATP-sensitive potassium channels (KATP channels) located on the membranes of pancreatic beta cells. These channels are composed of 2 main subunits: sulfonylurea receptor 1 (SUR1), which is encoded by the ABCC8 gene, and the inward-rectifier potassium ion channel (Kir6.2), encoded by the KCNJ11 gene. The closure of these channels leads to cellular depolarization and subsequent insulin release via calcium channel activation [13].

Significant genetic variations in these target genes, such as the ABCC8 gene, can markedly influence the response to sulfonylurea drugs. For instance, the Ser1369Ala polymorphism in the ABCC8 gene has been associated with differential therapeutic efficacy in various ethnic populations [14]. Research has demonstrated that this specific variant can impact the effectiveness of gliclazide, a common sulfonylurea, with notable associations found in Chinese patients, suggesting a significant modulation of drug response based on genetic makeup [15, 16]. However, other studies have provided conflicting results, indicating that the same polymorphism might not universally affect the response to sulfonylurea treatment across different populations [13].

In addition to the SUR1 gene, the KCNJ11 gene encoding Kir6.2 also exhibits polymorphisms that affect sulfonylurea efficacy. The E23K variant of KCNJ11 is particularly noteworthy; studies have shown it can influence both the risk of hypoglycemia and overall therapeutic response to sulfonylureas. For example, this polymorphism was associated with higher HbA1c reduction following gliclazide treatment in Caucasian populations and varied responses in treatment efficacy and hypoglycemia risk among different ethnic groups [15, 17].

Furthermore, the metabolism of sulfonylureas is predominantly facilitated by the cytochrome P450 enzymes, specifically CYP2C9, in the liver. Polymorphisms in the CYP2C9 gene, such as the *2 and *3 variants, have been found to significantly alter the pharmacokinetics of sulfonylureas. These genetic variants can lead to higher drug concentrations and prolonged drug activity, thereby modifying the risk of therapy failure and potentially enhancing glycemic control in patients treated with these drugs [18].

These insights underscore the crucial role of genetic profiling in optimizing the management of T2D with sulfonylureas. Understanding individual genetic differences in the ABCC8, KCNJ11, and CYP2C9 genes provides a foundational basis for personalized medicine approaches, aiming to tailor treatments according to patient-specific genetic backgrounds to maximize therapeutic efficacy and minimize adverse effects.

**Table 2. Pharmacogenomic Variants and Their Clinical Impact on Thiazolidinedione Therapy in Type 2 Diabetes [29]**

| Gene | SNP | Alleles | Clinical significance of variant | Adverse effect |
|---|---|---|---|---|
| CYP2C8 | rs10509681 | C/T | Influences pharmacokinetics of TZDs, related to edema | Edema |
| | rs78637571 | C/A | Affects rosiglitazone pharmacokinetics, associated with hypoglycemia | Hypoglycemia |
| | rs11572103 | A/T | Modulates pioglitazone pharmacokinetics | — |
| | rs11572080 | A/G | Alters rosiglitazone response and risk of edema | Edema |
| PPARG | rs1801282 | C/G | Associated with TZD response, impacts FPG, HbA1c, TG | — |
| PPARGC1A | rs8192678 | A/G | Influences response to rosiglitazone | — |
| | rs2970847 | C/T | Related to rosiglitazone response | — |
| ADIPOQ | rs266729 | C/G | Related to improved TZD response, affects FPG, HbA1c | — |
| | rs2241766 | A/C | Associated with rosiglitazone response, impacts FPG, HbA1c | — |
| | rs1501299 | G/T | Linked to changes in fasting glucose and HbA1c post-rosiglitazone therapy | — |

FPG — fasting plasma glucose; HbA1C — glycated hemoglobin; SNP — single nucleotide polymorphisms; TG — triglycerides; TZDs — thiazolidinediones

## Genetic variability and glinide response in diabetes treatment

Glinides, notably repaglinide, are medications used to stimulate insulin release in diabetic patients by targeting the ATP-sensitive potassium (KATP) channels on pancreatic β-cell membranes. These channels consist of SUR1 and Kir6.2 subunits, encoded by the ABCC8 and KCNJ11 genes, respectively. Detailed pharmacogenomic research indicates that specific genetic variants in these genes markedly influence the therapeutic response to glinides. Specifically, the ABCC8 rs1801261 single nucleotide polymorphism (SNP) exhibits variable effects based on its alleles; patients with the CT genotype show significant reductions in fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels compared to those with the more common CC genotype [19, 20]. Additionally, the CC genotype of the ABCC8 rs1799854 SNP is linked to improved insulin sensitivity, as shown by lower values in the homeostasis model assessment of insulin resistance (HOMA-IR). Similarly, for the KCNJ11 E23K variant (rs5219), individuals carrying the K allele (either E/K or K/K genotypes) have significantly reduced HbA1c and postprandial glucose levels, indicating a more favorable pharmacological response to repaglinide [21, 22]. These findings emphasize the necessity of integrating genetic testing into the treatment planning for diabetes, as they confirm that genetic polymorphisms can substantially alter drug efficacy and patient outcomes. This tailored approach to diabetes management could lead to more precise and effective treatment strategies, enhancing therapeutic success rates and patient quality of life.

## Pharmacogenomic insights into thiazolidinediones

The pharmacogenomics of thiazolidinediones (TZDs), which encompasses pioglitazone and rosiglitazone, has garnered attention due to its impact on the therapeutic outcomes in T2D management. These drugs, functioning as insulin sensitizers, are metabolized primarily by cytochrome P450 enzymes, particularly CYP2C8. Notably, the CYP2C83 haplotype, characterized by rs11572080 and rs10509681 polymorphisms, is associated with a decreased rosiglitazone area under the curve (AUC) and an altered risk of edema, while the CYP2C811 variant, marked by the rs78637571 stop-gain mutation, heightens rosiglitazone bioavailability. The rs11572103 variant, indicative of CYP2C8*2, also influences pioglitazone pharmacokinetics, particularly in African Americans [23, 24]. PPARG, the target receptor for TZDs, harbors the Pro12Ala polymorphism (rs1801282), consistently linked with a lower T2D risk and improved responses to pioglitazone, as shown by enhancements in fasting glucose, HbA1c, and triglycerides, although some studies contest this association. PPARGC1A variants such as Thr394Thr (rs2970847) and Gly482Ser (rs8192678) have been shown to have an influence on rosiglitazone response in Chinese T2D patients, but with no significant effect noted with pioglitazone [25, 26]. In the adiponectin encoding gene ADIPOQ, the rs266729 variant upstream of the gene correlates with better pioglitazone response, and the synonymous T45G polymorphism (rs2241766) is associated with pioglitazone response in Southern Chinese T2D patients. The intronic SNP rs1501299 also associates with fasting glucose and HbA1c reductions

**Table 3. Genetic Variants Influencing Response to DPP-4 Inhibitors and GLP-1 Receptor Agonist Therapies in Type 2 Diabetes [29]**

| Gene | SNP | Alleles | Chromosomal region | Molecular function | Clinical impact on therapy |
|---|---|---|---|---|---|
| GIPR | rs13306399 | C/G | 19q13.32 | Missense Cys46Ser | Alters GIP binding, affects GIP sensitivity |
| GIPR | rs13306403 | G/T | 19q13.32 | Missense Arg316Leu | Decreases GIP sensitivity |
| GIPR | rs1800437 | C/G | 19q13.32 | Missense Glu354Gln | Reduces GIPR signaling, linked to CVD |
| GLP1R | rs10305420 | C/T | 6p21.2 | Missense Pro7Leu | Modulates response to liraglutide |
| GLP1R | rs6923761 | A/G | 6p21.2 | Missense Gly168Ser | Influences DPP-4i efficacy, alters liraglutide response |
| KCNQ1 | rs163184 | C/A | 11p15.4 | – | Affects HbA1c reduction from DPP-4i treatment |
| TCF7L2 | rs7903146 | C/T | 10q25.2 | – | May reduce GLP-1 action on beta cells, influences response to linagliptin |

CVD — cardiovascular disease; DPP-4i — dipeptidyl peptidase 4 inhibitor; GIP — gastric inhibitory polypeptide; GIPR — gastric inhibitory polypeptide receptor; GLP-1 — glucagon-like peptide-1; SNP — single nucleotide polymorphisms

post-rosiglitazone therapy [27, 28]. These genetic findings inform the pharmacogenomic landscape of TZD responsiveness, indicating the potential of personalized medicine in enhancing the management of T2D by tailoring treatments based on individual genetic profiles.

Table 2 is simplified for clarity and focuses on the clinical implications of the genetic variants on the efficacy and side effects of TZD therapy in patients. The term "—" is used where there is no direct adverse effect mentioned or the effect is not clearly defined.

Genetic determinants of response to DPP-4 inhibitors and GLP-1 receptor agonists

In the treatment landscape of T2D, dipeptidyl peptidase 4 (DPP-4) inhibitors and GLP-1 receptor agonists have emerged as effective modalities, known for their low hypoglycemia risk and beneficial impact on patients' quality of life. These agents exploit the incretin pathway: DPP-4 inhibitors prolong the activity of incretins like GLP-1 and gastric inhibitory polypeptide (GIP) by preventing their rapid degradation, while GLP-1 receptor agonists directly stimulate the GLP-1 receptor, enhancing glucose-mediated insulin secretion.

Polymorphisms within the genes encoding the GIP receptor (GIPR) have been identified, such as rs13306399 (Cys46Ser), which alters GIP binding, and rs13306403 (Arg316Leu), which reduces GIP sensitivity in beta cells [30]. The rs1800437 polymorphism is linked to cardiovascular disease incidence and affects the receptor's signaling dynamics, with implications for incretin-based therapies [31]. Additionally, the intronic variant rs10423928 in the GIPR gene may influence the receptor's function and has been associated with changes in glucose levels and body composition markers in response to incretin effects [32].

For the GLP-1 receptor, the rs367543060 (Thr149Met) variant is noteworthy for its functional impact in vitro and on insulin response to GLP-1 in vivo [33]. The rs6923761 (Gly168Ser) SNP presents a complex picture: it is associated with a reduced insulin response to GLP-1, but it predicts greater efficacy of liraglutide treatment and favorable changes in weight and metabolic profiles. The haplotype including rs6923761 and rs10305420 (Pro7Leu) further illustrates the nuanced genetic impact on treatment efficacy with liraglutide [34]. Other variants such as rs3765467 (Arg131Gln) and rs10305492 (Ala316Thr) have been linked to beta-cell responsiveness and fasting glucose levels, respectively.

KCNQ1 gene polymorphisms also exhibit associations with GLP-1 and GIP release and responses to DPP-4 inhibitor treatment, as exemplified by the rs163184 G allele's association with lower HbA1c reduction. This reflects findings across different ethnicities and underscores the gene's role in both incretin release and insulin secretion.

Notably, TCF7L2, which may influence GLP-1 synthesis, harbors variants such as rs7903146 and rs12255372 that could attenuate GLP-1 action on beta cells [35], as shown by differential responses to the DPP-4 inhibitor linagliptin. This finding, however, is not uniformly supported across studies.

These genetic insights accentuate the importance of personalized medicine in T2D. By understanding the genetic determinants that modulate the response to DPP-4 inhibitors and GLP-1 receptor agonists, clinicians can better tailor treatments, improving efficacy and minimizing adverse effects, thereby advancing the paradigm of individualized therapy in diabetes care.

Table 3 encapsulates genetic variations that have been identified as influencing the efficacy and response to DPP-4 inhibitor therapy and GLP-1 receptor agonists. The GIPR gene's SNPs have been associated

**Table 4. Pharmacogenomic Influences on SGLT2 Inhibitor Efficacy and Metabolism [43]**

| Gene | SNP (rs number) | Clinical impact of genetic variation | Drug association | Notes on drug efficacy or metabolism |
|---|---|---|---|---|
| WFS1 | rs10010131 | Carriers of the A allele exhibit a decrease in body weight | Dapagliflozin | Weight reduction more pronounced in individuals with two A alleles |
| PNPLA3 | rs738409 | Associated with variations in liver fat content. CG/GG genotype linked with higher reduction in liver PDFF with combined therapy | Dapagliflozin + omega-3-carboxylic acids | Lower reduction in liver PDFF with dapagliflozin alone |
| UGT1A9 | rs72551330 | Higher dose-normalized steady-state AUC (AUC_ss) and lower M/P ratio for M5 metabolite | Canagliflozin | Indicates increased plasma exposure to canagliflozin in carriers |
| UGT2B4 | rsNot provided | Higher dose-normalized AUC_ss and lower M/P ratio for both metabolites | Not specified | Suggests variation in metabolism efficiency |
| SLC5A2 | rs3116650, rs3116149, rs11646054 | Changes in systolic blood pressure and fasting postprandial glucose levels | Empagliflozin | Allelic variations correspond to changes in drug efficacy and metabolic response |

AUC — area under curve; PDFF — proton density fat fraction; SNP — single nucleotide polymorphisms

with variations in the sensitivity and expression of GIP, which are essential for the incretin effect utilized by these therapeutic agents. Variants in the GLP1R gene, such as rs10305420 and rs6923761, show differential responses to liraglutide treatment and general DPP-4 inhibitor responses, influencing therapy outcomes. The KCNQ1 and TCF7L2 gene variants also play a role in treatment efficacy, indicating potential areas where personalized medicine can optimize T2D management by considering individual genetic backgrounds. Adverse effect like cardiovascular disease (CVD) is noted as a concern for the rs1800437 SNP in the GIPR gene.

## SGLT2 inhibitors: a shift in diabetes management and pharmacogenomic insights

SGLT2 inhibitors represent a significant advancement in the management of T2D, providing a mechanism to lower glucose levels with a lower risk of hypoglycemia and improving life quality for patients. Initially discovered through phlorizin, a non-selective SGLT inhibitor derived from apple tree bark, the development of selective SGLT2 inhibitors like dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin has revolutionized diabetes therapy. These modern drugs, structurally related to phlorizin, have minimal adverse effects and have proven to be highly effective in enhancing glycemic regulation and inducing weight loss through increased glucose elimination in urine.

Dapagliflozin stands out as a potent, orally active SGLT2 inhibitor that competes with glucose at the renal binding site, thereby blocking glucose reabsorption and promoting its excretion. This process is dose-dependent, leading to significant glucose excretion and serum uric acid reduction, with a noted oral bioavailability of 78% [36]. Despite its benefits, the use of dapagliflozin is carefully monitored due to possible side effects such as genital infections, vertigo, hypotension, and potential renal function deterioration. The drug's metabolism primarily involves oxidative reactions and glucuronidation, excluding the involvement of CYP isoenzymes, and its elimination is facilitated through both renal and biliary pathways.

Pharmacogenetic studies have delved into the interindividual variations in response to dapagliflozin. Notably, the WFS1 gene, coding for a transmembrane protein implicated in cellular homeostasis and calcium signaling, has been associated with weight loss in patients treated with dapagliflozin [37, 38]. Another gene, PNPLA3, related to lipid metabolism and NAFLD risk, has shown an interaction with the treatment's efficacy, especially regarding liver fat content [39].

Canagliflozin, another FDA-approved SGLT2 inhibitor, has been linked to a reduced risk of cardiovascular events and end-stage kidney disease. Its glucose-lowering action is dose-dependent, and its oral bioavailability is 65%. Metabolized into inactive O-glucuronide metabolites by UGT1A9 and UGT2B4, canagliflozin is also affected by genetic polymorphisms that influence the rate of glucuronidation and therapeutic responses. For instance, carriers of the UGT1A9*3 allele exhibit increased plasma exposure to the drug, suggesting a heightened sensitivity [40, 41].

Empagliflozin, known for its high selectivity for SGLT2, is notable for reducing cardiovascular mor-

tality in T2D patients. The drug demonstrates high oral bioavailability and is extensively metabolized by UGT isozymes, with its pharmacokinetic and dynamic profiles being affected by genetic variants within the SLC5A2 gene, which can alter patient responses, including blood pressure regulation and glucose levels [42].

In conclusion, the pharmacogenomics of SGLT2 inhibitors highlight the crucial role of genetic variations in dictating drug responses and potential adverse effects in T2D management. Personalized medicine approaches, therefore, necessitate an integration of genetic testing to tailor treatments, mitigate risks, and optimize clinical outcomes in diabetes care.

Table 4 captures the genetic variants across different genes that influence the pharmacodynamics and pharmacokinetics of various SGLT2 inhibitors. It highlights the impact of specific SNPs on clinical outcomes such as body weight, liver fat content, and metabolic changes such as glucose and uric acid levels. It is noted that while certain SNPs are directly linked to the metabolism of the drugs (UGT1A9 and UGT2B4), others (WFS1, PNPLA3, and SLC5A2) influence the response to the drugs, demonstrating the complex nature of pharmacogenomics in diabetes treatment.

## Embracing genomic diversity in diabetes care

As we decode the genetic intricacies underlying T2D, it is imperative to harness the power of pharmacogenetics to steer clinical decision-making towards a more personalized approach. The therapeutic landscape of T2D is complex, as is its genetic underpinning, but significant strides have been made to elucidate how genetic variability can influence treatment outcomes.

## Metformin: bridging genes and gastrointestinal tolerance

Metformin, the cornerstone of T2D management, presents a unique case where genetic variations in transporters like OCT1 (SLC22A1), PMAT (SLC29A4), and SERT (SLC6A4) significantly influence drug tolerance. Approximately 5–10% of patients experience gastrointestinal intolerance to metformin, which may stem from the high concentrations of the drug in the enterocytes, altered gut microbiota, or interference with bile acid reabsorption. Variants in the aforementioned transporters not only modulate the drug's absorption and distribution but also the risk of intolerance, underscoring the need for genetic considerations in metformin therapy.

## Sulfonylureas and the KATP channel: a genetic conundrum

Sulfonylureas operate by stimulating insulin secretion via the KATP channel, but genetic variations like those in ABCC8/KCNJ11 and TCF7L2 influence their effectiveness and safety. The response to sulfonylureas is significantly better in individuals with slower CYP2C9 metabolism, exemplifying how genetic factors can inform drug dosing and efficacy. The challenge remains in leveraging these insights to mitigate adverse effects such as hypoglycemia while optimizing glycemic control.

## Thiazolidinediones: navigating through genetic metabolism

For TZDs, the metabolic process governed by CYP2C8 and SLCO1B1 is critical. Genetic variants influencing these enzymes can modify the therapeutic effects and side effects of TZDs, as seen with rosiglitazone. This understanding could direct the choice of specific TZDs and predict weight gain responses in patients.

## DPP-4 inhibitors: uncovering genotype--influenced efficacy

DPP-4 inhibitors have shown variability in HbA1c reduction due to genetic differences near the CTRB1/2 gene. This variance elucidates the potential for genotype-guided therapy for DPP-4 inhibitors, highlighting the nuanced interplay between genetic makeup and drug response.

## Tailoring diabetes care by SGLT 2 inhibitors with genetic insights

Dapagliflozin, a SGLT2 inhibitor, offers an illustrative case of the potential for tailored medication based on genetic insights. The WFS1 gene, associated with the regulation of cellular homeostasis, when bearing the rs10010131 variant, can predict the degree of weight loss a patient might experience with dapagliflozin. Similarly, the PNPLA3 gene, with its rs738409 SNP, has been linked with changes in liver fat content, suggesting a nuanced interaction with dapagliflozin's efficacy, particularly when combined with omega-3 carboxylic acids in patients with specific genotypes like CG/GG. In the metabolism of canagliflozin, genetic variants like UGT1A93 (rs72551330) and UGT2B42 demonstrate their significance by modulating drug exposure and metabolism, highlighting the profound impact genetic variations have on therapeutic outcomes. Empagliflozin's response is similarly influenced by genotypic variations in SLC5A2, with SNPs like rs3116650, rs3116149,

and rs11646054 linked to modifications in blood pressure and glucose levels.

## The dawn of preemptive genotyping

As the field progresses, the case strengthens for the implementation of preemptive genotyping, which could enable the embedding of genetic data within medical records. This advancement would transform clinical decision-making, providing healthcare professionals with valuable insights into genetic predispositions that may impact the choice and dosage of T2D medications. It underscores a shift towards a model in which genetic data informs the prescription process, aiming to enhance therapeutic benefits and reduce the risk of ADRs.

## Conclusions

### A new paradigm in type 2 diabetes management

The future of diabetes treatment pivots on the integration of pharmacogenetics into the standard of care, marrying genetic data with clinical judgment to provide tailored treatments. While the genetic architecture of T2D is complex, driven by multiple variants with small effects, the clinical relevance of pharmacogenetic interactions cannot be overlooked. The emergence of low-cost genotyping platforms has paved the way for preemptive genotyping, making it feasible to consider genetic factors in real-time prescribing decisions.

The successful adoption of this paradigm will require a concerted effort to standardize processes that facilitate the use of genetic information in clinical settings. With the incorporation of preemptive panel genotyping and clinical decision support tools that synthesize genetic and phenotypic data, a future in which personalized medicine is the norm for T2D management is within reach. The implications are profound: a redefined approach to diabetes care where therapy is finely tuned to the individual's genetic profile, fulfilling the promise of truly personalized medicine in the era of pharmacogenomics.

## Article information

### Author contributions

SSS, AM, AT, BS: study conceptualization, data acquisition, manuscript preparation; SM, KB, AKR: data acquisition, manuscript preparation; SJ: study supervision, manuscript preparation

### Funding

None.

### Conflict of interest

The authors declare no conflict of interest.

## REFERENCES

1. Roden DM, Van Driest SL. Pharmacogenetics and Pharmacogenomics. In: Brunton LL, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition. McGraw-Hill Education; 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=3191§ionid=268215725 (12.04.2024).
2. Flannick J, Thorleifsson G, Beer NL, et al. Go-T2D Consortium, T2D-GENES Consortium. Loss-of-function mutations in SLC30A8 protect against type 2 diabetes. Nat Genet. 2014; 46(4): 357–363, doi: 10.1038/ng.2915, indexed in Pubmed: 24584071.
3. Marques SC, Ikediobi ON. The clinical application of UGT1A1 pharmacogenetic testing: gene-environment interactions. Hum Genomics. 2010; 4(4): 238–249, doi: 10.1186/1479-7364-4-4-238, indexed in Pubmed: 20511137.
4. Pulley JM, Shirey-Rice JK, Lavieri RR, et al. Accelerating Precision Drug Development and Drug Repurposing by Leveraging Human Genetics. Assay Drug Dev Technol. 2017; 15(3): 113–119, doi: 10.1089/adt.2016.772, indexed in Pubmed: 28379727.
5. Rollinson V, Turner R, Pirmohamed M. Pharmacogenomics for Primary Care: An Overview. Genes (Basel). 2020; 11(11), doi: 10.3390/genes11111337, indexed in Pubmed: 33198260.
6. Pearson ER. Diabetes: Is There a Future for Pharmacogenomics Guided Treatment? Clin Pharmacol Ther. 2019; 106(2): 329–337, doi: 10.1002/cpt.1484, indexed in Pubmed: 31012484.
7. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017; 60(9): 1577–1585, doi: 10.1007/s00125-017-4342-z, indexed in Pubmed: 28776086.
8. Umamaheswaran G, Praveen RG, Damodaran SE, et al. Influence of SLC22A1 rs622342 genetic polymorphism on metformin response in South Indian type 2 diabetes mellitus patients. Clin Exp Med. 2015; 15(4): 511–517, doi: 10.1007/s10238-014-0322-5, indexed in Pubmed: 25492374.
9. Xiao Di, Guo Yu, Li Xi, et al. The Impacts of SLC22A1 rs594709 and SLC47A1 rs2289669 Polymorphisms on Metformin Therapeutic Efficacy in Chinese Type 2 Diabetes Patients. Int J Endocrinol. 2016; 2016: 4350712, doi: 10.1155/2016/4350712, indexed in Pubmed: 26977146.
10. Zhou Y, Ye W, Wang Y, et al. Genetic variants of OCT1 influence glycemic response to metformin in Han Chinese patients with type-2 diabetes mellitus in Shanghai. Int J Clin Exp Pathol. 2015; 8(8): 9533–9542, indexed in Pubmed: 26464716.
11. Dujic T, Causevic A, Bego T, et al. Organic cation transporter 1 variants and gastrointestinal side effects of metformin in patients with Type 2 diabetes. Diabet Med. 2016; 33(4): 511–514, doi: 10.1111/dme.13040, indexed in Pubmed: 26605869.
12. Phani NM, Vohra M, Kakar A, et al. Implication of critical pharmacokinetic gene variants on therapeutic response to metformin in Type 2 diabetes. Pharmacogenomics. 2018; 19(11): 905–911, doi: 10.2217/pgs-2018-0041, indexed in Pubmed: 29914345.
13. Nikolac N, Simundic AM, Katalinic D, et al. Metabolic control in type 2 diabetes is associated with sulfonylurea receptor-1 (SUR-1) but not with KCNJ11 polymorphisms. Arch Med Res. 2009; 40(5): 387–392, doi: 10.1016/j.arcmed.2009.06.006, indexed in Pubmed: 19766903.
14. Klen J, Dolžan V, Janež A. CYP2C9, KCNJ11 and ABCC8 polymorphisms and the response to sulphonylurea treatment in type 2 diabetes patients. Eur J Clin Pharmacol. 2014; 70(4): 421–428, doi: 10.1007/s00228-014-1641-x, indexed in Pubmed: 24442125.
15. Li Q, Chen M, Zhang R, et al. KCNJ11 E23K variant is associated with the therapeutic effect of sulpho- nylureas in Chinese type 2 diabetic patients. Clin Exp Pharmacol Physiol. 2014;

41(10): 748–754, doi: 10.1111/1440-1681.12280, indexed in Pubmed: 25115353.
16. Li Q, Tang TT, Jiang F, et al. Polymorphisms of the KCNQ1 gene are associated with the therapeutic responses of sulfonylureas in Chinese patients with type 2 diabetes. Acta Pharmacol Sin. 2017; 38(1): 80–89, doi: 10.1038/aps.2016.103, indexed in Pubmed: 27694910.
17. Javorsky M, Klimcakova L, Schroner Z, et al. KCNJ11 gene E23K variant and therapeutic response to sulfonylureas. Eur J Intern Med. 2012; 23(3): 245–249, doi: 10.1016/j.ejim.2011.10.018, indexed in Pubmed: 22385882.
18. Zhou K, Donnelly L, Burch L, et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther. 2010; 87(1): 52–56, doi: 10.1038/clpt.2009.176, indexed in Pubmed: 19794412.
19. Niemi M, Backman JT, Kajosaari LI, et al. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. Clin Pharmacol Ther. 2005; 77(6): 468–478, doi: 10.1016/j.clpt.2005.01.018, indexed in Pubmed: 15961978.
20. Pei Qi, Liu JY, Yin JY, et al. Repaglinide-irbesartan drug interaction: effects of SLCO1B1 polymorphism on repaglinide pharmacokinetics and pharmacodynamics in Chinese population. Eur J Clin Pharmacol. 2018; 74(8): 1021–1028, doi: 10.1007/s00228-018-2477-6, indexed in Pubmed: 29748863.
21. Kalliokoski A, Backman J, Neuvonen PJ, et al. Effects of the SLCO1B1*1B haplotype on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. Pharmacogenet Genomics. 2008; 18(11): 937–942, doi: 10.1097/FPC.0b013e32830d733e, indexed in Pubmed: 18854776.
22. Dai XP, Huang Q, Yin JY, et al. Polymorphisms of the KCNQ1 gene are associated with the therapeutic responses of sulfonylureas in Chinese patients with type 2 diabetes. Clin Exp Pharmacol Physiol. 2012; 39(5): 462–468, doi: 10.1111/j.1440-1681.2012.05701.x, indexed in Pubmed: 22414228.
23. Daily EB, Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. Pharmacogenomics. 2009; 10(9): 1489–1510, doi: 10.2217/pgs.09.82, indexed in Pubmed: 19761371.
24. Martis S, Peter I, Hulot JS, et al. Multi-ethnic distribution of clinically relevant CYP2C genotypes and haplotypes. Pharmacogenomics J. 2013; 13(4): 369–377, doi: 10.1038/tpj.2012.10, indexed in Pubmed: 22491019.
25. Stage TB, Christensen MMH, Feddersen S, et al. The role of genetic variants in CYP2C8, LPIN1, PPARGC1A and PPARγ on the trough steady-state plasma concentrations of rosiglitazone and on glycosylated haemoglobin A1c in type 2 diabetes. Pharmacogenet Genomics. 2013; 23(4): 219–227, doi: 10.1097/FPC.0b013e32835f91fc, indexed in Pubmed: 23426382.
26. Dawed AY, Donnelly L, Tavendale R, et al. CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients With Type 2 Diabetes. Diabetes Care. 2016; 39(11): 1902–1908, doi: 10.2337/dc15-2464, indexed in Pubmed: 27271184.
27. Zhang KH, Huang Q, Dai XP, et al. Effects of the peroxisome proliferator activated receptor-γ coactivator-1α (PGC-1α) Thr394Thr and Gly482Ser polymorphisms on rosiglitazone response in Chinese patients with type 2 diabetes mellitus. J Clin Pharmacol. 2010; 50(9): 1022–1030, doi: 10.1177/0091270009355159, indexed in Pubmed: 20498286.
28. Li Z, Peng X, Wu Y, et al. The influence of adiponectin gene polymorphism on the pioglitazone response in the Chinese with type 2 diabetes. Diabetes Obes Metab. 2008; 10(9): 794–802, doi: 10.1111/j.1463-1326.2008.00905.x, indexed in Pubmed: 18494805.
29. Mannino GC, Andreozzi F, Sesti G. Pharmacogenetics of type 2 diabetes mellitus, the route toward tailored medicine. Diabetes Metab Res Rev. 2019; 35(3): e3109, doi: 10.1002/dmrr.3109, indexed in Pubmed: 30515958.
30. Fortin JP, Schroeder JC, Zhu Y, et al. Pharmacological characterization of human incretin receptor missense variants. J Pharmacol Exp Ther. 2010; 332(1): 274–280, doi: 10.1124/jpet.109.160531, indexed in Pubmed: 19841474.
31. Nitz I, Fisher E, Weikert C, et al. Association analyses of GIP and GIPR polymorphisms with traits of the metabolic syndrome. Mol Nutr Food Res. 2007; 51(8): 1046–1052, doi: 10.1002/mnfr.200700048, indexed in Pubmed: 17624916.
32. Mohammad S, Patel RT, Bruno J, et al. A naturally occurring GIP receptor variant undergoes enhanced agonist-induced desensitization, which impairs GIP control of adipose insulin sensitivity. Mol Cell Biol. 2014; 34(19): 3618–3629, doi: 10.1128/MCB.00256-14, indexed in Pubmed: 25047836.
33. Tokuyama Y, Matsui K, Egashira T, et al. Five missense mutations in glucagon-like peptide 1 receptor gene in Japanese population. Diabetes Res Clin Pract. 2004; 66(1): 63–69, doi: 10.1016/j.diabres.2004.02.004, indexed in Pubmed: 15364163.
34. Jensterle M, Pirš B, Goričar K, et al. Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: a pilot study. Eur J Clin Pharmacol. 2015; 71(7): 817–824, doi: 10.1007/s00228-015-1868-1, indexed in Pubmed: 25991051.
35. Gotthardová I, Javorský M, Klimčáková L, et al. KCNQ1 gene polymorphism is associated with glycaemic response to treatment with DPP-4 inhibitors. Diabetes Res Clin Pract. 2017; 130: 142–147, doi: 10.1016/j.diabres.2017.05.018, indexed in Pubmed: 28624668.
36. Boulton DW, Kasichayanula S, Keung CF, et al. Simultaneous oral therapeutic and intravenous $^{1}$ C-microdoses to determine the absolute oral bioavailability of saxagliptin and dapagliflozin. Br J Clin Pharmacol. 2013; 75(3): 763–768, doi: 10.1111/j.1365-2125.2012.04391.x, indexed in Pubmed: 22823746.
37. Fischer TT, Ehrlich BE. Wolfram Syndrome: a Monogenic Model to Study Diabetes Mellitus and Neurodegeneration. Curr Opin Physiol. 2020; 17: 115–123, doi: 10.1016/j.cophys.2020.07.009, indexed in Pubmed: 32864536.
38. Pereira MJ, Lundkvist P, Kamble PG, et al. A Randomized Controlled Trial of Dapagliflozin Plus Once-Weekly Exenatide Versus Placebo in Individuals with Obesity and Without Diabetes: Metabolic Effects and Markers Associated with Bodyweight Loss. Diabetes Ther. 2018; 9(4): 1511–1532, doi: 10.1007/s13300-018-0449-6, indexed in Pubmed: 29949016.
39. Machado CM, Leite NC, França PH, et al. PNPLA3 gene polymorphism in Brazilian patients with type 2 diabetes: A prognostic marker beyond liver disease? Nutr Metab Cardiovasc Dis. 2019; 29(9): 965–971, doi: 10.1016/j.numecd.2019.06.002, indexed in Pubmed: 31377187.
40. Francke S, Mamidi RN, Solanki B, et al. In vitro metabolism of canagliflozin in human liver, kidney, intestine microsomes, and recombinant uridine diphosphate glucuronosyltransferases (UGT) and the effect of genetic variability of UGT enzymes on the pharmacokinetics of canagliflozin in humans. J Clin Pharmacol. 2015; 55(9): 1061–1072, doi: 10.1002/jcph.506, indexed in Pubmed: 25827774.
41. Heo CUk, Choi CI. Current Progress in Pharmacogenetics of Second-Line Antidiabetic Medications: Towards Precision Medicine for Type 2 Diabetes. J Clin Med. 2019; 8(3): 393, doi: 10.3390/jcm8030393, indexed in Pubmed: 30901912.
42. Zimdahl H, Haupt A, Brendel M, et al. Influence of common polymorphisms in the SLC5A2 gene on metabolic traits in subjects at increased risk of diabetes and on response to empagliflozin treatment in patients with diabetes. Pharmacogenet Genomics. 2017; 27(4): 135–142, doi: 10.1097/FPC.0000000000000268, indexed in Pubmed: 28134748.
43. Kaur P, Behera BS, Singh S, et al. "The pharmacological profile of SGLT2 inhibitors: Focus on mechanistic aspects and pharmacogenomics". Eur J Pharmacol. 2021; 904: 174169, doi: 10.1016/j.ejphar.2021.174169, indexed in Pubmed: 33984301.