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Original Article

Short-Term Changes in Glycemic Parameters Following Proton Pump Inhibitor Therapy in Patients With Type 2 Diabetes Mellitus: A Retrospective Cohort Study

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Abstract

Background: Emerging evidence suggests that proton pump inhibitors (PPIs) may influence glucose metabolism through mechanisms such as gastrin-mediated stimulation of pancreatic β-cell activity and alterations in gut microbiota composition. However, clinical studies evaluating the metabolic effects of PPIs in patients with type 2 diabetes mellitus (T2DM) have yielded inconsistent findings. The present study aimed to evaluate short-term changes in glycemic parameters after initiation of PPI therapy in patients with T2DM and to explore clinical characteristics associated with reductions in fasting glucose.

Methods: This retrospective observational study included 66 adults with T2DM who were newly prescribed a PPI in a gastroenterology outpatient setting. Clinical and laboratory data were obtained from electronic medical records and verified through the national prescription monitoring system. Fasting glucose, postmeal glucose, glycated hemoglobin (HbA1c), and body mass index (BMI) were recorded at baseline and during a three-month follow-up period. Changes in glycemic parameters were analyzed using paired statistical tests, and logistic regression was used to identify factors associated with reductions in fasting glucose.

Results: The mean age of participants was 57.93 ± 10.90 years, and the mean BMI was 29.31 ± 2.98 kg/m². During the three-month follow-up period, mean fasting glucose decreased significantly from 132.12 ± 19.61 mg/dL to 122.13 ± 23.52 mg/dL ($p < 0.001$). Postmeal glucose and HbA1c levels showed numerical reductions but did not reach statistical significance. A decrease in fasting glucose was observed in 47 of 66 participants (71.2%). Patients who experienced fasting glucose reduction were significantly older, had lower BMI, and had a shorter duration of diabetes compared with those without reduction. Multivariate analysis demonstrated that older age, lower BMI, and shorter diabetes duration were independently associated with fasting glucose reduction.

Conclusions: PPI therapy was associated with a modest reduction in fasting glucose during short-term follow-up, whereas HbA1c and postmeal glucose levels did not change significantly. The observed association appeared to vary according to patient characteristics, particularly BMI and duration of diabetes. These findings suggest that metabolic responses to PPI therapy may differ across clinical subgroups of patients with T2DM and warrant further investigation in larger prospective studies.

Keywords: Diabetes Mellitus, Type 2, Proton Pump Inhibitors, Blood Glucose, Glycated Hemoglobin, Body Mass Index

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most commonly prescribed medications worldwide for the treatment of acid-related gastrointestinal disorders, including gastroesophageal reflux disease, peptic ulcer disease, and dyspepsia (1,2). Their mechanism of action involves irreversible inhibition of the gastric H^+/K^+-ATPase enzyme, resulting in potent and sustained suppression of gastric acid secretion (1,3). Owing to their high efficacy and favorable safety profile, PPIs are frequently prescribed for prolonged periods and are widely used in patients with multiple comorbidities, including type 2 diabetes mellitus (T2DM) (4,5).

In recent years, increasing attention has been directed toward the potential extra-gastric metabolic effects of PPIs, particularly their possible influence on glucose metabolism (5,6). Several biological mechanisms have been proposed to explain a potential interaction between PPI therapy and glycemic regulation. One

commonly discussed pathway involves PPI-induced hypergastrinemia, which may stimulate pancreatic β-cell activity and enhance insulin secretion (7,8). Experimental and clinical studies have suggested that elevated gastrin levels may promote β-cell regeneration and improve glucose tolerance (5–8). In addition to gastrin-mediated mechanisms, alterations in gastrointestinal pH and gut microbiota composition associated with PPI therapy may also influence metabolic pathways involved in glucose homeostasis (9).

Despite these mechanistic hypotheses, clinical evidence regarding the impact of PPIs on glycemic control remains inconsistent. Some randomized controlled trials and observational studies have reported modest improvements in fasting glucose or glycated hemoglobin (HbA1c) levels among patients with T2DM receiving PPI therapy (4,10,11). Conversely, other investigations have demonstrated minimal or no measurable effects on glycemic indices (12,13). Furthermore, several studies have suggested that the metabolic impact of PPIs may vary according to patient characteristics such as duration of diabetes, body mass index (BMI), baseline glycemic status, and concurrent antidiabetic treatments (4,10–13). These heterogeneous findings highlight the need for additional clinical data to clarify whether specific subgroups of patients with T2DM may experience metabolic changes during PPI therapy.

Given the widespread use of PPIs among patients with diabetes, understanding potential interactions between these medications and glucose metabolism may have important clinical implications. The present study aimed to investigate the association between PPI therapy and short-term changes in blood glucose levels in patients with T2DM. In addition, we sought to explore whether specific clinical characteristics, including age, BMI, and duration of diabetes, were associated with a greater likelihood of fasting glucose reduction among PPI users.

METHODS

Protocol and Search Strategy

This retrospective observational study used routinely collected clinical data from patients who attended the gastroenterology outpatient clinics of Atılım University and Medicana International Ankara Hospital between January 2021 and December 2022. The study was designed as a within-subject before–after analysis evaluating changes in glycemic parameters following initiation of PPI therapy in patients with T2DM. Clinical and laboratory data were obtained from the hospital electronic medical record system. Medication exposure and prescription continuity were verified through the national electronic prescription monitoring system maintained by the Republic of Türkiye Ministry of Health (e-Nabız). The primary objective was to evaluate short-term changes in fasting and postmeal glucose levels, as well as glycated hemoglobin (HbA1c), following initiation of PPI therapy during routine clinical care.

Participants

Adult patients aged 18 years or older with a confirmed diagnosis of T2DM who were newly prescribed a PPI during the study period were eligible for inclusion. Patients were required to have available baseline clinical data and at least one follow-up evaluation within approximately three months after initiation of PPI therapy. Patients with diabetic gastroparesis, rheumatologic diseases requiring immunosuppressive therapy, chronic kidney disease stage 3 or higher, active malignancy, or acute systemic illness during the observation period were excluded. Individuals receiving anti-ulcer medications other than PPIs were also excluded. To minimize potential confounding related to prior drug exposure, patients who had used PPIs before the index prescription were not included. In addition, patients who discontinued PPI therapy during the follow-up period, experienced prolonged hospitalization, or had substantial changes in their antihyperglycemic treatment regimen were excluded. Verification of medication exposure, treatment continuity, and potential therapy changes was performed through review of the national prescription database and hospital outpatient registries.

PPI Exposure Assessment

PPI therapy was prescribed for routine clinical indications, including dyspepsia, gastritis, gastroduodenitis, or gastroesophageal reflux disease. The most commonly prescribed PPIs were lansoprazole 40 mg, esomeprazole 40 mg, and pantoprazole 40 mg. The type of PPI prescribed was recorded; however, the study was not designed to compare metabolic effects between individual PPI agents. Continuous PPI use for approximately three months was verified using the national electronic medication monitoring system and physician outpatient records. Diagnostic indications for PPI prescriptions were identified using International Classification of Diseases (ICD) codes K29 and K30 recorded in the hospital information system.

Clinical and Laboratory Measurements

Baseline demographic and clinical characteristics, including age, sex, BMI, duration of diabetes, and comorbid conditions, were extracted from the electronic medical record at the time of PPI initiation. Laboratory measurements included fasting glucose (FG), postmeal glucose (PMG), and HbA1c. BMI values were calculated using height and weight measurements recorded during outpatient visits. Baseline laboratory parameters were

defined as the most recent measurements recorded prior to initiation of PPI therapy. Follow-up laboratory data were obtained from subsequent outpatient visits occurring approximately one, two, and three months after initiation of PPI treatment when available. HbA1c and BMI measurements were primarily evaluated at baseline and at month three because intermediate measurements were not routinely performed in clinical practice.

To explore clinical predictors of glycemic response, patients were categorized according to the direction of change in fasting glucose between baseline and the third month of follow-up. Patients demonstrating a decrease in fasting glucose were classified as the glucose reduction group, whereas those without a decrease were classified as the non-reduction group. The magnitude of reduction was not used as a classification criterion; instead, the analysis focused on identifying baseline characteristics associated with the presence or absence of fasting glucose reduction.

Sample Size Estimation

Before data extraction, a minimum sample size of 62 participants was estimated using G*Power software (version 3.1.9.7), assuming an effect size of 0.70, a significance level (α) of 0.05, and a statistical power of 95% (1−β = 0.95). A total of 66 eligible patients met the inclusion criteria and were included in the final analysis.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS for Windows (version 17.0; IBM). The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Continuous variables with normal distribution are presented as mean ± standard deviation, whereas non-normally distributed variables are reported as median values with minimum and maximum ranges. Categorical variables are summarized as frequencies and percentages. Changes in glycemic parameters before and after PPI therapy were evaluated using paired-sample t-tests. Comparisons between patients with and without fasting glucose reduction were performed using chi-square tests for categorical variables and independent sample tests for continuous variables as appropriate. To identify factors associated with fasting glucose reduction, logistic regression analyses were performed including clinically relevant variables such as age, BMI, and duration of diabetes. Receiver operating characteristic (ROC) curve analysis was conducted as an exploratory analysis to evaluate the discriminatory ability of age, BMI, and diabetes duration for predicting fasting glucose reduction at month three and to identify potential cutoff values. All statistical tests were two-tailed, and a p value of less than 0.05 was considered statistically significant.

RESULTS

Study Characteristics

A total of 66 patients with type 2 diabetes mellitus were included in the analysis. The study population consisted of 31 men and 35 women, with a mean age of 57.93 ± 10.90 years. Age distribution did not differ significantly between male and female participants (p = 0.756). The median duration of diabetes was 6 years (range: 1–29 years). The mean baseline BMI was 29.31 ± 2.98 kg/m². The most common indications for PPI therapy were dyspepsia (24.24%), acute gastritis (21.21%), gastroduodenitis (19.69%), and gastroesophageal reflux disease (15.2%). The prescribed PPIs included lansoprazole (n = 23), esomeprazole (n = 21), pantoprazole (n = 19), and rabeprazole (n = 3). The mean follow-up duration after initiation of PPI therapy was 86 days.

Changes in Glycemic Parameters

Changes in glycemic parameters during the three-month follow-up period are summarized in **Table 1**. Mean fasting glucose decreased significantly from 132.12 ± 19.61 mg/dL at baseline to 122.13 ± 23.52 mg/dL at month three (p < 0.001), corresponding to an approximate reduction of 6%. Postmeal glucose levels demonstrated a numerical decline during follow-up but did not reach statistical significance (p = 0.126). Similarly, HbA1c decreased modestly from 8.15 ± 1.07% at baseline to 8.00 ± 1.09% at month three, although this change was not statistically significant (p = 0.146). BMI remained stable during the study period (29.31 ± 2.98 vs. 29.24 ± 3.06 kg/m²; p = 0.899).

Frequency of Fasting Glucose Reduction

A decrease in fasting glucose at month three was observed in 47 of the 66 participants (71.2%). In this

Table 1. Changes in Glycemic Parameters After Initiation of Proton Pump Inhibitor Therapy.

Variable	Baseline	Month 1	Month 2	Month 3	P value (baseline vs month 3)
Fasting glucose (mg/dL)	132.12 ± 19.61	126.28 ± 25.01	124.46 ± 25.73	122.13 ± 23.52	<0.001
Postmeal glucose (mg/dL)	183.84 ± 31.92	175.96 ± 53.44	187.80 ± 55.64	174.33 ± 51.99	0.126
HbA1c (%)	8.15 ± 1.07	NA	NA	8.00 ± 1.09	0.146
BMI (kg/m²)	29.31 ± 2.98	NA	NA	29.24 ± 3.06	0.899

HbA1c, glycated hemoglobin A1c; BMI, body mass index

Table 2. Comparison of Two Groups After Proton Pump Inhibitor Therapy.

Variable	Reduction (+) N=47	Reduction (−) N=19	P value
Age (years)	59.82 ± 10.18	53.26 ± 11.47	0.026
Sex (male/female)	22 / 25	9 / 10	1.000
BMI (kg/m²)	28.44 ± 2.17	31.45 ± 3.63	0.003
Baseline fasting glucose (mg/dL)	134.68 ± 20.95	125.78 ± 14.40	0.054
Fasting glucose Month 1	125.12 ± 26.11	129.15 ± 22.46	0.558
Fasting glucose Month 2	123.74 ± 27.40	126.26 ± 21.62	0.722
Fasting glucose Month 3	112.70 ± 17.74	145.47 ± 19.64	<0.001
Baseline PMG	184.23 ± 30.19	182.89 ± 36.72	0.879
PMG Month 1	174.91 ± 51.34	177.15 ± 59.52	0.754
PMG Month 2	171.53 ± 59.53	181.05 ± 45.35	0.535
PMG Month 3	169.27 ± 52.96	186.84 ± 46.32	0.211
Baseline HbA1c (%)	8.17 ± 1.07	7.63 ± 1.12	0.395
HbA1c Month 3 (%)	8.01 ± 1.16	7.74 ± 0.86	0.274
Diabetes duration (years)	6.70 ± 4.64	10.63 ± 5.95	0.005

PMG, postmeal glucose; HbA1c, glycated hemoglobin A1c; BMI, body mass index

subgroup, the mean reduction in fasting glucose was 15.78%. Conversely, 19 patients (28.8%) did not demonstrate a reduction in fasting glucose during the observation period.

Comparison Between Reduction and Non-Reduction Groups

Clinical and laboratory characteristics of patients with and without fasting glucose reduction are presented in **Table 2**. Patients in the reduction group were significantly older than those in the non-reduction group (59.82 ± 10.18 vs. 53.26 ± 11.47 years, p = 0.026). Baseline BMI was also significantly lower in the reduction group (28.44 ± 2.17 vs. 31.45 ± 3.63 kg/m², p = 0.003). In addition, patients demonstrating fasting glucose reduction had a significantly shorter duration of diabetes (6.70 ± 4.64 vs. 10.63 ± 5.95 years, p = 0.005). Baseline fasting glucose levels were slightly higher in the reduction group; however, this difference did not reach statistical significance (p = 0.054). During follow-up, fasting glucose levels progressively declined in the reduction group, reaching 112.70 ± 17.74 mg/dL at month three, whereas fasting glucose increased to 145.47 ± 19.64 mg/dL in the non-reduction group (p < 0.001). Postmeal glucose levels tended to decrease in the reduction group and increase slightly in the non-reduction group, although these differences did not reach statistical significance. HbA1c levels also demonstrated minor changes in both groups but remained statistically non-significant.

Predictors of Fasting Glucose Reduction

Logistic regression analysis was performed to evaluate potential predictors of fasting glucose reduction among PPI users (**Table 3**). In univariate analysis, age (p = 0.030), duration of diabetes (p = 0.029), and BMI (p = 0.002) were significantly associated with glucose reduction. Multivariate logistic regression analysis confirmed that older age (p = 0.001), shorter duration of diabetes (p = 0.045), and lower BMI (p = 0.005) were independently associated with a greater likelihood of fasting glucose reduction following PPI therapy.

Receiver Operating Characteristic Analysis

Receiver operating characteristic (ROC) curve analysis was performed as an exploratory analysis to assess the discriminatory ability of age, BMI, and diabetes duration for predicting fasting glucose reduction at month three among PPI users. The positive outcome was defined as a decrease in fasting glucose at month three compared with baseline. Age demonstrated modest discriminatory ability, with an area under the curve (AUC) of approximately 0.64 (95% CI 0.51–0.76). An optimal cutoff value of 57 years yielded a sensitivity of 66% and a specificity of 34%. Patients older than 57 years showed a higher rate of fasting glucose reduction than those aged 57 years or younger (81.6% vs. 59.3%, p = 0.048). BMI demonstrated stronger predictive

Table 3. Logistic Regression Analysis of Factors Associated with Glucose Reduction Following Proton Pump Inhibitor Therapy.

Variable	Univariate OR	95% CI	P value	Multivariate OR	95% CI	P value
Age	0.946	0.900–0.995	0.030	1.658	1.242–2.213	0.001
Diabetes duration	1.044	0.963–1.132	0.029	1.046	0.972–1.125	0.045
BMI	1.484	1.158–1.902	0.002	0.909	0.851–0.972	0.005

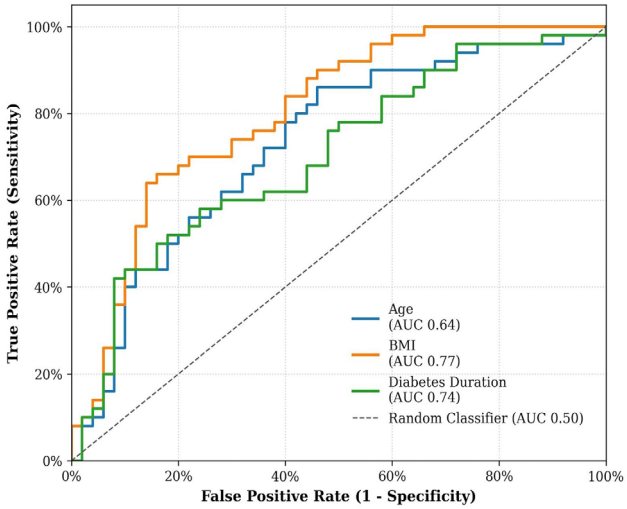

Figure 1. Receiver operating characteristic (ROC) curves for age, BMI, and diabetes duration as predictors of fasting glucose reduction at month 3 among proton pump inhibitor users with type 2 diabetes mellitus.

performance, with an AUC of approximately 0.77 (95% CI 0.64–0.88). A cutoff value of 29.40 kg/m² provided a sensitivity of 74.5% and a specificity of 68.4% for identifying individuals likely to experience fasting glucose reduction. Diabetes duration also showed predictive value, yielding an AUC of approximately 0.74 (95% CI 0.61–0.86). A cutoff value of 6.5 years was identified, indicating that patients with longer diabetes duration were less likely to demonstrate improvement in fasting glucose levels ($p < 0.001$). The ROC curves are presented in **Figure 1**.

DISCUSSION

The present study evaluated short-term changes in glycemic parameters following initiation of proton pump inhibitor therapy in patients with type 2 diabetes mellitus. The primary finding was a significant reduction in fasting glucose during the three-month follow-up period, whereas postmeal glucose and HbA1c levels did not demonstrate statistically significant changes. In addition, exploratory analyses suggested that certain patient characteristics, including older age, lower BMI, and shorter duration of diabetes, were associated with a higher likelihood of fasting glucose reduction during PPI therapy.

Interest in the potential metabolic effects of PPIs has increased in recent years, although the available clinical evidence remains heterogeneous (4,10–13). Some randomized controlled trials and observational studies have reported modest improvements in glycemic parameters among patients receiving PPI therapy, while other studies have found minimal or no measurable metabolic effects (10,11,14). In the present cohort, fasting glucose reduction was observed in more than two-thirds of participants, suggesting that PPI exposure may be associated with short-term changes in fasting glycemic regulation in a subset of patients. However, the absence of a significant change in HbA1c indicates that the overall impact on long-term glycemic control may be limited within the relatively short observation period.

Several biological mechanisms have been proposed to explain a potential interaction between PPIs and glucose metabolism. One commonly discussed pathway involves PPI-induced hypergastrinemia (15–17). Gastrin has been suggested to stimulate pancreatic β-cell activity and may contribute to enhanced insulin secretion under certain physiological conditions. Experimental studies have demonstrated that increased gastrin levels may promote β-cell regeneration and improve insulin production, potentially contributing to improved glucose regulation (15,16,18). In addition to gastrin-mediated mechanisms, PPI therapy may influence metabolic pathways through alterations in gastrointestinal pH and gut microbiota composition, both of which have been implicated in glucose homeostasis (9,19,20). However, because biomarkers such as insulin, C-peptide, proinsulin, gastrin levels, or indices of insulin resistance were not measured in the present study, these mechanistic explanations remain speculative.

An important observation of the present study is that the glycemic response to PPI therapy appeared to vary according to baseline patient characteristics. Individuals who demonstrated fasting glucose reduction had lower BMI and shorter duration of diabetes compared with those without reduction. These findings may be biologically plausible because longer diabetes duration is often associated with progressive decline in pancreatic β-cell function, while higher BMI is frequently linked to greater insulin resistance. Under such conditions, therapies that primarily influence insulin secretion might have greater metabolic impact in individuals with relatively preserved β-cell function. Nevertheless, these findings should be interpreted cautiously because the observational design does not allow causal inference.

Interestingly, older age was also associated with a greater probability of fasting glucose reduction in this cohort. The underlying mechanism remains unclear. One possible explanation is that age-related differences in pharmacokinetic or pharmacodynamic responses to PPIs may influence systemic metabolic effects of these drugs (21,22). Alternatively, age-related differences in metabolic characteristics or treatment patterns may contribute to this observation. Because these factors were not specifically investigated in the present study, further research is required to clarify the relationship

between age and metabolic responses to PPI therapy.

Despite the observed reduction in fasting glucose, neither postmeal glucose nor HbA1c levels changed significantly during the study period. This finding may be explained by the relatively short follow-up duration. HbA1c reflects average glycemic exposure over approximately two to three months, and modest short-term reductions in fasting glucose may not necessarily translate into detectable HbA1c changes during a limited observation period. In addition, variability in postprandial glucose measurements obtained during routine clinical practice may reduce the ability to detect subtle changes in postmeal glycemic responses.

The findings of the present study should also be interpreted in the context of previous research addressing the metabolic effects of PPIs. While some studies have suggested potential improvements in glycemic parameters among PPI users, others have reported neutral results. Differences in study design, patient populations, baseline glycemic status, duration of therapy, and concurrent antidiabetic treatments may contribute to the variability observed across studies (6,12,23). The present investigation provides real-world observational data suggesting that fasting glucose reduction may occur in a subset of patients with T2DM during short-term PPI therapy.

Several limitations of this study should be acknowledged. First, the retrospective observational design limits the ability to establish causal relationships between PPI therapy and changes in glycemic parameters. Second, the sample size was relatively modest and derived from a single clinical center, which may limit the generalizability of the findings. Third, mechanistic biomarkers such as insulin, C-peptide, proinsulin, gastrin levels, or indices of insulin resistance were not available, preventing direct evaluation of potential physiological pathways underlying the observed associations. Fourth, dietary adherence and lifestyle factors during the study period could not be fully standardized and may have influenced glycemic outcomes. Finally, although major changes in antidiabetic therapy were excluded, subtle variations in medication adherence or clinical management cannot be completely ruled out in a real-world observational setting.

Despite these limitations, the present study provides additional clinical insight into the potential metabolic effects of PPI therapy in patients with T2DM. The findings suggest that short-term PPI therapy may be associated with modest reductions in fasting glucose in a subset of patients, particularly those with lower BMI and shorter duration of diabetes. However, these observations should be considered hypothesis-generating rather than definitive evidence of a therapeutic metabolic effect.

Future prospective studies with larger sample sizes and longer follow-up durations are needed to better clarify the relationship between PPI therapy and glucose metabolism. Studies incorporating detailed metabolic biomarkers and standardized glycemic measurements may further help determine whether specific subgroups of patients with T2DM could experience clinically meaningful metabolic changes during PPI therapy.

CONCLUSION

In this retrospective cohort study of patients with type 2 diabetes mellitus, initiation of proton pump inhibitor therapy was associated with a modest reduction in fasting glucose during short-term follow-up, while postmeal glucose and HbA1c levels did not change significantly. The findings suggest that the glycemic response to PPI therapy may vary according to baseline clinical characteristics, particularly body mass index and duration of diabetes. Although these results provide real-world evidence that a subset of patients with T2DM may experience short-term improvements in fasting glucose following PPI therapy, the observational design and limited sample size preclude causal inference. Larger prospective studies incorporating detailed metabolic assessments are required to clarify the potential role of PPIs in glucose metabolism and to identify patient populations that may derive metabolic benefit.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the institutional ethics committee (Approval No: BSH 2022/19_a). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent to Participate: Because the study was retrospective and based on routinely collected clinical data, written informed consent was not required.

Availability of Data and Materials: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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approved the final manuscript.

Use of Artificial Intelligence: Artificial intelligence (AI) tools were used solely for language editing and improvement of the manuscript. No AI tools were used in the study design, data collection, data analysis, or interpretation of the results. The authors take full responsibility for the content of the manuscript.

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