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ORIGINAL ARTICLE

Postoperative Pain Following Endodontic Treatment in Patients With Type 2 Diabetes Mellitus: A Prospective Non-Randomized Clinical Trial

ABSTRACT

Aim: *Diabetic patients may exhibit altered responses to nerve stimulation due to diabetes-related neurological damage. This prospective, non-randomized, parallel, blinded clinical trial evaluated postoperative pain following endodontic treatment by comparing two groups of patients—with and without type 2 diabetes mellitus (T2DM).*
Methodology: *Eighty adult patients were included: 40 with T2DM and 40 without T2DM. At baseline, glycated hemoglobin (HbA1c) levels were recorded. Endodontic treatment was performed, and root canals were irrigated with 2.5% sodium hypochlorite solution. Postoperative pain was assessed by a blinded researcher at 6, 12, 24, and 72 hours using a Numerical Rating Scale (NRS, 0–10).*
Results: *Within the first 6 hours, 19 patients in the T2DM group and 24 in the control group reported pain ($p = 0.429$). After 12 hours, 11 T2DM patients and 19 control patients experienced pain ($p = 0.165$). At 24 hours, 9 patients with T2DM and 11 in the control group reported pain ($p = 0.930$). After 72 hours, 5 patients from each group reported pain ($p = 0.186$). No significant differences in pain intensity were observed between the groups at 6 hours ($p = 0.139$), 12 hours ($p = 0.169$), 24 hours ($p = 0.387$), or 72 hours ($p = 0.687$). However, regression analysis revealed that patients with T2DM had lower odds of experiencing postoperative pain (OR = 0.19; 95% CI = 0.04–0.77), regardless of sex, age, preoperative pain, tooth type, treatment modality, or sealer extrusion.*
Conclusions: *Although no statistically significant differences in pain intensity were observed between groups, patients with T2DM exhibited lower odds of reporting postoperative pain. These exploratory findings may indicate a trend toward reduced postoperative discomfort in this population, warranting further investigation through larger randomized trials.*

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Introduction

Diabetes mellitus (DM) is a multifaceted metabolic disorder currently affecting over 537 million individuals worldwide, with projections indicating an increase to 783 million by 2045 (1). Type 2 DM (T2DM) is the most prevalent form, primarily associated with impaired insulin secretion from pancreatic beta cells or insulin resistance (2).

Diabetic patients may exhibit altered responses to nerve stimulation due to diabetes-induced neurological damage. The pathophysiological mechanisms affecting metabolic and intracellular signaling pathways remain underexplored(3-5).

Moreover, DM induces metabolic alterations in the dental pulp, compromising its vascular and sensory structures(6). As such, T2DM is considered a critical factor influencing pulpal and periapical pathology in terms of susceptibility, progression, healing, and even prevalence. It is thus regarded as a potential modulating factor in endodontic disease(7) .

Postoperative discomfort is observed in up to 60% of cases following endodontic procedures and is a major contributor to behavioral changes that negatively affect emotional well-being and daily functioning, including occupational tasks, household activities, sleep, eating habits, and verbal communication (8).

Factors associated with post-endodontic pain include age, sex, molar involvement, and the mandibular arch; however, the relationship between systemic health and postoperative discomfort has been rarely investigated in the literature (9). Studies indicate that pain intensity typically peaks within the first 24 hours after treatment and significantly subsides over the following three days (10, 11).

Given the high prevalence of postoperative pain, often reflecting an ongoing inflammatory process, identifying its underlying causes and predictive factors is essential for enabling clinicians to implement effective strategies to reduce its incidence and improve patient comfort. Therefore, the objective of this clinical trial was to evaluate and compare the incidence of postoperative endodontic pain in individuals with and without type 2 diabetes mellitus. The primary research hypothesis was that individuals with type 2 diabetes mellitus would exhibit a significantly different incidence and intensity of postoperative endodontic pain compared to non-diabetic individuals, possibly due to diabetes-associated neurological and inflammatory alterations.

Materials and Methods

Study design and population

This prospective, non-randomized, parallel, blinded clinical trial was conducted at the Dental School Clinic of the Federal University of Amazonas, Manaus, Brazil, between November 2018 and November 2022. The study included patients requiring endodontic treatment. Ethical approval was obtained from the Research Ethics Committee of the Federal University of Amazonas (CAAE No. 97436918.0.0000.5020), and the trial was registered in the Brazilian Registry of Clinical Trials (REBEC) (UTN: U1111-1228-6794). The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines(12) and complied with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Sample size calculation

Sample size calculation indicated that a total of 80 patients (40 in each group) were required to detect a 30% difference between groups, assuming a significance level of $\alpha = 0.05$ and a power of 80%. The expected prevalence of postoperative pain was set at 60%, based on a previous clinical trial conducted at the same institution (10).

The study included adult men and women aged 18 years or older, with or without type 2 diabetes mellitus (T2DM), who required endodontic treatment for vital or necrotic permanent teeth without periapical lesions, excluding third molars (Table 1). Patients were excluded if they had periodontal disease, were pregnant, had hypersensitivity to or were using anti-inflammatory or antibiotic medications during treatment, were

Table 1.

Clinical and demographic data of patients recruited (baseline).

Variable	Without diabetes (n= 40)	With diabetes (n=40)	p-value
Mean age	32.7±12.63	54.53±10.68	*<0.001
Glycated hemoglobin	5.07±0.61	7.98±2.46	*<0.001
Gender			
Women	23 (57.5%)	24 (60.0%)	0.820
Men	17 (42.5%)	16 (40.0%)	
Arterial hypertension			
Yes	2 (5.0%)	20 (50.0%)	***<0.001
No	38 (95.0%)	20 (50.0%)	
Extrusion of filling material			
Yes	4 (10.0%)	15 (37.5%)	***0.041
No	36 (90.0%)	25 (62.5%)	
Maxillary teeth			**0,002
Molar	13 (32.5%)	12 (30.0%)	
Premolar	2 (5.0%)	2 (5.0%)	
Anterior	2 (5.0%)	5 (12.5%)	
Mandibular teeth			*<0,001
Molar	18 (45.0%)	3 (7.5%)	
Premolar	-	-	
Anterior	5 (12.5%)	18 (45.0%)	
Preoperative pain (NRS)	3.95±3.82	3.37±3.61	*0.044
Pulp diagnosis			
Vital	27 (67.5%)	12 (30 %)	**0.001
Non-vital	13 (32.5%)	28 (70 %)	

**p<0.05, Mann-Whitney test **p<0.05, Chi-square test ***p<0.05, Fisher's exact test*

immunocompromised, or had teeth with periapical pathology or endodontic complications, such as canal calcifications, internal or external resorption, incomplete root formation, perforations, longitudinal or vertical root fractures, or cases that could not be completed in a single session. These exclusion criteria were implemented to eliminate confounding factors that could influence pain perception or interfere with the analysis of postoperative pain scores.

Patients using anti-inflammatory drugs were only included after a minimum wash-out period of 7 days. In case of postoperative pain, they were instructed to contact the research team, who would provide a standardized prescription if necessary. All medication use during the follow-up period was recorded.

Group allocation procedure

To determine the metabolic control status of the patients, glycated hemoglobin (HbA1c) levels were recorded prior to treatment. Patients were divided into two groups according to the criteria established by the American Association of Clinical Endocrinologists (AACE)(13). The experimental group consisted of individuals with a medical history of type 2 diabetes mellitus and an HbA1c level ≥ 6.5%, while the control group included participants with an HbA1c level < 6.5% (13).

A total of 130 patients were recruited. Of

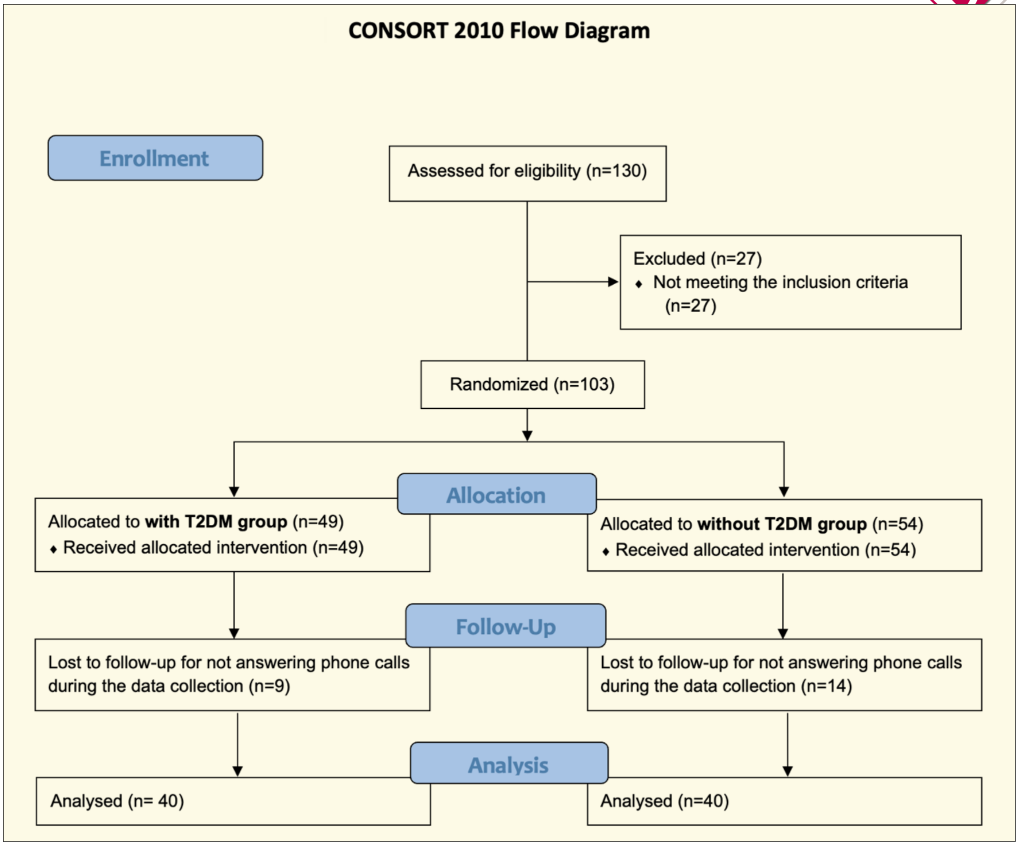

Figure 1
Flow diagram for clinical trials

these, 13 were excluded due to the presence of systemic disorders other than arterial hypertension, 10 were excluded because their teeth did not require endodontic treatment, and 4 were excluded due to endodontic complications. During the clinical trial, an additional 23 patients were excluded for failing to respond to telephone calls during outcome data collection (Figure 1).

Treatment protocol

The protocol was carried out in three phases. During the first phase, baseline and diagnostic data were collected, including glycated hemoglobin (HbA1c) levels to determine group allocation and preoperative pain assessment using the Numerical Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain). Diabetic patients were instructed to adhere to their prescribed medications to maintain stable blood glucose levels. Eligible participants provided written informed consent. In the second phase, endodontic treatment was performed. All procedures were carried out in the morning. The third phase involved analysis of the outcome-related data. The endodontic protocol was standardized across both groups and performed by a certified endodontic specialist. Anesthesia was administered using 3.6 mL of 2% lidocaine with 1:100,000 epinephrine (Alphacaine; DFL Indústria e Comércio Ltda., Rio de Janeiro, Brazil) via inferior alveolar nerve block for mandibular teeth or terminal infiltration for maxillary teeth. Following rubber dam isolation, access to the pulp chamber was performed, and the apical working length was determined using an electronic apex locator (Romiapex A-15; Romidan Ltd., Kiryat Ono, Israel) set to 0.0 mm from the apical foramen, with confirmation by periapical radiography. Root canal preparation was carried out using the WaveOne GOLD® system (Dentsply Maillefer, Ballaigues, Switzerland) according to the manufacturer's instructions.

For single-rooted teeth, instrumentation was performed up to size 45.05 (Large file); for bi-rooted teeth, up to size 35.06 (Medium file). In multi-rooted teeth (e.g., molars), instrumentation varied according to canal complexity and curvature: mesial canals were generally prepared to size 25.07 (Primary file), and distal canals to size 35.06. Files were introduced into the canals with short reciprocating strokes (3–4 mm) until

complete preparation of the cervical, middle, and apical thirds was achieved.
Apical patency was confirmed using a #10 K-file at the established working length. All instrumentation was performed with the XSmart Plus® motor (Dentsply Maillefer, Ballaigues, Switzerland) in reciprocating motion.
Throughout instrumentation, the canals were irrigated with 20 mL of 2.5% sodium hypochlorite solution (Asfer; São Caetano do Sul, São Paulo, Brazil), ensuring continuous presence of the irrigant within the canals. Irrigation was delivered using a Max-i-Probe 30-G needle (Dentsply Maillefer, Ballaigues, Switzerland) positioned 3 mm short of the working length, as measured with a silicone stop.
Prior to obturation, the canals were irrigated with 2 mL of 17% EDTA (Fórmula e Ação; São Paulo, Brazil), followed by 2.5% sodium hypochlorite. Final irrigation was enhanced using passive ultrasonic irrigation (PUI) for 1 minute with an E2 Irrisonic® ultrasonic tip (Helse, Brazil) attached to an ultrasonic unit (Altsonic Ceramic II; ALT Equipamentos, Ribeirão Preto, São Paulo, Brazil).
The canals were dried using absorbent paper points corresponding to the final instrument size used in apical preparation (WaveOne GOLD® system). For obturation, gutta-percha cones from the same system were coated with AH Plus sealer (Dentsply Maillefer, Ballaigues, Switzerland) and placed 5 mm short of the apical foramen. Thermoplasticized obturation was then performed using a McSpadden compactor (Dentsply Maillefer, Ballaigues, Switzerland), positioned 5 mm short of the working length.
The teeth were restored with glass-ionomer restorative cement, and a final radiograph was obtained. At the end of the procedure, patients were instructed on how postoperative pain would be monitored through follow-up telephone calls. They were also provided with printed instructions and a copy of the Numerical Rating Scale for reference.

Pain assessment

Postoperative pain was assessed via telephone calls at 6, 12, 24, and 72 hours after endodontic treatment by an evaluator blinded to group allocation. Pain intensity was measured using the Numerical Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain). While a specific Minimal Clinically Important Difference (MCID) for the NRS was not pre-defined for this exploratory study, a reduction of 2 points or a 30% decrease from baseline is generally considered clinically meaningful in pain research(14).
Patients were allowed to contact the researcher at any time if they had questions or concerns. No rescue medication was required for the management of severe pain.

Statistical analysis

The frequency of patients reporting postoperative pain was analyzed using the Chi-square test and Fisher's exact test. Comparisons of pain scores between the two groups at each time point were performed using the Mann–Whitney U non-parametric test. Multiple logistic regression analysis was used to examine the association between covariates and the occurrence of postoperative pain, estimating odds ratios (OR) and 95% confidence intervals (95% CI). Variables with $p<0.20$ in the bivariate analyses were included in the multiple model. The final multiple model was estimated using backward selection process, retaining the variables with $p<0.20$. All statistical analyses were conducted using Stata® SE, version 17 (StataCorp LLC, Texas, USA), with the significance level set at 0.05.

Results

Of the 130 patients initially considered eligible for the study, 27 were excluded for not meeting the inclusion criteria, and an additional 23 were excluded for not responding to the NRS questionnaire during follow-up (9 in the diabetes group and 14 in the non-diabetic group), as shown in Figure 1. These participants were lost to follow-up despite multiple contact attempts and were not included in the final analysis. No imputation methods were applied; thus, the results are based on complete case analysis. A total of 80 patients were included in the study, with 40 in each group.
In the diabetes group, the prevalence of postoperative pain was reported by 19 pa-

Table 2.

Descriptive analysis of postoperative pain in both groups at the four-time intervals assessed, mean ± SD (median, IQR).

NRS	6h	12h	24h	72h
Without diabetes	2.25±2.27 (1, 4.5)	1.43±2.14 (0, 2.5)	1.00±2.15 (0, 1)	0.30±0.91 (0, 0)
With diabetes	1.65±2.23 (0, 3)	0.85±1.55 (0, 2)	0.58±1.36 (0, 0)	0.18±0.59 (0, 0)
	p =0.139	p =0.169	p = 0.387	p = 0.687

**p<0.05, Mann-Whitney test.*

Table 3.

Measures of association between the independent variables and the occurrence of postoperative pain. Logistic regression for estimation of OR (95% CI).

Variable	Crude OR	Model 1	Model 2
Diabetes (ref.: no)	0.29 (0.11-0.79)*	0.05 (0.01-0.56)*	0.19 (0.04-0.77)*
Gender (ref.: women)	0.51 (0.19-1.32)[a]	0.31 (0.09-1.09)b	0.31 (0.10-0.99)*
Age	0.99 (0.96-1.02)	1.04 (0.98-1.10)	-
Extrusion of filling material (ref.: no)	1.19 (0.42-3.40)	2.39 (0.54-10.54)[a]	-
Glycated hemoglobin	0.94 (0.77-1.14)	1.39 (1.01-1.95)*	1.26 (0.94-1.70)[a]
Preoperative pain (NRS)	1.37 (1.14-1.65)**	1.38 (1.11-1.72)**	1.39 (1.14-1.69)**
Treatment (ref.: necro)	1.99 (0.79-5.05)[a]	1.11 (0.29-4.29)	-
Hypertension (ref.: no)	0.99 (0.36-2.76)	1.04 (0.21-5.04)	-

*a p<0.20; b p<0.10; * p<0.05; ** p<0.01*
Model 1: initial multiple model including all variables
Model 2: final multiple model estimated using backward selection process, retaining variables with p<0.20

tients (47.5%) within the first 6 hours, 11 patients (27.5%) at 12 hours, 9 patients (22.5%) at 24 hours, and 5 patients (12.5%) at 72 hours.

In the non-diabetic group, postoperative pain was reported by 24 patients (60%) within 6 hours, 19 patients (47.5%) at 12 hours, 11 patients (27.5%) at 24 hours, and 5 patients (12.5%) at 72 hours.

Postoperative pain intensity, measured using the Numerical Rating Scale (NRS), is presented in Table 2. No statistically significant differences were observed in pain intensity between the groups at any of the assessed time intervals.

The effects of the independent variables—sex, age, extrusion of filling material, glycated hemoglobin level, preoperative pain, and pulp diagnosis—on postoperative pain were evaluated using multiple logistic regression analysis. The odds of experiencing postoperative pain were significantly lower in patients with diabetes mellitus (OR = 0.19; 95% CI: 0.04–0.77), regardless of the other covariates included in the model. Variables with p<0.20 in the bivariate analyses were included in the multiple model. The final multiple model was estimated using backward selection process, retaining the variables with p<0.20. (Table 3).

Discussion

Previous endodontic clinical studies have focused on evaluating treatment success through apical healing(15, 16), which is a

recognized complication among diabetic patients (17, 18). The presence of postoperative symptoms in this population, particularly pain, also warrants attention, as it affects more than half of patients(10, 11) and remains a concern for clinicians(8).
In the control group, nearly half of the patients reported postoperative pain within the first 6 hours after treatment. Similar results were reported in studies with comparable designs conducted in the same geographic region(10, 11). In the experimental group, fewer diabetic patients reported pain at 6 hours, which may be related to altered nerve response in individuals with DM(4). This outcome differs from that of Ali et al. (19), who attributed increased postoperative pain during the first 12 hours to diabetes-related nerve damage, which can either exacerbate pain or cause an absence of symptoms.
The age disparity between groups in the present study aligns with findings by Cho et al. (20), who analyzed global diabetes prevalence. Their study found that most individuals with type 2 diabetes were older, with the highest prevalence in the 60–79 age group in high-income countries and 55–64 years in low-income countries. Age was included as a covariate in the multiple logistic regression model to account for its potential confounding effect. The association between T2DM and reduced postoperative pain remained significant after adjustment, suggesting that age did not substantially influence this relationship.
Given the well-established association between type 2 diabetes mellitus and hypertension(21), hypertension was not considered an exclusion criterion. The frequent coexistence of these conditions is due to shared pathophysiological mechanisms, particularly those involving obesity and insulin resistance(22). Epidemiological data highlight a high prevalence of hypertension among patients with type 2 diabetes, as well as increased risks of resistant hypertension and cardiovascular complications. According to the Framingham Heart Study, type 2 diabetes is associated with a two- to fourfold increased risk of hypertension, peripheral arterial disease, and myocardial infarction(23).
Regression analysis in this study indicated that systemic arterial hypertension did not influence patients' pain experience, although previous studies(24, 25)have shown that patients using angiotensin-converting enzyme (ACE) inhibitors may exhibit an increased pain threshold.
In our study, most participants in both groups were women, despite global data showing a higher prevalence of diabetes among men, with approximately 231.7 million male cases reported(20). A possible explanation is that women tend to seek healthcare services more frequently than men. According to the 2019 Brazilian National Health Survey(26), women reported accessing medical care more often than men.
In a prospective clinical trial, Ali et al.(19) evaluated 270 patients and found a positive correlation between preoperative and postoperative endodontic pain—patients who experienced pain before treatment were more likely to report pain afterward. This was also observed in the present study.
Diabetes mellitus has a direct impact on the structural integrity of dental pulp, causing histological changes in vascular and neural components. In diabetic patients, peripheral nerve glycosylation results in neurotoxicity, further aggravated by endoneurial microangiopathy. Increased intracellular glucose promotes mitochondrial oxidant release, reducing membrane potential and impairing energy production, which diminishes nerve conduction. Clinically, this manifests as reduced sensitivity to stimuli in the dental pulp and peripheral tissues(27), potentially explaining the lower average pain scores among diabetic patients observed in this study.
In cases of poorly controlled or long-standing diabetes, pulpal blood flow is significantly reduced due to vascular basement membrane thickening and diminished collateral circulation. Elevated levels of inflammatory mediators, such as kallikrein-nitrite, along with a reduced leukotactic response, contribute to pulpal inflammation and irreversible damage, including necrosis. These vascular changes also decrease oxygen saturation, creating an anaerobic environment conducive to bacterial proliferation(28).
In an in vitro study, Alsamahi et al.(6) found morphological differences in pulp tissue

from diabetic patients, including reduced cell density, fewer blood vessels, thicker vascular walls, increased calcification, and enhanced collagen deposition.

All dental groups were included in the study due to the difficulty in pairing patients by tooth type. Diabetic patients were found to have fewer teeth than controls, consistent with previous studies reporting that poorly controlled diabetes is associated with significant tooth loss due to increased caries and aggressive periodontal disease(29).

In the non-diabetic group, most treated teeth were molars, whereas in the diabetic group, the majority were incisors or canines. This discrepancy may explain the higher incidence of material extrusion in the diabetic group (37.5%) compared to the non-diabetic group (10.0%), likely due to the larger apical diameters of anterior teeth(30). The lack of statistically significant differences in postoperative pain between diabetic and non-diabetic patients undergoing single-session endodontic treatment was also reported by Anagha et al. (31). The results of this study should be interpreted considering its methodological limitations. Despite adjusting for potential confounding factors, challenges in matching groups due to population heterogeneity and the impossibility of randomization remain key limitations. Randomization is essential in clinical trials to ensure equal allocation and comparability between groups. However, because systemic condition was the main distinguishing factor, randomization was not feasible in this study.

The results of this study suggest a trend toward reduced postoperative pain in individuals with type 2 diabetes mellitus (T2DM). This observation may be associated with the neuropathic changes linked to T2DM. Diabetic neuropathy is a common complication of diabetes and can lead to altered pain perception, resulting in hypoalgesia or even analgesia in some cases(32, 33). Studies have indicated that diabetic neuropathy may affect the nerve fibers responsible for pain transmission, leading to decreased pain sensitivity(34). Furthermore, central mechanisms such as descending pain modulation may also be altered in patients with T2DM, contributing to variability in pain perception(35). It is important to note that the presence or absence of pain in patients with diabetic neuropathy can vary significantly, and factors such as the duration of diabetes, glycemic control, and the presence of other comorbidities may influence this perception(34). Therefore, although our findings suggest a potential reduction in postoperative pain among patients with T2DM, further studies are required to fully understand the underlying mechanisms and confirm these results.

From a clinical perspective, the observed trend toward reduced postoperative pain in patients with type 2 diabetes mellitus (T2DM) following endodontic treatment has meaningful implications for treatment planning and patient management. Specifically, these patients may require less analgesic intervention in the postoperative period. However, this diminished pain perception—likely influenced by diabetic neuropathy—should not be misinterpreted as an indication of improved healing. Instead, it underscores the need for careful postoperative follow-up to monitor healing progression and detect potential complications that may otherwise go unnoticed due to altered pain sensitivity. Diabetic patients constitute a heterogeneous group with diverse systemic characteristics, and currently, no specific endodontic protocol exists for this population. Anagha et al.(31) also demonstrated that one- or two-session endodontic treatment did not influence postoperative pain in diabetic patients. Therefore, future studies should aim to identify the most effective techniques, instruments, and materials for endodontic treatment in patients with diabetes to reduce postoperative pain and enhance clinical outcomes.

Conclusion

Considering the limitations of this study, individuals with type 2 diabetes mellitus may experience reduced postoperative pain following endodontic treatment compared to non-diabetic individuals. However, these findings should be interpreted with caution, as the study was exploratory in nature and may be limited by its statistical power.

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Declarations

Ethical approval
The study was approved by the Research Ethics Committee of the Federal University of Amazonas (CAAE n° 97436918.0.0000.5020) and registered in the Brazilian Registry of Clinical Trials (REBEC) (UTN: U1111-1228-6794).

Informed consent
Written informed consent to participate was obtained from all individual participants included in the study.

Data availability
No datasets were generated or analyzed during the current study.

Conflict of interest
All the authors report no conflicts of interest related to this study.

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