

# Influence of Glycemic Control on Peri-Implant Bone Healing: 12-Month Outcomes of Local Release of Bone-Related Factors and Implant Stabilization in Type 2 Diabetics

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## ABSTRACT

**Background:** The poor glycemic status seems to be an important factor affecting implant complication rates, including peri-implant bone loss.

**Purpose:** This trial evaluated the influence of glycemic control of type 2 diabetes mellitus (T2DM) patients on implant stabilization and on the levels of bone markers in peri-implant fluid during the healing.

**Materials and Methods:** Systemically healthy patients (SH,  $n = 19$ ), better-controlled T2DM (BCDM,  $n = 16$ ), and poorly controlled T2DM (PCDM,  $n = 16$ ) indicated for implant therapy were recruited. The implant stability quotient (ISQ) was determined at implant placement, 3, 6, and 12 months. Levels of transforming growth factor- $\beta$  (TGF- $\beta$ ), fibroblast growth factor (FGF), osteopontin (OPN), osteocalcin (OC), and osteoprotegerin (OPG) in the peri-implant fluid were quantified at 15 days, and 3, 6, and 12 months, using the Luminex assay.

**Results:** OPG and OPN levels were higher in SH at 12 months than at 15 days ( $p < .05$ ), whereas OC and TGF- $\beta$  were lower in PCDM at 12 months compared with the 15-day and 3-month follow-ups, respectively ( $p < .05$ ). Inter-group analyses showed lower OPN levels in PCDM compared with SH at 12 months ( $p < .05$ ). The ISQ was higher at 12 months when compared with baseline and 3 months in SH ( $p < .05$ ), whereas no differences were observed during follow-up in diabetics, regardless of glycemic control ( $p > .05$ ). No difference in ISQ was observed among groups over time ( $p > .05$ ).

**Conclusion:** Poor glycemic control negatively modulated the bone factors during healing, although T2DM, regardless of glycemic status, had no effect on implant stabilization.

**KEY WORDS:** biological markers, bone and bones, dental implants, diabetes mellitus, osseointegration

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## INTRODUCTION

Diabetes mellitus is a complex, chronic systemic illness, whose complications impact significantly on quality of life and longevity. Patients with type 2 diabetes mellitus (T2DM) have an increased risk of developing periodontitis, and poor glycemic control may negatively modulate osteo-immunoinflammatory mediators in the presence of periodontitis.<sup>1</sup> It creates a susceptibility condition that leads to periodontal attachment and tooth loss over time.<sup>2,3</sup> Implant therapy is an efficient form of dental rehabilitation that may benefit patients with

diabetes mellitus by improving masticatory function and dietary intake, which is critical for diabetic individuals.

However, experimental models have demonstrated that diabetes may lessen peri-implant bone formation.<sup>4-7</sup> In addition, clinical studies investigating implant success in T2DM patients with well-controlled glycemic status,<sup>8-11</sup> and unknown or poor levels of glycemic control,<sup>12-16</sup> have revealed varying levels of implant success, without a clear association with glycemic control. Recently, Khandelwal and colleagues<sup>16</sup> demonstrated predictable clinically successful implant placement even in diabetic patients lacking good glycemic control and support the application of dental implant therapy for patients having a broader range of glycemic control than has traditionally been proposed. However, it seems that a poor glycemic status is the most important factor affecting implant complication rates in T2DM patients, including peri-implant bone loss.<sup>14</sup>

Nevertheless, no controlled long-term clinical trial is available investigating the impact of glycemic control on the healing process around implants in T2DM patients. Therefore, this prospective case-controlled study compared the levels of key bone-related factors (transforming growth factor [TGF]- $\beta$ , fibroblast growth factor [FGF]), osteopontin [OPN], osteocalcin [OC], and osteoprotegerin [OPG]) in the peri-implant crevicular fluid of systemically healthy, better-controlled (BCDM), and poorly controlled patients with type 2 diabetes (PCDM) over 12 months, and evaluated implant stability during the same period. We hypothesized that better- and poorly controlled patients with diabetes and systemically healthy (SH) individuals exhibit distinct patterns of local bone-related markers, which could affect their potential for compromised healing and implant stabilization.

## MATERIALS AND METHODS

### Study Design

This study was designed as a prospective, case-controlled, examiner-blind clinical trial to evaluate the effects of glycemic control of type 2 diabetes on the levels of key bone markers in peri-implant fluid during the healing process around implants, and to determine

the impact of glycemic status on dental implant stabilization over 12 months.

### Population Screening

Patient recruitment started in April 2012 and was completed by the end of February 2013. The clinical procedures and evaluations were carried out between May 2012 and March 2014. Data entry and statistical analyses were performed by the end of April 2014. All the patients in the study were recruited from patients referred to Paulista University.

The inclusion criteria included: (1) patients aged between 35 and 70 years old; (2) with a posterior mandibular edentulous unitary area indicated for rehabilitation with dental implants; and (3) whose extractions had occurred at least 12 months before treatment. Patients with diabetes had to have T2DM, diagnosed by a physician, for at least the past 5 years. Such individuals were either under a dietary regimen and/or were using oral hypoglycemic agents (metformin or glybenclamin). Exclusion criteria were: (1) pregnancy; (2) lactation; (3) current smoking or ex-smokers; (4) other systemic conditions that could affect bone metabolism (e.g., immunologic disorders); (5) use of anti-inflammatory and immunosuppressive medications; (6) patients that required bone grafts before or concomitantly with implant surgery; and (7) a history of previous regenerative procedures in the area designated for implant therapy. Patients with major complications of DM (i.e., cardiovascular and peripheral vascular diseases [ulcers, gangrene, and amputation], neuropathy, and nephropathy) were also excluded.

All eligible patients were thoroughly informed of the nature, potential risks, and benefits of their participation in the study, and signed an informed consent document. This study was approved by the ethics committee of Paulista University (Protocol 601/11).

### Experimental Groups

Based on their systemic condition and glycemic status, 51 patients were divided into one of the following groups: (1) SH ( $n = 19$ ), without diabetes; (2) BCDM ( $n = 16$ ), diabetic patients with glycated hemoglobin (HbA1c) levels  $\leq 8\%$ ; and (3) PCDM ( $n = 16$ ), diabetic patients with HbA1c levels  $> 8\%$ .<sup>17</sup> All patients recruited received one dental implant. Thus, 51 implants were evaluated.

## Fasting Plasma Glucose and Glycated Hemoglobin Monitoring

A single laboratory (Clinical Analysis Laboratory, Paulista University) conducted the blood analyses of the patients, including fasting plasma glucose (FPG) and HbA1c monitoring. FPG was measured using the glucose oxidase method (milligrams per deciliter), and HbA1c (percentage) was measured by high-performance liquid chromatography.

## Treatment Protocol

Before implant therapy, patients were subjected to calculus removal, supragingival plaque control, and subgingival debridement, when necessary.

All surgery was performed by the same operator (A.C.) and all patients received a single-stage dental implant with external-hexagon connections. All implants used were of the same design with a 3.75 mm diameter and 8.5 mm to 11.5 mm length (SIN, São Paulo, Brazil). Surgical areas were anesthetized and mucoperiosteal incisions were made in the alveolar ridge mucosa. The surgical sequence followed the protocol described by the implant company. Suturing was done with interrupted sutures using absorbable polygalactin 5.0. Amoxicillin (2 g/1 h before the procedure), postoperative sodic-dipyrone (500 mg, every 6 h/2 days), and 0.12% chlorhexidine mouthwash (every 12 h/7 days) were indicated. The screw-retained prostheses were placed at 4 months.

## Implant Stability Analysis

The implant stability quotient (ISQ) was determined by resonance frequency measurements using Osstell® (Integration Diagnostics AB, Göteborg, Sweden) at implant placement and at 3, 6, and 12 months later. The measurements were performed in triplicate by the same examiner (B.G.).

## Bone-Related Factor Profile Assessment Using Multiplexed Bead Immunoassay (Luminex)

Peri-implant crevicular fluid was collected from implants using filter paper strips (Periopaper, Oraflow, Plainview, NY, USA) after 15 days, and 3, 6, and 12 months by the same examiner (B.G.), as previously described.<sup>18</sup> The fluid volume was measured using a calibrated device (Periotron 8000, Oraflow) and peri-implant fluid samples were stored at  $-20^{\circ}\text{C}$ .

The levels of TGF- $\beta$ , FGF, OPN, OC, and OPG in the peri-implant crevicular fluid were determined using human plex (HBNMAG-51K and TGFBMAG-64K, Millipore Corporation, Billerica, MA, USA) and the multiplexing instrument (MAGpix™, MiraiBio, Alameda, CA, USA). The samples were individually evaluated, adjusted for the fluid volume measured by the device, and the concentrations were estimated from the standard curve using a five-parameter polynomial equation and specific software (Xponent®, Millipore Corporation). The mean concentration of each biomarker was calculated and expressed as pg/mL.

## Reassessment Evaluations

Reassessment visits occurred every 15 days during the first month and then monthly until the 12th month. During each visit, postoperative healing complications (such as wound dehiscence, ulceration, or infection) and implant failure, if present, were recorded.

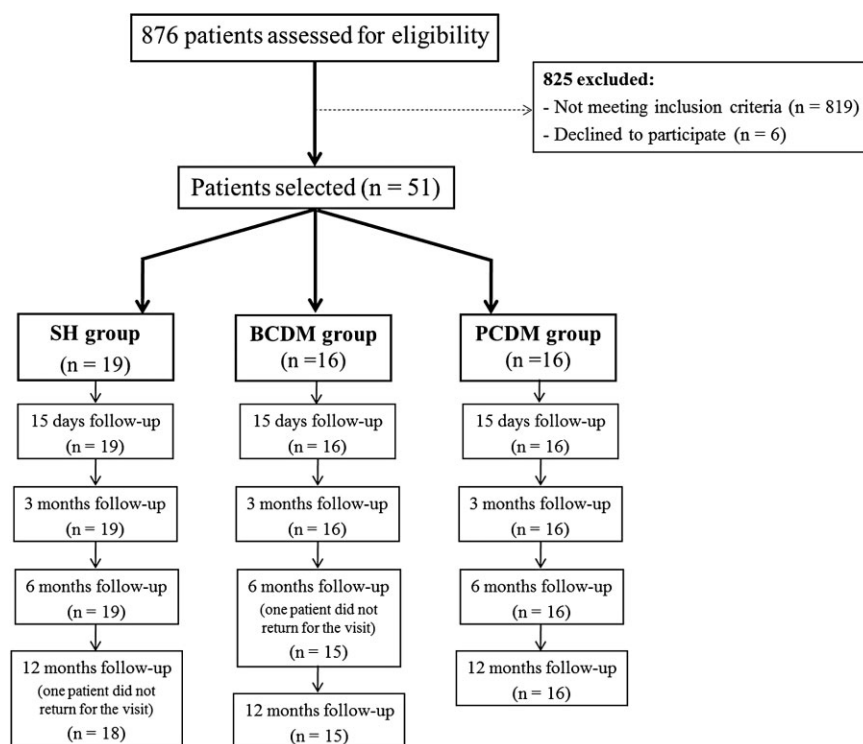
## Data Analysis

The number of patients included in the present study was based on previous investigations that found differences in the peri-implant and gingival levels of various bone-related and immune-inflammatory markers and on dental implant stability.<sup>1,18–20</sup>

All analyses were performed using SAS program release 9.3 (Cary, NC, USA). Data were first examined for normality using the Kolmogorov–Smirnov test, and the data that achieved normality were analyzed using parametric methods. Differences in the time of diagnostic of DM between poorly controlled and better-controlled patients with diabetes were compared using the Student's *t*-test. Differences in HbA1c and FPG levels among groups were compared using the Kruskal–Wallis and Dunn's test. The significance of differences in age and in the concentrations of the biomarkers among groups were compared using analysis of variance (ANOVA) and Tukey's test and the Kruskal–Wallis and Dunn's test, respectively. Repeated measures ANOVA and Tukey's test were used to detect intragroup and intergroup differences in the ISQ. An experimental level of significance was determined at 5% for all statistical analyses.

## RESULTS

Initially, 32 patients with type 2 diabetes and 19 patients without diabetes (28 men and 23 women; aged 37 to 70



**Figure 1** Flowchart of the study showing the patients enrolled in the prestudy phase and periodontal maintenance and the selection of individuals for the study phase. BCDM = better-controlled T2DM; PCDM = poorly controlled T2DM; SH = systemically healthy; T2DM = type 2 diabetes mellitus.

years) were selected. One better-controlled type 2 diabetic and one SH patient did not return for the 6 and 12-month visit, respectively, and therefore, intention-to-treat clinical analyses were performed for these participants (Figure 1).

There were no differences in the mean age and sex distribution among groups ( $p > .05$ ). As expected, T2DM patients, both BCDM and PCDM, presented higher HbA1c and FPG levels than SH individuals

( $p < .05$ ). Additionally, poorly controlled patients with diabetes demonstrated higher levels of HbA1c and FPG than better-controlled patients ( $p < .05$ , Table 1). No patients in any experimental group presented implant failure or clinical complications during the study.

### Biomarker Levels

Table 2 shows the levels of each biomarker evaluated for all groups. In the intra-group analyses, higher levels of

**TABLE 1** Demographic Characteristics of the Study Population (Mean  $\pm$  SD)

|                     | Patients with Type 2 DM |                                 |                                  |
|---------------------|-------------------------|---------------------------------|----------------------------------|
|                     | SH (n = 19)             | BCDM (n = 16)                   | PCDM (n = 16)                    |
| Age (years)         | 51.58 $\pm$ 7.74        | 54.91 $\pm$ 13.95               | 56.38 $\pm$ 13.69                |
| M/F                 | 10/9                    | 9/7                             | 9/7                              |
| HbA1c (%)           | 5.49 $\pm$ 0.71         | 7.22 $\pm$ 0.56 <sup>†</sup>    | 10.04 $\pm$ 1.15 <sup>†*</sup>   |
| FPG (mg/dL)         | 90.47 $\pm$ 7.82        | 143.44 $\pm$ 16.96 <sup>†</sup> | 193.88 $\pm$ 28.65 <sup>†*</sup> |
| DM duration (years) | —                       | 10.69 $\pm$ 5.71                | 10.86 $\pm$ 4.49                 |

\*Significant differences when compared with BCDM (Kruskal–Wallis and Dunn’s test;  $p < .05$ ).

<sup>†</sup>Significant differences when compared with SH (Kruskal–Wallis and Dunn’s test;  $p < .05$ ).

BCDM = better-controlled type 2 DM; DM = diabetes mellitus; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; PCDM = poorly controlled type 2 DM; SH = systemically healthy.

**TABLE 2** Mean ( $\pm$ SD) Concentrations (pg/ $\mu$ L) of Mediators of All Groups at Baseline, and at 3, 6, and 12 Months Post-Therapy

|              |      | 15 Days           | 3 Months          | 6 Months          | 12 Months          |
|--------------|------|-------------------|-------------------|-------------------|--------------------|
| OPG          | SH   | 27.8 $\pm$ 31.1   | 55.4 $\pm$ 54.0   | 78.4 $\pm$ 09.0   | 97.0 $\pm$ 91.2*   |
|              | BCDM | 24.7 $\pm$ 23.5   | 63.8 $\pm$ 140.9  | 46.2 $\pm$ 50.3   | 69.8 $\pm$ 87.3    |
|              | PCDM | 18.8 $\pm$ 14.8   | 51.6 $\pm$ 43.1   | 66.0 $\pm$ 76.8   | 53.1 $\pm$ 53.7    |
| OC           | SH   | 150.8 $\pm$ 169.7 | 278.5 $\pm$ 521.0 | 149.1 $\pm$ 149.7 | 143.3 $\pm$ 123.4  |
|              | BCDM | 92.1 $\pm$ 86.7   | 123.4 $\pm$ 122.7 | 113.2 $\pm$ 131.5 | 113.6 $\pm$ 117.0  |
|              | PCDM | 167.4 $\pm$ 125.4 | 121.7 $\pm$ 81.9  | 130.7 $\pm$ 130.7 | 69.7 $\pm$ 53.8*   |
| OPN          | SH   | 159.3 $\pm$ 220.3 | 165.2 $\pm$ 286.1 | 237.8 $\pm$ 293.3 | 388.8 $\pm$ 390.2* |
|              | BCDM | 121.5 $\pm$ 126.3 | 163.9 $\pm$ 219.7 | 136.0 $\pm$ 179.8 | 196.5 $\pm$ 323.5  |
|              | PCDM | 167.4 $\pm$ 176.2 | 156.4 $\pm$ 230.1 | 145.2 $\pm$ 117.7 | 121.0 $\pm$ 133.4† |
| FGF          | SH   | 45.3 $\pm$ 70.9   | 51.8 $\pm$ 93.7   | 62.9 $\pm$ 91.8   | 62.9 $\pm$ 74.9    |
|              | BCDM | 20.3 $\pm$ 16.8   | 31.6 $\pm$ 39.7   | 41.9 $\pm$ 64.7   | 30.6 $\pm$ 45.5    |
|              | PCDM | 26.2 $\pm$ 26.3   | 54.7 $\pm$ 46.2   | 34.4 $\pm$ 31.8   | 25.0 $\pm$ 23.3    |
| TGF- $\beta$ | SH   | 20.6 $\pm$ 21.6   | 28.5 $\pm$ 31.6   | 16.3 $\pm$ 18.3   | 36.0 $\pm$ 50.0    |
|              | BCDM | 17.6 $\pm$ 11.6   | 30.9 $\pm$ 63.9   | 29.9 $\pm$ 42.7   | 17.1 $\pm$ 15.4    |
|              | PCDM | 29.0 $\pm$ 23.0   | 33.9 $\pm$ 26.8   | 19.1 $\pm$ 25.0   | 18.1 $\pm$ 16.6‡   |

\*Represents significant intragroup differences from 15 days by Friedman test,  $p < .05$ .

†Represents significant intergroup differences by Kruskal–Wallis test,  $p < .05$ .

‡Represents significant intragroup differences from 3 months by Friedman test,  $p < .05$ .

BCDM = better-controlled type 2 diabetes mellitus; FGF = fibroblast growth factor; OC = osteocalcin; OPG = osteoprotegerin; OPN = osteopontin; PCDM = poorly controlled type 2 diabetes mellitus; SH = systemically healthy; TGF- $\beta$  = transforming growth factor  $\beta$ .

OPG and OPN were observed in the peri-implant fluid of systemically healthy patients at the 12-month follow-up when compared with 15 days ( $p < .05$ ), whereas OC and TGF- $\beta$  levels were decreased after 12 months when compared with the 15-day and 3-month follow-ups, respectively, in poorly controlled diabetics ( $p < .05$ ). Intergroup comparisons exhibited inferior levels of OPN in poorly controlled diabetics when compared with nondiabetic controls at the 12-month reevaluation ( $p < .05$ ).

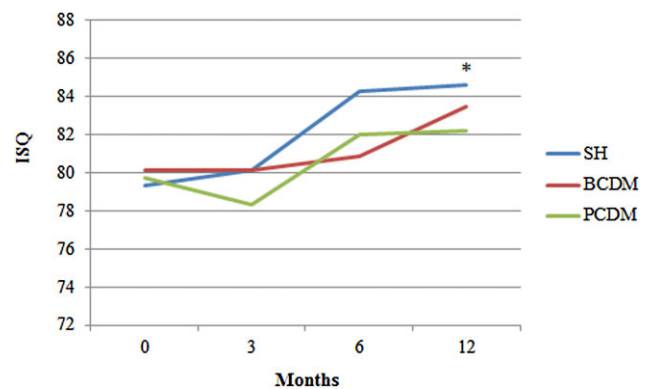
### Resonance Frequency Analysis

In the resonance frequency analysis, the ISQ was significantly higher at 12 months ( $84.62 \pm 4.72$ ) when compared with baseline ( $79.36 \pm 4.60$ ) and 3 months ( $80.11 \pm 5.51$ ) in SH patients ( $p < .05$ ), whereas no ISQ differences were detected during follow-up in type 2 diabetics, regardless of glycemic status ( $80.17 \pm 6.44$ ,  $80.13 \pm 4.21$ ,  $80.86 \pm 5.22$ , and  $83.5 \pm 4.30$ , for better-controlled diabetics at baseline, 3, 6, and 12 months, respectively; and  $79.77 \pm 5.72$ ,  $78.33 \pm 6.79$ ,  $82.00 \pm 5.81$ , and  $82.20 \pm 6.83$ , for poorly controlled diabetics at same periods, respectively) ( $p > .05$ ). No differ-

ences in implant stability among groups were observed over the healing period ( $p > .05$ ) (Figure 2).

### DISCUSSION

Bone remodeling is a critical aspect of implant survival in response to the functional demands exerted on the implant restoration and supporting bone, especially in



**Figure 2** Implant stability quotient at baseline and after 3, 6, and 12 months. \*Different from baseline and 3 months in systemically healthy patients (ANOVA/Tukey's test,  $p < .05$ ). BCDM = better-controlled T2DM; ISQ = implant stability quotient; PCDM = poorly controlled T2DM; SH = systemically healthy.

patients with diabetes, as the relationship between glycemic control and the development of microvascular and macrovascular complications is well established,<sup>21</sup> and may compromise healing capacity.<sup>1,22–26</sup> Thus, this study evaluated the effect of glycemic control of T2DM on the local levels of key bone markers in peri-implant fluid during the healing process around dental implants, and also determined the impact of glycemic status on implant stabilization over 1 year. In general, although the results of the present study revealed that diabetic patients with compromised glycemic control exhibit a distinct profile of bone-related factors that could impair bone repair, the current study failed to identify a significant difference in implant stability patterns among groups during the 12-month integration period following implant placement. Additionally, no differences in implant failure or clinical complications were observed among groups during the study.

Consistent with our results, successful implant placement has been demonstrated in diabetic patients regardless of glycemic status.<sup>13–16</sup> However, most of these studies presented only short-term outcomes with about a 4-month follow-up after implant placement.<sup>13,15,16</sup> When the follow-up period ranged from 1 to 12 years, a significant correlation between HbA1c values and peri-implantitis and peri-implant bone loss was observed, although the number of failures was limited.<sup>14</sup>

Although it is important to investigate the impact of glycemic control on peri-implant repair over a long-term follow-up period, as performed in the present study, the early phase of implant healing – the first 4 weeks – seems to be critical, especially when considering diabetics with inadequate glycemic control. In general, the minimum implant stability occurs at 2 to 4 weeks following implant placement, representing the transition from primarily bone resorption to bone formation, thus initiating the osseointegration phase.<sup>15,16,27</sup> In the current trial, the resonance frequency analysis was performed during implant placement and during the 12 months following implant surgery. However, studies with shorter reevaluation periods after implant placement (16 weeks) showed that patients with HbA1c  $\geq 8.1\%$  had a greater maximum decrease in stability from the initial measurement and required a longer period for the return of stability to the baseline level.<sup>15</sup> The results of the current study demonstrated that at 3 months (12 weeks), although there was no significant difference among groups in term of stability,

poorly controlled diabetics had a tendency to show lower stability when compared with the other groups and the ISQ levels were lower than those obtained at baseline. Oates and colleagues<sup>15</sup> also demonstrated that individuals with HbA1c  $\geq 8.1\%$  tended to show less improvement in stability from baseline to 12 weeks, with few implants returning to or exceeding baseline stability levels after this period, when compared with nondiabetics and diabetics with better glycemic control.

Additionally, according to the resonance frequency analysis of the present study, the ISQ level was significantly higher at 12 months when compared with baseline and 3 months in systemically healthy patients, whereas no ISQ differences were observed during follow-up in diabetic groups, regardless of glycemic control. Previous investigations with longer reevaluation periods showed that implant stability gradually increased after 3, 6, and 12 months in SH patients.<sup>28,29</sup> In our study, this outcome regarding the long-term stability of the osseointegrated interface could be related to the higher peri-implant levels of OPG and OPN observed at 12 months in nondiabetic individuals when compared with baseline levels. Whereas OPG binds to RANKL and prevents binding to its membrane receptor (RANK) present in the preosteoclasts, modulating bone maturation and resorption,<sup>30</sup> OPN is related to the binding of basic elements to the extracellular bone matrix and bone mineralization.<sup>31</sup> Interestingly, the results of the current investigation also revealed higher OPN levels at 12-month follow-up in SH patients when compared with poorly controlled diabetics. Hyperglycemia and oxidative stress related to diabetes are able to negatively influence the Wnt signaling pathways, which is crucial for osteoblast differentiation and for bone repair,<sup>32,33</sup> and it seems that the OPG exerts an important role in this pathway.<sup>34</sup> Thus, it could be suggested that the peri-implant OPG increasing in diabetics to a lesser extent than in healthy patients throughout the present study could be related to the inhibition of Wnt signaling pathway. However, further investigations are required to support this hypothesis.

Data from the present investigation also revealed that the peri-implant fluid of patients with poor glycemic control showed lower TGF- $\beta$  and OC levels at the 12-month reevaluation when compared with earlier follow-ups. The TGF family is linked to osteoblastic proliferation, differentiation, activity, and collagen synthesis.<sup>35</sup> Besides having an important impact on bone

formation, OC plays a vital role in the regulation of glucose metabolism.<sup>36–38</sup> Lee and colleagues<sup>39</sup> revealed that OC acts as a hormone that regulates glucose metabolism and fat mass, showing that OC-knockout mice display decreased  $\beta$ -cell proliferation, glucose intolerance, and insulin resistance. In the Kanazawa and colleagues<sup>40</sup> study, the serum OC level was significantly and negatively correlated with glycemic control in both men and postmenopausal women with T2DM, in line with the findings of the current investigation. According to Okazaki and colleagues,<sup>23</sup> the improvement of poorly controlled T2DM glycemic status modulated bone turnover, reducing markers for bone resorption and increasing OC.

Altogether, the peri-implant fluid outcomes of this study showed that important osteogenic and/or bone mineralization markers were downregulated in poorly controlled diabetics, suggesting that diabetic patients with inadequate glycemic control present a different local pattern of bone biomarkers, which could compromise the host response during the healing process around dental implants. Accordingly, in a population of poorly controlled diabetic patients, biochemical markers of bone resorption were reduced in association with improved glycemic control, suggesting that hyperglycemia in T2DM patients has an adverse impact on bone metabolism.<sup>22,23</sup> Other studies also demonstrated that hyperglycemia is related to changes in insulin levels and augmented advanced glycation end-products (AGEs) and pro-inflammatory cytokines that may alter bone physiology, disturbing remodeling and resulting in bone loss.<sup>1,41</sup>

A critical aspect when comparing the findings of this study with previous data from investigations of implant therapy in diabetic patients is the lack of a clear definition of glycemic control in these studies,<sup>10,12,42,43</sup> limiting the development of specific evidence-based strategies for the care of T2DM patients. Further, few studies have compared a T2DM population with non-diabetic control individuals,<sup>42,44</sup> as performed in the current trial. Interestingly, data from these studies also failed to demonstrate a difference in implant failure between diabetics and systemically healthy patients, consistent with our findings.

In conclusion, while the peri-implant fluid results of this trial demonstrated that poor glycemic status negatively influences the profile of local bone markers over 12 months, dental implant stability when assessed on a

long-term basis does not seem to be influenced by glycemic control. Although the present study and previous investigations have reported successful outcomes of implant therapy in patients with high levels of HbA1c,<sup>15,16,45</sup> most authors insist on an HbA1c of less than 8% before implant surgery is carried out.<sup>46–48</sup> Thus, professionals should encourage T2DM patients to have good glycemic control before dental implant rehabilitation. However, while there is knowledge about the importance of maintaining a rigorous glycemic status to reduce diabetic complications, most individuals with diabetes mellitus still present inadequate glycemic control with elevated HbA1c levels.<sup>49,50</sup> Importantly, this study offers additional information for the application of dental implant therapy in patients with poorly controlled diabetes, highlighting a tendency toward lower implant stability during the initial healing phases, and suggesting that the impact of hyperglycemia on implant integration can be successfully accommodated with longer follow-ups. Nevertheless, it is essential to note that a worse glycemic status has been associated with more implant complications in assessments conducted up to 12 years following dental implant placement.<sup>14,51</sup> Although the present study has revealed that the pattern of release of bone markers in peri-implant fluid is altered by glycemic control, the role of hyperglycemia in bone healing related to dental implants is not completely established and further studies are needed to determine the effects of these alterations on the rate of implant failure and complications in this patient profile.

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