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The influence of conventional non-surgical periodontal treatment in glycemic control of patients diagnosed with diabetes mellitus and periodontitis - review of literature

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• Conflicts of interest: none declared.

Abstract

Objective: to review the literature on the influence of conventional non-surgical periodontal treatment (CPT) in terms of glycemic control in diabetic patients diagnosed with periodontitis. **Material and Methods:** we used the descriptors Diabetes mellitus, Periodontitis and Therapy, in English, to search the PubMed database, from 2015 to 2019. A total of 233 articles were found, and after reading all abstracts, we selected 25 related to the subject and fully read them. Literature reviews, in vivo research and clinical trials without systemic analysis of patients, especially regarding glycemic tests, or aimed at evaluating drug effects, were excluded. **Results:** most of the selected clinical trials prospectively analyzed the present association. Twenty studies indicated the CPT may positively influence in glycemic control in patients diagnosed with DM and periodontitis. Proinflammatory cytokines are known to increase peripheral cellular resistance to insulin action and to have a causal relationship with DM. The present result was associated with the potential of CPT, performed through supra and subgingival scraping, to reduce the local microbial load and, consequently, the massive concentration of inflammatory mediators in the free gingival groove or periodontal pocket, reducing their spread. **Conclusion:** CPT has systemic benefits by facilitating glycemic control in patients with diabetes. It is suggested the visits to the dentist should be recorded in the treatment of diabetic patients.

Keywords: Diabetes mellitus, Periodontitis, Therapy.

Introduction

Diabetes Mellitus (DM) is a chronic disease characterized by a deficiency in insulin production in the pancreas or resistance to the acitvity of this hormone.[1] The consequent serum hyperglycemia, in turn, is associated with vascular changes, especially in microcirculation,[2] with decreased salivary flow[3] and host immune defense dysfunction,[4] contributing to the precariousness of intraoral pathological conditions in affected individuals. Thus, chronic inflammatory diseases, especially periodontal pathologies of infectious origin, such as periodontitis, may be favored in decompensated diabetic patients.[5]

Periodontitis is a worldwide infectious disease associated with tooth loss.[6] It is a chronic inflammatory process that is mostly nonspecific and destructive, installed in response to bacterial antigens from the dental biofilm. Clinically, specific signs are observed as a result of bone resorption and periodontal ligament destruction, such as the formation of a periodontal pocket, and inflammatory parameters, such as edema and redness of the gingival tissue.[7]

The literature has been consistent regarding the faster rate of progression of clinical signs of periodontitis and lower responsiveness to periodontal treatment in patients with decompensated DM.[5] In addition, some studies suggest an inverse sense of the present association, so that glycemic control is difficult due to the presence of a consistent infectious-inflammatory process in periodontitis, deducing a two-way character of the interrelationship between the two diseases. In this last sense, the data have not been completely elucidated, but it is suggested that the degree of periodontal inflammation is directly related to the difficulty of glycemic control in DM.[5,8]

Considering that both diseases are remarkably prevalent worldwide and frequently associated with each other, allied to the knowledge that non-surgical conventional periodontal treatment (CPT) in patients with periodontitis has the advantages of low cost, easy access and relative simple accomplishment, favoring

periodontal healing and reducing local inflammation,[9] this study aimed to review the current scientific literature regarding the influence of CPT on the glycemic control of patients diagnosed with DM and periodontitis, highlighting the importance of reviewing the pathological mechanisms involved in both diseases.

Material and methods

The search was performed in March 2018. We searched for scientific papers in the PubMed database through the descriptors Diabetes mellitus, Periodontitis and Therapy, registered in Mesh. These were combined through Boolean operators as follows: Diabetes mellitus and Periodontitis and Therapy. From 223 results published from 2015 to 2019, 25 articles were selected which included results from clinical trials or data analysis that directly investigated the effect of CPT on glycemic control in diabetic patients. Studies including description of case report, literature reviews, as well as in vivo research and clinical trials without systemic analysis of patients, especially for tests related to glycemic control, or studies that aimed to evaluate drug effects primarily were excluded from the studied sample.

For the initial selection of articles, their abstracts were read and then the selected scientific papers were read in full and compiled into a table for comparison and discussion of the data.

Results

Among the 25 studies selected, a total of 23 were prospective clinical trials[10-32] containing varying number of samples (minimum 24 and maximum 330 patients examined), which were composed of individuals with adult ages (minimum 18 years and maximum of 85 years) systemically healthy, diabetic and/or diagnosed with periodontitis. In these studies, patients were assessed at baseline and at 1, 3 or 6 months after periodontal treatment. Regarding the individuals diagnosed with diabetes, the studies referred to subtype 2 (DM2), except one that included patients with DM1 and DM2.[32]

Of the remaining 2 selected studies, one retrospectively evaluated data from systemic and dental health records of 14551 patients[33] and the other investigated financial costs through a spreadsheet of patients with diabetes treated or not for periodontal disease.[34] In both of them, the advantages of performing CPT in diabetic patients were observed.

In all prospective clinical trials (n = 23), patients were evaluated periodically for plaque index (PI), gingival bleeding index (GBI), probing depth (PD), clinical insertion level (CIL) and bleeding on probing (BP). The systemic parameters evaluated were mainly fasting blood glucose, percentage of glycated hemoglobin (HbA1C) and serum levels of inflammatory mediators. Among these, the HbA1C test was more used to evaluate DM glycemic control. In addition, serum concentrations of inflammatory mediators and/or C-reactive protein (CRP) were evaluated in 10 studies and compared to glycemic te sts.[11,15,16,18,21,22,25,26,28,30]

Regarding prospective clinical trials, CPT improved periodontal conditions in PI, GBI, BP, CIL and/or PD, but in a minority there were no improvements in CIL and/or PD.[14,19,22,24,27] With regard to the influence of CPT on glycemic control in patients with diabetes and periodontitis, it was found that 06 studies,[11,15,22,23,30,32] out of these 23 clinical trials,[10-32] did not detect any benefit from reductions in periodontal inflammatory parameters, obtained after CPT, on glycemic tests, especially HbA1C. However, such manuscripts correspond to a small number of studies among the whole sample in the present review.

Among the 10 prospective clinical trials that assessed the correlation between CPT and the level of systemic inflammation, six studies found reductions in serum concentrations of inflammatory mediators and/or CRP during the post-CPT reassessment period.[16,21,25,26,28,30] Nevertheless, in one study no serum reduction in HbA1C levels and improvements in glycemic control in diabetic patients were observed,[30] even though the plasma concentration of IL-17 was decreased by CPT.

The results of the selected scientific papers, as well as their methodologies, are compiled in Table 1 for better understanding.

Discussion

DM is a systemic disease of multiple etiology characterized by compromised glucose metabolism and chronic hyperglycemia.[35,36] Subtype 1 (DM1) is defined as an autoimmune disease caused by the destruction of pancreatic β cells responsible for insulin production and release, mediated by macrophages and T lymphocytes.

Whereas subtype type 2 DM (DM2) seems to be more prevalent compared to the former[36] and in fact, in great majority of the studies selected in this review (Table 1) patients were diagnosed with DM2, in which insulin resistance is the etiology as well as consequence of this disease, since it is favored by the inflammatory characteristics observed with the evolution of hyperglycemia.[35]

Regardless of etiology, from the generation of free radicals and reactions known as glycation, in which Advanced Glycosylation End-products (AGEs) develop through the interaction between reducing sugars or oxidized lipids, a generalized inflammatory reaction is established in DM. AGE receptors are found in macrophages and endothelial cells, and their activation provides for the activation of nuclear factor kappa-B (NF-KB) in these cells, which is a key factor in gene transcription for inflammatory mediators with concomitant production of proinflammatory cytokines,[35,37,38] such as TNF-α and IL1, as well as reactive oxygen species.[35] Corroborating these findings, clinical trials contemplated in the present review (Table 1) observed elevated serum levels of pro-inflammatory mediators in decompensated diabetic patien ts.[11,15,16,18,21,22,25,26,28,30] Associated with this serum overexpression of inflammatory mediators, hyperglycemia also compromises the immune defense system by interfering phagocytic capacity of neutrophils and macrophages.[35,39]

Additionally, chronic hyperglycemia associated with oxidative stress also culminates in alteration of the vascular antiatherogenic profile, resulting in vascular thickening by smooth muscle cell proliferation, platelet aggregation, monocyte adhesion, and additional proinflammatory cytokine production. In fact, DM contributes to atherosclerotic events and cardiovascular diseases, among other ischemic changes such as retinopathy.[2,40] Moreover, DM is one of the major systemic diseases that favors chronic and infectious inflammatory processes,[5,41] respectively by exacerbation of inflammatory response and impaired phagocytosis.

Hence, periodontitis stands out as an exacerbated host immune response to a chronic microbial challenge, represented by the accumulation of dental biofilm composed of a variable microbiota.[5,7] In the pathogenesis of this disease, the activation of resident leukocytes after recognition of molecular patterns of bacteria present in dental biofilm, such as lipopolysaccharide (LPS), culminates in the production and local release of cytokines such as TNF-α, IL1-β, IL-6, IL-17, as well as prostaglandins (PGs), especially PGE2.[8,42] Such mediators are responsible for inducing vascular changes and leukocyte migrations, as well as for propagating the inflammatory process, which should result in tissue resolution and repair, inducing phagocytosis of bacteria by specialized leukocyte cells such as neutrophils and macrophages.[42]

There are biological bases that justify the influence of DM on the severity of the clinical signs of periodontitis[5,41] and, in fact, for diabetic patients diagnosed with periodontitis to acquire periodontal stability, they must concomitantly obtain and maintain regularization of their glycemic status. When it comes to the influence of periodontal inflammation on the severity of DM, it is important to note that chronic inflammatory diseases, characterized by high serum concentration of inflammatory mediators, such as rheumatoid arthritis, are associated with the development of DM.[43] Anti-inflammatory drugs have been reported to reverse insulin resistance due to hyperglycemia, so that inflammation is not only a consequence of DM, but also an important causal factor.[43,44]

Thus, the low cost and easily accessible CPT possibly becomes of high value in contributing to glycemic control in patients with diabetes and periodontitis, due to its ability to reduce local microbial load and, consequently, the inflammatory process. Corroborating with this information, our findings showed that, in all clinical trials analyzed, periodontal treatment was able to improve one or more clinically analyzed inflammatory periodontal parameters.

The chronic periodontal inflammatory process may influence other systemic conditions by the fact that inflammatory mediators, once produced near the free gingival groove and periodontal pocket, as well as periodontal bacteria, are able to reach the systemic circulation and spread.[8] This statement was corroborated by clinical trials selected in the present review that specifically analyzed serum concentrations of inflammatory mediators and/or CRP, noting that diabetic patients with periodontitis have higher systemic inflammation compared to periodontally healthy diabetic patients[16,21,25,26,28,30] and that root debridement has better results than supragingival scraping alone,[11,26] indicating that the deeper the CPT, the better the systemic results, beyond those sites. In this context, it is noteworthy that proinflammatory cytokines have been related to grea-ter peripheral cellular resistance to insulin action, as well as apoptosis of β-pancreatic cells, resulting in lower glucose metabolism and, consequently, difficulty in glycemic control.[35,46,47,48] In fact, high serum levels of inflammatory cytokines due to DM alone potentiate the pathogenesis of the disease as a feedback mechanism.[35,48]

Besides that, a serum elevation of IL-10 and osteoprotegerin (OPG),[10,19] and a plasma reduction of kappa B nuclear factor activating receptor (RANKL) 19 ligand after CPT was associated with improvements in HbA1C rates. IL-10 is an anti-inflammatory cytokine associated with tissue repair,[10] while OPG is a soluble protein present in plasma with antiosteoclastogenic effects and whose production by osteoblasts is negatively influenced by pro-inflammatory cytokines such as TNF-α and IL-1β.[19] Whilst, RANKL is a ligand expressed in osteoblastic and lymphocyte cells that,

Table 1. Methodology description and main results of selected clinical trials

Method: Prospective clinical study. Patients were divided into three groups: (1) periodontally and systemically healthy patients; (2) patients with periodontitis and systemically healthy; (3) patients with periodontitis and DM2. All patients were treated periodontally in a conventional manner.	
Author	**Results**
Acharya *et al*., 2015	CPT reduced fasting blood glucose and serum HbA1C levels in diabetic patients, while increasing those of IL-10 in groups 2 and 3.
Xu *et al*., 2016	TPC increased serum OPG levels and reduced RANKL and HbA1C levels in patients of group 3, with correlations of RANKL/OPG ratio and plasma HbA1C concentrations.
Method: Prospective clinical study. Patients diagnosed with DM2 and periodontitis were divided into two groups according to the treatments they underwent: (1) patients receiving supragingival therapy; (2) patients who would receive supra and subgingival therapies.	
Author	**Results**
Artese *et al*., 2015	CPT did not reduce serum HbA1c, TNF-α, IL-8 and IL-17 levels in either group. MCP-1 levels were significantly reduced in both groups. Serum IL-6 levels were significantly reduced only in the sub-gingival treatment group.
Masi *et al*., 2018	CPT reduced circulating LPS levels, oxidative stress and serum levels of HbA1c and IFN-γ, TNF-α, IL-6, CRP and E-selectin, except for IL-6 and CRP. The results were superior in all analyzes for the subgingival scraping group.
Method: Prospective clinical study. Patients diagnosed with DM2 and periodontitis were divided into two groups according to CPT modality: (1) patients were treated at two consultations within 24 hours. (2) patients were treated at four or five appointments at a frequency of 1 session per week.	
Author	**Results**
Quintero *et al*., 2018	CPT in both forms of therapy was beneficial for glycemic control and reduced fasting blood glucose and serum CRP and HbA1c levels, but stratification of appointments appeared to be interesting for patients with HbA1c levels greater than 9%.
Method: Prospective clinical study. Patients were divided into four groups: (1) periodontally and systemically healthy patients; (2) patients with periodontitis and systemically healthy; (3) periodontally healthy patients with DM2; (4) patients with periodontitis and DM2. All patients were treated periodontally in a conventional manner.	
Author	**Results**
Altamash *et al*., 2016	CPT reduced serum HbA1C levels in diabetic patients.
Method: Prospective clinical study. Patients diagnosed with DM2 and periodontitis were divided into two groups: (1) periodontally treated patients and (2) periodontally untreated patients.	
Author	**Results**
Mammen *et al*., 2015	CPT reduced insulin sensitivity, with associated reduction in insulin resistance, fasting blood glucose and serum HbA1c levels.
Geisinger *et al*., 2016	CPT did not significantly reduce serum HbA1C, fasting blood glucose and biomarkers levels (IL-6, IL-8, TNF-α, IL-10, CRP, E-selectin, VCAM), except for serum levels of E-selectin.
Koçak *et al*., 2016	CPT reduced serum levels of HbA1c and IL-1β, IL-6, IL-8, ICAM and VCAM.
Salman *et al*., 2016	CPT reduced serum levels of HbA1c.
Goel *et al*., 2017	CPT reduced serum levels of HbA1c.
Kapellas *et al*;. 2017	CPT did not significantly reduced serum levels of HbA1c and CRP.
Mizuno *et al*., 2017	CPT did not significantly reduce serum HbA1c and glycated albumin levels between the two groups. Nevertheless, the treated group obtained better serum levels of oxidative stress at 3 months after periodontal therapy, with reductions in reactive oxygen species metabolites.
Wang *et a*l., 2017	CPT reduced serum levels of HbA1c and TNF-α.
Mauri-Obradors *et al*., 2018	CPT reduced fasting blood glucose and serum HbA1c levels. Regarding microbiological counts (Aa, Pi, Pg and Tf), a clear reduction in bacterial periodontal count was determined in some patients, but it was not clear which type of bacterial species involved was related to the improvement of DM2-related parameters.
Tsobgny-Tsague *et al*., 2018	CPT reduced serum levels of HbA1c.
Vergnes *et al*., 2018	CPT did not significantly reduced serum levels of HbA1c, either for DM1 or DM2.
Method: Prospective clinical study of a sample of patients diagnosed with DM2 and periodontitis. These were treated periodontally and baseline times of 1 month or 6 months after therapy were compared with each other.	
Author	**Results**
Hayashi *et al*., 2017	CPT reduced serum HbA1c, TNF-α and CRP levels, as was observed for urinary NAG and albumin levels. There was a tendency to decrease in fasting blood glucose and immunoreactive insulin levels, but without statistical significance.
Sundar *et al*., 2018	CPT reduced serum HbA1c levels in patients with compensated or unbalanced diabetes.
Method: Prospective clinical study in which patients diagnosed with obesity and periodontitis were divided into two groups: (1) patients with poorly controlled DM2; (2) patients without DM2. All patients were treated periodontally in a conventional manner.	
Author	**Results**
Taşdemir *et al*., 2016	CPT reduced fasting blood glucose and serum HbA1c levels, with even higher reduction levels for the DM2 group. No significant differences were observed in serum CRP, TNF-α, Pentraxim-3 and IL-6 concentrations, except for serum TNF-α levels.

Method: Prospective clinical study in which patients diagnosed with periodontitis were divided into two groups: (1) systemically healthy; (2) patients with DM2. All patients were treated periodontally in a conventional manner.	
Author	**Results**
Sundaram *et al*., 2017	CPT reduced fasting blood glucose and serum HbA1c levels in the intragroup analysis. However, in the intergroup comparison, it was observed that there was no significant difference in glycemic levels, but such rates were significantly higher in decompensated diabetic patients.
Sunandhakumari *et al*., 2018	CPT reduced serum IL-17 levels, but without significant reduction in glycemic tests (fasting and postprandial blood glucose, as well as HbA1c) in both groups.
Method: Prospective clinical study in which individuals were divided into 5 groups: (1) and (2) 2 diabetic patients with good glycemic control, submitted or not to CPT / (3) and (4) 2 diabetic patients with poor glycemic control, submitted or not to CPT / (5) non-diabetic patients with periodontitis who received CPT.	
Author	**Results**
Kaur *et al*., 2015	CPT reduced serum HbA1c levels in diabetic patients.
Method: Retrospective study in which 14551 patients had their data verified regarding systemic health and dental treatment. Patients were analyzed for level of glycemic control in diabetic or pre-diabetic patients according to HbA1c and were classified into categories based on the frequency of use of dental services for one year.	
Author	**Results**
Saito *et al*., 2017	CPT was associated with improved periodontal conditions. DM2-related glycemic test rates were significantly lower for individuals who received periodontal treatment compared to those who did not receive dental treatment. Overall, periodontal treatment was significantly associated with decreased HbA1c.
Method: A spreadsheet model was constructed for the benefits of periodontal therapy for patients with newly diagnosed DM2 and periodontitis. With regard to the costs for this, the authors compared the outcomes of DM2 treatment including or not CPT. Costs for each patient group were estimated as the cost of any periodontal treatment (including maintenance therapy) plus the cost of replacing missing teeth due to periodontitis, as well as cost savings (negative costs) resulting from any improvement in HbA1c.	
Author	**Results**
Solowiej-Wedderburn *et al*., 2017	The analysis indicated that CPT increases the overall costs associated with the management of periodontal disease. However, the health benefits attributable to reductions in HbA1c in DM2 patients are sufficient to justify the additional costs in most patients.

Twenty-five clinical studies were selected for this literature review, 23 prospective clinical trials. 1 retrospective study and 1 study investigating the financial advantages of conventional periodontal treatment (CPT) for diabetic patients. Conventional Non-Surgical Periodontal Treatment (CPT), Diabetes mellitus (DM), Percentage of glycated hemoglobin (HbA1C), Plaque Index (PI), Gingival Bleeding Index (GBI), Probing Depth (PD), Clinical Insertion Level (CIL), Probing bleeding (PB), oral hygiene instruction (OHI), lipopolysaccharide (LPS), interleukin (IL), tumor necrosis factor (TNF), monocyte chemoattractant protein (MCP), diabetes mellitus (DM), C-reactive protein (CRP), N-acetyl-β-D-glycosaminidase (NAG), intercellular adhesion molecule (ICAM), vascular adhesion molecule (VCAM), interferon (IFN).

by binding to its RANK receptor, which is located on the surface of osteoclasts, initiates the activation of intracellular pathways culminating in osteoclast differentiation.[19] These results are in accordance with the literature, in which oral infection by periodontal pathogenic bacteria stimulated RANKL expression in local osteocytes in wild mice, and such expression was significantly higher in diabetic animals.[49]

Indeed, the literature has indicated a close proximity of the immune and bone systems, so that pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 increase the RANKL/OPG ratio. Resolution of periodontal inflammation by CPT could result in a reduction in the RANKL/OPG ratio and, consequently, a reduction in the rate of inflammatory bone resorption. Furthermore, a causal relationship between improvement in serum HbA1C levels and elevated plasma IL-10 and OPG concentrations and reduced RANKL has been proposed.[10,19] However, the mechanisms underlying this regulation are unclear and require more studies, though it is clear such increased concentrations may be indirectly related to lower AGE formation, as a result of reduced systemic inflammation.

Based on these evidences, although six results[11,15,22,23,30,32] did not specifically show improvements in glycemic tests after CPT, two of them indicate a reduction in serum concentration of inflammatory markers such as IL-6,[11] or oxidative stress[23] systemically and, therefore, do not contradict the systemic benefits of controlling periodontal inflammation. It is suggested that differences in manual skill among researchers during the periodontal examination and treatment phases, as well as in the sample number between studies, in the individual factors of the patients involved or in the reevaluation time may perhaps justify the contradictory results, specifically related to blood glucose control tests.

Conclusion

From the association of scientific data in the present literature review, it was found that the reduction of periodontal inflammatory parameters, obtained exclusively by CPT, can influence the glycemic control of diabetic patients.

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