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Review

Diabetes and Non-Surgical Periodontal Therapy: What Can We Hope for?

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Abstract: Diabetes and periodontal disease share the same inflammatory pattern. Both these pathologies, if left untreated, lead to a cytokine storm that carries pro-inflammatory factors throughout the body. Periodontitis has recently been assumed to be the sixth complication of diabetes and the latest studies suggest a biunivocal connection between these two conditions. Most recent evidence-based studies propose that having a controlled periodontal situation with proper and timely therapy could improve glycemic management in diabetic patients. In order to provide the newest findings on this topic, a systematic literature research was performed on PubMed following the PRISMA statement. The keywords used were: "*Diabetes; Periodontitis; Non-surgical periodontal therapy*". Only free full texts and abstracts in English were enrolled considering a time range of the last 10 years, from 2011 to 2021. A total of 308 studies arose from the first search, and only 73 were strictly related to our topic, while 235 were excluded. The bidirectional link between diabetes and periodontitis is well known. To the best of our knowledge, in the last 10 years there is increasing evidence that non-surgical periodontal treatment is associated with improved glycemic control. Further studies are needed to empower this relation.

Keywords: diabetes; periodontitis; non-surgical periodontal therapy; new periodontal classification; dentistry; supportive periodontal therapy

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1. Introduction

Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycemia that is caused by an inherited and/or acquired deficiency in insulin production and/or action [1]. Chronic hyperglycemia stimulates the monocyte/macrophage system, which leads to a cytokine storm that causes tissue damage and low-grade inflammation. It can also alter the immune competence of the host by modifying the chemotaxis system, with a significant impact on injury healing [2]. Periodontitis is a chronic multifactorial inflammatory disease that can cause, if untreated, non-reversible damage to the supportive structures (periodontal ligament, cementum, and alveolar bone) surrounding the teeth and consequent tooth loss [3]. One of the major determinants of the development and progression of periodontal disease is represented by an increased concentration of pathogenic bacteria within the dental plaque, which activates a massive noxious immune response [4]. The presence of some bacterial surface molecules, for instance lipopolysaccharides (LPS), causes the release of cytokines and other inflammatory mediators that stimulates the discharge of the matrix metalloproteinases (MMPs), finally leading to extracellular matrix remodeling and bone destruction [5]. Thus, periodontal disease is a medical condition in which both bacterial antigens and products and the immune system of the host are very important and are linked together. Recent studies have clearly proven that the effects of all these molecules and inflammatory cells do not only affect the oral cavity but have an important impact on the overall health of a human being [6].

The relationship between DM and periodontitis has been studied in the literature for over 70 years. Several studies in various populations have shown that individuals with diabetes tend to have a higher prevalence of and more severe periodontitis than nondiabetics [7]. Periodontal disease is the most prevalent oral complication in patients with type 2 DM [8] and advanced glycation end products (AGE) have a major role in its pathogenic pattern: these special proteins bind to specialized receptors (RAGE) on the endothelium cells and on the monocytes–macrophages, leading to the production of cytokines, growth factors, expression of adhesion molecules, and production of procoagulant activity, which establish negative effects on periodontal tissues [9]. The accumulation of AGEs in the periodontal tissues is also likely to play a role in upregulating periodontal inflammation in individuals with diabetes via the production of inflammatory mediators such as IL-1β, TNF-α, and IL-6 [10]. As was stated by De Miguel-Infante et al. in their observational study using data from the National/European Health Interview Surveys from 2003 to 2014 in Spain, the prevalence of periodontal disease was higher among people suffering from diabetes than among non-diabetics [11]. On the other hand, chronic periodontal disorders are associated with glycemic metabolism, and can appear alongside increased glycated hemoglobin (Hb1Ac) and serum high-sensitivity-C-reactive protein (hsCRP) levels in patients with type 2 DM [12]. According to these results, Quintero et al. performed a randomized clinical trial, proving that periodontal therapy has a very important role in HbA1c reduction in patients with type 2 DM, poor glycemic control, and chronic periodontitis [13]. In relation to the meta-analysis of Li Q. et al. on randomized controlled trials, non-surgical periodontal treatment can moderately reduce the HbA1c percentage level in type 2 diabetic patients [14]. The aim of this study is to report on the connection between these two different low grade inflammatory diseases, DM and periodontitis, focusing on the eventual effects of non-surgical periodontal therapy on glycemic control in diabetic patients.

The new classification of periodontal diseases [15] marks a turning point that aligns the diagnostic criteria of periodontal and peri-implant diseases with the emerging scientific evidence of the last decade. Starting from a clear definition of "periodontal health" and gingival inflammation, it identifies a patient affected by periodontal disease, introducing new elements to the previous classification of 1999 [16]. Periodontal disease may occur with different levels of severity (staging) that lead the clinician to the diagnosis, and staging is largely dependent on the complexity of disease management; on the other hand, grading provides further information about the biological features of the disease (analysis of the rate of disease progression based on the history of the patient, assessment of the risk for further progression, etc.) [17]. Furthermore, the new classification of periodontal diseases also includes common systemic diseases and conditions that can affect the periodontal system, such as uncontrolled DM.

2. Materials and Methods

This systematic review was conducted in order to underline the correlation between periodontitis and diabetes. The review followed the guidelines detailed in the PRISMA statement [18]. A literature search was performed in the PubMed database using the search terms "Periodontitis" AND "Diabetes" or "Non-Surgical Periodontal Therapy" and "Diabetes". We considered studies published between 2011 and 2021 that were focused on non-surgical periodontal therapy, such as scaling and root planing (SRP). The studies were selected using the following inclusion criteria: English language, publication between 2011 and 2021, free full text. The following types of articles are included: clinical trials, meta-analyses, randomized controlled trials, reviews, and systematic reviews.

3. Results

The search conducted identified 308 articles. Based on the title, 107 articles were selected. After reading the abstracts, 49 works met the inclusion criteria (Figure 1) as reported in Table A1.

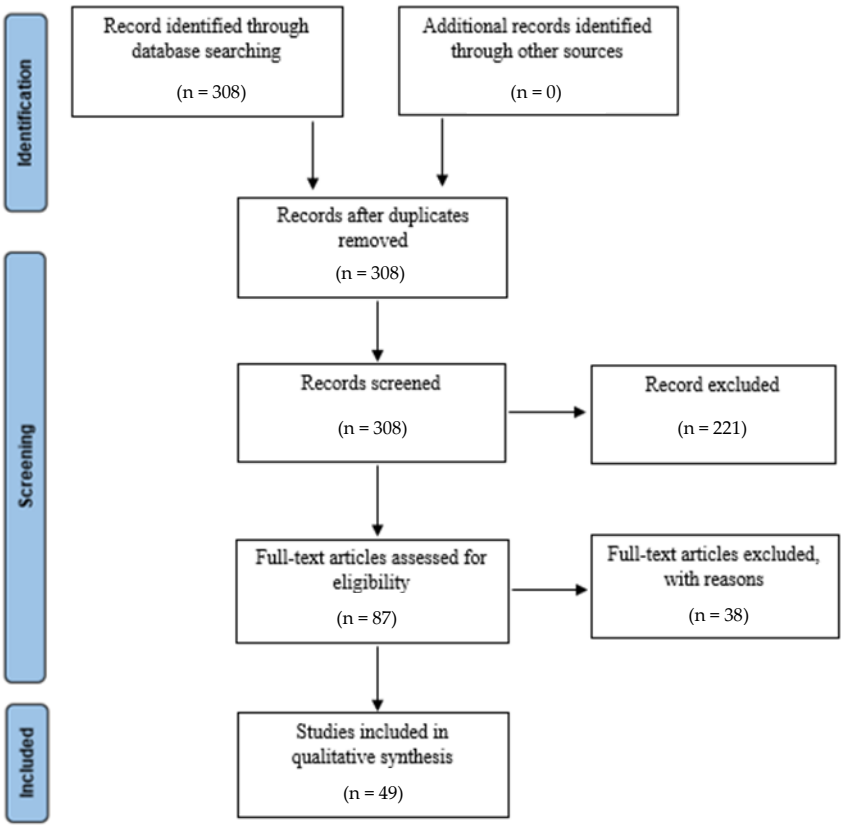

Figure 1. Study methodology following the PRISMA statement.

A correlation between advanced periodontitis and elevated blood C-reactive protein (CRP) levels in patients with type 1 diabetes was found; however, periodontal treatment did not significantly reduce CRP values, even in the patients with the best response to this treatment. This finding is to be expected because periodontal disease acts as any other chronic infection or inflammatory process in the body. Periodontitis produces bacteremia and the host responds with elevated levels of interleukin-6 (IL-6).

Non-surgical periodontal treatment is very effective at reducing periodontal inflammation. Periodontal improvement was followed by a reduction in CRP values but not to a significant level. More studies are needed to clarify the benefits of periodontal treatment in patients with type 1 diabetes and to relate inflammatory mediators with periodontal progression and diabetic complications [19]. A genetic link has been observed between periodontics and gestational diabetes mellitus (GDM) and some studies have postulated the possible existence of genetic polymorphism between inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6; insulin resistance; and periodontitis such that their derangement may concurrently cause periodontitis and GDM. Periodontitis can be associated with the development of GDM and this strong evidence of association has great implications for public health, especially for pregnant women, and this can suggest a new intervention strategy for professionals in both dental medicine and obstetrics and gynecology [20].

4. Discussion

DM and chronic periodontitis are common chronic diseases in adults all over the world. DM is a heterogeneous group of disorders and it is characterized by high blood glucose levels due to defects in insulin secretion, insulin action, or both [21]. As stated by the European Federation of Periodontology (EFP), periodontitis is a chronic inflammatory disease that is triggered by bacterial microorganisms and involves severe chronic inflammation that causes the destruction of the tooth-supporting apparatus and can lead to tooth loss [22]. It starts with gingival inflammation and, if left untreated, leads to a radical

change in the metabolism of the periodontal tissues, resulting in the loss of periodontal support [23].

The two-way relationship between these two inflammatory conditions has been extensively studied over the last 50 years, not only as DM is a risk factor for periodontitis, but also because periodontitis could have a negative effect on glycemic management [24]. The major role of diabetes in the onset of periodontal disorders has been unequivocally confirmed [25], and diabetic individuals compared with non-diabetic ones have approximately a threefold increased risk of developing periodontitis [26].

Taylor et al. illustrated a sixfold increased risk of worsening glycemic control in patients with severe periodontitis and type 2 diabetes when compared with patients with type 2 diabetes without periodontitis [27]. Although most studies on the relationship between these two conditions have focused on mechanisms by which glycemic metabolic may cause periodontal damage (chronic periodontitis has been identified as the sixth complication of diabetes alongside retinopathy, nephropathy, neuropathy, macrovascular disease, and poor wound healing) [28], a growing body of evidence has examined the converse relationship too.

A randomized controlled trial in a sub-Saharan Africa population, conducted by Tsobgny-Tsague et al. in 2018 to establish whether non-surgical periodontal treatments have an impact on glycated hemoglobin in patients with T2DM or not, showed a massive improvement in glycemic control with a remarkable reduction in HbA1c [29]. A meta-analysis of nine studies involving 485 patients reported a significant reduction in HbA1c of 0.46% following periodontal treatment [30]. In 2010, the Cochrane Collaboration reported on studies that investigated the relationship between periodontal treatment and glycemic control in people with diabetes [31]. Three studies were included in this meta-analysis, which reported a significant reduction in HbA1c of 0.40% 3–4 months after conventional periodontal therapy: the authors concluded that there is some evidence of improvement in metabolic control in patients with diabetes after treating periodontal disease.

Although many studies have reported a positive relation between periodontal treatment and metabolic control, some have found different results. The 6-month single-masked randomized multi-center clinical trial performed by Engebretson SP. et al., published in 2014 concluded that non-surgical periodontal therapy does not improve glycemic control in patients with DM and moderate to advanced chronic periodontitis; the use of non-surgical periodontal therapy in order to reduce HbA1c levels in patients with T2D was not supported [32]. Another 2013 randomized controlled clinical trial by Santos et al. did not find a significant reduction in HbA1c in either of the two groups in the study; one treated with curettage and the other with curettage plus chlorhexidine [33]. In 2014, another randomized controlled trial, designed to prove whether treatment of periodontitis affects HbA1c values in the Mexican-American population, concluded that there were no statistically significant differences in the change in HbA1c levels between the control and test groups [34].

Even though there are still differing opinions surrounding this issue, the systematic review with two meta-analyses conducted by Baeza M. et al. in 2019 indicated that conventional periodontal treatment, such as SRP, can augment metabolic control and decrease systemic inflammation in patients with DM type 2 by reducing the serum levels of HbA1c and CRP, respectively [35]. Another case–control report from Stewart J. E. et al. in 2002, aiming to assess the effects of periodontal treatment on glycemic control in patients with T2DM, showed that HbA1c levels significantly decreased in the treatment group compared to a non-treatment control group [36].

Supportive periodontal therapy (SPT) is strictly linked with domiciliary oral care. Among the desirable future goals there is the idea of enhancing antioxidant action using postbiotics. These compounds include any microbial fermentation product released by, or produced through, the metabolic activity of a microorganism that is able to exert a direct or indirect beneficial effect on the host [37]. Promising results have been observed regarding the use of paraprobiotics as a support for SRP in terms of reducing clinical indexes and microbiological aspects related to periodontopathic bacteria [38].

5. Conclusions

Diabetes and periodontitis are closely connected. To the best of our knowledge, in the last 10 years there is increasing evidence that non-surgical periodontal treatment is associated with improved glycemic control. Further high-quality studies are needed to further clarify this relation.

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Appendix A

Table A1. Articles matching inclusion criteria.

Authors	Year	Conclusions
Anton D.M. et al.	2021	Combined non-surgical periodontal treatment and systemic treatment with melatonin provided additional improvements to severe periodontal condition and the glycemic control of patients with diabetes type 2 when compared to non-surgical periodontal treatment alone.
Baeza M. et al.	2020	SRP has an impact on metabolic control and reduction of systemic inflammation of patients with T2D.
Bazyar H. et al.	2020	It was observed that synbiotic supplementation with non-surgical periodontal therapy may be beneficial in improving inflammatory, antioxidant, and periodontal status in T2DM patients with CP.
Bian Y. et al.	2021	The combination therapy of periodontal curettage and root planing exerted beneficial effects on moderate-to-severe chronic periodontitis in patients with type 2 diabetes mellitus, which holds the potential to maintain the level of blood glucose and improve the quality of life of the patients.
Borgnakke W.S. et al.	2014	Nonsurgical periodontal therapy did not improve glycemic control in patients with type 2 DM.
Botero J.E. et al.	2016	Highly heterogeneous short-term studies with small sample size suggest that periodontal treatment could help improve glycaemic control at 3 months in patients with type 2 diabetes and periodontitis. However, longer term studies having sufficient sample size do not provide evidence that periodontal therapy improves glycaemic control in these patients.
Chen L. et al.	2014	Non-surgical periodontal treatment can effectively improve periodontal status, circulating inflammatory status, and metabolic control of diabetic patients with moderate to severe periodontitis.
Chen Y.F. et al.	2021	Periodontal therapy significantly contributed to glycemic control in T2DM patients, especially in patients with higher baseline HbA1c level.
Corbella S. et al.	2013	The meta-analysis showed that non-surgical periodontal treatment improves metabolic control in patients with both periodontitis and diabetes.
DPTT study group et al.	2013	It is not clear if the treatment of periodontal disease affects glycemic control in patients with T2DM.

Table A1. *Cont.*

Authors	Year	Conclusions
Engebretson S.P. et al.	2013	Nonsurgical periodontal therapy did not improve glycemic control in patients with type 2 diabetes and moderate to advanced chronic periodontitis. These findings do not support the use of nonsurgical periodontal treatment in patients with diabetes for the purpose of lowering levels of HbA1c.
Engebretson S. et al.	2013	The modest reduction in HbA1c observed as a result of periodontal therapy in subjects with type 2 diabetes is consistent with previous systematic reviews. Despite this finding, there is limited confidence in the conclusion due to a lack of multi-centre trials of sufficient sample size are lacking.
Garde S. et al.	2019	Periodontal treatment reduces total cholesterol and triglycerides in 3 months follow-up.
Gay I.C. et al.	2014	No statistically significant differences were found in the changes of HbA1c levels between test and control groups.
Hungund S. et al.	2012	There is a definite reduction in HbA1c level in diabetic patients after conventional non-surgical periodontal treatment.
Jain A. et al.	2019	Scaling and root planning treatment leads to modest improvement in glycemic status and periodontal parameters in T2DM patients with chronic periodontitis at 3-4 months.
Javed F. et al.	2014	Non-surgical periodontal therapy (NSPT) reduces gingival crevicular fluid (GCF) levels of proinflammatory cytokines in dogs with and without diabetes; however, chronic hyperglycemia seems to retard the effect of NSPT on GCF cytokine concentration.
Jayakumar Sunandhakumari V. et al.	2018	Within the limits of the study, it can be concluded that the IL-17 level is positively correlated with the periodontal condition of the patient, HbA1c levels, and the fasting blood sugar level. Nonsurgical periodontal therapy plays an effective role in reducing the Th17 related cytokine (IL-17) in plasma both in systemically healthy chronic periodontitis and in chronic periodontitis with well-controlled Type 2 DM patients.
Joseph R. et al.	2017	Periodontal inflammation could affect the glycemic control in otherwise systemically healthy individuals. Periodontal therapy improved periodontal health status and decreased glycosylated haemoglobin levels, thus reducing the probability of occurrence of inflammation induced prediabetes in patients with chronic periodontitis.
Joshi A. et al.	2019	Resistin levels are increased in diabetes related periodontitis. However, post treatment a similar response can be seen between healthy and well controlled diabetics. Hence, resistin can be used as an inflammatory biomarker for diabetes related periodontal disease.
Katagiri S. et al.	2012	As BOP is a marker of total gingival inflammation, these results suggest that NSPT with topical antibiotics in patients with mild periodontitis might improve glycemic control by resolving periodontal inflammation. Such treatments might be insufficient for the amelioration of insulin resistance in T2D patients with severe periodontitis.
Li Q. et al.	2015	The moderate reduction in HbA1c after the non-surgical therapy in patients with T2DM is consistent with previous systematic reviews. However, more large scale and high-quality RCTs are necessitated to confirm these results.
Liew A.K. et al.	2013	The meta-analysis suggested that non-surgical periodontal treatment was associated with a reduction in HbA1c%.
Llambés F. et al.	2012	Non-surgical periodontal treatment couldn' t reduce high sensitivity-CRP values, however, it was found an association between advanced periodontitis and elevated blood hs-CRP levels in patients with type 1 diabetes.
Mirnić J. et al.	2013	Level of glycemic control don't significantly affect the periodontal therapy outcome in diabetics.
Mishra V. et al.	2016	Visfatin levels are highest in individuals with both periodontal disease and diabetes even after periodontal therapy. Individuals with T2DM may be at higher risk of developing periodontal disease.
Mizuno H. et al.	2017	In T2DM patients, non-surgical periodontal treatment improved systemic oxidative stress balance and quality of life, but did not decrease HbA1c levels at 3 months follow-up.

Table A1. *Cont.*

Authors	Year	Conclusions
Moeintaghavi A. et al.	2012	Non-surgical periodontal therapy could improve metabolic control in diabetic patients.
Munjal A. et al.	2019	There is definitely a positive effect of non-surgical periodontal therapy on HbA1c levels in type 2 diabetes patients with chronic periodontitis.
Naiff P. et al.	2018	The periodontal therapy may help to reduce the risk of systemic complications in diabetes patients.
Nana Nana A.R. et al.	2021	Non-surgical periodontal therapy of chronic periodontitis in individuals without diabetes is associated with increased insulin sensitivity and decreased serum CRP levels.
Ndjidda Bakari W. et al.	2021	Non-surgical periodontal therapy is effective in the improvement of glycaemic control in patients with diabetes and periodontitis for up to 3 months. However, questions remain about this beneficial effect over a longer period of time.
Ogawa H. et al.	2014	Treatment of periodontal disease and reduction of oral inflammation may have positive effects on the diabetic condition, although evidence for this remains somewhat equivocal.
Pérez-Losada F.L. et al.	2016	The majority of clinical trials showed that radicular curettage and smoothing, whether associated with antibiotics or not, can improve periodontal conditions in patients with diabetes mellitus. Few studies suggest that this periodontal treatment improves metabolic control. However, there is no clear evidence of a relation between periodontal treatment and improved glycemic control in patients with type 2 diabetes mellitus.
Rabelo M.S. et al.	2021	Periodontal treatment reduced local inflammatory markers, specifically IL-1B and IFN-γ, irrespective of the diabetes status. Periodontal treatment had no significant effect on serum levels of the inflammatory markers evaluated in this study.
Saengtipbovorn S. et al.	2014	The combination of lifestyle change and dental care in one program improved both glycemic and periodontal status in the elderly with type 2 diabetes.
Schmalz G. et al.	2018	Salivary aMMP-8 chairside findings were not associated with common parameters used for periodontal risk assessment in patients receiving SPT.
Schoenfeld E.R. et al.	2014	This study demonstrated the successful collaboration of different healthcare groups to recruit and conduct a study involving participants with two different chronic diseases. Data obtained during screening helped to highlight the success of using different recruitment methods to recruit a diverse participant population based upon gender, race and ethnicity.
Silva-Boghossian C.M. et al.	2014	SRP associated with a rigorous maintenance program improved the periodontal status and reduced the levels of putative periodontal pathogens at 3 months' evaluation in individuals with DM2 and inadequate metabolic control compared with systemically healthy individuals.
Simpson T.C. et al.	2015	There is low quality evidence that the treatment of periodontal disease by SRP does improve glycaemic control in people with diabetes.
Sun W.L. et al.	2011	Periodontal intervention can improve glycemic control, lipid profile and insulin resistance, reduce serum inflammatory cytokine levels and increase serum adiponectin levels in moderately poorly controlled type 2 DM patients.
Suresh R. et al.	2019	Based on the results of this Non-Randomized Clinical Trial, it can be concluded that TSSA levels do decrease after non-surgical periodontal therapy in chronic moderate periodontitis patients with and without NIDDM and we may consider TSSA as a novel biomarker in progression of periodontal disease and diabetic status.
Tsobgny-Tsague N.F. et al.	2018	Non-surgical periodontal treatment markedly improved glycaemic control with an attributable reduction of 2.2 points of HbA1c in poorly controlled T2D patients in a sub Saharan setting.
Teshome A. et al.	2016	There is a significant reduction of Glycated hemoglobin and Fasting plasma glucose level on type 2 diabetic and periodontal patients with non-surgical periodontal therapy.
Wang S. et al.	2017	Periodontal therapy relieved the periodontal inflammatory status, which in turn caused reductions in insulin-antagonizing adipokines and increases in insulin-sensitizing adipokines that were reflected by an improvement in glycemic control in T2DM patients with chronic periodontitis.

Table A1. *Cont.*

Authors	Year	Conclusions
Wang T.F. et al.	2014	In conclusion, adding doxycycline to periodontal therapy with SRP does not significantly improve metabolic control in patients with T2DM and chronic periodontitis. Currently, available evidence is insufficient to support a significant association between periodontal therapy and metabolic control in T2DM patients with PD, however, evidence suggests that periodontal therapy itself improves metabolic control.
Wang M.M. et al.	2019	Periodontal mechanical treatment may elevate serum IL-6 levels in the short term but might reduce the whole inflammatory state in the long term.
Wehmeyer M.M. et al.	2013	This small trial demonstrates successful cooperation between dentists and nephrologists and successful recruitment, treatment, and retention of dialysis patients with periodontitis. Larger studies with longer follow-up are needed to determine whether treatment can improve markers of inflammation and morbidity.
Zare Javid A. et al.	2020	The adjunctive effects of melatonin and non-surgical periodontal therapy may improve inflammatory and antioxidant parameters in T2DM patients with periodontal disease.

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