12 Update on the Bidirectional Link Between Diabetes and Periodontitis

Leila Salhi and Michèle Reners

Abstract

Aim: To provide an update on the evidence on the bidirectional relationship between periodontitis and diabetes.

Methods: This narrative review was focused on recent studies between 2015 and 2020. The literature search was performed on PubMed. The inclusion criteria were systematic reviews, consensus reports and controlled trials assessing the effect of diabetes on periodontitis, the effect of periodontitis on diabetes, and the influence of periodontitis non-surgical treatment on diabetes.

Results: Data concerning the influence of periodontitis on diabetes, and the influence of diabetes on periodontitis were summarized in descriptive tables.

Conclusion: The control of hyperglycemia in the prevention of periodontitis and the control of periodontitis systemic inflammation in the prevention of diabetes, should be take into account in the treatment planning of both diseases.

Keywords

Periodontitis · Diabetes · Periodontitis non-surgical treatment

Abbreviations

AGEs	Advanced Glycation Endproducts)
CI	Confidence Interval
EFP	European Federation of Periodontology
HR	Hazard Ratio
PNST	Periodontal Non-Surgical Treatment
RR	Relative Risk (or Risk Ratio)
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
VEGF	Vascular Endothelial Growth Factors
WHO	World Health Organization
ORCA	European Organization for Caries Research
RAGE	Receptor for Advanced Glycation Endproducts
OPG	Osteoprotegerin Ratio
PMNs	Polymorphonuclear Leucocytes

L. Salhi (✉)
Department of Periodontology, Buccal Surgery and Implantology, University of Liège, Liège, Belgium
e-mail: l.salhi@chuliege.be

M. Reners
Private Practice, Paroliège, Liège, Belgium
e-mail: mreners@gmail.com

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Highlights

Periodontitis and diabetes presented bidirectional influence:

- People with diabetes have an increased risk for periodontitis prevalence and tooth loss;
- People with periodontitis have an increased risk for systemic inflammation and diabetes onset.

The treatment of periodontitis reduces HBA1c, CRP, TNF-α, IL-6 level, contributing to the control of diabetes of glycemia and prevent further complications.

Considerations For Practice

- All diabetic patients should be screened for periodontal disease and should receive information about how to prevent and to treat periodontal disease
- It might be relevant, for patients with poor response after periodontal treatment, to propose the screening of diabetes by their doctor.
- The periodontal non-surgical treatment lead, after 3 months, to a significant decrease of HBA1c

Patient Summary

A good oral health contributes to a better control of diabetes.

A well-controlled diabetes contributes to oral health and avoid periodontitis. Prevention is the best way to keep diseases away.

Regularly visit your doctor and your dental practitioner for screening diabetes and periodontal disease.

12.1 Introduction

According to the world health organization (WHO), diabetes is a chronic metabolic disease that affects more than 422 million of adults worldwide (Tonetti et al. 2013), including 59.3 million of European people aged from 20–79 years (Atlas 2019). This global epidemic disease occurs when the pancreas fails to produce enough insulin or, when the body becomes resistant to insulin. Both of these conditions are characterized by hyperglycemia in the blood with a decrease of glucose storage in the liver, but also a limited use of glucose by other cells and organs as retina, heart and kidney. Additionally, hyperglycemia induces the expression of the vascular endothelial growth factors (VEGF), advanced glycation endproducts (AGEs), and oxidative stress (Nardi et al. 2020) that negatively impair the microvascularisation and increase the risk of diabetes complications. The adverse events involved in the disease concern microvascular complications (retinopathy, nephropathy and neuropathy), macrovascular complications (coronary artery disease, peripheral arterial disease and stroke)(Skyler et al. 2017). Additionally, during pregnancy, gestational diabetes can provoke eclampsia with preterm birth and baby with low birth weight (Tonetti et al. 2013; Atlas 2019). Besides, diabetes has been widely associated with the increase of sensibility to infection (foot ulcers) (Alavi et al. 2014; Everett and Mathioudakis 2018) and periodontal disease (Preshaw and Bissett 2013, 2019).

Periodontitis is a chronic inflammatory disease characterized by gram negative bacteria organized in a dental plaque biofilm within microbial dysbiosis leads to a chronic non-resolving and destructive inflammatory response (Jepsen et al. 2017; Meyle and Chapple 2015) that induces local inflammation and progressive destruction of the supporting tissues around teeth (Meyle and Chapple 2015; Schenkein 2006; Haffajee and Socransky 1994; Amano 2010a, b). Approximately 50% of the adult population suffers from this chronic disease (Eke

et al. 2016), and severe periodontitis affects 11.2% of the population (Kassebaum et al. 2014). Moreover, due to mastication and tooth brushing, the periodontal pathogens or/and their sub-products (SPs) are able to disseminate (Forner et al. 2006) from the pocket depth to the blood circulation, inducing a systemic inflammation with an extra-oral metastatic infection (Van Dyke and van Winkelhoff 2013; Loos 2005; Chapple et al. 2013; Szulc et al. 2015; Tonetti et al. 2013; Mealey 1999; van Winkelhoff and Slots 1999). This pathway contributes to the relationship between periodontitis and chronic non-communicable diseases as cardiovascular diseases and diabetes (Chapple et al. 2013; Tonetti et al. 2013; Sanz et al. 2018; Salhi et al. 2019; Salhi et al. 2020).

Periodontitis and diabetes are two associated diseases with a well-described bidirectional influence (Preshaw and Bissett 2019; Sanz et al. 2018; Preshaw et al. 2012; Kumar et al. 2014; Taylor 2001). This review aims to support the bidirectional influence of these two diseases.

12.2 Method

This narrative review was focused on recent studies between 2015 and 2020. The literature search was performed on PubMed, and inclusion criteria were systematic reviews, consensus reports and controlled trials assessing the relationship between periodontitis and diabetes, and the influence of periodontitis non-surgical treatment on diabetes.

12.3 Results

This narrative review aims to highlight the updated literature on the bidirectional link between periodontitis and diabetes. Three questions were asked: (1) what is the effect of diabetes on periodontitis?, (2) what is the effect of periodontitis on diabetes?, and (3) what is the effect of periodontal non-surgical treatment on diabetes? The above-described search were summarized respectively in Tables 12.1, 12.2 and 12.3.

Table 12.1 Effect of diabetes on periodontitis

Authors	Study design	Conclusion
Dicembrini et al. (2020)	Systematic review on 5 studies	T1DM is a relevant risk factor for the development of PD. The prevalence of PD in type 1 diabetes was 18.5%
Nardi et al. (2020)	Systematic review on 8 studies	The microvasculature of the periodontium is affected in diabetic patients towards the overexpression of VEGF
Herrmann et al. (2019)	Controlled study on 20 patients with chronic periodontitis T2DM + CP patients with type 2 diabetes mellitus and chronic periodontitis; CP: Systemically healthy participants with chronic periodontit Patients with type 2 diabetes Systemically healthy patients	Overexpression of PMN's in patients with T2DM
Sanz et al. (2018)	Consensus report	Poor glycaemic control in diabetes is associated with poorer periodontal status and outcomes
Nascimento et al. (2018)	Systematic review and meta-analysis on 13 studies	Diabetes increased the risk of incidence or progression of periodontitis by 86% (RR 1.86 [95% CI 1.3–2.8])
Chapple et al. (2017)	Consensus report	Hyperglycaemia drives oxidative stress and advanced glycation end-pro-ducts that can trigger a hyper inflammatory state and periodontitis

T1DM type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *PD* periodontal disease, *VEGF* vascular endothelial growth factors, *PMN's* polymorphonuclear leucocytes

Table 12.2 Effect of periodontitis on diabetes

Authors	Study design	Conclusion
Jensen et al. (2020)	Systematic review and meta-analysis on 23 studies	Risk markers for periodontal disease, PI, GI, BOP, PD and CAL were found to be more pronounced among children and adolescents with T1DM compared to healthy control
Rapone et al. (2020)	Systematic review and meta-analysis on 10 studies	PI and GI parameters affects the impacts of uncontrolled diabetes
Nguyen et al. (2020)	Systematic review on 14 studies	Higher risks for diabetic ($p < 0.001$) Retinopathy (odds ratios -OD: 2.8–8.7) Neuropathy (OD: 3.2–6.6) Nephropathy (OD: 1.9–8.5) Cardiovascular complications (OD: 1.28–17.7)
Graziani et al. (2018)	Systematic review and meta-analysis on 20 studies	Periodontitis has a significant impact on the control, the incidence and the complications of diabetes. The hazar ratio (HR) to develop diabetes in periodontitis compromised patient is 1.29; 95% CI, 1.11–1.46, $p < .0001$)
ZiuKaite et al. (2018)	Systematic review and meta-analysis on 27 studies	Periodontitis influence both the prevalence and odds of having diabetes
Sanz et al. (2018)	Consensus report	Periodontitis is associated with dysglycaemia and increased insulin resistance in people with diabetes, as well as increased risk for incident diabetes and diabetes complications
Abariga et al. (2016)	Systematic review and meta-analysis on 10 studies	periodontitis is associated with a significant increased risk for gestational diabetes mellitus compared to women without periodontitis

PI plaque index, *GI* gingival index, *BOP* bleeding on probing, *PD* pocket depth and *CAL* clinical attachment loss

Table 12.3 Effect of periodontal non-surgical treatment on diabetes

Authors	Study design	Conclusion
Baeza et al. (2020)	Systematic review and meta-analysis on 9 studies	Scaling and root planing reduces the blood concentration of HbA1c and CRP ($p < 0.01$).
El-Makaky et al. (2019)	RCT on 88 patients with chronic periodontitis and uncontrolled diabetes	Non-surgical periodontal treatment reduces the level of HbA1c ($p < 0.001$)
Cao et al. (2019)	Systematic review and meta-analysis on 14 studies	Periodontal treatment induces the decrease of the HbA1c% in T2DM
Garde et al. (2019)	Systematic review and meta-analysis on 7 studies	Periodontal therapy induces the changes of total cholesterol and triglycerides levels in patients with type 2 DM
Nishioka et al. (2019)	RCT on 74 patients with borderline T2DM	After periodontal therapy, lower BOP (%) is associated with significant improvements in fasting serum insulin
Lima et al. (2019)	Systematic review on 15 studies	Periodontal therapy has beneficial effects on the level of IL-6
Sanz et al. (2018)	Consensus report	Periodontal therapy improves serum HbA1C levels
D'Aiuto et al. 2018	RCT on 264 patients with T2DM	After periodontal treatment, the HbA1c was 0·6% (95% CI 0·3–0·9; $p < 0.0001$) lower in the test group than in control
Kocher et al.2019	Prospective controlled study on Periodontitis patients With normal HbA1c Prediabetes Unknown diabetes	Non-surgical periodontal treatment leads to the decrease of HbA1c in pre-diabetic patients from 5.9% (95% CI, 5.9% to 6.0%) to 5.4% (95% CI, 5.3% to 5.5%)
Tsobgny-Tsague et al. (2018)	RCT on 30 patients with T2DM	Non-surgical periodontal treatment induced a reduction of HbA1c levels from 9.7 ± 1.6% at baseline to 6.7 ± 2.0% 3 months after NSPT ($p < 0.001$)

(continued)

Table 12.3 (continued)

Authors	Study design	Conclusion
Madianos et al. (2017)	Meta-analysis of 7 RCT	Reduction in HbA1c at 3–4 months was reported ranging from −0.27% (95% CI: −0.46, −0.07, p = 0.007) to −1.03% (95% CI: 0.36, −1.70, p = 0.003)
Mauri-Obradors et al. (2017)	RCT on 90 patients with T2DM	Non-surgical periodontal treatment induced a reduction of HbA1c levels (p < 0.05)
Mizuno et al. (2017)	RCT on 40 patients with T2DM	Non-surgical periodontal treatment improved systemic oxidative stress
Hasuike et al. (2017)	Systematic review and meta-analysis on 13 studies	Periodontal treatment in diabetic patients reduces the level of HbA1c
Simpson et al. (2015)	Systematic review on 34 studies	Periodontal therapy leads to the reduction in HbA1c (p = 0.003).
Artese et al. (2015)	Systematic review on 9 studies	Periodontal treatment leads to a significant decrease of both TNF- α and CRP level (p < 0.001)
Kaur et al. (2015)	RCT on 100 patients with T2DM.	Non-surgical periodontal therapy improved glycemic control, with the decrease of HbA1c decreased by 10.8%

RCT randomized controlled trial, *HbA1* haemoglobin A1c or glycated haemoglobin, *TNF* tumor necrosis factor, *CRP* C reactive protein

12.3.1 Effect of Diabetes on Periodontitis

The effect of diabetes on periodontitis is summarized in Table 12.1. Recent systematic reviews (Nguyen et al. 2020; Dicembrini et al. 2020; Nascimento et al. 2018), controlled prospective trials (Herrmann et al. 2020) and consensus reports (Sanz et al. 2018; Chapple et al. 2017) highlighted that diabetes impairs periodontitis. Diabetes significantly increased the incidence (Dicembrini et al. 2020; Nascimento et al. 2018) and the progression of periodontitis with a relative risk (RR) of 1.86 ([95% CI 1.3–2.8]) (Nascimento et al. 2018). Indeed, diabetic patients harbored significantly worst periodontal status with lower outcomes than healthy patients (Sanz et al. 2018; Dicembrini et al. 2020). Furthermore, the pathophysiological processes involved in the relationship, were mechanisms that trigger hyper inflammatory state and periodontitis, as the impairment of microvasculature (Nascimento et al. 2018), the over-expression of PMN'S (Herrmann et al. 2020), oxidative stress and the advanced glycation end-products (Chapple et al. 2017).

12.3.2 Effect of Periodontitis on Diabetes

The effect of periodontitis on diabetes is summarized in Table 12.2. Recent systematic reviews with meta-analysis (Jensen et al. 2021; Rapone et al. 2020; Nguyen et al. 2020; Graziani et al. 2018; Ziukaite et al. 2018; Abariga and Whitcomb 2016), consensus report (Sanz et al. 2018) confirm that periodontitis impairs diabetes. Periodontitis, with associated risk markers (Jensen et al. 2021; Rapone et al. 2020) as plaque index, probing depth, gingival index, impairs both the incidence (Graziani et al. 2018; Ziukaite et al. 2018) and the complications of diabetes (Sanz et al. 2018; Nguyen et al. 2020; Graziani et al. 2018). Patients with periodontitis present significant higher risk of developing diabetes with a hazard ratio (HR) of 1.29; 95% CI, 1.11–1.46, p < .0001 (Graziani et al. 2018). The dysregulation of glycemia and the increased insulin were the mechanisms involved in the relation of periodontitis on diabetes (Sanz et al. 2018).

12.3.3 Effect of Periodontal Non-surgical Treatment on Diabetes

The effect of periodontal non-surgical treatment on diabetes is summarized in Table 12.3. Recent systematic reviews with meta-analysis (Baeza et al. 2020; Cao et al. 2019; Lima et al. 2019; Garde et al. 2019; Madianos and Koromantzos 2018; Hasuike et al. 2017; Simpson et al. 2015; Artese et al. 2015), randomized controlled trials (Kaur et al. 2015; Mizuno et al. 2017; Mauri-Obradors et al. 2018; Tsobgny-Tsague et al. 2018; D'Aiuto et al. 2018; Nishioka et al. 2019; El-Makaky and Shalaby 2020), controlled prospective trials (Kocher et al. 2019) and consensus report (Sanz et al. 2018) confirm the positive effect of periodontal non-surgical treatment (PNST) on diabetic outcomes. Among assessed parameters, PNST significantly decreased the blood concentration of glycated haemoglobin (HbA1c) (Sanz et al. 2018; Baeza et al. 2020; Cao et al. 2019; Madianos and Koromantzos 2018; Hasuike et al. 2017; Simpson et al. 2015; Kaur et al. 2015; Tsobgny-Tsague et al. 2018; D'Aiuto et al. 2018; El-Makaky and Shalaby 2020; Kocher et al. 2019; Mauri-Obradors et al. 2015), total cholesterol, triglycerides (Garde et al. 2019) and insulin (Nishioka et al. 2019). Furthermore, the blood level of biomarkers related to inflammation (IL-6,TNF- α and CRP) (Baeza et al. 2020; Lima et al. 2019; Artese et al. 2010) and oxidative stress (Mizuno et al. 2017) were also significantly decreased after PNST.

12.4 Discussion

Periodontitis and diabetes are two associated diseases with a well-described bidirectional influence (Preshaw and Bissett 2019; Sanz et al. 2018; Preshaw et al. 2012; Kumar et al. 2014; Taylor 2001). Nonetheless, distinction must be made between the tree categories of diabetes (Atlas 2019). The type 1 diabetes mellitus (T1DM) occurs most frequently in children and young people with genetic and environmental factors. However, the increase of overweight and obesity in young people raise the prevalence of diabetes type 2 diabetes in this population. T1DM is characterized by an autoimmune reaction that leads to the destruction of the insulin-producing beta cells of the pancreas (pancreatic islet cells) (Paschou et al. 2018). Indeed, the lymphocytes T recognize the B cells of the pancreas as non-self-cells, and therefore destroy them. As a result, a little quantity or the absence of insulin is secreted (Paschou et al. 2018; Wang et al. 2019; Smith et al. 2017). Therefore, in order to maintain the appropriate blood level of glucose and to avoid the complications of diabetes, a daily injection of insulin is needed.

On the contrary, the type 2 diabetes mellitus (T2DM) occurs most frequently in elderly population, with obesity being a major risk factor in addition to complex genetic and environmental etiology (Chan et al. 1994; Colditz et al. 1995). Furthermore, the increment of overweight, obesity and sedentary lifestyle in young people increase the apparition of the disease in this population. T2DM is characterized by inadequate use of insulin from the body enhancing insulin resistance and leading to elevated levels of glucose in blood (Atlas 2019).

Gestational diabetes happens to women with hyperglycemia during the beginning of pregnancy, but also to women presenting insufficient insulin secretion to overcome the diminished action of insulin due to hormone production by the placenta (Atlas 2019). Nevertheless, once hyperglycemia occurs, diabetic people present the same complications as the micro- and the macro-vascular complications (Skyler et al. 2017), the sensibility to infection (Alavi et al. 2014; Everett and Mathioudakis 2018), as well as periodontitis (Preshaw and Bissett 2013, 2019), but with different rate of progression (Skyler et al. 2017). Regarding patients with T2DM, they have higher risk to suffer from severe form of periodontitis (Genco and Borgnakke 2013; Albert et al. 2012; Lalla et al. 2006) (Table 12.1), and in the other way, patients with periodontitis presented a higher risk to develop T2DM (Demmer et al. 2008; Chapple et al. 2013; Borgnakke et al. 2013) (Table 12.2).

Diabetic patients present an increased risk of the incidence and the progression of periodontitis by 86% (Nascimento et al. 2018). As described in 2017 (Chapple et al. 2017) by the consensus report of the joint workshop the European Federation of Periodontology (EFP) and the European Organization for Caries Research (ORCA), the absence of the control of glycemia leads to hyperglycemia that enhance the expression of AGE-RAGE complex (Advanced Glycation Endproducts- Receptor for Advanced Glycation Endproducts) in periodontal tissues. Its expression triggers an hyper inflammatory state and promotes periodontitis. Subsequently, an elevation of proinflammatory mediators (PIM) such as TNF-α, IL-1βIL-6, NF-kβ, osteoprotegerin ratio (OPG), oxidative stress (ROS) and immune dysfunction as with the overexpression of the polymorphonuclear leucocytes (PMNs) (Herrmann et al. 2020) occur that contribute to the destruction of connective tissue surrounding the teeth, and the progression of periodontitis (Sanz et al. 2018; Nascimento et al. 2018; Herrmann et al. 2020; Chapple et al. 2017; Polak and Shapira 2018). Additionally, the recent systematic review of Nardi et al. (Chapple et al. 2017) supported that in diabetic patient, the microvasculature of periodontium is affected by the overexpression of vascular endothelial growth factor (VEGF) that enhances periodontitis progression. As emphasized recently by the consensus report by the International Diabetes Federation and the European Federation of Periodontology (Sanz et al. 2018) poor glycaemic control is associated with poorer periodontal status and outcomes.

Furthermore, recent systematic reviews (Sanz et al. 2018; Nguyen et al. 2020; Graziani et al. 2018; Ziukaite et al. 2018) describe the influence of periodontitis on both the prevalence of diabetes and the risk to develop further complications. Indeed, in patients affected by the disease, the presence of bacteria or their metabolites (LPS) induce the host secretion inside the bloodstream of pro-inflammatory cytokines (TNF-α, IL-6, CRP, oxygen radicals) involved in the increase of systemic inflammatory state and in the impairment of insulin signaling and resistance (Sanz et al. 2018; Graziani et al. 2018; Polak and Shapira 2018). Therefore, as described in the recent consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation (IDF) and the European Federation of Periodontology (EFP) (Sanz et al. 2018), periodontitis is associated with dysglycaemia and insulin resistance by increasing the HBA1c, and as a result, augmenting the risk of diabetes development and its complications. Likewise, in the update of Polak et al. 2017 (Polak and Shapira 2018), it was underlined that periodontitis systemic inflammation contributes to the undercontrolled diabetes and its complications. Additionally, the periodontitis chronicity elicits cytokine sensitivity, contributing to the increase of diabetes (Sanz et al. 2018; Graziani et al. 2018; Polak and Shapira 2018) and, according to the recent systematic review of Nguyen et al. (Nguyen et al. 2020), contribute to the long-term complications of diabetes, as retinopathy, neuropathy, nephropathy and cardiovascular adverse events. Besides, as well-described, the periodontal non-surgical treatment leads to significant decrease of blood biomarkers related to diabetes, as HBA1c, CRP, TNF-α, IL-6 (Cao et al. 2019; Garde et al. 2019; Madianos and Koromantzos 2018; El-Makaky and Shalaby 2020; Kocher et al. 2019). These clinical observations support both the negative effect of periodontitis on diabetes and the positive effect of periodontitis treatment on diabetes (Tables 12.2 and 12.3).

12.5 Conclusion

This review supports the bidirectional link between diabetes and periodontitis. Furthermore, it is relevant to bring in light the role of the prevention and the control of hyperglycemia in the prevention of periodontitis, and the control of periodontitis systemic inflammation in the prevention of diabetes.

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