



DIABETES, GUM HEALTH AND PERIODONTAL DISEASE: STATE OF THE EVIDENCE ON THE BIDIRECTIONAL LINK

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INTRODUCTION

The last two decades have seen an increased awareness of a bidirectional link between periodontal disease, particularly the severe form known as periodontitis (PD) and diabetes.¹ There is an inherently greater risk of developing PD in patients who have diabetes, while PD may impair glycemic control in diabetes and increase the risk of diabetes-related complications.^{1,2} The risk for diabetes onset is also greater in individuals who have PD.¹

Accordingly, more communication is required between healthcare professionals and patients with diabetes regarding this potentially destructive inflammatory disease.³ In a recent survey carried out with diabetes and periodontology experts, it transpired that there is a significant opportunity to inform patients living with diabetes about gum health, as around half of them had never received any information on gum health, while for those that had, they were more likely to have received information only from their dentist.⁵ There is a clear need for diabetes healthcare professionals to talk about periodontal disease with their patients, to regularly examine their patients for any signs of periodontal disease (gingivitis or periodontitis), and to promptly refer patients to a dental professional whenever necessary.⁶

A CLOSER LOOK AT PERIODONTITIS

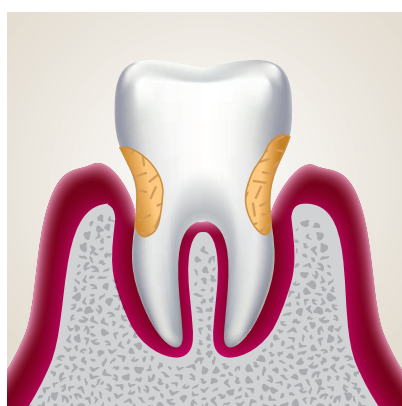


Figure 1. Periodontitis can damage gums, teeth and surrounding tissues

Inflammation is a key cause of periodontal disease and of the development of its worst manifestation (i.e. periodontitis). Periodontal disease occurs when the gums become infected with bacteria, usually caused by a build-up of plaque on the teeth.^{7,8} If not removed, bacteria in the plaque can cause gum tissue inflammation, leading to redness, bleeding on brushing, swelling and soreness, as well as bad breath (halitosis).

The early and reversible form of periodontal disease is called gingivitis and can be readily treated by improved dental hygiene (e.g. flossing), plaque removal by the dentist (e.g. scale and polish), or by using an antiseptic mouthwash.¹ Gingivitis affects between 50%

and 90% of the world's population.⁹ Swollen gums may also be caused by other factors, such as smoking, immune-suppressing drugs, infections such as herpes and HIV, hormonal changes during pregnancy, stress, and metabolic diseases such as diabetes.⁸

If the bacteria spreads below the gum line, periodontitis can occur⁸ – a severe inflammatory disease where the inflamed gums pull away from the teeth to form infected pockets, and the body's immune system is triggered to fight the infection. Over time, the inflammatory mediators released by the infection stimulate the maturation of macrophages in osteoclasts, a cell type deputised to bone resorption. The bone supporting the gum recedes. (Figure 1). The teeth can become loose and may need to be removed. Periodontitis is estimated to affect 50% of adults worldwide, and is especially prevalent in older populations, affecting 70–90% of people over the age of 60 years.³



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BIDIRECTIONAL LINK BETWEEN DIABETES AND PERIODONTITIS

Periodontitis is considered to be the 'sixth major complication' of diabetes.¹⁰ Many studies have confirmed their bidirectional relationship – diabetes increases both the prevalence and severity of PD, particularly in cases of poor glycemic control, while PD can adversely affect glycemic control in patients living with diabetes and increase the risk of complications.^{2,7,11-14} Thus, management of PD is particularly important and has been associated with improvements in glycemic control.^{2,11,15,16}

DIABETES INCREASES THE RISK OF PERIODONTITIS

While the overall prevalence of periodontal disease (i.e. including both gingivitis and PD) appears to be the same in patients living with diabetes and the general population. There is however a much higher prevalence of severe periodontal disease – periodontitis – in diabetes^{3,14,17,18} (Figure 2). Type 2 diabetes in particular can be considered a risk factor for PD.¹³

Furthermore, the poorer the glycemic control, the greater the prevalence of severe PD.^{17,19,20} In individuals with poorly-controlled diabetes, the risk of severe PD was significantly higher than in those without diabetes (odd ratio 2.9); even in patients with better glycemic control, the prevalence of PD was higher (odds ratio 1.56).²⁰

To further highlight the bidirectional nature of the relationship, a significantly higher proportion of patients diagnosed with PD also have diabetes (75.6%) compared with non-PD individuals (22.4%).²¹ The severity of PD has an impact on the prevalence of diabetes, as patients with moderate or severe PD were 2.9- or 3.4-fold more likely to have diabetes compared with other PD patients.²¹

MECHANISMS FOR INCREASED PREVALENCE OF PD IN DIABETES

Poorly-controlled diabetes has consistently been shown to be a systemic risk factor for PD, characterized by significant inflammation of both epithelial and connective tissues.^{2,22} There is a good rationale for the increased prevalence of PD in diabetes:

- The microorganisms in subgingival tissues are similar between patients with diabetes and patients without diabetes; therefore, the risk of PD is most likely increased because of diabetes-induced alterations in the immunoinflammatory response caused by bacteria.²³
- The functioning of neutrophils is often inadequate in diabetes, leading to impairments in neutrophil adherence, chemotaxis and phagocytosis that damage the ability of the body to kill the bacteria, allowing it to persist in the periodontal pocket.²³
- The hyperinflammatory response seen in diabetes results in elevated levels of proinflammatory cytokines such as interleukins (IL), tumor necrosis factor alpha (TNF- α), C-reactive protein (CRP), and fibrinogen in the gingival crevice.^{2,6,23,24} For example, levels of IL-1 β are significantly higher in patients living with diabetes with PD compared to healthy individuals with chronic PD.²⁵

PREVALENCE OF GINGIVITIS AND PERIODONTITIS AMONG THE GENERAL POPULATION AND PATIENTS WITH DIABETES

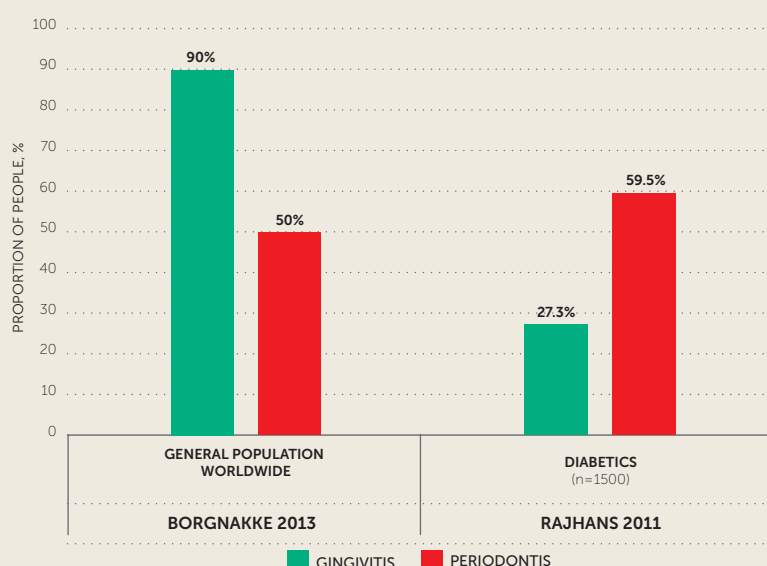


Figure 2. The prevalence of periodontitis is significantly higher in patients with diabetes (although the overall prevalence of periodontal disease is similar)^{3,17}



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Furthermore, cytokine levels are related to the level of glycemic control in patients with diabetes; levels of IL-1 β in gingival crevice fluid have been reported to be almost twice as high in patients with diabetes and PD whose HbA1c was >8% compared with those with better glycemic control (HbA1c <8%).²⁶

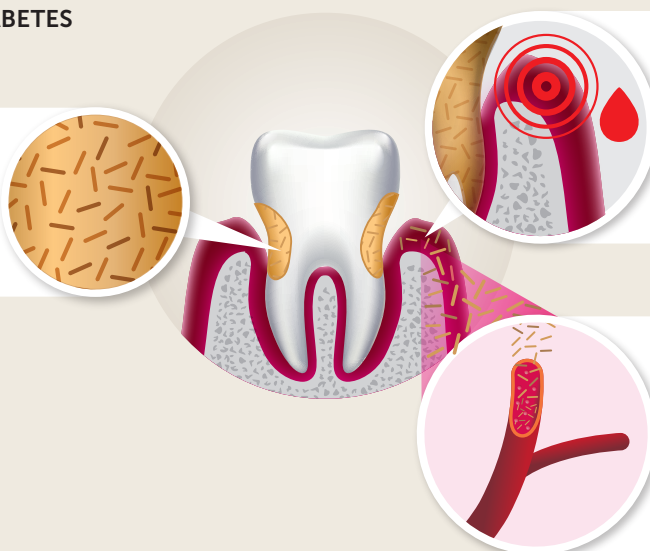
All of these alterations in the immune response in patients with diabetes, particularly the elevated levels of proinflammatory cytokines in the periodontal environment, results in an increase in periodontal inflammation, periodontal ligament destruction, bone loss, and subsequent tooth loss.^{23,30}

PATHOPHYSIOLOGY OF INCREASED PREVALENCE OF PD IN DIABETES

PLAQUE

BACTERIA IN DENTAL PLAQUE CAUSE SEVERE GUM INFLAMMATION

- Inflamed gums pulling away from teeth
- Infected periodontal pockets
- Gum tissue and bone loss



DIABETES

DIABETES INCREASES INFLAMMATORY MEDIATORS AND ADVANCED GLYCATION END-PRODUCTS IN PERIODONTAL TISSUES*

- Tissue homeostasis, wound healing, and vessel regeneration are affected in periodontal tissues, causing periodontitis

* (e.g. interleukins, TNF- α , CRP, fibrinogen, collagenase)

SYSTEMIC CIRCULATION

PERIODONTITIS TRIGGERS MORE INFLAMMATORY MEDIATORS, WHICH MOVE INTO THE SYSTEMIC CIRCULATION AND INCREASE THE INFLAMMATORY BURDEN IN DIABETES

- Tissue homeostasis, wound healing, and vessel regeneration also affected in other body systems (e.g. heart, kidneys), affecting glycemic control and increasing diabetic complications and mortality

Figure 3. Bidirectional link between diabetes and periodontitis - Mechanism of action

- Production of matrix metalloproteinases such as collagenase is elevated in patients with diabetes.²³ These inflammatory mediators are critical components of tissue homeostasis and wound healing and are produced by cells throughout the periodontal tissues.²⁷ Increased levels adversely affect collagen homeostasis and wound healing in the periodontium.²³
- Hyperglycemia also contributes to the increased expression of receptors for advanced glycation end-products (AGEs) in the gingival tissues of patients with diabetes.^{6,28} These end-products increase oxidative stress within the body⁶ and are a critical factor in many complications of diabetes.²⁴ The harmful effects of AGEs observed in other organs in the body may also be seen in periodontal tissues.²⁹ For example, microvascular changes that are a hallmark of many diabetic complications also occur in the periodontium, including abnormal growth and impaired regeneration of vessels.²⁴

PERIODONTITIS HAS ADVERSE EFFECTS ON GLYCEMIC CONTROL

Diabetes and PD share many similarities in pathobiology, and both alter the systemic immunoinflammatory response.²⁴ In fact, the systemic inflammation that occurs in PD may represent an additional factor contributing to the cumulative inflammatory burden in patients with diabetes,^{3,31} leading to poor glycemic control and exacerbating diabetic complications.^{19,32} A systematic review of the evidence has confirmed the adverse effects that PD has on glycemic control and on diabetes outcomes.³



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In brief, people with periodontal disease have:³

- 1. Greater risk of developing poorer glycemic control**
(True for both patients with Type 2 diabetes and patients without diabetes)
- 2. Greater risk for developing diabetes-related complications**
(True for both patients with Type 1 and Type 2 diabetes)
- 3. Greater risk of diabetes onset**
(For patients without diabetes)

1. PD LEADS TO POOR GLYCEMIC CONTROL IN DIABETES

The higher levels of circulating pro-inflammatory mediators (e.g. TNF- α , CRP, mediators of oxidative stress) observed in patients with diabetes and PD may affect the control of diabetes.² Severe PD in diabetes is associated with increased blood glucose levels, expressed as HbA1c.^{1-3,12} In one study in patients with diabetes, a six-fold increased risk of worsening of glycemic control was observed over 2 years in patients with severe PD at baseline compared to patients with no PD.^{24,33} Poor glycemic control has also been reported in three cohort studies,² where patients with Type 2 diabetes and PD had significantly higher HbA1c levels compared to those without PD. The risk was even greater if glycemic control was poor at baseline. The increased risk occurs mainly because, similar to diabetes itself, PD triggers the production of inflammatory mediators (e.g. TNF- α , IL-6, CRP) in the periodontal tissues, which then enter the systemic circulation.^{7,24} Systemic inflammation leads to a prolonged inflammatory response that ultimately increases insulin resistance and aggravates glycemic control.^{7,24}

2. PD INCREASES THE RISK FOR DIABETIC COMPLICATIONS

There is evidence to suggest that there is a direct relationship between the severity of PD and diabetes complications.^{1,2} Inflammatory mediators (e.g. TNF- α , IL-6) and bacterial products (e.g. bacterial lipopolysaccharides) induce acute phase proteins such as CRP, fibrinogen and serum amyloid.⁷ These factors,

which can easily be detected in patients and which are elevated in the presence of PD, can be harmful to the heart, kidney and other organs.⁷ For example, the risk of diabetic retinopathy is greater in patients with PD (odds ratio 1.2-2.8), with a correlation between the severity of PD and retinopathy.² The presence of severe PD in patients with diabetes is associated with increased mortality and morbidity from heart and kidney disease,^{2,7} with a greater risk for cardiorenal complications such as macroalbuminuria, end-stage renal disease, calcification of atherosclerotic plaques, and carotid intimamedial thickness.^{1,3} In patients with diabetes dependent on insulin, the presence of severe PD led to the onset of one or more major cardiovascular, cerebrovascular or peripheral vascular events in 82% of patients, compared with 21% of patients with no or mild PD.³⁴

Accordingly, the overall risk of cardiorenal mortality has been found to be 3.5 times higher in patients with Type 2 diabetes and severe PD compared to those with mild or no PD, after accounting for all other risk factors (Figure 4).³⁵ The death rate from ischemic heart disease was 2.3 times higher, while the mortality rate for diabetic nephropathy was 8.5 times higher in patients with severe PD.³⁵ Furthermore, severe PD in younger patients with diabetes (35–54 years) was associated with a much higher hazard ratio (14.8) compared with older patients (≥ 55 years, hazard ratio 3.3), and a higher proportion of cardiorenal deaths.³⁵

Therefore, it is essential that patients with diabetes are examined for the presence of PD and referred to a dental professional for treatment; the risk of poor glycemic control and diabetic complications needs to be discussed in patients with diabetes with PD.¹

3. PD CAN LEAD TO THE DEVELOPMENT OF DIABETES

Even in people who don't have diabetes, the inflammatory mediators that are released in PD can induce or perpetuate an elevated systemic chronic inflammatory state that can worsen glycemic control.^{3,7,24} In people without diabetes, progression of PD over 5 years has been associated with increasing HbA1c (by 0.143%, compared with 0.005% in patients without PD¹) and impaired glucose tolerance.^{1,2} Over time, the increased blood glucose levels contribute to insulin resistance and increase the chances of



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SEVERITY OF PERIODONTITIS AND RISK OF DIABETIC RELATED COMPLICATIONS AND MORTALITY

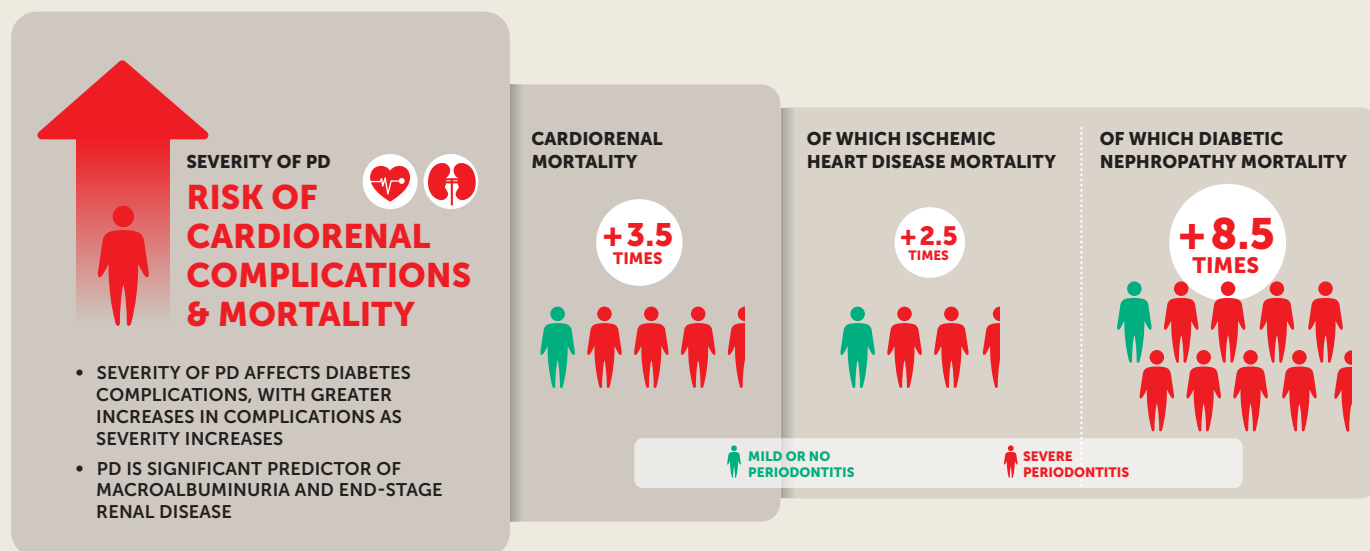


Figure 4. Severe periodontitis and tooth loss in diabetes is associated with a significantly higher risk of diabetes-related complications,^{1,2} and ultimate a significantly greater risk of cardiorenal mortality, attributed to greater ischemic heart disease and diabetic nephropathy (based on number of deaths per 1,000 person-years of follow-up)³⁴

developing diabetes.^{2,3,7,24} The risk of pre-diabetes is significantly higher in people with PD (hazard risk 1.29).² Moderate to severe PD is associated with an increased risk of diabetes onset, with the risk increasing as the severity of PD increases.¹ The presence of PD may also significantly increase the risk of gestational diabetes in pregnant women.³⁶

TREATMENT OF PERIODONTITIS IN DIABETES IS IMPORTANT

It is established that PD can worsen glycemic control and increase the risk of diabetes-related complications.^{1,3} It is recommended that diabetes and dental specialists be aware of the signs of PD in their patients.¹ PD should be regarded as a complication of diabetes – but one that can be treated.

Any treatment that reduces periodontal inflammation may help to restore insulin sensitivity and improve metabolic control.²⁴ It has been suggested that in diabetes, every 1% reduction in HbA1c (an established outcome measure of diabetes treatment¹) is associated with a relative risk reduction of 21% for any diabetes-related endpoint, 21% for diabetes-

related deaths, 14% for myocardial infarction, and 37% for microvascular complications.³⁷ Therefore, it is important to treat PD in patients with diabetes.

Therapies used to treat periodontal disease include non-surgical debridement techniques such as oral hygiene regimen, scaling and root planing (SRP), local or systemic antimicrobial therapy (i.e. antibacterials and antibiotics) and, in more severe cases, surgical treatments such as gingivectomy and flap surgery.¹⁶ It is important to note that periodontal disease has a tendency to recur; therefore, it is essential that patients practice meticulous oral hygiene to remove the dental plaque on a daily basis, and have professional SRP on a regular basis.⁷

TREATING PD CAN REDUCE THE INFLAMMATORY BURDEN IN DIABETES

The main aim of PD therapy is to reduce inflammation, which is particularly important in patients with diabetes who already have a large inflammatory burden. Systematic reviews investigating the effect of PD therapy on serum inflammatory mediators have determined that in patients with diabetes and PD, periodontal interventions

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EFFECT OF PERIODONTAL TREATMENT ON GLYCEMIC CONTROL IN DIABETES: RESULTS FROM SYSTEMATIC REVIEWS & META ANALYSES

ANALYSIS	NUMBER OF STUDIES (PATIENTS)	TYPE OF DIABETES	PD INTERVENTION	CONTROL	FOLLOW-UP	GLYCEMIC CONTROL VS. CONTROL
Teshome 2017 ⁴⁵	7 (940)	Type 2	SRP ± antibiotics or mouthwash	No treatment	Minimum 3 months	↓ HbA1c: mean difference 0.48% after 3 months, 0.53% at end of intervention ↓ FPG: mean difference 8.95 mg/dl at end of intervention
Pérez-Losada 2016 ³⁹	13 (1912)	Type 2	Radicular curettage & smoothing ± antibiotics or mouthwash	Various, including active PD therapy	3–12 months	↓ HbA1c: significant decrease in 7 studies
Li 2015 ⁴⁰	9 (1066)	Type 2	SRP, curettage, debridement	Various, including active PD therapy	3–6 months	↓ HbA1c: effect size –0.27% at 3 months
Simpson 2015 ⁴⁶	35 (2565)	Type 1 or 2 (33 studies Type 2 only)	Mechanical debridement, surgical treatment, antimicrobial	No treatment or alternative PD therapy	3–12 months	↓ HbA1c: 0.29% lower 3–4 months post-treatment, 0.02% lower after 6 months – need for ongoing PD treatment
Sun 2014 ⁴¹	8 (515)	Type 2	'Periodontal treatment'	'Control'	3–6 months	↓ HbA1c: mean difference 1.03% at 3 months, 1.18% at 6 months
Wang 2014 ³⁸	4 (143)	Type 2	SRP plus oral doxycycline	SRP alone or no treatment	3–4 months	↓ HbA1c in both groups, with no differences between interventions; reduction of 0.71–1.5% with intervention, 0.43–0.95% with control
Corbella 2013 ⁴²	15	Type 1 or 2	Non-surgical periodontal treatment	No treatment	3–6 months	↓ HbA1c: mean difference 0.38% after 3–4 months, 0.31% after 6 months
Liew 2013 ⁴³	6 (473)	Type 2	SRP, curettage, debridement	No treatment	Minimum 3 months	↓ HbA1c: absolute difference 0.41%; 0.64% difference in studies without adjunctive antibiotics
Teeuw 2010 ⁴⁴	5 (371)	Type 2	SRP ± antibiotics	No treatment	3–9 months	↓ HbA1c: mean difference 0.40% at end of intervention ↓ FPG: mean difference 2.30 mg/dl at end of intervention

Table 1. Periodontal Treatment Effect on HbA1c: Systematic Reviews & Meta Analyses 2000–2017

significantly reduced serum levels of TNF- α and CRP compared with no PD treatment.^{2,31} These results have important implications for metabolic control, as treatment of PD could help to reduce the long-term risk of diabetes-related complications.

TREATING PD CAN IMPROVE GLYCEMIC CONTROL

Many studies have looked at the effect of PD treatment on glycemic control in diabetes (mainly Type 2), and several meta-

analyses of the data have been performed (Table 1). Overall, the results indicate that periodontal treatment (including adjunctive antimicrobials) improves glycemic control in diabetes, as assessed by HbA1c and fasting plasma glucose.^{1,2} The improvement in HbA1c (0.27–0.48%) after PD treatment correlates with the increase in HbA1c that can be attributed to PD in Type 2 diabetes (0.29%).² Treatment with SRP, for example, leads to an approximate 0.4% reduction in HbA1c at 3 months – a clinical impact that



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is equivalent to adding a second drug to a pharmacological regime for diabetes.^{1,2} If such reductions following PD therapy could be sustained over the long term, they could contribute to reduced diabetes-associated morbidity and mortality.^{1,2} However, currently there is no evidence to suggest that effects (of SRP, for example) are sustained after 6 months,¹⁶ and the available data does not show a difference between the therapies used to treat PD.^{16,38} Regular examination for PD is necessary, and it has been recommended that in clinical practice, ongoing professional periodontal treatment will be required to maintain clinical improvements in blood sugar levels over time.¹⁶

NEED TO IMPROVE AWARENESS OF THE LINK BETWEEN DIABETES AND PD

Clearly, prompt treatment of periodontal disease, particularly moderate and severe PD, is essential to mitigate glycemic problems that may occur in diabetes. The bidirectional relationship between diabetes and PD means that diabetes specialists need to be aware of and check for symptoms of periodontal disease in their patients. If symptoms are found, the potential for poor glycemic control and increased risk of diabetes complications should be discussed, and the patient should be referred for treatment with a dental specialist.^{1,6} A collaborative approach is ideal for patients with diabetes and periodontal disease, as closer collaboration can result in a significant improvement in HbA1c and fasting plasma glucose.⁴⁵

Suggested guidelines for use in diabetes practice, as per "Consensus Report and Guidelines" jointly published by the International Diabetes Federation and the European Federation of Periodontology in 2017²

- Inform patients that:
 - The risk of periodontitis is increased by diabetes
 - Periodontitis may adversely affect glycemic control
 - Periodontitis may increase the risk for diabetes complications (e.g. cardiovascular and kidney disease)

- Perform a thorough oral examination for any signs of periodontal disease as part of the initial evaluation in all patients with Type 1, Type 2 or gestational diabetes
- Perform subsequent periodontal examinations in newly diagnosed patients as part of ongoing management of diabetes, even if no signs of periodontal disease are found
- Refer patients with overt periodontitis (including loose teeth not associated with trauma and/or gingival abscesses or gingival suppuration) to a dental professional
- Provide oral health information to all patients with diabetes
- Refer children 6–7 years and up to a dental professional for annual oral screening

CONCLUSIONS

There is a bidirectional relationship between diabetes and PD, mainly caused by the production of inflammatory mediators in both diseases. The prevalence and severity of PD is increased in patients with diabetes, particularly in patients whose glycemic control is poor, while the periodontal inflammation caused by severe PD can add to the inflammatory burden in diabetes. The presence of severe PD in patients with diabetes can impair glycemic control and increase the risk of cardiorenal complications and mortality.

In summary, PD should be considered a complication of diabetes and should be treated accordingly. Diabetes specialists need to be aware of PD symptoms and examine all patients for any signs, referring to a dental specialist where necessary. Providing information about the importance of improving periodontal health to patients, as well as regular oral examinations, should form an integral part of overall diabetes management – prompt management of PD supports the management of diabetes.



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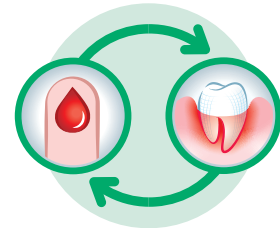
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ORAL HEALTH SHOULD BE INCLUDED IN THE COMPLETE CARE OF PATIENTS WITH DIABETES ^{1,2,3}

- Patients living with diabetes have an inherently greater risk of developing severe periodontal disease⁴: they are 2-3 times more likely to develop Periodontitis, making Periodontitis the 6th complication of diabetes⁵
- Periodontal disease (PD) in patients living with diabetes may also lead to impaired glycemic control and increase the risk of diabetes-related complications.⁵ Increased mortality and morbidity from heart and kidney disease is documented in patients with Type 2 diabetes with PD
- The risk for diabetes onset is greater in individuals who have Periodontitis.⁵



**BREAK
THE CYCLE**

MANAGING THE ORAL HEALTH OF PATIENTS WITH DIABETES: CHECK AND REFER

There is a clear need for diabetes healthcare professionals to:^{3,6}

- Talk about oral health with their patients
- Regularly examine their patients for mild or severe forms of periodontal disease (gingivitis or periodontitis)
- Promptly refer patients to a dental professional whenever necessary.⁵

INVESTIGATE THE PRESENCE OF PERIODONTAL DISEASE AT EVERY VISIT:

- Ask your patient about signs and symptoms of periodontal disease
- Inform patients that if Periodontitis is untreated it can negatively impact metabolic control and may increase the risk of diabetic complications including cardiovascular and kidney failure
- Inform patients that successful periodontal therapy may have a positive impact on metabolic control and diabetic complications

INFORM YOUR PATIENTS ABOUT ORAL HEALTH SYMPTOMS OF UNTREATED PERIODONTITIS:

Less saliva, causing dry mouth; inflamed bleeding gums during brushing or eating; problems tasting foods, susceptibility to infections in the mouth or delayed wound healing in the mouth

REFER PATIENT TO A HYGIENIST, DENTIST OR PERIODONTIST DEPENDING ON THE GRAVITY OF THE PROBLEM

- Ascertain that periodontal care and maintenance are being provided
Refer for immediate care patients showing signs of periodontal disease
Recommend annual periodontal check up for patients with no signs
Refer to trusted oral care practitioners with knowledge of Diabetes mellitus (DM) and PD.
- Encourage patients who have extensive tooth loss to pursue dental rehabilitation to restore adequate mastication for proper nutrition



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Ensure
**ORAL
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is included in
the complete
care of
patients
living with
diabetes



There is a need of people living with diabetes to attentively manage their oral health. It will help them better control their glycaemia and reduce the risk of diabetic complications.

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