Journal of Dental Sciences 19 (2024) 1338–1347

Available online at www.sciencedirect.com

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journal homepage: www.e-jds.com

Review article

Interplay between diabetes mellitus and periodontal/pulpal-periapical diseases

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Received 31 January 2024; Final revision received 21 March 2024
Available online 5 April 2024

KEYWORDS
Apical periodontitis;
Diabetes;
Microorganism;
Pathogenesis;
Periodontitis;
Inflammatory cytokines

Abstract This longevity of life expectancy has indirectly led to an increase in the number of chronic diseases such as periodontitis, apical periodontitis (AP), and diabetes mellitus (DM) in the aging society, thus affecting people's quality of life. There is an interaction between periodontitis/AP and DM with a two-way relationship. Although type 1 and 2 diabetes (T1DM, T2DM) have different etiologies, glycemic control may affect the infection, inflammation and tissue healing of periodontitis and AP. Non-surgical periodontal treatment may influence the glycemic control as shown by decrease of HbA1c level in T2DM patient. However, the effect of periodontal treatment on glycemic control in T1DM and root canal treatment/apical surgery on T1DM and T2DM patients awaits investigation. DM may affect the periodontal and periapical tissues possibly via altered oral microbiota, impairment of neutrophils' activity and host immune responses and cytokine production, induction of oxidative stress etc. While periodontitis associated systemic inflammation and hyperlipidemia is suggested to contribute to the control of T2DM, more intricate studies are necessary to clarify the detailed mechanisms. The interactions between DM (T1DM and T2DM) and periodontitis and AP are therefore reviewed to provide a basis for the treatment of subsequent patients with pulpal/periodontal disease and diabetes. A two-pronged approach of medical and dental treatment is needed for the

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https://doi.org/10.1016/j.jds.2024.03.021
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management of these patients, with emphasis on blood glucose control and improving oral hygiene and periodontal maintenance care, to ensure the best treatment outcome.
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Introduction

Chronic diseases are currently the leading cause of death worldwide, in every region, and in all socioeconomic classes.[1] The prevalence of chronic diseases is rapidly increasing worldwide because of aging in the global population and the changes in modern lifestyles. Periodontitis and diabetes are both chronic inflammatory diseases that are now common in the world, and both diseases pose a major public health concern. This is the reason why the relationship between periodontitis and diabetes has been of great interest. A national study in the United States found that the prevalence of diabetes was twice as high in patients with periodontitis as in those without periodontitis.[2] Epidemiological studies have also shown that diabetes is one of the major risk factors for periodontitis, especially in the setting of poor glycemic control.[3] Furthermore, periodontal disease is also considered to be a co-morbidity of diabetes.[4]

In terms of the common chronic disease, the diabetes global prevalence rate in adults (20–79 years) was 6.4% in 2010, affecting about 285 million adults, and is expected to continue to increase to 7.7% by 2030, affecting 439 million adults.[5] These figures suggest that diabetes is no longer a problem in individual countries, but has become a worldwide issue that requires attention. Diabetes not only impacts the quality of life but also increases socioeconomic costs, hence international coordination and efforts are needed to stop the global diabetes epidemic and its complications.

Two important oral diseases currently contribute to the global burden of chronic disease, one of which is dental caries with/without pulpal/periapical diseases and the other is periodontal disease.[6] However, in dentistry, periodontal disease is still one of the most important oral health burdens besides caries. For these reasons, the management of periodontitis in diabetic patients is particularly important. In order to improve the quality of life and treatment outcomes for patients with periodontitis and diabetes, a collaboration between the medical and dental specialties is necessary to better utilize the healthcare system and resources to achieve the best possible outcomes. This allows for the most efficient way to utilize the healthcare system and resources to ensure the best possible treatment outcome, with less labor and financial costs. The World Health Organization has just published the 'Political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases' in a report by the Director General on January 11th, 2022.[7] The Report includes an updated draft Global Oral Health Strategy WHA74.5, which suggests improving political and resource commitment to oral health by including a guaranteed minimum share of public health expenditure exclusively for national oral health programs. National targets for 2025 and process indicators for the prevention and control of noncommunicable diseases (NCDs) should be set based on national situations, taking into consideration the nine voluntary global targets for NCDs, in addition to increasing efforts to address NCDs, including cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes, as part of universal health coverage (UHC).[7]

Diabetes mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder caused by a defect in the production or action of insulin or both, resulting in reduced or complete failure to utilize sugar and resulting in hyperglycemia. Prolonged hyperglycemia can cause damage to organs, including the retina, kidneys, nervous system, heart and blood vessels.[8] There are several types of diabetes, the most common of which are type 1, type 2 diabetes and gestational diabetes.[9,10]

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM), also known as autoimmune diabetes mellitus or insulin dependent diabetes mellitus (IDDM), is an organ-specific autoimmune disease caused by an absolute deficiency of insulin. The deficiency of insulin results from the attacking and destroying pancreatic beta cells by lymphocytes and other immune cells.[11–14] It is also known as juvenile diabetes because the onset of symptoms usually occurs in childhood or adolescence. However, symptoms do not always appear in childhood or adolescence, and may occur at a much later age.[9,10] In 70–90% of patients, the loss of islet beta cells is the result of T1DM-related autoimmunity and is accompanied by the formation of T1DM-related autoantibodies. T1DM is associated with non-pathogenic autoantibodies or enzymes, such as islet cell autoantibodies (ICA), antibodies against insulin (IAA), glutamic acid decarboxylase (GAA or GAD), and protein tyrosine phosphatase (IA2 or ICA512), that appear months or years before the onset of symptoms.[15,16] These autoantibodies and enzymes have been considered as biomarkers to predict the development of T1DM. It is not clear what triggers the first appearance of autoantibodies targeting β-cells and more studies are needed to explore the mechanisms.

Environmental factors may also influence T1DM, and viruses or environmental toxins may contribute to the progression of T1DM by inducing isletitis or by activating the immune system through molecular mimicry of islet

autoantigens.[17] Isletitis refers to an inflammatory infiltrate found in the islets of Langerhans in the pancreas. The use of antibiotics has also been implicated in the pathogenesis of T1DM,[18] but their role remains unclear.

Type 2 diabetes mellitus

Diabetes mellitus can be due to dysfunction of insulin production (T1DM) or decrease in insulin sensitivity (T2DM). Type 2 diabetes mellitus (T2DM), also known as non-insulin-dependent diabetes mellitus (NIDDM), is the most common form of the three major types of diabetes mellitus (accounting for more than 90% of all cases). NIDDM is characterized by impaired carbohydrate, lipid, and protein metabolism due to diminished insulin secretion, insulin resistance, or a combination of both. The main cause of this condition is the progressive impairment of insulin secretion from the beta cells of the pancreas, usually in skeletal muscle, liver, and adipose tissue, which is known as insulin resistance.[19] Because T2DM most often occurs in adulthood, it is also known as adult-onset diabetes. But today more and more children are being diagnosed with T2DM, probably due to the increasing prevalence of childhood obesity.[20]

The causes of T2DM are complex and are related to risk factors such as age, genetics, race, and ethnicity, as well as environmental factors such as diet, physical activity, and smoking.[21] All of these factors reduce insulin sensitivity in target organs and affect the insulin-producing pancreatic beta cells. Thus, T2DM is a series of dysfunctions involving insulin insensitivity resulting in hyperglycemic symptoms combined with insufficient insulin secretion and excessive or inappropriate glucagon secretion.[22]

T2DM is a complex chronic disease that requires ongoing medical care, patient self-management, and control of multiple risk factors to normalize blood glucose levels, lipids, and blood pressure in order to prevent or minimize acute and long-term microvascular (including retinopathy, nephropathy, and neuropathy) and macrovascular complications (such as heart attacks and strokes).[23]

Periodontal disease

Periodontal disease is a disease that affects the gums, supporting connective tissue, and alveolar bone due to bacterial infection, causing the destruction of periodontal supporting tissues and resulting in tooth movement, and even tooth loss in severe cases. Due to changes in people's lifestyles, periodontal disease has become one of the most common chronic diseases. However, in addition to pathogenic microorganisms in biofilms, genetic and environmental factors also contribute to a higher risk of periodontal disease, especially the use of tobacco.[24] Periodontal diseases can be graded into 4 levels of severity, ranging from mild to severe: gingivitis, mild periodontitis, moderate periodontitis, and severe periodontitis.[25]

Gingivitis is the mildest form of periodontal disease and is caused by the accumulation of bacterial biofilm in or near the gingival sulcus, although gingivitis does not affect the underlying supporting structures of the teeth and is reversible.[26] Periodontitis, on the other hand, causes loss of connective tissue and supporting bone which is the main cause of tooth loss in adults. Therefore, the control of bacterial biofilm and other risk factors has been recommended to stop the progression of periodontal disease.

The association between periodontal disease and diabetes mellitus

Diabetes is a complex disease with many variables, including periodontal disease, that can influence its development. Although the exact mechanism of bidirectional interaction between periodontal disease and diabetes is not fully understood, poor glycemic control and prolonged hyperglycemia have been implicated as risk factors for periodontal disease (Fig. 1).[27] Although some researchers have suggested that there is no significant association between diabetes and gingival inflammation,[28] an association between diabetes and periodontitis does exist as reported in other studies.[29,30] Although most studies have focused on T2DM, T1DM appears to have the same effect in increasing the risk of periodontitis. One study of systematic review showed that the proportion of T1DM with periodontitis was more than doubled in patients with T1DM compared with nondiabetic individuals.[31] In addition, periodontitis appeared to be more severe in T1DM as evaluated by clinical attachment level (CAL), and the severity of periodontitis is strongly associated with glycemic control.[31] The prevalence of periodontitis was two to four times higher in T1DM patients with normoglycemic controls than in nondiabetics. Poor glycemic control in diabetes, as well as smoking and inadequate oral hygiene, were reported with an increased risk of severe periodontal destruction in T1DM.[2,32] Another study has also examined the effects of the interaction between periodontitis and T1DM on the alveolar bone, mandibular condyle, and tibia using an animal model and found that T1DM exacerbates the alveolar bone loss in rats with periodontitis by approximately 3-fold compared to normal rats.[33] All these results suggest an association between T1DM and periodontitis.

A two-way association between T2DM and periodontitis has been reported,[34] with a significantly higher prevalence of periodontitis in patients with T2DM and vice versa. A significantly worse periodontal status, as reflected by deeper periodontal pockets and more attachment loss, was found in patients with T2DM compared to those without T2DM (Fig. 1).[35] To know the effect of periodontal treatment on the control of DM, serum glycated hemoglobin (HbA1c) level is popularly used as marker of blood sugar control in the last 2—3 months.[36] HbA1c is a predominant glycated hemoglobin with an attached sugar moiety, and high plasma glucose may elevate the HbA1c levels.[36] It has been demonstrated that intensive periodontal care (by scaling, subgingival curettage, periodontal surgery and maintenance care) for 12 months may obviously decreased the HbA1c levels by 0.5%, relative to scaling only group in T2DM patients with moderate to severe periodontitis.[37] Improved periodontal health after non-surgical periodontal treatment in T2DM patients, as indicated by significant decreases in plaque index, gingival index, probing depth, clinical attachment level, gingival recession, and bleeding on probing, may decrease the HbA1c levels

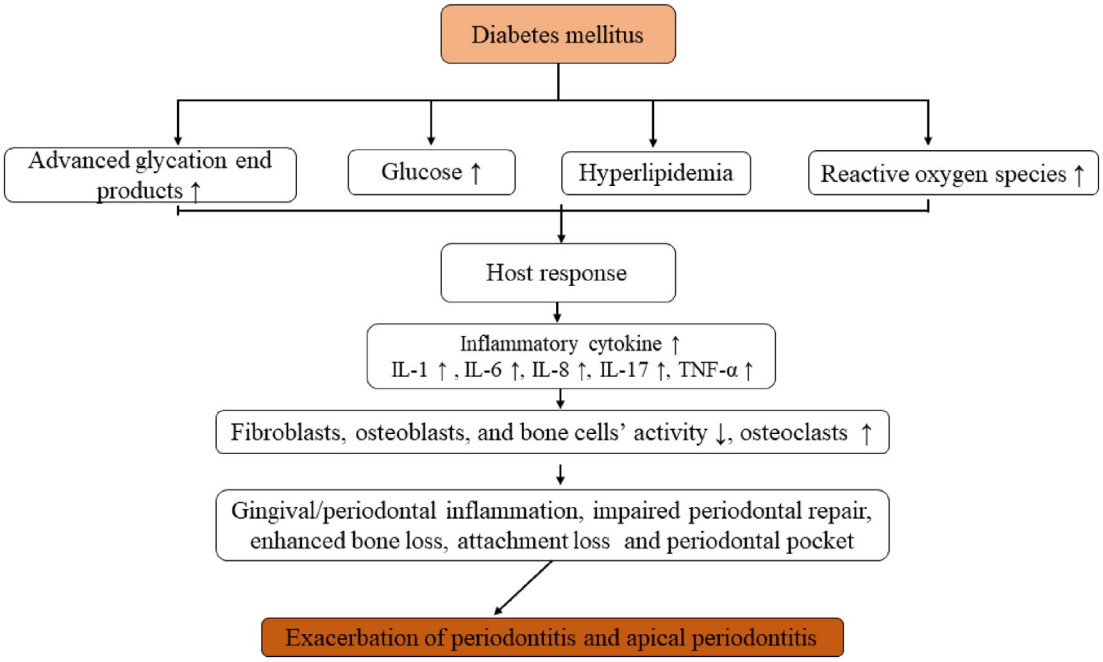

Figure 1 Diabetes increases the levels of glucose, advanced glycation end products, hyperlipidemia, and reactive oxygen species in periodontal tissue, leading to increased inflammation and affecting fibroblasts, osteoblasts, and osteoclasts, thereby enhancing tissue inflammation, attachment loss, periodontal pocket formation, and alveolar bone resorption.

significantly.[38] The authors concluded that non-surgical periodontal treatment is associated with improved glycemic control in T2DM patients in Turkey.[38] Other report also suggests that periodontal treatment with subgingival instrumentation may reduce the HbA1c levels by 0.3–0.5% after 3–12 months of follow up.[39] A 3–6 months follow-up study in Sweden found that T2DM patients showed a reduction of HbA1c value after non-surgical and surgical periodontal treatment.[40] However, 3–12 months after periodontal surgery, the HbA1c level decreased in T1DM patients, but not in T2DM patients as studied in Lithuania.[41] Simpson et al. collected the data of 35 studies with 3249 participants and found that periodontal treatment really reduces the HbA1c value 3–6 months after treatment in T2DM patients.[42] But only one study on T1DM patients was conducted and the results for this point are not conclusive. This indicates that in untreated periodontitis and apical periodontitis (AP), the infection of pathogenic microorganisms in the periodontium and root canal may induce inflammatory mediators' production, hyperlipidemia. Further bacterial invasion and systemic inflammation may affect the blood sugar control, and provoke the exacerbation and complications of DM (Fig. 2, Left). Elimination of pathogenic microorganisms by non-surgical and surgical periodontal/root canal treatment may remove dental plaque and pathogenic bacteria, and decrease the inflammatory cytokine levels. Remove periodontal and periapical inflammation can decrease systemic inflammation and thereby improve glycemic control as well as DM-related complications (Fig. 2, Right). Reduce bacterial infection, bacteremia, oxidative stress, periodontal inflammation, immune responses and systemic inflammation (such as decreased serum C-reactive proteins, and other inflammatory markers), as well as improve the insulin sensitivity, beta cells' function and vascular functions by intensive periodontal treatment are the possible mechanisms responsible for its reduction of serum HbA1c levels and more adequate glycemic control.[37,43] More studies are necessary to clarify whether periodontal treatment may reduce HbA1c and control of DM in T1DM patients. Moreover, mechanisms responsible for the control of T2DM by periodontal treatment should be addressed.

On the other hand, a comprehensive oral examination study of 1500 diabetic patients was conducted. The information and history of all patients were collected to determine the relationship between diabetes and periodontal disease. They found that the poorer the glycemic control and the longer the duration of diabetes, the higher the prevalence and severity of periodontal disease.[44] They reported that the prevalence of periodontal disease in diabetic patients was 86.8%. Both T1DM and T2DM may affect the two major periodontal diseases, gingivitis and periodontitis. However, despite all these intensive studies, the exact relationship between diabetes and periodontal disease is not yet fully understood. It seems more reasonable from the available data that patients with diabetics are more likely to have periodontal disease than non-diabetics.

The association between apical periodontitis and diabetes mellitus

Apical periodontitis (AP) is an umbrella term for chronic infectious lesions at the apical region of the tooth and its surrounding tissues, including the periodontium and alveolar bone, due to various causes. Inflammatory reactions, such as inflammation or suppuration, may occur in the

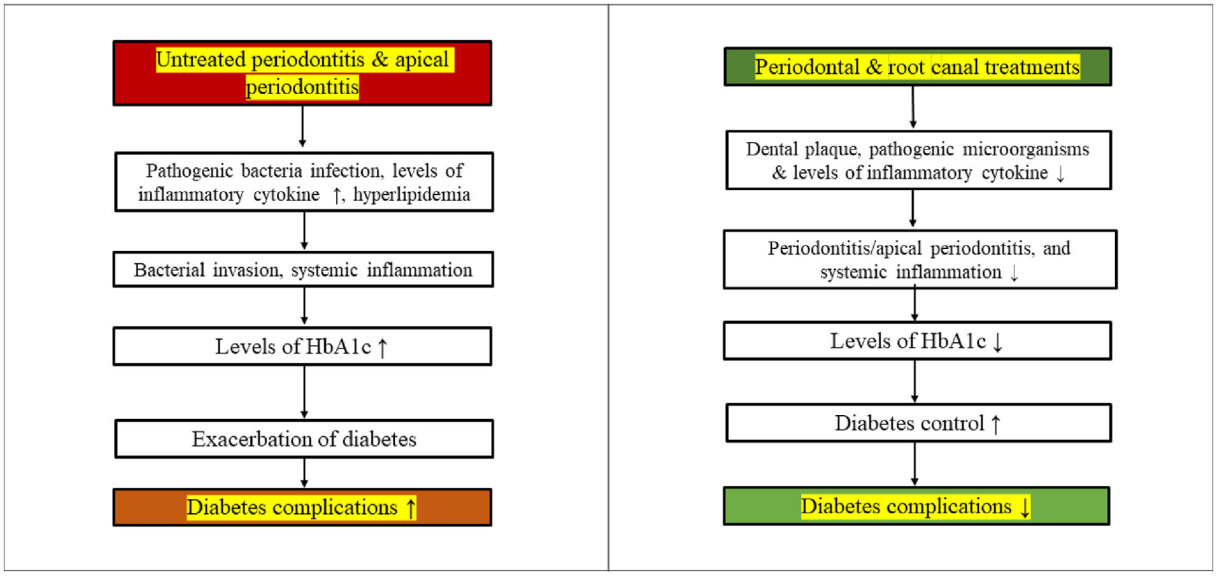

Figure 2 (Left) In patients with untreated periodontitis and apical periodontitis, pathogenic microorganisms, pro-inflammatory mediators and cytokines are elevated, which leads to a state of systemic inflammation that in turn leads to increased HbA1c levels and increased diabetic complications. (Right) In patients with treated periodontitis and root canal, the levels of dental plaque, pathogenic bacteria, pro-inflammatory mediators and cytokines are reduced, which leads to a reduced systemic inflammatory state, resulting in lower HbA1c levels and a lower incidence of diabetic complications.

periapical tissues due to infection by various Gram-negative bacteria, *Staphylococcus aureus*, or *Streptococcus*.[45,46] In addition to infection, a sudden physical injury can also cause trauma to the periapical tissues and further develop periapical inflammation. Depending on the duration of the disease, it can be divided into acute and chronic apical periodontitis, both of which can cause toothache. Apical periodontitis could recur if it is not treated thoroughly. It is well established that there is a strong association between systemic diseases and oral diseases, and that they share many related risk factors.[47,48] As the medical and dental communities continue to analyze the possible link between AP and systemic health, more and more findings describing the association between AP and certain systemic diseases have been reported.[49] However, in addition to systemic diseases, AP can also be affected by periodontal disease. Conversely, AP can lead to destruction of surrounding periodontal tissues, resulting in periodontal disease. Although many microbial pathogens are common in both periodontal disease and AP, endodontic infections have received much less attention. For these reasons, this article also discusses the association between AP and diabetes.

Although several studies have demonstrated an association between AP and diabetes, the exact relationship between diabetes and AP has not yet been elucidated. One study showed that 7% of teeth in diabetic patients had AP compared to 4% in those individuals without diabetes.[50] In another study, it was reported that 14.6% of those with AP had T2DM, which is about twice as many as those without AP (7.6%).[51] Furthermore, AP was also found to be more severe in those with poor glycemic control.[51,52] All of these studies suggest that the prevalence of AP is indeed higher in patients with diabetes and that T2DM and poor glycemic control are significantly associated with AP.[51,52] Another study comparing the success of root canal therapy (RCT) between T2DM and non-diabetic patients found that the periapical scores were significantly decreased in both the diabetic and non-diabetic groups after root canal therapy at the 12-month follow-up.[53] However, periapical healing was significantly less in the diabetic group compared to the non-diabetic group. In addition, the HbA1c levels were found to increase at each follow-up after RCT in the diabetic group.[53] The authors concluded that diabetes may have a negative impact on the outcome of endodontic treatment in regard to periapical healing. Unexpectedly the HbA1c levels in patients with T2DM elevated even after non-surgical endodontic treatment.[53] Most of the studies support the association of AP with diabetes (Fig. 1). More studies should be conducted to clarify the non-surgical endodontic treatment and surgical endodontic treatment on HbA1c level and glycemic control of T1DM and T2DM patients in different countries.

Not only the association between T1DM and AP, but also the prevalence of RCT and AP in T1DM and non-diabetic individuals were analyzed in the Brazilian population.[54] The radiographic records of individuals with T1DM and age- and sex-matched non-diabetic subjects were examined. They found that the mean number of RCT per individual was 1.44 $\pm$ 1.14 in T1DM patients and 0.81 $\pm$ 1.03 in non-diabetic subjects. The prevalence of AP was 58% in T1DM patients, while only 15% in nondiabetic participants. The prevalence rate of RCT, AP, and RCT with AP was higher in patients with T1DM than in non-diabetic patients, suggesting an association between RCT and AP and T1DM. Recently, a systematic review and meta-analysis including 1087 patients and 2226 teeth in 15 studies was conducted. Diabetes showed a higher rate of apical periodontitis in endodontically-treated teeth than the healthy subjects at

tooth level. DM increased the probability of apical periodontitis in endodontically-treated teeth by 3-folds relative to healthy control.[55] This implied that DM may possibly impair the apical infection/inflammation and healing response (Figs. 1 and 2). However, more prospective epidemiological studies are needed to better define the association between endodontic inflammatory disease and DM. Nevertheless, there are relatively few well-designed longitudinal studies and clinical trials on endodontically relevant topics in the relationship of diabetes, the evidence for such association is not yet certain. It is difficult to determine the true association between periapical inflammatory disease and diabetes because of the obvious shortcomings of these studies in terms of sample size calculation, classification of diabetes, methods of procurement of diabetic status, use of training courses, and assurance of inter- and intra-examiner agreement.[56] More well-designed longitudinal studies and clinical trials could provide more scientific evidence.

Mechanisms of inter-relationship between diabetes and periodontitis/AP

There is considerable evidence that diabetes is a risk factor for gingivitis, periodontitis, and alveolar bone resorption possibly due to impairment of host immune defense, neutrophil activity, cytokine inflammatory responses, oxidative stress, production of advanced glycation end-products, imbalance of osteogenic/osteoclastic activity, and changes in oral microorganisms and more others (Fig. 1).[57–59] The glycemic control is an important determinant of this relationship. Patients with poorly controlled DM showed elevated levels of IL-1β, TNF-α, IL-6, RANKL/OPG and oxygen metabolites in gingival tissues.[58] These poorly controlled DM patients are shown to have greater risk for periodontal destruction, have more severe periodontal disease, and are more likely to develop severe periodontitis than patients with well-controlled diabetes.[3,31,32,44] Diabetes mellitus affects both innate and specific immune response cells, both of which are thought to contribute to periodontitis. Neutrophils make up the majority of cells in the gingival crevice. However, overactive or dysregulated neutrophils may release inflammatory toxic substances or tissue-degrading enzymes, which can lead to periodontal tissue damage.[60–63]

Macrophages are another cell type associated with the pathogenesis of periodontal disease. It has been suggested that diabetes increases the production of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) by macrophages, which may contribute to the pathogenesis of periodontal disease.[64] There are M1 and M2 macrophages, which promote Th1 and Th2 responses, respectively.[65] M1/M2 designates the two main and contradictory activities of macrophages, in which M1 activity retards cellular proliferation surrounding the tissue leading to tissue damage. In contrast, M2 activity encourages cell proliferation and accelerates wound healing and tissue repair.[66] It has been demonstrated that the induction of M2 macrophage activities could prevent alveolar bone loss around murine molar through the inoculation of *Porphyromonas gingivalis* and ligature.[67] Periodontitis induced in these mice was found to be associated with an increase in M1 macrophages that enhance inflammation and a decrease in M2 macrophages that stimulate the repair and reduction of inflammation. In a study investigating the abnormal cell responses in diabetic wound healing found that diabetes may increase M1 macrophage polarization, thereby increasing susceptibility to periodontal disease and its severity of the periodontal disease.[68] In addition to neutrophils and macrophages, dendritic cells are also associated with periodontal disease. Diabetes may affect periodontitis by modulating dendritic cells, thus altering periodontal bone loss by increasing Th1 or Th17 lymphocyte production or decreasing regulatory T cell formation.[69] All these events may predispose to chronic inflammation, progressive tissue breakdown, and impair of tissue healing activity.[70]

The mechanisms responsible for the effect of periodontitis/AP on the control and progression of DM are unexpectedly not so clear. Periodontal inflammation, bacteremia and endotoxemia with associated increase of IL-1β and TNF-α, systemic inflammation and hyperlipidemia are considered to be the possible reasons leading to pancreatic beta cells' dysfunction (Figs. 1 and 2).[58,70] Hyperlipidemia may affect DM and periodontitis via their influence on inflammatory cytokine production and insulin secretion, whereas DM and periodontitis may also result in hyperlipidemia.[71] Therapeutic control of hyperlipidemia is suggested for clinical management of DM and periodontitis,[71] and even for AP. Patients with DM and periodontitis are shown to have higher levels of circulation CRP, TNF-α and oxidative stress factors. Periodontal treatment may reduce these inflammatory factors.[68]

Impact of diabetes on the oral microbiota

The oral microbiota is one of the most complex microbial communities in the human body.[72,73] The oral microbiota is of course associated with many oral diseases, but in recent years more and more literature has shown that the oral microbiota is closely related to human health conditions, such as diabetes, cardiovascular disease, and cancer.[74,75] The bacterial counts of *Tannerella forsythia* and *Treponema denticola* were reported to be increased in DM patients relative to healthy control.[76] Recently an increase in the bacterial load of *Fusobacterium*, *P. gingivalis* and *T. forsythia* was reported in the oral cavity of patients with diabetes,[77,78] perhaps due to altered glucose metabolism in pre-DM and DM patients,[58] leading to advanced glycation end-products (AGEs) formation and oxidative stress.[78] Recent development of next generation sequencing (NGS) technology help us to compare the difference of oral microbiome in non-diabetic and diabetic patients with or without periodontitis. Metagenomic analysis of salivary microorganisms has found a higher bacterial load of *Streptococci*, *Veillonella*, *Actinomyces*, *Fusobacterium* and *Rothia* in T2DM patients relative to healthy controls.[79] The other study also found an increased *P. gingivalis*, *P. melatinogenica* and bacterial metabolites such as cadaverine, l-(+)-leucine, N-acetyldopamine and 3,4-dimethylbenzoic acid etc., but not *Streptococci mutans* in T2DM patients without evident oral diseases when compared to healthy subjects.[80]

Less reports have addressed this point in T1DM. An analysis of oral microorganism in 12—19 y/o T1DM patients in USA showed that HbA1c level was inversely associated with the yellow/other cluster (microorganisms that are not associated with periodontal disease) among youth with T1DM.[81] The microbial diversity in children/adolescent patients with DM and periodontitis was higher than DM and periodontitis alone in India. Poor glycemic control also increased the biofilm formation in both DM and DM with periodontitis patients.[82] Pachonski et al. have found that T1DM children and poorly controlled (HbA1c $>$ 7.5%) T1DM children showed evident increase in the number of bacterial strains relative to healthy control.[83] T1DM patients with/without adequate glycemic control also showed more dental plaque formation than healthy control.[84] Changes in oral microorganisms in children and adolescents with T1DM also showed a higher prevalence of cariogenic and periodontopathic bacteria such as *Actinomyces* spp., *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *S. mutans*, *Veillonella*, and *Lactobacillus* than healthy control.[85] Interestingly little is known about the effect of T2DM and T1DM on the pulpal and root canal microorganisms. A positive association between DM (T1DM + T2DM) with *P. gingivalis* and *P. Endodontalis* has been reported.[86] The other study reported no association between DM and three root canal microorganisms including *Pseudoramibacter alactolyticus*, *Propionibacterium propionicum*, and *Prevotella nigrescens* in teeth with persistent apical lesions.[87] But the samples size is relatively small with only 6 DM patients in both studies. From above reports, more studies on the effect of T1DM to changes of oral microorganisms in the saliva, pulp/root canal and periodontal regions should be further investigated.

Directions for periodontal treatment

Periodontal and periapical infection and inflammation may possibly affect the glycemic control. Clinically periodontal treatment and oral hygiene maintenance care may effective improve the treatment outcome, oral health-related quality of life, oral self-care behavior and glycemic control in patients with T2DM.[88,89] There is now much evidence of a causal relationship between periodontal disease and diabetes and that glycemic control has an impact on the progression of the periodontal disease. In addition to the impacts of diabetes on the two types of immune systems, namely the innate and the adaptive immune responses, that cause periodontitis, uncontrolled diabetes also appears to have an influence on bone density. For example, patients with either T1DM or T2DM have an increased risk of bone fracture compared to those without diabetes,[90] and patients with poor glycemic control and those treated with insulin have a higher risk of bone fracture.[91] Animal studies have also shown that rats with diabetes and periodontitis have significantly more alveolar bone loss but fewer fibroblasts, osteoblasts, and osteocytes than rats with periodontitis only.[92] Increased pro-osteoclastogenic mediators was found in cultured cells derived from diabetic (hyperglycemic) mice and peripheral blood cells of DM patients.[93] These results suggest that diabetes may negatively affect periodontal tissue by increasing osteoclast formation and enhancing apoptosis of fibroblasts, osteoblasts and bone cells in periodontal tissue.[92,93] In addition, as mentioned above, diabetes may also alter the composition of the microbiota in the oral cavity, making pathogenic bacteria more pathogenic. It is known that periodontal disease is highly complex, including microbe—microbe interactions, microbe—host interactions, and systemic disease effects. Many epidemiological studies showed the effect of diabetes on periodontal disease, but there are many extraneous factors such as the degree or duration of hyperglycemia and the use of medications that can lead to discrepancies in the data or in the discrimination, so more precise and consistent studies are needed to confirm these findings and to provide more accurate medical treatment for clinical periodontal disease. Recent study in southern Taiwan further found that DM patients in rural and suburban area showed lower incidence of periodontitis, showing underdiagnosis of periodontitis or underutilization of dental care in this region.[94] Therefore, more follow-up studies with high precision and consistency are needed to confirm these points and provide more accurate medical treatment for clinical periodontal therapy to improve their quality of life.

Conclusion

There is an interplay between periodontitis/AP and DM with a two-way association. DM may influence the infection, inflammation and tissue healing of periodontitis and AP. Periodontal treatment may improve the glycemic control especially in T2DM patients possibly by reducing periodontal infection/inflammation, bacteremia and endotoxemia with associated elevation of IL-1β and TNF-α, systemic inflammation and hyperlipidemia that may impair the function of pancreatic beta cells. But the clinical studies for the effect of root canal on glycemic control in T1DM and T2DM patients, as well as the effect of periodontal treatment on glycemic control in T1DM patients are limited and should be further addressed. DM may influence the periapical and periodontal diseases possibly via changes in pathogenic microorganisms, impairment of neutrophils' activity and host immune responses and cytokine production, induction of oxidative stress etc. DM may affect salivary and periodontal microorganisms especially in T2DM patients. But the effect is still not confirmed in root canal microorganisms. While periodontitis associated systemic inflammation and hyperlipidemia is suggested to contribute to the control of T2DM, more intricate studies are necessary to clarify the detailed mechanisms.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

The authors would like to thank Prof. Eddie Hsiang-Hua Lai for his comments on this manuscript. This study was supported by Chang Gung Memorial Hospital (CMRPF1G0101, CMRPF1G0102, CMRPF1F0071, CMRPF1H0061, CMRPF1H0062,

CMRPF1H0063, CMRPF3E0022, CMRPF3E0023, NMRPF3E0041, NMRPF3E0042, NMRPF3E0043, NMRPF3H0061, NMRPF3H0062, NMRPF3H0071, NMRPF3H0072, NMRPF3H0073, CMRPF1K0071, CMRPF1K0072, NMRPF3L0031, NMRPF3L0032, ZMRPF3L0121, NMRPF3L0041, NMRPF3L0042, ZMRPF3L0111, ZMRPF3L0121, ZMRPF3M0051, ZMRPF3M0061, CMRPF1M0081), the Ministry of Science and Technology, Taiwan (MOST104-2314-B-255-010-MY3, MOST106-2314-B-002-033-MY2, MOST106-2314-B-002-034-MY2, MOST107-2314-B-255-009-MY3, MOST107-2314-B-255-008-MY2, MOST108-2314-B-002-043-MY3, MOST110-2314-B255-002-MY3, MOST110-2314-B-255-003-MY3; MOST111-2314-B002-109-MY3, MOST111-2314-B002-107-MY3), National Taiwan University Hospital (NTUH101-S1862, NTUH102-S2180, NTUH103-S2368, NTUH104-S2658, NTUH106-S3467, NTUH106-UN-001, NTUH107-003875, NTUH108-004156, NTUH110-S4815) & Kaohsiung Medical University (KMU-Q111004, KMU-110KK040, KMU-DK(A)-110002, KMUH111-1T09).

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