Periodontal disease: A silent factor in the development and progression of diabetic retinopathy

Lomelí Martínez SM et al. Periodontal disease

Abstract
The global increase in the prevalence of type 2 diabetes mellitus (T2DM) and its complications presents significant challenges to public health. Recently, periodontal disease (PD) was recognized as a factor that is likely to influence the progression of T2DM and its complications due to its potential to exacerbate systemic inflammation and oxidative stress. In this editorial, we commented on the article published by Thazhe Poyil et al in the very recent issue of the World Journal of Diabetes in 2024, which investigated the correlation between PD and diabetic retinopathy (DR) in patients with T2DM, with emphasis on the association amongst periodontal swollen surface area, glycated hemoglobin (HbA1c), interleukin-6 (IL-6), and lipoprotein(a). The findings in the study by Thazhe Poyil et al are significant as they demonstrate a strong link between PD and DR in patients with T2DM. This correlation highlights the importance of addressing periodontal health in diabetes management so as to potentially reduce the risk and severity of DR, a complication of diabetes. The integration of periodontal evaluation and treatment into diabetes care protocols may lead to improved glycemic control and better overall outcomes for patients with T2DM. A few studies that have established an interconnection between PD and diabetic complication, specifically DR, in patients with DM2. This editorial was aimed at discussing some of the most notable studies in this regard. Emphasized was placed on the different mechanisms that suggest a bi-directional relationship between PD and T2DM, where the presence of periodontal inflammation negatively influenced glycemic control and contributed to the development and progression of DR through shared inflammatory and vascular mechanisms. This article highlights the importance of collaboration amongst diabetes specialists, ophthalmologists, periodontists, and public health professionals so as to
advance the prevention, early detection, and treatment of PD and DR. This will improve the health and quality of life of patients with DM2. Moreover, the editorial highlights the need for further research on the specific molecular and immunological mechanisms that underlie the link between periodontitis and DR, with identification of common inflammatory biomarkers and signaling pathways. This is expected to facilitate effective direction of therapeutic objectives, thereby improving the management of diabetes and its complications through integrated care that incorporates oral health.

**Key Words:** Type 2 diabetes mellitus; Periodontal disease; Periodontitis; Diabetic retinopathy


**Core Tip:** In this editorial, we commented on the observational study by Thazhe Poyil et al published in the recent issue of the *World Journal of Diabetes* in 2024, in which the correlation between periodontal disease (PD) and diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM) was investigated. We discussed some of the most notable studies, with emphasis on the different mechanisms that suggest a bi-directional relationship between PD and T2DM, where the presence of periodontal inflammation negatively influenced glycemic control and contributed to the development and progression of DR through shared inflammatory and vascular mechanisms.

**INTRODUCTION**

The surge in diabetes mellitus (DM) cases over the last three decades has escalated into a critical global health challenge, with DM emerging as a leading cause of morbidity and mortality worldwide. Presently, over 420 million people are grappling with type 1
or type 2 diabetes (T2D), a figure resulting from quadrupling of the value in 1980, and it has been projected to surpass 500 million at the end of the next decade. The factors that contribute to this surge in DM are unhealthy dietary patterns, sedentary lifestyles, obesity, and genetic predispositions[3]. The chronic complications of DM encompass macrovascular issues which are the foremost contributors to DM-related mortality, while microvascular complications significantly impact quality of life of DM patients. Glycemic control and blood pressure control have demonstrated efficacy in mitigating certain microvascular complications, notably ocular lesion, i.e., diabetic retinopathy (DR). In contrast, factors such as smoking, alcohol consumption, hyperlipidemia, and periodontitis heighten the risk of DR[2].

Diabetic nephropathy (DR) affects the retinal microvasculature, and it correlates primarily with glycemic control, duration of diabetes, and hypertension. This complication (DR) severely compromises vision, and it has emerged globally as a leading cause of blindness. Diabetic nephropathy (DR) manifests in two stages: Non-proliferative DR (characterized by capillary hyperpermeability, macular edema, ischemia, hemorrhage, and microaneurysms), and proliferative DR (an advanced stage marked by retinal neovascularization, vitreous hemorrhage, and fibrovascular proliferation). Although various treatments are used to delay DR progression, it has been shown that the control of hemoglobin (HbA1c) levels and management of hypertension are effective in preventing or impeding accelerated development of the disease[3,4].

Periodontal disease (PD) is a prevalent oral disease which affects 20%-50% of the population, and it is ranked amongst the top common conditions in the world[5]. There has been a significant surge in the incidence of PD, a situation which has earned it global public health recognition. Although the pathogenesis of PD is multifactorial, the primary cause stems from formation of pathogenic bacterial biofilm. This results in dense immunoinflammatory infiltrates that damage soft tissues and, in severe cases, lead to tooth detachment due to loss of periodontal support[6]. Beyond local symptoms such as inflammation and pain, PD-associated bacterial infections release
proinflammatory cytokines such as interleukin 1β (IL-1β), IL-6, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), prostaglandin E2, and receptor activator of nuclear factor κB ligand as autoimmune responses, all of which contribute to systemic health issues[7]. The association of PD with non-oral diseases such as DM, cardiovascular disorders, and certain cancers underscores its systemic impact[8,9]. Individuals with T2D who have severe PD have 3.2-fold higher risk of mortality than those with mild or no periodontitis[5]. This indicates that individuals with type 2 DM (T2DM) are more susceptible to developing PD and are likely to experience more severe forms of periodontitis than non-diabetic individuals[10]. Moreover, the raised levels of proinflammatory cytokines in diabetic patients may reach the gum and exacerbate existing PD, thereby indicating the likelihood of a bidirectional relationship between periodontitis and diabetes mellitus[11].

The present editorial emphasizes the critical need to comprehend the interplay amongst PD, DM, and DR development, with highlights on how periodontal health profoundly influences diabetic complications. It advocates for a comprehensive, multidisciplinary approach to public health assessment, in recognition of the systemic implications and interconnected pathways amongst PD, DM, and DR.

ASSOCIATION BETWEEN DR AND PD

The correlation between PD and the onset of DR may be elucidated through several mechanisms. The association of PD with increased levels of IL-6, CRP, and fibrinogen contributes to heightened insulin resistance. Furthermore, oxidative stress induced by PD exacerbates tissue damage and cellular demise. Studies have shown that PD triggers gradual increases in the level of vascular endothelial growth factor (VEGF) within the gingival crevicular fluid[12]. Periodontitis leads to atherosclerosis, resulting in retinal hypoxia and the formation of fragile, leaky vessels which result in retinal detachment. Additionally, systemic inflammation markers such as C-reactive protein, TNF-α, IL-1b, and IL-6 are associated with altered lipid homeostasis and increased levels of adipose tissue macrophages. This leads to higher lipid concentrations in the bloodstream and
ectopic fat deposits in the endothelium, thereby potentially triggering retinal hypoxia and DR. However, this connection has not been completely validated, despite results of individual studies suggesting an association between diabetic DR and periodontitis.

In the recent 2024 issue of the World Journal of Diabetes, Thazhe Poyil et al. published an interesting paper titled “Correlation of periodontal inflamed surface area with glycated hemoglobin, interleukin-6 and lipoprotein(a) in type 2 diabetes with retinopathy”. This cross-sectional study analyzed the correlation between PD and DR in patients with T2DM. Eighty patients with T2DM were included in the study (40 patients with DR and 40 without retinopathy). The periodontal parameters evaluated were Plaque Index (PI), percentage of sites with bleeding on probing (BOP), probing pocket depth, gingival recession, clinical attachment loss (CAL), periodontal inflamed surface area (PISA), and systemic parameters such as glycosylated HbA1c, IL-6, and lipoprotein (a) [(Lp (a)]. The results showed that the proportion of periodontitis was higher in T2DM with DR (47.5%) than in T2DM without DR (27.5%), with a significant difference in the severity of PD between both groups (P = 0.05). Periodontitis severity, CAL, PISA, IL-6, and Lp (a) were higher in the T2DM group with DR. A significant difference was observed in the mean percentage of sites with BOP between T2DM with DR (69%) and T2DM without DR (41%). Moreover, HbA1c was positively correlated with CAL (P = 0.001) and PISA (P ≤ 0.001) in the studied subjects. Additionally, there were positive correlations between PISA and IL-6 (P < 0.0001); PISA and Lp (a) (P < 0.001); CAL and IL-6 (P < 0.0001), and CAL and Lp (a) (P < 0.001). The authors proposed that in view of the bidirectional link between periodontitis and DM, it is most likely that the presence of DR contributed to the severity of periodontal destruction, and that periodontitis might have influenced the progression of DR.

In a cross-sectional study conducted by Tandon et al. on 213 South Indian patients diagnosed with DM2, 66.2% of the population had DR, while approximately 91% had PD. It was found that the presence of moderate-to-severe PD increased 1.6 folds the risk of having DR. Patients with proliferative DR had significantly higher gingival plaque indices than those with non-proliferative DR or those without DR. These findings
established a significant association between the presence and severity of DR and PD in patients with DM2. This correlation implies that recognizing the link between these two conditions could help identify potentially sight-threatening retinopathy in diabetic patients who visit the dental clinic with PD.

On the other hand, in an interesting cross-sectional study on the association between PD and DR, Veena et al\textsuperscript{[12]} investigated 200 adult T2DM patients with DR of varying severity. The severity of PD was assessed using clinical parameters, and HbA1c and serum creatinine levels were measured before DR treatment. The authors found a statistically significant association between the duration of diabetes and the severities of DR and PD. The severity of PD was directly correlated with the severity of DR, with higher plaque and gingival indices in patients with proliferative DR. A significantly higher association of HbA1c level was found between the group with DR and the group without DR. This is similar to the results from the study by Thazhe Poyil et al\textsuperscript{[14]}, indicating worse glycemic control in the presence of DR. The study by Veena et al\textsuperscript{[12]} suggests the likelihood of a plausible relationship between DR and PD, which highlights the importance of prevention and control of PD as an integral part of diabetes management strategies. In addition, there were significant associations between serum creatinine and the severities of DR and PD, unlike in the studies by Tandon et al\textsuperscript{[15]} and Thazhe Poyil et al\textsuperscript{[14]} in which kidney function was not evaluated.

It is important to highlight that Thazhe Poyil et al\textsuperscript{[14]} measured PISA (which estimates periodontal inflammatory load), as well as levels of IL-6 and Lp (a). Lp (a) and IL-6 were positively correlated with PISA and PD. This contrasts with the studies by Tandon et al\textsuperscript{[15]} and Veena et al\textsuperscript{[12]}, in which these inflammation and lipid markers were not evaluated. Despite the methodological differences in sample sizes, with Veena et al\textsuperscript{[12]} having a larger sample size ($n = 200$) than Thazhe Poyil et al\textsuperscript{[14]} ($n = 80$) and Tandon et al\textsuperscript{[15]} ($n = 213$), the periodontal and systemic parameters evaluated in the three studies indicated a significant association between the presence and severity of PD and DR in DM2 patients. This association could be attributed to shared inflammatory mechanisms. The more severe the DR, the higher the proportion and severity of PD. These findings
suggest that incorporating periodontal therapy into comprehensive diabetes management would be beneficial in improving glycemic control and preventing the progression of diabetic complications.

**FUTURE PERSPECTIVES**

The study by Thazhe Poyil *et al.*\(^{[14]}\) posits the existence of a bi-directional link between periodontitis and T2DM. This suggests that the presence of DR contributes to increased periodontal destruction, and *vice versa*. These findings are noteworthy as they underscore inflammation as a common component in the pathogenesis of periodontitis and DR. Moreover, the findings emphasize the importance of dental care in the management of patients with T2DM, especially those having complication with DR. These findings pave the way for several crucial avenues for future research in diabetes management.

It would be beneficial to integrate research projects with adequate longitudinal design and appropriate adjustments for confounding factors, in order to identify the specific molecular and immunological mechanisms that underlie the bidirectional link between periodontitis and DR. The need for studies that determine common inflammatory biomarkers, signaling pathways, and epigenetic changes connecting these conditions should be emphasized. This will allow for effective direction of therapeutic objectives.

The bidirectional link between periodontitis and DM suggests that good periodontal health must be considered for the adequate management of diabetes\(^{[16,17]}\). However, more research is essential in order to evaluate whether periodontal health has the potential to improve glycemic control and prevent the progression of DR to some extent. Additionally, there is need for studies on the benefit of incorporating periodontal evaluation into the diagnosis and management guidelines for DR. This would contribute to identifying patients at higher risk of DR. An interesting aspect would be to evaluate the impact of periodontal treatment on the long-term outcomes of DR such as disease progression, need for laser treatment, and risk of vision loss. These
will provide a more solid foundation for the potential advantages of periodontal management in patients with diabetes.

Oral dysbiosis, inflammation, and destruction of the periodontium are characteristics of periodontitis\[^{16}\]. Recent studies suggest that oral dysbiosis generated by periodontitis may result in chronic and repetitive discharge of periodontal microbes and their byproducts into the bloodstream, leading to systemic inflammation and creating or exacerbating insulin resistance and diabetes complications\[^{16}\]. However, more research is needed to fully understand these links. In this sense, it would be important to investigate the role of the oral microbiota in the relationship between periodontitis and diabetes complications, including DR.

A multidisciplinary approach that integrates diabetes specialists, ophthalmologists, periodontists, and public health experts should be proposed for the management of diabetes and its complications. The implementation of this comprehensive management will ensure better prevention strategies, as well as early diagnosis and treatment of periodontitis and DR, thereby ultimately improving treatment outcomes and quality of life of patients. Similarly, it would be beneficial to promote the development of educational strategies for raising awareness among health professionals and patients, especially on the importance of oral health in the management of diabetes and the prevention of diabetes complications.

However, there may be challenges and barriers to effective integration of periodontal health into the management of DM. One of the main challenges is the lack of awareness amongst patients and health professionals about the importance of periodontal health and its impact on DM, and *vice versa*. In addition, limited availability of resources, especially in low-resource areas, makes it difficult to embark on regular periodontal health assessments and necessary interventions. For comprehensive management, there is need for collaboration amongst dentists, endocrinologists, diabetologists, and other health professionals. However, this may be limited by lack of effective referral systems or communication between different specialties. In addition, patients may not perceive PD as a priority, especially if they are focused more on another aspect of diabetes such
as blood glucose control. Thus, they may not follow recommendations for periodontal treatment, which, apart from being expensive, is not always covered by health insurance, thereby limiting access for some patients. Addressing these challenges requires a collaborative, multidisciplinary approach that prioritizes education of the patient, healthcare integration, and accessibility to affordable treatments.

Ultimately, more research is essential in order to understand the pathophysiological mechanisms that connect the complex relationship between EP and DR while unravelling the clinical implications. Additionally, it is necessary to ensure collaboration amongst health professionals, social workers, and community organizations, in order to develop a comprehensive approach that addresses the needs of DM patients.

CONCLUSION
There is a significant association between the severity of periodontitis and the presence and severity of DR, indicating that patients with T2DM and DR experience greater burdens of PD. This suggests that, not only is periodontitis more prevalent and severe in these patients, but it may also play a role in the progression of DR through shared inflammatory and vascular mechanisms. These findings highlight the importance of adopting a multidisciplinary approach to the management of DM by incorporating the evaluation and treatment of periodontitis as essential components of comprehensive care. Integrating dental care into the management of DM may offer significant opportunities to improve glycemic control and mitigate the risk and progression of DM-related complications. Future research is needed to further investigate the underlying mechanisms linking periodontitis and DM, including the identification of common inflammatory biomarkers and signaling pathways. This is expected to facilitate the development of more effective therapeutic strategies targeting these shared pathological processes, thereby improving health outcomes for patients with T2DM. The integration of dental care into the management of DM not only promises to improve glycemic control and mitigate the progression of its complication, but also represents a
transformative opportunity for enhancing public health outcomes and quality of life of DMT2 patients. These advantages underline the importance of a multidisciplinary approach in the treatment of this complex disease.

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