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Review Article

Dentistry Section

Unraveling the Intricacies: Pioneering Insights into the Interplay of the Gut and Oral Microbiome in Diabetes and Periodontal Disease

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ABSTRACT

Exploring the intricate interplay between two prevalent chronic conditions, diabetes mellitus and periodontal disease, reveals a bidirectional relationship. Recent evidence underscores the pivotal influence of the microbiome, particularly the gut and oral microbiome, in shaping the pathogenesis of both diabetes and periodontal disease. The present comprehensive review aimed to elucidate the current understanding of how these microbial communities contribute to the development and progression of diabetes, especially when compounded by periodontal disease. However, emerging evidence suggests a complex bidirectional relationship between these two conditions. The microbiome's involvement in these conditions unfolds through multifaceted mechanisms, with microbial dysbiosis influencing systemic inflammation, insulin resistance, and periodontal tissue degradation. The authors explored the dynamic crosstalk between the gut and oral microbiome, shedding light on how alterations in these microbial ecosystems may exacerbate the interconnected manifestations of diabetes and periodontal disease. Furthermore, present review unraveled the potential therapeutic implications for targeted interventions. By dissecting the microbiome-driven pathways, authors identified the promising avenues for precision medicine and tailored therapies. This exploration opens new vistas for developing strategies that leverage the microbiome to mitigate the impact of diabetes with periodontal disease. As the authors navigated this complex terrain, the manuscript underscores the urgency of a holistic understanding and targeted modulation of the microbiome to revolutionise treatment paradigms for these intertwined chronic conditions. The present manuscript aimed to review the current understanding of the role of the gut and oral microbiome in the development and progression of diabetes with periodontal disease.

Keywords: Bidirectional relationship, Chronic conditions, Diabetes mellitus, Pathogenesis, Therapeutic implications

INTRODUCTION

In the expansive landscape of health research, the intricate relationship between diabetes mellitus and periodontal disease has sparked increasing interest, prompting a quest for deeper understanding. While each condition has been extensively studied in isolation, emerging evidence suggests a complex interplay that extends beyond conventional paradigms. Within this intricate web of connections, the microbiome, specifically the gut and oral microbiome, emerges as a central player influencing the pathogenesis of both diabetes and periodontal disease. Diabetes affects approximately 463 million people worldwide, and its prevalence is expected to increase to 700 million by 2045 [1]. On the other hand, periodontal disease, a chronic inflammatory condition affecting the supporting structures of the teeth, affects a large proportion of the population, with severe periodontitis affecting 11.2% of the global population [2].

Traditionally, these conditions have been studied independently, focusing on their respective aetiologies and management strategies. However, recent research [2,3] has shed light on the role of the microbiome, particularly the gut and oral microbiome, in the pathogenesis and progression of chronic diseases, including diabetes and periodontal disease. The microbiome refers to the complex community of microorganisms, including bacteria, fungi, viruses, and other microbes, residing in and on the human body.

The microbiome has emerged as a key player in maintaining human health and has been implicated in various physiological processes, including metabolism, immune modulation, and inflammatory responses. Perturbations in the microbiome composition and function, termed dysbiosis, have been associated with the development of several chronic diseases, including obesity, cardiovascular disease, inflammatory bowel disease, and cancer [3,4].

Microbiome as a Key Player in Chronic Diseases

The gut microbiome, the collection of microorganisms residing in the gastrointestinal tract, plays a crucial role in human health. It is estimated that the gut harbours trillions of microorganisms, representing hundreds of species [5]. The gut microbiome contributes to digestion, vitamin synthesis, and the metabolism of dietary components that are otherwise indigestible by human enzymes [6]. Additionally, it interacts closely with the host immune system, influencing the development and regulation of immune responses [7].

Dysbiosis of the gut microbiome has been implicated in the pathogenesis of diabetes mellitus. The alterations in the gut microbial composition in individuals with type 2 diabetes are characterised by a decrease in butyrate-producing bacteria [8]. This dysbiosis is associated with increased gut permeability, chronic low-grade inflammation, and insulin resistance [9]. The gut microbiome has also been linked to the regulation of glucose metabolism through the production of Short-chain Fatty Acids (SCFAs) and modulation of bile acid metabolism [10,11]. These findings highlight the role of the gut microbiome in the development and progression of diabetes.

The oral microbiome comprises diverse microorganisms inhabiting the oral cavity, including bacteria, viruses, fungi, and archaea. It is a

dynamic ecosystem influenced by factors such as diet, oral hygiene practices, and systemic conditions [12]. The oral microbiome is essential for maintaining oral health, but dysbiosis can contribute to the development of various oral diseases, including periodontal disease [13]. Many studies have demonstrated alterations in the oral microbiome in individuals with periodontal disease [14,15]. Shifts in microbial composition, such as an increase in periodontopathogenic bacteria (e.g., Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola), have been associated with periodontal inflammation and disease severity [14,15]. The dysbiotic oral microbiome triggers an exaggerated host immune response, leading to chronic inflammation and tissue destruction in the periodontium [16]. Moreover, the oral microbiome is not confined to the oral cavity but can serve as a reservoir for potential pathogens that may translocate to distant sites, contributing to systemic inflammation and the pathogenesis of various systemic diseases, including diabetes [1].

Diabetes Mellitus and Periodontal Disease: An Overview

Diabetes Mellitus:

I. **Definition and classification:** Diabetes mellitus is a chronic metabolic disorder characterised by hyperglycaemia (high blood glucose levels) resulting from defects in insulin secretion, insulin action, or both [5]. Insulin, a hormone produced by the pancreas, regulates glucose metabolism in the body. There are several types of diabetes mellitus, including:

- **Type 1 diabetes:** This form of diabetes results from an autoimmune destruction of the pancreatic beta cells, leading to an absolute deficiency of insulin production. It typically manifests in childhood or early adulthood and requires lifelong insulin therapy [5].
- **Type 2 diabetes:** Type 2 diabetes is the most common form and occurs when the body becomes resistant to the action of insulin or fails to produce enough insulin to meet the body's needs. It is strongly associated with obesity, a sedentary lifestyle, and unhealthy dietary habits. Initially, it can often be managed with lifestyle modifications, oral medications, or injectable medications, but some individuals may eventually require insulin therapy [5].
- **Gestational Diabetes Mellitus (GDM):** GDM occurs during pregnancy and is characterised by elevated blood glucose levels that were not present before pregnancy. It increases the risk of complications for both the mother and the baby, and in some cases, GDM may progress to type 2 diabetes later in life [5].

Epidemiology and impact on oral health: Diabetes mellitus has reached epidemic proportions worldwide, affecting people of all ages and ethnicities. According to the International Diabetes Federation (IDF), , in 2019, approximately 463 million adults (20-79 years) were living with diabetes, and this number is projected to rise to 700 million by 2045 [17]. The impact of diabetes on oral health is significant, with several oral complications associated with the disease:

- **Periodontal disease:** Individuals with diabetes have an increased risk of developing periodontal disease, a chronic inflammatory condition that affects the supporting structures of the teeth. Diabetes impairs the body's ability to control infection and inflammation, leading to an exaggerated immune response to oral pathogens. This dysregulated immune response contributes to the destruction of the periodontal tissues and exacerbates periodontal disease [18].
- **Impact of glycaemic control on periodontal disease:** Poor glycaemic control and elevated blood glucose levels can exacerbate the progression and severity of periodontal disease. Hyperglycaemia provides a favourable environment for bacterial growth, impairs immune responses, and compromises tissue repair, leading to increased susceptibility to oral infections and periodontal tissue destruction [3].
- **Dental caries:** Diabetes can also increase the risk of dental caries (tooth decay). Elevated blood glucose levels provide an optimal environment for acid-producing bacteria, leading to demineralisation of the tooth enamel and the development of dental caries [3].
- **Xerostomia:** Xerostomia, or dry mouth, is another common oral manifestation of diabetes. Reduced salivary flow, resulting from neuropathy or other diabetes-related factors, can contribute to oral discomfort, difficulty in chewing and swallowing, and an increased risk of dental caries and oral infections [19].

Periodontal disease

II. **Definition and stages:** Periodontal disease is a chronic inflammatory condition that affects the supporting structures of the teeth, including the gums, periodontal ligament, and alveolar bone. It is caused by a complex interaction between oral bacteria and the host immune response. The disease progresses through several stages:

- **Gingivitis:** Gingivitis is the earliest stage of periodontal disease and is characterised by inflammation of the gingiva. It is reversible with appropriate oral hygiene measures and professional dental care [20].
- **Periodontitis:** If left untreated, gingivitis can progress to periodontitis, a more severe form of the disease. Periodontitis is characterised by the destruction of the periodontal tissues, including the formation of periodontal pockets, loss of connective tissue attachment, and bone resorption. It can lead to tooth mobility and eventual tooth loss [20].

Epidemiology and impact on glycaemic control: Periodontal disease is prevalent globally, with varying rates depending on geographic location and population groups. According to a systematic review, the global prevalence of severe periodontitis (stage III or IV) was estimated to be 11.2% [20]. Studies have investigated the bidirectional relationship between periodontal disease and glycaemic control in individuals with diabetes [21].

- **Impact of periodontal disease on glycaemic control:** Periodontal inflammation and infection can adversely affect glycaemic control in individuals with diabetes. The chronic inflammation associated with periodontitis leads to the release of inflammatory mediators and cytokines, which can induce insulin resistance and impair glucose uptake by cells [20]. Furthermore, the oral pathogens associated with periodontal disease can release proinflammatory molecules that may contribute to systemic inflammation and insulin resistance [22].

Gut Microbiome

Composition and functions: The gut microbiome is a diverse community of microorganisms that reside in the gastrointestinal tract. It consists primarily of bacteria but also includes archaea, viruses, fungi, and other microbes. The composition of the gut microbiome is influenced by various factors, including diet, host genetics, age, and environmental exposures [23]. The gut microbiome performs essential functions that contribute to human health. It aids in the digestion and metabolism of dietary components that are otherwise

indigestible by the host, such as dietary fibers and complex carbohydrates [23]. The gut microbiome also produces metabolites, such as SCFAs, through fermentation processes. SCFAs, such as butyrate, acetate, and propionate, have been shown to provide energy for the host, regulate gut barrier function, and modulate immune responses [9].

Influence on glucose homeostasis and inflammation: The gut microbiome plays a critical role in glucose homeostasis and inflammation, which are closely linked to the development and progression of diabetes. Alterations in the gut microbial composition, known as dysbiosis, are associated with impaired glucose metabolism and insulin resistance, particularly in individuals with type 2 diabetes. Dysbiosis in individuals with diabetes is characterised by a reduction in beneficial bacteria such as Bifidobacterium and Akkermansia muciniphila and an increase in potentially harmful bacteria such as Firmicutes [24,25].

The gut microbiome can influence glucose metabolism through several mechanisms. For instance, SCFAs produced by gut bacteria can improve glucose tolerance and insulin sensitivity by enhancing the production of incretin hormones, promoting gut hormone secretion, and regulating hepatic glucose production [6,7]. Additionally, the gut microbiome can modulate inflammation in the gut and systemically. Dysbiosis can lead to increased gut permeability, allowing the translocation of bacterial components such as Lipopolysaccharides (LPS) into the bloodstream. LPS, in turn, triggers systemic inflammation and impairs insulin signaling [26].

Oral Microbiome

Composition and functions: The oral microbiome consists of a wide range of microorganisms, including bacteria, viruses, fungi, and archaea, that inhabit the oral cavity. The oral microbiome is influenced by various factors, including oral hygiene practices, diet, genetics, and the local oral environment [4]. The oral microbiome performs essential functions in maintaining oral health. It contributes to the formation of dental biofilms (plaque) and plays a role in various oral processes, including the metabolism of dietary components, modulation of the host immune response, and maintenance of oral tissue homeostasis [27].

Influence on periodontal health and systemic inflammation: The oral microbiome has a significant impact on periodontal health and can influence systemic inflammation, which is relevant to the bidirectional relationship between periodontal disease and diabetes. In periodontal health, the oral microbiome consists predominantly of commensal bacteria that contribute to maintaining a balanced ecosystem. However, in the presence of poor oral hygiene practices and other risk factors, dysbiosis can occur, leading to an overgrowth of periodontopathogenic bacteria (e.g., Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola) [28]. These bacteria initiate and sustain an inflammatory response in the periodontium, resulting in the destruction of the supporting tissues of the teeth, including the periodontal ligament and alveolar bone [22].

Moreover, periodontal disease is not limited to the oral cavity. The dysbiotic oral microbiome and the locally produced inflammatory mediators can translocate into the systemic circulation, contributing to systemic inflammation. The translocation of oral pathogens and their associated virulence factors, such as LPS, can trigger immune responses and systemic inflammation, potentially affecting distant organs and tissues [23].

Impact of Diabetes on the Gut and Oral Microbiome

Dysbiosis and altered microbial composition: Diabetes has been associated with alterations in the gut and oral microbiome, leading to dysbiosis. In individuals with diabetes, there is a shift in the composition of the gut microbiota, characterised by a decrease in microbial diversity and changes in the relative abundance of specific bacterial taxa [14,23]. These changes include a reduction in butyrate-producing bacteria, such as Faecalibacterium prausnitzii and Roseburia spp., and an increase in opportunistic pathogens, such as Enterobacteriaceae [5].

Similarly, diabetes can also impact the oral microbiome. Studies have shown that individuals with diabetes have an altered oral microbial composition, with an increase in pathogenic bacteria associated with periodontal disease, such as Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola [6,29]. Additionally, individuals with diabetes may exhibit a higher prevalence of Candida species in the oral cavity, contributing to the risk of oral infections [30].

Influence on glucose metabolism and insulin resistance: The dysbiotic oral microbiome and the associated systemic inflammation may also influence glucose metabolism and insulin resistance. Systemic inflammation, triggered by oral pathogens and their virulence factors, can lead to insulin resistance through the impairment of insulin signaling pathways. Additionally, the systemic inflammatory state can contribute to chronic low-grade inflammation, which has been implicated in the development and progression of insulin resistance [8,31].

Moreover, the dysbiotic oral microbiome and periodontal disease have been associated with increased systemic oxidative stress. Oxidative stress can further contribute to insulin resistance by impairing insulin signaling and promoting chronic inflammation [32].

Targeting the Gut Microbiome

Probiotics, prebiotics, and dietary interventions: Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host. They can help restore the balance of the gut microbiome by promoting the growth of beneficial bacteria and inhibiting the growth of harmful bacteria. Probiotics commonly used in clinical studies include strains of lactobacillus and bifidobacterium species [33].

Studies have shown potential benefits of probiotics in individuals with diabetes. Probiotic supplementation has been associated with improved glycaemic control, reduced insulin resistance, and decreased systemic inflammation [34]. For example, a systematic review and meta-analysis indicated that probiotic interventions significantly reduced fasting blood glucose levels and Glycated Haemoglobin (HbA1c) levels in individuals with type 2 diabetes [35].

Non digestible dietary fibers, known as prebiotics, selectively promote the growth and functioning of beneficial bacteria in the gastrointestinal tract. They can be found in foods such as whole grains, fruits, vegetables, and legumes. Prebiotics can support the growth of beneficial bacteria, such as bifidobacteria and lactobacilli, in the gut [36]. Dietary interventions, such as adopting a high-fiber diet or consuming specific foods rich in beneficial bacteria (e.g., fermented foods like yogurt and kimchi), can also positively impact the gut microbiome. These dietary strategies can provide substrates for the growth of beneficial bacteria and promote a more diverse and balanced gut microbiome composition [37].

Targeting the Oral Microbiome

Oral hygiene practices and antimicrobial therapies: Maintaining proper oral hygiene practices is crucial for promoting oral health and modulating the oral microbiome. Regular brushing and flossing help remove dental plaque, which is a biofilm that can harbor harmful bacteria. Effective plaque control is essential for preventing and managing periodontal disease [38].

In addition to good oral hygiene practices, antimicrobial therapies can be used to target specific pathogens in the oral microbiome. For example, antimicrobial mouthwashes containing chlorhexidine or essential oils can help reduce the bacterial load in the oral cavity and improve periodontal health. However, it is important to use antimicrobial therapies judiciously and under the guidance of dental professionals to minimise the risk of antimicrobial resistance and disruption of the oral microbiome [38].

Integrated approaches and multidisciplinary care: Given the bidirectional relationship between the gut and oral microbiome in diabetes with periodontal disease, integrated approaches and multidisciplinary care are crucial for effective management. Collaboration between dental and medical professionals is essential to ensure comprehensive care. This includes regular communication and sharing of patient information to address the interplay between periodontal health, glycaemic control, and systemic inflammation. Coordinated treatment plans that target both the gut and oral microbiome can yield better outcomes.

In addition, patient education plays a vital role in promoting oral and gut health. Educating individuals with diabetes about the importance of maintaining good oral hygiene practices, dietary modifications, and adherence to medical and dental treatments can empower them to actively participate in their own care.

Furthermore, ongoing research is needed to better understand the complex interactions between the gut and oral microbiome in diabetes with periodontal disease. Future studies should explore novel therapeutic interventions targeting the microbiome, such as personalised approaches based on individual microbial profiles, and evaluate their effectiveness in improving glycaemic control, periodontal health, and overall well-being.

CONCLUSION(S)

In conclusion, the symbiotic relationship between the gut and oral microbiome in individuals with diabetes and periodontal disease emphasises the significance of addressing both microbial ecosystems in their management. Dysbiosis in these microbiomes can substantially impact glycaemic control, systemic inflammation, and insulin resistance. Integrating targeted interventions, such as probiotics, prebiotics, and oral hygiene practices, offers promising avenues for enhancing outcomes and underscores the need for a holistic approach to patient care, recognising the pivotal role of microbiome modulation in mitigating the complexities of diabetes with periodontal disease.

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