REVIEW

Alterations in the Oral Microbiome of Diabetic Patients and Their Impact on Dental Caries: A Critical Review

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Abstract

Introduction: India is the second largest country affected by diabetes mellitus after China. Majority of diabetes patients are associated with oral complications. Diabetes patients have reduced salivary flow rate, which can invariably increase the progression of acid-producing microorganisms. This is a contributing factor for the initiation and progression of dental caries in diabetic individuals. It synthesizes evidence showing that diabetic individuals, especially those with poor glycemic control, exhibit oral microbial diversity and a shift toward pathogenic bacteria compared to nondiabetic individuals. While the association between diabetes and periodontal disease has been extensively documented, the impact of diabetes-induced microbial dysbiosis on dental caries development remains insufficiently elucidated.

Objective: This review aims to comprehensively evaluate the alterations in the oral microbiome of diabetic patients, delineate their potential role in caries pathogenesis, and identify gaps that warrant further investigation.

Significance: Understanding these mechanisms may contribute to the development of targeted preventive and therapeutic strategies, advancing precision oral healthcare for individuals with diabetes.

Key-words: Deep dental caries, Diabetes mellitus, oral microbes, salivary pH, biodiversity, health service, social welfare, deep learning method, prevalence

Key message: Despite growing recognition of the oral microbiome's role in systemic health, there are certain gaps in the literature regarding the interrelationship between diabetes-associated microbial dysbiosis and dental caries pathogenesis. First, most available studies have focused predominantly on periodontal outcomes. Second, there is considerable heterogeneity in existing study design leading to inconsistent results, Third, few investigations have integrated clinical caries indices with microbiome profiling, which restricts the ability to establish causal or mechanistic associations. This review seeks to bridge these gaps by critically synthesizing available evidence across molecular, microbiological, and clinical studies to provide a comprehensive understanding of how diabetes alters the oral microbial ecosystem and contributes to cariogenic processes.

Introduction

The oral cavity harbours a complex and dynamic microbial ecosystem composed of highly organized structural and functional communities known as biofilms. Within these biofilms, microorganisms coexist symbiotically, communicating through quorum sensing mechanisms that regulate gene expression, nutrient exchange, and collective defence against competing species and antimicrobial agents.[1] The stability of this microbial community is maintained by saliva, which provides an optimal pH, essential nutrients, and host-derived factors necessary to sustain ecological balance.[2,3] Any disturbance in salivary composition, pH, or flow rate can disrupt this equilibrium, leading to dysbiosis and the onset of oral diseases such as dental caries and periodontitis.[4]

Diabetes mellitus, particularly Type 2 Diabetes Mellitus (T2DM), is a prevalent metabolic disorder associated with persistent hyperglycaemia and systemic complications. In the oral environment, diabetes is known to alter salivary flow, increase glucose concentration, and impair host immune defence, thereby creating conditions conducive to microbial imbalance.[5] Studies have demonstrated that individuals with T2DM exhibit notable changes in the composition of saliva and the bacterial diversity within supragingival plaque compared with non-diabetic individuals.[6,7] These alterations are

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indicative of oral microbial dysbiosis, which may play a critical role in the pathogenesis of dental caries and other oral infections.

Dental caries is a chronic, biofilm-mediated disease characterized by the demineralization and destruction of tooth structure resulting from acid production by fermentative microorganisms.[8] In diabetic patients, elevated levels of fermentable carbohydrates and glucose in saliva enhance bacterial metabolism, increase acidogenic potential, and accelerate caries formation.[9,10] However, the specific microbial shifts across various stages of caries progression in individuals with T2DM remain inadequately characterized.

Given the rising prevalence of diabetes and its potential to modify oral microbial ecology, it is imperative to understand how these changes influence caries susceptibility. Therefore, this review aims to critically analyse the alterations in oral microbial flora associated with initial, moderate, and deep carious lesions in patients with Type 2 Diabetes Mellitus and to discuss the advanced microbiological and molecular methods employed to identify these microbial variations.

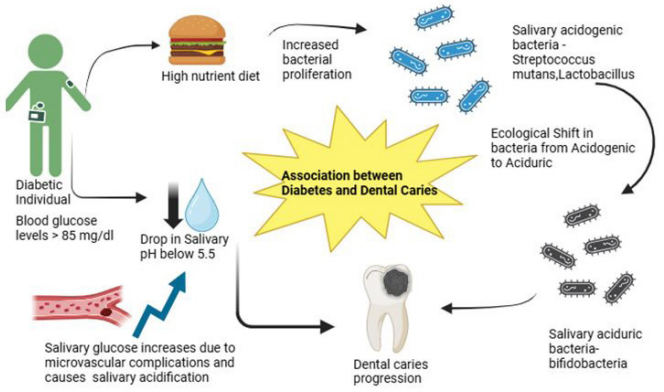


Fig. 1: Diabetic patients have very high blood glucose levels >85 mg/dl. This elevated blood glucose level ultimately increases the glucose levels in the saliva that causes a fall in salivary pH from 6.5 to below 5.5. Salivary pH drop below 5.5 results in ecological shift of oral microbes from acidogenic to aciduric resulting in excessive acid production leading to demineralisation of hydroxyapatite and caries progression. The high nutrient availability in diabetic patients also helps in bacterial proliferation eventually leading to caries formation.

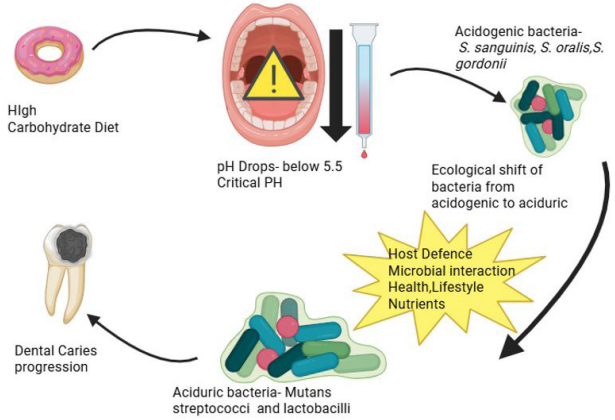


Fig 2: Role of bacteria and influence of various risk factors in caries formation.

Association between Diabetes and Oral Bacteria:

The relationship between diabetes and bacteria has been extensively studied, with scientific research providing strong evidence of how oral bacteria can influence the onset, progression, and management of diabetes.[11,12]

Diabetic patients are more prone to develop dental caries since the greater number of meals these patients are subjected to translates into a greater daily supply of nutrients. This can influence the proliferation of microorganisms in the oral cavity and maintain a lower salivary pH, a risk factor for developing dental caries.(Fig 1) Several factors contribute to the decrease in pH: the low concentration of bicarbonate, the greater accumulation of dental plaque and saliva with high cariogenic load, and an increased concentration of salivary glucose, possibly related to microvascular complications, and damage to the basal membrane of salivary glands leads to endothelial dysfunction and the glucose molecule is easily released to the existing saliva.[13,14] Given the heterogeneity of the diabetic population and the different risk factors, a dietary assessment is also extremely important. It allows analysing the frequency of ingestion of cariogenic products high or low to identify this parameter as a risk or protective factor, respectively. Diabetic patients who present better dietary habits, such as reduced intake of cariogenic products, have better nutritional control and are motivated and willing to cooperate towards a healthier lifestyle.

Importance of aciduric and acidogenic bacteria:

Acidogenic and aciduric bacteria are both types of bacteria related to their ability to survive and function in acidic environments, but they have distinct characteristics:

Acidogenic Bacteria:

Acidogenic bacteria are microorganisms that produce acids as byproducts of their metabolism, especially when they break down carbohydrates or other substrates. The primary feature of acidogenic bacteria is their ability to ferment sugars (like glucose) and convert them to lactic acid, acetic acid, and butyric acid. When non-mutant streptococci such as S. San-

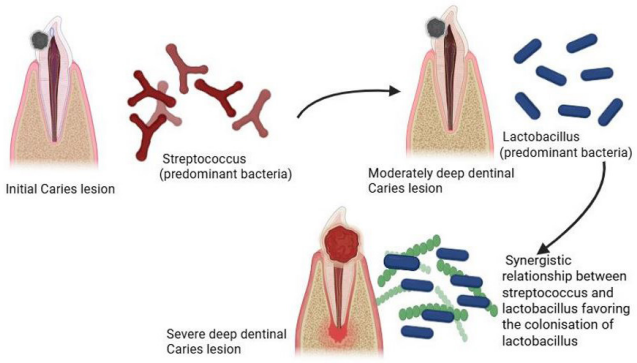


Fig 3: Oral microbes commonly found in initial, moderate and deep carious lesion.

Table 1: Most Common bacteria found in diabetic and non diabetic individuals and novel methods to identify them.

S.no	Author /year	Most common bacteria involved in Diabetic patients	Most common bacteria involved in non-diabetic patients	Inference	Methods to identify bacteria
1.	Almeida-Santos et al. 2021[40]	At phylum level- Fusobacteria-6% Actinobacteria-9% Proteobacteria-16% Bacteroidetes- 22% Firmicutes (45%) “, At the class level - *Bacilli* and *Bacteroidia* are the dominant classes in both groups (50%) *Betaproteobacteria* was higher in the diabetics group At genus level- Neisseria (5%)” Prevotella (14%)”, and Streptococcus (29%) “,.	At phylum level- Fusobacteria-6% Actinobacteria-9% Proteobacteria (16%) Bacteroidetes (22%)”,”, Firmicutes (45%) “, *At class level-Deltaproteobacteria* (*Spirochaetes*, *Mollicutes*, and *Synergistia*) were higher in the control group *Streptococcus* (29%) is the most abundant genus, present in all subjects, followed by *Neisseria* (5%) *Prevotella* (14%) .	No changes between diabetic and non diabetic group	RNA sequencing method
2.	Lee et al. 2022[41]	Fusobacteria (6%) Actinobacteria (9%)” Proteobacteria (16%)” Bacteroidetes (22%)” Firmicutes (45%) “,	Firmicutes is most common at phylum level while Streptococcus is most common at the genus level.	No difference in diabetic and non-diabetic groups	DNA sequencing method,
3.	Ali et al. 2021[42]	Staphylococcus hominis Enterobacter cloacae “, Staphylococcus pasteuri” Proteus mirabilis”,, Streptococcus mutans”, and Bacillus mojavensis”, Streptococcus pasteurianus”. Staphylococcus epidermidis”,	NA	Diabetes mellitus changes the environment and changes the microbial population.	DNA sequencing method,
4.	Sun et al. 2020[28]	*Treponema denticola*, *Prevotella nigrescens*, *Streptococcus sanguis*, *Streptococcus oralis*, and *Streptococcus intermadius increased in T2DM patients*	*Actinomycetes*, *Fusobacterium*, *Pigmentiphaga* in the T2DM group were similar to those of the healthy group	Shift in microbial population seen in relation to supragingival plaque. No significant difference in subgingival plaque.	RCT study, n = 133); BMI was observed for each group.
5.	Matsha et al. 2020 [5]	Fusobacteria (14%) and Actinobacteria (10%) were significantly more abundant in subjects with diabetes,	Actinobacteria were more abundant in those with prediabetes	No significant difference in both groups.	DNA sequencing method,
6.	Chen et al. 2020[13]	Neisseria”, Streptococcus”, Haemophilus”, and Pseudomonas”,	NA		RNA sequencing,
7	Anbalagan et al 2017 [26]	Streptococcus (95.8%), Veillonella (72.2%, , Neisseria (87.5%) , Rothia (63.6%), Actinomycetes (25%), Fusobacterium (21%), and Pigmentiphaga (12.5%) in Type 2 diabetes patients.	Streptococcus (26.1%), Veillonella (21.9%), Neisseria (16.9%), Haemophilus (10.7%), Actinomycetes (2.6%), Rothia (3.1%), Oribacterium (1.7%) in healthy patients	No significant difference. Microbial load high in diabetics and not in non diabetics.	16s rRNA

8	Yujiao Li, et al, 2023[36]	Treponema denticola, Aggregatibacter segnis, Rothia mucilaginosa, Fusobacterium nucleatum, Catonella morbi, Porphyromonas gingivalis, Treponema vincentii, Parvimonas micra, and Morococcus cerebrosus were significantly overrepresented in the T2DM group. Neisseria flavescens, Capnocytophaga granulosa, Prevotella melaninogenica, Capnocytophaga_ sp, and Capnocytophaga_sp in supragingival plaque in T2DM.	Prevotella aur antiaca and Lautropia mirabilis enriched in healthy individuals. Actinomyces massiliensis, Corynebacterium durum, Propionibacterium propionicum, Actinomyces johnsonii, Streptococcus sanguinis, Actinomyces naeslundii, Lautropia mirabilis, Rothia aeria, and Cardiobacterium hominis	There is a significant difference between the oral microflora in T2DM and healthy individuals.	Metagenomics DNA extraction.

No significant changes in bacteria in both groups at phylum level, significant difference exists in the microbes between diabetic and non diabetic individuals.

guinis, S. oralis, S. mitis, S. gordonii, and Actinomyces are exposed to an acidic environment, their acidogenicity rises. This acid-induced adaptation of bacteria can be primarily due to H+ -ATPase activity that removes protons from cells and maintains an acidic pH for bacteria to thrive.[15] This microbial acid-induced adaptation by bacteria might cause caries formation. Acidogenic bacteria contribute to the lowering of pH in their environment, which can create an acidic environment conducive to the growth of other acid-tolerant bacteria. (Fig 2)

Aciduric Bacteria:

Aciduric bacteria are specifically adapted to survive and thrive in acidic environments (low pH). They are not necessarily acid producers but can tolerate and grow in acidic conditions. They often possess mechanisms to neutralize acid or to maintain an internal neutral pH (e.g., proton pumps and buffer systems). Even though the non-mutant Streptococcus species have acidogenicity and acid-induced adaptation, the mutant Streptococci and Lactobacillus species are highly competitive under severe acidic conditions.[16] Lactobacillus and mutant Streptococcus do not show loss of viability or delay in growth.

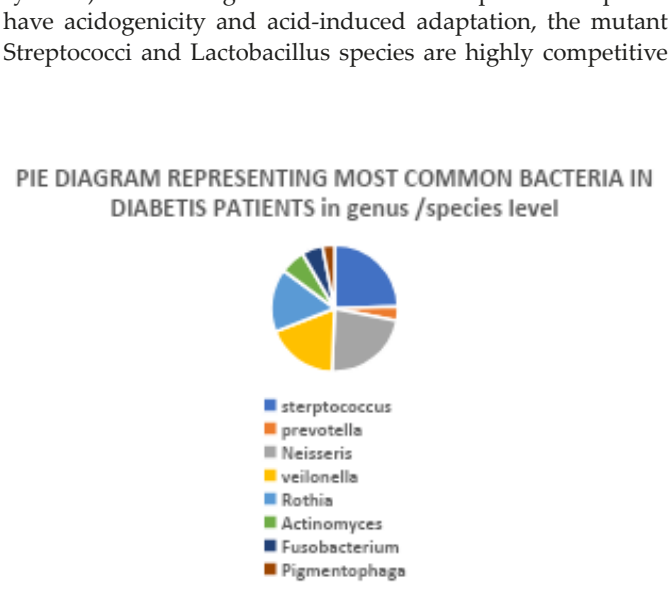
Key Differences:

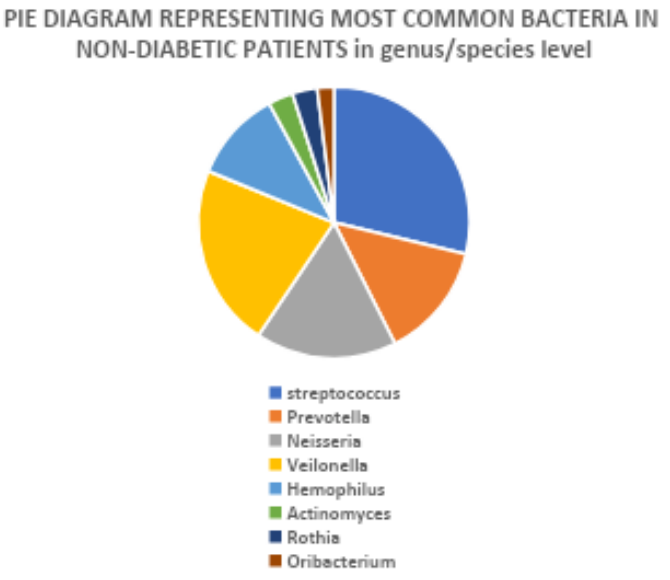
- Acidogenic bacteria produce acids during metabolism, contributing to acidic conditions.
- Aciduric bacteria can survive and grow in acidic environments, but they don't necessarily produce acids themselves.

Both types of bacteria are significant in areas like oral health, gastrointestinal health, and fermentation processes.

The underlying mechanism involved in the shift of bacteria from commensals to pathogens in all the carious lesions.

Acidic stress is recognized as a major biological challenge for oral microorganisms. Among various dietary components, fermentable carbohydrates exert the greatest influence on the





Pie chart representing most common bacteria in genus/species level in diabetic and nondiabetic patients

oral microbial ecosystem. As proposed by Quivey et al. (2000),[17] bacteria adapt to the acidic conditions through several strategies: (1) reducing the permeability of their cell membranes to protons; (2) increasing the activity of proton-pumping H^+-ATPase enzymes to expel excess protons; (3) activating the arginine deiminase pathway, which generates alkaline compounds from arginine; and (4) synthesizing stress-response proteins that protect cellular enzymes and genetic material from acid damage. These adaptive responses facilitate the loss of calcium and phosphate, contributing to the initiation and progression of caries.[18,19] A clear variation in microbial communities is seen between acidic and neutral pH zones. Acidic regions are dominated by low-diversity bacteria, especially Lactobacillus species such as L. fermentum, L. rhamnosus, and L. crispatus. Conversely, neutral pH areas tend to support a richer microbial diversity, including species like Alloprevotella tanerrae, Leptothrix, Sphingomonas, and Streptococcus anginosus.[20,21] Acid-tolerant (aciduric) bacteria are capable of thriving under these low pH conditions. For example, Streptococcus mutans is known to increase the expression of certain proteins under acid stress. Western blotting with specific antibodies identified proteins such as HPr, Enzyme I, Enzyme II^man of the phosphoenolpyruvate phosphotransferase system (PTS), and the L-subunit of the H^+/ATPase.[21,22] Conversely, bacteria that are typically associated with a healthy oral environment are more sensitive to acidic conditions and are thus outcompeted when fermentable carbohydrates are frequently consumed.[22]

Bacteria in initial, moderate and deep carious lesions:

The most common bacteria associated with initial caries lesion is found to be streptococcus because of the greater affinity to the smooth surface lesions and abundance of extracellular polysaccharides.[23] The predominant organisms in deep carious lesions are seen to be Lactobacillus. This is due to the fact that the capacity of adherence to the deep carious lesion is stronger than that of the smooth surface caries lesion.[24] Hence, Lactobacillus is more involved in caries progression rather than initiation. As the caries lesion progresses deeper, there is a synergistic relationship between Streptococcus and Lactobacillus, favouring the colonisation of Lactobacillus since it has the capacity to withstand the acidic environment in deep dentinal caries.[25] (Fig 3)

Based on the current research, the following inferences can be drawn about differences in oral microbial composition between diabetic and non-diabetic groups:

1. Streptococcus, Prevotella, Veillonella, and Rothia:

- **Higher abundance in diabetics:** Studies consistently show that genera such as Streptococcus, Prevotella, Veillonella, and Rothia are more abundant in diabetic patients compared to non-diabetics.[26]
- In the above data, these genera also show higher maximum percentages in diabetics (e.g., Streptococcus up to 95.8%, Veillonella up to 72.2%, Rothia up to 63.6%) than in non-diabetics (Streptococcus 26.1–29%, Veillonella 21.9%, Rothia 3.1%).[26]

2. Actinomycetes/Actinomyces and Oribacterium:

- Actinomyces (referred to as Actinomycetes) and Oribacterium are present in both groups, but their relative abundance is generally lower compared to the previously mentioned genera. There is no consistent evidence of a significant difference between diabetics and non-diabetics for these genera.[26,27]

3. Neisseria and Haemophilus:

- Higher in diabetics: Neisseria and Haemophilus are generally found in greater abundance in diabetic individuals.[27]
- our data reflect this, with Neisseria showing a wide range but often higher in diabetics (up to 16.9%) compared to non-diabetics (as low as 5%).

4. Fusobacterium and Pigmentiphaga:

- Fusobacterium shows moderate abundance in diabetics (21%), but is not highlighted as a distinguishing genus in most comparative studies.[27,28]
- Pigmentiphaga is less commonly reported in the literature and does not appear as a key differentiator between the groups.[28]

5. General Patterns:

- Diabetics: Increased abundance of genera associated with inflammation and dysbiosis (Streptococcus, Prevotella, Veillonella, Rothia).[28]
- Non-diabetics: Higher abundance of genera often linked to oral health and less inflammation (Neisseria, Haemophilus).[28]

Novel Tools for Detection of caries:

Recent advancements in pyrosequencing have enabled researchers to investigate the differences in microbial communities between caries-free and caries-active individuals by analysing plaque and saliva samples. The use of 454 sequencing technology has provided insight into the bacterial populations present in dentinal caries and revealed how microbial diversity is influenced by the pH within cavitated dentine lesions.[29,30] It was observed that pH significantly impacted the composition of approximately 42% of the bacteria associated with dentinal caries. Additionally, machine learning approaches specifically Random Forest (RF) analysis—were applied to distinguish bacterial species that are characteristic of dentinal caries environments with either acidic or neutral pH levels.[30]

Artificial intelligence, particularly through convolutional neural networks (CNNs), is revolutionizing dentistry by analysing microscopic images of dental biofilms to identify bacterial colonies and differentiate between acidogenic and non-cariogenic bacteria based on morphology.[30] The integration of AI with computer-aided diagnosis (CAD) systems is helping dentists achieve more consistent and objective caries detection and risk assessment, minimizing subjective differences between practitioners.[30]

Genomic Sequence of oral microbes and its role in caries progression:

In terms of dental caries, certain genes within cariogenic bacteria, particularly Streptococcus mutans, play a crucial role in carbohydrate metabolism and acid production:

- *Phosphoenolpyruvate-dependent sugar:* phosphotransferase systems (PTS): These genes encode sugar trans-

porters that facilitate the efficient uptake of glucose, fructose, sucrose, and other carbohydrates for rapid metabolism.[31]

- *Glycolytic pathway genes:* S. mutans relies heavily on glycolysis, converting sugars directly into acid, creating acidic pH that contributes to enamel demineralization.[32]
- *Glycosyltransferase genes (gtfB, gtfC, gtfD):* These enzymes transform sucrose into extracellular glucans, promoting the formation of dense biofilms that retain acid and support cariogenic activity.[33]
- *glg operon (glgA, glgB, glgC, glgD, glgP):* This operon regulates the synthesis and breakdown of intracellular polysaccharides (IPS), allowing the bacteria to store energy and continue acid production even in the absence of external sugar sources.[34]
- *Cxatabolite control protein A (ccpA):* This regulatory gene manages carbohydrate catabolite repression, ensuring a balanced expression of metabolic genes and coordinating the bacteria's energy needs with acid generation.[35,36]

Together, these genetic systems equip S. mutans and other cariogenic microbes with the metabolic adaptability needed to thrive in low-pH environments and actively contribute to the progression of dental caries.[37-42]

Conclusion

India is the second-largest nation with a high number of diabetic patients in the world. One in four people in the world with diabetes is from India, making our country the most affected in the world. Currently, the diagnosis for diabetes is only through a blood test, which is very invasive, painful, and takes time to acquire the results. Understanding the genome sequence of cariogenic microbes can make diagnosis simple and effective. This review highlights the most common oral microbes in diabetic individuals, methods to identify the oral microbes, and novel diagnostic aids for the detection of early dental caries and the possibility of using oral microbes as biodetectors for personalized monitoring and risk assessment of diabetes mellitus.

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