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Review Article: Oral Microbiota and it's Role in Dental Caries

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Abstract: The oral microbiomes, specifically, have a significant impact on an individual's health. The oral cavity contains over 500 bacterial species from multiple phyla, which can exist as either commensals or pathogens. Streptococcus mutans is recognized as a significant pathogen in the development of dental caries through biofilm formation. The objective of this review is to provide a comprehensive understanding of the role that S. mutans in the development of dental caries.

Introduction:

The term "microbiota" apply to the collection of valuable and/or harmful microorganisms that reside a certain host, hence it is associated with its composition and taxonomy. Conversely, the term "microbiome" refers to the complete set of genomic material of the microbiota, also known as the "metagenome". This phrase encompasses the physiology and metabolism of the microbiota[1]. A microbiota consists of a wide range of prokaryotic organisms, including bacteria and archaea, as well as fungi, protozoa, and viruses. The bacterial component of microbiota, known as "bacteriota/bacteriome," is the most extensively researched. However, it is often mistakenly used interchangeably with the terms "microbiota/microbiome" in a simplified manner[2].The human microbiome significantly influences an individual's state of health and overall well-being. Recently, much research has been conducted to study and classify the various microbial communities that inhabit the human body. Among all the locations, the human mouth contains one of the most varied microbiomes in the human body[3].

Oral Microbiomes:

The human oral microbiome comprises the bacteria found in the mouth and its surrounding structures, including the lower part of the esophagus. These structures offer separate microbial environments that encompass the teeth, gingiva, tongue, hard and soft palates, cheeks, and lips. Anatomical structures that are next to each other, such as the tonsils, pharynx, Eustachian tube, middle ear, trachea, lungs, nasal cavity, and sinuses, can serve as a habitat for different bacteria.

The oral cavity is extensively inhabited by microorganisms, making it one of the most strongly colonized areas of the body[4].The oral microbiota can be characterized as a diversified set of microorganisms[5]. The oral cavity possesses the second most intricate microbiota in the human body, following the gut[6].

The oral sites exhibited the lowest diversity in abundance and symmetry of species, as well as diversity when comparing microbiotas among individuals. This indicates that oral communities had a higher degree of similarity in terms of bacterial composition compared to communities in

other body sites. The utilization of DNA for the identification of oral bacteria has revealed that the oral microbiota is far more intricate and varied than once believed[7].

After birth, the microbiota undergoes a lengthy process of development, eventually forming a diverse and complex ecosystem as the individual ages. Various research investigations have established a connection between the structure and formation of the oral microbiome in children and their parents as well as other relatives[8].These organisms exhibit location specificity or host specificity and can be either temporary or persistent[9]. These organisms possess defensive properties against the infiltration of other disease-causing species, or are linked to both oral and systemic illnesses.

Over 500 distinct bacterial species are capable of residing in the mouth cavity, however certain ones cannot be cultivated because of their particular need for nutrients and sensitivity to oxygen[10]. Based on molecular investigations, these organisms are classified into numerous phyla: Bacteroidetes, Firmicutes, Tenericutes, Actinobacteria, Proteobacteria, Euryarchaeota, Chlamydiae, and Spirochaetes. Frequently encountered species include of streptococci, actinomycetes, veillonella, diphtheroids, and gramme negative anaerobic rod[9].

The oral cavity contains a variety of bacteria, including Gram-positive bacteria such as Lactobacillus, Actinomyces, Eubacterium, Corynebacterium, Staphylococcus, Peptostreptococcus, Streptococcus, and Enterococcus. Additionally, there are Gram-negative bacteria such as Aggregatibacter (formerly Actinobacillus), Prevotella, Wolinella, Leptotrichia, Prophyromonas, Eikenella, Haemophilus, Capnocytophaga, Bacteroides, Tannerella, Treponema, Fusobacterium, and Campylobacter. Additional potentially harmful bacteria found in the oral cavity include Streptococcus pneumoniae, Streptococcus pyogenes, Neisseria meningitidis, Haemophilus influenzae, and certain members of the Enterobacteriaceae family, as documented by Bowen and Koo[11].

The oral microbiomes of individuals exhibit a high amount of specificity at the species level. However, there are little geographical variations observed in the overall human oral microbiome[10].

Furthermore, oral microbiota diversity is significantly influenced by biological and cultural factors such as nutrition, mouth cleanliness, health status, genetics, and lifestyle[12]. Furthermore, the presence of tobacco, alcohol, catechol, and reactive oxygen species is a contributing factor to the diversity in the makeup of oral bacterial populations[13].

Factors that affect the stability of the microbiota [14]

1-Aging : The human microbiota has undergone evolutionary changes during an extensive period of microbe-human symbiotic interaction spanning hundreds of thousands of years. Several years ago, research demonstrated that the composition of microorganisms in the mouth changes over time as an individual ages. Colonization commences at birth with the initiation of dynamic microbial colonization of the oral cavity. The composition of the dominant phylum undergoes

changes throughout childhood and adolescence, and reaches a rather stable state during adulthood. However, the composition of the nasopharyngeal microbiota in young infants changes periodically according to the seasons.

Streptococcus mutans and Streptococcus sanguinis colonies the teeth upon their initial emergence. Certain species of Streptococcaceae exhibit strong adhesion to the gingival mucosa and cheeks, but not to the hard tissues. The composition of the gingival mucosa facilitates the growth of anaerobic organisms. The oral microbiota becomes more intricate as individuals age. During puberty, the process of colonization by Bacteroidetes and Spirochetes commences. Furthermore, the microbiota can be quantitatively altered by factors such as age and clinical states. For instance, the rise in the number of Streptococcus anginosus bacteria in saliva that occurs with age is likely regulated due to its established association with disorders like cancer.

2-Location : The composition of the human microbiome varies considerably depending on the specific anatomical site. The gastrointestinal (GI) tract contains a large number of microorganisms, although its microbial diversity at the phylum level is less extensive compared to that of the oral cavity. At least 15 different phyla have been found in the oral cavity, with the most common ones being Fusobacteria, Actinobacteria, Proteobacteria, Bacteroidetes, and Spirochaeta. The Streptococcus genus is the most prevalent in most sites, followed by Haemophilus spp. in the buccal mucosa, Actinomyces spp. in the supra gingival plaque, and Prevotella spp. in the subgingival plaque. The gastrointestinal (GI) tract microbiota is mostly made up of the Bacteroidetes and Firmicutes phyla, with additional components including Actinobacteria, Proteobacteria, and Verrucomicrobia.

3-Environment : The oral microbiome has the ability to influence the equilibrium of the mouth cavity. The interactions among the resident microorganisms are influenced by local environmental fluctuations and the nutrition of the host. The mouth cavity provides a highly conducive habitat for different bacteria due to the presence of nourishing flakes of epithelium and secretions. The commensal resident flora consists of planktonic bacteria, which are derived from many microorganisms, as well as the remnants of apoptotic eukaryotic cells. This flora colonizes hard and moist surfaces, hence inhibiting the colonization of external germs. The composition of microbiota is influenced by various factors such as temperature (ranging from 33 to 37°C), smoking, alcohol consumption, pH levels (which are neutral on the tongue and mucosal surfaces and alkaline in gingival crevices), redox potential (which is positive in the main oral sites and negative in gingival crevices), air pressure, and light exposure. The oral microbiota plays a crucial role in the host's immune system by keeping antibody levels in saliva low and aiding in the production of vitamins.

Oral microbiome and oral diseases : Dental caries, periodontal disease, tooth loss, and lip and oral malignancies are the most common oral disorders. These disorders are among the most common non-communicable illnesses worldwide. They impact health, society, and the economy in spite of be treatable. Early childhood, youth, adulthood, and adult age are influenced. The oral microbiota has the ability to generate metabolites within the mouth, which

can have an impact on the progression of oral illnesses[10]. While caries and periodontitis are really caused by bacteria, they do not fit the traditional definition of infectious diseases. This is because they arise from a multifaceted interplay between the commensal microbiota, the sensitivity of the host, and external variables like food and smoking.

Periodontitis is believed to occur due to an abnormal inflammatory response to the usual microorganisms in the body, which is worsened by the presence of certain bacteria linked with the condition. Functionally, there seems to be a lot of unnecessary repetition within the oral microbiota. To fully comprehend the interactions between the host and the microbiome, it may be necessary to priorities functional diversity rather than phylogenetic diversity[10].

Dental caries is the prevailing chronic infectious disease in the oral cavity. Bacteria are the primary causative agents, and symptoms encompass the erosion of dental hard tissues. It's the second most common reason people lose their teeth, and it can happen to anyone affecting all individuals regardless of age, gender, race, religion and geographic location[11].The prevalence of dental caries is in children are more likely than adults and this problem is strongly linked to the mouth microbiota and consuming sweets frequently before bedtime[12]. In contrast to healthy persons, the oral microbiota found on the surface of dental caries exhibits more complexity and lower diversity, potentially as a result of the acidic environment.

Dental plaque, a thin, persistent microbial film, accumulates on tooth surfaces. Microorganisms in dental plaque ferment carbohydrates, particularly sucrose, to produce acids that demineralize inorganic materials and deliver enzymes called proteolytic that disintegrate organic tooth substances, causing dental caries. Dental plaque traps acids formed on tooth surfaces, preventing saliva from washing them[13].

Bacteria like Streptococcus mutans, Streptococcus sobrinus, and Lactobacilli are more frequent in cavities[9]. As a while as, Prevotella spp., Dialister spp., and Filifactor spp. have been identified by advanced sequencing technologies as potential contributors to the development and advancement of dental caries. Although there is a strong link between Streptococcus mutans and cavities[14].

When individuals refrain from eating, bacteria acquire resources from our saliva and gingival reticular fluid, which contain abundant glycoproteins[15]. Bacteria metabolize these glycoproteins, breaking them down into constituent sugars and proteins. Bacteria can obtain energy for survival through the process of metabolizing carbohydrates and proteins. Metabolism involves the breakdown of carbohydrates and proteins by bacteria into tiny molecules that are either acidic or basic. When the host is not eating, these tiny molecules with acidic and basic properties counterbalance each other, resulting in a neutral state of the mouth. Nevertheless, upon consumption of sugar or starch, acid genic bacteria will dominate. The initiation of weak acid production will lead to the corrosion of the teeth.

Dental caries is the process of demineralization and degradation of the hard tissues of the teeth, including the enamel, dentin, and cementum. The occurrence of dental caries is mostly

determined by the duration of tooth surface exposure to acidic by-products produced during bacterial fermentation. A chalky white spot on the tooth, referred to as a micro cavity, is an initial indication of demineralization of the tooth enamel. An inactive caries is indicated by a lackluster brown spot, which ultimately results in the formation of cavities or voids on the teeth and inflammation of the gums.

The condition commonly presents with clinical symptoms such as pain and discomfort during mastication, impaired facial mobility, tooth sensitivity, jaw pain, tooth surface discoloration, facial inflammation, and mild pyrexia. Bad breath and unpleasant tastes can also be symptoms of dental caries. These oral infections can be either acute or persistent. During the acute stage of dental caries, the decay spreads horizontally, leading to a fast deterioration of the pulp tissues. The discomfort is severe, and the dentin has a pale yellowish hue. Chronic caries exhibits less horizontal expansion, and the progression of tooth pulp involvement occurs at a significantly slower rate. Hence, the cavity is superficial and does not involve any pulp tissue. Oral pain is typically not associated with this particular type of tooth decay.

Other forms of infection caused by plaque include inflammation of the gum tissue (gingivitis), gum recession (retraction of gum tissue), bleeding gums, and more severe periodontal diseases caused by the loss of gum tissue and underlying bone. If dental caries are not treated for a long time, there is a possibility of developing bacteremia, which can then increase the chances of getting an opportunistic heart valve endocarditis.

Moreover, it has been suggested that highly pathogenic strains of S. mutans may contribute to the exacerbation of ulcerative colitis. It is important not to exclude such possibilities without a precise pathological explanation.

Oral biofilms formation : Biofilms are complex assemblages of diverse microorganisms, enclosed inside a matrix of polymers that exist between the cells. These bacteria have the ability to attach to or settle on various surfaces, such as the tooth enamel, the lining of the mouth, and the saliva[16].

The colonization of oral surfaces is a deliberate process in which bacterial species are chosen based on their ability to adhere, leading to effective colonization when bacteria can thrive in the specific environment. The oral bacteria can access all the surfaces in the mouth, including teeth and various types of mucosa, due to the flow of saliva. However, the specific properties of different tissues decide which species of bacteria are capable of attaching to and establishing colonies on them. The adherence features mentioned in the text may be influenced by the coevolution of microbe-microbe interactions, such as syntrophic (where one species uses the metabolic products of another as a source of nutrition), aggregation (the attachment of different bacterial species to each other using specific molecules), antagonism (where certain bacteria inhibit the adherence or growth of other species), and communication (specifically, quorum sensing). These features also involve adaptation to the host, as discussed by [17] and [18].

Dental biofilms form through successive waves of colonization, with their variety progressively expanding over time. Initial colonizers adhere to a thin layer generated by the host's salivary glycoproteins on the surface of the tooth using their fimbriae[19]. Subsequently, they alter the habitat, facilitating the attachment and subsequent establishment of additional species[20].

Initially, there is a process of co aggregation between the genera Firmicutes and Actinobacteria, specifically including Streptococcus, Veillonella, and Actinomyces. Subsequently, Fusobacterium engage in interactions with the aforementioned first colonizers (Palmer, 2014). Colonizers play a beneficial role in preserving dental health by building a complex interdependency among its members and contributing to the preservation of biofilm resilience[20].

Failure to maintain oral hygiene can lead to the recognition of polysaccharide or protein receptors on the early colonizers by bacteria, resulting in their attachment. Consequently, a fully developed biofilm arises beneath the gum line, known as subgingival plaque, which is composed of around 5-25% bacterial cells and 75-95% matrix[19]. Initially, homeostasis is sustained through the prevalence of Firmicutes and Actinobacteria. Over time, harmful substances like endotoxin and lytic enzymes build up and enter the gingivae, causing irritation and inflammation. The host's immunological response causes an increase in the depth of the periodontal fissures and enhances the secretion and flow of gingival reticular fluid[21].

The serum ultra-filtrate contains a high concentration of protein and stimulates the proliferation of proteolytic bacteria, specifically Fusobacterium and Prevotella[21]. Prevotella dominates the transition from the first supra gingival plaque (which is aerobic and facultative) to the anaerobic environment of mature and subgingival plaque. In addition, Fusobacterium forms physical connections between the early colonizers and period onto pathogens[22].This is the initial phase in the development of an intricate and extremely varied community of microorganisms in the area beneath the gum line[23].

Consequently, the disruption of microbial balance leads to a condition known as symbiosis, which facilitates the growth of harmful pathogens and subsequently results in the occurrence of disease[24].The harmful alteration in the natural equilibrium of the microbiota is caused by the excessive proliferation of native pathogens within the existing microbiota, rather than being a result of external infection[25].

Streptococcus : The mouth cavity is initially colonized by Streptococcus bacteria, which are acquired shortly after birth. This early colonization is crucial for the development of the oral microbiota[26].There are more than 100 types of oral Streptococci bacteria that can inhabit the mouth and upper respiratory tract of humans. These bacteria colonies shortly after birth and are important for the development of the normal oral microflora. They are usually harmless and live in harmony with the human body, but can cause infections in other parts of the body or in the mouth, particularly in people with weakened immune systems or the elderly.

Although early efforts to characterize the oral microbiome depended on methods that involved growing microorganisms in a lab, the use of 16S rRNA sequencing has allowed for the identification of over 700 different microbial species that inhabit the mouth. Approximately 50% of these species are deemed non-cultural using existing techniques.

Pathogenic Streptococci are recognized as the cause of invasive infections in humans, which remain one of the most severe diseases in modern medicine[27]. Hence, there is growing recognition of the detrimental impact of the Streptococci genus on human health, as it is responsible for a substantial number of global human infections.

Classification: To better understand this genus, researchers have classified it into eight distinct groups: mitis, sanguinis, anginosus, salivalius, downei, mutans, pyogenic, and bovis. This classification was achieved through gene clustering, as well as phylogenetic and gene gain/loss analyses, as described by Richards[28]. The mitis and sanguinis groups, which consist of S. oralis, S. mitis, S. gordonii, and S. sanguinis, are the main organisms that initially settle on the tooth surface. They are typically regarded as commensals, although all of them have been associated with cases of infective endocarditis.

Identification : Streptococci, being Gram-positive bacteria, are of great significance in both industry and medicine due to their essential role. The typical microorganisms do not have the ability to move or make spores. Unlike the Staphylococci, they are primarily facultative anaerobes that do not possess the catalase enzyme. The growth of these organisms typically necessitates the use of intricate culture medium. These encompass a wide range of aerobic and anaerobic bacterial species. A significant number of bacteria exhibit fastidiousness in their dietary needs, making them challenging to cultivate and identify in a laboratory setting. Additionally, a considerable portion of these bacteria are obligate anaerobes.

Streptococci are categorized into three classes, namely alpha, beta, and gamma hemolytic, based on their ability to cause the breakdown of red blood cells. Beta-hemolytic Streptococci are responsible for the full destruction of blood cells. They have been categorized into 20 categories based on Lancefield grouping. Lancefield grouping is a classification system that categories serotypes based on the particular carbohydrates found in the cell wall. The alpha-hemolytic and beta-hemolytic Lancefield group A and group B Streptococci play significant roles in the pathogenesis of numerous disorders from a medical perspective[29].

Lannes-Costa et al., [30] found that although the genus Streptococci has both beneficial and important characteristics, specific species are responsible for various types of infections ranging from sub-acute to chronic, such as meningitis, pneumonia, pharyngitis, endocarditis, and dental caries. Specific cellular and extracellular factors are also implicated in the development of the disease.

Virulence factors: Streptococcus possesses various virulence factors that contribute to its ability to colonies different areas of the human body, evade the immune system, destroy host

tissues, and manipulate the host's immune response. These factors include surface proteins for adhesion and invasion, extracellular enzymatic proteases, and toxins that are delivered to both the cell surface and extracellular environments[31]. Several vaccine candidates are presently under consideration to safeguard against infectious illnesses caused by Streptococci. Oral microorganisms can enter the bloodstream not just through invasive treatments like dental extractions and oral surgery, but also through routine activities like chewing, brushing, and flossing.

Streptococci found in the mouth : Oral streptococci are categorised into four species groups: anginosus, mitis, salivarius, and mutans groups[32].Categorization Based on chemotensive and genotypic data, particularly the examination of DNA base pairing and the 16-RNA gene sequence.

The mutant group consists of S. mutans, S. sobrinus, S. downeii, S. rattus, S. macacaes, and S. cricetus[33].It is classified as part of the Streptococcus group Viridans, specifically including S.mutans, S.sanguis, S.salivarius, and S.mitis[34].

The Streptococcus mutans, S. rati, and S. sobrinus, are abundant on the surface of the teeth. S. salivarius is primarily found on the tongue and is one of the main producers of alkali in the mouth[35]. On the other hand, S. sanguinis is part of the natural oral microbiota found in humans. S. mitis has been regarded as innocuous, residing in the pharynx[36].Various studies on these species recognized as a leading colonizer in the development of dental plaque. Although, S.mutans is recognized as a significant pathogen in the development of dental caries, particularly in relation to the initiation of the disease[37].

Streptococcus mutans : Streptococcus mutans belongs to a group of mutans streptococci which includes S. sobrinus. The colony morphology of S. mutans appears uneven or jagged when cultivated on plates with mitis salivarius agar, which is a specialized medium designed to selectively promote the growth of mutans streptococci.

S. mutans is categorized into serotypes c, e, f, and k. Serotype c is the predominant type in the oral cavity, accounting for around 70-80% of cases, while serotype e makes up approximately 20%. Conversely, the occurrence rates of serotypes f and k in the oral cavity are rather little, with a prevalence of under 5% [38].

Pathogenicity: S. mutans is a frequently seen kind of oral streptococci that plays a crucial part in causing oral disorders, such as periodontal infections[39]. Bacteria that create biofilms have the potential to cause periodontitis, which is an inflammatory illness caused by infection in the gums, the bone surrounding the tooth, and the tissue beneath it[40]. Consequently, it is a prevalent public health issue affecting both children and adults[41].

The etiology of S. mutans pathogenesis include biofilm formation, alterations in several proteins, synthesis of extracellular polysaccharides, and acidgenesis, resulting in demineralization of tooth enamel and the development of caries[42]. As awhile as the abnormal physiological processes

that occur in the body, leading to the development of diseases or disorders. Oral streptococci, which are part of the oral microbial community, have the ability to produce biofilms[43].

Biofilm generation is the primary factor in the pathogenesis of S. mutans, resulting in the erosion of tooth enamel and the development of caries. The genes atpF, gtfB, gtfC, gtfD, gtf, LuxS, comAB, comCDE, and comX are involved in the regulation of biofilm formation[44]. S. mutans exhibits a strong correlation with dental caries.

The organism use sucrose as a substrate for the synthesis of polysaccharides, including dextran, a sophisticated extracellular polysaccharide, and glycoproteins. These polysaccharides facilitate the organism's ability to strongly adhere to dental enamel and other organisms. As a result, the accumulation of organisms occurs, which generate elevated levels of acid from the sugars in their diet. These acids induce demineralization and disintegration of enamel, resulting in tooth caries. These conditions result in the exposure of the dental pulp, leading to pulpitis, pulpal necrosis, periapical abscess, and acute alveolar abscess[45].

If S. mutans is present in the saliva of an infected person and is mixed with food or drinks, it has the potential to cause an oral infection. An elevated count of S. mutans in saliva, above 10^5 colony forming units, increases the likelihood of transmitting the pathogenic bacterium to an unaffected individual, particularly children.

Virulence factors: S. mutans utilize carbohydrates to facilitate adherence and the production of biofilms on tooth surfaces[46].Biofilm production is influenced by various parameters, including co aggregation adhesion and nutrient flow, which can impact gene expression and growth rate[47].

Streptococcus mutans as an agent of dental carries :S. mutans possesses specific characteristics that significantly contribute to the development of dental caries[48]. These traits include the ability of S. mutans to metabolize different carbohydrates and convert them into acidic byproducts, leading to a reduction in pH levels. Furthermore, S. mutans possesses the ability to synthesize and accumulate intracellular polysaccharides derived from diverse carbohydrates. These polysaccharides can subsequently be metabolized by the bacteria, leading to continual acid production. Streptococcus mutans have the capability to generate extracellular polysaccharides, specifically dextran, that contribute to the sticky and cohesive characteristics of dental plaque on the tooth surface. S.mutans have the capacity to utilize glycoproteins derived from saliva that are present on the surfaces of teeth.

The caries infection process initiates with the adherence of S. mutans to the tooth surface. This is due to the presence of the glucosyltransferase (Gtf) enzyme in S. mutans, which enables the breakdown of sucrose into significant amounts of glucans. Glucose is a hydrophilic adhesive solution that promotes the clustering of S. mutans and its adherence to the tooth enamel. Glucan binding protein (Gbp) enables the adherence of S. mutans to other bacteria, hence promoting the

formation of plaque. In addition, S. mutans produces organic acids by the breakdown of sucrose. S. mutans metabolizes sucrose to produce lactic acid.

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