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Review Article

Relevance of Oral Microbiome – A Narrative Review

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Abstract

Microbial community of the oral cavity is considered as complex, second only to the gut microbiome. Oral cavity is exposed to inhaled and ingested microbes that consist of more than 700 species of bacteria, fungi, viruses, archaea and protozoa. Oral microbiome composition differs with individuals and with the micro habitat. However, the principal function of the microbiome remains similar in every individual. The commensal microbiome maintains oral and systemic health with delicate balance. If the balance or equilibrium is altered, both oral and systemic diseases can be developed. This is an attempt to give a narrative review on the basics of oral microbiome.

Keywords: Oral Microbiome; Oral Microbiota; Oral Diseases; Systemic Diseases; Microbial Dysbiosis; Probiotics; Oral Care; Bio Film

Introduction

Antonie van Leeuwenhoek, a Dutch microscopist, wrote a letter to the Royal Society stating as follows: "I didn't clean my teeth for three days and then took the material that had lodged in small amounts on the gums above my front teeth… I found a few living animalcules". He made the observations on the plaque which was collected from the front teeth using a self designed single lens microscope. He could see different microorganisms and later drew them in a note book (1670) [1-3].

From that point of time, the microorganisms caught the attention of many thinking individuals. As the time progressed, these organisms were named differently. Oral microflora and oral microbiota were the synonyms popularly used. Lederberg and Mccray coined the presently popular term oral microbiome that signifies the ecological community of commensals - symbiotic and pathogenic microorganisms that share the human body space [4].

Oral microbiome consists of a huge community of microorganisms that include bacteria, fungi, viruses, archaea and protozoa [5]. Oral cavity provides a number of distinct habitats where the microorganisms get harboured viz. teeth, gingival sulcus, dorsum of the tongue, palate and nearby contiguous areas like tonsils, oesophagus, pharynx, eustachian tube, middle ear, trachea, lungs etc. The oral surfaces usually get coated with the widely discussed bacterial biofilm. Mouth has a favourable environment of temperature 37^0C and pH 6.5-7 which can nurture bacterial growth [6]. Gut associated microbiome is the most complex microbial community in the human body and the second one is the oral cavity. Oral cavity is constantly exposed to both inhaled and ingested microbes which amounts to nearly 700 species of which 54% were identified and cultivable, 14% not identified but cultivable and 32% not identified and cultivated [7].

The foetus in the womb is considered as sterile but recent observations have established the presence of oral microorganisms in the amniotic fluid of majority of the pregnant women. When the baby is delivered, maternal transmission of microorganisms happens at the uterus. Mouth of the baby is usually sterile but the baby gets inoculated from the first feeding and from the atmosphere. Eruption of teeth that happens subsequently, provide ecological niches with diverse characteristics and acquisition of microflora begins [8,9].

Under healthy conditions oral microbiome maintains a commensal relationship with its environment just like other body parts such as gut, skin or vagina. Certain opportunistic microorganisms belonging to the microbiome can turn into pathogens and can cause various oral and systemic diseases. Dental caries, periodontal diseases, endodontic disease, osteitis and tonsillitis thus caused can contribute towards disruptions in the balance of oral microbiota which is known as dysbiosis. By definition it is an imbalance in bacterial composition, changes in metabolic activities or changes in bacterial distribution within the microbiome. The effect of dysbiosis can be listed as follows: 1. loss of beneficial bacteria, 2. overgrowth of pathogenic bacteria and 3. Loss of bacterial diversity. Dysbiosis can extend its effect in initiating and worsening various systemic conditions viz. metabolic, cardio vascular, oral mucosal and respiratory diseases. Pre term childbirth, obesity, colon cancer and psychiatric diseases are also included in the list of systemic diseases [10-12].

Evolution of oral microbiome

Oral microbial residents have not colonised in a random fashion but in fact they have co-evolved with humans for millions of years. The relationship between the microbiome and the host is influenced by the life style factors such as diet, tobacco, stress etc. Change in the environment that has happened during human evolution has influenced the microbiome composition. To be specific, use of fire, beginning of agriculture, processing of food, use of refined sugar and antimicrobial therapy are factors that have changed the composition of microbiome in due course of time. Oral hygiene practice that has become popular towards the last decade of 19^{th} century, adequately supported by the findings of Miller as well as the modern life style of consuming acidic drinks, alcohol consumption and cigarette smoking are all factors that changed the oral eco system [13,14]. Increased intake of dietary carbohydrate favoured streptococcus mutans and it eventually promoted dental caries. Consumption of processed food which was considered as a sign of sophistication, enormously increased and finally ended up with dysbiosis and oral diseases.

Saliva and oral microbiome

Conventional functions of saliva which are popularly recognised, are mastication and swallowing. Saliva and gingival crevicular fluid provide nutrients for microbial growth and contains components with antimicrobial functions. Maintenance of the ecological

equilibrium of the resident microbiota is controlled by vital enzymes and proteins contained in the saliva. The protein content regulates the oral microbiome through promoting colonisation of the commensal bacteria and eliminates pathogenic bacteria. Saliva can harbour one hundred million of microorganisms per millilitre and these are derived from the oral mucosal surfaces. In individuals who are suffering from pulmonary diseases, periodontitis, arthritis, cardio vascular diseases and diabetes can alter general composition of microbiota. Viral infections like herpes, influenza and SARS-CoV can also alter the oral microbiome. Candida and inflammation due to oral lichen planus can also alter the composition of oral microbiome. Saliva has a major role in the formation of salivary pellicle and through that microorganisms get colonised. Saliva has a different role of antimicrobial activity manifested through the proteins and peptides which are contained in its composition. Saliva buffers oral pH and prevents growth of acid loving pathogens. Oral health is dependent on the maintenance of oral microbiome and symbiosis. Salivary gland hypofunction, low salivary pH and altered salivary composition disturbs the composition of the oral microbiome and eventually leads to dysbiosis and associated oral diseases [15-18].

Composition of the oral microbiome

There are many species of microorganisms in the oral cavity which include more than 700 different bacteria, fungi, archaea, viruses and protozoa [19,20]. Oral bacterial species mainly include the *phyla Actinobacteria*, *Bacteroidetes*, *Chlamydia*, *Euryarchaeota*, *Fusobacteria*, *Firmicutes*, *Proteobacteria*, *Spirochaetes*, and *Tenericutes* [21]. These make up over 90% of the detected microbes. Approximately hundred species of fungi exist in the oral cavity belonging to genera *Aspergillus*, *Aureobasidium*, *Candida*, *Cladosporium*, *Cryptococcus*, *Fusarium*, *Gibberella*, *Penicillium*, *Rhodotorula*, and *Schizophyllum*, as well as the order *Saccharomycetales* [22]. In addition to the above, Archaea, viruses and protozoa are also present in the oral cavity but in lesser abundance. Archaea are single celled microbes, primarily methanogens that produce methane. Archaea contribute to oral infections viz. periodontitis, dental caries, inflammation of pulp and peri-implantitis. Their presence is proved in biofilms and are related to various gastrointestinal disorders. According to some authors, archaea are non-pathogenic. Elaborate research is required to understand and throw more light on the archaea fully well [23,24].

Oral virome consists of eukaryotic viruses and bacteriophages that target specific bacterial species. Common eukaryotic viruses in the oral cavity of healthy adults include Herpesviridae, Papillomaviridae, Anelloviridae, and Redondoviridae. Anelloviridae are the most common, and the newly discovered Redondoviridae as the second most common. Even though viruses are the dominant infectious agents, the research profile on them so far obtained is very limited. Some researchers have attributed a commensal status for the viruses [25,26].

Protozoa, primarily *Entamoeba gingivalis* and *Trichomonas tenax*, are common residents of the oral microbiome, often found in dental plaque, saliva, and periodontal pockets, in conditions of poor oral hygiene. These single-celled eukaryotes may be considered as commensals but have strong links to periodontal diseases. They can cause degradation of tissues, shelter harmful bacteria, and potentially influence systemic health, though their exact role is still researched. They spread through salivary contact, sharing items, or kissing and are often found alongside major periodontal pathogens like *Porphyromonas gingivalis*. Studies have found that there is a correlation between increase in protozoa and progression of periodontal disease. This area warrants further research to get more evidence. Other than periodontal disease, Protozoans are related to oral cancers and cardiovascular diseases [27].

Factors influencing the oral microbiome

Diet

Diet is the essential source of nutrients which are required for survival, growth and energy. Nutrients are divided into two viz. macro nutrients and micronutrients. Macronutrients consist of carbohydrates, proteins, fats and water. Carbohydrates are the primary energy sources found in grains, fruits and vegetables. Proteins are essential for building and repairing of tissues and which are present in meat, eggs, beans and nuts. Fats provide concentrated energy, protect organs and absorb certain vitamins. Water is considered as a macronutrient because it is required in large quantity for hydration and metabolic process. Micronutrients are required in small quantities but critical for body functions. Vitamins and minerals are included in this category of nutrients.

Dietary macronutrients and diet types can influence the oral microbiome. Sugars and starches favour the growth of acid producing bacteria like Streptococcus mutans which are mainly

responsible for generating dental caries. Some specialised bacteria help in breaking down glycoproteins and sugars which help in the utilisation of nutrition. Nitrate rich diet can promote proliferation of nitrate reducing bacteria and which cause production of nitric oxide. Nitric oxide acts as a vasodilator and can control the blood pressure. Anti-oxidants and anti-inflammatory compounds contained in fruits and vegetables can modulate the immune response in the oral cavity and balance between different bacterial species are maintained through that. This may be used in the control of periodontal disease [28-30].

Smoking and oral microbiome

Smoking can disrupt the oral microbiome by reducing the beneficial bacteria and increasing the pathogens. As a result, the risk of oral diseases ranging from periodontal diseases to oral cancer increases. Smoking creates anaerobic conditions, compromised immune responses, altered salivary pH and the toxic effects of cigarette smoke exert an antibacterial effect. Nicotine contained in tobacco increases the virulence of microorganisms through the stimulation of the concerned genes. Biofilm formation is also increased along with this. The possibility of an increase in oral diseases do happen with smoking habit. Smoking causes oxygen level decrease and which is favourable for anaerobic bacteria. Increase in free iron levels and inhibition of oral peroxide activity further enhances anaerobic bacterial growth. Smoking can cause a decrease in proteobacteria and increase in firmicutes and actinobacteria. In fact, smoking can drastically cause a shift in the composition of oral microbiome. The mouth becomes more susceptible to infections and can cause functional changes linked to general health issues. Smoking increases the risk of mortality and quitting smoking can restore oral and general health [31-33].

Alcohol and oral microbiome

All over the world, every year, three million people die because of alcohol related reasons. This number amounts to more than 5% of global deaths. There are gender differences in both alcohol consumption and alcohol related mortality and morbidity. While 52% of men consume alcohol, only 35% of women are in the habit of drinking. The per capita consumption of alcohol is 8.2 litres for men and 2.2 litres for women (per year) [34].

India faces unique challenges of illicit liquor and rising teenage binge drinking both leading to significant mortality rate. In the state of Kerala, 135 road accidents and 11 deaths happen every day. In India 2.6 to 5 lakhs deaths happen due to cardio vascular diseases, liver cirrhosis, various forms of cancer and alcohol related road accidents. Alcohol and its metabolic byproduct acetaldehyde are toxic to human cells. Alcohol and tobacco have a synergistic effect on the risk of oral cancer [35].

Alcohol alters the oral environment quite conducive to the proliferation of pathogenic microorganisms. Also, it disrupts the structure of oral microbiome causing periodontitis which by itself can alter the oral microbial flora. Alcohol induced gut dysbiosis has a cascading effect on oral dysbiosis. Zhao., *et al*. have observed that chronic alcohol consumption disrupts the gut microbiota composition. Reduction in beneficial commensals like Bacteroidetes and Firmicutes and increase in gram negative proteobacteria and gram positive actinobacteria do happen. This eventually leads to liver disease, cardio vascular diseases and other systemic conditions [36]. Alcohol consumption causes changes in oral microbiota like increased presence of Neisseria, streptococcus and Prevotella. Assessment of these microorganisms serve as an indicator of alcohol induced liver damage [36].

Poor oral hygiene, dental plaque, antibiotic resistant microorganisms

Poor oral hygiene causes accumulation of dental plaque and proliferation of pathogenic bacteria. This will result in an imbalance in the oral microbiome. Systemic diseases and autoimmune disorders can alter the pH and which favour overgrowth of pathogens and along with that the host defences weaken. Indiscriminate use of antibiotics can disrupt the balance with the beneficial oral microorganisms. Changes that happen with the helpful microorganisms may lead to overgrowth of candida. In the oral microbiome, antibiotic resistant genes get transferred through horizontal gene transfer contributing to the problem of antibiotic resistance [38].

Oral microbiome and oral diseases

Dental caries

Caries is associated with dysbiosis of the microbiota contained in the dental plaque and which belong to three classes viz. biofilm forming, acid producing and acid tolerant. S. mutans has all the three traits and are frequently isolated from carious lesions. Hence it was considered as the primary aetiologic agent that causes dental caries. S. mutans has an ability to produce extra cellular glucans from sucrose and considered as the driver for biofilm

formation and dysbiosis. The role of S. mutans in caries has been questioned by some research workers. Their argument was that it was not present in some of the lesions of caries. However, when it is present along with carious lesions, there is an undeniably strong correlation [39,40].

A recent discovery is that nitrate reducing bacteria viz. *Rothia Neisseria* and Haemophilus are closely related to good dental health. Nitrate acts as an anticaries prebiotic by feeding beneficial oral bacteria, which convert nitrate into nitrite, then to nitric oxide, thereby raising salivary pH (neutralizing acid) and using decay-causing lactate as fuel. This process prevents tooth decay. Nitrate-reducing bacteria (like *Rothia*, *Neisseria*) are the probiotics that perform the nitrite conversion, making them ideal for oral care products to promote a healthy mouth microbiome, reduce harmful bacteria, and fight cavities. This may lead to newer preventive methods for dental caries surpassing fluorides and oral hygiene methods [41,42].

Periodontal disease

The supporting tissues of the teeth are highly vascularised and the constantly flowing gingival crevicular fluid contains neutrophils and other immune cell types. These cells maintain a balance between the subgingival microorganisms and adaptive responses of the host. Changes in the microbiome or the host lead to inflammation viz. gingivitis and periodontitis. Gingivitis is a reversible state where as periodontitis leads to irreversible bone resorption [43].

Recent analyses have revealed that bacteria other than *Porphyromonas*, *Treponema* and *Tannerella* species, *Filifactor alocis*, *Peptoanaerobacter stomatis* and *Saccharibactere* are also potential periodontal pathogens. Recent microbiome studies have revealed an association between periodontitis and virome. The community of viruses in the mouth is significantly altered in periodontitis with viruses like Redontoviruses and anello viruses like TTV. Viruses are key players in periodontal infections possibly demanding new therapeutic strategies. Hypertension which very often coexists with periodontitis indicates the virome's role and require further research to obtain more information. But the primary focus still remains on both supra and subgingival biofilms. The concern still remains on the 500 species of microorganisms present in the biofilms [44-46].

Oral cancers

Epidemiological studies have established many well-defined risk factors related to cancers like age, heredity, diet, use of tobacco, chronic viral infections and inflammation. Bacterial infection and its contribution to cancer did not receive wide recognition in the earlier days. In the 1980s Marshall and Warren found a relationship between Helicobacter pylori and gastric cancer. They could not convince the scientific community fully well because majority of them believed that life style caused the ulcers. In 1994, H.Pylori became the first bacterial species, officially recognised by WHO, as a definite cause of cancer in humans. There is a carcinogenic link between oral bacteria and oral squamous cell carcinoma (OSCC). It was established that surfaces of OSCC harbour higher levels of Porphyromonas and Fusobacterium when compared to contiguous healthy mucosa [47].

Many viruses promote cancer through genetic mechanisms. 10-15% of cancers that affect human beings are caused by seven viruses that include Epstein bar virus, Hepatitis B virus, Human T lymphotropic virus-I, Human papilloma virus, Hepatitis C virus, Kaposi sarcoma herpes virus and Merkel cell polyoma virus [48]. Correlation has been established between periodontitis and numerous forms of cancers viz. leukaemia, cancers of digestive tract, pancreas, prostate, lung and breast. There is a clear positive correlation between periodontal disease and oral cancer [49].

To explain the link between oral microbiome dysbiosis and oral cancer, several biological mechanisms have been proposed. Chronic inflammation is a central pathway that leads to continuous activation of host immune responses, production of pro-inflammatory cytokines, and generation of reactive oxygen and nitrogen species. These mediators can induce DNA damage, promote genomic instability and enhance epithelial cell proliferation and finally facilitating malignant transformation. Additionally, certain oral bacteria can directly interfere with cell signalling pathways, inhibiting apoptosis and promoting tumour cell survival and invasion. Microbial metabolism also plays a crucial role in carcinogenesis. Oral microorganisms are capable of converting ethanol to acetaldehyde, which is a recognized carcinogen and proves the ill effects of alcohol consumption. Other microbial by-products, such as volatile sulphur compounds and nitrosamines, may exert genotoxic effects on oral epithelial cells. Furthermore,

some bacteria have been shown to modulate epithelial barrier function, facilitating deeper microbial penetration and sustained inflammatory responses within the tumour microenvironment [50].

The relationship between the oral microbiome and oral cancer involves complex interactions between microbial communities, host immunity and environmental risk factors such as tobacco and alcohol use. Dysbiosis of the oral microbiome is strongly associated with oral carcinogenesis but further studies are required to establish undeniable links.

Oral microbiome and systemic diseases

Oral microbiome which consists of a complex community of microbes can significantly affect the systemic health. Dysbiosis (imbalance) of the microbiome is proved to be linked to cardio vascular issues, gastro intestinal disorders, diabetes, Alzheimer's disease, autoimmune diseases like rheumatoid arthritis, cancers and respiratory infections. There are different methods through which bacteria get translocated. Pathogenic oral bacteria like Porphyromonas gingivalis enter the blood stream from inflamed gingiva and can affect distant targets like heart, brain and joints. Oral infections can trigger systemic inflammation leading to inflammatory bowel disease and rheumatoid arthritis. Oral microbiota reaches the gut very easily and disrupts the microorganisms in the gut, eventually leading to inflammation and colorectal cancer. Oral bacteria and their byproducts can modulate the immune system and provoke systemic immune responses. This highlights the importance of oral care in providing overall wellbeing. Systemic diseases and the related microorganisms of the oral microbiome are given below: [52].

- Gastro intestinal disorder – *P. gingivalis, F. nucleatum*
- Cardiovascular diseases (Atherosclerosis) – *P. gingivalis, T. denticola*, *T. forsythia*, *Prevotella intermedia*, *Prevotella nigrescens*
- Diabetes mellites – *Capnocytophaga*, *P. gingivalis*, *T. forsythia*
- Obesity – Proteobacteria, Chloroflexi, Firmicutes
- Alzheimer's disease – *P. gingivalis*, *T. forsythia*, *T. denticola*
- Parkinson's disease – *P. gingivalis*
- Rheumatoid arthritis – *P. gingivalis*

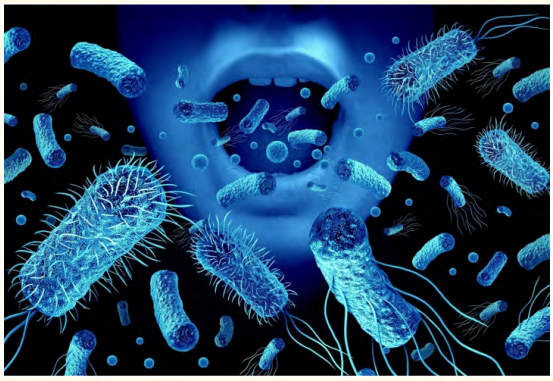

Figure 1: Oral microbiome. https://www.news-medical.net/news/20240724/Oral-gut-axis-How-mouth-bacteria-impact-your-overall-health.aspx

Conclusions

Human oral cavity harbours a diverse microbial ecosystem presently referred to as 'Oral microbiome'. It consists of bacteria, fungi, viruses, archaea and protozoa. This microbial community maintains oral health and contributes significantly towards oral as well as systemic diseases. Oral microbiome is dominated by bacteria which amounts to more than 700 identified species. There are distinct oral sites viz. dorsum of tongue, supra and sub gingival plaque, saliva and oral mucosa which serve as ecological niches for specific microbial communities. Oral microorganisms exist predominantly in biofilms popularly known as plaque.

The composition and stability of the microbiome is modulated by different factors like the age and immune status of the host, diet, habits like smoking and alcohol consumption, systemic conditions like diabetes and oral hygiene practices. Use of antibiotics can cause dysbiosis by the suppression of beneficial commensals and promotion of opportunistic pathogens.

Dysbiosis characterised by an imbalance in the oral microbiome can cause diseases like dental caries (predominant microorganisms – *Streptococcus mutans*, *Lactobacillus*), periodontal diseases (*porphyromonas gingivalis*, *treponema denticola*), peri implantitis (microbiome shift similar to periodontitis), oral candidiasis (candida albicans) and halitosis (*P. gingivalis, P. oralis, treponema denticola, fusobacterium*). There is definite evidence for association of oral microbiome and systemic diseases like cardio vascular diseases, diabetes mellitus, diseases of GI tract, rheumatoid arthritis and Alzheimer's disease.

Traditional culture methods can identify only a fraction of the oral microbiome. Modern methods like 16S rRNA gene sequencing has expanded our understanding of the oral microbiome. In future, personalised assessment of the microbiota and the host response will be done to identify subjects at high risk. This may lead to a shift from conventional practice of treating oral diseases through elimination of microbiota to a proactive management of oral health where the host and the microbiome will be considered as a single ecologic system.

Definitions of some key terms used in this review*.

Term	Definition
16S ribosomal RNA (16S rRNA)	An RNA molecule (approximately 1500 nucleotides long) that is part of the small subunit of the ribosome in prokaryotes. 16S rRNA has both highly conserved regions, common to all prokaryotes, and hypervariable regions that are unique to particular species
Biofilm	A sessile community of microbes characterized by cells that are attached to a surface or to each other and embedded in a matrix of extracellular polymeric substances20
Dysbiosis	A condition in which the normal microbiome population structure is disturbed, often through external burdens such as disease states or medications
Gene sequencing	A laboratory method to determine the precise order of nucleotides within a DNA molecule, enabling scientists to decipher genetic information that is carried in a particular DNA segment (for example, the 16S rRNA gene)
Holobiont	The host organism and all its symbiotic microbial residents1
Microbiome	The sum of microbes, their genetic information, and the environment in which they interact
Microbiota	All living microbial organisms constituting the microbiome
Next-generation sequencing (NGS)	An umbrella term to describe a number of different modern high throughput sequencing technologies
Phenotype Probiotics	The observable physical characteristics of an organism, for example, appearance, behaviour or clinical presentation Probiotics are live microorganisms, like beneficial bacteria and yeasts, that provide health benefits when consumed in adequate amounts, primarily by supporting a healthy gut microbiome, improving digestion, and bolstering the immune system. Found in fermented foods (yogurt, kimchi, kefir) and supplements, they work by balancing the good microbes in your body,
Species	Coherent and distinct groups of bacteria that have been isolated, cultured and named
Symbiosis	Two or more species living closely together in a long-term relationship

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Conflict of Interest

The authors declare that they do not have any conflict of interest.

Author Contributions

All the authors have contributed equally towards the preparation of this review.

All the authors have read and agreed to the published version of the manuscript.

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