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ABSTRACT
Microbes continue to live on and within human beings. Intestinal microbial imbalance has a close relationship with human health and disease. This review article targets on the communication between human microbiome and host in order to provide an overview of the microbial role in biological processes and in major human diseases such as infectious diseases, liver diseases, gastrointestinal cancers, metabolic diseases, respiratory diseases, mental or psychological diseases, and autoimmune diseases. Hence research is necessary for understanding the role of microbiome in health and disease which pave the way for treatment approaches in clinical practice.

KEY WORDS: Microbial flora, Health, Systemic diseases

1. INTRODUCTION

Microbiome is a complex of various species of microorganisms such as Streptococcus, Neisseria, Veillonella, Actinomyces and other obligate anaerobes.[1] The oral microbiome plays a crucial role to health resulting in oral and systemic disease. It is situated within biofilms in the oral cavity, creating an ecosystem which maintains health. All human body consist of characteristic microbiome which is mandatory in maintaining homeostasis. These bacteria have a basic character of synthesizing vitamins like B and K, helping in digestion, and inhibiting bacterial colonization, but can likely to induce disease in case of imbalance with a shift in the equilibrium state granting pathogens to manifest and cause disease. Oral microflorae can create dental plaques and also causes dental caries and periodontal disease.[2] A vital equilibrium persist between dental plaque bacteria and innate host defence system. The human microbiome is classified into core microbiome and variable microbiome. The core microbiome is present in all individuals and is composed of predominant species which are under healthy conditions at various body parts.[3]

2. MICROBIAL FLORA IN HEALTHY CONDITION

In oral cavity, teeth, gingival sulcus, tongue, cheeks, hard and soft palates, and tonsils provides a supportive environment for microbial survival. It accommodates huge species of bacteria which donate to the health and physiological status of the oral cavity namely the resident flora, supplemental flora and transient flora. The residential flora comprises of organisms which are usually present in a specific area at

a particular age. Supplemental flora consists of species that are constantly present but in low numbers (< 1%). Transient flora has both nonpathogens and pathogens that populate skin or mucous membrane for a certain period of time. Intraorally there are two types of surfaces where bacteria can colonize; the hard surfaces of teeth and the soft tissue of the oral mucosa.[4] Microbiome commonly present in different sites in oral cavity. They are:

- Gingival crevices: spirochetes, vibrios and S. melaninogenicus (optimal redox potential and anoxygenic environment helps in growth of these microorganisms).11
- Dorsal tongue and in saliva: Streptococcus salivarius
- Buccal mucosa: Streptococcus mitis
- Teeth: Streptococcus sanguinis

Saliva maintains the microbial ecology since it is an important nutritional source for microorganisms and contains proteins and glycoproteins. Saliva prevents microbial communities with immunoglobulins and lactoferrins hence growth of pathogenic microorganisms is inhibited. [5]The human microbiota attacks host physiology to a great extent. Trillions of microbes such as bacteria, archaea, viruses, and eukaryotic microbes colonize the human body. Microbiotic composition and function varies depending on different sites, age, gender, races, and diet of the host. Host-bacterial relationship have developed into a beneficial one. Symbiotic bacteria metabolize indigestible compounds, provide essential nutrients, protect against colonization by opportunistic pathogens, and donate to the formation of intestinal architecture[6]. For instance, the intestinal microbiota plays an important role in the digestion of certain foods which are indigestible by stomach and small intestine and maintains energy homeostasis. These foods are dietary fibres such as xyloglucans, which are seen in vegetables and can be digested by a specific species of bacteroides. [7]. However, not all microbiota lead to health benefits but some induce inflammation under certain conditions.

3. MICROBIAL FLORA IN DISEASED CONDITION

Bacteria causing oral diseases: Porphyomonas gingivalis (periodontal diseases) and Streptococcus mutans (dental caries). Caries and periodontal diseases are caused due to poor oral hygiene and high sugar based diet where constant recolonization by pathogenic bacteria occur[8]. Kigure et al have stated that high concentration of P. gingivalis and Treponema denticola in the periodontal pockets of adults causes periodontitis.[9]

PATHOPHYSIOLOGY

Bacterial adhesion to the tooth surface develops increased populations of microorganisms in the oral cavity. Apart from bacteria, proteins and glycoproteins from the saliva, also adhere to the tooth surface (referred to as conditioning film)

Chemistry of the tooth surface is altered thus encouraging adhesion of other microbial species.

Biofilm thickens and gradients develop within the biofilm.

These environmental changes develop different types of bacteria (such as primary colonizers include Streptococcus, Actinomyces, Neisseria and Veillonella and secondary colonizers include Fusobacterium nucleatum, Prevotella intermedia and Capnocytophaga species) in different regions of the biofilm.

Periodontitis: Causative organisms shows hemolysis and thereby affecting the attachment of gums with the teeth.[9]

Dental caries: Sucrose helps S. mutans colonize. S. mutans break sucrose down to glucans where it builds a biofilm which is different from normal biofilms. This biofilm increases porosity and permit acids to diffuse into the enamel causing pH drop which leads to dental caries.[8]

Oral cancer: Third disease which receives a substantial attention. It is the sixth most prevalent cancer where 300,000 people are affected every year[10]. Most patients with oral cancer have poor oral hygiene. Several studies states that poor oral hygiene and tooth loss increases the risk of gastric, pancreatic and other cancers.

Oral cavity and microflora

Oral flora plays a major role in dental infections. This is partly in response to food intake and also by oral hygiene measures (brushing and flossing). Dental plaque usually accumulates in hard surfaces of teeth and gingival crevices. Microbial flora is a complex structure containing microbes, microbial products, food particles, host secretions and host cells.

4. MICROBIAL FLORA AND SYSTEMIC DISEASES

Oral cavity is the main access to the human body where microorganisms has the capacity to spread to different body parts.[11]Pathogens in the oral cavity can be identified in blood cultures since they destroy and pass through oral mucous membranes and periodontal pockets. Pathogens in the blood stream modifies proper immune responses or provide deregulated amounts of inflammatory mediators causing disease at different body sites. Persistent inflammation and bacterial attacks causes severe systemic diseases (diabetes and cardiovascular disease).[12,13] This correlation supports the importance of oral microbiome to overall health.

Microbial Flora and Liver Diseases:

GIT and Liver

Correlation between GI tract (GIT) and liver as well as persistent exposure of liver to gut-derived factors involving bacteria and bacterial components thus promoting the use of the term “gut-liver axis”. The intestinal microbiome provides ethanol, ammonia, and acetaldehyde; these products control liver function through endotoxin release or liver metabolism. Modified intestinal microbiota plays a major role in inducing and progressing liver damage as well as in direct injury derived from different causal agents (viral, toxic and metabolic agents) [14] through mechanisms (activation of Kupffer cells by bacterial endotoxins). Gut microbiota promotes the pathogenesis of liver cirrhosis complications, such as infections, spontaneous bacterial peritonitis, hepatic encephalopathy, and renal failure.

Acute-on-chronic liver failure (ACLF) syndrome

- Characterized by acute decompensation of cirrhosis, with 28-d mortality.
- Based on the final clinical outcome at 90 d, it was identified as gut dysbiosis in ACLF patients.
- Correlations between specific bacterial families and inflammatory cytokines in ACLF patients was observed.[15]

Microbial Flora in GIT Disorders:

Gastric cancer

- Risk factor: H.pylori associated chronic inflammation (loss of acid-producing parietal cells develops gastric atrophy, metaplasia, dysplasia, and carcinoma) .
- Eliminating H. pylori before onset of chronic atrophic gastritis protects gastric cancer.
- H. pylori determinants such as cytotoxin related antigen A and vacuolating cytotoxin increases the risk of cancer [16].

Colorectal cancer

- Recent researches explain the relation between gut microbiome and colon cancer.
- Etiology: Microbial dysbiosis.

- Comparatively, pathological imbalance has been observed in microbial community in adenomas than controls.
- Fusobacterium nucleatum, a periodontal pathogen, helps in progression from adenomas to cancer. Bacteroides massiliensis, Bacteroides ovatus, Bacteroides vulgatus, and Escherichia coli (E. coli) also involve in progressing advanced adenomas to cancer.
- Mechanism: promotion of inflammation and the induction of tumorigenesis.
- Associated Microbiota: Pseudomonas, Helicobacter, Acinetobacter and butyrate-producing bacteria [17].
- Management: Butyrate which is produced by species Lachnospiraceae and Ruminococcaceae is protective against colonic neoplasia. High fiber intake reduces the risk of developing colon malignancy because of the production of butyrate. Because butyrate produces a tumour-suppressing effect by stimulating apoptosis, inhibiting proliferation, causing epigenetic changes in gene expression, and modulating inflammatory responses and cytokine levels[18].
- Dietary control or antibiotic treatment controls gut microbiome.

Oesophageal cancer

- Recent studies had stated that chronic inflammation in oesophagus caused by gastroesophageal reflux is closely associated to oesophageal adenocarcinoma.
- Regional variance in its incidence appears to be correlated with economic development. Hence, researchers have proposed that morbidity might be related to the use of antibiotics worldwide [19].

Microbial flora and metabolic disorders

- Gut microbiome is influenced by the use of antibiotics and lifestyle of the human host, involving exercise, diet, and hygiene measures.
- Obesity and its related metabolic complications including type 2 diabetes (T2D) and cardiovascular disease have become a common health problem worldwide and are considered to be the complications of a complex multidirectional communication among host genetics, diet, environment and gut microbiota[20].

Obesity

- Communication among gut microbiota and host genotype or dietary changes plays a crucial role in contributing obesity and related metabolic disorders.
- Several studies have indicated that diet alters the composition and function of microbes in humans.
- Phenotypic differences in the dietary groups contribute differences in microbiota composition. Evidence has been shown that gut microbiota is important in interaction between diet and the development of metabolic diseases [21].

Type 2 Diabetes

- It is a prevalent global metabolic disorder. Studies indicate that a modified gut microbiome characterized by lower diversity and resilience is correlated with diabetes.
- Mechanism: May be associated with microbiota translocation from the gut to the tissues, thus resulting inflammation.
- Pedersen et al. [22] proposed that human gut microbiome influence serum metabolome and promote insulin resistance through certain species such as Prevotella copri and Bacteroides vulgates.
- The gut microbiota directly affects Type2Diabetes by its effect on amino acid metabolism. Hence recent antidiabetic treatment strategies target bacterial strains which leads to imbalance in amino acid metabolism.
- Management: Metformin (oral hypoglycaemics) is widely used as an antidiabetic drug[23].

Microbiota and other diseases

Modified human microbiota are involved in the pathogenesis of other diseases, such as severe asthma, food allergies and autism. The complex microbiota-host interactions are dynamic which involves several mechanisms such as immune, hormonal, and neural pathways. Hence microbial changes result in dysregulation of host homeostasis and it also increases susceptibility to these diseases.

Allergic diseases

- Antibiotic-driven low diversity in gut microbiota intensify susceptibility to allergic asthma.
- Mode, place of delivery and infant feeding also alters GI microbiota composition which subsequently increases the risk of atopic manifestations.
- Bunyavanich et al. [24]discovered that infants with gut microbiota enriched in Clostridia and Firmicutes at a host age of 3–6 months are correlated to the resolution of cow's milk allergy (CMA) by 8 years.

Psychiatric diseases

- It is a severe threat to human health. It happens due to combination of biological, psychological, and environmental factors.
- Gut-brain axis maintains normal brain and GI function. This axis involves a number of systems such as endocrine system, neural system, metabolic system, and immune system.
- Studies proposes the gut microbiota's role in autism as a part of the gut-brain axis
- Autism spectrum disorder (ASD) is associated with a modified gut microbiota and low relative abundances of the mucolytic bacteria Akkermansia muciniphila and Bifidobacterium spp. Are identified in the faeces of children with autism [25].

5. TREATMENT

Antibiotics

In future, use of antibiotics need genomic analysis of oral microbiome to identify microbes and to find whether they will respond to specific treatments.

Probiotics and Prebiotics

They strengthen the beneficial microflora hence body can fight against causative agents. Therapeutic antibiotics and probiotics are limited because of unawareness of oral microbiome.

Vaccination

Dental caries: Proteins in colonization of teeth by Streptococcus mutans produces antibodies for arresting cariogenic process.

Periodontal vaccines: Currently not available but some antigenic targets have been found.[26]

6. CONCLUSION

Microbial flora maintains both oral and systemic homeostasis in the body. Salivary flow and biofilms on hard and soft tissue maintain microbial equilibrium in the oral cavity and protects pathogenic microbes from manifesting. Alteration in oral homeostasis causes pathogenic event leading to oral disease. Oral disease causes spread of infection to body parts resulting in systemic diseases such as cardiovascular disease, diabetes, etc. Good oral hygiene and stable oral biofilms maintains the body and prevents spread of infection to others. Personalized medicine and personalized dental medicine are developed based on microbiome analysis.

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