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Case Report

Oral –Gut Microbium and Impact on Systemic Health: Systematic Reviews

Shaimaa Hussein Rafat Kotb*

[1]*Alazher University, Faculty of Dentistry, Departement of Oral Medicine ,Periodontology, Oral Diagnosis and Dental Radiology, Assuit branch, Egypt.*
[2]*Ministry of Health and Population, Egypt*

Corresponding author: Shaimaa Hussein Rafat Kotb
Alazher University ,Faculty of Dentistry, Departement of Oral Medicine, Periodontology, Oral Diagnosis and Dental Radiology, Assuit branch, Egypt, Ministry of Health and Population, Egypt
E-mail: shaymarafat.dental@gmail.com, **Tel:** +201062051669

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Abstract

Impact of health awareness affect positively on healthy longer life. Gut microbiota homeostasis has a great effecacy on regulate various immunological functions and homeostasis . The oral cavity and gut are the two largest microbial habitats, playing a major role in microbiome-associated diseases. oral microbiota transfere commonly to the gut . Pathogenic microbiota of oral and oropharyngeal is porphormonous gingivalis which reach the stomach through swallowed saliva, nutrients and drinks . Periodontal disease (PD), a severe form of gum disease, is the most prevalent chronic infection in humans and is associated with complex microbial synergistic dysbiosis in the subgingival cavity . Immune system of the body interacts with the microbes as the plaque extends and propagates below the gingival sulcus . Once the bacteria reach the gingival sulcus, it can enter the blood stream and affect various areas of the human body. The polymicrobial nature of periodontal disease, if left untreated, promotes chronic inflammation, not only within the oral cavity, but also throughout the human body. Alterations seen in the concentrations of healthy gut microbiota may lead to systemic alterations, such as gut motility disorders, high blood pressure, and atherosclerosis.Hence this review discuss about oral –gut microbiota which play a major role in intiating and progreesion of systemic diseases.

Objective: To thorough the light on the importance of oral –gut relation and its impact on improving systemic general health.

Methods: A systematic literature review depends on collecting data from an evidence-based studies. Searches were made of tewenty electronic databases: the Cochrane Oral Health Group's Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, Scopus and Web of science ,MEDLINE(PubMed).

Summary: Dysbiosis of the oral microbiota in geriatric patients have a great impact on the balanced composition of the gut microbiota and so affect on immunity system and General systemic health. Diet consider as a modulating factor to modify microbial community for better health results and longer healthy life.

Conclusions: Understanding the bidirectional relation between oral –gut microbiota on precise diagnosis/prognosis and effective treatment on general health condition .there is a new strategy to use noval probiotic to modulate microbiota state for better control microbiome-associated diseases and so improve people health condition.

Keywords :
Gut microbiota , oral microbiota . Immunity . Dysbiosis . Disorder . Health span . Aging . Elderly periodontal diseases ,Dental caries . GI disease; GI cancer, systemic health.

Introduction:

Improved longer life is associated with the development of public health awareness .Keeping older people healthy has become an emergent global direction .Aging is related to the inefficient removal of hypo-functional or dead cells, which is related to immune dysfunction and immune disorders .Therefore, there is a higher occurrence rate of some diseases in older people than in younger ones, particularly metabolic syndrome and immune hypofunction . The word geriatric most common word used these days in practice clinic ,It is largely refers to multifactorial health disorders^ that happen when the accumulation damages in multiple systems [1,2].

The gut is the largest and the most well-characterized microbial ecosystem in the human body, which harbors about 500 to 1000 species . The human gut microbiota is known to be established early in life and can then be changed by age and environments, such as diet and nutrition, similar to the human oral microbiome .Thus, both oral and gut microbiomes that are primarily responsible for energy intake and metabolic processing necessary for human survival . Both of them directly reflect the health status of the host. [3].

Gut microbiota in the human starts from infancy and is influenced by many factors, including maternal condition, delivery mode, and contact with the mother. Dysbiosis of gut microbiota during infancy increases the risk for allergic diseases, such as allergic rhinitis, atopic eczema, asthma, and may increase the risk of acquiring immune disorders, such as diabetes, cancer during later stages of lifeThe composition of the infant gut microbiota is unstable during the first year of life. The feeding mode is considered a key factor that affects the gut microbiota composition during this period. During the first 2 years of life, children obtain their microbiota from surrounding people, their diet, and the environment. This period is categorized by rapid development of the immune system. The adult-like gut microbiota is established 3 years after birth. At this stage, the gene function of the infant gut microbiome changes from early lactate utilization to adult plant polysaccharide breakdown, and vitamin biosynthesis . The improvement in the gut microbiota throughout infancy has been a curiosity due to its importance in development of a strong immune system [4,5,6].

Our own body immune system is also depend¬ent on a perfectly functioning gut microbi¬ome, because the immune system located in the gut area is part of the entire defense sys¬tem (Marchesi et al. 2016). According to that , the microbiome there helps to prevent the settlement of pathogenic germs. A constant training of the immune system takes place in the gut .The composition of the gut microbiota can be altered as a result of exposure to antibiotics, infection, stress, or environmental factors, which can influence the physiology of the host over the long term .Role of gut microbiota affects the gut–brain axis interaction through neural, immunological, and neuro-endocrine mechanisms such as aging-related neurodegenerative diseases [7,8].

The human digestive system consists of the GI tract and the accessory digestive organs, including liver and pancreas. The GI tract is well-lined by the mucous membrane,beginning at the mouth and ending at the gut—more precisely, the anus. Thus, the oral cavity and gut are anatomically continuous regions connected through the GI tract. Moreover, both sites are also chemically connected, since saliva and digested food pass through the GI tract .the oral and gut microbiomes are highly diverse and concomitantly show unique signatures distinguished from each habitat. the oral and gut microbiomes have closely connected so bidirectional interaction can mutually shape and/or reshape the microbial ecosystem of both habitats, finally modulating physiological and pathological processes in the GI system [9].

Gut–brain axis communication is regulated by microbial metabolites, the vagus nerve, gut hormonal signaling pathways, the metabolism of amino acids, and the immune system .The microbiota regulates the release and synthesis of gamma amino butyric acid, dopamine, norepinephrine, and serotonin along with altering the levels of neurotransmitters. Various events, such as physical stress, can dysregulate the gut–brain axis by influencing the action of the hypothalamic–pituitary–adrenal axis, which regulates the stress response [10,11].

Aging is a pathophysiological process accompanied by reduced intestinal motility, which, affects the homeostatic relationship between the host and gut microbiota .The aging-linked weakening,

such as chewing problems, teeth loss, damaged sense of taste and smell, and physical disability, leads to alterations in lifestyle and diet. These changes result in a reduced consumption of foods containing protein and fiber, which, affects the structure, function, and composition of the gut microbiota importance of the dietary patterns affects directly on the equilibrium of the oral microbiota [12].

Immunosenescence is the dysfunction of the immune system as we get older . It is contribute to increased morbidity and mortality in the elderly. Immunosenescence promote bacterial overgrowth on epithelial cell surfaces, damage to the barrier function of gut microbiota . A gut infection caused by toxigenic microorganisms is a paradigm of bacterial-induced autoimmune disease . Some bacterial toxins, such as the toxin from Bacteroides fragilis, CagA from H. pylori, cytotoxic necrotizing factor 1, and colibactin from Escherichia coli disturb cell growth or directly damage DNA [13].

The oral cavity presents approximately 700 species of microorganisms . dental hygiene is another important factor that shapes the oral microbiome, since the oral cavity is directly open to the outside environment The commensal microbiota plays an important role in maintaining oral and systemic health. Commensals in the gut are known to be essential for the development of the structures of the gut and for appropriate development of local and systemic immunity .The simple presence of the oral microbiota in the mouth inhibits colonisation by pathogens [14].

Periodontal disease or periodontitis is a chronic immunoinflammatory pathology of periodontium also considered a bacterial disease with a multifactorial cause. The pathogens that cause periodontitis are mainly anaerobic Gram-negative bacteria, such as Porphyromonas gingivalis. This bacterium destroys tooth-supporting tissue, resulting in tooth loss if left untreated periodontal disease is associated with an increased risk of various metabolic, inflammatory, and autoimmune diseases, such as type 2 diabetes, atherosclerotic vascular diseases, and rheumatoid arthritis.. The high immune response due to the presence of periodontal bacteria leads to high production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), as a response from the host immune system .Periodontitis is also associated with increased serum levels of C-reactive protein (CRP) and decreased anti-inflammatory markers such as interleukin-10.This results in a first stage of severe gingival inflammation, followed by irreversible loss of the tooth supporting tissues [15,16].

Although Oral microbiota like P. gingivalis,seen in periodontitis,otherwise it may affect intestinal dysbiosis also .The periodontopathogen A. actinomycetemcomitans may alter the gut microbiota but P. gingivalis and A. actinomycetemcomitans are not the only periodontopathogens that can translocate to extraoral sites. Actually, a large variety of oral species can reach the intestinal microbiota through swallowing, regardless of the periodontal status, these bacteria seems to colonize in the gut when the microbiota here is dysbiotic. Anyhow, severe diseases and genetic susceptibility of the host may promote ectopic colonization of oral bacteria. The large amounts of swallowed dead bacteria from the mouth may stimulate several pathogens in the gut (necrotrophy) and create a new phenotype by upregulation of bacterial virulence genes (necroviru-lence) and increased cytotoxicity. [17].

Periodontitis may affect non-alcoholic fatty liver disease (NAFLD)the most common form of chronic liver disease. In addition, the gut microbiota has been mediate the development and progression of NAFLD. Thus, in patients with liver cirrhosis, a major change in the gut microbiota was due to the massive invasion of the gut by oral bacteria . There is a strong correlation of the severity of liver cirrhosis with an abundance of the invading bacteria indicate that oral bacteria other than P. gingivalis could also play a role in the pathology of liver cirrhosis [18].

Periodontal disease has a close relation to increased risk of cancer affecting distant organs .Furthermore, specific oral microbiome dysbiosis patterns have been related to several types of cancer. augmented colonization of the oral microbiome by T. forsythia and P. gingivalis have been implicated in esophageal cancer ,P. gingivalis and A. actinomycetemcomitans have been linked to pancreatic cancer and Fusobacterium and Porphyromonas have been implicated in colorectal cancer among others. Schwabe et al. proposed that the synergistic effects that eukaryotic and human cells take in human metabolism inside the oral cavity, once imbalanced, could result in the progression of carcinogenesis.

There is an increasing evidence suggesting that certain oral bacteria can contribute to oral and gastrointestinal cancers such as , P. gingivalis can be implicated in precancerous gastric and colon cancer lesions. Epidemiological studies have shown that there is an increased risk for such cancers in both men and women with periodontal disease or tooth loss .P. gingivalis up-regulates specific receptors on oral squamous cell carcinoma ,cells and keratinocytes, induces epithelial-to-mesenchymal transition of oral epithelial cells, and activates metalloproteinase- 9 and interleukin-8 in cultures of carcinoma cells . [19]

Pathogenesis of oral microbium in gingivitis ,periodontitis and dental caries reveals that oral microbiome possesses fascinating role affecting human systemic health beyond the oral cavity. In fact, oral microbiome products, microorganisms and inflammatory molecules could reach distal organism systems and organs through two different ways, mainly by the bloodstream and the digestive tract that influence the occurrence and progression of human systemic diseases [20].

Tooth decay is the most prevalent non-communicable pathology at a global scale.This microbial disease caused by the bacteria of the bacterial plaque .It is consider as an irreversible demineralization of the tooth hard tissues: enamel and dentin. This process occurs through anaerobic metabolism of sugars ingested in the diet, especially following consumption of sucrose .the importance of the dietary patterns affects directly on the equilibrium of the oral microbiota . A propriate dietary recommendations needed to manage the expanding global burden of tooth decay [21,22].

The main bacteria strain which considered cariogenic due to the production of acids and demineralization of the dental structure was S. mutans . in recent decades, a more complex composition of the bacterial community associated with caries in its different stages and now includes the presence of Streptococcus sobrinus, S. salivarius, S. parasanguinis, Actinomyces and Lactobacillus spp. at the onset of caries . This bacteria stimulates epithelial production of IL-6, INF-γ, and TNF-α which leads to local inflammatory processes that degrade oral gingival tissue and subsequently allow for bacterial access into the vasculature. This auto-destruction of the oral tissue–blood barrier allows for dissemination of bacteria and their byproducts into the bloodstream, and enables access to coronary atherosclerotic plaques. Bacteria found in atherosclerotic plaques also form complex biofilms that mirror dental plaques and consist of three stages of colonization with F. nucleatum serving as a bridging species. [23,24].

Some oral bacteria implicated as causative agents of pneumonia include P. gingivalis, P. intermedia, A. actinomycetemcomitans, Capnocytophaga, Eikenella corrodens, and S. constellatus .Oral pathogens are thought to play two indirect roles in the pathogenesis of pneumonia: modification of the oral cavity's innate immunity and cytokine production. Enzyme secretion caused by periodontal pathogens degrades mucins and the salivary pellicle. This reduces the body's ability to clear pathogenic respiratory bacteria from the mouth and also exposes adhesion sites that allow them to bind to structures in the oral cavity.

The cytokines produced by the oral immune response to periodontal bacteria (e.g., IL-1α, IL-1ß, IL-6, IL-8, TNF-α) can be aspirated and travel to the lower respiratory tract. Once in the lower respiratory tract, these cytokines can cause recruitment of inflammatory cells that damage respiratory epithelium and increase susceptibility to respiratory pathogen colonization [25].

Microbial dysbiosis or alterations of the host microbial community might also trigger the development of autoimmune diseases, a distinct and multifaceted category of chronic diseases. An evidence link between an individual's microbiota and autoimmunity .Toll-like receptors (TLRs) are important membrane-bound proteins found on the surface of many different immune cells. These receptors recognize specific structures of invading microorganisms such as lipopolysaccharide (LPS), peptidoglycan, flagellin and nucleic acid, but also damage-associated patterns (DAMPs) that are released from the host's dying cells, that is, oxidative stress and heat shock proteins (O'Neill, 2008). The activation of TLRs leads to upregulation of inflammatory cytokines and chemokines promoting an inflammatory immune response. It has been proposed that there is a synergy between autoantigen–autoantibody immune complexes in the activation of TLRs through microbial PAMPs and endogenous ligands resulting in autoimmunity (Hurst and von Landenberg, 2008). Indeed, the presence of PAMPs in tissues after an infectious period has been linked to autoimmunity . Sjogren diseases,systemic lupus erthematosis ,crohns diseases and rheumatoid arthritis are most common autoimmune diseases can be produced . Indeed, this review literature provides support for our thinking that imbalances of the microbial composition may be the missing link in the etiology of autoimmune disease, and may help in early diagnosis of autoimmune disease [26,27]..

Nowadays , scientist thorough the light on the importance of balanced diet which prevent or promote the development of caries .In general, fiber-rich foods are stimulate the flow of saliva, buffering pH and protecting teeth in reduce the risk of tooth decay by reducing the adhesion of bacteria, inhibiting their growth, or by reducing the ability of bacteria to form biofilm .There are also several studies on the relationship of vitamins and periodontal disease, especially those with antioxidant capacity and with effects on the immune system, as well as those involved in bone metabolism, seem useful for the prevention or improvement of periodontal disease, highlighting the action in oral health of the vitamins C and D [28].

Good oral hyigiene and non surgical periodontal treatment consider an conventional approach

to improve oral –gut microbium outcomes . Broad-spectrum antimicrobial mouthwashes such as chlorhexidine are often used to control dysbiosis . There ia another approach by using a noval Probiotic intervention According to the World Health Organization (WHO), probiotics are live microbes that confer a sufficient heath advantage to the host. Probiotics exert their favorable effects on the health of the host by producing neurotransmitters, immunomodulating, improving barrier function, and affecting the host gut microbiota and cellular component of the gut– brain axis. Among the probiotics used to target the gut microbiota, Lactobacillus and Bifidobacterium are the most extensively investigated in various clinical trial. Probiotic therapy promotes longevity in mice by suppressing chronic low-grade inflammation in the colon (Matsumoto et al. 2011). Recent evidence suggests that use of probiotics is safe for most of the population, but may cause an unfavorable infection in older people if there is damage to the intestinal mucosa [29,30,31]

Results: There is a strong positive bidirectional correlation of oral –gut microbiota and systemic disease .

Table 1: Composition of the gut microbiota in different geriatric diseases: From: Origination, change, and modulation of geriatric disease-related gut microbiota during life.

Disease	Microbiota composition	Reference
Parkinson's disease	Increased↑ Ralstonia Decreased↓ Helicobacter pylori Prevotellaceae Blautia Coprococcus Roseburia Faecalibacterium	(Scheperjans et al. 2015; Parashar et al. 2017)
Immunosenescence	Increased↑ Bacteroides fragilis E. coli Helicobacter pylori	(Nguyen et al. 2016)
Rheumatoid arthritis	Increased↑ Prevotella Decreased↓ Bacteroides bifidobacteria Clostridium coccoides Eubacterium rectale	(Nakayama et al. 2015; Vaahtovuo et al. 2008)
Metabolic syndrome	Increased↑ Prevotella Lactobacilli Proteobacteria Decreased↓ Bacteriodes Catenibacteriu	(Kelly et al. 2016)

Table 2: Main factors influencing the compositions of the oral microbiota.

Age	Host and Habitat	Environment	Biofilm Maturation
-Changes in the host and its habits -Microevolution	Genetic factors Diet and lifestyle	Surface 1 Immune system	Environment Oxygen Probiotics

-Horizontal transfer of Microorganisms	Changes in host defenses Broad spectrum antibiotics	Nutritional status Oral hygiene	Oral hygiene Microbial
-Changes in diversity interactions	Hormonal balance	pH Environment Cell flaking in the mucosa Density	Immune response
Tooth, mucosa, subgingival groove, tongue			Salivary flow and Gingivalcrevicularfluid

Table 3. Systemic diseases and pathologies related to dysbiosis of the oral microbiome.

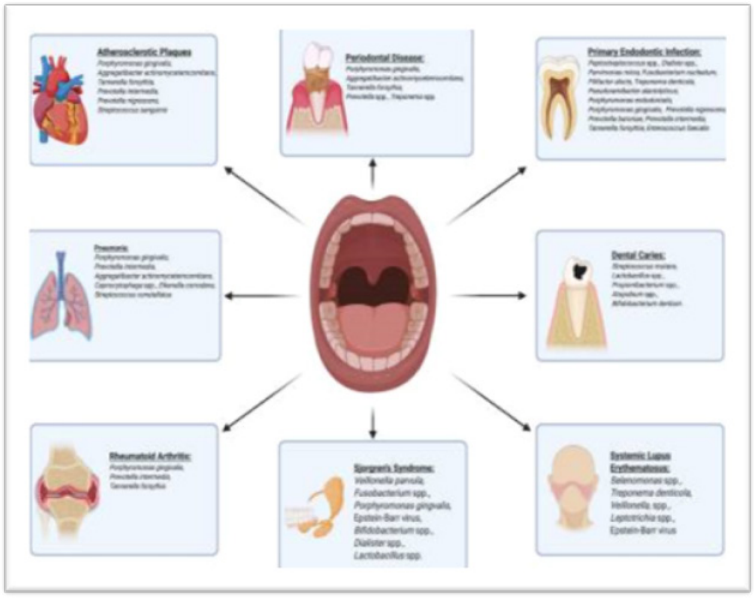
Autoimmune Diseases	Metabolic and Inflammatory Diseases	Cancer Diseases	Neurodegenerative Disorders
Rheumatoid arthritis [42,73]	Non-alcoholic hepatic	Colorectal cancer steatosis (F. nucleatum)	Multiple sclerosis
Sjögren syndrome, systemic lupus erythematosus [32]	Insulin resistance, diabetes, atherosclerosis [74]	Pancreatic cancer (P. gingivalis and A. actinomycetemcomitans)	
Inflammatory boweldisease [29]	Chronic kidney disease Hypertension, stroke, obesity	Gastrointestinal cancer [32] Head and neck tumors Oral cancer [75]	Alzheimer's disease

Discussion:

The oral and gut microbiomes are dynamic microbial communities that are of interest to nurse scientists as they noninvasively provide information related to disease and may be targets for future therapeutic interventions.The diversity and composition of microbiota (healthy microbiota profile) are dynamics, depending not only on the host physical status, genotype and immune phenotype, but also on the environmental factors like diet, antibiotic usage and lifestyle behaviors. These environmental factors may adversely alter gut ecosystem (dysbiosis) that is frequently associated with increased susceptibility to infections as well as to non-communicable diseases like obesity, metabolic syndromes (e.g., diabetes and cardiovascular diseases), allergy and other inflammatory auto immune diseases. Emerging evidence from recent studies demonstrate the existence of a bidirectional communication route linking gut and microbiota with Oral cavity (Vasapolli et al., 2019), and the taxonomic characteristics of the oral and gut microbiome may be more similar than previously realized, when analyzed at the strain level (Schmidt et al., 2019). Additionally, strain-level analysis provided evidence that these oral-gut bacterial community similarities resulted from passive translocation of the oral microbiome bacteria to the gut microbiome through saliva(Schmidt et al., 2019). This suggests the oral microbiome may be modulated by good oral hygiene, periodontal treatment therapy and using a novel probiotic interventional target for manipulating the gut microbiome through the oral microbiome's downstream influence. probiotics help ameliorating oral bacteria-elicited gastrointestinal disorders (44,45). Probiotics shown an impact on systemic metabolic disorders including diabetes, obesity, hypertension, and hyperlipidemia. Probiotic supplementation with Lactobacillus and Bifidobacterium to patients with T2D resulted in lower HbA1C scores and decreased LDL and total cholesterol levels .In patients with a body mass index greater

than 25, probiotic administration of multiple Streptococcus, Lactobacillus, and Bifidobacterium species resulted in weight reduction and a significant increase in Lactobacillus plantarum in the gut microbiota .A meta-analysis of pre-hypertensive and hypertensive patients given probiotic-fermented milk with various strains of Lactobacillus was associated with significantly reduced systolic and diastolic blood pressures .A study of probiotic supplementation with several strains of Lactobacillus, Bifidobacterium, and Streptococcus found significant shifts in the gut microbiota following probiotic treatment, namely an overall increase in the total aerobes and anaerobes, Bifidobacterium, Lactobacillus, and Streptococcus levels. Conversely, a reduction in Bacteroides, Coliforms, and E. coli was also observed [31,32,33]. probiotic bacteria exert an immunomodulatory effect and have the potential to communicate and interact with a series of immune cells (e.g., DCs, lymphocytes, epithelial cells, monocytes, and macrophages). The immune response generally comprises the innate immune response and adaptive immune response. Immunomodulatory effects of probiotics are mainly due to the induction of the release of cytokines including interleukins, transforming growth factor (TGF), tumor necrosis factors (TNFs), interferons (INFs), and immune cells released chemokines, which further regulate the immune system furthermore acting against infection and cancer cells, inducing the release of IL-12, which stimulates the NK cells and produces the Th1 cells [34].

Figure 1: Oral bacteria are linked to numerous oral and systemic diseases, highlighting the importance of oral microbial homeostasis in the maintenance of health and prevention of pathology.



Summary :

The oral microbiota presents a crucial factor, since it is in contact with the external environment. This is fundamental factor is modifiable and can improve or destroy the individual health . Gut microbiota identified as an important metabolic organ that provides us with important pathways, directly affect on the human body bio-transforms dietary components. Hence current nutrition intervention studies looking at the impact of diet on human oral, gut ,systemic health and the diseases risk.

Conclusion :

the importance of bidirectional relation between the oral - gut dynamic microbial community and the effect of diet as a modulatory capacity on health and pathological state. This study indicate that changes in the oral microbiome may not only affect the presence and severity of oral lesions but also the underlying imbalances in pathogenesis of systemic diseases, including autoimmune RA, SS, CD, and SLE. Factors that affect the balance between the immune system and composition of microbiota lead to dysbiosis and may lead to loss of tolerance and subsequent autoimmune disease. Improvment of oral hygiene should be the primary goal . Noval Probiotics can be used to improve the microbiota equilibrium in the host oral- gut, will serve as immunomodulators, growth promoters, and to inhibit pathogenic infections is crucial from a practical point of view. Impact of this issue will raise awareness about improving oral health condition especially in geriatric patients for longer healthy life .

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