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ORAL MICROBIOME: A SYSTEMIC PROBLEM

***Luay Thanoon Younis**

Center of Studies for Preclinical Sciences, Faculty of Dentistry, Universiti Teknologi MARA, Sungai Buloh Campus, 47000 Sungai Buloh, Selangor, Malaysia.

***Corresponding Author: Dr. Luay Thanoon Younis**
Center of Studies for Preclinical Sciences, Faculty of Dentistry, Universiti Teknologi MARA, Sungai Buloh Campus, 47000 Sungai Buloh, Selangor, Malaysia.

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ABSTRACT

Oral microbiotas play a crucial role in development of oral diseases, such as, tooth decay and periodontal disease. They are also known to participate in disease initiation and progression not only limited to the oral cavity, but at other distant sites. Poor oral health associates statistically with prevalence of many types of cancer, such as oral, pancreatic and gastrointestinal cancer. Shifting of microbiome composition is also associated with human disease such as heart disease and causes adverse effect on pregnancy. This mini-review reveals the connections of oral bacterial dysbiosis with oral and systemic problems.

KEYWORDS: Oral microbiome, oral health, cancer, heart disease, pregnancy.

INTRODUCTION

The human body is inhabited by over 100 trillion microbial cells living in symbiosis with their host.[1,2] The oral cavity is colonised by a numerous microbial communities of more than 700 microbial species as well as commensal and opportunistic bacterium, fungi and viruses. They are living in a symbiotic relationship with one another and the host immune system.[3,4]

The oral environment is known to be involved in the pathogenesis and development of various diseases such as bronchitis, pneumonia, diabetes, heart disease, and dementia.[5] Because the oral cavity acts as the bodily entrance for air and food, it is constantly exposed to foreign substances, including bacteria and viruses. A large number of bacteria are endemic to the oral cavity, and indigenous oral flora act to prevent the settlement of foreign bacteria and maintain the normal oral physiological environment.[6]

It is well known that many chronic inflammatory conditions are sequelae of imbalance between host-microbiota interactions, which consequently result in a dysbiotic community, uncontrolled immune responses, and ultimately disease aftermath.[7]

Oral Microbiome and Cancer

Certain types of cancer have been correlated with an altered microbial profile, such as oral, gastric,[8] lung,[9,10] pancreatic and colonic malignancies.[11,12] Alteration in oral microbiome could be significant in cancer and other chronic diseases, through direct metabolism of chemical carcinogens, alteration of tumor microenvironment, induction of genotoxic responses and induction of chronic inflammation.[13,16] Bacteria are also thought to be part of the carcinogenic process through inhibition of apoptosis, activation of cell proliferation, promotion of cellular invasion, and production of carcinogens.[17,18]

Oral microbiome and Oral Squamous Cell Carcinomas

Most oral cancers are oral squamous cell carcinomas (OSCCs), representing up to 80-90% of all malignant neoplasms of the oral cavity.[19,21] Though the advances of therapeutic approaches, percentages of morbidity and mortality of OSCC are still high and have not improved significantly during the last 30 years. Percentages of morbidity and mortality in males are 6.6/100,000 and 3.1/100,000 respectively, while in females the same percentages are 2.9/100,000 and 1.4/100,000.[20-22]

OSCC is a disease that arises from both host genetics and environmental factors; tobacco and alcohol consumption, betel quid chewing, and human papillomavirus infection are well-known risk factors.[2,5,23,24] Inflammation was found to be a key feature in many chronic diseases including cancer.[13,25,26] Previous studies found that the effect of bacteria on OSCC progression can be explained by the inflammation-induced DNA damage in epithelial cells caused by microorganism-secreted endotoxins.[27-29]

In response to bacterial endotoxins, during inflammation, immune and non-immune cells release large amount of cytokines and growth factors that may influence carcinogenesis of gastrointestinal malignancies.[30] In general, infection-driven inflammations have been estimated to be involved in the pathogenesis of

approximately 15–20% of human tumors.[31] Hence inflammation caused by infections might be one of the most important preventable causes of cancer.[31]

Some specific species have been identified to associate with occurrence of OSCC, such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Prevotella intermedia* (1-4).[8,32,34] It was found that specific bacterial taxa, such as *Veillonella*, *Fusobacterium*, *Prevotella*, *Porphyromonas*, *Actinomyces*, *Clostridium*, *Haemophilus*, *Enterobacteriaceae*, and *Streptococcus* spp., are correlated with oral cancer and epithelial precursor lesions.[35] Other reports suggested increased abundance levels of *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *Streptococcus mitis* in the saliva of individuals with OSCC incidence.[8,34]

Oral Microbiome and Oropharyngeal Cancer

Due to the close proximity of oral cavity and oropharynx, abundance changes in oral microbiota may provide useful information on tumourigenesis.[36] In the oral cavity, there are several distinct microbial habitats such as periodontal pockets and the surface of teeth and cheeks, where tongue is the most populated niche because of its fissured and pappillated surfcase.[37] Microorganisms inhabiting the dorsum of the tongue may travel through saliva to colonise other regions in the oral cavity.[37] Microbes in the tongue include *Veillonella atypica*, *Porphyromonas gingivalis*, *Selenomonas spp*., *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *Capnocytophaga spp*. and many more.[37,38] Distinctive microbes residing in the oropharynx include *Strep. pyogenes*, *Strep. pneumoniae*, *Haemophilus influenza* and *Haemophilus parainfluenzae*.[39] There are also numerous microbes that could be found in the oral cavity, but not in the oropharynx such as *Strep. feacalis*, *E.corrodens*, *Enterobacteriaceae*, *Actinomyces*, *Lactobacilli*, *Veillonella* & *Treponema*.[40,42] One of the viruses which have been implicated in cancer is the human papillomavirus (HPV) which is the most common sexually transmitted infection where the virus can be transmitted to oral cavity during sex. HPV has been identified as an etiologic agent for oropharyngeal cancer.[43,44]

Oral Microbiome and Colorectal Cancer

Previous studies found that alterations in oral microbiota were linked with colorectal cancer (CRC) and notably higher abundance of putative oral bacteria on colonic tumours.[45] *Fusobacterium* species (a group of non-spore-forming, anaerobic gram-negative bacteria) are a part of the normal human oral and intestinal microbiota.[46] The species of the *Fusobacterium* genera are highly heterogeneous, and some of them have been recognized as opportunistic pathogens involved in periodontitis,[47] inflammatory bowel disease,[45,48,49] pancreatic abscess,[50,51] and hepatic abscess.[52,53]

Fusobacterium nucleatum is frequently identified in studies of CRC bacterial culture with other oral microbes such as *Porphyromonas* gingivalis. Interestingly, *F. nucleatum* and *P. gingivalis* are synergistically promoting oral cancer progression.[54,55] Previous studies of the two periodontal pathogens have revealed several virulence mechanisms that enhance the survival and carcinogenesis of both bacteria.[56] The specific virulence characters include the abilities to invade the gut submucosa and epithelium, disrupt oncogene signaling, disrupt cell-cell adhesion, promote inflammation, and inhibit natural killer and cytotoxic T cells, promoting tumor proliferation and progression.[56,58] Other than *Fusobacterium* and *Porphyromonas*, there several other oral indigenous and periodontopathic bacteria are frequently identified in the cancerous colon. These bacteria, including members of the *Peptostreptococcus*, *Prevotella*, *Parvimonas*, and *Gemella* genera.[48,59]

Oral Microbiome and Pancreatic Cancer

Carcinoma of exocrine pancreas is the fourth leading cause of cancer deaths, worldwide. Pancreatic cancer is an aggressively lethal cancer; 94% of pancreatic cancer patients succumb to their disease within 5 years from diagnosis.[60] The colonies of bacteria found in pancreatic tumour tissue would certainly reveal the direct causal link between oral microbiome and pancreatic carcinogenesis.

Periodontitis is associated with a local overly aggressive immune response and a spectrum of systemic effects. Subjects with periodontal disease or having high count of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* also tended to have excess risks for pancreas cancer.[61,63] Furthermore, it was found that *P. gingivalis* is also associated with risk in subjects not exhibiting overt periodontal disease, hence, it is a strong indicator that microbial factors play a role in orodigestive carcinogenesis independent of their association with periodontal disease.[64]

It was reported that a high number of bacteria present in the calcified pancreatic duct epithelium and in pancreatic abscess.[51,65,67] Pancreatic tissues were found to be colonised by known members of the oral microbiome.[68,69] This can explained by the fact that bacterial dissemination may occur from the mouth to the pancreas through the colon and via bacterial translocation, general circulation, biliary duct, duodenum, and the lymphatic system.[65,70,72]

Oral Microbiome and Cardiovascular Diseases

Bacteria the inhabiting the oral cavity my translocate into the blood stream through the inflamed gingiva and play a role in the atherogenesis.[73] Previous studies suggested that bacteria from the oral cavity, and perhaps even the gut, may correlate with disease markers of atherosclerosis.[74] Chronic inflammatory periodontal diseases are among the most common human infections with 10–15% of the population experiencing advanced

forms of the disease.[75] It was reported that Individuals with periodontitis may have an increased risk of developing a cardiovascular disease, such as coronary artery disease, stroke, myocardial infarction, and atherosclerosis even after adjusting for classical cardiovascular-risk factors.[76,78] Other reports showed that the bacterial burden of *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Treponema denticola*, and *Tannerella forsythia* in subgingival plaque samples was associated with carotid intima-media thickening.[73,79]

It was found that gingival ulceration in periodontitis may result in bacteraemia which trigger the release of inflammatory cytokines that provoke an additional inflammatory stimulus for atherosclerotic plaque formation in the endothelium.[80,81] Activation of the endothelium also results in the release of chemotactic cytokines, further attracting monocytes or other cells that form a vicious cycle leading to plaque formation.[82,83]

Due to the recent advances in microbial identification and analyses techniques, a number of oral bacteria have been independently found in atherosclerotic plaque samples from coronary artery disease patients.[83,84] In meta-analysis study, it was concluded the presence of 23 oral commensal bacteria, either individually or in coexistence, within atherosclerotic plaques in patients undergoing carotid endarterectomy, catheter-based atherectomy, or similar procedures. of these 23 bacteria, 5 microbes (*Campylobacter rectus*, *Porphyromonas gingivalis*, *Porphyromonas endodontalis*, *Prevotella intermedia*, *Prevotella nigrescens*) are unique to coronary plaques, while the other 18 are additionally present in non-cardiac organs, and associate with over 30 non-cardiac disorders.[83] Other type of bacteria in the oral cavity such as *Anaeroglobus* could be associated with symptomatic atherosclerosis.[85]

Interestingly, improvement in oral hygiene and periodontal status has been shown to slow progression of increased intima-media thickness in the common carotid artery in a 3-year longitudinal study.[86]

Oral Microbiome and Pregnancy

The oral cavity, like the gut, skin and vagina, is a major microbial habitat in our body, thus can serve as a potential reservoir for microbial infections.[87] Significant evidence supports an association between periodontal pathogens and preterm birth, preeclampsia, stillbirth and low birthweight.[88,90]

Pregnancy-associated gingivitis is highly prevalent, affecting 30–75% of the pregnant population, which goes away after delivery.[91] Studies in both humans and animals have demonstrated that oral bacteria can translocate to the pregnant uterus through hematogenous transmission.[87] Blanc et al. (2015) reported that women with periodontitis showed a higher prevalence of periodontopathogens detected in their placentas compared to those from women without periodontitis. The study concluded that oral bacteria may be normally present in the placenta, however, the levels of certain oral pathogens in the placenta would highly depend on the mother's periodontal state.[92] The virulence properties assigned to specific oral pathogenic bacteria, for example, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Filifactor alocis*, *Tannerella forsythia*, *Prevotella intermedia*, *Prevotella nigrescens* *Campylobacter rectus*, and others, render them as potential collaborators in adverse outcomes of pregnancy.[68,93,94] Studies have shown that some of the idiopathic preterm births were probably caused by uncultivated or difficult to-culture microorganisms.[95] *Bergeyella* and *F. nulceatum* are common to the human oral cavity. However, investigations have shown that when they migrate to other distant sites in our body, such as the uterus, they become harmful and could cause preterm birth or stillbirth.[87]

It has been shown that periodontal pathogens provoke the release of inflammatory cytokines and mediators which elicit intrauterine inflammation.[96,97] Furthermore, Offenbacher et al. (2006) revealed the potential benefits of periodontal treatment on pregnancy outcomes and suggest that periodontal therapy may lead to a 3.8 fold reduction in the rate of preterm births.[90]

CONCLUSION

The oral cavity is the biggest exposed opening or entrance which allow the microbiome into the deepest parts of human body. Billions of microbiome are entering our body daily. These microbiome are carried by food, drinks, contaminated hands, etc., but our body immunity doesn't make it easy for these invaders to cause a disease. There are several prerequisite factors must be available to enhance the pathogenesis of the microbiome to cause a local or systemic problem.

Conflict of Interest

No conflict of interest exists.

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