Oral Health: A Guide for Your Health as a Periodontist’s Point of View

Vinay H. Vadavadgi¹, Amit Mani¹, Neeta S. Padmawar²* and Lingraj Harihar³

¹Department of Periodontology, Rural Dental College, Pravara Institute of Medical Sciences (Deemed to be University), India.
²Department of Pediatric & Preventive Dentistry, Rural Dental College, Pravara Institute of Medical Sciences (Deemed to be University), India.
³Department of Oral Medicine, Diagnosis & Radiology, P.M.N.M Dental College & Hospital, Bagalkot, India.

Authors’ contributions

This work was carried out in collaboration among all authors. Author VHV managed the literature searches and wrote the first draft of the manuscript. Author AM guided during designing manuscript. Author NSP managed the literature searches and reviewed of final draft of the manuscript. Author LH managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i32A31716

Editor(s):
(1) Dr. Aurora Martínez Romero, Juarez University, Mexico.
(2) Karnati Praveen kumar reddy, SEGi University, Malaysia.
(2) Rosario Almanzar, Instituto Tecnologico de Santo Domingo, Dominican Republic.

Reviewers:
http://www.sdiarticle4.com/review-history/70084

Received 10 April 2021
Accepted 15 June 2021
Published 17 June 2021

ABSTRACT

Dental caries and Periodontitis are the most commonly reported dental diseases. These can lead to loss of tooth structure and compromising the functions of teeth like mastication and thus affecting the overall health. Periodontitis is inflammation of periodontium resulting in loss of periodontal ligament attachment, bone destruction, tooth mobility and ultimately tooth loss. This is caused by the microorganisms present in the oral biofilm. One cubic millimeter of dental plaque contains about 100 million bacteria. At present almost more than 500-600 different varieties of bacteria have been identified in the oral cavity. Key periopathogens are the group of periopathogens that are responsible for the commencement and progression of periodontal disease as well as failed periodontal therapy. A. actinomycetemcomitans, Tannerella forsythia and Porphyromonas gingivalis are the established key-pathogens in the various periodontal diseases.

*Corresponding author: E-mail: opneeta23@gmail.com;
Through blood stream, these micro-organisms can be transported to various organs or system in the human body and causing and affecting overall health negatively. Endotoxins produced by these key perio-pathogens are associated with the non-oral diseases. It is a proven fact that periodontal health plays an important role in general health status in mankind. Periodontal pathogens can affect the systemic diseases and conditions adversely and can lead to unfavourable outcomes. Patients with cardiovascular diseases showed pathogens having same DNA as periodontal pathogens. In periodontitis patients, inflammatory mediators produced can trigger the hyperglycaemia. In pregnant women, premature birth and low birth weight is found linked with poor periodontal health. This paper highlights the role of periodontal health in various systemic diseases and conditions for better treatment planning and prevention of the adverse outcomes.

Keywords: Periodontitis; key pathogens; systemic health; adverse effect.

1. INTRODUCTION

Dental caries and Periodontitis are the most commonly reported dental diseases. These can lead to loss of tooth structure and compromising the functions of teeth like mastication and thus affecting the overall health.

Periodontitis is inflammation of periodontium resulting in loss of periodontal ligament attachment, bone destruction, tooth mobility and ultimately tooth loss. This is caused by the microorganisms present in the oral biofilm. The destruction of the periodontium is associated with the presence of gram-negative anaerobic bacteria localized in the subgingival region, and include typically Porphyromonas gingivalis (Pg), Prevotella intermedia (Pi), Actinobacillus actinomycetemcomitans (Aa), and Bacteroides forsythus (Bf) are the initiator for periodontal diseases and Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Prevotella intermedia, Campylobacter rectus, Peptostreptococcus micros, Eikenellacorrodens are required for the progression of the disease [1].

Periodontitis can be mild, moderate or severe type depending upon the clinical and radiographic presentations. According to a survey in 2013, the prevalence of mild periodontitis was found in 35% and moderate to severe periodontitis in 11% of study population [2].

In severe periodontitis cases, along with severe clinical manifestations; elevated levels of inflammatory mediators like CRP, hyperfibrinogenemia, moderate leukocytosis and IL-1 and IL-6 were found as compare to healthy counterparts [3,4,5,6,7].

In 1900 a British Doctor William Hunter based upon his clinical experience postulated a concept of “focal infection” in which he emphasized on the there is a link between oral pyemia and systemic health. He further said that if infected tooth is extracted or removed, general health of an individual improved [8].

Through blood stream, micro-organisms causing periodontitis can be transported to various organs or system in the human body and causing and affecting overall health [9]. Endotoxins produced by gram negative anaerobic microorganisms are associated with the non-oral diseases [10].

1.1 Periodontal Pathogens

One cubic millimeter of dental plaque contains about 100 million bacteria. At present almost more than 500-600 different varieties of bacteria have been identified in the oral cavity [11]. These bacteria grow on the tooth surface, gingival margin and subgingival margin. Among these bacteria, only small amount of bacteria can cause periodontal disease [12]. These bacteria can be anaerobes, aerobes, capnophiles and microaerophiles; but most of periodontal pathogens are anaerobes and this contribution depends on environment of the periodontal pocket. These possible etiological pathogens should have ability to grow subgingivally, produce enzymes and toxins and or antigens and inflammatory mediators which will commence inflammatory reaction leading to injury or destruction of periodontal tissue [13,14]. key perio-pathogens are the group of perio-pathogens that are responsible for the commencement and progression of periodontal disease as well as failed periodontal therapy. A. actinomycetemcomitans, Tannerella forsythia
and Porphyromonas gingivalis are the established key pathogens in the various periodontal diseases [15]. Other than these species, subgingival species like Prevotella intermedia, Prevotella nigrescens (formerly P. intermedia), Bacteroides forsythus, Fusobacterium nucleatum, Campylobacter rectus, Eikenella corrodonens, Treponema denticola, Micromonas micros (formerly Peptostreptococcus micros) and some other species are also present subgingivally.

This article gives a glimpse of the relation between periodontal pathogens and various systemic conditions like cardiovascular disease, diabetes mellitus, osteoporosis, colon cancer, premature deliveries etc.

2. MECHANISM OF EFFECT OF PERIODONTAL PATHOGENS ON SYSTEMIC HEALTH

Exact Pathophysiology of impact of periodontal diseases on system health is explained through following two mechanisms-

1. Direct Mechanism: During the progression of periodontitis of chronic type, the epithelium becomes inflamed and ulcerated creating the first hand access for the periodontal pathogens into the bloodstream. Thus these systemically circulating bacteria having direct contact with some organs and causing or affecting the systemic outcome [16].

For example (eg) Periodontal bacteria have been detected in thrombi of acute myocardial infarction.

2. Indirect mechanism: Periodontal pathogens or the chemicals produced by them begins inflammatory changes which may show systemic consequences indirectly. Now it is proven fact inflammation is among triggering factors which can cause or initiate systemic illness like cardiovascular disease, diabetes type 2, rheumatoid arthritis. Thus chronic inflammatory responses caused by periodontitis may influence the pathogenesis of inflammatory based diseases [17,18].

For eg. Level of C-reactive protein (CRP) is an indicator for systemic inflammation and CRP values are increased in individuals with periodontitis.

3. PERIODONTITIS & ITS CONNECTIONS WITH VARIOUS SYSTEMIC DISEASES AND CONDITIONS:

3.1 Periodontitis & Cardiovascular Diseases

Globally main cause of death is cardiovascular diseases [19]. Main etiology of these cardiovascular diseases is thickening of arteries called as atherosclerosis. It occurs due to deposition of calcium and fatty materials resulting in plaque formation thus causing hardening and stiffening of the arteries. Complications of this atherosclerosis depends upon location and amount of deposits. Some most common complications are angina, myocardial infarction, stroke, or aneurysm [20].

The association between periodontal disease and atherosclerotic cardiovascular disease is independent of other known confounding risk factors [21]. The link between the periodontal disease and atherosclerotic cardiovascular disease is direct and is not related to other associated risk factors. Periodontal disease plays direct role in pathophysiology of atherosclerosis (ATH) by causing thromboembolic events and furnishing systemic needs through liposachharides and inflammatory cytokines. Streptococcus sanguis and Porphyromona gingivalis caused platelet aggregation and activation by the expression of collagen-like platelet aggregation-associated proteins. These aggregated proteins play a role in atheroma formation and thromboembolic events directly or indirectly [22].

Bahekar et al. [23] carried of a meta-analysis of five studies which included 86092 persons and concluded that persons with periodontitis had higher chances of developing coronary heart disease than healthy persons. They also found that this relation is not depend of confounding risk factors.

Another case control study, which included 1423 individuals, showed more than double the risk of frequency of occurrence of cardiovascular disease in individuals with periodontitis [23].

Some studies evaluated the contents like bacterial DNA, antibodies in atheromatous plaque samples. They confirmed the presence of DNA of bacteria namely P. gingivalis most frequently followed by A. actinomycetemcomitans, T. forsythia,
Eikenellacorrodens, Fusobacterium nucleatum and Campylobacter rectus [24,25]. Haraszthy et al. identified periodontal pathogens in human carotid atheromas. They found 26% for P. gingivalis, 18% for Aggregatibacter actinomycetemcomitans, and 14% for P. intermedia. They also found that more than 40% of atherosclerosis have more than one periodontal pathogen [26].

This finding suggest that these micro-organisms can travel from oral cavity to distant organs in the body [25,26].

In individuals having high plasma levels of fibrinogen & Tumour Necrosis Factor-alpha(TNF-alpha) and having periodontal disease, they showed increased thickness of carotid intima-media thickness (IMT). Thus increasing the chances of atherosclerosis [27,28,29,30].

Further studies required to evaluate the impact of the improved periodontal health and condition on the cardiovascular condition.

### 3.2 Periodontal Disease & Diabetes Mellitus

Diabetes mellitus is a metabolic disorder which is marked by increase in blood levels of sugar known as hyperglycemia. This occurs due to faulty or defective secretion or activity of insulin [31].

Diabetes mellitus is classified into three types depending upon signs & symptoms as-type 1, type 2 and gestational. Type 1 Diabetes Mellitus is caused by wasting or destruction of beta-cells within the islets of Langerhans of the pancreas causing complete insulin deficiency. Type 2 diabetes mellitus starts due to insulin resistance and slowly progressing towards pancreatic beta-cell failure whereas in gestational type of diabetes mellitus results due to glucose intolerance during pregnancy [32].

Pathophysiology of periodontal disease and diabetes mellitus is considerably alike, that both the diseases are inflammatory in origin and in both increased levels of AGEs cause marked destruction. Thus both the conditions results in production of inflammatory mediators like IL-18 and CRP or IL-18 and IL-6 [33,34].

In diabetic patients, hyperglycemia is caused due to increased levels of advanced glycation endproducts (AGEs) in the serum [35]. These AGEs causes production of inflammatory mediators by activation of endothelial cells and monocytes. If AGEs gets deposited/accumulated in the gingiva, they cause increased vascular permeability, increased disintegration of collagen fibers and faster impairment of nonmineralized connective tissue as well as of bone [36]. Similar observations were done by many researchers stating that severe periodontal destruction resulting in tooth loss occurs in patients with uncontrolled diabetes [37,38,39].

In patients of severe periodontitis with diabetes mellitus, due to production of inflammatory mediator’s sugar level may get affected.

Thus periodontitis and diabetes mellitus share dual relationship and their prognosis is interlinked but more studies are required to prove and understand the progression and therapeutical outcomes.

### 3.3 Periodontitis & Pneumonia

Pneumonia is an infection of the lungs. Etiology of this infection can be bacteria, mycoplasma, viruses, fungi, or parasites. Bacterial pneumonia can be classified as community-acquired pneumonia and hospital-acquired (nosocomial) pneumonia. Nosocomial pneumonia, generally occurs within 48–72 hours of admission to a hospital or nursing home, can be subdivided into two subtypes: ventilator-associated pneumonia (VAP) and non-VAP.

Many oral pathogens have been identified in lung infection. Some of these are including A. actinomycetemcomitans, Actinomyces israelii, Capnocytophaga spp, Chlamydia pneumoniae, E. corrodens, F. nucleatum, Fusobacterium necrophorum, P. gingivalis, P. intermedia and Streptococcus constellatus. Saliva and dental plaque in patients with periodontal disease are the major source for spreading these pathogens to the lower airway [40,41,42].

When the pathogens in patients admitted in intensive care unit were compared, it was observed that genetic structure of the pathogens from dental plaque had similarity to the genetic structure of pathogens isolated from bronchoalveolar lavage fluid. Thus it can be concluded that the dental plaque can act as a stock for respiratory pathogens [43].

Many authors suggested that oral and respiratory bacteria from the dental plaque lean out into the
saliva and then travel to the lower respiratory tract and lungs provoking infection [44,45].

Second mechanism suggested was cytokines and enzymes produced due to periodontal inflammation in the oral biofilm may get transferred into the lungs triggering local inflammatory response in the lung and encouraging colonization of pathogens and the actual lung infection [44,45].

Another possible way of pulmonary infection is through entry of airborne micro-organisms through respiration or circulation of microorganisms through bacteria from local infection.

Individuals with low salivary flow, diminished cough reflex, swallowing disorders, with poor oral hygiene or poor oral health care habits or physical disabilities are at higher risk of developing lung infections as compare to healthy persons [44].

Gomes-Filho et al observed that the patients with periodontal diseases are three time more susceptible to the nosocomial pneumonia as compare to individuals with healthy periodontium [46].

Porto AN et al examined forty individuals who had orotracheal intubation. And observed that pathogens like A.actinomycetemcomitans, P. gingivalis and T. forsythia were present in large quantity. In this study both dentulous and edentulous individuals were included. Thus it can be concluded that oral cavity has favourable conditions for accumulation and growth of pathogens [47].

Poor oral health, dental plaque, or oropharyngeal bacterial colonization have been associated with the occurrence of pneumonia in hospitalized or ICU patients [45,48,49].

In nursing care home for elderly, individuals with high plaque scores, bacterial presence in saliva and colonization in oropharynx was found to be associated with pneumonia [50,51].

Dentulous individuals have higher risk of developing pneumonia and respiratory tract infections than edentulous individuals [50,51].

Use of chlorhexidine topically in ventilated patients reduces the chances of development of pneumonia and diminishes the doses of systemically administered antibiotics thus shorten the time period for mechanical ventilation in ICU patients. Early use of topical chlorhexidine in intubated patients can reduce the colonized oral bacterial count and postpone the onset of VAP [52,53,54,55,56].

Recently in a study it was observed that use of povidone iodine in combination of mechanical oral health care in ventilated patients reduces the risk of pneumonia [57].

Thus it can be concluded that oral health status can affect the lungs negatively but with proper oral health care severity of adverse outcomes can be reduced.

### 3.4 Periodontal Disease And Osteoporosis

Osteoporosis is a skeletal disease which is characterized by reduced bone density and bone quality resulting in decreased bone strength, making it vulnerable for fracture [58].

Both osteoporosis and periodontal disease has similarity that both results in bone resorption. Age, estrogen deficiency and smoking are the common threats for the systemic as well as oral osteopenia [59,60,61].

Increased bone resorption can be due to surge in systemic / local osteoclastic activity or due to cellular or cytokine effects in both diseases [62].

In periodontitis, gingiva shows thick layer of infiltration by mononuclear leucocytes, T lymphocytes and monocytes or osteoclast like progenitor cells [63]. In periodontal infection, osteoclast formation occurs due to interaction between T cells and monocyte/lymphocyte progenitor cells. This is the most important event in periodontal infection [64].

When gene sequencing was examined in advanced periodontitis patients, it was found that RANKL mRNA was increased whereas osteoprotegerin (OPG) mRNA was downregulate/decreased in the gingival [64].

Nagasawa et al observed that increased OPG mRNA was due to LPS from P. gingivalis and A. actinomyecetemcomitans, thus it can be correlated that LPS-stimulated OPG may be responsible for the osteoclast formation in periodontitis [65].

Gram negative bacteria associated with periodontitis may aggravate the RANKL activity
and thus causing osteoclast activation hence initiating the osteoporosis in periodontitis patients. This was observed by Teng YTA et al and Jiang Y et al in their studies also [66,67].

In women, Estrogen deficiency was main etiological factor associated with osteoporosis [68].

Estrogen regulates cytokines production that is essential for bone metabolism as well as modulation of host response to inflammation through factors like as IL-1 alpha, IL-1 beta, TNF-alpha, and macrophage colony-stimulating factor (M-CSF). Hence estrogen deficiency results in increased osteoclasts population thus resulting disparity in bone metabolism leading to reduced bone mineral density (BMD) [69].

In Periodontitis host's proinflammatory response is activated through engagement of cytokines and prostanoids causing activation of osteoclasts and resulting in bone resorption. In gingivitis, elevated levels of IL-1 beta, TNF-alpha, IL-6, and IL-8 were associated with bone resorption. Thus proving interlink between periodontal disease and estrogen deficiency [70,71].

Wactawski-Wende et al.110 determined a strong and consistent association between alveolar crestal height (ACH) and osteoporosis through measurements of bone density and ACH in postmenopausal women [72].

Stefen Renvert et al observed that 61.1% patients with Rheumatid arthritis showed signs and symptoms of periodontitis as compare to control group-33.7% [73].

Lozano et al in their case control study observed significant prevalence of periodontal disease in rheumatoid arthritis patients as compare to control group. They also observed that in rheumatoid arthritis group, severity of clinical signs and symptoms were more as compare to control group [74].

Still the question remains unclear whether periodontitis causes osteoporosis or vise versa. Further studies are required to evaluate the exact role of periodontitis in osteoporosis occurring in Rheumatoid arthritis.

3.5 Oral and Colorectal Cancer

Cancer is the cause of death for every fourth person, which adds to emotional and financial burden. In 1990, Helicobacter pylori was the first pathogen to be identified as the one of the etiological factor in human gastric cancer [75]. Thus it was the first bacterial pathogen to be associated with cancer in humans [76,77].

Yao QW et al in their study of 3183 patients, found that the individuals with periodontitis had higher risk of developing oral cancer [78].

Michaud DS et al found positive relationship in patients with periodontitis and cancer of pancreas, head, lung and neck [76].

Wen BW et al examined one million Taiwanese individuals and concluded that individuals who had periodontitis have higher risk of developing cancer than individuals with gingivitis [79].

P. gingivalis pathogen responsible for the periodontal disease was found in higher level in patients of oral squamous cell carcinoma (oscc) and esophagus squamous cell carcinoma as compare to healthy patients [77,80].

In animal study model, Binder Gallimidi A et al evaluated possible role of periodontal pathogens in the instate of the oral cancer and they observed that periodontal pathogens P. gingivalis & P. nucleatum trigger tumorigenesis through unmediated linkage with oral epithelium [81].

In OSCC, P. gingivalis causes invasion and metastasis of oral squamous cell through matrix metalloproteinase 9 (pro-MMP9) expression. Periodontal pathogen F. nucleatum does not play any role [80].

Ha NH et al. observed that the aggressiveness of oral cancer is affected by P. gingivalis positively. They also observed that chronic & recurrent exposure of P. gingivalis causes augmentation of aggressiveness of oral cancer by triggering epithelial mesenchymal transition-like changes in the cells [82].

Colorectal carcinoma (CRC) is the fourth most common carcinoma diagnosed and cause of deaths in cancer patients. In CRC patients, high numbers of F. nucleatum and Clostridium difficile were found in intestinal microbiota. [83]

Warren RL evaluated 130 specimens of CRC patients and specimen showed presence of Gram-negative anaerobic oral pathogens such as Fusobacterium, Leptotrichia and Campylobacter [84].
When human colonic adenoma site and surrounding healthy tissue in CRC patients and healthy patients were evaluated, it was found that F. nucleatum colonizes were more in number in CRC patients. Even stools of CRC patients showed high number of F. nucleatum as compare to healthy patients [85,86].

F. nucleatum not only migrate to human instetinal tract but also colonize their triggering severe inflammation [83,87].

In a mouse study of CRC, it was found that F. nucleatum not only affects the constitution of lumen microbiota and moderate the secretion of cytokines and activate tumorigenesis-related pathway [86].

These all finding suggest that F.nucleatum causes changes in microenvironment which favours the advancement of CRC.

In summarization, it can be concluded that P. gingivalis and F. nucleatum have positive correlation in development of various carcinoma like oscc, crc etc. and this relationship can be used for early detection and better prognosis. To evaluate this further studies are required.

3.6 Alzheimer's Disease

Alzheimer's disease (AD) is a neurological disorder which causes progressive and irreversible]

Alzheimer's disease develops due to different response of brain to inflammatory process and this occurs through complement activation and cytokine and chemokine expression [88].

This occurs due to emergence of synaptotoxic amyloid plaques and hyperphosphorylated tau proteins in the area of the brain designated to the advances cognitive functions [89].

AD is emerged by the development of extracellular amyloid β-peptide (AβP) plaques and intraneuronal neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein which results into loss of neuronal synapses gradually and ultimately neuronal degeneration with diminution of essential neurotransmitters [88].

Inflammation is the common factor associated with periodontitis and Alzheimer's disease. In AD. activated glial cells causes crucial increase in inflammatory cytokines [90].

AD can show early or late onset. Early onset AD is due to genetic linkage; whereas late onset or sporadic AD is caused due to combination of genetic and environmental factors. Age, education, high fat diet, hypertension, diabetes, history of head trauma, and susceptibility genes such as apolipoprotein E (APOE) and periodontitis are the elements which influence AD negatively.

The linkage between periodontitis and AD can be explained by two mechanism-

i) Micro-organisms associated with periodontitis causes increased levels of proinflammatory cytokines as host response. This procedure causes production of various cytokines and pro-inflammatory mediators in systemic circulation, resulting in systemic or peripheral inflammation. These pro-inflammatory mediators can cross the BBB and entering the cerebral regions. This results in activation of microglial cells and adverse reactions causing neuronal damage.

ii) According to second mechanism, microorganisms associated with the dental plaque biofilm directly enters in the brain through blood stream or via peripheral nerves. These micro-organisms illicit inflammatory response in central nervous system. This response is initiated due to interplay between neurons and glial cells. This interaction results in release of different cytokines like IL family, TNF-α, transforming growth factor-β, and chemokines (monocyte chemotactic protein, IL-8, macrophage migration inhibitory factor, and monokine induced by γ-interferon) which are identified as biomarkers for AD [91].

Cytokines like TNF-alpha plays major role in in neurodegenerative disease. TNF-α aggravates the inflammatory process, causing in gliosis, demyelination, blood brain barrier (BBB) deterioration, and cell death [92,93].

Seulggie Choi MD et al in their study found that individuals with Chronic periodontitis have higher risk of developing dementia and AD [94].
Increased levels of antibodies for A. actinomycetemcomitans, P. gingivalis, T. forsythia, F. nucleatum and P. intermedia were detected in individuals with AD compared with healthy persons [90,95].

It can be summarized that poor oral hygiene specially periodontitis can be a risk factor for AD but still question arises that what comes first and further longitudinal studies required for the evaluation of the relationship between periodontitis and AD.

3.7 Adverse Pregnancy Outcomes

Females with maternal infection are at higher risk of unfavourable pregnancy outcomes like preterm labour, preterm premature rupture of the membranes, pre-eclampsia, miscarriage, intrauterine growth retardation, low birthweight, stillbirth, and neonatal sepsis [96].

Hormonal changes occurring during pregnancy increases the risk of developing to gingivitis and periodontitis by 40% in pregnant women than non-pregnant women [96].

The association between oral health status and unfavourable pregnancy outcome is explained by two mechanisms-

i) Oral pathogens directly move from unhealthy mouth or oral cavity and crossing the placenta ,reaches in the intra-amniotic fluid and fetal circulation [97].

ii) Second mechanism can be systemic circulation of endotoxins or inflammatory mediators released in periodontal disease can strike adversely on development of the fetus or cause spontaneous abortion [98].

F. nucleatum is the frequently occurred oral pathogen in placental and fetal tissues [99].

Han YW et al reported a case of stillbirth where they found F. nucleatum was moved and travelled to the uterus from the mouth when mother suffered from respiratory infection during pregnancy [100]. In many studies, F. nucleatum was frequently identified in amniotic fluid and cord blood from of preterm birth and neonatal sepsis cases [101,102].

F. nucleatum, P. gingivalis and other oral species were oftenly detected in intrauterine infection, thus proving that these micro-organisms can migrate from oral cavity [102,103].

But in mice model study, it was found that of P. gingivalis has negative impact on pregnancy, LPS from P. gingivalis confined placental development and fetal growth. And when antibodies against Pgingivalis administered ,it caused fetal loss [104,105].

The maternal-fetal interconnect hosts the immune tolerance to the fetus as well as produce strong host defence against infections. Placenta produces Toll-like receptors(TLRs) during normal pregnancy as a part of innate immunity. Increase in TLRs levels suggest that innate immunity activation against the periodontal pathogens like T. denticola and P. gingivalis [106,107,108,19].

Although more studies are required to evaluate the exact relationship and effect of the periodontal diseases and pregnancy outcomes. Results will help to combat and prepare better oral health care protocols during pregnancy.

4. CONCLUSION

Periodontal health has an impact on overall health directly or indirectly. Individuals with periodontal disease are at higher risk for developing systemic diseases than their healthy counterparts, this relationship can be dual. Present literature includes epidemiological , animal and clinical studies which reinforce the link between the periodontal pathogens, inflammation and bacteraemia in the systemic diseases. Further studies are required to explicate the exact role of periodontal health in various systemic diseases and it’s role in aggravating present systemic condition are required. But proper oral hygiene care and timely management of periodontal disease can have positive impact on the overall health leading to favouring or assuring outcomes.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.
REFERENCES

1. Christina Popova, Velitchka Dosseva-Panova, Vladimir Panov. Microbiology of periodontal diseases. A review, Biotechnology & Biotechnological Equipment. 2013;27(3):754-3759. DOI: 10.5504/BBEQ.2013.0027

2. Richards D. Oral diseases affect some 3.9 billion people. Evid Based Dent. 2013;14(2):35. DOI: 10.1038/sj.eds.6400925.[Pubmed]

3. Kweider M, Lowe GD, Murray GD, Kinane DF, McGowan DA. Dental disease, fibrinogen and white cell count; links with myocardial infarction? Scott Med J.1993 Jun;38(3):73-4. DOI:10.1177/003693309303800304.[Pubmed]

4. Ebersole JL, Machen RL, Steffen MJ, Willmann DE. Systemic acute-phase reactants, C-reactive protein and haptoglobin, in adult periodontitis. Clin Exp Immunol. 1997;107(2):347-52. DOI: 10.1111/j.1365-2249.1997.tb1162.x.[Pubmed]

5. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U (2000). Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol. 2000;71(10):1528-34. DOI:10.1902/jop.2000.71.10.1528[Pubmed]

6. Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS (2000). Acute-phase inflammatory response to periodontal disease in the US population. J Dent Res. 2000;79(1):49-57. DOI: 10.1177/0022034500790010701

7. Hutter JW, van der Venden U, Varoufaki A, Huffels RA, Hoek FJ, Loos BG. Lower numbers of erythrocytes and lower levels of hemooglobin in periodontitis patients compared to control subjects. J Clin Periodontol. 2001;28(10):930-6. DOI: 10.1034/j.1600-051x.2001.028010930.x[Pubmed]

8. Newman H N. Focal infection. J Dent Res 1996;75(12):1912-9. DOI: 10.1177/00220345960750120101[Pubmed]

9. Larjava H, Koivisto L, Hakkinen L, Heino J. Epithelial integrins with special reference to oral epithelia. J Dent Res 2011;90(12):1367-76. DOI:10.1177/0022034511402207[Pubmed]

10. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent Jr RL. Microbial complexes in subgingival plaque. J Clin Periodontol. 1998,25(2):134-44. DOI: 10.1111/j.1600-051x.1998.tb02419.x[Pubmed]

11. Paster BJ, Boches SK, Galvin JL, Ericson RE, Lau CN, Levanos VA, Saharsrabude A, FE. Dewhirst Bacterial diversity in human subgingival plaque. Bacteriol. 2001;183(12):3770-83. DOI: 10.1128/JB.183.12.3770-3783.2001.[Pubmed]

12. Haffajee AD, Socransky SS. Microbiol etiological agents of destructive periodontal diseases. Periodontol 2000;1994 5:78-111. DOI: 10.1111/j.1600-0757.1994.tb00020.x[Pubmed]

13. Gary C Armitage. Periodontal diagnoses and classification of periodontal diseases. Periodontol 2000;2000:34:9-21. DOI: 10.1046/j.0906-6713.2002.003421.x[Pubmed]

14. Brochut PF, Marin I, Baehni P, Mombelli A. Predictive value of clinical and microbiological parameters for the treatment outcome of scaling and root planning. J Clin Periodontol. 2005 Jul;32(7):695-701. DOI: 10.1111/j.1600-051x.2005.00730.x[Pubmed]

15. Slots J, Ting M. Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis in human periodontal disease: occurrence and treatment. Periodontol 2000. 1999 Jun;20:82-121. DOI: 10.1111/j.1600-0757.1999.tb00159.x[Pubmed]

16. Ohki T, Itabashi Y, Kohno T, Yoshisawa A, Nishikubo S, Watanabe S, et al. Detection of periodontal bacteria in thrombi of patients with acute myocardial infarction by polymerase chain reaction. Am Heart J 2012;163(2):164-167. DOI: 10.1016/j.ahj.2011.10.012[Pubmed]

17. Linden G J, McClean K, Young I, Evans A, Kee F. Persistently raised C-reactive protein levels are associated with advanced periodontal disease. J Clin Periodontol. 2008;35(9):741-747. DOI: 10.1111/j.1600-051x.2008.01288.x. Epub 2008 Jul 21[Pubmed]

18. Paraskevas S, Huisinga JD, Loos BG. A systematic review and meta-analyses on...
C-reactive protein in relation to periodontitis. J Clin Periodontol 2008; 35(4): 277-290.

DOI: 10.1111/j.1600-051X.2007.01173.x.[Pubmed]

19. World Health Organisation., World Heart Federation., World Stroke Organisation. Global atlas on cardiovascular disease prevention and control. Mendis S, Puska P, Norving B, editors. Geneva: World Health Organisation in collaboration with the World Heart Federation and the World Stroke Organisation; 2011.

20. Lewis Winning, Gerard J. Linden. Periodontitis and Systemic Disease: Association or Causality? Curr Oral Health Rep. 2017;4(1):1-7.

DOI: 10.1007/s40496-017-0121-7[Pubmed]

21. Maurizio S Tonetti, Thomas E Van Dyke, working group 1 of the joint EFP/AAP workshop .Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol. 2013 Apr; 84(4):S24-9.

DOI: 10.1902/jop.2013.1340019[Pubmed]

22. Herzberg MC, Meyer MW. Effects oral flora on platelets: Possible consequences in cardiovascular disease. J Periodontol. 1996;67:1138-42.

23. Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. Am Heart J 2007;154(5):830-7.

DOI: 10.1016/j.ahj.2007.06.037. Epub 2007 Aug 20. [pubmed]

24. Figuero E, Sanchez-Beltran M, Cuesta-Frechoso S, Tejerina JM, del Castro JA, Gutierrez JM, et al. Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. J Periodontol. 2011;82(10):1469-77.

DOI: 10.1902/jop.2011.100719. [Pubmed]

25. Pussinen PJ, Jousilahti P, Alfthan G, Palosuo T, Asikainen S, Salomaa V. Antibodies to periodontal pathogens are associated with coronary heart disease. Arterioscler Thromb Vasc Biol. 2003; 1:23(7):1250-4.

DOI:10.1161/01.ATV.0000072969.71452.87[Pubmed]

26. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. J Periodontol. 2000; 71(10):1554-60.

DOI:10.1902/jop.2000.71.10.1554[Pubmed]

27. Nakano K, Inaba H, Nomura R, Nemoto H, Takeda M, Yoshioka H, et al. Detection of cariogenic Streptococcus mutans in extirpated heart valve and atheromatous plaque specimens. J Clin Microbiol 2006;4(9):3313-7.

DOI: 10.1128/JCM.00377-06.[Pubmed]

28. Firatli E. The relationship between clinical periodontal status and insulin-dependent diabetes mellitus. Results after 5 years. J Periodontol. 1997;8(2):136-40. [PubMed: 9058330]

29. Hung HC, Willett W, Merchant A, Rosner BA, Acherio A, Joshipura KJ. Oral health and peripheral arterial disease. Circulation 2003;107(8):1152-7. [PubMed: 12615794]

30. Skyler J, Oddo C. Diabetes trends in the USA. Diabetes Metab Res Rev 2002;18 (3):S21-6. [PubMed: 1232498]

31. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998; 21(9):1414-31. [PubMed: 9727886]

32. Matthews DC. The relationship between diabetes and periodontal disease. J Can Dent Assoc. 2002;68(3):161-4. [PubMed: 11911811]

33. Thorand B, Kolb H, Baumert J, Koenig W, Chambless L, Meisinger C, Illig T, Martin S, Herder C. Elevated levels of interleukin-18 predict the development of type 2 diabetes: results from the MONICA/KORA Augsburg Study, 1984–2002. Diabetes 2005;54(10):2932-8. [PubMed: 16186395]

34. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, I Machtel EE, et al. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. J Periodontol. 1994;65:260–7. [PubMed: 8164120]

35. Westfelt E, Rylander H, Blohme G, Jonasson P, Lindhe J. The effect of
periodontal therapy in diabetics. Results after 5 years. J Clin Periodontol. 1996;23(2):92-100. [PubMed: 8849844]

37. Christgau M, Palitzsch KD, Schmalz G, Kreiner U, Frenzel S. Healing response to nonsurgical periodontal therapy in patients with diabetes mellitus: clinical, microbiological, and immunologic results. J Clin Periodontol. 1998;25(2):112-24. [PubMed: 9495610]

38. Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. J Clin Periodontol. 2001;28(4):306-10. [PubMed: 11314885]

39. Offenbacher S, Salvi GE. Induction of prostaglandin release from macrophages by bacterial endotoxin. Clin Infect Dis 1999; 28(3):505-13. [PubMed: 10194068]

40. Hajishengallis G, Wang M, Bagby GJ, Nelson S. Importance of TLR2 in early innate immune response to acute pulmonary infection with Porphyromonas gingivalis in mice. J Immunol 2008;181(6):4141-9. doi: 10.4049/jimmunol.181.6.4141.[PubMed]

41. Sonti R, Fleury C. Fusobacterium necrophorum presenting as isolated lung nodules. Respir Med Case Rep 2015;15:80. doi: 10.1016/j.rmcr.2015.05.011.[PubMed]

42. Williams MD, Kerber CA, Tergin HF. Unusual presentation of Lemierre’s syndrome due to Fusobacterium nucleatum. J Clin Microbiol 2003;41(7):3445-8. doi: 10.1128/JCM.41.7.3445-3448.2003.[PubMed]

43. Heo SM, Sung RS, Scannapieco FA, Haase EM. Genetic relationships between Candida albicans strains isolated from dental plaque, trachea, and bronchoalveolar lavage fluid from mechanically ventilated intensive care unit patients. J Oral Microbiol. 2011;3:6362. doi: 10.3402jom.v3i0.6362.[PubMed]

44. Scannapieco FA. Role of oral bacteria in respiratory infection. J Periodontol. 1999;70(7):793-802. DOI: 10.1902/jop.1999.70.7.793.[PubMed]

45. Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. Crit Care Med. 1992;20(6):740-5. DOI: 10.1097/00033246-199206000-00007.[PubMed]

46. Gomes-Filho IS, de Oliveira TF, da Cruz SS, Passos-Soares Jde S, Trindade SC, Oliveira MT, et al. Influence of periodontitis in the development of nosocomial pneumonia: a case control study. J Periodontol 2014;85(5):e82-90. DOI: 10.1902/jop.2013.130369.[PubMed]

47. Porto AN, Borges AH, Rocatto G, Matos FZ, Borba AM, Pedro FL, et al. Periodontal and microbiological profile of intensive care unit inpatients. J Contemp Dent Pract. 2016;17(10):807-814. DOI: 10.5005/jp-journals-10024-1935.[PubMed]

48. Garrouste-Orgeas M, Chevret S, Arlet G, et al. Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospective study based on genomic DNA analysis. Am J Respir Crit Care Med. 1997;156(5):1647-55. DOI: 10.1164/ajrccm.156.5.9604076.[PubMed]

49. El-Solh AA, Pietrantoni C, Bhat A, et al. Colonization of dental plaques: a reservoir of respiratory pathogens for hospital-acquired pneumonia in institutionalized elders. Chest. 2004;126(5):1575-82. DOI: 10.1378/chest.126.5.1575.[PubMed]

50. Williams DS, Kerber CA, Tergin HF. Unusual presentation of Lemierre’s syndrome due to Fusobacterium nucleatum. J Clin Microbiol 2003;41(7):3445-8. doi: 10.1128/JCM.41.7.3445-3448.2003.[PubMed]

51. Heo SM, Sung RS, Scannapieco FA, Haase EM. Genetic relationships between Candida albicans strains isolated from dental plaque, trachea, and bronchoalveolar lavage fluid from mechanically ventilated intensive care unit patients. J Oral Microbiol. 2011;3:6362. doi: 10.3402jom.v3i0.6362.[PubMed]

52. Scannapieco FA. Role of oral bacteria in respiratory infection. J Periodontol. 1999;70(7):793-802. DOI: 10.1902/jop.1999.70.7.793.[PubMed]

53. Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. Crit Care Med. 1992;20(6):740-5. DOI: 10.1097/00033246-199206000-00007.[PubMed]

54. Gomes-Filho IS, de Oliveira TF, da Cruz SS, Passos-Soares Jde S, Trindade SC, Oliveira MT, et al. Influence of periodontitis in the development of nosocomial pneumonia: a case control study. J Periodontol 2014;85(5):e82-90. DOI: 10.1902/jop.2013.130369.[PubMed]

55. Porto AN, Borges AH, Rocatto G, Matos FZ, Borba AM, Pedro FL, et al. Periodontal and microbiological profile of intensive care unit inpatients. J Contemp Dent Pract. 2016;17(10):807-814. DOI: 10.5005/jp-journals-10024-1935.[PubMed]

56. Garrouste-Orgeas M, Chevret S, Arlet G, et al. Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospective study based on genomic DNA analysis. Am J Respir Crit Care Med. 1997;156(5):1647-55. DOI: 10.1164/ajrccm.156.5.9604076.[PubMed]

57. El-Solh AA, Pietrantoni C, Bhat A, et al. Colonization of dental plaques: a reservoir of respiratory pathogens for hospital-acquired pneumonia in institutionalized elders. Chest. 2004;126(5):1575-82. DOI: 10.1378/chest.126.5.1575.[PubMed]

58. Williams DS, Kerber CA, Tergin HF. Unusual presentation of Lemierre’s syndrome due to Fusobacterium nucleatum. J Clin Microbiol 2003;41(7):3445-8. doi: 10.1128/JCM.41.7.3445-3448.2003.[PubMed]

59. Heo SM, Sung RS, Scannapieco FA, Haase EM. Genetic relationships between Candida albicans strains isolated from dental plaque, trachea, and bronchoalveolar lavage fluid from mechanically ventilated intensive care unit patients. J Oral Microbiol. 2011;3:6362. doi: 10.3402jom.v3i0.6362.[PubMed]

60. Scannapieco FA. Role of oral bacteria in respiratory infection. J Periodontol. 1999;70(7):793-802. DOI: 10.1902/jop.1999.70.7.793.[PubMed]

61. Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. Crit Care Med. 1992;20(6):740-5. DOI: 10.1097/00033246-199206000-00007.[PubMed]
patients. Intensive Care Med. 2000;26(9):1239-47. DOI: 10.1007/s001340000585.[PubMed]
54. Genuit T, Bochichio G, Napolitano LM, McCarter RJ, Roghman MC. Prophylactic chlorhexidine oral rinse decreases ventilator-associated pneumonia in surgical ICU patients. Surg Infect (Larchmt). 2001;2(1):5-18. DOI:10.1089/109629601750185316[Pubmed]
55. Koeman M, van der Ven AJ, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med. 2006;173(12):1348-55. DOI: 10.1164/rccm.200505-820OC. [PubMed]
56. Grap MJ, Munro CL, Elswick RK, Jr, Sessler CN, Ward KR. Duration of action of a single, early oral application of chlorhexidine on oral microbial flora in mechanically ventilated patients: a pilot study. Heart Lung. 2004;33(2):83-91. DOI:10.1016/j.hrthmg.2003.12.004.[PubMed]
57. Mori H, Hirasawa H, Oda S, et al. Oral care reduces incidence of ventilator-associated pneumonia in ICU populations. Intensive Care Med. 2006;32(2):230-236. DOI: 10.1007/s00134-005-0014-4.[PubMed]
58. Garnero P. Markers of bone turnover for the prediction of fracture risk. Osteoporos Int 2000;11(6):S55–65. [PubMed: 11193240]
59. Jeffcoat MK, Chestnut CH 3rd. Systemic osteoporosis and oral bone loss: evidence shows increased risk factors. J Am Dent Assoc 1993;124:49–56. [PubMed: 8227773]
60. Page RC, Sims TJ, Geissler F, Altman LC, Baab DA. Defective neutrophil and monocyte motility in patients with early-onset periodontitis. Infect Immun 1985;47(1):169–75. [PubMed: 3965394]
61. Genco RJ, Grossi SG. Is estrogen deficiency a risk factor for periodontal disease? Compend Contin Educ Dent Suppl 1998;22:S23–9. [PubMed: 12089758]
62. Amar S, Han X. The impact of periodontal infection on systemic diseases. Med Sci Monit 2003;9(12):RA291–9. [PubMed: 14646984]
63. Taubman MA, Kawai T. Involvement of T-lymphocytes in periodontal disease and in direct and indirect induction of bone resorption. Crit Rev Oral Biol Med 2001;12(2):125–35. [PubMed: 11345523]
64. Liu D, Xu JK, Figliomeni L, Huang L, Pavlos NJ, Rogers M, et al. Expression of RANKL and OPG mRNA in periodontal disease. Possible involvement in bone destruction. Int J Mol Med. 2003;11(1):17–21. [PubMed: 12469211]
65. Nagasawa T, Kobayashi H, Kiji M, Aramaki M, Mahanoda R, Kojima T, et al. LPS-stimulated human gingival fibroblast inhibits the differentiation of monocytes into osteoclasts through the production of osteoprotegerin. Clin Exp Immunol 2002;130(2):338–44. [PubMed: 12390325]
66. Teng YTA, Nguyen H, Gao X, Kong YY, Gorczynski RM, Singh B, et al. Functional human T-cell immunity and osteoprotegerin ligand control alveolar bone destruction in periodontal infection. J Clin Invest 2000;106(6):R59–67. [PubMed: 10995794]
67. Jiang Y, Mehta CK, Hsu TY, Aslailaibani FFH. Bacteria induce osteoclastogenesis via an osteoblast-independent pathway. Infect Immun 2002;70(6):3143–8. [PubMed: 12011008]
68. Jacobs R, Ghyselen J, Konincks P, van Steenberghe D. Long-term bone mass evaluation of mandible and lumbar spine in a group of women receiving hormone replacement therapy. Eur J Oral Sci 1996;104(1):10–6. [PubMed: 8653490]
69. Pacifi R. Cytokines, estrogen, and postmenopausal osteoporosis – the second decade. Endocrinology 1998;139(6):2659–61. [PubMed: 9607769]
70. Gemmell E, Marshall RJ, Seymour GJ. Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. J Periodontol2000;1997:14:112–43. DOI: 10.1111/j.1600-0757.1997.tb00194.x.[PubMed]
71. Baker PJ. The role of immune responses in bone loss during periodontal disease. Microbes Infect 2000;2(10):1181–92. [PubMed: 11008108]
72. Wactawski-Wende J, Hausmann E, Hovey K, Trevisan M, Grossi S, Genco RJ. The association between osteoporosis and alveolar crest height in postmenopausal women. J Periodontol 2005;76(11):2116–24. [PubMed: 16277584]
73. Renvert S, Berglund J.S., Persson, G.R. et al. The association between rheumatoid arthritis and periodontal disease in a population-based cross-sectional case-control study. BMC Rheumatol 2020;4:31 DOI: 10.1186/s41927-020-00129-4. [Pubmed]

74. Rodríguez-Lozano B, González-Febles J, Garnier-Rodriguez JL, et al. Association between severity of periodontitis and clinical activity in rheumatoid arthritis patients: a case-control study. Arthritis Res Ther. 2019;21(1):27. DOI: 10.1186/s13075-019-1808-z. [Pubmed]

75. Kim SS, Ruiz VE, Carroll JD, Moss SF. Helicobacter pylori in the pathogenesis of gastric cancer and gastric lymphoma. Cancer Lett 2011;305(2):228-38. DOI:10.1016/j.canlet.2010.07.014. [Pubmed]

76. Michaud DS, Fu Z, Shi J, Chung M. Periodontal disease, tooth loss, and cancer risk. Epidemiol Rev. 2017;39(1):49-58.doi: 10.1093/epirev/mxx006. [Pubmed]

77. Gao S, Li S, Ma Z, Liang S, Shan T, Zhang M, et al. Presence of Porphyromonas gingivalis in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Infect Agent Cancer. 2016;11:3. DOI: 10.1186/s13027-016-0049-x. [Pubmed]

78. Yao OW, Zhou DS, Peng HJ, Ji P, Liu DS. Association of periodontal disease with oral cancer: a meta-analysis. Tumour Biol. 2014;35(7):7073-7. DOI: 10.1007/s13277-014-1951-8. [Pubmed]

79. Wen BW, Tsai CS, Lin CL, Chang YJ, Lee CF, Hsu CH, et al. Cancer risk among gingivitis and periodontitis patients: a nationwide cohort study. QJM. 2014;1107(4):283-90. DOI: 10.1093/qjmed/hct248. [Pubmed]

80. Inaba H, Sugita H, Kuboniwa M, Iwai S, Hamada M, Noda T, et al. Porphyromonas gingivalis promotes invasion of oral squamous cell carcinoma through induction of proMMP9 and its activation. Cell Microbiol. 2014;16(1):131-45. DOI: 10.1111/cmi.12211. [Pubmed]

81. Binder Gallimidi A, Fischman S, Revach B, Bulvik R, Malutina A, Rubinstein AM, et al. Periodontal pathogens Porphyromonas gingivalis and Fusobacterium nucleatum promote tumor progression in an oral-specific chemical carcinogenesis model. Oncotarget. 2015;6:22613-23. DOI: 10.18632/oncotarget.4209. [Pubmed]

82. Ha NH, Woo BH, Kim DJ, Ha ES, Choi JI, Kim SJ, et al. Prolonged and repetitive exposure to Porphyromonas gingivalis increases aggressiveness of oral cancer cells by promoting acquisition of cancer stem cell properties. Tumour Biol. 2015;36(12):9947-60. DOI: 10.1007/s13277-015-3764-9. [Pubmed]

83. Fukugaiti MH, Ignacio A, Fernandes MR, Ribeiro Junior U, Nakano V, Avila-Campos MJ. High occurrence of Fusobacterium nucleatum and Clostridium difficile in the intestinal microbiota of colorectal carcinoma patients. Braz J Microbiol. 2015;46(6):1135-40. DOI:https://doi.org/10.1590/S1517-8382446201404665

84. Warren RL, Freeman DJ, Pleasance S, Watson P, Moore RA, Cochrane K, et al. Co-occurrence of anaerobic bacteria in colorectal carcinomas. Microbiome. 2013;1(1):16. DOI: 10.1186/2049-2618-1-16. [Pubmed]

85. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe. 2013;14(2):207-15. DOI:10.1016/j.chom.2013.07.007. [Pubmed]

86. Yu YN, Yu TC, Zhao HJ, Sun TT, Chen HM, Chen HY, et al. Berberine may rescue Fusobacterium nucleatum-induced colorectal tumorigenesis by modulating the tumor microenvironment. Oncotarget. 2015;6(31):36012-23. DOI: 10.18632/oncotarget.4506. [Pubmed]

87. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinska M, Strauss J, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012;22(2):299-306. [Pubmed]

88. Gaur S, Anghiotri R. Alzheimer's disease and chronic periodontitis: is there an association? Geriatr Gerontol Int. 2015;15(4):391-404. DOI: 10.1111/ggi.12425. [Pubmed]

89. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21(3):383-421.
90. McGeer PL, McGeer EG. Inflammation, autotoxicity and Alzheimer disease. Neurobiol Aging. 2001;22:799-809. DOI: 10.1016/s0197-4580(01)00289-5. [PubMed]

91. Kamer AR, Craig RG, Dasanayake AP, Brys M, Glodzik-Sobanska L, de Leon MJ. Inflammation and Alzheimer's disease: possible role of periodontal diseases. Alzheimers Dement. 2008;4(4):242-50. DOI: 10.1016/j.jalz.2007.08.004. [PubMed]

92. Lee KS, Chung JH, Choi TK, Suh SY, Oh BH, Hong CH. Peripheral cytokines and chemokines in Alzheimer's disease. Dement Geriatr Cogn Disord. 2009;28(4):281-7. DOI: 10.1159/000245156. [PubMed]

93. Park KM, Bowers WJ. Tumor necrosis factor-alpha mediated signaling in neuronal homeostasis and dysfunction. Cell Signal. 2010;22(7):977-83. DOI: 10.1016/j.cellsig.2010.01.010. [PubMed]

94. Montgomery SL, Bowers WJ. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. J Neuroimmune Pharmacol. 2012;7(1):42-59. DOI: 10.1007/s11481-011-9287-2. [PubMed]

95. Seulggie Choi MD, Kyuwoong Kim BSc, Jooyoung Chang MD, Sung Min Kim BSc, Seon Jip Kim RDH, Hyun-Jae Cho DDS, PhD, Sang Min Park MD, PhD, MPH Alzheimer's Disease or Vascular Dementia. J Am Geriatr Soc. 2019;67(6):1234-1239. DOI: 10.1111/jgs.15828. [PubMed]

96. Han YW, Wang X. Mobile microbiome: oral bacteria in extra-oral infections and inflammation. J Dent Res. 2013;92(6):485-91. DOI: 10.1177/0022034513487559. [PubMed]

97. Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. Alzheimers Dement. 2012;8(3):196-203. DOI: 10.1016/j.jalz.2011.04.006. [PubMed]

98. Vamos CA, Thompson EL, Avendano M, Daley EM, Quinonez RB, Boggess K. Oral health promotion interventions during pregnancy: a systematic review. Community Dent Oral Epidemiol. 2015;43(5):385-96. DOI: 10.1111/cdeo.12167. [PubMed]

99. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015;15(1):30-44. doi: 10.1038/nri3785. [PubMed]

100. Ebersole JL, Stevens J, Steffen MJ, Dawson lii D, Novak MJ. Systemic endotoxin levels in chronic indolent periodontal infections. J Periodontal Res. 2010;45(1):1-7. DOI: 10.1111/j.1600-0765.2008.01169.x. [PubMed]
preterm pregnancy outcome. J Periodontol. 2007;78(5):833-41. DOI: 10.1902/jop.2007.060201.[Pubmed]

108. Abrahams VM, Mor G. Toll-like receptors and their role in the trophoblast. Placenta 2005;26(7):540-7. DOI:10.1016/j.placenta.2004.08.010.[Pubmed]

109. Chaparro A, Blanlot C, Ramirez V, Sanz A, Quintero A, Inostroza C, et al. Porphyromonas gingivalis, Treponema denticola and Toll-like receptor 2 are associated with hypertensive disorders in placental tissue: a case-control study. J Periodontal Res. 2013;48(6):802-9. DOI: 10.1111/jre.12074.[Pubmed].

© 2021 Vadavadgi et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/70084