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REVIEW ARTICLE

Role of oral foci in systemic diseases: An update

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Abstract

Background: A current research disagreement middles about a theorized connection between chronic oral infections and the progress of adverse systemic health conditions. However, the gap between general and dental medicine is quickly closing, due to significant findings supporting the association between dental infections and systemic conditions such as cardiovascular diseases, type 2 diabetes mellitus, respiratory diseases, stroke, adverse pregnancy outcomes, osteoporosis, renal diseases, and gastrointestinal diseases. Relentless efforts have brought light on numerous advances in illuminating their etiopathological links. However, the majority of data about possible role or interlink between the infection and systemic disease is available in the form of case report or summary. As case reports are not the acceptable to many indexed scientific magazines, many these findings undergo unnoticed to researchers. The currently minimal accessible data provide only an indication of the actuality. **Aim:** This article highlights the Role of oral foci in systemic diseases. **Conclusion:** There is need of sincere work efforts on genetic relatedness of organisms, rather than their phenotypes, sophisticated sampling, detection, and analytical techniques to create the associations. To give insight to recent apprises of different systemic diseases as a consequence of primary oral infections and the pathogenesis link. The odontogenic bacteremia is likely to cause systemic and end organ infections, but such infections can easily resist by body defenses. It is important that role of good oral health and the risks associated with poor oral health should told to the individuals. **Clinical significance:** Dentists and medical practitioners should work together to provide comprehensive health care, thereby reducing the morbidity and mortality associated with oral infections.

Keywords: Adverse pregnancy outcomes, cardiovascular disease, diabetes mellitus, gastrointestinal disease, oral foci, osteoporosis, respiratory disease, renal disease, stroke

Introduction

General practitioner and dentists for years together have paid close attention to their own respective specialty fields, rather than a possible link between oral and systemic health. A current research controversy centers on a hypothesized connection between the presence of chronic oral infections and the development of adverse systemic health conditions. However, this link establishing fast due to substantial findings supporting the association between dental infections and various systemic conditions. The numerous case–control and epidemiologic studies suggest that people with periodontal disease have a unassumingly higher risk for myocardial infarction (MI)[1] than with people without periodontal disease. Few studies have also linked periodontal disease with adverse pregnancy outcomes,[1,2] diabetes mellitus (DM),[3] lung diseases such as pneumonia and chronic obstructive lung disease.[4] The dedicated efforts of researchers have helped in revealing the etiological and pathological links between these chronic inflammatory dental diseases and systemic conditions. This paper abridges the

available evidence in the literature on the possible mechanisms by which oral infections may be responsible for the initiation and progression of systemic diseases. Each section presents the current state of the field. This may help in increasing the awareness about the importance of the oral health, which is often neglected in developing countries.

Focal Infection and Focus of Infection

A focal infection is a localized or general infection caused by the dissemination of microorganisms or toxic products from a focus of infection. Focus of infection refers to a circumscribed area of tissue, which is infected with pathogenic microorganisms and is usually located near a mucous or cutaneous surface.[5] Due to the recent advance in classification and identification of oral microorganisms, some of which are commensal in the oral cavity which gives hint to health-care practitioners about the realistic assessment of the role of oral focal infection in systemic diseases. The oral cavity can act as gateway for microorganism to access the distant body organ through dissemination by taking advantage of compromised immunity. Currently, more than 6 billion bacteria, representing in excess of 700 species belonging to at least nine different phylae, are inhabited in the oral crevices.[6,7] The oral microbial flora, like most other resident floras of the human body, such as those of the skin and the gut, exhibits commensalism, a survival mechanism that benefits the microbes without harming the host. Nevertheless, these largely harmless commensal inhabitants of the human body have the propensity to become pathogenic in the event of compromised host defense mechanism. The presence of the organism in oral cavity environment is largely due to its difference in physiology and histology. For example, the thick, impermeable keratinized layers of the skin prevent entry of microorganism into the circulation from cutaneous flora. The periodic and continuous exfoliation of the superficial layer of epithelium at a quick rate decreases the chance of colonization by the bacterial flora. However, the formation of plaque over the tooth surface which is if left undisturbed can act as scaffold for the microorganism to grow, even in the presence of polymorphonuclear neutrophils in adjacent dentogingival junction and organized lymphatic system. The breach in thin subgingival epithelium can occur easily as oral mucosa in under continuous subjected to trauma due to various normal and paranormal functions such as mastication or eating. This can lead to dissemination of a bacteremia within the systemic circulation as due to the presence of high vascularity.[8] The Universal precautions Guidelines are developed for prevention and management of bacteremia of odontogenic origin, specifically advocating the use of prophylactic antibiotics while dental procedures.[9,10] However, focal bacteremia spread from the oral cavity may involve the number of other organs and body sites.

This evidence suggests that bacteria can gain entry into the bloodstream from oral cavity through a number of mechanisms and a variety of gateways:

1. The trauma to oral tissue caused during the various dental procedures such as periodontal prophylaxis, root canal instrumentation beyond the root apex and extra or intra-alveolar tooth extractions may produce a breakage in capillaries located in the vicinity of the plaque biofilms. This may open the doorway for bacteria to get entry into the systemic circulation. This is more profound in the individuals with poor oral hygiene, which has a higher microbial load leading to dissemination, during oral manipulative procedures.[11]
2. Although only a few distinct species were detected in experimental bacteremia despite the assembly of diverse resident bacteria within the periodontal biofilm, the possibility of the role of innate microbial aspects was suggested in the development of bacteremia.

Triggering Factors in Odontogenic Bacteremia

The dental factors that trigger in odontogenic bacteremia are mentioned in Table 1.

Systemic or End Organ Diseases with Oral Bacteria

The concept of the focal infection, introduced by Hunter in 1911, has recently generated the interest within the research communities, specifically concentrating on the impact of an oral infection on distant sites in the body[12] as well as has highlighted the relationship of oral disease to systemic conditions. Although results are not enough to be conclusive about the relationships between oral disease and systemic health,[13] health care should stay up-to-date of the recent knowledge about oral-systemic disease interrelationship and their possible risk influences as it will affect the outcome of the patient health-care treatment as well as should refer to dental specialists and medical providers as precautionary measure.

Cardiovascular Disease (CVD)

CVD are the largest cause of mortality worldwide. CVD encompasses coronary heart disease (CHD), as well as congestive heart failure, cerebrovascular disease and stroke, peripheral artery disease, carotid artery disease, and aortoiliac disease. CHD is responsible for the majority of deaths than CVD in India. Atherosclerosis is part of etiopathogenesis in

Table 1: Triggering factors in odontogenic bacteremia

Triggering factor
Chewing
Personal oral hygiene measures
Periodontal procedures
Tooth extraction
Orthodontic procedures
Endodontic procedures
Miscellaneous oral procedures

the development of CHD. The deposition of atherosclerotic plaques on the inner layer of walls of arteries characterized this process. Atherosclerosis and MI are closely related involving a complexity of genetic and environmental dynamics. The arterial inflammation has a definitive role in the development of atherosclerosis which is being debated over the last few years. Several epidemiological scholarly works have identified the association between high levels of acute phase reactants such as C-reactive protein (CRP), fibrinogen, serum Amyloid A, with atherosclerosis and an associated risk for development of CVD/CHD.[14] The concept of poor oral health, such as severe or chronic periodontal disease, may put down patient at risk of developing of a variety of systemic disease like CVD.[15-17] The inadvertent tooth brushing habit can result in increased blood level of CRP and fibrinogen;[18] indirectly play a role in coronary arterial plaque formation. Certainty, further evidence-based research studies are needed to affirm whether there is a strong relationship between periodontal disease, CVD and diabetes.[19] The studies conducted on patients with acute ischemic heart disease have shown, the positive correlation between various degrees of chronic periodontitis with higher levels of triglyceride and low-density lipoprotein (LDL) levels.[20] After the loss of few teeth as result of periodontitis, the remaining of teeth act as a source of infection putting the patient at risk for CHD. Holmlund *et al*. suggests that the presence of number of teeth could be one factor in deciding increased risk of mortality in CHD.[21] The periodontitis may add the infectious and inflammatory burden which may increase risk of cardiovascular events and stroke in susceptible person.[3]

The relationship between periodontitis and atherosclerosis has been explained by following pathophysiological mechanisms:

Direct Pathways

Periodontium has rich vascularity which gives a good environment for dissemination of oral microbes and their byproducts into circulatory system. Several triggering factors [Table 1] can induce bacteremias. The oral microbes can directly influence the cardiovascular events such as hypercoagulability, atherosclerosis. Various oral pathogens such as *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Treponema denticola,* and *Eikenella corrodens* have been isolated from atherosclerotic plaques.[22] *P. gingivalis* induces the expression of several cell surface receptors such as toll-like receptor (TLR-2/TLR-4), endothelial cell adhesion molecules, interleukin (IL)-8, IL-6, monocyte chemoattraction protein-1, and TLR-4.[23-26] The autoimmune mechanisms secondary to periodontal infections may influence the progression and development of atherosclerosis.[27]

Indirect Pathways

In patients with periodontal diseases produces certain inflammatory mediators such as CRP, matrix metalloproteinases. These have a positive association with atherosclerosis which is, in fact, an inflammatory disease, responsible for initiation of cardiovascular events.[28,29] Routine periodontal procedure act as potential triggers for dissemination of these inflammatory mediators in the blood circulation, leading to the development of transient bacteremia. During this state, there is release of bacterial virulence factors which called as lipopolysaccharides (LPS) are released in circulation.[30] The proinflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-α], IL-1 beta, IL-6, IL-8), activation of the fibrinolytic system, kallikrein-kinin generation and phospholipase A2 release are released as response. This leads to initiation of vast majority of events such as recruitment of inflammatory cells at site of large blood vessels especially, activation of platelet function.[31] Proinflammatory cytokines (TNF-α, IL-1, IL-6) initiate production of enzymes of NOX family belonging to NADPH oxidases. This increased NOX activity contributes to various pathologies, particularly CVD.[32] TNF-α induced effect on the regulation of endothelial adhesion molecule expression such as intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAM-1), as well as some of the integrins. These ICAMs and VCAM-1 stimulate compact adhesion of inflammatory cells at the vascular surface, whereas platelet endothelial cellular adhesion molecules-1 are implicated in extravasations of blood cells into the vessel and underlying tissue. The formation of atherosclerotic plaques occurs at the site of binding or stagnation of cells. In the absence of high-density lipoprotein which has antiatherogenic properties, there is a migration of leukocytes (diapedesis) to atherosclerotic plaques.[33]

Respiratory Infections/Diseases

A respiratory disease/infection involves the respiratory system affecting the lung and its anatomical parts. These could be a common cold to grave condition pneumonia or chronic obstructive pulmonary disease (COPD), which has significant role increased morbidity and mortality worldwide. Pneumonia is leading causes among the elderly, the majority of these patients are diagnosed as aspiration pneumonia. Pneumonia is an inflammation of the lungs parenchyma due to various etiological agents such fungus, virus, parasites, or bacterial infection.

Recent evidence has suggested that oral cavity act as foci of infection for the development of lung diseases such as aspiration pneumonia, COPD and lower respiratory tract infections.[34,35] The poor or inadequate maintenances of oral health in nursing home residents, elder subjects, intensive care unit patients and hospitalized individuals requiring mechanical ventilation can predispose them to the development of aspiration pneumonia. The pathogenesis of aspiration pneumonia is not clear. The oral cavity is contiguous with the trachea and may be a portal for respiratory pathogen colonization. Development of plaque often involves aggregation of many microorganisms or pathogens.[36,37] such as *Staphylococcus aureus, Pseudomonas aeruginosa, P. gingivalis,* and *A. actinomycetemcomitans.* There are

chances of aspiration of bacterial foci from the oral cavity and upper airway into the lungs, increasing the risk of development of the aspiration pneumonia.[38,39] Theses foci could be plaque or oral biofilm, residual root of the decayed teeth, residue in oral mucous epithelium and oral dryness as result of impaired oral function. Oral bacteria releases various enzymes which help them to adhere and colonize the mucosal surface.[36] The cytokine released from the epithelial cell cause the recruitment of chronic inflammatory cells, increasing the susceptibility of mucosa to the infections.[4] There are reports of increased incidence of aspiration pneumonia in patients on ventilators having periodontal infections or poor periodontal health status[40] which results increased mortality the elderly person.[41,42] During endotracheal intubation in the various procedure, there is aspiration of bacterial microbial flora from the oral mucosa or upper airways passage to respiratory mucosa, thereby increases the chance of developing the aspiration pneumonia.

DM

DM is a metabolic disorder affecting the metabolism of carbohydrates, lipids, and proteins, resulting in altered state of blood sugar. It is due to insulin deficiency as a result of pancreatic β-cell dysfunction or insulin resistance in cells.[43] Conversely, periodontitis may be a risk factor for worsening glycemic control among patients with diabetes and may increase the risk of diabetic complications.[44] Chronic periodontitis causes the imbalance between the host immune system and oral microbial flora resulting the increase in inflammatory response. To met a high level of immune response body system requires high level of energy, resulting in reduction in the glucose level at cellular level. The inflammatory cells release various cytokine such as TNF-α which exerts certain kind of stress situation at cellular level.[45,46] There is an association between the status of periodontitis, glucose intolerance, signs of metabolic diseases, and diabetes-associated complications, such as CVD.[47,48]

Recently, the role of certain oral microorganism present in in chronic periodontitis have been suggested in worsening the status of DM.[49] The persistent release of LPS from *P. gingivalis* and prolonged upregulation of TNF-α which may increase the severity of diabetes.[46] The chronic periodontitis, involving Gram-negative organisms specially *P. gingivalis, Tannerella forsythia,* and *P. intermedia*, have significantly higher levels of CRP and fibrinogen than those without periodontitis which may be associated with poor glycemic control.[50] Besides these factors, the virulence of *P. gingivalis* is critical in poor glycemic control.[51] Dental procedures as well as daily activities such brushing or chewing can produce bacteremia and endotoxemia in patients suffering from periodontitis. These events increase levels of inflammatory mediators such as IL-1, IL-6, and TNF-α in serum leading to chronic inflammatory state.[46] The inflammatory mediators play role in development of insulin resistance, under the influence of environmental factors such as decreased physical activity, poor nutrition, obesity, and infection.[52]

Adverse Pregnancy Outcomes

Preterm low-birth-weight (PLBW) is worldwide leading perinatal problems and has evident public health implications, due to the fact that their incidence does not decrease in spite of the many attempts at their prevention. Health of the pregnant women is an important factor influencing pregnancy outcome. Cervical incompetence or short cervical length, pre-eclampsia and numerous maternal infection, systemic like toxoplasmosis[53,54] and local infections such as bacterial vaginosis, chorioamnionitis, or uterine tract infections[55,56] pose greater risk to health of pregnant women. Various risk factors such as increasing age of women giving birth, ethnical origin, tobacco, socioeconomic disparities, maternal body-mass index, or multiple pregnancies are responsible for PLBW.[57,58] The majority of time cause of preterm birth remain unknown.[56] It is also possible that infectious processes occurring elsewhere in the body may contribute to neonatal morbidity and mortality.

Periodontal disease is a risk factor for adverse pregnancy outcome. There is a positive correlation between poor maternal periodontal health with PLBW babies.[59-61] Preterm birth incidence increases frequently with the severity of periodontitis.[62-64] This is linked to biological theories: (i) Bacterial spreading, (ii) inflammatory products dissemination, and (iii) role of feto-maternal immune response against oral pathogens.[61]

The bacterial spreading theory is based on the possible dissemination of oral bacteria including periodontal pathogens through blood circulation[65] to the amniotic fluid and leading to chorioamniotic infections. The frequent gingival inflammation of women presenting periodontal diseases,[66] especially pregnancy-associated gingivitis, facilitates bacteremia process.[67] Many analyses of amniotic fluid or placenta showed the presence of different oral pathogens such as *Bergeyella*, *Eikenella*,[67] *Fusobacterium nucleatum,* or *P. gingivalis.*[68,69] Inside uterus, these pathogens could provoke an inflammatory response. The increase of inflammatory cytokines or metalloproteases synthesis and the neutrophil activation could induce preterm birth process.[67]

The immune and genetic characteristics of fetus and pregnant women are one of the potential mechanisms linking periodontal diseases to preterm birth. Higher levels of periodontopathogen-specific immunoglobulin M in umbilical-cord blood in babies born preterm was found in the past.[70] This immune response against oral pathogens could evoke with an inflammatory response, and increases the risk significantly. In view of the possible adverse effects of periodontitis on pregnancy outcomes, it is important to promote good oral hygiene.

Stroke

Ischemic Stroke is caused due decrease in blood supply to the brain leading to death of brains cells. Reduction in blood supply is caused by the formation of clot formation or thrombus within these vessels. Various studies have correlated periodontal disease

with stroke.[71-73] Kim *et al*., in their case-control study, found a significant association of periodontitis with hemorrhagic stroke.[74] The inflamed periodontium or other intraoral pathologies, such as caries, or periapical osteitis releases periodontal pathogens, antigens, endotoxins, inflammatory cytokines and LPS into the systemic circulation. The oral pathogenic bacteria, cytokines, and LPS in the systemic circulation may promote atherosclerosis and affect blood coagulation, the function of platelets, and PG synthesis, thereby contributing to the onset of stroke. Majority case reports suggested the primary oral foci such as poor oral hygiene, periodontitis, dental abscesses, mucositis with oral ulcerations as a source of infection and contributing risk factor in the development of CNS disease.

Rheumatoid Arthritis (RA)

The etiology of RA which considered the autoimmune disease is unknown, however recently various environmental factors including hormones, dietary factors, infections, tobacco smoke as well as antigen and antibody interactions are linked to increased risk for RA. RA is characterized by the presence of an inflammation in the synovial membrane affecting joint architecture leading to reduced function. Periodontitis and RA share similar clinical and pathogenic characteristics as well as a strong relationship between severity of periodontal disease and RA.[74,75] The current paradigm for RA includes an initiating event (possibly a microbial exposure or a putative autoantigen) leading to significant synovial inflammation and tissue destruction. As for periodontitis, there is no direct proven cause and effect relation with the development of RA. Periodontal pathogen may responsible for the alteration of inflammatory response in susceptible host. Release of cytokines by inflammatory cells (T and B lymphocytes, neutrophils, and monocytes), could contribute to the development of RA.

Oral bacterial DNAs are detected in serum and synovial fluid of RA patients.[76] RA patients also were found to have a significantly higher level of IgG antibody against *P. gingivalis*, *P. intermedia,* and *Bacteroides forsythus*.[77] An association of *P. gingivalis* titres with RA-related autoantibody and CRP levels suggest that infection with this organism may play a role in the risk for and progression of RA.[78]

Osteoporosis

Osteoporosis is a systemic disease affecting the skeletal bone. It is characterized by loss of bone leading to bone fragility and fracture susceptibility. It is multifactorial disease of which inflammation is major factor. Recently, investigation on this aspect has linked the various inflammatory diseases with osteoporosis.[79] Oral inflammations such as chronic periodontal inflammation, oral osteoporosis, and systemic osteoporosis have inter-relation, but little is known about the mechanism behind such a relationship. Inflammatory mediators are suspected in bone loss through modulation of osteoclast function and osteoclastogenesis. It was suggested that chronic periodontal inflammation can act as source or reservoir of for numerous cytokines, e.g., IL-6.[80,81] These cytokine level are higher at local level but are highly variable in systemic or within serum. It is still unclear whether oral inflammation can cause to skeletal osteoporosis as cytokine level within serum are variable and cannot be linked with clinical parameter of periodontal inflammation.[82] Another possible mechanism which is contradictory or support link between chronic periodontitis and osteoporosis is there. Chronic periodontitis caused the stress and trauma leading to activation of other inflammatory pathways (for example, cyclooxygenase 2 and prostaglandin production. Increase in systemic level of inflammatory mediators may have a stimulating effect on osteoclasts, and thus inducing bone resorption at either at local level or distant level.[83]

Renal Diseases

Renal diseases are considered a worldwide public health problem, mainly due to its high morbidity and mortality. Glomerular nephropathies are sometimes attributed to oral foci of infection. Glomerular disease, e.g., acute post-streptococcal glomerulonephritis sometimes develops rapidly after an oral infection such as periapical granuloma or abscess, and chronic periodontitis. Indirect involvements of oral microorganisms in the development of this renal pathology were observed. Microorganism does not attack the kidney directly, but an infection causes the immune system to overproduction of antibodies, which enter the blood circulation and get deposited in the glomeruli, causing damage. Periodontal bacteria have known to cause immune reaction and might cause IgA nephropathy.[84] The type of microorganisms most commonly involved in urinary infections is *Escherichia coli*, although *Staphylococci* and *Streptococci* also may be cultured. Of the *Streptococci*, *Streptococcus hemolyticus* seems to be the most common. This *Streptococcus* is an uncommon inhabitant of dental root canals or periapical and gingival areas. *P. gingivalis* has shown an invasive trend toward endothelial cell cultures and may directly affect the glomeruli.[85] Ardalan *et al.*[86] have recently been suggested that periodontitis may be a neglected and treatable cause of glomerulonephritis.

Gastrointestinal (GI) Diseases

The oral cavity provides a doorway between the extra oral environment and the gastrointestinal tract. It facilitates both food ingestion and digestion. Gastrointestinal diseases have been periodically related to oral foci of infection. It has been proposed that the constant swallowing of oral microorganisms might lead to a variety of GI diseases. In most instances, however, the low pH of the gastric secretions is an adequate defense against such infection.

Helicobacter pylori is an important human pathogen linked to chronic gastritis, peptic ulcer, duodenal ulcers, gastric

malignancies and lymphoid tissue lymphoma. The exact pathway of transmission of *H. pylori* is not clear; however, it is suspected that oral cavity is most possible source of microorganism. *H. pylori* have been detected in plaque and saliva.[87-89] However, it is still controversial point and under study. It is believed that *H. pylori* belongs to the normal microbiota of the human oral cavity and maintains a commensal relationship with the human host. Conversely, it may be possible that presence of *H. pylori* in oral cavities may be a result of the ingestion of contaminated foods or as a secondary effect of gastroesophageal reflux.[87,90] Besides, there are many factors such as variations in the geography location of subjects, oral health status, intricacy of the oral microbiota and methods of detection, etc., which can affect progress of gastrointestinal disease.[87]

Conclusion

In this era of evidence-based medicine, a vast number of research studies have indicated that oral infection are a possible causal factor which can influence the progression of important systemic diseases. However, the majority are in the form of reports or as a summary of cases. Since they lack originality, a large number of them go unreported. The odontogenic bacteremia is likely to cause systemic and end organ infections, but such infections can easily resist by body defenses. It is important that role of good oral health and the risks associated with poor oral health should told to the individuals. Dentists and medical practitioners should work together to provide comprehensive healthcare, thereby reducing the morbidity and mortality associated with oral infections. There is need of much more work in this area to established strong association of oral microorganism with systemic disease causation. This will provide future direction to prepare guidelines of treatment of oral infection.

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