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ORAL FOCI OF INFECTION LEADING TO SYSTEMIC DISEASES—AN EMERGING PROBLEM IN MEDICINE

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ABSTRACT

The relationship between oral and general health has been increasingly recognised during the past two decades. Several epidemiological studies have linked poor oral health with cardiovascular disease, poor glycaemic control in diabetics, low birth-weight pre-term babies and a number of other conditions, including rheumatoid arthritis and osteoporosis. It is therefore important that the individuals should be made aware of the risks associated with poor oral health. Hence, dentists and medical practitioners should work together to provide comprehensive health care, thereby reducing the morbidity and mortality associated with oral infections.

KEYWORDS: Infection, Oral foci, Systemic disease.

INTRODUCTION

In 1900, William Hunter, a British physician, first suggested that micro-organisms found in the oral diseases were responsible for a wide range of systemic conditions. The concept of focal infection was evolved.[1] The teeth are the only nonshedding surfaces in the body, and bacterial levels can reach more than $10^{[11]}$ microorganisms per mg of dental plaque. Human endodontal and periodontal infections are associated with complex microfloras in which approximately 200 species (in apical periodontitis and more than 500 species (in marginal periodontitis) have been encountered. These infections are predominantly anaerobic, with gram-negative rods being the most common isolates. The anatomic closeness of these microfloras to the blood-stream can facilitate bacteremia and systemic spread of bacterial products, components, and immunocomplexes. A number of epidemiological studies have suggested that oral infection, especially marginal and apical periodontitis, may be a risk factor for systemic diseases.[2]

Definition

Foci of infection

Persistent infection with microorganisms and septic material constantly localized anywhere in the body, which on stimulation disseminates to other parts of the body causing diseases in remote parts.[3]

Oral foci of infection: Localized area of persistent infection containing microorganisms and septic materials in any part of the oral cavity, which on stimulation disseminates to other parts of the body causing diseases in remote parts.[3]

PATHWAYS LINKING ORAL INFECTION TO SECONDARY NONORAL DISEASE[2]

Three mechanisms or pathways linking oral infections to secondary systemic effects have been proposed. These are metastatic spread of infection from the oral cavity as a result of transient bacteremia, metastatic injury from the effects of circulating oral microbial toxins, and metastatic inflammation caused by immunological injury induced by oral micro- organisms.[2]

Metastatic infection

As previously discussed, oral infections and dental procedures can cause transient bacteremia. The microorganisms that gain entrance to the blood and circulate throughout the body are usually eliminated by the reticuloendothelial system within minutes (transient bacteremia) and as a rule lead to no other clinical symptoms than possibly a slight increase in body temperature. However, if the disseminated microorganisms find favorable conditions, they may settle at a given site and, after a certain time lag, start to multiply.[2]

Metastatic injury

Some gram-positive and gram-negative bacteria have the ability to produce diffusible proteins, or exotoxins, which include cytolytic enzymes and dimeric toxins with A and B subunits. The exotoxins have specific pharmacological actions and are considered the most powerful and lethal

poisons known. Conversely, endotoxins are part of the outer membranes released after cell death Endotoxin is compositionally a lipopolysaccharide (LPS) that, when intro- duced into the host, gives rise to a large number of pathological manifestations. LPS is continuously shed from periodontal gram-negative rods during their growth in vivo.[2]

Metastatic inflammation

Soluble antigen may enter the bloodstream, react with circulating specific antibody and form a macromolecular complex. These immunocomplexes may give rise to a variety of acute and chronic inflammatory reactions at the sites of deposition.[2]

PERIODONTAL DISEASE AFFECTS SUSCEPTIBILITY TO SYSTEMIC DISEASE[2]

The term periodontal disease is used to describe a group of conditions that cause inflammation and destruction of the attachment apparatus of the teeth (i.e., gingiva, periodontal ligament, root cementum and alveolar bone). Periodontal disease is caused by bacteria found in dental plaque and about 10 species have been identified as putative pathogens in periodontal disease, mainly gram-negative rods. *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis* and *Bacteroides forsythus* are the gram-negative bacteria most commonly associated with periodontitis Periodontitis lesions exhibit gingival inflammation as well as destruction of the periodontal ligament and alveolar bone. This leads to bone loss and apical migration of the junctional epithelium, resulting in the forma- tion of periodontal pockets.[2]

Subgingival biofilms

Subgingival biofilms constitute an enormous and continuing bacterial load. They present continually renewing reservoirs of LPS and other gram-negative bacteria with ready access to the periodontal tissues and the cir- culation. Systemic challenge with gram-negative bacteria or LPS induces major vascular responses, including an inflammatory cell infiltrate in the vessel walls, vascular smooth muscle proliferation, vascular fatty degeneration and intravascular co- agulation. LPS upregulates expression of endothelial cell adhesion molecules and secretion of interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and thromboxane, which results in platelet aggregation and adhesion, formation of lipid- laden foam cells and deposits of cholesterol and cholesterol esters.[2]

Periodontium as cytokine reservoir

The proinflammatory cytokines TNF- α, IL-1 α, and gamma interferon as well as prostaglandin E_2 (PGE_2) reach high tissue concentrations in periodontitis. The periodontium can therefore serve as a renewing reservoir for spillover of these mediators, which can enter the circulation and induce and perpetuate systemic effects. IL-1α favors coagulation and thrombosis and retards fibrinolysis. IL-1, TNF- α and thromboxane can cause platelet aggregation and adhesion, formation of lipid-laden foam cells and deposition of cholesterol. These same mediators emanating from the diseased periodontium may also account for preterm labor and low-birth-weight infants.[2]

SYSTEMIC DISEASES ASSOCIATED WITH ORAL INFECTION

Cardiovascular Disease

Cardiovascular diseases such as atherosclerosis and myocardial infarction occur as a result of a complex set of genetic and environmental factors. There are several proposed mechanisms by which periodontal disease may trigger pathways leading to cardiovascular disease through direct and indirect effects of oral bacteria.[2]

First, evidence indicates that oral bacteria such as *Streptococcus sanguis* and *Porphyromonas gingivalis* induce platelet aggregation, which leads to thrombus formation. These organisms have a collagen-like molecule, the platelet aggregation-associated protein, on their surface.[2]

The second factor in this process could be an exaggerated host response to a given microbial or LPS challenge, as reflected in the release of high levels of proinflammatory mediators such as PGE_2, TNF-alpha and IL-1. These mediators have been related to inter individual differences in the T-cell repertoire and the secretory capacity of monocytic cells. Typically, peripheral blood monocytes from these individuals with the hyper inflammatory monocyte phenotype secrete 3- to 10-fold-greater amounts of these mediators in response to LPS than those from normal monocyte phenotype individuals. Several investigators have suggested that genes that regulate the T-cell monocyte response and the host-microbe environment can directly trigger and modulate the inflammatory response. Patients with certain forms of periodontal disease, such as early-onset periodontitis and refractory periodontitis, possess a hyper inflammatory monocyte phenotype.[2]

A third mechanism possibly involves the relationship be-tween bacterial and inflammatory products of periodontitis and cardiovascular disease. LPS from periodontal organisms being transferred to the serum as a result of bacteremias or bacterial invasion may have a direct effect on endothelia so that atherosclerosis is promoted. LPS may also elicit recruitment of inflammatory cells into major blood vessels and stimulate proliferation of vascular smooth muscle, vascular fatty degeneration, intravascular coagulation and blood plate- let function. These changes are the result of the action of various biologic mediators, such as PGs, ILs and TNF- α on vascular endothelium and smooth muscle. Fibrinogen and WBC count increase noted in periodontitis patients may be a secondary effect of the above mechanisms or a constitutive feature of those at risk for both cardiovascular disease and periodontitis.[2]

Finally, oral infection can also cause tooth loss. Evidence has shown that edentulous persons with and without dentures and dentate individuals with missing teeth change their eating habits. They may thereby avoid certain nutritious foods because of difficulty in chewing and select high-calorie, high-fat food. When the foods cannot be well pulverized, this has an adverse effect on the internal absorption of nutrients. Such dietary preferences would predispose such individuals to the type of high-fat foods that are recognized as risk factors for cardiovascular disease.[2]

Stroke

Stroke is classified as either hemorrhagic or non-hemorrhagic stroke. Non-hemorrhagic stroke or ischemic stroke is usually caused by thromboembolic events and cerebrovascular atherosclerosis, whereas hemorrhagic stroke often results from a vascular bleed such as an aneurysm. Periodontal disease has been associated primarily with an increased risk of non-hemorrhagic stroke. Periodontal infection may contribute directly to the pathogenesis of atherosclerosis by providing a persistent bacterial challenge to the arterial endothelium, thereby contributing to the monocyte and macrophage driven inflammatory process that results in atheromatosis and the narrowing of the vessel lumen. Furthermore, periodontal infection may stimulate a series of indirect systemic effects, such as the elevated production of fibrinogen and CRP, which serve to increase the risk of stroke. Finally, bacteremia with PAAP- positive bacterial strains from the supragingival and subgingival plaque can increase platelet aggregation, thereby contributing to thrombus formation and subsequent thromboembolism, which is the leading cause of stroke.[4]

Diabetes Mellitus

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to an absolute or relative deficiency of insulin. Diabetes mellitus is characterized by metabolic abnormalities and long-term complications involving the eyes, kidneys, nervous system, vasculature, and periodontium. Diabetes is commonly categorized as type 1, or insulin dependent, and type 2, non-insulin dependent. The fundamental derangement in insulin-dependent diabetes is the hypoproduction of insulin due to destruction of the beta cells of the pancreas. In non-insulin-dependent diabetes, the derangement involves resistance of target tissue to insulin action.[2]

Although the precise etiology is still uncertain in both main types of primary diabetes, environmental factors interact with a genetic susceptibility to determine which of those with the genetic predisposition actually develop the clinical syndrome and the timing of its onset.

A model was presented by Grossi and Genco, in which severe periodontal disease increases the severity of diabetes mellitus and complicates metabolic control.[5] They propose that an infection-mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from LPS and products of periodontopathic organisms may amplify the magnitude of the advanced glycation end product (AGE)-mediated cytokine response that is operative in diabetes mellitus. The combination of these two pathways, infection and AGE-mediated cytokine upregulation, helps explain the increase in tissue destruction seen in diabetic periodontitis and how periodontal infection may complicate the severity of diabetes and the degree of metabolic control, resulting in a two-way relationship between diabetes mellitus and periodontal disease or infection.[2]

Respiratory infections

An association between oral conditions such as periodontal disease and several respiratory conditions has been noted. Several mechanisms can be envisioned to help explain how oral bacteria can participate in the pathogenesis of respiratory infection: 1) aspiration of oral pathogens (such as *P. gingivalis, A. actinomycetemcomitans*, etc.) into the lung; 2) periodontal disease-associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens; 3) periodontal disease-associated enzymes may destroy salivary pellicles on pathogenic bacteria; and 4) cytokines originating from periodontal tissues may alter respiratory epithelium to promote infection by respiratory pathogens.[6]

Periodontal Disease-Associated Enzymes in Saliva May Modify Mucosal Surfaces

Data suggest a mucosal alteration, perhaps the loss of fibronectin from the epithelial cell surface, promoted bacterial adhesion. Buccal epithelial cells from gravely ill patients, all colonized by *P. aeruginosa*, interacted with greater numbers of bacterial cells in vitro and possessed lesser amounts of surface fibronectin as determined by immunofluorescence. The removal of fibronectin (by exposure to proteases) may unmask mucosal surface receptors for respiratory pathogen adhesins. Other investigators have also pointed out an inverse relation between the amount of mucosal epithelial cell fibronectin and Gram-negative bacilli binding to these cells.[6]

Destruction of Protective Salivary Pellicles by Oral Bacteria

Recent evidence suggests that the respiratory pathogen *H. influenzae* binds to mucins contained within mucosal secretions. This binding may involve sialic acid residues. In the context of COPD, it is possible that subjects with poor oral hygiene may have elevated levels of hydrolytic enzymes (e.g. sialidase) in their saliva. These enzymes may process mucins, which reduce their ability to bind to and clear pathogens such as *H. influenzae*. Conversely, enzymes may process the respiratory epithelium to modulate adhesion of such pathogens to the mucosal surface.[6]

Salivary Cytokines May Alter Respiratory Epithelium

One mechanism proposed for the gross airway epithelial damage observed in COPD involves release of proinflammatory cytokines (i.e., IL-8) from the respiratory epithelium, resulting in the recruitment and infiltration by neutrophils, which subsequently release proteolytic enzymes and toxic oxygen radicals. The release of cytokines from the respiratory epithelium may be the result of the binding of respiratory pathogens or their products to the respiratory epithelial cells.[6]

Pregnancy Outcome

Low-birth-weight (LBW) infants (those weighing less than 2500 g at birth) are 40 times more likely to die in the neonatal period than normal-birth-weight (NBW) infants." Although about 7% of all infants weigh less than 2500 g at birth, they account for two thirds of neonatal deaths. Periodontitis is a remote gram-negative infection that may play a role in LBW. Periodontopathic organisms and their products may have wide-ranging effects, most likely mediated through stimulation of host cytokine production in target tissues.[7]

Animal studies suggest that remote reservoirs of gram-negative organisms and their products may have a negative impact on pregnancy outcome. P. gingivalis implanted in subcutaneous chambers during gestation caused significant increase in TNF-a and PGE levels. This localized subcutaneous infection resulted in a significant increase in fetal death and a decrease in fetal birth weight for those that remained viable, when compared with control animals that were not inoculated. There was a significant correlation between TNF-a and PGE levels, as well as fetal death and growth retardation. These data suggest that a remote, nondisseminated infection with P. gingivalis may result in abnormal pregnancy outcomes in this model.[7]

Central Nervous System

Existing proof links oral focal sepsis to trigeminal, atypical neuralgias, unilateral paralysis of the face and brain infarctions.[8,9] Infections and inflammations in the body alter the values of leukocytes, fibrinogen and coagulation factors, causing myocardial and brain infarctions.[10,15]

Any focal sepsis, including oral focal sepsis contains bacteria which can increase manifold and circulate into the blood stream causing life-threatening conditions, such as brain abscesses.[16] The postulated entry of oral microorganisms into the cranium maybe by, along the facial planes, hematogenous route—through general circulation, veins which lack valves, through cavernous sinus, lymphogenous route and indirectly by extraoral odontogenic infections. Bacterial lipopolysaccharide endotoxins and host- produced inflammatory cytokines may also aid in the development of atheroma's and thus infarctions.[14,15]

Eye

Uveitis or iritis is the most common manifestations of metastatic inflammation due to an immunologically exuberant host response in conjunction with oral foci.[16,17,18]

Skeletal System and GIT

Removal of dental focal sepsis has shown remarkable alleviation in the state of infectious arthritis.[19] Systemic allergy with increased levels of IgE was an important finding in patients with periapical periodontitis.[20,21] Oral infections have been seen to aggravate arthritis and Crohn's disease, while an improvement of symptoms follows the abolition of oral foci.[22,23]

Osteoporosis

Osteoporosis has been described as 'thin bones' or 'brittle bones'. Periodontal pathogens releases endotoxins and proinflammatory cytokines, IL-1 and IL-6 which results in uncoupling of normal bone homeostasis leading to increased osteoclastic activity and decreased bone density thereby causing osteoporosis.[24,25]

Skin

Rosacea is a long-term skin disorder, which involves the facial convexities, characterized by recurrent flushing, persistent erythema and telangiectasia. Removal of infectious foci specifically dental foci caused a major improvement and led to recovery.[26] In a case of neurodermatitis, when the foci were eliminated, it has been reported to have retreated from its severe form.[27]

CONCLUSION

Thus we see that oral infection, especially periodontitis, is a potential contributing factor to a variety of clinically important systemic diseases. If this is neglected it can lead to significant morbidity and mortality.

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