Review Article

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Risk Factors in Periodontal Disease Progression

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Abstract

Inflammatory periodontal disease is one of the most common diseases of mankind. Gingival inflammation is widespread, but advanced periodontitis is limited to relatively small groups of population. Microbial plaque deposits at the dentogingival interface initiate gingivitis. Progression to periodontitis is modified by several environmental, behavioral, biological and healthcare variables. The purpose of this paper is to summarize the available information on the influence of risk factors on progression of periodontitis.

Keywords: Inflammatory disease; Microbial deposit; Genetics; Smoking; Diabetes; socioeconomic factor; HIV.

Introduction

Risk factors are part of the causal chain for a particular disease or can lead to the exposure of the host to a disease. If a risk factor is absent or removed, a reduction in the probability of the disease occurrence is noted.

The risk factors can be defined as any environmental, behavioral or biologic factor that, when present, increase the likelihood that an individual will develop disease.[1] It is important to make the distinction that risk factors are associated with a disease but do not necessarily cause the disease. The interventional study gives the strongest evidence of casual relationship.[2]

Risk factors may be modifiable or non-modifiable. Modifiable risk factors are usually environmental or behavioral in nature whereas non-modifiable risk factors are usually intrinsic to the individual and therefore not easily changed. Non modifiable risk factors are also known as determinants. Evidence used to identify risk factors usually is derived from case reports, caseseries, case control study, cross sectional, longitudinal study and interventional study. All these studies can identify factors associated with a disease though they are not in strength. The longitudinal studies may be capable of identifying a casual relationship. The interventional studies give strongest evidence of a casual relationship and also provide benefit of elimination factor.[3]

Risk indicators are probable or putative risk factors that have been identified in cross sectional studies, but not confirmed through longitudinal studies. The term risk determinant / background which in sometime substitute for the term risk factors that cannot be modified.

Risk predictors/marker although associated increased risks for disease do not cause the disease. These factors also are identified in cross sectional and longitudinal studies.[4]

Microbial plaque is a crucial factor in inflammation of periodontal tissues, but, progression of gingivitis to periodontitis is largely governed by host based factors. Microbial films of particular composition will initiate chronic periodontitis. In certain individuals, their host response and cumulative risk factors predispose them to

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periodontal destruction. Systemic factors of patients influence the effectiveness of host response so that the rate of periodontal destruction may be significantly increased.

Smoking not only increases the risk for developing periodontal disease but also impairs the response to periodontal therapy. Stress and other psychosomatic conditions may have direct autoimmune effect of behavior mediated effects on body defenses. There is a convincing evidence from twin studies for a genetic predisposition to periodontal disease. The study has indicated that the risk of chronic periodontitis in twins has an inherited component. Much attention has been focused on the polymorphisms associated with the genes involved in cytokine production. Such polymorphisms have been linked to an increased risk for periodontal disease.

At present, sufficient amount of dependable information exists to begin risk assessment of periodontal disease. The purpose of this paper is to summarize the existing information about the role of risk factors in periodontitis. Longitudinal studies conducted to identify the potential risk factors are also presented.

Risk elements for periodontal diseases are categorized as follows[1]:

1. Risk factors for periodontal diseases
   - Tobacco smoking
   - Diabetes
   - Pathogenic bacteria
   - Microbial tooth deposits
2. Risk determinants for periodontal diseases
   - Genetic factors
   - Age
   - Gender
   - Socioeconomic status
   - Stress
3. Risk indicators for periodontitis
   - HIV/AIDS
   - Osteoporosis
   - Infrequent dental visits
4. Risk markers/predictors for periodontitis
   - Previous history of periodontal disease
   - Bleeding on probing

Tobacco smoking and Periodontal disease

A wealth of data has been presented demonstrating that of all the risk factors identified, cigarette smoking may be the environmental risk most strongly associated with periodontitis. In many of the studies, multivariate analyses indicated that smoking was an independent risk factor for periodontal disease, after controlling for oral hygiene, plaque, calculus, socioeconomic and demographic factors.

Further support for this, except that, smoking is a risk factor for periodontal disease, is provided by studies in which frequency of smoking or the consumption of a certain quality of cigarettes over a period of time, is positively correlated with increasing levels of risk of periodontal disease observed among current smokers as compared with ex-smokers, while the lowest risk is observed for those who never smoked.[2]

Smoking may play a role in the etiology of refractory periodontitis, as most individuals with refractory periodontitis are heavy smokers. There is sufficient evidence that smoking behavior delays healing and impairs the quality of repair after periodontal therapy. Smoking also increases the risk for osteoporosis, progressive attachment loss and tooth loss in younger individuals, early-onset periodontitis, heart disease, periodontal disease in diabetics, root caries, leukoplakia and oral cancer.

Health studies in 1990s examined the effect of smokeless (snuff or chewing) tobacco on periodontal health in certain demographic groups such as Native Americans, American baseball players who have a high rate of use of snuff and chewing tobacco. Use of chewing tobacco has long been associated with localized loss of attachment and oral

leukoplakia but not with severe periodontal destruction. Gingival recession and white lesions frequently occur at sites of placement of smokeless tobacco. In a case-control study, smokeless tobacco users matched for plaque and probing depth levels to non-tobacco subjects presented significantly higher gingival index scores and elevated prostaglandin E2 concentration in gingival crevicular fluid.

The mechanisms through which smoking tobacco deleteriously affects the periodontium remains obscure, although several possibilities have been described. Potential molecular and cellular mechanisms in pathogenesis of smoking associated periodontal disease include immunosuppression, exaggerated inflammatory cell responses and impaired stromal cell functions. In support of the concept that smoking exerts local effects, studies have shown that smokers with periodontal disease have less clinical inflammation and gingival bleeding compared with non-smokers. This tissue response may be due to the tobacco smoke by-product, nicotine, which exerts local vasoconstriction reducing blood flow, edema and clinical signs of inflammation.

Hanes *et al* reported that human gingival fibroblasts can bind and internalize nicotine and release it unmetabolised. In addition, nicotine and cotinine have been detected in gingival crevicular fluid and saliva.[3] Systemic alterations of the host response in cigarette smokers have been evaluated by several investigators and includes impaired chemotaxis and phagocytosis of both oral and peripheral neutrophil and reduced antibody production. In vitro studies have also provided evidence that nicotine can suppress the osteoblast proliferation while stimulating the alkaline phosphatase activity. Zambon *et al* examined the association between cigarette smoking and infection with periodontal pathogens than non-smokers. These investigators demonstrated that in a dose-dependent manner smokers who harboured significantly higher levels of B.forsythus were at a greater risk of infections with this periodontal pathogen than non-smokers.[4] Studies by Payne *et al* demonstrated that nicotine upregulates monocytic release of prostaglandin E2 and IL-1 in response to lipopolysaccharides and may contribute to the increased periodontal destruction in smokers, which in the presence of vasoconstrictive activities and hyperkeratotic response to physical heat and chemical stimuli could count for the presence of severe pockets and bone loss.[5]

The uptake of nicotine from snuff is dependent on the amount of nicotine, the p^H, and the buffering capacity. Localized oral manifestations, such as gingival recessions and mucosal lesions (snuff dipper's lesion) at the site of snuff placement, are common in users of moist snuff.[6]

Smoking behaviors have consistently associated with attachment loss. Smokers have a significant higher risk of developing chronic periodontitis and show a higher rate of destruction over time than non smokers.[1] There is a dose-effect relationship between cigarette smoking and severity of periodontal disease, such that heavy smokers and those with a longer history of smoking show more tissue destruction than the light smokers with shorter duration.[2] Studies showed that cigarette smoking is associated with a two fold to seven fold increased risk of having attachment loss compared with non smokers with pronounced risk in young smokers.[3]

Diabetes Mellitus

Epidemiological studies have shown that the risk for periodontitis in diabetes mellitus patients is greater than in non-diabetics. Type I and type II diabetes are now documented to significantly enhance susceptibility to severe periodontitis. Studies have shown the association of diabetes with periodontitis. One of these compares the outcome of studies of the Pima Indians residing in Arizona, who may have the worlds' highest prevalence of type II diabetes and in whom type I diabetes is virtually non-existent with a group of Danish men aged 20 to 40 years having type I diabetes. The prevalence of advanced periodontal

disease was substantially higher in both type I and type II diabetes than in non-diabetics. In the Pima Indian population, the onset of bone and attachment loss in those with diabetics was early and the rate of progression was almost three times than in non-diabetics. Those with retinopathy were almost five times likely to have advanced periodontitis than those without retinopathy. Calculus seems to be an important determinant especially in Pima Indian population, where teeth with more calculus were likely to have severe periodontal destruction than with little or no calculus.[7,8] A recent study by Golla *et al* shows that, diabetics have 15 times more risk of periodontal disease than nondiabetics.[9]

Diabetes enhances the risk for severe periodontitis by affecting the function of PMNs and by the formation of advanced glycosylation endproducts (AGEs) that bind to AGE receptors on critical target cell surfaces and lead to oversecretion of inflammatory mediators such as IL-1, tumor necrosis factor-alpha and prostaglandin E2.[10] A fundamental lesion is the thickening of the basement membrane of small vessels with non-enzymatic glycosylation of protein and accumulation of deposits within the vessel wall and on the luminal surfaces, thus altering the function of vascular wall collagen, resulting in deleterious complications.[11]

Type I collagen is the predominant extracellular matrix component of gingival tissue, periodontal ligament and alveolar bone. Metabolic dysregulation induced by diabetes mellitus has been associated with abnormalities of collagen turnover. Studies have shown reduced collagen synthesis and enhanced degradation of newly synthesized collagen, that has not been completely cross-linked, potentially leading to impaired wound healing. Several studies have reported an impaired metabolism of gingival and periodontal ligament fibroblasts under hyperglycaemic conditions resulting in lower mitotic activity and growth as well as increased collagen activity. In addition, osteoblasts from rats with experimentally induced diabetes display an impaired synthesis of bone matrix component. Thus taken collectively, alterations in connective tissue metabolism associated with diabetes may contribute to delayed wound healing and severity of periodontal disease. Lesions are seen more frequently in individuals having diabetes of long duration and poor metabolic control of hyperglycaemia.

Increased susceptibility to periodontal disease has been associated with impaired polymorphonuclear leukocyte functions. Several studies in diabetic animals and humans have reported defects in neutrophil chemotaxis, adherence, phagocytosis and bacterial killing suggesting that these dysfunctions may lead to impaired host response. Several possible explanations may account for altered neutrophil function *in vivo*, in the diabetic in periodontitis. Impaired polymorphonuclear leukocyte functions may result as a consequence of periodontitis associated with bacterial infections. Local lipopolysaccharides may alter oxidative burst capacity to impair killing. Neutrophil function is also influenced by systemic levels of lipids, especially unsaturated fatty acids. A few earlier studies reported that diabetes-associated changes in the periodontium may be due to a gram negative microbial flora. High levels of Capnocytophaga, Prevotella intermedia in diabetes is recorded.[12] The gingival fluid of diabetic patients has enhanced levels of ureas and glucose which may be responsible for the change in subgingival flora. When diabetes is induced in rats there is change in the flora from predominantly gram positive to gram negative cocci and rods. These organisms are associated with pathogenesis of periodontal pocket. The type I and type II D.M. significantly enhance one's susceptibility to severe periodontitis. The cross sectional case control and longitudinal studies indicate that diabetes is at present a possible risk factor for periodontal disease.

Pathogenic Bacteria

Studies evaluating the possible association between the presence of specific species of

putative periodontopathic bacteria which enhance the risk for periodontal deterioration fall into two categories; those that evaluate the frequency of association of the bacteria with periodontal status and those evaluating the strength of the association with periodontal deterioration. Wolff *et al* reported problems in identification and quantification of bacterial species and sampling of organisms. In cross-sectional studies, he distinguished between the disease active and inactive sites.[13]

Inspite of the complexities, most studies indicate an association between the presence of certain specific putative pathogens in the subgingival flora and various measures of periodontal deterioration. However, the interaction between the bacteria and numerous other factors such as poor oral hygiene, smoking and diabetes which are also associated with the disease complex remains poorly understood.

In a longitudinal study of 3052 sites in 886 patients, Wolff *et al* evaluated the relationship of five putative periodontal pathogens to periodontal status. They reported an odds ration 3.6 for P. gingivalis, 2.5 for A. actinomycetemcomitans, 2.1 for P. intermedia, 2.3 for E. corrodens and 1.4 for F. nucleatum. In an adult population, C. rectus and F. nucleatum, E.corrodens and P. intermedia were found in 50% of the subjects, while , A. actinomycetemcomitans and P. gingivalis were found in 25% and 14% respectively. They reported that Aa is found more frequently in younger and Pg in older individuals. A positive association between the presence of A. actinomycetemcomitans, P. gingivalis and C. rectus with alveolar bone loss was also noticed.[13] Of the five species studied by Malfarlane *et al* prevalence was observed to be lowest for P at 32% and highest for E. corrodens at 40%.[14]

A group of patients designated was as high risk based on the presence of P. gingivalis and A. actinomycetemcomitans in their subgingival flora at the baseline and another group designated as a low risk based on the absence of these flora at the baseline were observed longitudinally.

Haffajee *et al* reported that the presence of P.intermedia, C.rectus, B.forsythus and Peptostreptococcus micros and the absence of other species such as C.ochracia and Streptococcus sanguis II were excellent risk predictors for future disease progression in adult periodontitis. Aa, P.intermedia and P.gingivalis were found to be associated with disease progression.[15]

It is clear from the published evidence that specific species of predominantly gram negative anaerobic bacteria are involved in the etiology of periodontitis. Nevertheless, it is also clear that the presence of one or more of these species is not tantamount to disease; other host and environmental factors must also be involved.

Microbial Tooth Deposits and Oral Hygiene

Oral hygiene can favorably influence the ecology of the microbial flora in shallow to moderate pockets. Oral hygiene alone has little effect on sub gingival micro flora in deep pocket.[1] Comprehensive oral hygiene programs are effective in preventing or reducing the level of gingival inflammation in children and adults. These programs may not be viable in preventing aggressive periodontitis. Study also reported it may be difficult to achieve a level of oral hygiene in the general population to prevent chronic periodontitis with periodontal tissue destruction.[2]

The strong association of microbial deposits and poor oral hygiene with gingivitis has been clearly established. Axelsson reported the result of 15 years uncontrolled longitudinal study of gingivitis and periodontitis based on 375 individuals. All the individuals were on proper oral hygiene measures. All underwent scaling and root planning every 2 to 3 months for 9 years and twice a year for next 6 years. At the end of the study, none of the participants had clinically detectable loss of attachment. The inference of this study was that periodontitis can be prevented by the control of microbial deposits.[16]

Anatomic factors such as furcations, root

concavities, developmental grooves, cervical enamel projections, enamel pearls, bifurcation ridges as well as subgingingival and overhanging restoration margins may contribute in accumulation of microbial plaque ; thus predisposing the periodontium to disease. Although not clearly defined as risk factors for periodontitis, anatomic factors and restorative factors that influence plaque accumulation may play a role in disease susceptibility for specific teeth.[1]

Genetic Factors

Human periodontitis comprises a heterogenous group of infectious diseases that lead to pathologic destruction of periodontium. It is well known that periodontal disease may differ with respect bacterial etiology,host response and clinical disease progression. Disease onset progression depends upon the balance between homeostasis and destruction of periodontal tissue. Supporting evidence for genetic control of risk factors for some forms of periodontal disease comes from three primary resources:

- The consistent association of periodontitis with certain genetically transmitted traits.
- Twin studies of adult onset forms of periodontitis and
- Genetic studies of early onset forms of periodontitis

Sofaer *et al* conducted a study on 4098 twins pairs including 116 monozygotic and 233 dizygotic pairs. They reported that monozygotic twins (0.38) showed greater periodontal destruction when compared to dizygotic (0.16) twin pairs.[17] Melnick *et al* reported that LJP has an X-linked dominant mode of transmission.[18]

Studies in twins by Michalowicz have shown that genetic factors influence clinical influence clinical measures gingivitis, probing pocket depth, attachment loss and interproximal bone height.[19,20]

Hart and co-workers reported a detailed analysis of the literature, which support the autosomal mode of transmission of localized juvenile periodontitis. They also noted that it is likely heterogenous and indeed some rare X-linked forms may exist. Linkage analysis and identification of an abnormal gene will ultimately be needed to prove the genetic basis of this disease.[21]

A declaration was made by American Academy of Periodontology in 2001 that, genetic factor contributes to every human disease, increasing susceptibility or resistance or influencing interactions with environment. Inherent disorders in which susceptibility to periodontitis is increased are listed below:

Enzyme and Enzyme Inhibitor Defects

- Acatalasia, congenital erythropoietic porphyria, hypophosphatasia
- Alpha and antitrypsin deficiency

Leukocytic Defects

- Chediak-Higashi syndrome, glycogen storage disease, Leukocyte adhesion defects I and II.
- Cyclic and chronic neutropenia

Connective Tissue Disorders

- Ehlers-Danlos syndrome IV, VIII and IX.
- Chromosomal disorders
- Trisomy 21 (Down's syndrome)

Other Inherited Disorders

Alopecia, Epilepsy, mental subnormality, Papillon-Lefevre syndrome.

- Among enzyme and enzyme inhibitor defects, acatalasia, hypophosphatasia and α-1 antitrypsin deficiency are autosomal dominant traits while congenital erythropoietic porphyria is an autosomal recessive trait. The dental aspect of hypophosphatasia is characterised by the absence of cementum or presence of hypoplastic

cementum on the roots of primary teeth resulting in lack of periodontal ligament attachment. Functional defects in neutrophils comprise the largest group of genetically transmitted traits with enhanced susceptibility to periodontitis. Among these, chronic and cyclic neutropenia are autosomal dominant traits. Chediak-Higashi syndrome, glycogen storage disease, Leukocyte adhesion defects I and II are autosomal recessive. Other connective disorders enhance the susceptibility to periodontitis.

Mechanisms through which genetic factors are translated into enhanced susceptibility to periodontal destruction, although three possibilities are presented below:

A. Defect in PMN function has been identified and is manifested in approximately 75 percent of individuals with localized juvenile periodontitis. The defect is related to suppressed cell chemotaxis and phagocytosis. Van Dyke *et al* have demonstrated a defect in intracellular signaling and an abnormality on the surface of the glycoprotein.[22] Studies have showed a familial aggregation in localized and generalized aggressive periodontitis.[23]

B. The role of genetic factors may be manifested through the IgG2 antibody subclass response induced by antigens of periodontal pathogens. The bacterial species most strongly related to human periodontitis include A. actinomycetemcomitans, P. gingivalis and P. forsythus. The major serum antibody response induced by periodontal infection is of IgG2 subclass. Localized juvenile periodontitis patients have higher titers of specific IgG2 than patients with generalized juvenile periodontitis suggesting that higher titers may slow disease progression.

C. A third possible mechanism is through the Fc receptors expressed on the surfaces of phagocytic cells. There is strong evidence that normally functioning phagocyte cells comprise the key host defense mechanisms in fending off bacterial challenge. Human phagocytic cells express Fc receptors of three types including Fc-gamma RI(CD64), hFc-gamma RIIa (CD32) and gamma-RIIIb(cd16). Among these, only, hFc-gamma RIIa can recognize the Fc region of IgG2. Loos BG showed that the only polymorphisms associated with periodontitis in different ethnic groups were polymorphisms associated with the Fc-gamma receptor genes.

Some recent studies in the last decade have shown that, a weak association between single nucleotide polymorphisms in the IL-1 genes and chronic periodontitis exists. But, no genetic risk factors or markers are able to distinguish between aggressive periodontitis and chronic periodontitis.[10]

The major histocompatibility complex is a cluster of genes encoding the HLAs involved in cell recognition. It has also been found to be a useful marker for a number of diseases with a genetic predisposition. These cell-surface molecules have a key role in antigen presentation and activation of T cells. The polymorphisms of HLA can directly affect the binding capability of antigen peptides and thus affect the antigen-specific T-cell response. Since 1970, numerous reports have emerged regarding the associations between HLA class I and HLA class II antigens and periodontal diseases. Patients with aggressive periodontitis showed a positive association with HLA-A9 and a negative association with HLA-A2 and HLA-B5. No significant associations were found between HLA class II antigens and aggressive periodontitis.[10]

Age

Epidemiological studies have shown periodontal disease to be more prevalent in older age groups compared to younger age groups. The evidence demonstrates that manifestations of periodontitis are more frequently observed and more severe in older contrasted with younger persons. Whether the increased prevalence and the severity in older

persons results from lifetime accumulation of local irritants or a truly enhanced susceptibility to periodontal deterioration exists in them remains unresolved. In cross-sectional analysis of a recent epidemiologic study of 1426 individuals aged 25 to 74 years, of all the risk factors studied, age was the most strongly associated with clinical attachment level. The odds ratio for this association for persons aged 35-44 years was 1.2 and for subjects aged 65-74, it was 9.01. There was an even stronger association between age and alveolar bone loss; the odds ratio for subjects aged 35-44 years was 2.6, but for those in 67-74 years age group it was 24.08. In a patient population of 1783 at a large military treatment center in the United States, age was the most strongly associated of putative risks studied, with an odds ratio of 5.03.

A study was done by Brown *et al* to evaluate clinical attachment level over 18 months in people aged 65 and older adults. They found that in older adults, age was not related to attachment loss. Ismail *et al* conducted a follow-up study for 28 years. They found a non-significant trend that average attachment loss was greater in older individuals, though the trend was statistically non-significant. However, age was found to be significant in a multivariate model.

Abdellatif and Bart evaluated the relative importance of age and oral hygiene status as determinants of periodontitis in an epidemiological study. The rate of increase of periodontitis with increasing age across all age groups was much higher for those with poor oral hygiene than those with excellent oral hygiene. They concluded that the effect of the age on disease progression is negligible when good oral hygiene is maintained.

Medications

People take medications which may benefit their general health, but not necessarily their periodontal health. The effects of medications on periodontal health have been grouped into four categories:

a) Behavioural alteration of oral hygiene methods
b) Alteration of plaque composition
c) Effects on gingival tissues
d) Effects on salivary flow

Behavioural Alteration: Patients who take certain medication, have a depressant effect on CNS. Patients may not importance to oral hygiene practice. Hence they have a tendency towards increased plaque accumulation.

Common drugs which have such an effect include sedatives, tranquilizers, narcotic analgesics, acute metabolites and antihypertensives.

Alteration of Plaque Composition: plaque composition and p^H may be altered significantly by the dosage of drug administration. Liquid or chewable pharmaceutical preparation for children are made palatable by addition of sucrose, glucose and fructose as sweeteners. This might cause an alteration in p^H of plaque and its composition. Sugar metabolized by bacteria to acid end products lowers the p^H of plaque. The lowered p^H near the tooth surface cause ionic dissolution of the hydroxyapatite crystals increase roughness and enhance the ability for plaque to be more adherent. It has been shown that human plaque p^H decreased significantly after administration of liquid iron supplements and cough syrups.

Effects on Gingival Tissue: Phenytoin was the first drug reported to produce gingival enlargement. The incidene of gingival enlargement due to the drug ranges between 3% and 62% with a mean of 50%. Although the occurrence of gingival enlargement with this drug has been well established, its cellular and molecular mechanisms of action for this effect are unclear. A recent paper suggests that phenytoin augmented the expression of gene for the platelet derived growth factor-β, authors also showed that, gingival macrophages exposed to phenytoin secrete increased amounts of PDGF. The increase in PDGF may increase not only the proliferation of gingival cells but also alveolar bone cells. Gingival enlargement has also been associated

with a number of calcium channel blockers ncluding Nifedipine, Verapamil, Diltiazem and Oxodipine. Gingival enlargement is seen in approximately 5% of patients taking these medications. Gingival enlargement has also been reported with cyclosporine with an incidence of approximately 25%. It is also been postulated, that cyclosporine alters fibroblastic activity through effects on a variety of cytokines such as interleukins.

Effects on Salivary Flow: Adequate salivary flow is critical to the manintainance of health of oral soft tissues. It has been suggested that mouth breathers have modified plaque accumulation and associated soft tissue changes. A number of other agents produce xerostomia including antihypertensives, narcotic analgesics, tranquilizers, anti-metabolites, antihistaminics and vitamin D in larger dose. In addition to the effect of xerostomia on soft tissues, root surface caries may be more prevalent.

Body Mass: In adult population in Ljubijana, Slovenia using the CPITN methodology it was found that 45year and old over weight needed complex treatment more frequently than age matched subjects with normal or low body mass index. Saito and workers reported that relative risk for periodontitis was assessed by CPITN, after matching for age, sex, oral hygiene status and smoking history was significantly increased in overweight subjects in comparison to normal weight subjects.

Systemic Diseases

Grossi and coworkers studied the role of large number of systemic diseases as a risk indicator for periodontal disease in a population of 1,426 subjects aged 25 to 75 years residing in Erie county, New York. It was found that association of 17 systemic diseases and conditions to periodontal disease was rather high. These included allergy, hives, asthma, hay fever, high blood pressure, thyroid disease, gout, venereal disease, hepatitis, diabetes and angina. Out of these, only diabetes mellitus was found to be associated with more destructive periodontal disease. In a large study of 4000 subjects, of all the diseases assessed, only diabetes mellitus showed a statistically significant prevalence of periodontitis than other conditions.

Case control studies or case histories have provided hypotheses regarding the association of the association of these rare conditions with periodontal diseases. Some of the conditions are associated with neutrophil defects, such as Chediak-Higashi syndrome, Down syndrome and Papillon-Lefevre syndrome. AIDS has been shown to have an association with destructive periodontal disease.[17]

Gender

Periodontal disease is often reported in population studies to be more prevalent or severe in males than females of comparable age. Males were more affected by adult type of periodontitis, but females were more affected by refractory periodontitis. Males usually exhibit poor oral hygiene compared to females. However, when oral hygiene, socioeconomic status, age, are correlated with gender, males are found to be associated with more severe periodontal disease. The reason for gender difference is not clear.

It has been shown that more females seek dental treatment for esthetic reasons when compared to males. There are gingival inflammatory conditions found in females, which are relatively normal conditions, such as pregnancy gingivitis. In a recent study, women aged 50 to 64 years who were on estrogen replacement therapy had more gingival bleeding than women of same age who did not receive estrogen. These differences persisted even after adjusting for adjusting for other possible confounding factors such as higher education level and lower plaque accumulation.

Socioeconomic Status

Wide variations in socioeconomic status among the different populations were compared. Socioeconomic status of an individual is shown to influence his dietary

habits, health awareness including dental care as well as the frequency of dental visits. Therefore, gingivitis and poor oral hygiene can be attributed to lower socioeconomic status of an individual.[36,37,38] Studies have shown that in developing countries and industrialized countries periodontal disease may be associated with nutritional deficiencies.[39] However, when periodontal structure is adjusted for oral hygiene and smoking, the associations between lower socioeconomic and educational status and severe periodontal disease was not seen. Thus, lower socioeconomic status alone does not increase the risk for periodontal disease.[1]

Diet and Nutrition

Tissue integrity ultimately depends upon nutrition and, the periodontium is no exception to this. Immunological response such as cell-mediated immunity, humoral immunity, PMN phagocytic function and complement activation are reduced in protein energy malnutrition. Deficiencies of trace elements like Zinc will affect the integrity of gingival by altering the ability of host to eliminate infection.

In a study of The Third National Health And Nutrition Examination Survey (NHANES III), low calcium intake was found to be associated with increased risk of periodontal disease in young males, young females and older males. In the same study, a weak but statistically significant relationship was found between vitamin C intake and periodontal disease.

Studies of rural African population such as those in Nigeria compared high and low socioeconomic groups. Severe periodontal disease was seen in low socioeconomic groups even after correction of local factors like poor oral hygiene. They concluded that inadequate nutrition may lead to or enhance periodontal disease.

Ramfjord *et al* found that the periodontal condition of young men in India who exhibited the clinical symptoms of generalized mal-nutrition was not different from the condition of well-nourished individuals.

Another report from a prospective study of periodontal disease in a developed country such as United States demonstrated that periodontal disease is more severe in individuals of low socioeconomic status. However, more recent studies showed that periodontal status depends on oral hygiene, smoking and low socioeconomic status.

Minor nutritional deficiencies or imbalance failed to demonstrate any effect on periodontal disease in animal models. There is lack of longitudinal studies controlling for possible confounders for evaluation of nutrition as a risk factor.

Stress

Since the 1950's emotional factors have been identified in periodontal disease. It is now well established that psychological stress can down regulate the cellular response. Communication between central nervous system and immune system occurs via a complex network of bidirectional signal linking. Stress disrupts the homeostasis between the nervous, endocrine and the immune system which in turn alters immune functions.

The first available finding linking stress to periodontal condition were concerned with acute necrotizing ulcerative gingivitis after its diagnosis among soldiers during First World War. It has been suggested that, if a patients resistance was lowered by an inability to cope with stressful life events, then overt inflammatory periodontal disease may be manifested. Marcenes & Sheiham investigated whether periodontal status was associated with work stress and marital quality in 149 males employed parents of age 35 to 44 years. Pocketing and/or gingivitis were associated with higher scores for work related mental demands and low scores in marital quality if others variables including socioeconomic status and dental health behaviours were controlled for in the analysis. Military recruits with extreme personality traits or perception of high physical stress levels during basic combat training showed signs of gingival inflammation. Moss *et al* explored the

association between social factors and adult periodontitis by comparing self-reported information for daily strains such as job, financial strains and it was found that individuals who had elevated levels of serum antibody to B.forsythus scored high. Adult patients with periodontitis who are resistant to therapy are more stressed than those who respond to therapy. Patients with financial strain, distress, depression or inadequate coping mechanisms are more prone to severe loss of attachment. Also, caregivers of stressed and those with the condition themselves are prone to elevated biofilm levels and increased gingivitis.

The cellular and molecular interaction between the neuroendocrinal and immune system have been reviewed by Sternberg *et al*. It was well documented that corticosteroids exert inhibitory effects on several inflammatory cells including monocytes and macrophages, neutrophils, eosinophils and mast cells. These inhibitory effects are mediated through suppression of cytokines such as IL-1,2,3 and 6, tumor necrosis factor, interferon-gamma as well as through the inhibition of prostaglandin and leukotreines. According to McGlynn *et al* stress-released hormones present in the gingival crevicular fluid may provide a source of nutrients that promote subgingival growth of periodontal pathogens.

Present scientific evidence is sufficient to substantiate the hypothesis that the psychological factors are of etiological importance in the pathogenesis of periodontal disease.There are no psychoneuroimmuological studies to test whether the host defense system can be compromised by psychcoemotional stress.

HIV Infection

Human immunodeficiency virus (HIV) seropositive patients and those with the acquired immunodeficiency syndrome (AIDS) have been shown to experience a severe, painful and rapidly progressing form of periodontitis (NUP). The NUP was related to the degree of immunosuppression as determined by a CD4 lymphocyte count below 200cells/mm, indicating that alterations in the normal cellular immune response may be associated with increased periodontal disease by a modification of normal regulatory mechanisms.

In a prospective study of 20 months duration, of 114 male HIV positive cohorts, CD4 count < 200/mm conferred a 6-fold increased risk of attachment of 3mm or more compared with CD4 counts > 200/mm3. Excellent reviews have been published summarizing the oral findings in HIV infected subjects and these suggest that periodontitis in HIV infected individuals is likely to have a more common clinical and radiographic appearance than that associated with NUP. It is also apparent that the NUP may vary widely in HIV infected populations, depending on the stage of HIV infection, the amount of seropositivity, the individuals' lifestyle and the level of care, use of antiretroviral agents and other undefined factors. Because a similar manifestation may be seen in patients who are HIV-ve, it is possible that HIV infections share common pathogenic mechanisms with other systemic diseases and conditions.

The magnitude of the link between HIV and the progression of periodontitis has recently been questioned. However, some studies suggest that in immunocompromised HIV patients, pre-existing periodontitis may be exacerbated and thus HIV infection can be considered as a significant modifier of periodontitis. Current evidence does not support HIV seropositivity being a predictor for progressive periodontitis.[10]

Osteoporosis

Many of the studies conducted to date suggest that there is a relationship between skeletal osteoporosis and oral bone loss. Postmenopausal osteoporosis may result in dental osteopenia involving jaws, particularly the mandible. Groen *et al* suggested a relationship between dental osteopenia and periodontal disease, tooth mobility and tooth loss. They examined 29 dentate patients with

osteopenia and found 27 of them to have advanced periodontitis. A review of the relationship between osteopenia and oral bone loss and periodontal disease, concluded that osteopenia does play a role in the expression of periodontal disease. The review indicated a direct association between skeletal and mandibular osteopenia and loss of alveolar crestal height and tooth loss in postmenopausal women.

It has been hypothesized that systemic metabolic bone abnormalities that occur in osteopenia may locally enhance bone resorption caused by periodontal infection. the relationship between periodontal disease and osteoporosis needs to be evaluated in a larger population with adequate control of potential confounding variable such as gender, hormone intake, smoking, stress, race, age, diet, body mass, exercise and other systemic conditions. The interaction of several known and unknown risk factors may complicate the role of osteoporosis in attachment loss and bone loss. A recent assessment of osteoporosis in the jaws carried out using dual photon absorptimetry found that reduction in total skeletal mass is positively correlated with a reduction in mandibular bone density in women with osteoporosis. Kribbs *et al* showed that mandibular bone mass was significantly associated with skeletal bone mass in a population of nonosteoporotic women.

It is still questionable whether osteoporosis is indeed a risk factor for periodontitis, or simply a risk factor for alveolar bone loss. Prospective studies are needed to confirm or refute a causal relation between osteoporosis and periodontitis

Infrequent Dental Visit

Even though infrequent dental visits may be attributed to lower socioeconomic status, its role as a risk factor for periodonitits single handedly, is controversial. One study demonstrated an increased risk for severe periodontitis in patients who had not visited the dentist for 3 or more years, whereas another demonstrated that there was no more loss of attachment or bone loss in individuals who did not seek dental care compared with those who did over a 6-year period. Research is still going on regarding the same.[1]

A study of 14,690 individuals aged 15 to 74 years, demonstrated an odds ratio of 20.52 for the association between poor oral hygiene and periodontitis. They also found that periodontitis was much higher in those with poor oral hygiene when compared with good oral hygiene. Hence it was concluded that poor oral hygiene measures and infrequent dental visits may be risk factors for further attachment loss.

It is likely that the widely observed relation between socio-economic status and gingival health is a function of better oral hygiene among the better educated and greater frequency of dental visits among the more dentally aware. It is more likely that socio economic status, a complex and multifaceted variable that can include a variety of cultural factors confounding this relationship.

Additional longitudinal and interventional studies are necessary to determine if infrequency of dental visits is a risk factor for periodontal disease.[1]

Previous History of Periodontal Disease

A history of periodontal disease in previous life is a risk predictor of periodontal disease in future life. Patients with existing periodontal disease are at a more increased risk of periodontal disease in future life, whereas, patients free of periodontal disease at present are at decreased risk of periodontal disease.[1]

Bleeding on Probing

Bleeding on probing along with periodontal pocket serve as an excellent predictor of periodontal disease. But, lack of bleeding on probing is not an excellent indicator of periodontal health.[1]

Race

Though not included in the categories of risk elements for periodontal disease, some studies

have shown the association of race to periodontal disease. Beck *et al* showed that blacks had approximately three times more advanced periodontal destruction as compared to whites of the same age. In an analysis of risk indicator for black and whites, there were more indicators related to socioeconomic status for black than whites belonging to the same socioeconomic status group had no difference in periodontal disease. A recent study also shows that blacks are twice more susceptible than whites for periodontal disease.

Discussion and Clinical Application

In this paper, we have attempted to review reports dealing with risk factors associated with the progression of periodontal disease. It has been hypothesized that, all cases of gingivitis need not progress to periodontitis and that progressive loss of attachment occurs in cases exposed to risk factors. Many factors have been identified to have specific role in modifying the disease progression. An understanding of these factors is necessary to prevent and control periodontal disease in the population. The risk factors to which the subjects have been exposed may vary from population to population and hence a thorough knowledge of the risk factors is essential. Risk factors are also used as an aid in diagnosis of a condition if an individual is known to have a number of risk factors for a certain disease. The clinicians begin to think about a certain diagnosis, because the presence of risk factors increases the probability that the disease is present. If a risk factor can be modified, then the intervention may result in prevention of disease. Prognostic factors may or may not totally depend on risk factors. Because periodontitis is considered to have multiple etiology, successful intervention to ameliorate a risk factor may only partially reduce the likelihood of disease occurrence. Regarding the risk assessment, limited information is available. Several exposures including smoking, pathogenic bacteria and diabetes mellitus may play a role in the causation of periodontitis. None of this is sufficiently documented as a risk factor.

Clinical Implication

Decision making for periodontal therapy should encounter 3 different directions, namely diagnosis, periodontal risk assessment and prediction of disease progression.

After making diagnosis of the case, possible risk factors should be assessed. As described above factors are the major elements of periodontal risk assessment. The existence of one or more of these risk elements would probably modify the treatment plan.

Information concerning individual risk for developing periodontal disease is obtained through clinical examination, medical history, demographic data , dental history. Once a risk factor is identified, treatment plan may be modified accordingly. It is necessary to differentiate between modifiable factors, acquired and behavorial factors considered to be modified and age, gender and gene polymorphism were considered non modifiable background factors.

Whereas microbiota, smoking, diabetes mellitus, osteoporosis, HIV infection and psychological factors were considered as modifiable risk factors.

Some authors considered smoking, diabetes, pathogenic bacteria and microbial deposits as risk factors for periodontitis, whereas age, gender, SES, stress and genetic factors were considered as risk determinators and HIV infections, osteoporosis and infrequent dental visits were considered as risk indications for periodontal R.

However, according to recent agreement to accept SP bacteria, cigarette smoker, and diabetes mellitus as major established risk factors for periodontitis. The rest of risk elements for periodontitis.

The existence of one or more of these risk elements would probably modify the treatment path. For instance, regenerative periodontal therapies are usually not the first choice in patients who are heavy smokers or patients

with current history of uncontrolled diabetes.

It is important for development of a risk assessment method to assess the prognostic value of a treatment. Although several approaches have been developed. Current available methods for periodontal risk assessment for the evaluation of risk for both the incidence and progression of periodontitis should be emphasized with scientific evidence.

Further trials should be undertaken in order to facilitate the periodontal risk assessment and to confirm the power of involvement of several factors within the process.

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