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Effects of some risk factors and immunodeficiencies on the periodontium – a review

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Summary
The possible role systemic factors might play in initiating or modifying the progress of periodontal disease has been a controversial issue for some time. Gingivitis is initiated by microbial plaque deposits on the dento-gingival interface but progression to periodontitis is modified by several environmental, behavioural, biological and health care variables. The importance of the immune system in modifying the host response to plaque is well established and as such, the immune system is a risk factor for human and animal periodontal disease. This paper reviews the modifying risk factors for periodontal disease and examines the periodontal manifestations of subjects with primary and acquired immuno-deficiencies.

Keywords: *Effects, risk factors, immunodeficiencies, periodontium, review*

Résumé
Le role possible que les facteurs systemiques peuvent jouer dans l'initiation on la modification des progress des maladies periodontales a Ete l'object de contestations pour un certain temps. La gingivite est initiee par des depots de plaques microbiennes sur l'inter face dento-gingivale, mais la progression vers la periodontite est modifiee par plusieurs variables de sante tells l'environment, la conduite et la biologie L'importance du systeme immunitaire dans la modification la reponse hote aux plaques est belet bun etablie alors le systeme immunitaire est un facteur de risqué pour les maladies periodontales chez les homes et les animaux. Cette communication est une revue de la modification des facteurs de risqué des maladies peri-odontales et examine les manifestations periodontales des sujets ayant fes deficience primaries et l'immunodeficience acquise.

Introduction

The periodontium is a functional, biological unit supporting the tooth in the jaw and comprising of the gingiva, periodontal ligament, cementum and alveolar bone. Since the basic tissue elements are diverse, being composed of keratinized and non- keratinized epithelia and mineralised and non-mineralised connective tissues, many systemic conditions may affect the periodontium. Epidemiological studies have established that gingivitis is prevalent in children and that by the age of 15 years many have lost some bone around one or more teeth [1]. However, tooth loss as a result of periodontitis is not inevitable with increasing age, and disease progression may not occur in a steady, continuous fashion, having some periods of remission and periods of random bursts [2].

The precise manner by which the plaque organisms induce breakdown of the periodontal tissues is not known. Several theories have been proposed, none of which are mutually exclusive. The host defence system is made up of local tissue components, together with cosinophils, basophils and mast cells, neutrophils and monocytes, the immune response and serum factors such as the complement system [3]. The activities of these host defence mechanisms would appear to be both protective and destructive. An intact and normal functioning host response would appear to be compatible with slowly progressive periodontal disease. However, changes in the various components of the hosts response to deal with the bacterial challenge may alter the characteristics of the periodontal disease. Recent advances in immunology, genetics and cell biology have given a more detailed knowledge of the pathogenesis of periodontitis at both the cellular and molecular level [4,5]. For the purpose of this review, the systemic modifying factors will be discussed under two broad categories: risk factors and immunodeficiency states. Certain conditions, though rare, have been included to highlight the possibility of underdiagnosis of these conditions in our environment and to increase the level of knowledge in this field.

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Risk factors and periodontitis

Body mass index (BMI)

Using the Community Periodontal Index of Treatment Needs (CPITN) methodology, Skaleric and Kovac [6] found that 45year old over weight subjects needed complex treatment significantly more frequently than age-matched subjects with normal or low body mass index. After adjustment for age, sex and oral hygiene status, the relative risk for periodontitis was also found to be significantly increased in overweight subjects (BMI > 30) in comparison to normal weight subject [7].

Gender

Females were found to have a relative risk ratio for gingivitis significantly lower than males in an adult population of Tanzanians [8]. Hugoson *et al.* [9] also reported that significantly more males than females had higher gingivitis scores. Also in a study among Nigerians, Arowojolu *et al.* [10] found that more males had periodontal disease than females. Similarly, in a study by Hou *et al* [11] in Taiwan, the prevalence of molar furcation involvement was significantly higher in males than in females adult populations.

Social class

In a population of community-dwelling older adults with low socioeconomic status, trends in attachment loss over a 5-year observation period was followed by Beck *et al.* [12]. Similarly in Nigeria, in a study of effect of social class on the prevalence and severity of periodontal disease [13], adults with low socioeconomic status had significantly poorer periodontal status than those with high social class.

Education

Lower educational status was associated with higher prevalence of gingival recession among adults in Tanzania [8]. In a study by Gamonal *et al.* [14] among an adult population in Chile, only subjects who were periodontally healthy were in the group

with university education and they also had significantly lower prevalence of shallow and deep periodontal pockets. Similarly, in a longitudinal study of Oslo citizens over 15 years, an increased number of deep pockets as assessed by the Periodontal Treatment Need (PTN) system [15] was positively associated with a short duration of education of less than 10 years [16]. In a recent survey of periodontal disease in the United States by Oliver et al [17], it was reported that extensive and severe periodontitis was much more prevalent in people with less than a high school education.

Marital status

It has been reported that older single adults had a 3.07 times increased risk for periodontal disease compared to married adults [18]. Croucher *et al* [19] also found that marital status after adjustment for other variables, was significantly related to periodontitis.

Primary and acquired immunodeficiences and periodontitis

The immunodeficient individual can be classified as having either a primary or secondary immunodeficiency. Most primary immuno-deficiency disorders are caused by a single gene defect and may be manifested by defects in T- or B-cell development, phagocytic function or components of the complement system (WHO, 1997) [20]. Secondary or acquired immunodeficiency usually result from infections, malignancies or immuno-suppressive drug therapy [20].

A number of other conditions can also be attributed to immuno-suppression. These factors and conditions include smoking, ageing, malnutrition, stress, alcoholism. Iatrogenic causes include major surgery, use of immuno-suppressants, radiotherapy and chemotherapy. It is noteworthy to mention that the above stated classification of immnodeficiencies is arbitrary if such a deficiency results as a consequence of a metabolic disorder affecting the immune cells, for example, diabetes mellitus. An alternative approach will be to consider the conditions under some broad categories like haematological, hormonal, immunological, genetic, drug induced, psychosomatic, age and nutritional, but it should be appreciated that many fall within more than one category.

Primary immunodeficiencies

Due to the life threatening nature of these conditions, reports in relation to periodontitis are limited or non-existent [21]. However, with advances in medical care, an increasing number of patients with these conditions have a better life expectancy and as such, the dental profession is experiencing greater exposure to these subjects. Polymorphonuclear (PMN) deficiencies exhibit severe destruction of the periodontal tissues, which is a strong evidence that PMNs are an important component of the host's protective response to dental plaque. Quantitative deficiencies are generally accompanied by destruction of the periodontium of all teeth whereas qualitative defects are often associated with localized destruction affecting only the periodontium of certain teeth [22].

Phagocyte cell defects

These include:

(i) *Neutropenia:* where there is a decrease or absence of neutrophils [23]. These patients exhibit a very florid gingivitis with marked swelling, bleeding, sulcular ulceration and rapidly advancing periodontitis.

(ii) *Neutrophil specific granule deficiencies:* in which there is defective mobilisation and chemotaxis.

(iii) *Myeloperoxidase deficiencies:* in which there is lack or reduced amount of the enzyme.

(iv) *Malignant form of neutropenia:* (agranulocytosis, PMN count below 500 per ul), which is generally drug induced, there is ulceration and necrosis of the marginal gingiva.

Genetic disorders

Various disorders of neutrophil function are also associated with severe forms of periodontal disease. The congenital conditions under this category include

(i). *Chediak Higashi Syndrome (CHS)*
Presents with abnormal PMN's function. Increased severity of periodontal disease has been reported [23]

(ii). *Papillon Lefevre Syndrome*
Manifests as a defect of neutrophil adhesion. Evidence of increased periodontal disease has been reported [24].

(iii). *Down's Syndrome (Trisomy* [21])
Presents with defective chemotaxis of PMN's and monocytes. It manifests periodontal disease with increased severity [25,26].

(iv). *Hypophosphatasia*
Patients with this condition have a decreased serum alkaline phosphatase and the presence of phosphoethanolamine in the urine. The disease manifests with severe loss of alveolar bone and premature loss of the deciduous teeth [1].

Acquired immunodeficiencies and periodontitis

The acquired or secondary immunodeficiencies include a wide range of lymphocyte disorders, from those induced by viruses to those associated with lymphoid malignancies [20].

Viral infections

Viral infections such as human immunodeficiency virus (HIV), rubella virus and cytomegalo virus (CMR) compromise the host immune system. Of great concern, however, is the HIV in terms of its effect on the periodontal tissues [27,28]. In the terminal stages of this infection (AIDS) there is a depression of antibody and immune cell production which then renders the host susceptible to opportunistic bacterial, fungal and viral infections and it has been reported that affected individuals are at increased risk of destructive periodontitis [29]. HIV associated gingivitis (linear gingival erythema, LGE) with necrotising ulcerative periodontitis is seen in HIV patients with severe immuno-suppression [30].

Diabetes mellitus

Epidemiological studies have shown that some patients suffering from diabetes are at a greater risk for periodontitis compared to non-diabetic individuals [31].

There have been several reports that the level of risk may be modified by a number of factors such as age of onset, degree of metabolic control and the duration of the disease [32]. Diminished PMN function in terms of chemotaxis, diminished phagocytosis, intracellular killing and adherence, as well as impaired PMN function are all major contributory factors associated with an increased risk of periodontal destruction [32].

Leukaemia

Periodontal lesions have been observed frequently in patient

with leukaemia, particularly those with acute forms of thedisease [33] A high number of immature blast cells are present in peripheral blood and bone marrow in acute leukaemia, whilst in chronic leukaemias the majority of neoplastic cells are of a mature type. Periodontal manifestations of myeloid leukaemias include gingival enlargement (due to infilteration of the tissues by the malignant cells), in about 27% of patients and gingival bleeding in about 43% of patients [34].

Smoking

In smokers, defects of phagocytic activity of both PMNs and macrophages impair clearance of bacteria, and the compromised B-cell function may result in inappropriate humoral response [35]. Salvi *et al* [29] also reported that smokers are 2.5 to 7 times more likely to develop periodontitis than non-smokers. Smokers exhibit more severe disease and have a poorer response to periodontal treatment [36,37]. A recent longitudinal study by Faddy *et al* [38], using ante-dependence modeling has shown that the major effect of smoking may be due to inhibition of healing rather than enhanced destruction.

Pregnancy

Pregnancy causes a modification in the host's response to dental plaque. Several studies have shown that the incidence and severity of gingival redness, swelling, bleeding and exudation increase from the second month of gestation to the eighth month and then decrease [39,40]. Menstrual cycle, puberty and oral contraceptives all show clinical indications of hormonal effect on the gingiva and the periodontium.

Reports of fluctuations in gingivitis with phases of the menstrual cycle and increased gingival inflammation associated with puberty have been attributed to hightened response to plaque by increased concentration of circulating sex hormones in these conditions [1].

Stress

The incidence of acute necrotising ulcerative gingivitis (ANUG) increases during periods of stress [41]. Green *et al* [42] studied individual's life events' such as divorce, and bereavement, and concluded that increased stressful events led to a greater prevalence of periodontal disease. In a larger study of 1426 subjects, financial strain was found to be significantly associated with greater gingival attachment and alveolar bone loss after adjusting for age, gender and smoking [43]. The intervening physiological mechanisms between stress, and increased susceptibility to periodontal disease are not well understood and documented. Rose [44] reported that stress may increase the levels of circulating cortiosteroids which may have effects on the periodontium. A strong association has also been reported between levels of *Bacteroides forsythus* and periodontitis in subjects with high depression scores compared to subjects with low depression scores [45], thus suggesting a psychoneuro-immunological link between stress, *Bacteroides forsythus* antibody levels and periodontitis.

Nutrition

The relationship between nutrition and chronic periodontal disease remains a poorly understood and complicated issue. Children with severe protein deficiency were found to have more severe gingival inflammation and bone loss than healthy children and some improvement in the periodontal condition was obtained following protein supplementation [1]. Cell mediated, humoral immune and inflammatory responses such as PMN phagocytosis and complement activation are reduced in protein-deficient states [46].

Age

Although age should not be considered a systemic disease, there is much evidence correlating age and periodontal disease. Papapanou *et al* [47] reported that the prevalence of periodontitis increases with age. It is possible that immune alterations associated with increasing age may modify periodontal disease progression [48].

Drug induced disorders

(i) *Phenytoin* - Some degree of gingival enlargement is present in 36-67% of patients who take the anticonvulsant drug sodium 5, 5-diphenylhydantoinate (DPH, Phenytoin, Dilantin). The lesion exhibits site and age specificity. An acceptable theory is that gingival overgrowth is a result of the direct effects of phenytoin or its metabolites on the gingival tissues [49].

(ii) *Nifedipine* - It is used extensively in the management of angina and hypertension. Gingival hyperplasia often accompanies nifedipine use. Lucas *et al* [50] reported that nifedipine has its hyperplastic effect by increasing the ground substance in the connective tissue. Nifedipine and Phenytoin have been reported to have effects on calcium channels in cells and this may suggest a common pharmacodynamic mechanism, as other drugs with calcium-channel-blocking actions induce gingival hyperplasia, for example, cyclosporin-A.

Iatrogenic immunosuppression

i. *Cyclosporin-A (CsA)* – Cyclosporin – A acts solely on the cell-mediated immune responses by disrupting interleukin synthesis and formation of interleukin receptors on T-cells. It suppresses T helper cells with minimal effect on T-suppressor cells [51]. CsA is now used extensively in the prevention of organ transplant rejection [52]. A widely recognized side-effect of cyclosporin is gingival hyperplasia which clinically and histopathologically resembles phenytoin induced hyperplasia.

ii. *Azathioprine:* - Azathioprine suppresses the cell-mediated immune system but has little effect on the humoral response. A longitudinal study of periodontitis in patients on azathioprine and prednisolone (over a period of 2-4.5 years) revealed a significant increase in gingival inflammation compared to health, despite similar plaque levels [53].

Discussion

Bacterial plaque is the main aetiological agent in periodontal disease, but the exact form of disease progression is dependent on the host's defences on this challenge. Systemic risk factors and immunological conditions have been found to modify the normal defences and predispose individuals to specific forms and patterns of periodontal disease [1,3]. Certain systemic disorders produce well recognised gingival lesions (e.g. leukaemia) or patterns of bone loss (e.g. cyclic neutropenia). Most systemic disorders, however, usually do not produce such pronounced periodontal lesions and any precise evaluation of the role they may play in the pathogenesis of chronic periodontal disease is difficult to assess.

Reduction in number or function of PMNs generally results in increased rate and severity of periodontal destruction. Changes in hormone balance result in increased severity of plaque-induced gingival inflammation. Perhaps the most important reason for the difficulty in assessing the effects of systemic disorders is the episodic nature of periodontal destruction. It is now clear that disease progression may not occur in a steady, continuous fashion [2].

This review has shown the various risk factors and immunodeficient states that modify the progress of periodontal disease and it has also highlighted the biochemical and histological basis of such changes. It is hoped that this review has provided a greater challenge for the clinical management of the patients and has shown greater need for oral health education to dissuade patients from deleterious habits (e.g., smoking). For optimum periodontal care in these susceptible individuals, a need has arisen to provide intensive prophylactic oral health measures.

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