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Influence of Systemic Conditions on Periodontium- Exploring the Oral Systemic Connection: A Mini-Review

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Review Article

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ABSTRACT

Background: Understanding the etiology and pathophysiology of periodontal disease, due to its chronic infectio-inflammatory nature, demands acknowledging that these infections may affect processes elsewhere in the body. At the same time, acknowledging the interaction between oral diseases and some systemic conditions requires dentists and periodontists to direct their practice and knowledge not only to events strictly related to the oral cavity but also to systemic conditions and diseases that may change or interfere with established preventive and therapeutic approaches.

Aim: The aim of this literature review is to explore and understand the interrelationship and the influence of systemic diseases on periodontium thereby raising health practitioners' attention to the importance of oral health care on overall well-being, and underlining the necessity for a broader connection between medical and dental training.

Review results: This review paper discusses the underlying relationship and the etiopathology linking periodontal diseases and various systemic disorders.

Conclusion: Periodontitis is a continual source of infection and has been identified as a risk factor for several cardiovascular, pulmonary, endocrine, musculoskeletal, and reproductive system disorders. Oral health has an influence on overall well-being, and if comprehensive health care is to be realized, oral health should not be viewed as a distinct, remote, and less essential area of health that is completely unconnected to longevity and its quality. Medical and dental experts have a propensity to approach patient treatment from a localised rather than a systemic perspective. Given the growing body of evidence on the significance of oral infections like periodontitis in a variety of systemic diseases, it has become imperative to do a literature review on the issue.

Keywords: Diabetes, Drugs, Hormones, Periodontitis, Systemic Diseases, Vitamins.

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Introduction

It is rightly said that the mouth is the mirror of systemic health and disease. The manifestations of various diseases such as diabetes are reflected in the oral cavity. Periodontium is the main reflection manifested with various sign and symptoms. Inflammation of the periodontium leads to periodontal disease. It mainly refers to the inflammatory processes that occur in the tissues surrounding the teeth in response to bacterial accumulations, or dental plaque, on the teeth. The bacterial accumulations cause an inflammatory response from the body. The chronic and progressive bacterial infection of the gums leads to tissue attachment loss alveolar bone destruction. It has many states or stages, ranging from easily treatable gingivitis to irreversible severe periodontitis. The understanding of the etiology and pathogenesis of periodontal diseases and their chronic, inflammatory and infectious nature necessitates admitting the possibility that these infections may influence events elsewhere in the body. Periodontal disease is seen to be increased due to several risk factors: cigarette smoking; systemic diseases; medications such as steroids, anti-epilepsy drugs, and cancer therapy drugs; ill-fitting bridges; crooked teeth and loose fillings; pregnancy; and oral contraceptive use. In addition to these variables, any systemic disorder that triggers host antibacterial defense mechanisms, such as human immunodeficiency virus (HIV) infection, diabetes, and neutrophil disorders, will likely promote periodontal disease.[1]

The oral cavity is an open system exposed to the environment. Furthermore, the possibilities of foreign material entering the system from the oral cavity are heightened due to the constant intake of food and liquids through the mouth. Not too long ago, literature evidence began to suggest a possible link between chronic inflammatory periodontitis and a number of systemic diseases.[2] The concept that oral diseases could influence distant structures is, to a certain extent, a return to the theory of focal infection. The evidence supporting this theory dates from around 1900 and it was based on the expert opinion and personal clinical experience of a few physicians and dentists. Some reports of questionable scientific merit have also supported the influence of dental sepsis on systemic health.[3] The return of this concept since the end of the 80's has been investigated in a quite different scenario. Evidence suggests a bi-directional relationship between periodontitis and systemic diseases.[4]

With the development of an epidemiological approach, dental and medical researchers and clinicians conducted various studies in order to provide the relationship between oral diseases and systemic conditions with a more scientific approach. Chronic oral diseases such as periodontitis are a constant potential source of infections and have been considered as a separate risk factor for cardiovascular diseases, cerebrovascular diseases, peripheral arterial disease, respiratory diseases, and low birth weight.[5] In addition, periodontitis has been described as a potential risk for increased morbidity and mortality for diabetes, insulin resistance, rheumatoid arthritis, obesity, osteoporosis, and complications of pregnancy.[6] In fact, a case of pyogenic liver abscess caused by periodontal bacteria had been reported.[5] On the contrary systemic conditions such as hormonal factors, hematological and immunodeficiency disorders, stress, and nutritional disorders also play a pivotal role as risk factors for periodontal diseases.

Thus this literature review aims in unveiling the interrelationship between systemic diseases and periodontal disease thereby understanding the role of systemic diseases on periodontal disease status.

Periodontal Disease and Systemic Disease

The term Periodontal Medicine, as first suggested by Offenbacher (1996), 7 can be viewed as a broad term that defines a rapidly emerging branch of periodontology focusing on the wealth of new data establishing a strong relationship between periodontal health or disease and systemic health or disease.[7] It establishes the

association between periodontal diseases and other systemic diseases. Though researches in the previous years have tried to establish a link between periodontitis and systemic ailments suggesting the possible role of periodontal disease on systemic health, numerous studies in the past have also been performed by various researchers confirming the other side of the link between periodontal-systemic health. The influence of various systemic diseases on periodontal health has also been justified. This means the systemic disease may have an influence on an individual's periodontal health. It should be understood that any systemic ailment will primarily not initiate the periodontal disease, however, it can perpetuate or enhance the progression of the disease. Thus, these can act as the contributing factors or risk factors in periodontal disease progression. Few systemic disorders, having an impact on the periodontium are listed below:

I. Influence of Hormonal Changes on Periodontium

Hormones have seemed to exert a great influence on the periodontium and alter the immune response to local factors such as plaque and calculus. There is usually an exaggerated immune response, which increases the individual's chance of having an increased severity of the disease. Hormonal variations associated with other co-morbidities such as diabetes increases the likelihood of an individual developing an exaggerated immunoinflammatory response leading to gingivitis and periodontitis.

1 Diabetes mellitus

Diabetes mellitus is a chronic, metabolic disease leading to a hyperglycemic state, that is characterized by increasesed blood glucose levels. This condition can mainly occur due to impaired insulin secretion by the beta cells of the pancreas, or there is an impaired insulin uptake due to insulin resistance in the peripheral cells.

Diabetes and periodontitis seem to have a bidirectional relationship, the presence of one increases the likelihood of the other disease condition.[8] Diabetes mellitus can be broadly classified into three types. Type I diabetes is also known as Insulin Dependent Diabetes Mellitus (IDDM) occurs mainly due to impaired secretion of insulin. This defective secretion can be mainly due to autoimmune destruction of the secretory cells of the pancreas or due to any carcinogenic condition. This mainly occurs in younger individuals and comprises 5-10% of the total diabetic condition.[9] Type II diabetes, also known as Non-Insulin Dependent Diabetes Mellitus (NIDDM) is characterised by impaired insulin intake and due to insulin resistance. This mainly occurs in elderly individuals and comprises 80-85% of the total number of diabetic cases. The third form of diabetes mellitus is also known as gestational diabetes can occur during pregnancy and usually returns to normalcy, a few months after parturition. Sometimes, diabetes can also occur secondary to certain medications such as steroids, and due to genetic defects and syndromes such as acromegaly.[10]

Periodontitis is considered the sixth complication of diabetes.[11] The periodontal manifestations in diabetic patients can be characterised by severe gingival inflammation, multiple periodontal abscesses, deep periodontal pockets, loss of clinical attachment, rapid bone loss, and mobility of the tooth. The main mechanism behind this influence is thought to be due to the alteration in the host response to local factors, which leads to rapid periodontal destruction.

i. Effect of hyperglycemia on the host immune response

The chronic hyperglycemic state is thought to have an effect on the neutrophil function such as impaired adhesion, chemotaxis, and phagocytosis, hence increasing the disease susceptibility of the individual.[12] Advanced glycation end products (AGE's), which are mainly produced due to the non-enzymatic glycation reactions also enhances the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and the

respiratory burst mechanism of neutrophils, hence there is an increase in the reactive oxygen species production (ROS) which causes extensive connective tissue breakdown. The other mechanism by which AGE's can contribute to periodontal tissue destruction is by binding to the high-affinity receptors present on the surface of the macrophages (RAGE). This RAGE activation causes an increased production of proinflammatory cytokines such as IL - 1 and TNF-α which leads to periodontal tissue destruction.[13]

ii. Alteration in subgingival microflora

In patients with uncontrolled diabetes, there is an increased proportion of periopathogenic anaerobic microorganisms, spirochetes, motile rods with decreased levels of cocci in periodontal tissue. Patients with type I diabetes with periodontitis have been reported to have a subgingival flora composed mainly of Capnocytophaga, anaerobic vibrios, Actinomyces species, Porphyromonas gingivalis, Prevotella intermedia, and Aggregatibacter actinomycetemcomitans.[14] Due to the impaired host responses, there is an increased chance of the establishment of pathogenic microflora. Hyaluronidase activity is shown to be lowered in subgingival microbiota in periodontally diseases sites in diabetic patients.[15]

iii. Alteration in collagen metabolism

In periodontium, collagen homeostasis is markedly affected in uncontrolled diabetes. There is increased crosslinking of the Advanced Glycation End (AGE's) products with the collagen, making it less degradable by the proteolytic enzymes. There is also decreased collagen synthesis in diabetes.[16] As a result of this process of decreased old collagen breakdown and less new collagen formation, collagen in the tissues of poorly controlled diabetics is weaker and aged and hence is more susceptible to breakdown. There is impaired neutrophil migration across this aged collagen matrix, hence leading to a more inflammatory response.

iv. Oral Manifestations of Diabetes Mellitus

The following are the common oral manifestation seen in diabetic patients include decreased salivary secretion/xerostomia, altered taste sensation, thick, ropy saliva, increased susceptibility to dental caries, severe gingival inflammation, multiple periodontal abscesses, deep periodontal pockets, and increased loss of clinical attachment associated with rapid bone loss and increased teeth mobility.

2. Female Sex Hormones

Throughout the life of women, there is a frequent alteration in the levels of female sex hormones. These hormones play an important role in the initiation and progression of periodontal disease, as well as in the determination of therapeutic outcomes. Gingival alterations such as pubertal gingivitis, pregnancy gingivitis, and menopausal gingivostomatitis are associated with physiologic hormonal changes and are characterized by nonspecific inflammatory reactions with a predominant vascular component, leading clinically to a marked haemorrhagic tendency of the periodontium.

i. Puberty associated changes

Puberty is an intricate hormone-mediated process that leads to sexual maturation resulting in an individual capable of reproduction. It is also accountable for changes in the physical appearance and behavior of an adolescent, which is usually attributed to the increased levels of the steroid sex hormones, testosterone in males, and progesterone and estrogens in females. Puberty occurs between the average ages of 11 to 14 years in most women. During puberty, there is an exaggerated immunoinflammatory response of the periodontal tissues to local factors, which is comparatively less severe in otherwise normal conditions.[17] The gingiva appears erythematous, bluish red in colour, lobulated and retractable. It has a tendency for spontaneous bleeding. Puberty is also associated with higher bacterial counts especially P. intermedia in the subgingival

tissue. Kornman and Loesche postulated that this anaerobic organism may use ovarian hormone as a substitute for vitamin K growth factor as its substrate and thus is usually seen in the gingival sulcus of teenaged females.[18] Although the prevalence and severity of gingival disease are increased in puberty, gingivitis is not a universal occurrence during this period and it can be prevented with good oral hygiene.

ii. Menstrual cycle associated changes

Estrogen and progesterone are the two main steroid hormones produced by the ovaries during the menstrual cycle under the influence of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones modulate the gingival and periodontal tissue changes at the microscopic level. There is an increased tendency for gingival bleeding due to underlying gingival inflammation which is aggravated by an imbalance and/or increase in sex hormones.[19] Gingival tissue also appears to be more edematous and erythematous during the menstruating period. This is mainly attributed to the increased production of gingival exudates. Variations in the production rate and pattern of gingival collagen arrangement are also seen. Occasionally the menstrual period is also associated with an increase in tooth mobility which is usually negligible. The incidence of post-extraction osteitis has also been reported during the initiation of menstruation.[20] Intraoral recurrent aphthous ulcers, herpes labialis lesions, and candida infections are also often seen in some women as a cyclic pattern.

iii. Pregnancy associated changes

During pregnancy, there is a continued elevated level of both oestrogen and progesterone, which leads to complex periodontal changes that affect the therapeutic outcomes. During pregnancy, the hormonal influence causes decreased neutrophil chemotaxis, phagocytosis, and depressed antibody production.[17] There is extensive mast cell destruction by the increased level of sex hormones leading to elevated levels of histamine and proteolytic enzymes, which contribute to an exaggerated inflammatory response to local factors such as plaque. An increased number of periodontopathogens especially P. gingivalis and P. intermedia are found in the periodontium as these microbes use estrogen and progesterone as a substitute for menadione (Vitamin K growth factor) for their growth.[18] PGE2 synthesis is also increased during pregnancy. Gingival changes seen during pregnancy include erythematous edematous gingiva with a smooth and shiny surface. It may also have a raspberry-like appearance and an increased tendency to bleed. Pregnancy tumors appear as an isolated, hyperplastic, protruding, bright red overgrowth with mulberry–like surface which is usually seen during the second trimester of pregnancy.

iv. Menopause associated changes

During menopause, there is a decrease in estrogen levels all over the body. Thus, the effects of estrogen are reduced. This can lead to a condition known as menopausal gingivostomatitis. The periodontal manifestations include dry, pale to red gingiva that tends to bleed sometimes. Fissuring of the mucobuccal fold occurs. The patient complains of a dry, burning sensation throughout the oral cavity which is associated with extreme sensitivity to thermal changes and altered taste sensation.[21] microscopically, the gingiva exhibits atrophy of the germinal and prickle cell layers of the epithelium. In some instances, areas of ulceration are also noticeable.

v. Influence of Oral Contraceptives on Periodontium

Hormonal contraceptives are a successful method of birth control and plainly refer to supplements of synthetic female sex hormones. Hence, the effect of oral contraceptives in the periodontium is similar to those exerted in other conditions of hormonal variations such as pregnancy. During pregnancy hormonal level changes, which usually do not affect the healthy tissues in a clean mouth, but exaggerated immune response

is seen secondary to bacterial plaque, same is with oral contraceptives. There is an increase in gingival inflammation without increased loss of attachment and sometimes increased gingival melanin pigmentation can occur.

3. Parathyroid hormone (PTH)

The parathyroid hormone plays a pivotal role in the calcium homeostasis of the body. During a state of decreased plasma calcium levels, PTH is secreted by the parathyroid gland, which immobilizes calcium from the bone by stimulating osteoclast function and increases the calcium reuptake in the renal tubules thereby maintaining the normal calcium levels in the blood. Hyperparathyroidism is a condition characterized by increased PTH secretion which leads to the demineralization of the skeletal system and increased bone resorption. The bone proliferates into the enlarged bone marrow spaces leading to the formation of giant cell tumours, a condition, termed Von Recklinghausen's bone disease.[22] Oral changes include malocclusion and tooth mobility, radiographic evidence of alveolar bone resorption, widening of the periodontal space, and absence of lamina dura.

4. Corticosteroids

Cortisol is a major glucocorticoid produced by humans and is also known as the stress hormone. It has immunoregulatory effects and maintains vascular tone and electrolyte balance. It also helps in maintaining plasma blood glucose. When the person is under stress, the cortisol levels increase via the hypothalamic-pituitary-adrenal axis which is likely to version the periodontium. Systemic administration of cortisol may also lead to the demineralization of the alveolar bone, increased capillary dilation, hemorrhage in the connective tissue of the periodontium, and degradation of collagen fibres.[23] Hyperpigmentation of gingiva is seen as a classical sign of primary adrenal insufficiency, which may appear as irregular pale brown spots that vary in intensity. However, in humans, no effect on the incidence and severity of gingival and periodontal disease was noted with systemic administration of cortisone and adrenocorticotropic hormone (ACTH).[24]

5. Growth Hormone

Increased secretion of growth hormones from the pituitary gland (hyperpituitarism) results in a condition called gigantism (in children) and acromegaly (in adults). This syndrome is characterized by unequal growth of the facial bones and overdeveloped sinuses. The face and the size of the lips are greatly enlarged. A marked expansion of the alveolar process leads to an increase in the size of the dental arch which affects the spacing of the teeth. This in turn may lead to food impaction. Hypercementosis is another important feature associated with hypopituitarism. Hypopituitarism, on the other hand, results in decreased skeletal growth which further leads to crowding and malposition of teeth.[25] The periodontal tissues of experimental animals with artificially induced hypopituitarism have shown an increased gingival inflammation, resorption of the cementum in the molar furcation areas, reduced apposition of cementum, decreased osteogenesis, reduced vascularity, and cystic degeneration of the periodontal ligament with calcification of many of the epithelial rests.[26]

6. Thyroxine

Thyroxine is the major hormone secreted by the thyroid gland apart from calcitonin. Hypothyroidism leads to cretinism in children and myxoedema in adults. Myxoedema manifests as hyper keratinisation of the gingival epithelium with oedema and disorganization of the collagen bundles in the connective tissues. It is also accompanied by osteoporosis of the alveolar bone. In an animal study with thiouracil-induced hypothyroidism, results showed that in these test animals, the apposition of alveolar bone was retarded and the size of the haversian system was reduced but there was no evidence of periodontal disease.[27]

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II. Influence of Hematological Disorders on Periodontium

Hematological disorders can be classified into hemostatic disorders, red blood cell disorders and white blood cell disorders. The white blood cell or leukocyte disorders constitute the major proportion of hematological disorders affecting the periodontium. However, hemostatic and red blood cell disorders may also have a detrimental effect on the integrity of periodontium.

1. Leukaemia

Leukaemia is characterised by a marked increase in circulating white cell precursors or abnormal white blood cells. These cells mainly infiltrate into various lymphoid tissues and cause enlargement of these tissues such as the spleen, liver, and lymph nodes. Different types of leucocytes can be involved. These are granulocytes, and non-granulocytes such as monocytes and macrophages. The disease is of two main variants-acute and chronic leukaemia. Acute leukaemia is characterised by increased precursor cell circulation in the periphery and occurs in the younger age group. On the other hand, chronic leukaemia has circulating leucocytes which are well-differentiated and occur in older adults. In all forms of leukaemias, the normal marrow function is impaired, and thus anaemia, infections, and thrombocytopenia are more common.

Periodontal manifestations mainly include a leukemic gingival enlargement characterised by bluish red and cyanotic gingival appearance with rounding of the gingival margin.[27] This is mainly due to the leukemic cell infiltration into the gingival tissues. Gingival bleeding is seen as a common finding in both acute and chronic leukaemia. This can be attributed to the thin and atrophic gingival epithelium, with associated thrombocytopenia. The granulocytopenia resulting from the replacement of bone marrow cells by leukemic cells reduces the tissue resistance to opportunistic microorganisms which leads to ulcerations and infections. The tissue which is evidently altered becomes extremely susceptible to bacterial infection, causing necrosis and connective tissue breakdown. A marked improvement can be seen by systemic management of the disease and the administration of an effective oral hygiene program.

2. Erythrocyte disorders

The erythrocyte disorders do not affect the periodontium profoundly. The most common red blood cell (RBC) disorder that can be possibly manifested in the periodontium is anaemia. Anaemia mainly occurs due to a decrease in the circulating haemoglobin levels, which can be due to its decreased production, decreased RBC count, or abnormal RBC formation.

Aplastic anaemia is a form of normocytic-normochromic anaemia that results from a lack of bone marrow production of erythrocytes and other blood cells. The disorder may be genetic or acquired. The acquired form usually follows exposure to certain drugs, toxic chemicals, or ionizing radiation. As all bone marrow-derived cells are affected, including the defensive leukocytes and platelets, haemorrhage and infection are the major threats to patients with aplastic anemia. Oral manifestations include petechiae, gingival swelling and bleeding (often spontaneous), gingival overgrowth, and herpetic infections. Rapid bone loss has been reported and periodontal infections have led to severe, life-threatening systemic infections.

3. Thrombocytopenia

Thrombocytopenic purpura is a disorder of the platelets which can be idiopathic in nature or secondary to other disease conditions. It is characterised by a reduction in the number of circulating platelets. There are two forms of Idiopathic thrombocytopenic purpura (ITP) - acute and chronic. The oral manifestations of thrombocytopenia may be the first clinical sign of the disease. There is spontaneous gingival haemorrhage and prolonged bleeding after trauma and toothbrushing.

4. Coagulation Disorders

Coagulation disorders may not be directly associated with periodontal disease manifestation however can influence the treatment provided due to the increased hemorraghic tendencies. Supplementing haemostatic mechanisms by altering the anticoagulant therapy, platelet transfusions or clotting factor supplements should be considered, particularly prior to surgery.

III. Influence of Immunodeficiency Disorders on Periodontium

The immune system plays a vital role in the maintenance of normal health and the function of the host. The immune mechanisms are mainly mediated through white blood cells/leucocytes along with the protective epithelial barriers, bodily secretions, and other blood and tissue components such as macrophages, mast cells, dendritic cells, histiocytes, etc. Abnormalities arising in the functions of any of these components can initiate and propagate the disease process.

1. Leukocyte disorders

i. Agranulocytosis

Agranulocytosis chiefly refers to a reduction in the number of circulating granulocytes (neutrophils, eosinophils, monocytes, and basophils) in the blood. This can lead to severe infections such as ulcerative necrotizing lesions of the gingiva and oral mucosa, skin, gastrointestinal, and genitourinary tract infections. The intensity of the lesions is mainly correlated to the extent of the absence of inflammatory cells. There can be haemorrhagic changes in the gingival connective tissue and periodontal ligament with the destruction of the principal fibres, and the presence of fetid odour.[28] Osteoporosis of the cancellous bone with osteoclastic resorption is sometimes seen.

ii. Neutropenia

Neutropenia is an immunological disorder characterised by a decrease in the circulating levels of neutrophils. There are different types of neutropenia such as agranulocytosis, familial neutropenia, and chronic idiopathic neutropenia. An individual with an absolute neutrophil count (ANC) of less than 1500 cells per microliter is considered to be neutropenic. Periodontal manifestations in neutropenic patients include the appearance of inflamed and erythematous gingiva, with or without involving the gingival margin, gingival ulceration, periodontal attachment, and bone loss.[29] In advanced stages, ulceration, and necrosis of the marginal gingiva can be seen. This is associated with bleeding and the occasional involvement of the attached gingiva.

iii. Papillon-Lefevre syndrome

It is a rare autosomal recessive disorder characterized by a mutation in the Cathepsin C gene located on chromosome 11 (11q14 – q21). Cathepsin C is a protease molecule which is mainly found in the epithelium and on the surface of immune cells such as neutrophils. Their main function is to aid in proteolytic degradation and immune cell activation. Patients with Papillon – Lefevre syndrome have little or no cathepsin C activity. The syndrome is characterized by hyperkeratotic skin lesions, severe destruction of the periodontium, and in some cases, calcification of the dura.[30] There is an increase in the collagenolytic activity, which leads to connective tissue destruction and periodontal breakdown in both primary and permanent teeth.

iv. Chediak-Higashi syndrome

It is an autosomal recessive type of syndrome mainly characterised by failure of proper organelle formation in the cells. A mutation in the Lysosomal trafficking regulator gene (LYST) - the only gene known to cause this syndrome may be responsible for this phenomenon. There is a fusion of the azurophilic and specific granules

in the neutrophils which leads to abnormal mega body formation.[31] This leads to impaired neutrophil killing mechanisms, which can also be delayed or absent. The findings of this condition are similar to those of agranulocytosis. Patients may respond to periodontal therapy, leading to premature loss of both deciduous and permanent dentitions. It is characterized by decreased chemotaxis, degranulation, and microbial activity.

v. Down Syndrome

Down syndrome caused due to trisomy 21, is a chromosomal abnormality which leads to retardation in physical and mental development. These limitations lead to poor oral hygiene maintenance and lead severe periodontal breakdown. The clinical features manifests as deep periodontal pockets, and marked recession can be seen, especially in cases of high frenal attachment. There is an increase in the population of P. intermedia in the subgingival flora in the oral cavity of children with Down syndrome.[32]

vi. Lazy leukocyte syndrome

Impaired neutrophil chemotaxis is the hallmark feature of this syndrome. This can lead to increased susceptibility to infections and periodontal breakdown, causing severe forms of bone destruction and aggressive forms of the disease with rapid attachment loss.

vii. Leukocyte adhesion deficiency

Leukocyte adhesion deficiency (LAD) is a rare genetic disorder and is present since birth. Hence the survival rate of these children is usually less, and they usually die at a young age. LAD results from the inability to express an important cell surface integrin (CD18), which is necessary for leukocytes to adhere to the vessel wall and reach the site of infection. Hence the neutrophils are not able to escape the vasculature and reach the infected site. Cases of periodontal disease attributed to LAD are rare.

Leukocyte adhesion deficiency Type I: There is a deficiency of integrin β2 subunit (CD18) resulting in impairment in leukocyte function. This defect is usually associated with aggressive periodontitis.[33]

Leukocyte adhesion deficiency Type II: Neutrophils fail to express the ligand (CD15) for P and E selectins, resulting in impaired transendothelial migration in response to inflammation.

2. Antibody deficiency disorders

i. Agammaglobulinemia

Agammaglobulinemia, or hypogammaglobulinemia, is an immune deficiency disorder resulting from inadequate antibody production caused by a deficiency in B cells. It can be congenital or acquired deformity. Congenital agammaglobulinemia is caused by an X-linked, recessive gene. The gene is responsible for B-cell development. The only male population is affected. In the absence of mature B cells, patients lack lymphoid tissue and fail to develop plasma cells. Thus, the production of antibodies is also deficient. This disease is characterized by recurrent infections, including destructive periodontitis in children and in adults, with extensive bone and attachment loss.[34]

ii. Acquired immunodeficiency syndrome

It is caused by the human immunodeficiency virus (HIV) and is characterized by the destruction of the immune cells, rendering the patient susceptible to opportunistic infections. Periodontal findings in HIV-infected individuals are mainly seen as linear gingival erythema, necrotizing ulcerative gingivitis (NUG), severe localized periodontitis, and severe destructive necrotizing stomatitis.[35]

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III. Influence of Nutritional Deficiencies on Periodontium

A good diet is required for the maintenance of overall health and periodontium is no exception. Healthy nutritional status helps in maintaining a delicate balance between tissue destruction and renewal. A well-balanced diet contains all forms of necessary ingredients such as carbohydrates, fats, proteins, vitamins, and minerals. Out of all these constituents, vitamins play a major role in periodontal tissue balance.

1. Vitamin Deficiency

Vitamins have been defined as organic components in natural foods which are required in minute amounts for normal growth, maintenance, and reproduction. They are also called "miracle workers". They are classified as fat (A, D, E, and K) and water-soluble vitamins (B, C).

i. Vitamin A

Vitamin A deficiency leads to hyperkeratinisation and hyperplastic growth of the gingival epithelium with the proliferation of the junctional epithelium.[36] There is retardation of gingival wound healing also which can be seen. There is little information regarding the effects of vitamin A deficiency on the oral structures in humans.

ii. Vitamin B complex deficiency

B complex is composed of various forms of vitamin B. But the common oral changes to B-complex deficiencies are gingivitis, glossitis, glossodynia, angular cheilitis, and inflammation of the entire oral mucosa.[37] The gingivitis in vitamin B deficiencies is non-specific, as it is caused by bacterial plaque rather than by deficiency.

iii. Vitamin C (Ascorbic Acid) Deficiency

Vitamin C plays a major role in the formation of certain amino acids such as hydroxyproline and hydroxylysine, which are important for collagen formation. Vitamin C deficiency causes scurvy, which is characterized by haemorrhagic diathesis and retardation of wound healing.[38]

Following are the possible etiologic relationships between vitamin C and periodontal diseases.[39] the first etiologic relationship could be attributed to low levels of vitamin C influence the metabolism of collagen, there is an impaired ability of the periodontal tissues to repair and regenerate by itself. The second etiopathogenesis underlying the mechanism involves alveolar bone loss can occur as it interferes with bone formation. There is an increased permeability to oral fluids and endotoxins in the mucosa, thus making it more susceptible to infection. Increasing levels of vitamin C enhance both the chemotactic and the migratory action of leukocytes without influencing their phagocytic activity. Vitamin C is required to maintain proper periodontal microvasculature. It modulates the ecologic equilibrium of bacteria in plaque and thus increases its pathogenicity.

iv. Vitamin D deficiency

Vitamin D plays an important role in bone metabolism. In vitamin D deficiency, there is generalized bone resorption in jaws, and the marrow spaces appear haemorrhagic.[40] This deficiency may lead to osteoporosis of alveolar bone. Radiographically, there is generalized partial to complete disappearance of the lamina dura and reduced density of the supporting bone, and loss of bony trabeculae.

v. Vitamin E deficiency

No relationship has been demonstrated between deficiencies in vitamin E and oral disease but in experimental rats, systemic vitamin E appears to accelerate gingival wound healing.[41]

2. Protein deficiency

Deficiency in protein has not been much demonstrated in periodontal tissues. But in experimental animals, it causes the following changes: Degeneration of the connective tissue of the gingiva and periodontal ligament, osteoporosis of alveolar bone, retardation in the deposition of cementum and delayed wound healing. Protein deprivation adversely affects immunoglobulin A in saliva, PMN phagocytosis and complement activation, and both cell-mediated and humoral immune responses.[42] Severe protein deficiency (Kwashiorkor) or general starvation (Marasmus) has long been associated with glossitis, increase gingival inflammation, and alveolar bone loss.

V. Influence of Stress and Psychosomatic Disorders on the Periodontium

Stress has now become an integral part of everyday life. Several clinical studies have documented the relationship between psychosocial stress and chronic forms of periodontal diseases. Interestingly, it is now becoming apparent that the effect is not simply a matter of the presence of stress versus a lack of stress but rather the type of stress as well as the ability of the individual to cope with the stress that correlates with destructive periodontal disease. All individuals experience stress, but these events do not invariably result in destructive periodontitis.

The types of stress that lead to periodontal destruction appear to be more chronic or long-term and less likely to be controllable by the individual. The duration of the stressful life event will also have an influence on the total impact of the stress-induced disease destruction. The systemic reactions that affect the body generally or produce an interrelated nonspecific tissue change resulting from continued exposure to stress have been termed the general adaptation syndrome (GAS) by Selye.[43] Selye considered GAS to be the basis of the pathogenesis of various diseases. The three stages of this syndrome are-a) Initial response (alarm reaction); b) adaptation to stress (resistant stage); c) Final stage, marked by an inability to maintain adaptation to stress (exhaustion stage). Stress is known to alter immune responsiveness and increase the susceptibility to periodontal inflammation such as bleeding gums, erythematous gingiva appearing reddish in colour with a soft consistency.

VI. Influence of Other Systemic Conditions/Diseases on the Periodontium

1. Congenital Heart Disease

Congenital heart disease occurs in about 1% of live births and about 40% of dying without treatment. The most striking feature of congenital heart disease is cyanosis caused by the shunting of deoxygenated blood from the right to the left, resulting in a return of poorly oxygenated blood to the systemic circulation. In severe cases, cyanosis is obvious at birth, particularly in the Tetralogy of Fallot. risk of infective endocarditis because of turbulent blood flow in the heart and associated cardiovascular defects. The need for prophylactic antibiotics should be evaluated before dental therapy. In addition to the obvious cyanosis of lips and oral mucosa, oral abnormalities associated with cyanotic congenital heart disease include delayed eruption of both deciduous and permanent dentitions, increased positional abnormalities, and enamel hypoplasia. The teeth often have a bluish-white appearance with an increased pulp vascular volume.[44]

2. Hypophosphatasia

Hypophosphatasia is a rare familial skeletal disease characterized by rickets, poor cranial bone formation, craneostenosis, and premature loss of primary teeth, particularly incisors.[45] Patients have a low level of serum alkaline phosphatase, and phosphoethanolamine is present in serum and urine. Teeth are lost with no clinical evidence of gingival inflammation and show reduced cementum formation.

3. Metal Intoxication

The ingestion of metals such as mercury, lead, and bismuth in medicinal compounds and through industrial contact may result in oral manifestations caused by either intoxication or absorption without evidence of toxicity.

4. Osteoporosis

Osteoporosis is a systemic skeletal disease characterised by low bone density, increased bone fragility, and increased susceptibility to fracture. Women above 45 years of age are most commonly affected due to menopause. This is due to changes in the hormonal levels which influence bone metabolism. Oestrogen deficiency and osteoporosis are considered common risk factors for periodontitis in postmenopausal women. Controversy exists between the association of osteoporosis and periodontal disease and it is difficult to establish a relationship between them. Some of the common factors between them include bone loss, chronicity and both are multifactorial in nature.

VII. Adverse Effects of Systemic Drugs on the Periodontal Tissues

Drug-induced xerostomia may result in increased plaque and calculus formation. Drugs which can cause xerostomia include diuretics, antihypertensives, antipsychotics, and antidepressants. Drugs of abuse such as cannabis and cocaine can induce gingival leukoplakia and erythema. Drug-induced agranulocytosis may result in severe gingival necrosis resembling generalized necrotizing ulcerative gingivitis. Drugs implicated in causing agranulocytosis include phenothiazines, sulphur derivatives, indomethacin, and some antibiotics.

Therapeutic intake of sex hormones such as estrogen, progesterone has been reported to be associated with gingival enlargement. Drug-induced gingival overgrowth remains the most widespread unwanted effect of systemic medication on the periodontal tissues. Three groups of drugs most frequently implicated are – anticonvulsants (eg Phenytoin), immunosuppressants (eg. Cyclosporine) and antihypertensives (eg. Nifedipine). Some of the psychiatric medications can cause halitosis namely lorazepam, carbamazepine, amitriptyline, fluoxetine and haloperidol.

A number of drugs may induce unusual pigmentation in the oral cavity. Implicated drugs include minocycline, zidovudine, phenothiazines, bismuth, gold salts and anticancer drugs. Minocycline may produce a gray blue black pigmentation of alveolar mucosa and attached gingiva.

Conclusion

Various systemic diseases such as osteoporosis, cancer, cardiovascular diseases, stroke, diabetes, and respiratory diseases have proven to be a major risk factors for periodontal diseases. A good clinician considers the oral cavity as an important component of routine diagnosis, as a myriad of diseases manifest in the oral cavity. It is important to have a thorough understanding and knowledge about the various oral and periodontal manifestations of various systemic diseases for an early, effective diagnosis and to formulate a proper treatment protocol. Hence the timely detection and management of the underlying systemic diseases prior to the periodontal treatment would definitely prevent the disease progression thereby maintaining both, periodontal and systemic health in order to achieve an overall good clinical outcome.

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