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Ministry Of Higher Education

And Scientific Research

University Of Dyala

College Of Medicine

Department OF Pathology

RELATIONSHIP BETWEEN SEVERITY OF PERIODONTITIS AND CLINICAL ACTIVITY IN SLE PATIENTS

Research submitted by;

ALKHAZRAJI MAADH WISAM MAHMOOD

Supervised by;

Asist.Prof.Dr. Mustafa Gheni Taher

Abstract

A large number of research have shown a potential association among periodontal and autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (SLE). Similar mechanisms of tissue destruction regarding periodontitis and different autoimmune diseases have stimulated the study of a probable relationship between those conditions. This study objectives to review the literature about this potential association and their different pathogenic mechanisms. Considering that periodontal disease is a disorder characterised by inflammation influenced by infectious factors, including SLE, it is conceivable to suggest that SLE might affect periodontal disease and vice versa. However, this issue isn't yet absolutely elucidated and numerous mechanisms have been proposed to give an explanation for this association, as deregulation particularly in innate immune system, with action of phagocytic cells and proinflammatory cytokines such as IL-1B and IL-18 in both conditions' pathogenesis, leading to tissue destruction. However, research assessing the relationship between these diseases are scarce, and more research focused on common immunological mechanisms have to be conducted for further understanding.

Introduction and pathophysiology

Periodontal tissue includes the gingiva, periodontal ligaments, cementum, and alveolar bone. The presence of bacterial infections will be inducing inflammation in periodontal tissue, resulting in progressive attachment bone loss and aggravated if systemic manifestations are present [1]. Periodontal disease starts with inflammation of gums and could develop into periodontitis. Gingivitis is found only in gingival tissue around the teeth, while periodontitis is inflammation of periodontal tissue, which can spread into periodontal tissues, associated with bacteria supplied by biofilms on teeth. As a end result of periodontal disease can damage the structure of the jawbone, causing pain, disruption of activity at a more severe level, at the same time as bacterial infections continue to develop can cause systemic disease and death [2].

The main reason of periodontal disease is the presence of dental plaque. Dental plaque is a soft, yellow layer that attaches to the teeth surface. The content of dental plaque is various types of microorganisms, mainly bacteria. Plaques containing pathogenic microorganisms play an important role in causing and developing periodontal destructions. Periodontal breakdown takes place due to increasing number of gram-negative bacteria in gingival plaques, such as Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans initiate periodontal infection [3].

An increasing periodontal infection might be a result of numerous reasons, due to chronic process lasts long in a local site or systemic conditions. Systemic diseases that play a role in this condition are the presence of blood disorders, diabetes, and rarely discussed systemic lupus erythematosus (SLE). SLE is an autoimmune disorder with many clinical manifestations. SLE patients have immune system hyperactivity, which causes a decrease in the immune system's ability to fight bacteria and the elimination of foreign antigens decreases and increasing risk of infection. High autoantibodies cause hyperactivity of the immune system against the body's own cells resulting in wide tissue damage [4].

SLE has various clinical manifestations, including atherosclerosis, malignancy, infection, and manifestation in oral cavity. The manifestation of SLE in the oral cavity could be ulcerated lesions on the mucosa,

cavities, and damage to periodontal tissue, periodontitis. Xerostomia is observed 75%, ulcerated lesions 15-40%, cavities (33-60%) and periodontitis (60-93%) [5]. Whereas in Iraq, there has never been a studies that shows periodontal tissue conditions in SLE patients. This study aimed to evaluate periodontal tissue condition on systemic lupus erythematosus patients and their characteristics.

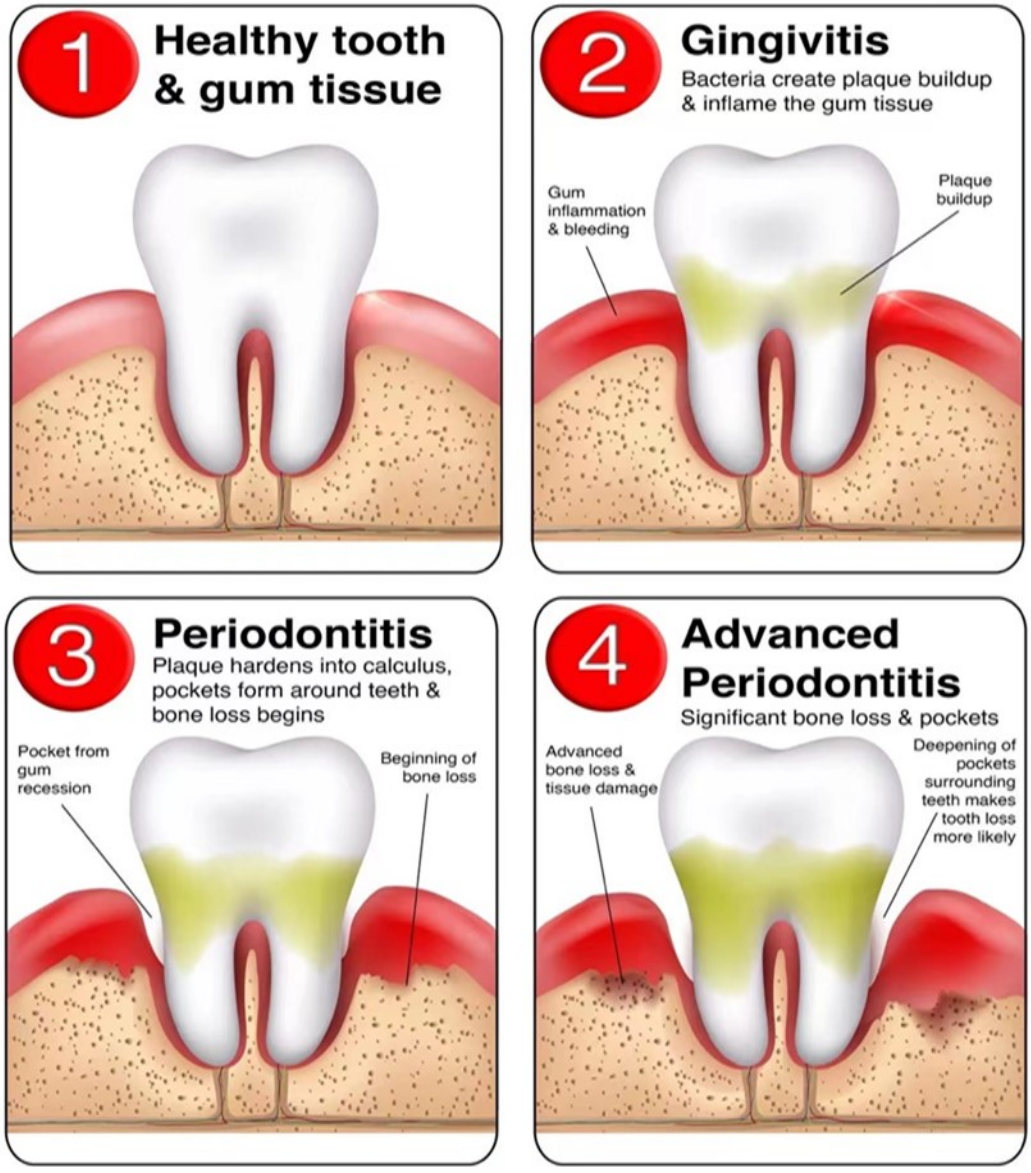

Figure 1 : the stages of gum disease

Etiology

Periodontitis has its onset and is perpetuated by a bunch of microorganism, predominantly gram-negative and anaerobes, that colonize the subgingival area. Today, it's already clear that these bacteria cause indirect tissue destruction, activating various mechanisms of host immunity [6].

it's believed that in SLE, a disease of unknown origin, there's an accumulation of disorders. Potential complications could also be related to hormonal imbalances, viral infections, impaired function of suppressor T cells, defective genetic control of immune responses, abnormal function of macrophages, B cell intrinsic defects, poor host response to an infectious agent, or a mixture of such elements [7].

Immune changes

In periodontal disease, host response has been traditionally mediate by T and B lymphocytes, neutrophils and monocytes/macrophages. These cells are triggered to provide inflammatory mediators, together with cytokines, chemokines, arachidonic acid metabolites and proteolytic enzymes, that collectively contribute to the degradation of tissue and bone reabsorption by activation of multiple degradation pathways [8] immunologic changes in SLE include B lymphocyte hyperactivity and lead to enhanced synthesis of immunoglobulins and antibodies, additionally leading to deposition of immune complexes and subsequent damage to connective tissue and to multiple organs. The interaction among hyperactive B cells, abnormally activated T cells and antigen presenting cells leads to synthesis of various inflammatory cytokines, apoptosis, auto-antibodies and immune complexes which, in turn, activate effector cells and the complement system, resulting in tissue injury and to damage that are the hallmark of clinical manifestations of systemic lupus erythematosus.

Periodontitis, though an infectious disease, exhibits very similar characteristics to SLE pathophysiology. a large number of B lymphocytes and plasma cells have also been detected in periodontal lesions. [9]

Previous studies have shown specific IgG responses against periodontopathogenic bacteria in inflamed gingival tissue and crevicular fluid [10] [11]

In periodontitis, tissue damage also derives from an excessive and unregulated production of various inflammatory mediators and destructive enzymes, in response to the presence of the bacterial biofilm.

Figue 2 : butterfly rash of SLE

Genetic and familial factors

In periodontal disease, hosts respond differently to bacterial invasion, and therefore the amount and quality of the biofilm cannot demonstrate the various responses [12] . Only 20% of the variability within the expression of periodontal diseases appears to be explained by the presence of pathogenic bacteria [13] . Recently, studies have recommended that a significant part of this response variation is the results of genetic predisposition[14] [15] .

Another risk factors, like smoking and diabetes, are already well established.Polymorphisms of interleukin-1 gene were described as the 1st genetic markers related to chronic periodontitis[16]Since then, variety of other polymorphisms are studied. Trevillato pc .. [17]for example, have demonstrated that IL-6 polymorphism is associated with susceptibility to chronic periodontal disease in Brazilian Caucasian patients.

Genetic and gene expression studies in patients with lupus have also discovered new genetic mutations and alterations in cytokines that may explain many features of the disease, as well as its genetic susceptibility. The Fcγ receptor (an immunoglobulin G receptor) gene family is one of the most studied, and has a significant role in the regulation of host reaction to bacterial challenge. [18]Polymorphisms in this receptor are related to some autoimmune diseases, such as SLE and juvenile idiopathic arthritis (JIA). There are some studies linking polymorphisms in this receptor also with periodontitis. Kobayashi T ... [19] found an increased frequency of FcγRIIa-R131 alleles in systemic lupus erythematosus and periodontitis patients, compared to healthy patients without periodontitis. in this study, the authors concluded that patients with SLE presenting polymorphism in FcγRIIa factor have a higher risk of developing periodontitis. This polymorphism is associated with a ligand deficiency with IgG2, which is common in periodontitis and SLE.

Cytokines as biomarkers

Several studies spot to cytokines as significant mediators related to the pathological process of periodontitis. bacterial products induce synthesis of pro-inflammatory cytokines like interleukin-1 beta (IL-1B), interleukin-6 (IL- 6), Interleukin-8 (IL-8) and tumor necrosis factor (TNF), primarily by macrophages. [20]

Among different cytokines, tumour necrosis factor and IL-1, mediators which will potentially participate in this process, stand out. These cytokines stimulate bone resorption by directly inducing the proliferation of osteoclast progenitors, and indirectly by stimulating the resorptive activity of mature osteoclasts and increasing collagenase synthesis. [21]

In SLE, IL-6, in addition to IL-1, TNF, IL-17 and IL-18, levels have been correlate with disease activity; and a predominance of Th2 response has been reported. [22] The balance among cytokines and their receptors may also be important, not only considering their absolute level .

Higher serum levels of IL-12 and IL-18 were identified in the study by Robak... [23] in lupus patients versus healthy patients, and this finding might indicate a pathogenetic role. However, their levels didn't correlate with disease activity and weren't responsive to immunosuppressive treatment.

IL-18, an IL-1 family member, is expressed in various cell types, including macrophages, T lymphocytes, B lymphocytes, and dendritic cells. Studies have shown that IL-18 plays a significant role in the pathological process of various autoimmune diseases, being strongly expressed both locally and systemically in adult patients with lupus. [24] other studies showed that serum levels of IL-18 were raised in adolescents with SLE which these levels correlate positively with SLEDAI index. On the opposite hand, there's scarce data regarding the presence and role of IL-18 in the periodontium. what's known is that gingival epithelial cells express this cytokine constitutively, producing it under in vitro stimulation. [25] The study by Miranda .. [26] showed raised serum levels of IL- 18 in patients with juvenile idiopathic arthritis and found a significant correlation between odontology measurements (periodontal pocket depth and clinical attachment level) and IL-18, indicating a possible role of this cytokine also in periodontitis.

Oral manifestations of SLE and periodontal disease

Involvement of the mouth is one of the diagnostic criteria for SLE (presence of mouth ulcers). In the study by Rhodus and Johnson [27], the prevalence of oral manifestations (including dry mouth, caries, mucositis, angular cheilitis, ulceration) was between 81.3 and 87.5%. All patients in the study had xerostomia and 93.8% had periodontitis. On the other hand, in the study by Khatibi [28], 54.3% of the patients had oral lesions and 28.1% had ulcers. The authors assert that the number of oral lesions decreases the longer the disease persists.This is because most of the lesions are in the active phase and as the disease progresses after diagnosis, control and treatment leads to greater stability of the disease moving to an inactive phase and therefore less prone to oral lesions. Lesions

Several studies have been published that implicate a possible association between periodontitis and rheumatoid arthritis (RA) [29] [30] and indicate a higher relative risk of periodontitis in these patients [30]

On the other hand, there are few studies examining periodontal involvement in patients with SLE. There are some case reports, such as B. A case of acute necrotizing ulcerative gingivitis (ANUG) in a patient with SLE,[31] periodontitis[32] and gingivitis. [33]

In Mutlu's study...[34] The authors found no evidence of a greater predisposition to periodontitis in patients with SLE compared to healthy controls. They identified shallower pockets in patients with SLE, a finding paralleling Figueredo's. [35] and this result could be related to the use of anti-inflammatory agents .

On the other hand, other authors found a greater incidence of periodontitis in patients with SLE than in healthy controls. [36] [37] [38]

In the study by Fabbri., [39] these authors observed for the first time a reduction in SLE activity using the SLEDAI index, parallel to a decrease in periodontal indices after periodontal treatment. Importantly, in this study, the control group, which also received immunosuppressive drug treatment for SLE, did not show a significant decrease in SLEDAI, showing a direct association between periodontal treatment and improvement in the index. Under similar conditions, improvement in

periodontal condition and systemic disease activity was also evident. Studies in patients with rheumatoid arthritis.

Biological plausibility

Periodontitis may be a critical factor in maintaining the inflammatory response that happens in SLE. In fact, infection has been considered a triggering factor for autoimmune diseases and in SLE, and this condition has been responsible for the maintenance of disease activity. many mechanisms are proposed to explain this connection, for example, an adjuvant effect of products of microorganisms. [40] in the study by Rose, [41] the injection of thyroglobulin and mycobacterium products induced the production of specific autoantibodies, as well as inflammatory thyroid lesions. In addition, infectious agents can interact with the immune system in several ways, for example, molecular mimicry, a change in apoptosis of host cells and exposure of camouflaged antigens to the immune system by certain microorganisms. All of those mechanisms might give rise to dysfunctions of the immune system.

Another potential mechanism is that the presence of changes in epithelial tissue cells. C-reactive protein contributes to hypercoagulation and will increase the expression of adhesion molecules in these cells. Its levels are elevated in patients with periodontal disease, and autoantibodies directed against this protein are raised in systemic lupus erythematosus patients, suggesting a potential binding route between these 2 conditions, additionally to being a risk factor for developing cardiovascular diseases. Moreover, as already mentioned, polymorphism in Fcγ receptor are related to periodontal disease and autoimmune diseases, such as rheumatoid arthritis and SLE. [18][19]

Inflammatory cytokines also seem to play a significant role during this interrelationship. they're usually involved in the vascular process (vascular occlusion and perivascular infiltrates) in patients with SLE. [42] Furthermore, changes in local levels of several pro-inflammatory cytokines such as IL-1, IL- 6 and tumor necrosis factor have been associated with a possible role in the process of periodontal disease. [43]

Elastase, an enzyme of the proteinase class, also seems to be involved within the association between periodontal disease and systemic lupus erythematosus. Figueredo ... [35] found greater activity of this enzyme in the gingival crevicular fluid of inflamed sites of SLE patients, even in the presence of lower levels of IL-18 and IL-1B. This greater activity suggests neutrophil hyperactivity in SLE, probably generated by a primary impact caused by increased IL-18 plasma levels in these patients.

the exact pathogenesis of SLE, as well as periodontitis, remains unknown. according to Marks and Tullus, [44] SLE in children and adults occurs in genetically susceptible individuals, in whom the inflammatory system is triggered because of a secondary stimulant (such as an environmental stimulus, p.ex. infection), leading to an abnormal cytokine environment. this modification in cytokines is additionally found in periodontitis, as reported by Figueredo CM,Ribeiro.. [45] and Rescala.. [46]

Cytokines play a significant role in the pathologic process of periodontitis. Today, several articles in this area were published, being of particular interest their use as biomarkers of disease activity. Measurements of those cytokines might serve as an alternative to help in identifying outbreak periods and for therapy response monitoring. In periodontics, measures such as pocket depth and clinical attachment level are used; however

these variables don't measure the activity of periodontal disease, only its consequence. the present goals are to identify a cytokine or a combination of cytokines to provide such information.

Influence of medications

Regarding the association between SLE and periodontal disease, the variation observed between studies can be partially explained by the influence of drugs .

Continued use of medication may mask or lessen the severity of periodontitis. The use of different drugs and in different dosages complicates the analysis of these patients because they have different clinical manifestations and therefore different treatments .

It is controversial whether the improvement observed in patients is a result of the periodontal treatment itself or the use of immunosuppressive drugs. It is known that the use of corticosteroids can have antagonistic functions, since this drug predisposes to infection and at the same time can mask the clinical features of infection due to its immunosuppressive and anti-inflammatory effects. [47]

In addition, it is important to consider other factors, e.g. socio-demographic data, disease duration, clinical activity, laboratory tests, etc., to be evaluated in order to homogenize the study groups as much as possible and thus allowing an evaluation of the influence of periodontal treatment on disease course, without the influence of other factors. These precautions were not observed in some studies such as Mutlu[34] and Kobayashi[19]. On the other hand in the study by Fabbri[39]. There was

concerns to evaluate the regime of medications used, the duration of the disease and the inflammatory markers in the patients .

Children and adolescents receiving immunosuppressants are at increased risk of developing systemic complications from oral infections [48]. The damping of periodontal infection progression, thanks to periodontal treatment would reduce levels of inflammatory markers such as IL6, TNF and C-reactive protein, which are common in SLE and periodontitis, and this would contribute to decrease the systemic inflammation in these patients[49]

Conclusion

Considering periodontal disease as a condition characterized by inflammation and stimulated by infectious factors along with SLE, it is reasonable to assume that SLE would affect the progression of periodontal disease and vice versa. Studies evaluating the connection between SLE and periodontitis are scarce. Further research focusing on the immunological mechanisms common to both diseases must be conducted to gain a better understanding. The assumption of a possible association between SLE and periodontitis and between SLE activity and periodontal destruction should be explored through longitudinal research for a better understanding of possible common pathogenic processes.

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