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Review article

Periodontitis and systemic lupus erythematosus☆

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ABSTRACT

A large number of studies have shown a potential association between periodontal and autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Similar mechanisms of tissue destruction concerning periodontitis and other autoimmune diseases have stimulated the study of a possible relationship between these conditions. This study aims to review the literature about this potential association and their different pathogenic mechanisms. Considering that periodontal disease is a disease characterized by inflammation influenced by infectious factors, such as SLE, it is plausible to suggest that SLE would influence periodontal disease and vice versa. However, this issue is not yet fully elucidated and several mechanisms have been proposed to explain this association, as deregulation mainly in innate immune system, with action of phagocytic cells and proinflammatory cytokines such as IL-1β and IL-18 in both conditions' pathogenesis, leading to tissue destruction. However, studies assessing the relationship between these diseases are scarce, and more studies focused on common immunological mechanisms should be conducted to further understanding.

Doença periodontal e lúpus eritematoso sistêmico

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RESUMO

Um grande número de estudos tem mostrado uma potencial associação entre doenças periodontais e doenças autoimunes, como artrite reumatoide e lúpus eritematoso sistêmico (LES). Os mecanismos de destruição tecidual semelhantes entre a periodontite e as demais doenças autoimunes têm estimulado o estudo de possíveis relações entre essas condições.

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O presente estudo tem como objetivo revisar a literatura acerca dessa potencial associação e dos seus diferentes mecanismos patogênicos. Considerando-se a doença periodontal uma doença de caráter inflamatório que sofre influência de fatores infecciosos, assim como o LES, é plausível sugerir que o LES influenciaria sua progressão, assim como a periodontite influenciaria a progressão do LES. Entretanto, essa questão ainda não é totalmente elucidada e vários mecanismos têm sido propostos para explicar tal associação, como desregulações, principalmente no sistema imune inato, com ações de células fagocíticas e de citocinas pró-inflamatórias, como IL-1β e IL-18, na patogênese de ambas as condições, o que contribui para a destruição tecidual. Existem, contudo, poucos estudos na literatura que avaliam a relação entre essas doenças e mais trabalhos focados nos mecanismos imunológicos comuns a ambas as condições devem ser feitos para um maior entendimento.

Introduction

Periodontitis is a chronic destructive inflammation that leads to the loss of supporting tissues of teeth and eventually even to tooth loss. The periodontal ligament and bone tissue are destroyed by an immune and inflammatory response to the presence of bacteria, particularly gram-negative ones, in the gingival sulcus. The severity of inflammation varies between individuals, irrespective of the degree of bacterial infection, suggesting that a dysregulation of the host inflammatory response may contribute to its existence.[1]

On the other hand, systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin, which affects the connective tissue and thus various organs in the body. The clinical manifestations of SLE vary with the severity of the disease, and its course may exhibit periods of exacerbation and remission.[2] SLE is characterized by immune responses against a large number of autoantigens, affecting more often women in the second and third decades of life.[3]

A large number of studies have shown a potential association between chronic periodontitis and autoimmune disease, especially rheumatoid arthritis,[4] as well as inflammatory bowel disease and glomerulonephritis.[5] A high prevalence of periodontitis has also been detected in patients with SLE.[6,7]

The similar mechanisms of tissue destruction for periodontitis and other autoimmune diseases have stimulated the study of potential associations between these conditions. In spite of presenting different etiologies, the existence of similar destructive mechanisms could explain an eventual association between periodontitis and SLE.[8] These potential mechanisms in common may involve deregulation, especially in the innate immune system, with action of phagocyte cells and of proinflammatory cytokines, such as IL-1β and IL-18, in the pathogenesis of both conditions, contributing to tissue destruction.[6,9]

The literature describing oral conditions of patients with lupus is scarce, and pertinent information is conflicting. Considering the possibility of SLE as a modifying condition of the periodontal health-disease process and the lack of information to clarify this interrelationship, our aim is to review the literature on SLE and a potential relationship with periodontal disease. Despite its high prevalence in rheumatoid arthritis, only a limited number of studies have examined oral conditions, in particular periodontal disease in SLE patients.[10,11]

Literature review and discussion

Definition

Periodontal disease is defined as any hereditary or acquired disorder of tooth surrounding and supporting tissues (periodontium). Periodontal disease has neoplastic, developmental, inflammatory, traumatic, metabolic or genetic origin. However, the term periodontal disease generally refers to those common inflammatory disorders of gingivitis and periodontitis, which are caused by pathogenic microorganisms in a biofilm or plaque that forms adjacent to the teeth. Gingivitis, the mildest form of periodontal disease, is highly prevalent and readily reversible with an effective oral hygiene. On the other hand, the inflammation that extends deep into tissues and causes loss of supporting connective tissue and alveolar bone is known as periodontitis. It results in the formation of a soft tissue pocket between the gum and root of the teeth and can result in tooth loss.[12]

On the other hand, systemic lupus erythematosus is an autoimmune disease that affects the connective tissue and may extend to various organs of the body. The clinical manifestations vary greatly between organs and systems and the course of the disease goes through periods of exacerbation and remission.[2,10]

Etiology

Periodontitis has its onset and is perpetuated by a group of bacteria, predominantly gram-negative and anaerobes, that colonize the subgingival area. Today, it is already clear that these bacteria cause indirect tissue destruction, activating various mechanisms of host immunity.[13]

It is believed that in SLE, a disease of unknown origin, there is an accumulation of disorders. Potential complications may be associated with 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 combination of such elements.[14]

Immune changes

In periodontal disease, host response has been traditionally mediated by T and B lymphocytes, neutrophils and monocytes/macrophages. These cells are triggered to produce inflammatory mediators, including cytokines, chemokines, arachidonic acid metabolites and proteolytic enzymes, which collectively contribute to the degradation of tissue and bone resorption by activation of multiple degradation pathways.[15]

Immunological changes in SLE include B lymphocyte hyperactivity and result in increased synthesis of immunoglobulins and antibodies, also resulting in deposition of immune complexes and subsequent damage to connective tissue and to multiple organs. The interaction among hypereactive B cells, abnormally activated T cells and antigen presenting cells leads to the production of various inflammatory cytokines, apoptosis, autoantibodies and immune complexes which, in turn, activate effector cells and the complement system, leading to tissue injury and to damage that are the hallmark of clinical manifestations of SLE.

Periodontitis, although 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.[16] Previous studies have demonstrated specific IgG responses against periodontopathogenic bacteria in inflamed gingival tissue and crevicular fluid.[17,18]

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.

Genetic and familial factors

In periodontal disease, hosts respond differently to bacterial invasion, and the quantity and quality of the biofilm cannot explain the different responses.[19] Only 20% of the variability in the expression of periodontal diseases seems to be explained by the presence of pathogenic bacteria.[20] Recently, studies have suggested that a significant part of this response variation is the result of genetic predisposition.[21,22] Other risk factors, such as smoking and diabetes, are already well established.[23] Polymorphisms of interleukin-1 gene were described as the first genetic markers related to chronic periodontitis.[24] Since then, a number of other polymorphisms have been studied. Trevillato et al.,[25] for instance, have demonstrated that IL-6 polymorphism is associated with susceptibility to chronic periodontitis in Brazilian Caucasian patients.

Genetic and gene expression studies in patients with SLE have also revealed new genetic mutations and alterations in cytokines that can explain several 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 an important role in the regulation of host immune response to bacterial challenge.[26] Polymorphisms in this receptor are related to some autoimmune diseases, including SLE and juvenile idiopathic arthritis (JIA). There are some studies linking polymorphisms in this receptor also with periodontitis. Kobayashi et al.[7] found an increased frequency of FcγRIIa-R131 alleles in SLE and periodontitis patients, compared to healthy patients without periodontitis. In this study, the authors concluded that patients with SLE presenting polymorphism in FcγRIIa gene 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 point to cytokines as important mediators associated with the pathogenesis of periodontitis. Bacterial products induce synthesis of proinflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), Interleukin-8 (IL-8) and tumor necrosis factor (TNF), mainly by macrophages.[27]

Among various cytokines, TNF and IL-1, mediators that can 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[28] and increasing collagenase synthesis.[29]

In SLE, IL-6, as well as IL-10, TNF, IL-17 and IL-18, levels have been correlated with disease activity; and a predominance of Th2 response has been reported.[30] The balance among cytokines and their receptors might also be important, not just considering their absolute level. Higher serum levels of IL-12 and IL-18 were identified in the study by Robak et al.[31] in SLE patients versus healthy patients, and this finding could indicate a pathogenetic role. However, their levels did not correlate with disease activity and were not 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 major role in the pathogenesis of various autoimmune diseases, being strongly expressed both locally and systemically in adult patients with SLE.[32] Areas et al.[33] showed that serum levels of IL-18 were increased in adolescents with SLE and that these levels correlated positively with SLEDAI index. On the other hand, there is scarce information about the presence and role of IL-18 in the periodontium. What is known is that gingival epithelial cells express this cytokine constitutively, producing it under in vitro stimulation.[34] The study by Miranda et al.[35] showed increased serum levels of IL-18 in patients with juvenile idiopathic arthritis and found a significant correlation between periodontal 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

Oral involvement is one of the diagnostic criteria for SLE (presence of oral ulcers). In the study by Rhodus and Johnson,[10] the prevalence of oral manifestations (dry mouth, dental caries, mucositis, angular cheilitis, ulceration, among others) ranged from 81.3 to 87.5%. All study patients exhibited xerostomia, and 93.8% had periodontitis. On the other hand, in the study by Khatibi et al.[36] 54.3% of patients had oral lesions, and 28.1% presented with ulcers. These authors emphasize that

with a longer disease duration, the number of oral lesions decreases. This occurs because most lesions are found in the active period, and that with the course of the disease after diagnosis, the control and treatment lead to a greater stability of the disease, progressing to an inactive phase and thus tending to a smaller number of oral lesions.

Several studies implying a potential association between periodontitis and rheumatoid arthritis (RA) were published,[4,5] and suggested a higher relative risk of periodontitis in these patients.[5] On the other hand, studies evaluating periodontal involvement in SLE patients are scarce. There are some case reports, as a case of acute necrotizing ulcerative gingivitis (ANUG) in a patient with SLE,[37] periodontitis[38] and gingivitis.[39] In the study by Mutlu et al.,[11] the authors did not find evidence for a greater predisposition to periodontal disease in SLE patients versus healthy controls. They identified shallower pockets in patients with SLE, a finding paralleled by Figueredo et al.,[40] and this result could be related to the use of anti-inflammatory agents. On the other hand, other authors found greater presence of periodontal disease in SLE patients than in healthy controls.[6,41,42] In the study by Fabbri et al.,[1] these authors observed for the first time reduction of SLE activity with the use of SLEDAI index, in parallel with a drop of periodontal indexes after periodontal treatment. Importantly, in this study the control group, which also received treatment with immunosuppressive drugs for SLE, showed no significant drop in SLEDAI, demonstrating a direct association between periodontal treatment and index improvement. Improvement in periodontal status and systemic disease activity was also evident in similar studies on patients with rheumatoid arthritis.[43,44]

Biological plausibility

Periodontitis can be a critical factor in maintaining the inflammatory response that occurs in SLE. In fact, infection has been regarded as a triggering factor for autoimmune diseases[45] and in SLE, and this condition has been responsible for the maintenance of disease activity. Several mechanisms have been proposed to explain this connection, for example, an adjuvant effect of products of microorganisms.[45] In the study by Rose,[46] 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 instance, molecular mimicry, a change in apoptosis of host cells and exposure of camouflaged antigens to the immune system by certain microorganisms. All of these mechanisms may give rise to dysfunctions of the immune system.[47]

Another potential mechanism is the presence of changes in endothelial cells. C-reactive protein contributes to hypercoagulation and increases the expression of adhesion molecules in these cells. Its levels are elevated in patients with periodontal disease, and autoantibodies directed against this protein are also increased in SLE patients, suggesting a possible binding route between these two conditions, in addition to being a risk factor for developing cardiovascular diseases.[48] Moreover, as already mentioned, polymorphism in Fcγ receptor have been associated with periodontitis and autoimmune diseases, such as rheumatoid arthritis and SLE.[7,26]

Inflammatory cytokines also appear to play an important role in this interrelationship. They are often involved in the vascular process (vascular occlusion and perivascular infiltrates) in patients with SLE.[49] Furthermore, changes in local levels of several pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α have been associated with a possible role in the process of periodontal disease.[50] Elastase, an enzyme of the protease class, also appears to be involved in the association between periodontal disease and SLE. Figueredo et al.[40] 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-1β. This greater activity suggests neutrophil hyperactivity in SLE, possibly generated by a primary effect caused by increased IL-18 plasma levels in these patients.

The exact pathogenesis of SLE, as well as periodontitis, is still unknown. According to Marks and Tullus,[51] SLE in children and adults occurs in genetically susceptible individuals, in whom the inflammatory system is triggered due to a secondary stimulus (such as an environmental stimulus, p.ex. infection), resulting in an abnormal cytokine environment. This change in cytokines is also found in periodontitis, as reported by Figueredo et al.[52] and Rescala et al.[53]

Cytokines play an important role in the pathogenesis of periodontitis. Today, many articles in this area were published, being of particular interest their use as biomarkers of disease activity. Measurements of these cytokines could 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; but these variables do not measure the activity of periodontal disease, only its sequels. The current 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 diseases, the divergence observed between studies may be explained in part by the influence of medication. The continued use of drugs might mask or mitigate the severity of periodontal disease. The use of different drugs and in different dosage complicates the analysis of these patients, since they exhibit different clinical manifestations and, therefore, different treatments. The controversy is whether the observed improvement in patients is a result of periodontal treatment itself, or of the use of immunosuppressive medication. It is known that the use of corticosteroids may exhibit antagonistic functions, since this drug predisposes to infection and, at the same time, may mask clinical characteristics of the infection as a result of its immunosuppressive and anti-inflammatory effects.[2]

Also, it is important to evaluate other factors, such as socio-demographic data, disease duration, clinical activity, laboratory tests, among others, to homogenize as much as possible the study groups, 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 et al.'s[11] and Kobayashi et al.'s.[7] On the other hand, in the study by Fabbri et al.,[1] there was a concern to evaluate the regime

of medications used, duration of disease and inflammatory markers among patients.

Children and adolescents under treatment with immunosuppressive drugs are at a higher risk of developing systemic complications from oral infections.[54] The damping of periodontal infection progression, thanks to periodontal treatment, would decrease the levels of inflammatory markers such as IL-6, TNF-α and C-reactive protein, which are common to SLE and periodontitis, and this would contribute to decrease the systemic inflammation in these patients.[48]

Conclusion

Considering periodontal disease as a condition characterized by inflammation and influenced by infectious factors, such as SLE, it is reasonable to suggest that SLE would influence the progression of periodontal disease, and vice versa. Studies evaluating the relationship between SLE and periodontitis are scarce. More studies focused on the immunological mechanisms common to both conditions must be conducted, to obtain a better understanding. The hypothesis of a possible link between SLE and periodontitis and between SLE activity and periodontal destruction need to be investigated by longitudinal studies, for a better understanding of possible common pathogenic processes.

Conflicts of interest

The authors declare no conflict of interests.

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