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Brief communication

Is there an association between systemic lupus erythematosus and periodontal disease?☆

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ABSTRACT

Periodontal disease results from the interaction between pathogenic bacteria that colonize supragingival and subgingival biofilms and the host, triggering an inflammatory response, with systemic effects leading to immune-mediated destruction of the attachment apparatus and loss of supporting alveolar bone. Immunological pathways and predisposing genetic factors common to periodontal disease and rheumatic diseases, including systemic lupus erythematosus, have been described. Case reports have suggested greater severity of periodontal disease in patients with systemic lupus erythematosus. However, studies evaluating the influence of the treatment of one disease on the clinical and laboratory manifestations of the other have yielded conflicting results.

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Há associação entre o lúpus eritematoso sistêmico e a doença periodontal?

Palavras-chave:
Lúpus eritematoso sistêmico
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Periodontite crônica

RESUMO

A doença periodontal resulta da interação entre bactérias patogênicas que colonizam os filmes supra e subgengival e o hospedeiro e deflagram uma resposta inflamatória local, com efeitos sistêmicos, que leva à destruição imunomediada dos tecidos de sustentação dos dentes e do osso alveolar. Vias imunológicas e fatores genéticos predisponentes comuns

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à doença periodontal e às doenças reumáticas, entre elas o lúpus eritematoso sistêmico, vêm sendo descritos. Relatos de caso sugeriram maior gravidade da doença periodontal em pacientes com lúpus eritematoso sistêmico. No entanto, estudos que avaliaram as influências do tratamento de uma sobre as manifestações da outra apresentaram resultados conflitantes.

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Introduction

Currently, the relationship between connective tissue diseases and periodontal disease (PD) has been the subject of much discussion.[1]

PD is a group of infectious and inflammatory diseases that result from the interaction between periodontal pathogens present in supragingival and subgingival biofilms and the host, generating an inflammatory response of variable intensity, which can lead to immune-mediated destruction of the attachment apparatus and loss of supporting alveolar bone. Gingivitis, the most common form of periodontal disease, is an inflammatory process characterized by erythema, edema and gingival bleeding. Periodontitis is characterized by gingival inflammation accompanied by an inflammatory response by the host, which results in destruction of the attachment apparatus and loss of supporting alveolar bone and that have systemic effects. The changes found in dental evaluation of periodontitis are an increase in probing depth (probing pocket depth – PPD), which reflects the distance from the bottom of the pocket to the gingival margin, the presence of clinical attachment loss (CAL), which measures the position of the soft tissue in relation to the cemento-enamel junction, and the occurrence of gingival bleeding on probing (BOP), mobility and tooth and alveolar bone loss.[2]

The existence of immune pathways and of a genetic predisposition common to PD and connective tissue diseases, among these systemic lupus erythematosus (SLE), is recognized and has been described.[1]

In this brief communication, we reviewed studies published in English or Portuguese, which investigated possible associations between PD and SLE, found through a systematic search in PubMed/Medline and LILACS databases, using the terms “Lupus Erythematosus, Systemic” and “Periodontitis”, “Periodontitis, Chronic” or “Periodontitis, Adult”. There was no restriction about the search period. Twenty-two articles from PubMed/Medline and five articles from LILACS were found. Thirteen original articles that dealt with the topic were included in this review.[3–15] A manual search of the references of included articles was carried out, and five articles were selected.[16–20]

Studies of association between SLE and periodontal disease

Case reports suggesting that clinical and therapeutic associations between SLE and PD have been published since the 1980s,[3–5] reporting a greater severity of PD in patients with SLE, probably associated with immunosuppression caused by the disease, or its treatment.

The frequency of periodontitis in SLE patients varied in different studies, between 60 and 93.8% (Table 1).[6–11] A Japanese study reported that SLE patients had a higher frequency of PD *versus* the general population of that country,[9] but no study has compared the frequency of PD with a control group (healthy volunteers). The variability of the frequency of periodontitis found in different studies is probably associated with the use of different criteria for its diagnosis, or to differences in patient groups with SLE with regard to disease severity or activity. Thus, the question of frequency of periodontitis in patients with SLE remains an open one, and controlled studies are needed for setting up whether periodontitis is actually more common in SLE patients.

Several authors evaluated the severity of PD in SLE patients compared to healthy volunteers, or to patients with PD without SLE, and their results were conflicting. Periodontal parameters were found to be: similar,[9,10,12,13] less severe,[9,10,13–15] or more severe[16–18] (Table 2).

These controversial data prompted some questions as: immunosuppression induced by SLE or its treatment would increase, would not affect, or would reduce the infectious and inflammatory periodontal destruction? The studies that found lower severity of periodontal parameters in SLE suggest a smaller immune-mediated periodontal destruction associated with immunosuppressive drugs.[9,10,13–15] However, the composition bias of the control group, consisting primarily of patients referred for specialized treatment and potentially with more serious periodontitis, was not controlled. Studies were also published that suggest a greater severity of PD in patients with SLE, especially when the disease is active.[16–18] Then, immunosuppression would increase the periodontal decay associated with chronic infection? This point also is not defined and requires further studies that include patients with active and inactive SLE, evaluating the influence of SLE activity and of the immunosuppressive treatment on periodontal parameters, with the inclusion of a control group representative of the general population, with people with and without PD.

Biological basis of the association between SLE and PD

In PD, the gum infection triggers a series of immune responses that involve the participation of immune cells and cytokines, that results in the destruction of the attachment apparatus and alveolar bone loss. A study reported an increase of serum levels of C-reactive protein (CRP) and of salivary

Table 1 – Periodontitis frequency in patients with SLE.

Study	Number of patients with SLE	Frequency of periodontitis observed	Frequency of periodontitis in general population
Rhodus and Johnson[6]	16	93.8%	Not reported
Novo et al. [7,8]	30	60%	Not reported
Kobayashi et al. [9]	60	70%	30–40%
Kobayashi et al. [10]	71	64.8%	Not reported
Fabbri et al. [11]	55	89%	Not reported

and serum levels of various cytokines, including: IL-1α, IL-1β, IL-6, IL-8, TNF-α, TNF-β, IFN-γ (inflammatory) and IL-10 (anti-inflammatory).[19]

The receptors for the constant region of immunoglobulin G (FcγR) participate in the immune response, facilitating phagocytosis by opsonization and acting in antibody-dependent cellular cytotoxicity and in the activation of the toxic granule release by inflammatory cells. There is evidence of an association between certain genetic polymorphisms of genes encoding these receptors and infectious and autoimmune diseases. Kobayashi et al. [9,10] found higher expression of FcγRIIa-R131 allele in patients with SLE and periodontitis *versus* patients with SLE but without periodontitis, and also healthy volunteers.[9] These authors have also shown that patients with SLE and periodontitis exhibited the combination of polymorphisms FcγRIIa-R131 and FcγRIIB-232T more often than SLE patients without periodontitis, patients with periodontitis but without systemic disease, and healthy volunteers. Combined alleles also were associated with greater severity of periodontal parameters in patients with SLE.[10]

On the other hand, so far, studies have not identified an association between periodontitis or periodontal evaluation parameters and evidence of inflammatory activity (ESR and/or CRP) in SLE or SLEDAI.[13,16]

Table 2 – PD severity classification in SLE patients and the influence of treatment of a disease over the other.

Study	Study design	Patients included	Assessed outcomes	Results
Mutlu et al.[14]	Case–control	27 SLE 25 controls	PPD	Lower in SLE.
Meyer et al.[12]	Case–control	46 SLE 50 controls	VPI, GBI, BOP%	Similar.
Kobayashi et al.[9]	Case–control	42 SLE + PD 42 PD	PPD, CAL, SP%, BOP%	Smaller PPD, CAL and BOP% in SLE. Similar SP% and BOP%.
Souza[13]	Case–control	16 JSLE 14 controls	VPI, GBI, CAL, PPD	Lower percentage of sites with PPD ≥3 mm in JSLE. Similar VPI, GSI and percentage of sites with CAL ≥2 mm. Active JSLE presented higher VPI and GSI *versus* inactive JSLE.
Miceli et al.[15]	Case–control	17 JSLE 14 controls	PPD	Lower percentage of sites with PPD ≥4 mm in SLE.
Kobayashi et al.[10]	Case–control	46 SLE + PD 48 PD	PPD, CAL, BOP%, SP%	Lower PPD, CAL, BOP%, and SP% in SLE. Similar SP%.
Fernandes et al.[16]	Case–control	48 JSLE 48 controls	VPI, GBI	Higher in JSLE. Cumulative prednisone dosage correlated to VPI and GBI.
Umbelino Jr. et al.[17]	Case series	155 SLE	Dental calculus, gingival bleeding, periodontal pockets.	Gingival bleeding and periodontal pockets were greater in SLE patients, when compared to epidemiological data from general population.
Meyer et al.[18]	Case series	46 SLE	Oral mucosa lesions, teeth loss, gingival inflammation.	Greater in patients with severe SLE.
Sales et al.[20]	Series of cases submitted to clinical treatment of PD.	6 SLE + PD	Bacterial plaque, BOP% and PPD, SLEDAI, CRP.	Improvement of periodontal parameters with no changes of SLEDAI.
Fabbri et al.[11]	Randomized, controlled trial on PD treatment.	49 SLE + PD: 32 treated 17 untreated	PPD, CAL, GBI, SLEDAI, CRP, ESR.	Improvement of periodontal parameters and SLEDAI on treatment group

SLE, systemic lupus erythematosus; PD, periodontal disease (periodontitis); PPD, probing pocket depth; VPI, visible plaque index; GBI, gingival bleeding index; ABL, alveolar bone loss; SP%, percentage of sites with plaque; BOP%: percentage of sites with bleeding on probing; JSLE, juvenile systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; CRP, C-reactive protein; CAL, clinical attachment level; ESR, erythrocyte sedimentation rate.

Two studies examined inflammatory cytokines in gingival crevicular fluid (which can be found in periodontal pockets) and in serum. Souza[13] found higher crevicular fluid levels of total and free elastase and lower crevicular fluid levels of IL-18, but higher serum levels of IL-18 in patients with juvenile SLE *versus* control group. CAL showed a negative correlation with crevicular fluid IL-18 levels ($r = -0.5$; $p < 0.05$), suggesting that this cytokine could have a protective effect on the tissue destruction associated with PD. In the study by Miceli et al.,[15] healthy adolescents had higher levels of IL-1-β in crevicular fluid *versus* patients with juvenile SLE who were evaluated for presence of periodontal disease.

Two studies evaluated the association between the presence of antineutrophil cytoplasmic antibodies (ANCA) and periodontitis in subjects without rheumatic disease and in patients with SLE or rheumatoid arthritis (RA).[7,8] Half of the subjects with periodontitis were positive for ANCA. Among the 18 patients with SLE and periodontitis, 83.3% were positive for ANCA. Half of the patients with RA had periodontitis, but this disease was not associated with a higher occurrence of ANCA. The significance of the association between ANCA and periodontitis in healthy subjects or in patients with SLE remains unclear.[7,8]

In summary, there is evidence of a common genetic predisposition (shared polymorphisms) of SLE and PD, which could explain the association between these two conditions. Still, at least from a theoretical point of view, there are pathophysiological mechanisms common to PD and LES that need to be better described and understood, because they may represent prospects for future therapeutic approaches.

Specific treatment and influence on SLE and periodontal disease

Fernandes et al.[16] found a positive correlation between the cumulative dose of corticosteroids and increases in plaque and gingival bleeding rates in patients with juvenile SLE (respectively, $r = 0.385$, $p = 0.01$; $r = 0.471$; $p = 0.001$), but did not identify an association with the use of antimalarials or immunosuppressive agents (Table 2).[16]

Two studies evaluated the influence of the treatment of PD on SLE activity (Table 2). Sales et al.[20] selected six patients with SLE (mean of SLEDAI = 3.5) and PD. The patients underwent non-surgical treatment of periodontitis and were reassessed 45 days after its completion. There was significant improvement in their periodontal indices. SLEDAI and CRP levels did not change significantly after periodontal treatment.[20]

Fabbri et al.[11] selected 49 patients with active SLE and PD, divided into two groups: one group with treatment of PD performed during the study ($n = 32$) and a group whose treatment of PD was delayed for a time after completion of the study. There was no significant difference in baseline SLEDAI in treated and control groups. Patients were reassessed 3 months after the treatment of PD, when a significant reduction in SLEDAI was observed in the treatment group (5.9 ± 4.2 *vs.* 3.4 ± 3.3, $p = 0.04$), but did not occur in the untreated group.

No significant differences were noted in ESR or CRP in both groups (Table 2).[11]

The highest cumulative dose of corticosteroids, given local and systemic immunosuppressive and metabolic effects of these agents (with an interference in bone metabolism), could be associated with the worst outcome of the infectious process and, consequently, with greater periodontal destruction in patients with SLE and PD. Studies are needed to establish whether the concomitant use of immunosuppressants would have a protective effect or, on the contrary, would contribute to greater periodontal destruction in SLE and PD patients.

Studies evaluating the influence of PD treatment on SLEDAI in SLE patients showed conflicting results. One study, which showed no change in SLEDAI, included a small number of patients without high activity of the disease.[20] Another study evaluated a greater number of patients with active SLE, all on monthly intravenous infusions of cyclophosphamide and corticosteroids, and showed significant decline in SLEDAI, compared to baseline, in patients treated for periodontitis, which did not occur in the group untreated for this disease; this suggests a possible role of the treatment of periodontitis in the control of active SLE.[11] This result is quite interesting, because it opens up promising prospects in SLE approaches, however it must be confirmed by prospective controlled studies. Theoretically, the control of chronic infection related to PD could reduce the degree of activation of the immune system, favoring the response of SLE to the immunosuppressive treatment.

Conclusion

The data about possible associations between SLE and PD are controversial. The good clinical practice, however, recommends attention to the oral health of patients with SLE, ideally with periodic dental evaluation. In the event of PD identification, its treatment should be performed, as it can positively influence the however of SLE. Further studies will be needed to establish the association between SLE and PD, as well as their biological basis, and to clearly define the effect of treatment of a condition over the other.

Conflict of interests

The authors declare no conflicts of interest.

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