Review article

Periodontal disease in pediatric rheumatic diseases

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ABSTRACT
Gingivitis and periodontitis are immunoinflammatory periodontal diseases characterized by chronic localized infections usually associated with insidious inflammation. This narrative review discusses periodontal diseases and mechanisms influencing the immune response and autoimmunity in pediatric rheumatic diseases (PRD), particularly juvenile idiopathic arthritis (JIA), childhood-onset systemic lupus erythematosus (C-SLE) and juvenile dermatomyositis (JDM). Gingivitis was more frequently observed in these diseases compared to health controls, whereas periodontitis was a rare finding. In JIA patients, gingivitis and periodontitis were related to mechanical factors, chronic arthritis with functional disability, dysregulation of the immunoinflammatory response, diet and drugs, mainly corticosteroids and cyclosporine. In C-SLE, gingivitis was associated with longer disease period, high doses of corticosteroids, B-cell hyperactivation and immunoglobulin G elevation. There are scarce data on periodontal diseases in JDM population, and a unique gingival pattern, characterized by gingival erythema, capillary dilation and bush-loop formation, was observed in active patients. In conclusion, gingivitis was the most common periodontal disease in PRD. The observed association with disease activity reinforces the need for future studies to determine if resolution of this complication will influence disease course or severity.

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Doença periodontal em doenças reumáticas pediátricas

RESUMO
Gingivite e periodontite são doenças periodontais imunoinflamatórias caracterizadas por infecções localizadas crônicas geralmente associadas a uma inflamação insidiosa. Essa revisão narrativa discute doenças periodontais e mecanismos que influenciam a resposta imune e a autoimunidade na área das doenças reumáticas pediátricas (DRP), particularmente a artrite idiopática juvenil (AIJ), lúpus eritematoso sistêmico juvenil (LESJ) e dermatomiosite juvenil (DMJ). Foi notada maior frequência de gengivite nessas doenças em comparação com controles sadios, enquanto casos de periodontite foram achados raros.
Em pacientes com AII, a gengivite e a periodontite estavam relacionadas a fatores mecânicos, artrite crônica com incapacitação funcional, desregulação da resposta imunoinflamatória, dieta e medicamentos, principalmente corticosteroides e cicloserina. Em pacientes com LESJ, a gengivite estava associada a períodos mais longos da doença, doses elevadas de corticosteroides, hiperativação dos linfócitos B e elevação da imunoglobulina G. São escassos os dados sobre doenças periodontais na população com DMJ; nos pacientes ativos, foi observado um padrão gengival singular, caracterizado por eritema gengival, dilatação dos capilares e formação arbustiforme. Em conclusão, gengivite foi a doença periodontal mais comum em pacientes com DRP. A associação observada com a atividade da doença reforça a necessidade de futuros estudos, com o intuito de determinar se a resolução dessa complicação irá influenciar o curso ou a gravidade da doença.
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more prominent. The reasons for the host response fails to control periodontal infection or to inhibit disease progression are not well understood, but the disruption of host homeostasis by periodontal pathogens may be a major contributory factor.

Gingivitis pathogenesis is characterized initially by a vascular response with increased fluid and inflammatory cell infiltration in gingiva with perivascular lymphocytic infiltrate and macrophage cells deposition. Lymphocytes are predominantly T cells with a CD4:CD8 ratio of approximately 2:1. Clinical signs of oral inflammation including bleeding, swelling and redness of the gingiva may occur in these patients.

The persistence of this inflammatory response results in chronic gingivitis with collagen degradation but without any dental attachment loss. Gingivitis may progress to periodontitis, but this only occurs in 10% to 15% of the population and may be associated with environmental factors and/or genetic susceptibility. The immunological mechanism underlying periodontal development involves a shift to a B-cell/plasma-cell response with high levels of interleukin-1 (IL-1) and interleukin-6 (IL-6) production, increased chemokine production by macrophages [IL-1β, tumor necrosis factor-alpha (TNF-α) and IL-17] and a consequent enhanced osteoclastogenesis with connective tissue destruction and alveolar bone loss.

Cytokines may also modulate the action, differentiation, and survival of cells outside the immune system. In this regard, nervous system cells expressing neurotransmitters related to neurogenic inflammation are known to allow neuroplastic changes that are observed in chronic pain. In fact, severe periodontal disease was reported by our group to be related to refractory craniofacial pain.

**PD and systemic diseases**

Regarding periodontal pathogens, the dental plaque is a complex biofilm with a relevant role in the pathogenesis of PD and can serve as a reservoir of microbes with local and systemic consequence. The systemic exposure to periodontal pathogens, their toxins, and periodontal derived/elicted inflammatory mediators may have a deleterious effect in different organ or systems. Three mechanisms by which periodontal infection may influence systemic health have been described: metastatic infection (caused by translocation of Gram-negative bacteria from the periodontal pocket to the bloodstream), metastatic injury (such as vascular lesions from the effects of circulating microbial toxins and pro-inflammatory mediators) and metastatic inflammation (due to the immunological response to the periodontal pathogens and their toxins).

Indeed, pathogen manipulation may perturb otherwise homeostatic host-bacterial interactions, thereby leading to non-protective and non-resolving chronic inflammation. This condition can cause systemic inflammation that has been recognized as an essential component of different multifactorial diseases, including chronic inflammatory rheumatic diseases.

**Gingivitis and periodontitis may also induce a variety of immunological alterations with circulating immune complexes due to the failure of autoimmune regulation and tolerance, contributing the onset and progression of systemic autoimmune and rheumatic diseases.**

**Periodontal diseases in pediatric rheumatic diseases**

Reports of PD in PRD are restricted to juvenile idiopathic arthritis, childhood-onset systemic lupus erythematosus and juvenile dermatomyositis.

Tables 1 and 2 include clinical studies of periodontal diseases in pediatric rheumatic diseases.

### Juvenile idiopathic arthritis (JIA)

There is a negative impact on oral health in JIA patients due to mechanical factors, chronic arthritis with functional disability, dysregulation of the immunoinflammatory response, diet and medications.

Several studies reporting that JIA could be a risk factor for gingivitis or periodontitis and these pediatric conditions were included in the current system classification of PD. In this regard, chronic arthritis with upper limb disability and reduced mandibular mobility due to temporomandibular joint involvement was reported to be an important contributing factor for PD in our JIA patients. Furthermore, a significant increased level of poor oral hygiene in patients with JIA was found. On the other hand, one study showed that if cofactors (such as: age, gender and smoking) are included, the microbial plaque (and not the JIA diagnosis) is related to periodontitis.

It has been suggested that the association between JIA and periodontal disease might be caused by a common dysregulation of the immunoinflammatory response. Increased values of IL-10, and TNF-α in unstimulated blood-cell culture...
and IL-1Ra in stimulated blood-cell culture were observed in generalized periodontitis, JIA and RA, indicating that these cytokines are shared by these diseases. In the same way, patients with generalized periodontitis may present elevated levels of traditional markers of inflammation, such as neutrophils, leukocytes, CRP and ESR, similar to observed in patients with JIA and RA.

Moreover, allele variation of IL-1 gene cluster modify the cytokine profiles of patients with aggressive periodontitis as JIA, suggesting that this group shared genetic background for cytokines profiles.

In fact, the increased serum levels of IL-18 and IL-1β in JIA patients accompanied by a similar subgingival microbiota suggest that the increased frequency of incipient attachment loss observed in these patients might be due to their altered systemic inflammatory response, making them more susceptible to PD.

Additionally, for periodontitis, as well as for JIA, associations to HLA classes I and II alleles were reported, and HLA-DRB3 could be a common putative risk for JIA and chronic periodontitis among females. In fact, the immune response to bacteria is influenced by human leucocyte anti-

| Table 1 – Clinical studies of periodontal diseases in juvenile idiopathic arthritis |
|----------------------------------|-----------------|--------------------|
| Diseases                        | Country         | Number of patients and healthy controls | Clinical and immunological findings |
| Walton et al., 200028           | UK              | Review             | Negative impact of poor oral health |
| Miranda et al., 200337          | Brazil          | 32 JIA patients and 24 controls | JIA adolescents presented more periodontal attachment loss than healthy controls |
| Welbury et al., 200335          | UK              | 149 JIA patients and 149 controls | Increased level of poor oral hygiene and dental decay in JIA |
| Savioli et al., 200432          | Brazil          | 26 JIA patients and 13 controls | Gingivitis in JIA patients associated with upper limb disability |
| Ahmed et al., 200431            | UK              | 55 patients and 55 controls | Gingivitis score was significantly higher in JIA compared to controls |
| Miranda et al., 200535          | Brazil          | 38 JIA patients and 29 controls | Increased serum IL-18 and IL-1β in JIA patients increased susceptibility to PD |
| Havemose-Poulsen et al., 200538 | Denmark         | 10 JIA, 23 RA, 45 aggressive periodontitis patients and 25 controls | Peripheral blood cytokine profile and cytokine secretion pattern were showed in by JIA, RA and generalized aggressive periodontitis |
| Miranda et al., 200639          | Brazil          | 18 JIA adolescents and 14 controls | No clinical or laboratory differences in periodontal inflammation were found in JIA patients and controls |
| Havemose-Poulsen et al., 200640 | Denmark         | 10 JIA, 23 RA, 45 aggressive periodontitis patients and 25 controls | Elevated levels of traditional markers of inflammation were observed in generalized aggressive periodontitis, JIA and RA. |
| Reichert et al, 200646          | Germany         | 78 JIA patients and 75 controls | JIA was not a risk factor for periodontitis |
| Reichert et al., 200747         | Germany         | 110 JIA patients (50 of them generalized aggressive periodontitis), 102 JIA with chronic periodontitis | HLA-DRB3n was common risk indicator for JIA and chronic periodontitis in females |
| Havemose-Poulsen et al, 200748  | Denmark         | 10 JIA, 23 RA, 45 aggressive periodontitis patients and 25 controls | Variation of alleles of the IL-1 gene cluster modified the cytokine profiles of patients with aggressive periodontitis and chronic arthritis |
| Synodinos et al, 200849         | Ireland         | Review             | Caries and periodontal disease related to diet, disease activity and similar inflammatory process pattern |
| Leksel et al, 200850            | Sweden          | 41 JIA patients and 41 controls | JIA patients showed worse periodontal condition compared to controls |
| Silva et al, 201251             | Brazil          | 16 JIA patients and 11 controls | Lower alveolar bone density in JIA patients |

JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis; PD, periodontal disease; UK, United Kingdom; USA, United States of America.

| Table 2 – Clinical studies of periodontal diseases in pediatric rheumatic diseases |
|----------------------------------|-----------------|--------------------|
| Diseases                        | Country         | Number of patients and healthy controls | Clinical and immunological findings |
| JDM                             | USA             | 5 JDM patients     | Gingival telangiectases |
| Ghali et al., 199952            | Hungary         | 34 JDM patients    | Gingival telangiectases |
| Marton et al., 200553           | Brazil          | 26 JDM patients and 22 controls | Unique gingival pattern associated with cutaneous disease |
| Savioli et al., 201054          | Brazil          | 48 C-SLE patients and 48 children | C-SLE patients had inadequate oral hygiene, gingivitis and temporomandibular joint dysfunction |
| Fernandes et al., 200755        | Brazil          | 16 C-SLE patients and 14 controls | Increased elastase activity suggested hyperactivity of neutrophils |

JDM, juvenile dermatomyositis; C-SLE, childhood-onset systemic lupus erythematosus; USA, United States of America.
en (HLA) polymorphism and individual peptide binding capability of cell surface HLA receptors. Furthermore, bacterial mimicry between bacteria and certain HLA molecules could lead to autoimmune reactions or to mechanisms of cross-tolerance. Patients with JIA showed also lower alveolar bone density compared to healthy controls, without correlation with rheumatologic and periodontal clinical parameters. The generalized bone loss in arthritis has been suggested to an increase of osteoclastic activity and a reduction in the process of bone formation. Reduced physical activity and inadequate calcium and vitamin D intake can influence this reduction in bone mineral density.

Microbial challenge, environmental immune response modifiers and host genetic variation can have local and systemic repercussion. These effects will induce changes in connective tissue and bone metabolism resulting in the clinical features observed in JIA with PD (Fig. 2).

The most important factor associated with PD in JIA is medication. In this regard, cyclosporine may result in gingival enlargement, ulceration or bleeding. Glucocorticoids may have induced osteoporosis, and this therapy may also delay wound healing and increased risk of gingival infection, however the effect of this medication in alveolar bone is unknown in JIA. Despite the immunosuppressive treatment, the majority of JIA patients presented mild gingivitis without loss of connective tissue attachment, and periodontitis was rarely described. In addition, JIA patients under anti-TNF blockage had a higher frequency of sites with increased probing depth and a lower frequency of sites with bleeding on probing, however experimental studies suggested that these drugs might inhibit radiographic progression.

**Juvenile dermatomyositis (JDM)**

Periodontal diseases were rarely reported in JDM population, and the two most important factors present in these patients are: reduction of mandibular mobility and gingival alterations. Alterations in the masticatory system have been identified in JDM patients, such as: hyposalivation, mucosal alterations, mainly in the form of telangiectasia, and weakness of the masticatory muscles. The reduction of mandibular mobility, particularly mouth opening in active JDM patients reinforces the possibility that this finding is an additional manifestation of JDM in the masticatory system and a consequence of muscle weakness.

One relevant aspect evidenced in JDM patients was a unique gingival pattern, characterized by gingival erythema, capillary dilation and bush-loop formation (similar to periungual capillary changes observed in nailfold capillaroscopy) associated with cutaneous disease activity. This finding reported by our group was distinct from PD, suggesting that gingiva is a possible target tissue for JDM.

**Childhood-systemic lupus erythematosus (C-SLE)**

PRD were also rarely reported in C-SLE population. One study observed that C-SLE patients had an inadequate oral hygiene with higher incidence of gingivitis and without periodontitis. The most important risk factors for gingivitis were longer disease duration and higher cumulative dose of prednisonemas. In C-SLE patients, active elastase was observed in gingival crevicular fluid (GCF) from inflamed sites, even in the presence of significantly lower levels of IL-18 and IL-13. In contrast, the plasma levels of IL-18 and the erythrocyte sedimentation rate were significantly higher in this group of patients. The increased elastase activity suggests neutrophils hyperactivity in C-SLE patients, possibly induced by a priming effect caused by the high IL-18 plasma levels.

**Conclusions**

In conclusion, gingivitis was the most common periodontal disease in PRD. The underlying mechanism is multifactorial and includes mechanical factors, chronic arthritis with functional disability, dysregulation of the immunoinflammatory response, diet and medications, particularly corticosteroids. The observed common association with disease activity in all reported diseases reinforces the need for future studies to determine if resolution of this complication could influence disease course or severity. In addition, there are some evidence that gingiva may be a target tissue in pediatric autoimmune rheumatic disease.

**Take-home messages**

The most important periodontal disease observed in pediatric rheumatic diseases was gingivitis.

Periodontitis was rarely reported in pediatric rheumatic diseases.

Periodontal diseases in JIA patients are multifactorial related to mechanical factors, functional disability, dysregula-
tion of the immunoinflammatory response, diet and medica-
tions.

A gingival pattern, characterized by gingival erythema, capillary dilation and bush-loop formation associated with cutaneous disease activity was observed in JDM.

Gingivitis associated with longer disease period and high doses of corticosteroids was observed in C-SLE patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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