REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Review article

Periodontal disease in pediatric rheumatic diseases

Gisele M.C. Fabri[a,b], *Cynthia Savioli*[a], *José T. Siqueira*[a], *Lucia M. Campos*[c], *Eloisa Bonfá*[d], *Clovis A. Silva*[c,d,*]

[a]*Dentistry Division, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil*
[b]*Faculdade de Odontologia, Universidade Federal de Juiz de Fora, MG, Brazil*
[c]*Paediatric Rheumatology Unit, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil*
[d]*Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil*

ARTICLE INFO

Article history:
Received on 4 October 2013
Accepted on 23 November 2013

Keywords:
Gingivitis
Periodontitis
Periodontal diseases
Juvenile idiopathic arthritis
Childhood-onset systemic lupus erythematosus
Juvenile dermatomyositis

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.

Doença periodontal em doenças reumáticas pediátricas

Palavras-chave:
Gengivite
Periodontite
Doenças periodontais
Artrite idiopática juvenil
Lúpus eritematoso sistêmico juvenil
Dermatomiosite juvenil

RESUMO

Gengivite 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.

* *Corresponding author.*
E-mail: clovis.silva@hc.fm.usp.br (C.A. Silva).

0482-5004/$ - see front matter.
http://dx.doi.org/10.1016/j.rbr.2013.11.004

Em pacientes com AIJ, 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 ciclosporina. 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.

Introduction

Gingivitis and periodontitis are immunoinflammatory periodontal diseases characterized by chronic localized infections usually associated with insidious inflammation.[1]

Periodontal diseases (PD) can cause systemic inflammation, and it was demonstrated to be an essential underlying component of several inflammatory and immune mediated diseases, such as atherosclerosis,[2] diabetes mellitus[3] and systemic autoimmune rheumatic diseases.[4] In adults with rheumatoid arthritis (RA), PD was associated with disease activity and severity[5] with a striking similarity between both diseases with regard to genetic susceptibility and pathogenesis.[6]

PD is also relevant for pediatric rheumatic diseases (PRD), since poor oral health is a risk factor for systemic infection and inflammation in general population and may be more important in patients with immune dysregulation under immunosuppressive drugs.[7]

Therefore, we performed a narrative review and we conducted a series of literature searches in the MEDLINE/PubMed database for English language articles focusing on PD in patients with PRD. The search strategy included a combination of medical subject headings and keywords. The search terms that we used were "periodontal disease", "gingivitis", "pediatric rheumatic diseases", "juvenile idiopathic arthritis", "juvenile rheumatoid arthritis", "juvenile systemic lupus erythematosus", "childhood-onset systemic lupus erythematosus" and "juvenile dermatomyositis". The search covered the period between 1970 and 2012, and included clinical studies, systematic reviews and animal studies. All articles identified were full-text papers.

Periodontal diseases in children and adolescents

Plaque-induced PD has been classified into three subtypes: healthy (absence of plaque induced PD), gingivitis (presence of gingival inflammation without loss of connective tissue attachment) and periodontitis (presence of gingival inflammation with loss of connective tissue and alveolar bone).[8] Gingivitis is an inflammatory response to bacteria of the dental biofilm, without loss of dental attachment, and its prevalence among schoolchildren ranged from 40% to 100%.[9-12] Periodontitis is a widespread infection affecting the tooth support of 10%-15% of the general population.[13] The incidence of periodontitis in pediatric population is generally 1%.[14]

Children and adolescents can develop PD as a consequence of a local or a systemic factor. Local factors include: plaque, calculus, orthodontic appliances and dental anomalies (such as: enamel projections, enamel pearls). Systemic factors include: malnutrition, gender, race, hormones, smoking, systemic diseases and immunosuppressive drugs.[15-17]

The more common form of PD in pediatric population is gingivitis. This gingival abnormality is characterized by a local inflammatory response to microbial challenge without bone resorption. However, it is crucial to note that young subjects with overt gingival inflammation more frequently exhibit periodontal attachment loss than adolescents without gingival inflammation and gingivitis always appears to precede the development of periodontitis.[2,15]

Most cases of periodontitis described in children and adolescents occur as manifestation of systemic diseases, such as Papillon-Lefevre syndrome, hypophosphatasia and leukocyte adhesion deficiency. These diseases induce an impaired immune system, that compromise microbial plaque response and increase the likelihood of periodontal bone loss and premature teeth loss associated with severe and generalized periodontitis during or immediately after eruption of the primary teeth.[15-17]

Pathogenesis of PD

The tooth is an organ with peculiar characteristics in the organism. It is a hard structure that has one portion immersed in connective tissue and another part is exposed to the external environment, susceptible to bacterial colonization (Fig. 1). In addition, bacteria or their products continually interact with gingival epithelium to stimulate a host response.[18] An inflammatory infiltrate (mainly comprised of neutrophils or polymorphonuclear leukocytes) is usually present, even in the absence of clinically obvious inflammation in order to maintain periodontal homeostasis.[19]

The bacteria associated with PD comprise a group of Gram-negative anaerobic organisms, among which the so-called "red complex" pathogens, especially *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*, are

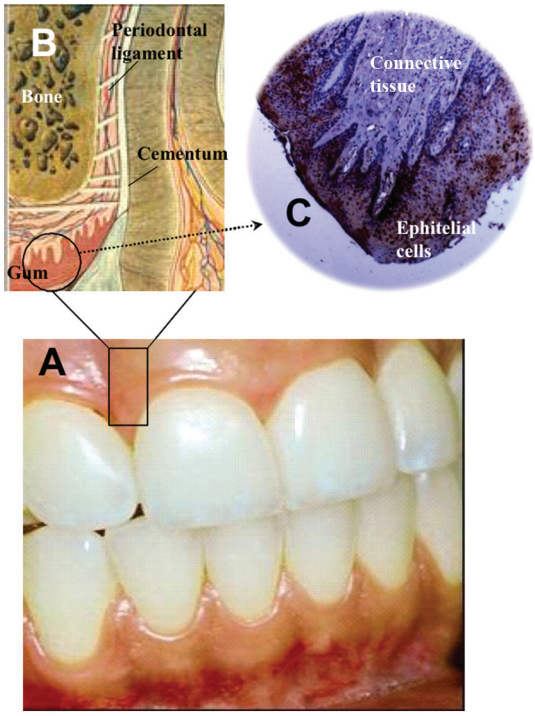

Fig. 1 – Periodontal tissues anatomy. (A) Clinical examination of healthy gingiva; (B) Periodontal tissues; (C) Histological characteristics of gingival

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.[20]

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.[19] 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.[19] 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-1b, tumor necrosis factor-alpha (TNF-α) and IL-17][21,22] and a consequent enhanced osteoclastogenesis with connective tissue destruction and alveolar bone loss.[22]

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[23] 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.[24]

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.[25] The systemic exposure to periodontal pathogens, their toxins, and periodontal derived/elicited 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).[25]

Indeed, pathogen manipulation may perturb otherwise homeostatic host-bacterial interactions, thereby leading to non-protective and non-resolving chronic inflammation.[26] This condition can cause systemic inflammation that has been recognized as an essential component of different multifactorial diseases, including chronic inflammatory rheumatic diseases.[27]

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.[4]

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.[28-30]

Several studies,[29-34] 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.[8] In this regard, chronic arthritis with upper limb disability and reduced mandibular mobility due to temporomadibular joint involvement was reported to be an important contributing factor for PD in our JIA patients.[32] Furthermore, a significant increased level of poor oral hygiene in patients with JIA was found.[35] 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.[36]

It has been suggested that the association between JIA and periodontal disease might be caused by a common dysregulation of the immunoinflammatory response.[37] Increased values of IL-10, and TNF-α in unstimulated blood-cell culture

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., 2000[28]	UK	Review	Negative impact of poor oral health
Miranda et al., 2003[37]	Brazil	32 JIA patients and 24 controls	JIA adolescents presented more periodontal attachment loss than healthy controls
Welbury et al., 2003[35]	UK	149 JIA patients and 149 controls	Increased level of poor oral hygiene and dental decay in JIA
Savioli et al., 2004[32]	Brazil	26 JIA patients and 13 controls	Gingivitis in JIA patients associated with upper limb disability
Ahmed et al., 2004[31]	UK	55 patients and 55 controls	Gingivitis score was significantly higher in JIA compared to controls
Miranda et al., 2005[55]	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., 2005[38]	Denmark	10 JIA, 23 RA, 45 aggressive periodontitis patients and 25 controls	Peripheral blood cytokine profile and citokine secretion pattern were showed in by JIA, RA and generalized aggressive periodontitis
Miranda et al., 2006[33]	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, 2006[39]	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, 2006[36]	Germany	78 JIA patients and 75 controls	JIA was not a risk factor for periodontitis
Reichert et al., 2007[43]	Germany	110 JIA patients (50 of them generalized aggressive periodontitis),102 JIA with chronic periodontitis and 102 controls	HLA-DRB3n was common risk indicator for JIA and chronic periodontitis in females
Havemose-Poulsen et al, 2007[40]	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, 2008[29]	Ireland	Review	Caries and periodontal disease related to diet, disease activity and similar inflammatory process pattern
Leksel et al, 2008[34]	Sweden	41 JIA patients and 41 controls	JIA patients showed worse periodontal condition compared to controls
Silva et al, 2012[48]	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			
Ghali et al., 1999[60]	USA	5 JDM patients	Gingival telangiectases
Marton et al., 2005[58]	Hungary	34 JDM patients	Gingival telangiectases
Savioli et al., 2010[59]	Brazil	26 JDM patients and 22 controls	Unique gingival pattern associated with cutaneous disease
C-SLE			
Fernandes et al., 2007[64]	Brazil	48 C-SLE patients and 48 children	C-SLE patients had inadequate oral hygiene, gingivitis and temporomandibular joint dysfunction
Figueredo et al., 2008[65]	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.

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.[38] 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.[39]

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.[40]

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.[33]

Additionally, for periodontitis,[41] as well as for JIA,[42] 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.[43] In fact, the immune response to bacteria is influenced by human leucocyte anti-

gen (HLA) polymorphism[44,45] and individual peptide binding capability of cell surface HLA receptors.[46] Furthermore, bacterial mimicry between bacteria and certain HLA molecules could lead to autoimmune reactions or to mechanisms of cross-tolerance.[47]

Patients with JIA showed also lower alveolar bone density compared to healthy controls, without correlation with rheumatologic and periodontal clinical parameters.[48] 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.[49,50]

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.[51,52] Long-term use of methotrexate in rats with PD enhanced alveolar bone destruction.[53] Glucocorticoids may have induced osteoporosis,[54] and this therapy may also delay wound healing and increased risk of gingival infection,[28] 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.[32,37,55] 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,[56] however experimental studies suggested that these drugs might inhibit radiographic progression.[57]

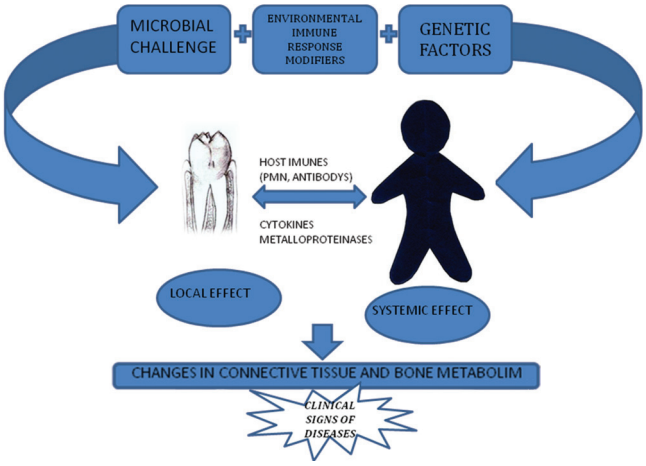

Fig. 2 – Similarities between periodontal diseases and pediatric rheumatic diseases: Microbial challenge, environmental immune response modifiers and genetic factors have critical role in pathogenesis of both diseases. The host inflammation, with production of antibodies, polymorphonuclears (PMN), cytokines and metalloproteinase, has local and systemic effect and trigger changes in connective tissue and bone metabolism with remarkable clinical signs of diseases

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.[58,59]

Alterations in the masticatory system have been identified in JDM patients, such as: hyposalivation, mucosal alterations, mainly in the form of telangiectasia,[58-63] and weakness of the masticatory muscles.[58] 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.[59]

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.[59]

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 prednisone.[64]

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.[65]

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 medications.

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.

Acknowledgments

This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (grants 2008/58238-4 to CAS, 2009/51897-5 to EB and CAS, and 2010/12035-5 to GMCF), Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq (301411/2009-3 to EB, and 472155/2012-1 to CAS), Federico Foundation (to EB and CAS) and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" of USP to CAS.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Ali J, Pramod K, Tahir MA, Ansari SH. Autoimmune responses in periodontal diseases. Autoimmun Rev. 2011;10:426-31.
2. Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. J Periodontol. 2004;75:1046-53.
3. Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. J Periodontol. 2013;84:S135-52.
4. Takakubo Y, Konttinen YT. Immune-regulatory mechanisms in systemic autoimmune and rheumatic diseases. Clin Dev Immunol. 2012;941346.
5. Al-Katma MK, Bissada NF, Bordeaux JM, Sue J, Askari AD. Control of periodontal infection reduces the severity of active rheumatoid arthritis. J Clin Rheumatol. 2007;13:134-7.
6. Kaur S, White S, Bartold PM. Periodontal disease and rheumatoid arthritis: a systematic review. J Dent Res. 2013;92:399-408.
7. Cullinan MP, Seymour GJ. Periodontal disease and systemic illness: will the evidence ever be enough? Periodontol 2000. 2013;62:271-86.
8. Armitage GC. Periodontal diagnoses and classification of periodontal diseases. Periodontol 2000. 2004;34:9-21.
9. Sheiham A, Netuveli GS. Periodontal diseases in Europe. Periodontol 2000. 2002;29:104-21.
10. Baelum V, Fejerskov O, Karring T. Oral hygiene, gingivitis and periodontal breakdown in adult Tanzanians. J Periodontal Res. 1986;21:221-32.
11. Baelum V, Fejerskov O, Manji F. Periodontal diseases in adult Kenyans. J Clin Periodontol. 1988;15:445-52.
12. Gjermo P, Rösing CK, Susin C, Oppermann R. Periodontal diseases in Central and South America. Periodontol 2000. 2002;29:70-8.
13. Jenkins WM, Papapanou PN. Epidemiology of periodontal disease in children and adolescents. Periodontol 2000. 2001;26:16-32.
14. Loe H, Brown LJ. Early onset periodontitis in the United States of America. J Periodontol. 1991;62:608-16.
15. Albandar JM, Rams TE. Risk factors for periodontitis in children and young persons. Periodontol 2000. 2002;29:207-22.
16. Cabanilla L, Molinari G. Clinical considerations in the management of inflammatory periodontal diseases in children and adolescents. J Dent Child. 2009;76:101-8.
17. Alrayyes S, Hart TC. Periodontal disease in children. Dis Mon. 2011;57:184-91.
18. Handfield M, Baker HV, Lamont RJ. Beyond good and evil in the oral cavity: insights into host-microbe relationships derived from transcriptional profiling of gingival cells. J Dent Res. 2008;87:203-23.
19. Kinane DF, Podmore M, Murray MC, Hodge PJ, Ebersole J. Etiopathogenesis of periodontitis in children and adolescents. Periodontol 2000. 2001;26:54-91.
20. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. J Clin Periodontol. 1998;25:134-44.
21. Hajishengallis G. Complement and periodontitis. Biochem Pharmacol. 2010;80:1992-2001.
22. Ohlrich EJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease. Aust Dent J. 2009;54:S2-10.
23. Bartold PM, Walsh LJ, Narayanan AS. Molecular and cell biology of the gingiva. Periodontol 2000. 2000;24:28-55.
24. Fabri GM, Siqueira SR, Simione C, Nasri C, Teixeira MJ, Siqueira JT. Refractory craniofacial pain: is there a role of periodontal disease as a comorbidity? Arq Neuropsiquiatr. 2009;67:474-9.
25. Teng YT. The role of acquired immunity and periodontal disease progression. Crit Rev Oral Biol Med. 2003;14:237-52.
26. Hajishengallis G. Complement and periodontitis. Biochem Pharmacol. 2010;80:1992-2001
27. Scrivo R, Vasile M, Bartosiewicz I, Valesini G. Inflammation as "common soil" of the multifactorial diseases. Autoimmun Rev. 2011;10:369-74.
28. Walton AG, Welbury RR, Thomason JM, Foster HE. Oral health and juvenile idiopathic arthritis: a review. Rheumatology (Oxford). 2000;39:550-5.
29. Synodinos PN, Polyzois I. Oral health and orthodontic considerations in children with juvenile idiopathic arthritis: review of the literature and report of a case. J Ir Dent Assoc. 2008;54:29-36.
30. Walton AG, Welbury RR, Foster HE, Thomason JM. Juvenile chronic arthritis: a dental review. Oral Dis. 1999;5:68-75.
31. Ahmed N, Bloch-Zupan A, Murray KJ, Calvert M, Roberts GJ, Lucas VS. Oral health of children with juvenile idiopathic arthritis. J Rheumatol. 2004;31:1639-43.
32. Savioli C, Silva CA, Ching LH, Campos LM, Prado EF, Siqueira JT. Dental and facial characteristics of patients with juvenile idiopathic arthritis. Rev Hosp Clín Fac Med São Paulo. 2004;59:93-8.
33. Miranda LA, Braga F, Fischer RG, Sztajnbok FR, Figueredo CM, Gustafsson A. Changes in periodontal and rheumatological conditions after 2 years in patients with juvenile idiopathic arthritis. J Periodontol. 2006;77:1695-700.
34. Leksell E, Ernberg M, Magnusson B, Hedenberg-Magnusson B. Intraoral condition in children with juvenile idiopathic arthritis compared to controls. Int J Paediatr Dent. 2008;18:423-33.
35. Welbury RR, Thomason JM, Fitzgerald JL, Steen IN, Marshall NJ, Foster HE.Increased prevalence of dental caries and poor oral hygiene in juvenile idiopathic arthritis. Rheumatology. 2003;42:1445-51.
36. Reichert S, Machulla HK, Fuchs C, John V, Schaller HG, Stein J. Is there a relationship between juvenile idiopathic arthritis and periodontitis? J Clin Periodontol. 2006;33:317-23.

37. Miranda LA, Fischer RG, Sztajnbok FR, Figueredo CM, Gustafsson A. Periodontal conditions in patients with juvenile idiopathic arthritis. J Clin Periodontol. 2003;30:969-74.
38. Havemose-Poulsen A, Sørensen LK, Stoltze K, Bendtzen K, Holmstrup P. Cytokine profiles in peripheral blood and whole blood cell cultures associated with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol. 2005;76:2276-85.
39. Havemose-Poulsen A, Westergaard J, Stoltze K, Skjødt H, Danneskiold-Samsøe B, Locht H et al. Periodontal and hematological characteristics associated with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol. 2006;77:280-8.
40. Havemose-Poulsen A, Sørensen LK, Bendtzen K, Holmstrup P. Polymorphisms within the IL-1 gene cluster: effects on cytokine profiles in peripheral blood and whole blood cell cultures of patients with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol. 2007;78:475-92.
41. Machulla HK, Stein J, Gautsch A, Langner J, Schaller HG, Reichert S. HLA-A, B, Cw, DRB1, DRB3/4/5, DQB1 in German patients suffering from rapidly progressive periodontitis (RPP) and adult periodontitis (AP). J Clin Periodontol. 2002;29:573-9.
42. Thomson W, Donn R. Juvenile idiopathic arthritis genetics – what's new? What's next? Arthritis Res. 2002;4:302-6.
43. Reichert S, Stein J, Fuchs C, John V, Schaller HG, Machulla HK. Are there common human leucocyte antigen associations in juvenile idiopathic arthritis and periodontitis? J Clin Periodontol. 2007;34:492-8.
44. Buckley CE 3rd, Dorsey FC, Corley RB, Ralph WB, Woodbury MA, Amos DB. HL-A-linked human immune-response genes. Proc Natl Acad Sci USA. 1973;70:2157-61.
45. Greenberg LJ, Gray ED, Yunis EJ. Association of HL-A 5 and immune responsiveness in vitro to streptococcal antigens. J Exp Med. 1975;141:935-43.
46. Rammensee HG, Friede T, Stevanoviic S. MHC ligands and peptide motifs: first listing. Immunogenetics. 1995;41:178-228.
47. Avakian H, Welsh J, Ebringer A, Entwistle CC. Ankylosing spondylitis, HLA-B27 and Klebsiella. II. Cross-reactivity studies with human tissue typing sera. Br J Exp Pathol. 1980;61:92-6.
48. Silva TL, Braga FS, Sztajnbok FR, Souza AA, Silva FB, Fischer RG et al. Reduction in alveolar bone density of patients with juvenile idiopathic arthritis. Rev Bras Reumatol. 2012;52:38-43.
49. Silva L, Freitas J, Sampaio L, Terroso G, Pinto JM, Veludo V et al. Vitamin D measurement in Portuguese patients with fragility fractures. Acta Reumatol Port. 2010;35:352-7.
50. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-A review of recent evidence. Autoimmun Rev 2013. Epub ahead of print.
51. Seymour RA. Dentistry and the medically compromised patient. Surgeon. 2003;1:207-14.
52. Lucas VS, Roberts GJ. Oro-dental health in children with chronic renal failure and after renal transplantation: a clinical review. Pediatr Nephrol. 2005;20:1388-94.
53. Yoshinari N, Kameyama Y, Aoyama Y, Nishiyama H, Noguchi T. Effect of long-term methotrexate-induced neutropenia on experimental periodontal lesion in rats. J Periodontal Res. 1994;29:393-400.
54. Seguro LP, Rosario C, Shoenfeld Y. Long-term complications of past glucocorticoid use. Autoimmun Rev. 2013;12:629-32
55. Miranda LA, Fischer RG, Sztajnbok FR, Johansson A, Figueredo CM, Gustafsson A. Increased interleukin-18 in patients with juvenile idiopathic arthritis and early attachment loss. J Periodontol. 2005;76:75-82.
56. Leksell E, Ernberg M, Magnusson B, Hedenberg-Magnusson B. Intraoral condition in children with juvenile idiopathic arthritis compared to controls. Int J Paediatr Dent. 2008;18:423-33.
57. Di Paola R, Mazzon E, Muià C, Crisafulli C, Terrana D, Greco S et al. Effects of etanercept, a tumour necrosis factor-alpha antagonist, in an experimental model of periodontitis in rats. Br J Pharmacol. 2007;150:286-97.
58. Márton K, Hermann P, Dankó K, Fejérdy P, Madléna M, Nagy G. Evaluation of oral manifestations and masticatory force in patients with polymyositis and dermatomyositis. J Oral Pathol Med. 2005 Mar;34:164-9.
59. Savioli C, Silva CA, Fabri GM, Kozu K, Campos LM, Bonfá E et al. Gingival capillary changes and oral motor weakness in juvenile dermatomyositis. Rheumatology. 2010;49:1962-70.
60. Ghali FE, Stein LD, Fine JD, Burkes EJ, McCauliffe DP. Gingival telangiectases: an underappreciated physical sign of juvenile dermatomyositis. Arch Dermatol. 1999;135:1370-4.
61. Rider LG, Atkinson JC. Images in clinical medicine. Gingival and periungual vasculopathy of juvenile dermatomyositis. N Engl J Med. 2009;9:360.
62. Gonçalves LM, Bezerra-Júnior JR, Gordón-Núñez MA, Libério SA, Cruz MC. Oral manifestations as important symptoms for juvenile dermatomyositis early diagnosis: a case report. Int J Paediatr Dent. 2011;21:77-80.
63. Sanger RG, Kirby JW. The oral and facial manifestations of dermatomyositis and calcinosis. Report of a case. Oral Surg Oral Med Oral Pathol. 1973;35:476-88.
64. Fernandes EG, Savioli C, Siqueira JT, Silva CA. Oral health and the masticatory system in juvenile systemic lupus erythematosus. Lupus. 2007;16:713-9.
65. Figueredo CM, Areas A, Sztajnbok FR, Miceli V, Miranda LA, Fischer RG et al. Higher elastase activity associated with lower IL-18 in GCF from juvenile systemic lupus patients. Oral Health Prev Dent. 2008;6:75-81.