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Characteristics and relationship of periodontal disease with juvenile idiopathic and rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory disease of the joints. It is correlated with periodontal disease due to similar factors that exist in both diseases. The present study assessed the relationship of periodontal disease with RA and juvenile idiopathic arthritis (JIA).

Materials and Methods: In this case-control study, 30 RA and 30 JIA patients along with similar number of matched controls were selected among patients referred to Imam Khomeini Hospital, Tehran, Iran. Periodontal parameters including pocket depth (PD), clinical attachment level (CAL), O'Leary and Bay plaque index (PI) and bleeding on probing (BOP) were determined in cases and controls. Erythrocyte sedimentation rate, number of painful and inflamed joints and severity of disease were evaluated in RA and JIA patients. Mann-Whitney U-test nonparametric, Spearman and Pearson's correlation coefficients, and Chi-square tests were used as statistical analysis ($\alpha = 0.05$).

Results: PD (4.17 vs. 3.6 mm; $P < 0.0001$), CAL (4.89 vs. 4.18 mm; $P < 0.002$), percentage of sites with PD >4 mm (58.83% vs. 44.33%; $P < 0.002$), percentage of sites with CAL >3 mm (74.13% vs. 64.4%; $P < 0.001$), percentage of sites with BOP (9.67% vs. 6.87%; $P < 0.0001$) and PI index (85.73% vs. 80.63%; $P < 0.0001$) were significantly higher in RA patients than controls. In this group, direct and significant correlations were found between serologic findings, disease severity and number of painful and inflamed joints with periodontal factors. In JIA patients, no significant relationships were found between JIA findings and periodontal parameters.

Conclusion: Considering the limitations of this study, there was a relationship between RA and periodontal disease. Severity of periodontal disease increases in patients with RA, while no increased risk of periodontal disease or its severity was observed among JIA patients.

Key Words: Juvenile, rheumatoid arthritis, periodontitis, case-control studies

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that mainly attacks joints. It often leads to the destruction of the joint due to the presence of inflammatory agents in the synovial fluid.[1] It is one of the most common forms of arthritis afflicting approximately 1% of the world's population[2] with a female to male ratio

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of 3:1.[3] The etiology of RA is yet to be completely identified, but some arteriogenic stimulants seem to be responsible for activating the inflammatory response in this disease. Infections, mediators like cytokines, impaired function of immunoglobulins and the immune system have also been suggested as the possible mechanisms involved.[1]

Juvenile idiopathic arthritis (JIA) was suggested by the International League of Association for Rheumatology in 1997 as a substitute for the terms juvenile chronic arthritis and juvenile RA.[4] JIA is a type of chronic arthritis with an onset before the age of 16 years.[2,5] It is a major connective tissue disorder in children and adolescents (with an incidence rate of 0.07-4.01 in 1000 adolescents and a female predilection).[6,7] Etiology of JIA is unknown, but the role of immune system disorders in this respect has been documented.[2,4] Increased production of cytokines, immunogenetic diseases, and some viral infections are among the proposed etiologies.[2] In these two forms of arthritis, increased levels of various cytokines such as interleukin-1 (IL-1), interleukon-2 receptor (IL-2r), IL-6, tumor necrosis factor alpha (TNF-alpha) and interferon gama (IF gama) are detected in the synovial fluid and serum of patients.[8,9] Apparently, these cytokines stimulate the synovial cells to release hydrolytic enzymes like collagenase that is, the main culprit in tissue destruction process.[2,10] Low-level of T helper 2 (Th2) in RA and JIA patients results in prolonged inflammation[11] and development of systemic signs of inflammation such as increased serum level of acute phase proteins.[1,3]

On the other hand, periodontitis is a chronic disease associated with the destruction of tooth-supporting structures like collagen fibers and alveolar bone. It is caused by a group of pathogenic microorganisms, and its continuation depends on the body's inflammatory and immune responses.[2,10] Periodontitis is the inflammation of the periodontal tissues associated with the destruction of gingiva and connective tissue attached to the tooth and is manifested in three general forms of chronic, aggressive and as a manifestation of systemic disease.[12] At present, scaling and root planning, periodontal flap, and antimicrobial therapy as an adjunct to mechanical debridement are offered to treat periodontal patients.[12]

Similar pathophysiologic mechanisms have been observed in RA, JIA, and periodontitis.[1] In addition to the involvement of bone and connective tissue in these conditions, host's immune system and function of neutrophils play a significant role in JIA and periodontitis.[1,4,12,13] Also, in all three conditions, cytokines and their receptors like IL1 β, IL2, IL6, prostaglandin E2 and TNF alpha play a role in tissue destruction and bone loss.[1,14] Polymorphism of IL1α, IL1β and IL4 genes has been observed in both JIA and periodontitis[15-18]

Association of HLA-DR4 alleles in genetic structure of RA and aggressive periodontitis patients are among other similarities of these conditions.[19-21] Use of nonsteroidal anti-inflammatory drugs for treatment of RA and JIA decreases the progression of periodontal disease and associated bone loss in patients suffering from arthritis;[22] however, this correlation can be an outcome of the upper limb movement limitations that result in patients' decreased ability to maintain their oral and dental hygiene.[4,23] Temporomandibular joint (TMJ) involvement in some RA and JIA patients can cause limited access to the oral cavity.[3,23] What is the mechanism.[4] Recently, studies conducted on the relationship of these two diseases have reported controversial results. In some studies, more severe periodontal conditions have been reported in RA and JIA patients as compared to healthy controls.[24-29]

Considering the little information regarding the relationship between periodontal disease and JIA and controversial correlations with RA, the present study aimed to determine the relationship of periodontal disease with RA and JIA.

MATERIALS AND METHODS

This case-control study was conducted on RA and JIA patients presenting to the Rheumatology and Pediatric Clinics of Imam Khomeini Hospital in Tehran, Iran during 2012-2013. The controls were healthy subjects that matched our cases in terms of age and gender. The sample size of the study was determined based on similar previous studies and consult of statistion. Adult controls were selected from the available patients presenting to a private practice office. Juvenile controls were chosen among the patients of a pediatric dental office. All subjects consented to participate in the study and related examinations. Data were collected through observation, examination, and interview and the obtained results were recorded in a questionnaire. A total of 30 adult RA patients who had been referred consequently to the Rheumatology Clinic of Imam Khomeini Hospital were selected, and their arthritis was

confirmed by an experienced rheumatologist according to the The American Rheumatism Association Criteria.[3] Also, 30 adolescents (below the age of 16) whose JIA diagnosis had been confirmed by a pediatrician were chosen in the pediatric clinic of Imam Khomeini Hospital. These two groups comprised the case groups.

The control group included 30 healthy adults selected among those presenting to a private practice office and 30 healthy adolescents (below the age of 16) presenting to a pediatric dental office. The controls were matched with cases in terms of age and sex. Understudy sample size was determined according to the most relevant study[2] (with10% increase to adjust for possible patient loss). The exclusion criteria were pregnancy, smoking, and any other systemic disease affecting periodontal conditions and use of antibiotics in last 6 months. All patients attending the study were thoroughly informed about the study and related examinations and a written informed consent was obtained from them. All data about their rheumatologic conditions in RA group were obtained by a rheumatologist and the questionnaire for joint pain, and inflammation was filled out for patients.

As previously mentioned, rheumatoid workup was performed on JIA patients by a pediatric rheumatologist and joint pain and inflammation questionnaire was filled out for them.

Periodontal examinations of patients were done within 10-15 days after rheumatologic examinations in the Rheumatology clinic of Imam Khomeini Hospital by a trained dental student. Examinations were done at the rheumatology and pediatric wards and clinics using a Williams probe. Since some of the patients were hospitalized, all subjects were examined on the hospital bed using a headlight. Measurements for plaque index (PI), bleeding on probing (BOP), pocket depth (PD) and clinical attachment level (CAL) were performed for all teeth except for the third molars and maximum values of indexes were recorded for each tooth. Erupting teeth in adolescents were not included in the measurement. Prior to the study, intra-examiner calibration was done through repeated examinations by the student and their accuracy was confirmed by a periodontist. All participants filled out the demographic characteristics and medical/familial history forms. Test subjects also completed the patient assessment (PA)[30] form and Children Health Assessment Questionnaire (CHAQ)[2] approved by the American College of Rheumatology in order to determine disease severity from their point of view.[30,31]

Eventually, erythrocyte sedimentation rate (ESR) was performed for case subjects (RA and JIA patients) to determine the amount and severity of inflammation.

The following indexes were also compared between case and control groups: Mean percentage of PI, mean percentage of sites with BOP, mean percentage of sites with CAL >3 mm, mean percentage of sites with PD >4 mm, mean CAL values, mean rate of PD, and TMJ status (pain, inflammation/swelling).

In the case groups, correlations between periodontal parameters and ESR, number of painful or inflamed joints, patient assessment scores, and CHAQ scores as the indexes for determining the severity of arthritis were evaluated.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 16 software (SPSS Inc., Chicago, IL, USA). Mean, standard deviation, standard error, minimum and maximum values of the variables were determined and reported for both groups of case and control. Comparison of periodontal indexes in the two groups was done using Mann-Whitney U nonparametric test. The correlations between periodontal indexes, serologic findings of disease and patients' assessment of disease severity were evaluated and compared using Spearman and Pearson's correlation coefficients (in case of the normal distribution). Gender frequency in the case and control groups was analyzed with Chi-square test. $P \leq 0.05$ was considered as statistically significant.

All participants provided written informed consent and study protocol was thoroughly explained to them. Also, participation in the study was voluntarily, and patients received oral health care instructions. It should be mentioned that examinations required for this study did not interfere with patients' treatments and all examinations were done under the supervision of a specialist. This study was approved by the Ethics Committee of Research Council, School of Dentistry, Shahid Beheshti Medical University.

RESULTS

This study was done on 30 healthy adults, 30 healthy adolescents and 30 adults with RA and 30 patients with JIA. Of a total of 60 adults, 48 (80%, 24 of cases

and 24 of controls) were females and 12 subjects (20%, 6 cases and 6 controls) were males.

In adult RA patients, mean ESR was 22.53 ± 5.99 (range 11-32), mean patient assessment score was 15.69 ± 3.55 (range 10.5-25), mean number of inflamed joints was 3.0 ± 1.44 (range 1-6), and mean number of painful joints was 13.1 ± 2.07 (range 10-19). The mean age of RA subjects was 42.73 ± 7.49 years (range 29-55 years). In the adult control group of RA, the mean age of subjects was 42.63 ± 7.64 (range 29-56). No statistically significant difference was detected between the 2 groups in terms of age.

Kolmogorov-Smirnov test demonstrated that case and control data lacked normal distribution. Therefore, comparison of the RA and healthy groups in terms of periodontal parameters was done with Mann-Whitney U-test [Table 1]. This test demonstrated that the PD ($P < 0.0001$), CAL ($P < 0.002$), percentage of sites with PD >4 ($P < 0.002$), percentage of sites with CAL >3 ($P < 0.001$), percentage of sites with BOP ($P < 0.0001$) and PI index ($P < 0.0001$) values in adult RA patients were significantly higher than those of controls.

Table 2 demonstrates the significant and insignificant correlations between understudy variables in adult RA patients using Spearman's rank correlation coefficient. Numbers of swelled and painful joints were significantly correlated with CAL >3, PD >4 and BOP. Other results are shown in Table 2.

Table 1: Comparison of periodontal parameters in control and RA patients

Periodontal parameters	RA	Control	*P*
PI (mean) (SD)	85.73 (4.95)	80.63 (4.51)	<0.001
BOP (mean) (SD)	9.67 (2.94)	6.87 (1.48)	<0.001
PD (mean) (SD)	4.17 mm (0.67)	3.6 mm (0.48)	<0.001
CAL (mean) (SD)	4.89 mm (0.95)	4.18 mm (0.58)	<0.001
Mean percentage of site with CAL >3 (SD)	74.13 (12.78)	64.4 (8.07)	<0.001

SD: Standard deviation; PI: Plaque index; BOP: Bleeding on probing; PD: Pocket depth; CAL: Clinical attachment level; RA: Rheumatoid arthritis

The mean age of adolescent controls was 13.4 ± 1.55 years. This rate in patients with JIA was 13.43 ± 1.45 years. Except for BOP that was significantly higher in JIA patients than controls ($P < 0.001$), no significant differences were observed between the two groups in terms of PD, CAL, sites with CAL >3 and PI [Table 3]. The difference between the two groups in terms of age was not significant.

Table 4 demonstrates significant and insignificant correlations between understudy variables in JIA patients using Pearson's correlation coefficient.

DISCUSSION

In this study, periodontal parameters including PD, CAL, percentage of sites with PD >4 mm, percentage of sites with CAL >3 mm, percentage of sites with BOP and PI index were significantly higher in RA patients than controls. In this group, direct and significant correlations were found between serologic findings, disease severity and number of painful and inflamed joints with periodontal factors. In JIA patients, no significant differences were detected between the two groups regarding periodontal parameters with the exception of BOP, which was significantly higher in cases. In this group, no significant correlations were found between JIA findings and periodontal parameters.

Such a result was not found in the provided reference. that article focused on gene polymorphism and was totally lab based. A copy of referred article is attached. The order of references might be scrambled.

Some studies present different results on the other hand. Welbury *et al*.[25] found significant higher PI in JIA patients. Higher and different PI and PD scores can be a reason for the difference. In Reichert *et al*. study,[4] although PI and mean percentage of sites with CAL >3.5 were higher in JIA group, there was no difference between patients and controls in number of people having at least one site with CAL.3.5, which was considered as periodontitis.

Table 2: The results of Pearson's correlation coefficient in evaluation of the correlation between different variables in RA patients

Severity of rheumatoid disease	PI	BOP	CAL >3	PD >4	CAL	PD
Amounts of ESR	*P*<0.0013	*P*<0.005	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001
PA	*P*=0.43	*P*=0.39	*P*=0.198	*P*=0.071	*P*=0.285	*P*=0.35
Number of swelled joints	*P*=0.628	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001
Number of painful joints	*P*=0.377	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001

PI: Plaque index; BOP: Bleeding on probing; PD: Pocket depth; CAL: Clinical attachment level; PA: Patient assessment; ESR: Erythrocyte sedimentation rate; RA: Rheumatoid arthritis

Table 3: Comparison of periodontal parameters in control and JIA patients

Periodontal parameters	JIA	Control	*P*
PI (mean) (SD)	53.07 (5.6)	53.43 (5.79)	Not significant
BOP mean) (SD)	10.57 (2.43)	6.03 (1.16)	*P*<0.001*
PD (mean) (SD)	2.64 mm (0.33)	2.52 mm (0.34)	Not significant
CAL (mean) (SD)	2.79 mm (0.3)	2.77 mm (0.33)	Not significant
Mean percentage of site with CAL >3 (SD)	41.3 (9.8)	41.63 (10.69)	Not significant

SD: Standard deviation; PI: Plaque index; BOP: Bleeding on probing; PD: Pocket depth; CAL: Clinical attachment level; JIA: Juvenile idiopathic arthritis; *Severity of rheumatoid disease.

Table 4: The results of Pearson's correlation coefficient in evaluation of the correlation between different variables in JIA patients

Periodontal parameters	PI	BOP	CAL >3	CAL
ESR	*P*=0.601	*P*=0.932	*P*=0.432	*P*=0.481
CHAQ	*P*=0.583	*P*=0.595	*P*=0.072	*P*=0.142

PI: Plaque index; BOP: Bleeding on probing; CAL: Clinical attachment level; ESR: Erythrocyte sedimentation rate; CHAQ: Children Health Assessment Questionnaire

In this study, even though we found that periodontal factors were significantly different between RA and healthy controls, but this difference might be somehow as a result of the difference in PI between two groups. We knew that all confounding factors such as PI are better to be matched between case and control groups, but it needs a large number of patients in each group, which is a difficult challenge for studies to have sufficient numbers of the samples, especially JIR patients. That is, why there are few studies evaluating periodontal conditions in JIA patients. Periodontal disease usually has a chronic entity that needs some time to be identified by routine clinical examination, and lower ages of JIA patients might inhibit enough time for the presentation of this time elapsing disease. Prevalence and severity of periodontal diseases in juvenile ages are low, and few cases of aggressive periodontal diseases could be seen in these periods of ages.

There was no significant difference between CAL in JIA group and healthy controls in this study. In adults, although the difference between CAL exists between two groups, but our limitation in patient number did not allow us to match the groups by determining a cutoff point or use multivariate tests. A limited number of studies have classified their patients regarding CAL.[32]

The present study is one of the few studies that evaluated the periodontal condition in both RA and JIA patients, and as far as we know, it is the only one in Iran evaluating this relation in JIA patients.

Radiographic examination was not performed in this study, and most of JIA patients were in their mixed dentition period. Considering the possibility of localized aggressive periodontitis in the age range of 14-17 in JIA patients, we could not exactly recognize this disease and discriminate it from chronic periodontitis. Due to low prevalence of aggressive types of periodontal diseases, there are few chances to find any possible relationships between aggressive periodontitis and arthritis especially juvenile type of the disease. There are few, if any, studies evaluating relationships between aggressive periodontitis and JIA and the rationale of this relationship is yet to be cleared.

On the other hand, considering both aggressive and chronic periodontitis in the relation between periodontitis and rheumatoid arthritis may probably show different results. Considering the difference between immunologic and pathologic nature of these two types of periodontitis might be helpful in future studies.

As it was mentioned before, in evaluating the relationship between periodontal disease and rheumatoid arthritis, the role of cytokines and inflammatory mediators should be considered. In RA and JIA, inflammatory mediators reflect the disease activity and respond to treatment.[31] All these inflammatory factors have been reported in aggressive periodontitis and are related to disease severity and specific periodontal pathogens.[33-36]

Some authors found a slight increase in Th1 cytokine such as IL-2 and IFNγ in destructed periodontal tissues.[37] Since some studies suggest that, T-cell characteristics are the same in some respects in RA or JIA and periodontal disease[38] more investigation in this relation is needed.

Another pathogenic relation that needs more consideration is neutrophils' role in the pathogenesis of both diseases and impaired neutrophilic response in RA or JIA and periodontal disease.[17,39]

Some studies have considered the role of genetic components in the susceptibility to both diseases. HLA subtypes and genes that are not in the HLA region association may contribute to the relationship between RA or JIA and periodontal disease.[23,40]

CONCLUSION

Periodontal parameters including PD and CAL were significantly higher in RA patients than controls with direct and significant correlations between serologic findings, disease severity and number of painful and inflamed joints. In JIA patients, no significant differences were detected between the two groups regarding periodontal parameters except BOP and no significant correlations were found between JIA findings and periodontal parameters. Specifically, longitudinal multi center studies are necessary to consider confounding factors including stress, nutritional factors and lifestyle and their correlation with periodontitis and RA at the same time. Last but not least, a close cooperation between dentists and rheumatologists is required to improve patient status.

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Conflicts of interest
The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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