



## Periodontitis in rheumatoid arthritis patients, abundance and association with disease activity

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### Abstract

**Background:** There are some discrepancy in association between activity of rheumatoid arthritis (RA) and periodontitis. The aim of this study was to evaluate the periodontal status of outpatients with RA.

**Methods:** The study was conducted in 2013-14 in a rheumatology clinic in Sari, north of Iran on 74 patients with RA. Evaluation of RA disease activity was according to disease activity score 28 (DAS28). Periodontitis was evaluated by probing depth (PD), gingival index (GI), clinical attachment level (CAL index), plaque index (PI), and panoramic X-ray. Statistical analysis included independent t-test and Mann-Whitney U test for quantitative, and chi square and OR for qualitative variables and evaluation of RA activity and periodontitis severity.

**Results:** The mean±SD of age and disease duration were 47.01±8.1 and 8.93±8.6 years, respectively and the mean±SD number of teeth was 20.70±6.8. Twenty-seven (36.5%) patients had moderate to severe disease. Forty-seven cases (63.5%) were found with periodontitis and 14 (12.2%) were identified to have moderate to severe periodontitis, unrelated to disease activity (p=0.22). For active/inactive periodontitis OR =1.33 (95% CI: 0.46 - 3.87) was computed. There was no association between RA disease activity and number of teeth, CAL, PI, PD, and GI, (p>0.05).

**Conclusion:** About 60% of RA patients suffered from periodontitis, but there was not any significant relation between RA disease activity and severity of periodontitis. Periodontitis may interfere with management and follow up of RA, so periodic periodontal examination is suggested in these patients.

**Keywords:** Rheumatoid arthritis, Periodontal diseases, Disease activity score

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### Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder with synovitis and joint destruction. (1). The prevalence of RA in Iran in 2014 was found to be 0.33% (2). Periodontitis is defined by gingival inflammation and bleeding, alveolar bone loss, periodontal pocket formation, gingival recession and, in later phases, tooth mobility and loss (3).

The concept of a relationship between periodontitis (PD) and RA was first suggested about 50 years ago and several studies demonstrated an epidemiological association between them (4). A high prevalence of periodontal

disease was reported in patients with rheumatoid arthritis and some RA patients even experience severe periodontal disease (5-7). Patients with RA also have higher CAL index, more tooth loss and periodontitis (8, 9).

There are some controversies about the association between RA activity/severity and periodontal diseases (5, 7, 10). Both RA and PD show similar pathophysiological mechanisms and risk factors. Probably in RA patients some microorganisms such as *P. gingivalis* have correlations with CRP and Anti CCP (6). Also, control of periodontal infection and gingival inflammation in patients

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#### ↑What is “already known” in this topic:

High prevalence of periodontal disease was reported in patients with rheumatoid arthritis and it may be RA activity/ severity associated with periodontal diseases. Control of periodontal infection and gingival inflammation in patients with periodontal disease could reduce the severity or activity of RA.

#### →What this article adds:

About two thirds of RA patients were found with periodontitis and unrelated to disease activity (p=0.22). Because of this remarkable frequency, periodic examination of periodontal status in RA patients seems necessary.

with periodontal disease could reduce the severity or activity of RA (11, 12), by lowering inflammatory products and markers or reduce exposure of the joints structures to bacteria and their toxins(13). Moreover, non-surgical periodontal treatment was found to be associated with significant reductions in ESR and a trend towards a reduction in TNF- $\alpha$  titers, GCF IL-1beta amounts and DAS scores without any evidence of an effect on RF, C-reactive protein, anti-CCP antibodies and IL-6 (12, 14).

It seems that the role of periodontitis in RA patients is important for several reasons as follows:

- 1) It may interfere with RA treatment and its efficacy (15),
- 2) Because of associations between periodontitis and cardiovascular disorders, and susceptibility of RA patients to cardiovascular events (16),
- 3) Many patients with RA are treated by bisphosphonates (BP) for management of osteoporosis, and potentially they are prone to jaw necrosis even with oral BP (17) especially in presence of periodontitis (18),
- 4) Difficulties in patients follow up because of interference with inflammatory lab tests (19). Also, RA patients may be more prone to periodontitis because of salivation difficulties due to sicca symptoms or dental hygiene related to hands involvement (20, 21).

The purpose of this study was to describe periodontal status in patients with RA and evaluation of association between severity of periodontitis and activity of RA.

## Methods

### Study population

The study was a cross sectional study conducted from May 2013 to September 2014 on out-patients with RA attending a rheumatology clinic in Sari, North of Iran. A rheumatologist consecutively screened patients for possible inclusion.

### Selection criteria

RA was defined according to American college of rheumatology (ACR), 1988(22), and the patients were divided for disease activity in two groups according to disease activity score (DAS 28): score >3.2 moderate to severe and  $\leq$ 3.2 mild or in remission(23). Patients with definite RA, age  $\geq$ 30 years and teeth count  $\geq$ 15 who provided informed consent, were included. Exclusion criteria were using antibiotics during the last 3 months, smoking, diabetes mellitus, and pregnancy. The sample size was estimated 39 patients in each group according to previous studies (20, 21, 24).

### Ethics approval

This study was approved by Vice chancellor for Research and Technology and Ethics Community of Mazandaran University of Medical Sciences. The patients who agreed to participate in the study, signed the informed consent forms. During the study period we had the opportunity to contact the patients by telephone.

### Examiner calibration

The periodontist was calibrated for intraexaminer re-

peatability before the examination and five patients enrolled for this aim. Clinical parameters were assessed in left mandibullary and maxillary first and second premolars of each patient. Duplicate measurements (N=320) were performed with an interval of 5 days for two records. The intraclass correlation coefficients as a measure of intra-examiner reproducibility were 0.85, 0.82, 0.88, and 0.80 for PD, CAL, GI, and PI, respectively.

### Data collection

Demographic data, duration of RA, medications and disease activity according to DAS 28 were recorded and patients were referred to periodontist. All clinical measurements were carried out by a calibrated examiner who was blinded for RA activity level. The patients were evaluated for probing depth (PD), clinical attachment level (25), gingival index(GI) (Loe) (26), plaque index (PI) (Loe and Silnes) (27) and panoramic X-ray.

CAL is the measurement of the position of the soft tissue in relation to the cemento enamel junction (CEJ) by the probing depth and the distance from the gingival margin to the CEJ(28). Periodontitis was considered mild if CAL was 1-2 mm, moderate if it was 3-4 mm and severe if it was  $\geq$ 5 mm. For measuring PI, mean amount of plaque for four surfaces of teeth was calculated and graded as 0 (without any plaque) to 3 (severe and abundant plaque material) (27).

The GI was scored based on the gingival inflammation in the marginal and inter proximal tissues separately on the basis of 0(normal gingiva) to 3(severe inflammation – marked redness and edema, ulceration with tendency to spontaneous bleeding) (26).

The Williams periodontal probe was used to measure the parameters. A panoramic radiograph was obtained by Cranex D ® (Soredex, Helsinki, Finland).

### Statistical analysis

Statistical analysis included independent t-test and Mann-Whitney U test for quantitative, and chi square and OR for qualitative variables and evaluation of RA activity and periodontitis severity. The  $p < 0.05$  was considered as statistically significant and quantitative variables are presented as mean $\pm$ SD.

## Results

### Demographic and basic data

One hundred eleven subjects were asked to participate in the study of whom 78 agreed. Four patients withdraw the study. The refusal rate was 33.3%.

The mean $\pm$ SD age and duration of RA were 47.01 $\pm$ 8.1 and 8.93 $\pm$ 8.6 years, respectively and the mean $\pm$ SD number of teeth was 20.70 $\pm$ 6.8. There were 68 (91.9%) female patients and 76.4% were seropositive for RF, 76.9% for anti CCP and 98.6% were glucocorticoid users.

The patients were divided for RA disease activity according to DAS 28 scores; 47 (63.5%) were considered as RA in remission or mild disease and 27 (36.5%) were identified with moderate to severe disease. The two groups were different in ESR, DAS scores and VAS because of disease activity but similar in age and duration of

**Table 1.** Demographic and Baseline Characteristics of Patients with Rheumatoid Arthritis

| Variable                               | Remission or mild RA (N=47) | Moderate to severe RA (N=27) | p      |
|--|-----------------------------|------------------------------|--------|
| Age (years), mean±SD                   | 46.31±8.4                   | 48.34 ± 7.7                  | 0.34   |
| Duration of illness (years), mean±SD   | 8.72±8.3                    | 9.33±9.3                     | 0.78   |
| Dose of prednisolone (mg/day), mean±SD | 5.22± 1.8                   | 6.86± 2.6                    | 0.03   |
| Methotrexate user, N (%)               | 39(84.8%)                   | 23(92%)                      | 0.16   |
| Hydroxychloroquine user, N (%)         | 20(43.5%)                   | 17(68%)                      | 0.03   |
| DAS 28, mean±SD                        | 2.31±0.8                    | 4.02±1.4                     | <0.001 |
| ESR(mm/h), mean±SD                     | 22.70± 15.78                | 32.30±16.5                   | 0.017  |
| VAS, mean±SD                           | 12.55±16.1                  | 50.76 ±29.7                  | <0.001 |

**Table 2.** Dental examination characteristics of patients with rheumatoid arthritis

| Variable        | Remission or mild RA (N=47) | Moderate to severe RA (N=27) | p    |
|-----------------|-----------------------------|------------------------------|------|
| Number of teeth | 21.70±6.7*                  | 18.96±6.8                    | 0.09 |
| GI              | 0.85±0.5                    | 0.96±0.6                     | 0.43 |
| PI              | 0.94±0.4                    | 1.06±0.5                     | 0.23 |
| PD              | 1.28±0.5                    | 1.50±0.8                     | 0.18 |
| CAL             | 1.33±0.19                   | 1.44±2.7                     | 0.08 |

\* mean±SD

illness.

The dose of steroids and usage of hydroxychloroquine sulfate were different in two groups because of high levels of disease activity (Table 1).

In dental examination, 47 (63.5%) patients were diagnosed with periodontitis and 14 (12.2%) had moderate to severe periodontitis, unrelated to disease activity ( $p=0.22$ ). The t-test and nonparametric Mann-Whitney U test showed no significant difference in periodontal status between the two groups (Table 2).

Number of teeth, CAL, PI, PD and GI were not associated with RA disease activity ( $p>0.05$ ). For active/inactive periodontitis OR= 1.33 (95% CI. 46-3.87) was computed.

## Discussion

In this study 63.5% of patients with RA had suffered periodontitis with 12.2% moderate to severe periodontitis, unrelated to disease activity ( $p= 0.22$ ). About 18.5% of patients with active RA have suffered from moderate to severe periodontitis. It was not significantly different in patients with active disease, but it demonstrates a high prevalence of severe periodontitis in this type of patients.

Some studies reported the prevalence of moderate and severe periodontitis as 42-48% and 46-57%, respectively (5, 20, 29). Older age, sex, previous or current smoking and high level of plaque score were associated with severe periodontal disease. In this study, the mean age of patients were below 50 years of age and patients who were smokers and had diabetes mellitus were not included in the study. On the other hand, the refusal rate was 33.3% which may be because the patients who completed the study had appropriate self-care. All these factors may show why patients had milder forms of periodontitis.

Among the patients 12.2% had moderate to severe periodontitis. This frequency was reported to be higher in other studies; for instance it was 51% in USA (5), 69.2% in Australia (24), and 94% in France(20). These discrepancies could be explained by selection of older patients, longer duration of RA, more RA activity, and methods of dental examination in these studies. One limitation of latter study was that it did not consider the effect of the types of biotherapies on oral clinical parameters(20). In current study we recorded and analyzed them and did not find any

relation between different kinds of DMARDs and severity of periodontitis ( $p> 0.05$ ).

The present study did not show any evidence of a link between the periodontitis and DAS28 scores, but a considerable number of patients with moderate to severe activity RA suffered from moderate to severe periodontitis too. These results are similar to some previously published studies (20, 29, 30), but can be due to of small sample size, therefore, future studies with more precipitants are needed to clarify the association.

The actual role of periodontitis in the pathogenesis of RA and the underlying mechanisms are not well understood. In mice models, repeated oral inoculations of periodontal pathogens (*P. gingivalis* and *Prevotella nigrescens*) induced periodontitis and alveolar bone resorption, and T cell responses toward Th17 phenotype without affecting Th1 (10). It was suggested that the ability of *P. gingivalis* to augment collagen-induced arthritis in mouse model, is dependent from the expression of a unique *P. gingivalis* peptidylarginine deiminase, which converts arginine residues in proteins to citrulline (31).

It seems even in patients with early RA, a greater number of missing teeth, higher CAL and greater bleeding on probing could occur (32). Elevated levels of IL-1, IL-6 and TNF-alpha have some roles in progression of periodontitis (33). There are some evidences of the involvement of periodontitis in the pathogenesis of T cell-driven arthritis through induction of Ag-specific Th17 response (10). The gingival crevicular fluid (GCF) concentrations of interleukin (IL)-1beta, IL-4, IL-10, matrix metalloproteinase (MMP)-8, MMP-13, and TNF $\alpha$  were reported to be higher in patients with RA than in healthy controls without chronic periodontitis(34). *P. gingivalis*, the major periodontal pathogen associated with the etiology of chronic periodontitis, likely fulfils a significant role in the pathogenesis of RA and citrullination of proteins resulting in immune dysregulation and autoimmune responses (33, 35). Immunity to *P. gingivalis*, is significantly associated with the presence of RA-related autoantibodies and CRP in individuals at risk of RA. Infection with this organism may play a key role in the loss of tolerance to self-antigens and pathogenesis of RA (19, 36).

Up to our knowledge, this is the first study about perio-



dentitis and RA in Iranian patients. Further studies and clinical evaluations are needed on epidemiology and mechanism of action to confirm the role of oral microbes and periodontitis in systemic inflammation and RA. The limitations of present study included small sample size and the number of patients who discontinued the study. Despite explaining about the study, encouraging the patients to participate and providing free care, out of 111 only 74 patients (69.4%) completed the study. It may be due to cultural or economic reasons, therefore, people should be provided with ample training to enhance their knowledge about the importance of dental care.

### Conclusion

In this study about 60% of RA patients suffered from periodontitis. This rate highlights the need for adequate dental care. We did not find any significant association between the activity of RA disease and severity of periodontitis, but due to the interference of periodontitis with management and follow up of RA activity, periodic periodontal examination is suggested in these patients. According to the frequency of periodontitis and some physiological hypotheses, clinical trials should be considered necessary to assess if periodontal treatment could improve RA biological and clinical parameters.

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### Conflict of Interests

The authors declare that they have no competing interests.

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