Study of chronic periodontitis in rheumatoid arthritis patients and its relation to serum anticitrulinated peptide antibody levels

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Background
Recently discovered evidence suggests that periodontitis might have a direct role in initiating and sustaining the immunoinflammatory responses in rheumatoid arthritis (RA), besides the risk factors that are common to both conditions.

Aim
The aim of this study was to determine the prevalence of chronic periodontitis in a cohort of Egyptian RA patients and their first-degree relatives and siblings compared with a control group and its relation to serum anticitrulinated peptide antibody (ACPA) levels.

Patients and methods
This study was carried out on three groups: group I included 100 patients with RA who fulfilled the 2010 ACR/EULAR classification criteria for RA and had less than 5 years' disease duration. They were recruited from the Rheumatology Unit and Rheumatology Outpatient Clinic at Alexandria Main University Hospital. Group II included 50 first-degree relatives and siblings of RA patients who were free of clinical joint disease, and group III included 50 age-matched and sex-matched healthy subjects referred for general dental treatment at the Dental Clinic of Alexandria Main University Hospital. RA disease activity was assessed by applying Disease Activity Score 28, and the functional state of the patients was assessed by applying the Health Assessment Questionnaire. All subjects underwent a dental examination, including Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Plaque Index (PI), and modified Gingival Index. The ACPA levels in serum were evaluated in group I, group II, and group III participants with periodontitis.

Results
Group I patients had significantly more periodontitis than group II ($P<0.001$) and group III ($P<0.001$). There was a statistically significant difference between group I and group II in PPD ($P<0.001$), CAL ($P<0.001$), and PI ($P<0.001$) and a statistically significant difference between group I and group III in PPD ($P=0.001$), CAL ($P=0.006$), and PI ($P=0.002$). In group I, 82 (82%) patients had positive serum ACPA (^{3}20 U/ml), compared with only four (8%) subjects in group II and none of the controls in group III. There was a statistically significant difference between group I and group II in serum ACPA level ($P<0.001$), as well as between group I and group III ($P<0.001$).

Conclusion
Our study shows an association between RA and chronic periodontitis. Individuals with RA are more likely to experience periodontitis.

Keywords:
anticitrulinated peptides antibodies, periodontitis, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that predominantly affects multiple peripheral joints. It is characterized by joint swelling and tenderness [1] resulting in progressive destruction of cartilage and bone in multiple joints [1].

Despite the recent advances in molecular pathogenesis its etiology is almost completely unknown. It is regarded as a complex multifactorial disease in which multiple genes and environmental factors act in concert to cause pathological events [2].

The potential impact of RA and many systemic disorders on the periodontium is well documented,

and recent evidence suggests that periodontal infection may significantly enhance the risk for various systemic diseases including RA [3,4].

Chronic periodontitis has been defined as 'an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment loss, and bone loss' [5]. Periodontal pocket formation is usually a sequel of the disease process [6].

RA demonstrates remarkably similar patterns of soft-tissue and hard-tissue destruction as in chronic periodontitis. Chronic periodontitis shares a common immune inflammatory profile with RA [7,8] and might have a direct causal role by initiating and sustaining the immune-mediated inflammatory response in RA, besides the genetic, environmental, and behavioral factors that are common to both conditions [9–14].

Although the etiologies of these two chronic inflammatory diseases are separate, the underlying pathological processes are of sufficient similarity to warrant consideration of the hypothesis that individuals with RA are more likely to experience periodontitis and that the severity of periodontitis will be higher in RA patients [15].

Patients and methods

This study was carried out on three groups: group I included 100 patients with RA fulfilling the 2010 ACR/EULAR [16] classification criteria for RA and of less than 5 years' disease duration. They were recruited from those attending the Rheumatology Unit and Rheumatology Outpatient Clinic at the Alexandria Main University Hospital. Group II included 50 first-degree relatives and siblings of RA patients who were free of clinical joint disease, and group III included 50 age-matched and sex-matched healthy individuals who were referred for general dental treatment at the Dental Clinic of Alexandria Main University Hospital.

Informed consent from all patients was obtained as required by the Declaration of Helsinki before the commencement of the study. This study was approved by the Independent Ethics Committee.

Exclusion criteria included being a smoking, presence of diabetes mellitus, having undergone periodontal treatment (including prophylaxis) and/or antibiotic therapy over the past 3 months, having faulty prosthesis and fillings, and being pregnant or lactating.

RA disease activity was evaluated by applying the Disease Activity Score 28 (DAS 28), which involves four parameters [erythrocyte sedimentation rate (ESR) version] [17–19]. The functional state of the patients was assessed by applying the Health Assessment Questionnaire (HAQ) [20,21].

All participants underwent a dental examination to detect and classify periodontal disease according to American Academy of Periodontology 1999 [22] on the basis of Probing Pocket Depth (PPD) [23], Clinical Attachment Loss (CAL) [23], Plaque Index (PI) [24], and modified Gingival Index (GI) [25].

Laboratory assessments included evaluation of acute-phase reactants, ESR, and C-reactive protein (CRP) levels.

Anticitrulinated peptide antibody (ACPA) levels in serum were evaluated for group I, group II, and group III with periodontitis by means of ELISA [26].

Statistical analysis

The data were analyzed statistically using the statistical package for the social sciences (SPSS software package, version 20.0; IBM; IBM Corp., Armonk, NY) and Microsoft excel (Microsoft; Microsoft Redmond campus, Redmond, Washington, United States). Qualitative data were described using number and percentage. Quantitative data were described using range (minimum and maximum), mean, SD, and median. The tests used were Spearman's correlation coefficient, χ^2-test, Mann–Whitney test, Kruskal–Wallis test, Fisher's exact or Monte-Carlo test, and *F*-test (analysis of variance). *P* less than 0.05 was accepted as statistically significant.

Results

Measures of disease activity and functional disability in rheumatoid arthritis patients

The disease activity state in RA patients was assessed by applying DAS 28 and every patient had a score that was a sum of different clinical and laboratory parameters. Two percent of patients were in remission, 2% had low disease activity, 34% had moderate disease activity, and 62% had high disease activity (mean DAS 28: 5.67±1.38) (Table 1).

Functional disability was assessed using HAQ. Thirty-two percent of patients had no disability, 26% had mild disability, 8% had moderate disability, and 34% had severe disability (mean HAQ: 1.62±0.93).

Periodontal disease diagnosis and site-specific scores in periodontitis cases in a comparison between the studied groups

Group I patients had significantly more periodontitis than group II ($P<0.001$) and group III subjects ($P<0.001$); 66% of patients in group I had periodontitis compared with 22% of subjects in group II and 30% of subjects in group III. There was no statistically significant difference between group II and group III regarding affection with periodontitis ($P=0.362$) (Tables 2 and 3).

On comparing the studied groups regarding site-specific scores (Table 3), we found a statistically significant difference between group I and group II in PPD ($P<0.001$), CAL ($P<0.001$), and PI ($P<0.001$) and a statistically significant difference between group I and group III in PPD ($P=0.001$), CAL ($P=0.006$), and PI ($P=0.002$). No statistically significant difference between group II and group III in terms of PPD ($P=0.938$), CAL ($P=0.135$), or PI ($P=0.504$) was detected. No statistically significant difference was detected between the three studied groups with respect to GI ($P=0.074$).

Table 1 Measures of disease activity and functional disability in group I (rheumatoid arthritis patients) ($n=100$)

Variables	*N* (%)
DAS 28	
Remission (<2.6)	2 (2.0)
Low (<3.2)	2 (2.0)
Moderate (≥3.2–<5.2)	34 (34.0)
High (≥5.2)	62 (62.0)
Min.–max.	2.52–7.97
Mean±SD	5.67±1.38
Median	5.74
HAQ (0–3)	
No disability (0–1.25)	32 (32.0)
Mid disability (>1.25–1.75)	26 (26.0)
Moderate disability (>1.75–2)	8(8.0)
Severe disability (>2)	34 (34.0)
Min.–max.	0.0–3.0
Mean±SD	1.62±0.93
Median	1.69

DAS 28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; min., minimum; max., maximum.

In group I, the mean PPD was 4.88±1.43, mean CAL was 4.26±1.92, mean GI was 2.16±0.53, and mean PI was 2.17±0.62.

In group II, mean PPD was 2.76±0.78, mean CAL was 1.90±0.70, mean GI was 1.91±0.64, and mean PI was 1.50±0.45.

In group III, mean PPD was 3.10±1.05, mean CAL was 2.78±1.28, mean GI was 1.85±0.45, and mean PI was 1.65±0.31 (Table 3).

Measurement of serum anticitrulinated peptide antibody level and its comparison between periodontitis cases in the three studied groups

Serum ACPA levels were measured in all group I and group II subjects and in subjects with periodontitis in group III (Tables 4–6).

In group I, 82 (82%) patients had positive serum ACPA (^{3}20 U/ml), compared with only four (8%) subjects in group II and none of the subjects in group III. There was a statistically significant difference between group I and group II ($P<0.001$) and between group I and group III ($P<0.001$). No statistically significant difference was detected between group II and group III ($P=0.117$) (Table 4).

The mean serum ACPA level in group I was 296.01±500.02 U/ml, that in group II was 7.42±9.35 U/ml, and that in group III was 9.04±5.72 U/ml. There was a statistically significant difference between group I and group II ($P<0.001$). A statistically significant difference was also detected between group I and group III ($P<0.001$). No statistically significant difference was detected between group II and group III ($P=0.374$) (Table 5).

Periodontitis was higher in ACPA-positive RA subjects, as 54 (81.8%) periodontitis cases in group I had positive serum ACPA compared with only two (18.2%) periodontitis cases in group II and none in group III. A statistically significant difference was detected between group I and group II ($P<0.001$) and between group I and group III ($P_2<0.001$).

Table 2 Comparison between the studied groups according to periodontal disease diagnosis

Periodontal diseases	Group I ($n=100$) [*N* (%)]	Group II ($n=50$) [*N* (%)]	Group III ($n=50$) [*N* (%)]	χ^2	*P*
Chronic gingivitis	34 (34.0)	39 (78.0)	35 (70.0)	32.850*	<0.001*
Periodontitis	66 (66.0)	11 (22.0)	15 (30.0)		
Significant difference groups		$P_1<0.001^*$, $P_2<0.001^*$, $P_3=0.362$			

*Statistically significant at $P\leq0.05$.

Table 3 Comparison between the studied groups according to site-specific scores in periodontitis cases

Site-specific scores	Group I periodontitis cases (n=66)	Group II periodontitis cases (n=11)	Group III periodontitis cases (n=15)	Test of significance	P
PPD (mm)					
Min.–max.	3.0–8.30	1.30–3.60	2.0–4.60	$^{KW}\chi^2$=34.645*	<0.001*
Mean±SD	4.88±1.43	2.76±0.78	3.10±1.05		
Median	4.60	3.0	2.60		
Significant difference between groups		P_1<0.001*, P_2<0.001*, P_3=0.938			
CAL (mm)					
Min.–max.	1.0–7.66	0.60–2.60	1.50–5.0	$^{KW}\chi^2$=17.873*	<0.001*
Mean±SD	4.26±1.92	1.90±0.70	2.78±1.28		
Median	4.20	2.0	2.60		
Significant difference between groups		P_1<0.001*, P_2=0.006*, P_3=0.135			
GI					
Min.–max.	1.0–3.50	1.0–2.75	1.25–2.50	F=2.683	0.074
Mean±SD	2.16±0.53	1.91±0.64	1.85±0.45		
Median	2.25	1.75	2.0		
No statistical significant difference between groups was detected					
PI					
Min.–max.	1.0–3.0	1.0–2.0	1.25–2.0	F=10.107*	<0.001*
Mean±SD	2.17±0.62	1.50±0.45	1.65±0.31		
Median	2.50	1.50	1.50		
Significant difference between groups		P_1<0.001*, P_2=0.002*, P_3=0.504			

CAL, Clinical Attachment Loss; GI, modified Gingival Index; min., minimum; max., maximum; PI, Plaque Index; PPD, Probing Pocket Depth. $^{KW}\chi^2$: Chi square for Kruskal Wallis test, Sig. bet. grps was done using Mann Whitney test. *Statistically significant at $P \leq 0.05$.

Table 4 Comparison between the studied groups according to detection of serum anticitrulinated peptide antibody

Variables	Group I (n=100) [N (%)]	Group II (n=50) [N (%)]	Group III (n=15) [N (%)]	χ^2	P
Serum ACPA					
Negative	18 (18.0)	46 (92.0)	50 (100.0)	142.765*	<0.001*
Positive	82 (82.0)	4 (8.0)	0 (0.0)		
Significant difference between groups		P_1<0.001*, P_2<0.001*, P_3=0.117			

ACPA, anticitrulinated peptide antibody. *Statistically significant at $P \leq 0.05$.

Table 5 Comparison between the studied groups according to serum anticitrulinated peptide antibody level

Variables	Group I (n=100)	Group II (n=50)	Group III (n=15)	$^{KW}\chi^2$	P
Serum ACPA (U/ml)					
Min.–max.	3.80–2565.0	1.80–44.90	2.10–17.0	95.434*	<0.001*
Mean±SD	296.01±500.02	7.42±9.35	9.04±5.72		
Median	118.25	4.0	10.90		
Significant difference between groups		P_1<0.001*, P_2<0.001*, P_3=0.374			

ACPA, anticitrulinated peptide antibody; min., minimum; max., maximum. *Statistically significant at $P \leq 0.05$.

No statistically significant difference was detected between group II and group III (P=0.169) (Table 6).

Correlation between anticitrulinated peptide antibody level in serum and Disease Activity Score 28, Health Assessment Questionnaire, erythrocyte sedimentation rate, C-reactive protein, and site-specific scores in group I patients with periodontitis

Serum ACPA was negatively correlated with DAS 28 and HAQ and all site-specific scores (PPD, CAL, GI, and PI), and positively correlated with ESR and CRP, but none was statistically significant (Tables 7 and 8).

Correlation between anticitrulinated peptide antibody level in serum and site-specific scores in group II and group III subjects with periodontitis (Table 8)

In group II, there was a negative correlation between serum ACPA and PPD, CAL, and PI with no statistical significance. In contrast, the correlation between serum ACPA and GI was positive, but there was no statistical significance.

Table 6 Positive serum anticitrulinated peptide antibody in periodontitis cases in the studied groups

Variables	Group I periodontitis cases (n=66) [N (%)]	Group II periodontitis cases (n=11) [N (%)]	Group III periodontitis cases (n=15) [N (%)]	χ^2	P
Positive Serum ACPA	54 (81.8)	2 (18.2)	0 (0.0)	43.909*	<0.001*
Significant difference between groups		P_1<0.001*, P_2<0.001*, P_3=0.169			

ACPA, anticitrulinated peptide antibody. *Statistically significant at $P \leq 0.05$.

Table 7 Correlation between serum anticitrulinated peptide antibody and different parameters in periodontitis cases in group I (rheumatoid arthritis patients)

	Serum ACPA	
Group I	r_s	P
DAS 28	–0.087	0.487
HAQ	–0.108	0.389
ESR	0.116	0.352
CRP	0.207	0.134

ACPA, anticitrulinated peptide antibody; CRP, C-reactive protein; DAS 28, Disease Activity Score 28; ESR, erythrocyte sedimentation; HAQ, Health Assessment Questionnaire; r_s, Spearman coefficient. No statistically significant values were detected in this table.

In group III, there was a significant negative correlation between serum ACPA and CAL (P<0.001) and PI (P=0.044). There was a positive correlation with PPD and negative correlation with GI, but none was of statistical significance.

Correlation between site-specific Clinical Attachment Loss and erythrocyte sedimentation rate

There was a significant positive correlation between site-specific CAL and ESR (Fig. 1).

Correlation between site-specific scores and Disease Activity Score 28 in group I patients with periodontitis

There was a correlation between RA disease activity and periodontal disease severity and activity as reflected by positive significant correlation between DAS 28 and CAL and GI (Figs 2 and 3).

Discussion

Diseases like RA result in the (patho)physiological citrullination of structure proteins and in an increased accumulation of citrullinated proteins [27]. The reduced immunotolerance of these patients to citrullinated proteins seems to be a key problem, and hence there is an increased development of autoantibodies [27].

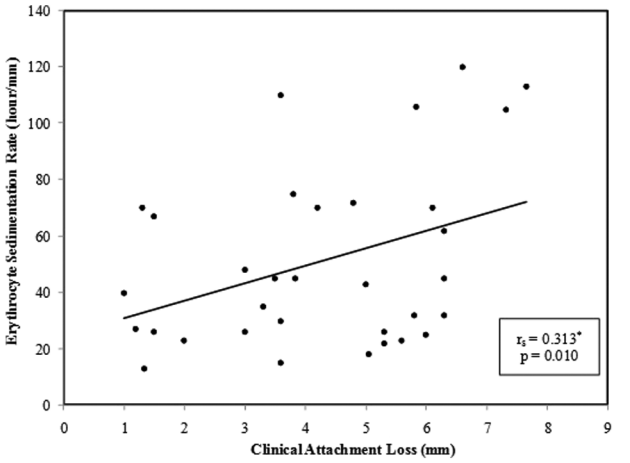
Whereas citrullination is associated with inflammation in general, the development of antibodies against them (ACPA) is specific to RA. The high specificity of ACPA is therefore most likely the result of an abnormal humoral response to these proteins. ACPA is produced locally in the inflamed synovium [28],

Table 8 Correlation between serum anticitrulinated peptide antibody and site-specific scores in periodontitis cases in the studied groups

	Serum ACPA			
Site-specific scores	Group I	Group II	Group III	Total
PPD				
r_s	–0.057	–0.063	–0.400	0.343*
P	0.648	0.854	0.140	0.001*
CAL				
r_s	–0.099	0.123	–1.000*	0.172
P	0.429	0.718	<0.001*	0.101
GI				
r_s	–0.231	0.005	–0.205	–0.003
P	0.063	0.989	0.463	0.975
PI				
r_s	–0.180	–0.205	–0.527*	0.129
P	0.147	0.546	0.044*	0.221

ACPA, anticitrulinated peptide antibody; CAL, Clinical Attachment Loss; GI, modified Gingival Index; PI, Plaque Index; PPD, Probing Pocket Depth; r_s, Spearman coefficient. *Statistically significant at $P \leq 0.05$.

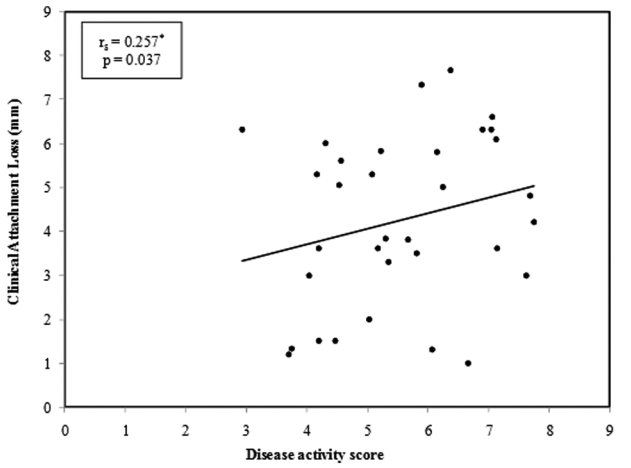
Figure 1



Correlation between site-specific Clinical Attachment Loss and erythrocyte sedimentation rate in periodontitis cases in group I (rheumatoid arthritis patients).

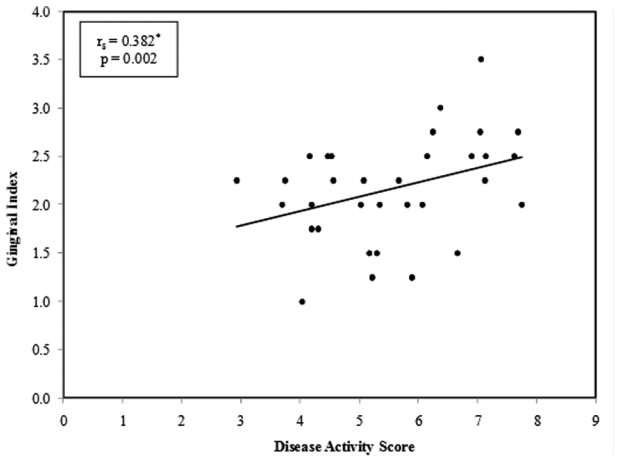
suggesting that the resulting immune complexes are directly involved in the disease pathogenesis of the chronic inflammation in the rheumatoid joint. Whether there is local ACPA production in the periodontium and in the bronchoalveolar compartment still not established, despite high ACPA reactivity in serum samples of aggressive periodontitis patients has been reported [29].

Figure 2



Correlation between Disease Activity Score 28 and site-specific Clinical Attachment Loss in periodontitis cases in group I (rheumatoid arthritis patients).

Figure 3



Correlation between Disease Activity Score 28 and site-specific Gingival Index in periodontitis cases in group I (rheumatoid arthritis patients).

Prevalence of periodontal disease and site-specific scores in periodontitis cases in a comparison between the studied groups

In our study, RA patients had significantly more periodontitis than did controls, as 66% of RA patients had periodontitis compared with 22% of subjects in group II and 30% of subjects in group III.

Although periodontal destruction is frequently seen among family members, suggesting a genetic basis for the susceptibility to periodontal disease [6], this was not detected in our study as there was no statistically significant difference between the control groups (II and III) regarding the prevalence of periodontitis. This may be due to the young age of group II subjects in our study. Also the familial background of group III subjects was not known.

To date, a large number of clinical studies [30–37] have indicated a potential positive association between the occurrence of periodontitis and RA.

De Pablo *et al.* [37] found that RA patients had about a two-fold increase in periodontitis. Also, Mercado *et al.* [32] indicated that the incidence of RA in patients suffering from periodontitis is 3.95% compared with 1% prevalence in the general population.

Only few authors observed no association between the occurrences of these diseases [38].

In patients with RA, disability in the upper extremities of the body and reduced manual dexterity might impair oral hygiene and thereby increase the risk for caries, periodontitis, and tooth loss [39]. However, impaired oral hygiene is unlikely to fully explain the positive association between RA and periodontitis [36].

In the present study, RA subjects had more PPD ($P<0.001$) and CAL ($P<0.001$) compared with non-RA subjects, and the difference was statistically significant. No statistically significant difference was detected between group II and group III.

Regarding PPD, our study was similar to that of Abdelsalam *et al.* [40], as a statistically significant difference in the mean pocket depth between their study group (RA patients) and control group (age-matched and sex-matched healthy volunteers) was detected: a mean pocket depth greater than 4 mm was observed in 10% of the study group versus 1.25% of the control group, which indicated the presence of deeper pocket depth in RA patients.

These results also agreed with those of Mercado *et al.* [33], Mikael and Sigvard [41], Pischon *et al.* [36], and Mayer *et al.* [1].

The increased occurrence and severity of periodontitis in RA subjects compared with controls may be due to the common features of an underlying dysregulation of the inflammatory mechanism that predisposes these individuals to advanced, aggressive, and severe forms of either disease [7].

Regarding CAL, a significant difference was observed between our RA subjects and controls. The results agreed with those of Ishi Ede *et al.* [42], Mikael and Sigvard [41], and De Pablo *et al.* [37].

Our RA subjects had more plaque deposits than control groups. This was in agreement with the

findings of Ishi Ede *et al.* [42] and Bozkurt *et al.* [43], who demonstrated a high prevalence of sites with dental plaque in their studies. This may be attributed to the fact that those patients directed their attention mainly at their serious illness while neglecting their oral health.

On the other hand, Abdelsalam *et al.* [40] found no statistically significant difference in the PI between their RA patients and the control group, which is in agreement with Mercado *et al.* [33] and Mayer *et al.* [1].

No significant difference was found in GI between the three studied groups in our study. We did not exclude any medications in our study; thus, RA cases were taking NSAIDs, which in turn reduces gingival inflammation [34].

This is similar to the findings reported by Mercado *et al.* [33] and Ishi Ede *et al.* [42], but it disagrees with the findings by Mayer *et al.* [1], who found a higher prevalence of sites with gingival inflammation in RA patients compared with the control group. Also, Kässer *et al.* [31] found greater gingival bleeding in RA subjects than in controls.

Some studies have failed to demonstrate meaningful differences in clinical indices of oral hygiene between individuals with or without RA [31,33]. They related this to the fact that a single assessment of oral hygiene at a study visit might not reflect the long-term oral hygiene status of an individual [43].

In our study, there was a positive correlation between RA disease activity and periodontal disease severity and activity as reflected by a positive significant correlation between DAS 28 and both CAL and GI.

A positive significant correlation between CAL and ESR was also found.

This was in agreement with the findings of Abou-Raya *et al.* [35] and Kobayashi *et al.* [44], who have reported that periodontal disease severity goes hand in hand with RA disease activity.

Measurement of serum anticitrulinated peptide antibody level

Citrullination of proteins occurs under inflammatory conditions and results in the production of anticitrullinated antibodies. ACPA can be used as a marker of RA and is rarely present in the absence of RA (0–2%) [45].

Two studies, Pischon *et al.* [36] and Dissick *et al.* [46], investigated the levels of anticyclic citrullinated protein (anti-CCP) antibodies in periodontal and RA patients. One study reported anti-CCP antibody levels as a percentage, and the other reported the levels as U/ml. None of the studies reported statistically significantly higher levels of anti-CCP antibodies in patients with periodontal disease and RA. The results of these studies do not provide good evidence for a correlation between increased levels of anti-CCP antibodies and the presence of periodontal disease and RA [47].

A study of patients with RA and chronic periodontitis found an association between seropositivity for anti-CCP antibodies and increased severity of periodontitis [46].

In a recent study, a small group of patients with chronic periodontitis was examined for the presence of anti-CCP antibodies in serum, and only one patient out of 20 was found to be seropositive [48].

In the present study, positive serum ACPA (^{3}20 U/ml) was detected in 82% of RA patients and in only 8% of group II subjects; ACPA was not detected in group III subjects.

Periodontitis was higher in ACPA-positive RA subjects, as 81.8% of periodontitis cases in group I had positive serum ACPA. Only 18.2% in group II and none among periodontitis cases in group III had positive serum ACPA.

Serum ACPA levels did not correlate with RA disease activity (assessed by DAS 28), functional disability (using HAQ), ESR and CRP levels in RA patients, or with periodontal disease scores in periodontitis cases in the three studied groups.

In the periodontitis cases in group III, ACPA was absent in the serum. A short duration of periodontitis may be a possible explanation. These subjects should be followed up for development of serum ACPA.

In group II, four relatives had ACPA in their serum; two of them had periodontitis.

The presence of serum ACPA in first-degree relatives and siblings may precede the occurrence of RA and these subjects are considered at high risk for RA.

Conclusion

In conclusion, our study shows an association between RA and chronic periodontitis. Individuals with RA are more

likely to experience periodontitis. The CAL is higher in subjects with RA and correlates with RA disease activity. This may be due to a common genetic predisposition as both RA and chronic periodontitis are associated with the same *HLA* gene complex that regulates monocytic cytokine response. Chronic periodontitis shares a common immune inflammatory profile with RA, and both result from a common underlying disregulation of the host immunoinflammatory response.

Periodontium is a possible site for protein citrullination and hence autoantibody formation. Thus, careful screening of periodontitis subjects with a history of arthritis or arthralgia would be promising for the early detection and treatment of this chronic debilitating disease.

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Conflicts of interest
There are no conflicts of interest.

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