Periodontal Condition of Patients With Autoimmune Diseases and the Effect of Anti-Tumor Necrosis Factor-α Therapy

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Background: The aim of this study is to evaluate the effect of autoimmune diseases (AIs), as well as anti-tumor necrosis factor-α (TNF-α) therapy on the clinical and immunologic parameters of the periodontium.

Methods: Thirty-six AI patients (12 rheumatoid arthritis [RA], 12 psoriatic arthritis, and 12 systemic sclerosis) were recruited together with 12 healthy (H) and 10 RA patients receiving anti-TNF-α therapy (RA+). Periodontal indices including plaque index, gingival index (GI), probing depth (PD), and bleeding on probing (BOP) were measured, and gingival crevicular fluid (GCF) was collected from five deepest pockets using papers strips. The TNF-α level was analyzed using enzyme-linked immunosorbent assay. Analysis of variance test was used for statistical comparison between groups, whereas Pearson linear correlation coefficient test was used to examine the association between TNF-α and periodontal status indices.

Results: The three AI subgroups were very similar in clinical and immunologic parameters. GI was greater in the AI patients compared to the H and RA+ groups (1.91 ± 0.54, 1.21 ± 0.67, and 1.45 ± 0.30, respectively, $P = 0.0005$). AI patients exhibited significantly more BOP than H and RA+ (46.45% ± 17.08%, 30.08% ± 16.86%, and 21.13% ± 9.51%, respectively, $P = 0.0002$). PD in H and RA+ groups were lower than in the AI (3.47 ± 0.33, 3.22 ± 0.41, and 3.91 ± 0.49 mm, $P = 0.0001$). Number of sites with PD >4 mm was higher in AI patients compared to H and RA+ (42.44 ± 17.5 versus 24.33 ± 15.62 versus 33.3 ± 6.6, $P = 0.0002$). GCF TNF-α was higher among the AI patients (1.67 ± 0.58 ng/site) compared to 1.07 ± 0.33 ng/site for the H group and 0.97 ± 0.52 ng/site for the RA+ group ($P = 0.0002$). A significant positive correlation was found between PD and TNF-α levels in the GCF ($r = 0.4672$, $P = 0.0002$), BOP ($r = 0.7491$, $P = 0.0001$), and GI ($r = 0.5420$, $P = 0.0001$).

Conclusions: Patients with AI diseases have higher periodontal indices and higher TNF-α levels in GCF than H controls. Anti-TNF-α treatment appears to reverse this phenomenon. *J Periodontol 2013;84:136-142.*

KEY WORDS

Arthritis, rheumatoid; chronic periodontitis; gingival crevicular fluid; scleroderma, systemic; tumor necrosis factor-alpha.

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with a prevalence of 1% in the population and is associated with significant morbidity and functional disability.[1] It is characterized by inflammatory infiltrate in the synovial tissue that leads to joint destruction and impaired function.[2] Psoriatic arthritis (PA) is another type of inflammatory arthritis that develops in ≤30% of people who have psoriasis.[3] Systemic sclerosis (SSc) is a chronic autoimmune disease (AI) characterized by widespread vascular alterations, inflammation, auto-antibodies production, and fibrosis in skin and internal organs. The estimate prevalence is one to two cases per 10,000 of the population.[4] A common oral complication of SSc is constriction of the oral orifice with progressively limited mouth opening.[5] SSc is associated with an increased risk of salivary hypofunction and consequently increasing incidence of dental caries, oral ulcers, and fungal infections.[6,7]

Likewise, periodontitis is a chronic inflammatory process accompanied by the destruction of surrounding connective tissue and alveolar bone.[8]

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There is an increased evidence of the association between periodontitis and RA.[9] These data suggest that patients with RA have an increased risk of periodontitis and show greater tooth loss and significantly greater clinical attachment loss (AL) than healthy (H) individuals.[9-15] However, very little information is available on the association of yet another chronic joint disease; i.e., PA and periodontal status. Some studies have assessed the relationship between SSc and periodontal conditions.[16-18]

Despite differences in the clinical course, most of inflammatory cytokines and mediators involved in AI are comparable to those that drive periodontal disease. More importantly, the balance between different cytokines and growth factors in AI and periodontitis is similar: higher levels of proinflammatory mediators, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, and low levels of anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β.

TNF-α is one of the key cytokines in the inflammatory process. It is present in serum and inflammatory tissues; its levels correlate with disease activity and the degree of tissue damage.[19] TNF-α contributes to the upregulation of osteoclastogenesis and the downregulation of osteoblastogenesis.[20] Furthermore, TNF-α may stimulate the release of other proinflammatory cytokines, such as IL-1 and IL-6, that in turn may activate polymorphonuclear cells and macrophages and increase the release of reactive oxygen species, which contribute to tissue damage.[21]

TNF-α blocking agents are widely used for managing severe RA and PA.[22] In animal studies of periodontitis, TNF-α blockade inhibited inflammatory progression toward the osseous crest, recruitment of osteoclastic cells, and bone loss and connective tissue attachments.[23-26] Likewise, studies in humans suggested that anti-TNF-α therapy may reduce the severity of periodontitis.[15,27]

The null hypothesis was that patients with AI have worse periodontal conditions and anti-TNF-α therapy has a beneficial effect on periodontal parameters.

The purpose of this study is to evaluate the effect of AI and anti-TNF-α therapy on clinical and immunologic parameters of periodontal disease.

MATERIALS AND METHODS

Patient Selection

Forty-six consecutive adult AI patients (16 males and 30 females, aged 48 to 53 years) attending the outpatient clinic at B. Shine Rheumatology Unit at the Rambam Health Care Campus, Haifa, Israel, were recruited to this study. Written informed consent was obtained from all participants before commencement of the study which took place from February, 2011 to November, 2011. Prior to study commencement, the protocol was approved by the institutional review board (Helsinki Declaration Committee) of Rambam Medical Center, Haifa.

Patients were required to fulfill the American College of Rheumatology criteria for RA, PA, or SSc.[28-30] Patients <18 years of age and pregnant or lactating women were not included. Individuals were also excluded if they received medications, such as antibiotics, within the previous 6 months or had periodontal treatment in the past 12 months.

Participants were sorted into three groups of 12 individuals each: RA patients (mean age: 48.2 ± 12.0 years), PA patients (mean age: 48.7 ± 10.4 years), and SSc patients (mean age: 48.4 ± 9.3 years). None of these patients received anti-TNF-α therapy currently or in the past. Another group (RA+) included 10 patients with RA (mean age: 53.6 ± 6.2 years) who received a 3 mg/kg infusion of the anti-TNF-α drug infliximab every 8 weeks. A control H group included 12 patients (mean age: 51.5 ± 9.97 years) without AI disease who were examined in the Department of Periodontics. Some of these patients were treated in our department afterwards. Smoking status was recorded for all participants. Data regarding AI patients' clinical features (activity of joint inflammation, erosive joint changes, joint contraction, esophageal involvement, and skin involvement) and laboratory parameters (acute-phase reactants and immunologic abnormalities) were collected from medical records. Joint status was assessed for the RA and PA patients using composite disease activity score (DAS 28) based on erythrocyte sedimentation rate (mm/1th hour).[31,32] Patient clinical status was assessed by rheumatologists (AB-G, YB-M).

Periodontal Examination

Periodontal examination was performed by two calibrated examiners (YM and RE). Assessment of clinical parameters included the following: 1) probing depth (PD); 2) plaque index (PI); [33] 3) gingival index (GI); [34] and 4) full-mouth bleeding score (FMBS). To avoid contamination of the filter paper strips with blood, GI, bleeding on probing (BOP), and PD were measured after the gingival crevicular fluid (GCF) collection. The deepest pockets were identified in an early screening session. All periodontal parameters were measured in all teeth excluding third molars. PD was recorded at six sites per tooth using a manual periodontal probe. FMBS was derived from calculating bleeding within 30 seconds from probing, at six sites per tooth (either present or absent); the mean bleeding percentage for each patient was calculated.

TNF-α Sampling and Assay

GCF samples were collected from the five deepest periodontal pockets. First, supragingival plaque was

carefully removed using curets,[§] after which the sample sites were isolated with cotton rolls. Each sterile paper strip[‖] was inserted to the pocket for 30 seconds. Samples were wrapped in aluminum foil and stored at –20°C. All specimens were masked before the laboratory assay.

Total TNF-α level in GCF was determined using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kit[¶] as described previously by our group.[15] Briefly, filter papers were unwrapped and inserted into a sterile test tube containing 1.0 mL distilled water. The tubes were left to stand at room temperature for 30 minutes and then agitated every 5 minutes to facilitate extraction of the sample from the filter paper. A monoclonal antibody specific for TNF-α was precoated on a microplate. Standards and samples were pipetted into the wells and the immobilized antibody bound the cytokine. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for TNF-α was added to the wells. The absorbance values were determined by using an ELISA reader at 450 nm. A standard curve was constructed by using standards provided in the kit and the cytokine concentration was calculated from this standard curve. The color intensity results were obtained using a microplate reader[#]).

Statistical Analyses

Means ± SD of the clinical and immunologic parameters were calculated. Analysis of variance (ANOVA) with Fisher least significant difference (LSD) test was used to test the differences between the clinical periodontal parameters and TNF-α level in the GCF among the groups. The Pearson correlation coefficient test was used to analyze the correlation between TNF-α level in the GCF and the various periodontal parameters. Results were considered significant statistically at $P<0.05$.

RESULTS

The mean age, sex, smoking status, DAS 28, and disease duration of the patients are shown in Table 1. Patient age ranged from 22 to 76 years (mean: 49.62 ± 9.4 years).

There was no difference in the medication protocol between RA+ and the other AI groups, except for the anti-TNF-α therapy. The mean duration of infliximab therapy was 26 ± 8 months without statistical significance.

The proportions of patients in each periodontal disease category, according to the American Academy of Periodontology classification of periodontal disease, did not vary significantly among the study groups (data not shown).[35] Forty-six patients (79%) had moderate-to-advanced chronic periodontitis (CP), nine (16%) had slight CP, and three (5%) had gingivitis.

Table 2 presents comparison of clinical and immunologic parameters between all groups. Mean PD was significantly lower in the H (3.47 mm) and RA+ (3.22 mm) groups compared to the AI patients: 3.93, 4.06, and 3.74 mm for the RA, PA, and SSc groups, respectively ($P = 0.0002$). Likewise, the number of sites with PD >4 mm was significantly lower in the H and RA+ groups compared to the AI patients. Moreover, FMBS and GI were significantly higher in these three groups compared to the H and RA+ groups. Patients who received anti-TNF-α therapy had the lowest levels of TNF-α in the GCF (0.97 ± 0.52 ng/site) compared to the H, RA, PA, and SSc groups (1.07 ± 0.33, 1.42 ± 0.46, 1.97 ± 0.61, and 1.65 ± 0.57 ng/site, respectively; $P = 0.0,001$). Similarly, these values for the H controls (1.07 ± 0.33 ng/site) were significantly lower than that of all the other AI groups except for the RA+ group.

Because the three AI subgroups were very similar, we have compared them to the H and RA+ groups (Table 3). All the periodontal and inflammatory parameters were higher in the AI group compared to the H and RA+ groups: PD, 3.91 ± 0.49 versus 3.47 ± 0.33 and 3.22 ± 0.41, respectively ($P = 0.0001$); number of sites with PD >4 mm, 42.44 ± 17.5 versus 24.33 ± 15.62 versus 33.3 ± 6.6, respectively ($P = 0.0002$); FMBS, 46.45% ± 17.08% versus 30.08% ± 16.86% and 21.13% ± 9.51%, respectively ($P = 0.0002$); GI, 1.91 ± 0.54 versus 1.21 ± 0.67 and 1.45 ± 0.30, respectively ($P = 0.0005$). PI was slightly lower in the H group (1.41 ± 0.8) compared with the AI (1.81 ± 0.49) and RA+ (1.95 ± 0.42) patients. These differences were borderline significant ($P = 0.058$).

A significant positive correlation was observed between PD and percentage FMBS ($r = 0.749$; $P = 0.0002$). Weak positive correlations were also observed between PD and TNF-α level ($r = 0.4672$; $P = 0.0002$) and GI and TNF-α level ($r = 0.542$; $P = 0.0001$). However, such correlations were not observed between TNF-α level and any of the other clinical parameters (Table 4).

DISCUSSION

In the present study, the authors demonstrate that periodontal indices in the three AI groups (RA+ group was excluded [Tables 3 and 4]) were very similar and significantly higher than in the H controls. Mercado et al.[14] reported significantly higher prevalence of moderate-to-severe periodontitis in individuals with RA compared to H controls. They also

§ Gracey curets, Hu-Friedy, Chicago, IL.
‖ PerioPaper, ProFlow, Amityville, NY.
¶ Human TNF-α/TNFSF1A Immunoassay, R & D Systems, Minneapolis, MN.
# Sunrise microplate reader, Magellan Tecan, Männedorf, Switzerland.

Table 1.

Patient Characteristics

Variable	H	RA	PA	RA+	SSc	*P* value*
No. of patients	12	12	12	10	12	NS
Age (years) mean ± SD	51.5 ± 9.97	48.2 ± 12.0	48.7 ± 10.4	53.6 ± 6.2	48.4 ± 9.3	NS
Female/male ratio	7/5	7/5	7/5	7/3	9/3	NS
Smokers (%)	25	16.6	25	30	16.6	NS
Disease duration (years) mean ± SD	NA	5.0 ± 2.1	8.9 ± 5.1	16.3 ± 14	7.2 ± 6.9	0.013†

NA = non-applicable; NS = statistically non-significant.
* ANOVA with Fisher LSD test.
† RA+ different from RA but not from SSc or PA.

Table 2.

Comparison of Clinical and Immunologic Parameters Between Groups (mean ± SD)

Variable	H	RA	PA	RA+	SSc	*P* value*
PD (mm)	3.47 ± 0.33	3.93 ± 0.66	4.06 ± 0.36	3.22 ± 0.41	3.74 ± 0.36	0.0002†
No. of sites with PD >4 mm	24.33 ± 15.62	44.5 ± 20.22	43.08 ± 14.35	33.3 ± 6.63	39.75 ± 18.61	0.0005†
FMBS (%)	30.08 ± 16.86	46.03 ± 17.78	55.5 ± 16.14	21.13 ± 9.51	37.83 ± 13.46	0.0000‡
GI (0 to 3)	1.21 ± 0.67	2.06 ± 0.42	2.14 ± 0.46	1.45 ± 0.30	1.51 ± 0.53	0.0000§
PI (0 to 2)	1.41 ± 0.82	1.86 ± 0.38	2.13 ± 0.26	1.95 ± 0.42	1.45 ± 0.54	0.0045‖
TNF-α (pg/mL)	1.07 ± 0.33	1.42 ± 0.46	1.97 ± 0.61	0.97 ± 0.52	1.65 ± 0.57	0.0001¶

* ANOVA with Fisher LSD test.
† RA+ and H groups are different from all others except themselves.
‡ RA+ different from all others except H; H different from all others expect RA+ and SSc.
§ RA+ and H groups are different from RA and PA only.
‖ H and SSc different from all other groups but not from each other.
¶ RA+ different from all others except H; H different from all others expect RA groups.

Table 3.

Clinical and Immunologic Parameters Between Between H, AI, and RA+ Groups (mean ± SD)

Variable	H	AI	RA+	*P* value*
PD (mm)	3.47 ± 0.33	3.91 ± 0.49	3.22 ± 0.41	0.0001†
No. of sites with PD >4 mm	24.33 ± 15.62	42.44 ± 17.5	33.3 ± 6.6	0.0002†
FMBS (%)	30.08 ± 16.86	46.45 ± 17.08	21.13 ± 9.51	0.0002†
GI (0 to 3)	1.21 ± 0.67	1.91 ± 0.54	1.45 ± 0.30	0.0005†
PI (0 to 2)	1.41 ± 0.82	1.81 ± 0.49	1.95 ± 0.42	0.0548‡
TNF-α (pg/mL)	1.07 ± 0.33	1.67 ± 0.58	0.97 ± 0.52	0.0002†

* ANOVA with Fisher's LSD test.
† RA+ and H groups are different from AI but not from each other.
‡ Statistically non-significant.

Table 4.

Correlation Between PD and Clinical, Demographic or Immunologic Parameters

Variable	All Patients (n = 58) (*r*, *P*)	AI (n = 36) (*r*, *P*)	RA+ (n = 10) (*r*, *P*)	H Controls (n = 12) (*r*, *P*)
TNF-α (pg)	0.4672,* 0.0002	0.3509,* 0.0359	0.3296, 0.3524	0.5413, 0.0692
FMBS (%)	0.7491,* 0.0001	0.6534,* 0.0001	0.3712, 0.2909	0.7683,* 0.0022
PI (0 to 2)	0.2632, 0.0459	0.2643, 0.1193	–0.4423, 0.2005	0.7286,* 0.0047
GI (0 to 3)	0.5420,* 0.0001	0.3285, 0.0504	0.4950, 0.1458	0.6882,* 0.0093
Age (years)	–0.0877, 0.5124	0.0535, 0.7566	0.0346, 0.9244	0.062 0.8407
Disease onset (years)	–0.1943, 0.1438	–0.2775, 0.1013	–0.1617, 0.6555	NA, NA

NA = non-applicable.
* Statistically significant (Pearson correlation coefficient test).

demonstrated that periodontitis patients had higher prevalence of RA compared to the general population. Other studies have shown that RA may be associated with tooth loss and periodontitis.[11,36] A case-control study by Leung et al.[18] reported that patients with SSc exhibited higher levels of periodontal inflammation and wider radiographic periodontal ligament spaces than age- and sex-matched controls. Also, higher prevalence of periodontal disease has been reported among SSc patients.[7] Moen et al.[37] reported that higher variety and concentrations of oral bacterial deoxyribonucleic acids (DNAs) were found in synovial fluid compared to serum of RA and PA patients. They suggested that synovial inflammation in RA and PA may favor trapping of oral bacterial DNAs, suggesting a perpetuating effect of oral pathogens in joint inflammation. Chronic inflammatory diseases, such as RA, PA, and periodontitis, are likely to share pathogenic mechanisms of inflammation-mediated solid-tissue destruction.[38] The expression of proinflammatory cytokines, such as TNF-α, leads to propagation of the inflammation and release of a high level of inflammatory mediators that result in bone destruction.[39] Therefore, AIs, such as RA, PA, SSc, and periodontal disease, may share similar patterns of etiopathogenesis or destruction pathway, thus potentially inducing each other.

Levels of TNF-α in the AI groups (1.67 pg/mL) were significantly higher than in the H controls (1.07 pg/mL). This phenomenon was negated in the patients treated with TNF-α blockers (0.97 pg/mL). Scala et al.[40] analyzed serum samples from 54 SSc patients and 20 matched H controls and found significantly increased levels of IL-6, TNF-α, and monocyte chemoattracive protein-1. Inhibition of TNF-α in vitro has been shown to reduce IL-1 activity and the production of growth factor (GM-CSF), IL-6, and IL-10. Therefore, placing TNF-α farther up the hierarchy, making this cytokine an attractive target for therapy in inflammatory conditions.[38] Studies have shown that inhibition of TNF-α activity leads to clinical improvement in both RA and periodontitis.[15,41] Garlet et al.[42] reported that TNF-α receptor p55-deficient mice developed less severe periodontitis in response to *Aggregatibacter actinomycetemcomitans* infection, which was characterized by significantly less alveolar bone loss and a higher acute-phase response with higher levels of C-reactive protein in the serum. In a longitudinal study, Pers et al.[27] reported a reduction in AL after anti-TNF-α therapy. Nonetheless, the multitude of severe side effects (demyelenation, lymphoma, systemic lupus, congestive heart failure, aplastic anemia)[43] associated with TNF-α antagonists makes the current use of this agent in patients with periodontitis a risk not worth taking.

A possible weakness in this study may be that the RA+ group was not matched for disease duration (RA+ was markedly longer than the other AI groups), but patients did not show differences in their immune profile (rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies), disease activity (according to DAS 28), or current disease-modifying antirheumatic drug use. Although disease duration was markedly longer in the RA+ group, both clinical and immunologic parameters were comparable to the H group. The duration of anti-TNF-α treatment was 1 to 3 years (not statistically significant). We did not find any correlation between any periodontal parameter and the duration of the anti-TNF-α therapy. The relatively short duration of anti-TNF-α administration may explain the lack of significant correlation between the clinical and biochemical data.

Biyikoğlu et al.[44,45] found that, despite the long-term usage of corticosteroids and non-steroidal anti-inflammatory drugs, similar GCF matrix metalloproteinase-8, matrix metalloproteinase-13, prostaglandin E_2, plasminogen activator inhibitor-2, and IL-1β, and levels in patients with RA and systemically

H counterparts suggest that RA may create a tendency to overproduce these enzymes.

A strong positive correlation was observed between PD and FMBS (r= 0.7491; P= 0.0001), GI (r= 0.542; P= 0.0001), and TNF-α (picograms) (r= 0.467; P= 0.0002). Clinical periodontal measurements, mainly PD and BOP, continue to be the most widely used parameters not only for the diagnosis but also for determining the activity and prognosis of periodontal diseases.[46] Moreover, GCF provides an accurate representation of tissue and serum concentrations of inflammatory mediators.[47] Nilsson and Kopp[48] found that, in patients with RA, high plasma levels of TNF-α were related to gingival BOP, more AL, and deeper pockets compared to those with low plasma levels. Kurtiş et al.[49] investigated the presence of TNF-α in the GCF and the clinical parameters in patients with chronic or aggressive periodontitis. They detected a positive statistical correlation between AL and TNF-α levels (r=0.487; P <0.001) and also found a correlation with other clinical parameters, such as PD, PI, and GI.

CONCLUSIONS

Patients with AI have higher indices of periodontal disease and TNF-α levels in GCF than H individuals. Anti-TNF-α treatment in patients with AI seems to hinder this phenomenon. Although the high cost and long-term safety profile associated with infliximab negate its current use in periodontal therapy, future generations of anti-TNF-α agents (preferably locally administered) may be incorporated into out host modulation armamentarium.

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