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Serum cytokine levels and periodontal parameters in ankylosing spondylitis

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Background and Objective: Multiple studies support the role of periodontal disease in contributing to the chronic systemic inflammatory burden in a variety of diseases, including ankylosing spondylitis (AS), in the progression which the inflammatory process plays an important role. We assume that patients with AS are more likely to have periodontal disease than healthy individuals. The aim of this study was to determine the possible relationship between inflammatory periodontal diseases and AS by evaluating clinical periodontal parameters and serum cytokine levels.

Material and Methods: Forty-eight adults with AS (35 women and 13 men; age range 18–56 years; mean age 34.27 years) and 48 age- and sex-matched systemically healthy control subjects participated in the study. The clinical periodontal parameters, venous blood and Bath Ankylosing Spondylitis Disease Activity Score were obtained, and serum C-reactive protein, tumour necrosis factor-α and interleukin-6 (IL-6) levels were evaluated.

Results: There was statistically no significant difference in the frequency of periodontitis between AS patients and the control group. Furthermore, there was no significant difference in probing depth, clinical attachment level and plaque index, and the only significant clinical difference between groups was in levels of bleeding on probing ($p < 0.001$). Serum concentrations of IL-6, tumour necrosis factor-α and C-reactive protein in the AS group were significantly higher than those in the control group ($p < 0.001$). In the AS group, there was a correlation between serum IL-6 levels and clinical attachment level ($p < 0.001$).

Conclusion: The results of present study suggest that bleeding on probing was the only different periodontal parameter between the AS and the control group, and the periodontal status of patients with AS may be affected by IL-6 levels.

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Periodontal disease is an inflammatory disease process resulting from the interaction of a bacterial attack and host inflammatory response, which results in the elevation of local and systemic proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (1). All forms of inflammatory periodontal disease associated with the accumulation of B and T lymphocytes as well as monocytes and neutrophils can be pronounced as chronic inflammation and, if left untreated, irreversible tissue damage can occur in the bone and soft tissue surrounding teeth, leading to tooth mobility and ultimately to the loss of teeth (2). Owing to the multifactorial nature of periodontal disease, which is modified by a number of systemic, environmental and microbiological factors, the severity and consequences vary between affected individuals despite the fact that the

same amount of dental plaque is detected.

According to Golub *et al*. (3), both periodontopathic bacteria and the systemic inflammatory response are responsible for the cascade of destructive events in chronic destructive periodontitis. Furthermore, multiple studies suggest that periodontal disease contributes to the chronic systemic inflammatory burden in a variety of diseases, such as coronary heart disease (4), chronic kidney disease (5), diabetes mellitus (6), rheumatoid arthritis (7) and, recently, ankylosing spondylitis (AS; 8).

Ankylosing spondylitis is a chronic inflammatory rheumatic disease affecting the axial skeleton, including the sacroiliac joints and spine and also the peripheral joints and entheses (9). The factors affecting the progress of AS have not yet been established. Advanced AS can be associated with severe functional impairment, work disability and a compromised quality of life (10). The prevalence of AS in the general population is 0.1–1.4% (11).

The inflammatory process plays an important role in disease progression in AS, as well as in inflammatory periodontal disease. Several studies have reported the systemic elevation of proinflammatory cytokines in AS patients, describing significantly higher levels of IL-6 (12–16) and TNF-α (13,16,17) in serum and of TNF-α in *in vitro* cultures of stimulated peripheral blood mononuclear cells from AS patients (18) compared with healthy control subjects. A similar profile of cytokines has also been shown in the pathogenesis of periodontitis (19). In addition, C-reactive protein (CRP) is an acute-phase protein synthesized mainly in the liver and regulated primarily by the concentration of circulating IL-6. Although CRP is not always elevated or is mildly elevated in severe cases of AS (20), it may be a weak common inflammatory marker for both diseases, because persistently increased CRP concentrations have been associated with destructive periodontal disease (21,22).

Although similarities in the pathogenesis of AS and inflammatory periodontal diseases are conspicuous, possible interactions between these two diseases are not well documented, and the mechanism underlying the possible interaction remains unclear. The aim of the present study was to determine the possible relationship between inflammatory periodontal diseases and AS by evaluating clinical periodontal parameters and serum cytokine levels.

Material and methods

Forty-eight adults with AS (AS group; 35 women and 13 men; age range 18–56 years; mean age 34.27 years) were assessed at the Department of Rheumatology of Gaziantep University, Faculty of Medicine, and these individuals randomly participated in the investigation between October 2010 and March 2011. Patients with AS were diagnosed by the rheumatologist (Y.P.) and confirmed by the second rheumatologist (A.M.O.) in accordance with the modified New York Criteria (23). These classification criteria include: (i) low back pain for more than 3 mo that improves with physical exercise, but no relief with rest; (ii) limitation of lumbar spine motion in sagittal and frontal planes; (iii) decreased chest expansion (corrected for age and sex); (iv) unilateral sacroiliitis grades 3–4; and (v) bilateral sacroiliitis grades 2–3. Either (iv) or (v) and any one of the clinical symptoms (i)–(iii) have to be found.

Disease activity in patients with AS was assessed by the Bath Ankylosing Spondylitis Disease Activity Score (BASDAI; 24), and their body mass index (BMI) was calculated as weight/height^2 (in kilograms per metre squared). All of the AS patients who participated in this study were under medication with TNF-α antagonists, disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) at the time of examination. A group of 48 age- and sex-matched systemically healthy control individuals (with no signs of AS and other systemic diseases; control group; 35 women and 13 men; age range 18–54 years; mean age 33.33 years) were included who attended Gaziantep University, Faculty of Dentistry from October 2010 to March 2011. Ethical approval was gained from the Ethical Committee for the Use of Human Subjects in Research, Gaziantep University, Gaziantep. Exclusion criteria for the AS group were a history of other systemic conditions (pregnancy etc.) or diseases except AS. Exclusion criteria for both groups were history of periodontal treatment within the last 6 mo and antibiotic or corticosteroid administration within the last 3 mo. Patients who had < 18 teeth in the mouth and current smokers were excluded from the study. Written informed consent was obtained from all participants before the study.

Periodontal parameters

All participants were evaluated clinically at their first visit to the Periodontology Department at the Gaziantep University, Faculty of Dentistry by the same clinician (U.S.) to assess the following periodontal measurements. All dental variables were assessed at six different sites (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual and disto-lingual) of each tooth present, excluding wisdom teeth. Clinical measurements of periodontal parameters included plaque index (25), probing pocket depth, clinical attachment level and percentage of bleeding on probing. All assessments were carried out using the Williams periodontal probe. The diagnosis was based on the clinical and radiographic criteria stated and described in the 1999 Consensus Classification of Periodontal Diseases. The criteria for chronic periodontitis was as follows: at least four teeth with a probing pocket depth ≥ 5 mm, with clinical attachment level ≥ 2 mm at the same time (26). Clinical periodontal characteristics and demographic variables of patients with AS and control subjects are shown in Table 1.

Measurements of serum cytokines and CRP levels

After periodontal evaluation, peripheral venous blood samples were obtained from all participants. Serum was isolated from the blood by

Table 1. Characteristics and clinical periodontal and rheumatological parameters of individuals with and without ankylosing spondylitis (AS)

Parameters	AS group (n = 48)	Control group (n = 48)	p-Value
Age [years; mean ± SD (range)]	34.27 ± 9.73 (18–56)	33.33 ± 9.67 (18–54)	Matching criteria
Gender (male/female)	35/13	35/13	Matching criteria
Body mass index (kg/m^2; mean ± SD)	23.54 ± 2.01	22.60 ± 1.88	0.011*
Chronic periodontitis frequency % (n)	37.5 (18)	29.2 (14)	0.518
Probing depth (mm; mean ± SD)	3.17 ± 0.82	3.15 ± 0.90	0.789
Clinical attachment level (mm)			
Mean ± SD	2.35 ± 1.93	2.04 ± 1.81	0.430
Median [interquartile range]	2.70 [3.06]	2.2 [2.07]	
Plaque index (mean ± SD)	1.60 ± 0.61	1.53 ± 0.52	0.689
Bleeding on probing (%)	46.77 ± 3.17	33.09 ± 2.98	0.001**
BASDAI (mean ± SD)	5.36 ± 1.59	NA	
Erythrocyte sedimentation rate (mean ± SD)	18.08 ± 8.50	NA	
Duration of AS (years; mean ± SD)	5.04 ± 6.13	–	
NSAIDs % (n)	77 (37)	–	
Tumour necrosis factor-α antagonists % (n)	21 (10)	–	
DMARDs % (n)	56 (27)	–	
Newly diagnosed % (n)	8 (4)		

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Score; DMARDS, disease-modifying antirheumatic drugs; NA, not applicable; and NSAIDs, nonsteroidal anti-inflammatory drugs.
*$p < 0.05$, **$p < 0.001$.

centrifugation at 1500g for 20 min, and stored at −80°C until used. The C-reactive protein was determined by nephelometer (Dade Behring Marburg GmbH, Mahburg, Germany; CRP range 0–5 mg/L), and erythrocyte sedimentation rate was measured using the Westergren method.

Proinflammatory cytokine (IL-6 and TNF-α) concentrations in the patients' serum were determined by ELISA (DIAsource ImmunoAssays, Nivelles, Belgium) according to the manufacturer's instructions. The detection range for the IL-6 assay was 23.3–2560 pg/mL, with a sensitivity of 2 pg/mL, and the detection range for the TNF-α assay was 7–518 pg/mL, with a sensitivity of 0.7 pg/mL. A wavelength of 450 nm was used for measurement in both assays. All samples obtained from AS patients and healthy control subjects were above the detection limit for TNF-α, IL-6 and CRP.

Statistical analyses

Sample size was estimated using a power calculation based on 30% increase in frequency of periodontitis in the AS group. It was estimated that at least 40 patients would be required to detect a significant difference between control and AS groups at 80% power level and an α error of 5%. Mann–Whitney U-tests were used to assess the differences in clinical parameters and serum cytokine and CRP levels between the AS and the control group. The Spearman rank correlation coefficient was used to determine the relationship between clinical periodontal parameters and serum cytokine and CRP levels. From the logistic regression analysis, odds ratios (ORs) were calculated with a 95% confidence interval (CI). A value of $p < 0.05$ was considered to be significant. Analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was considered significant.

Results

Comparisons between patients with AS and systemically healthy control subjects

The characteristics of the population and of the AS and control groups are shown in Table 1. Significant differences in age and sex (matching variables; $p < 0.05$) were not observed. The frequency of periodontitis was 37.5% (18 of 48) in the AS group and 29.2% (14 of 48) in the control group. The difference was not statistically significant (Table 1). Furthermore, there were no significant differences between the groupsin probing pocket depth, clinical attachment level or plaque index. The only significant clinical difference between AS patients and systemically healthy individuals was in bleeding on probing ($p < 0.001$). The BASDAI and erythrocyte sedimentation rate levels were higher in the AS group. The BMI was 23.54 ± 2.01 kg/m^2 in the AS group and 22.60 ± 1.88 kg/m^2 in the control group, and there was a statistically significant difference between groups ($p < 0.05$).

Serum concentrations of IL-6, TNF-α and CRP in the AS group were significantly higher than those in the control group ($p < 0.001$; Table 2.

Correlation between molecular variables, BASDAI and clinical periodontal parameters

In the AS group, there was a correlation between serum IL-6 levels and clinical attachment level ($p < 0.001$; Table 3), whereas there was no correlation detected between TNF-α or CRP levels and any of the clinical periodontal parameters (data not shown).

Logistic regression analyses

In logistic regression analyses, we examined the association of AS with

Table 2. Serum cytokine and C-reactive protein levels in individuals with and without AS

Parameters	AS group (n = 48)	Control group (n = 48)	p-Value
Interleukin-6 (pg/mL)	28.65 ± 13.00	6.28 ± 3.94	0.001**
Tumour necrosis factor-α (pg/mL)	17.45 ± 14.66	9.36 ± 4.60	0.001**
C-reactive protein (mg/L)	30.67 ± 20.07	3.87 ± 0.91	0.001**

**$p < 0.001$.

Table 3. Correlation between serum interleukin-6 levels and clinical periodontal parameters and age; each cell contains Spearman's rho value for pairs of variables and probability that correlation is significant in patients with ankylosing spondylitis (AS)

AS group (n = 48)	Age (years)	Plaque index	Bleeding on probing	Probing depth	Clinical attachment level
Interleukin-6	0.138–0.351	0.150–0.308	0.269–0.064	0.242–0.098	0.677–0.000**

** Correlation is significant ($p < 0.001$).

the odds of clinical attachment level > 3 mm as defined in a previous study (8) (Table 4). We entered age, sex, BMI and IL-6 into the logistic regression model. In this analysis, only age remained as a significant predictor of clinical attachment level > 3 mm, and no relationships were detected between AS status, IL-6 level, BMI and clinical attachment level > 3 mm. The logistic regression model was significant ($p = 0.001$); the correlation coefficient of the model was 0.737. Sensitivity of the model was 88.2% and specificity 88.7%.

Discussion

The present study is believed to be the first to evaluate clinical parameters and the potential role of proinflammatory cytokines in the relationship between periodontal disease and AS. The periodontal status is affected by systemic inflammation, which leads to the hypothesis that the disease activity of AS may affect periodontal conditions. There are scarce data regarding the periodontal status of AS patients (8,27). In the present study, the frequency of periodontitis was similar and statistically not different in AS patients and systemically healthy control subjects. The results of this study indicate that periodontal destruction, as determined by probing pocket depth and clinical attachment level, was not significantly affected by disease activity in AS patients. Our results were not consistent with the results of Pischon *et al*. (8), who concluded that probing pocket depth and clinical attachment levels were significantly different between AS patients and healthy control subjects. The discrepancy between the results of the studies can be explained by the multifactorial nature of the aetiology of periodontal disease and variable periodontal status of the control groups. The results of present study suggest that in AS periodontal destruction is more strongly influenced by factors other than the total burden of systemic inflammation. Some previous studies have also reported that systemic inflammation is not the major component of destruction in periodontal disease (28–30). Our findings were similar to these studies.

In the present study, to eliminate the confounding factors that affect periodontal status, distinct inclusion criteria for the groups of this study population were followed, and a homogeneous AS group was attempted through a definite diagnosis by the physician and through the elimination of potential shared confounders, such as smoking and diabetes mellitus, which are conditions believed to be involved in the development and/or progression of periodontal disease and levels of serum cytokines. Although age and sex differences and potential confounders were eliminated, BMI values were significantly higher ($p < 0.05$) in the AS group, and this may have affected the serum cytokine levels and periodontal status (31). Ten patients with AS (21%) were using TNF-α antagonists and, according to Briot *et al*. (32), anti-TNF-α treatment can be responsible for higher BMI values in AS patients, and the higher BMI values in AS group can be interpreted as an effect of disease therapy.

There was no statistically significant difference between the two groups in plaque index levels. These data are in contrast with the findings of Pischon *et al*. (8). The disability of patients with AS may be related to high plaque levels, but the poor oral hygiene of the control group may also be the determinant factor in the similarity of the plaque index values within groups. In a previous study, Pischon *et al*. (8) suggested that the prevalence of

Table 4. Logistic regression analysis

Characteristics	Clinical attachment level > 3 mm (n = 34)	Clinical attachment level ≤ 3 mm (n = 62)	p-Value	Odds ratio (95% confidence interval)
AS [n (%)]				
Yes	20 (58.8%)	28 (45.2%)	0.323	4.286 (0.240–76.67)
No	14 (41.2%)	34 (54.8%)	–	1.0 (reference)
Sex [n (%)]				
Male	25 (73.5%)	45 (72.6%)	0.434	0.503 (0.090–2.815)
Female	9 (26.5%)	17 (27.4%)	–	1.0 (reference)
Age (years; mean ± SD)	42.94 ± 6.64	28.790 ± 7.03	0.001	1.364 (1.178–1.580)
Body mass index (kg/m^2; mean ± SD)	23.70 ± 1.66	22.72 ± 2.07	0.482	0.834 (0.504–1.382)
Interleukin-6 (pg/mL; mean ± SD)	21.00 ± 16.68	15.52 ± 13.33	0.783	0.986 (0.893–1.089)

periodontal disease was increased in AS patients, but our results showed no difference between two groups in the clinical attachment level and probing pocket depth. However, similar to the study of Pischon *et al*.(8), bleeding on probing scores were significantly elevated in the present study. Administration of DMARDs, NSAIDs and TNF-α antagonists has commonly been used in the treatment of AS. It has been reported that patients with rheumatoid arthritis (another chronic inflammatory rheumatic disease) were less likely to have periodontal destruction if they were treated with DMARDs (30). Pers *et al*. (28) reported exaggerated gingivitis following administration of TNF-α antagonists in rheumatoid arthritis patients, and the results of the present study are consistent with their study regarding elevated bleeding on probing levels in AS patients, in whom administration of TNF-α antagonists is common. Furthermore, TNF-α antagonists and NSAIDs have been demonstrated to be beneficial in the treatment of periodontitis (28,33,34). The common use of these drugs for many years may mask the destructive periodontal effects of AS; thus, the possible difference between AS patients and healthy control subjects may not be detectable as a result.

Periodontal conditions are affected by several systemic conditions, which leads to the hypothesis that the disease activity of AS may be involved in progression of periodontal disease (35,36). The disease activity in AS patients can be evaluated by BASDAI, erythrocyte sedimentation rate and CRP. In general, erythrocyte sedimentation rate and CRP correlate poorly with disease activity evaluated by BASDAI, especially in patients with exclusive axial disease (37). In ankylosing spondylitis, erythrocyte sedimentation rate, CRP and even BASDAI cover the concept of disease activity only partly (38). In our study, higher levels of CRP and BASDAI were detected in the AS group, but there were no correlations between BASDAI or CRP levels and periodontal parameters (data not shown).

As an indicator of inflammation, the finding of systemic elevation of proinflammatory cytokines is in keeping with several other studies on AS describing significantly higher levels of IL-6 (12–16) and TNF-α (13,16,17) in serum of AS patients when compared with healthy control subjects. In the present study, IL-6 and TNF-α levels were elevated in the AS group compared with the control group (17.45 ± 14.66 vs. 9.36 ± 4.60 pg/mL and 28.65 ± 13.00 vs. 6.28 ± 3.94 pg/mL, respectively; $p < 0.001$). These results were consistent with the findings of previous studies (12–17).

Although there was no significant difference in clinical attachment level and probing pocket depth between systemically healthy and AS groups, an evaluation of the AS group separately can help us to asses the relationship between AS and periodontal disease in more depth. There were no significant correlations between periodontal parameters and TNF-α concentrations in the AS group (data not shown). This can be explained by the high rate of medication use in the AS group, as most of these medications might affect the levels of TNF-α. There was, however, a significant positive correlation between IL-6 concentrations and clinical attachment level. In AS patients, the periodontal destruction may be related to circulating IL-6 levels instead of TNF-α levels. Elevated levels of IL-6 may lead to a possible increase in the number and duration of exacerbation periods in the pathogenesis of periodontitis, which may explain the correlation between IL-6 levels and clinical attachment level in AS patients.

In the logistic regression analysis, no relationships were detected between AS status, IL-6 levels and BMI when odds ratios were evaluated, considering clinical attachment level > 3 mm (Table 4). These results are in contrast to a previous study (8). This difference can be explained by different patient groups with different medication use.

Drug treatment may mask any potential effects of AS activity on periodontal status. The patients were diagnosed a mean of 5.04 ± 6.13 years before the study, and most of the patients were using these medications (DMARDs, NSAIDs and TNF-α antagonists). In AS patients, the effects of these drugs on periodontal parameters are still unknown, so follow-up studies are needed to evaluate the exact effects. Another limitation of present study was the cross-sectional design and the number of participants in the study. Further studies are needed with a different design, and larger patient groups are necessary in order to evaluate the relationship between AS and periodontal disease.

Conclusion

Within the limitations of present study, it can be concluded that bleeding on probing was the only different periodontal parameter between the AS group and as the control group, and the periodontal status of the patients with AS may be affected by IL-6 levels.

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