Periodontal Disease in Patients with Ankylosing Spondylitis: myth or reality?

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Although the relation between periodontitis (PD) and systemic disorders (e.g. cardiovascular diseases, diabetes and rheumatoid arthritis) is widely accepted, the association with ankylosing spondylitis (AS) is inconsistently mentioned. We prospectively examined the relationship between periodontal disease and AS, focusing on the rate and course of PD, factors associated with severity and the impact of anti-TNF-α treatment on inflammatory status. Standard assessments performed twice (week 0, week 24) included an extensive dental evaluation (plaque index, gingival index, bleeding on probing, periodontal pocket depth, clinical attachment loss), inflammatory parameters and AS activity scores (BASDAI, ASDAS-CRP). More than half of AS presented with impaired periodontal health at baseline (mild to moderate PD) meaning increased sites with dental plaque, abnormal bleeding, increased periodontal pocket depth and clinical attachment loss. Significant positive correlation between presence and severity of PD, AS activity and systemic inflammation (CRP) was reported at baseline ($p<0.05$). A final analysis performed at 24 weeks revealed significant improvement in periodontal status, inflammatory parameters and AS activity, suggesting efficacy of TNF inhibitors directed not only against systemic, but also on local (articular, periodontal) inflammation ($p<0.05$). Patients with AS are at risk to develop periodontal disease, particularly those with high levels of systemic inflammation. Benefits of anti-TNFα therapy in the particular settings of AS patient and concomitant periodontal disease should be validated through further studies in larger cohorts.

Keywords: ankylosing spondylitis, periodontitis, TNF antagonists

Ankylosing spondylitis (AS) and periodontal disease (PD) are chronic inflammatory disorders that share local and systemic inflammatory as well as destructive events, targeting specific tissues such as joints and enthesis in AS, while periodontal tissues in PD [1-3]. The underlying pathobiologic pathways emphasize a complex immune dysregulation with excess of pro-inflammatory cytokines including TNF-α and IL-6 in both articular and periodontal environments, indicating potential association of these entities [1-5].

Periodontitis or periodontal disease remains an inflammatory infectious condition characterized by an immunologically mediated damage of tissues surrounding and supporting the teeth accompanied by chronic gingival inflammation driven by pathogenic bacteria in the dental plaque [2, 5-7]. Progressive attachment loss, alveolar bone resorption, soft tissue pockets formation between the gingiva and the tooth root and/or gingival recession are typically reported as subsequent steps in the long-term course of the disease [6-8].

Although three main criteria are largely accepted for the clinical diagnosis of periodontitis, including clinical attachment loss (CAL), bleeding on probing (BOP) and pocket probing depth (PPD), a uniform definition of the diagnostic threshold has not yet been established. Thus, the true rate of periodontitis in general population largely varies according to the definition used [4, 5, 7, 9].

Ankylosing spondylitis is a chronic inflammatory rheumatic disorder, affecting mainly the axial skeleton and, with a lesser extent, peripheral joints, enthuses, eyes, bowels and skin, causing inflammation and tissue damage as a result of an autoimmune process in a genetically background (HLA-B27, genes for IL-23 and ERAP-1) [1]. While inflammation is the initial step in the immunopathogenesis of the disease involving the bone-cartilage interface, cartilage erosions and additional osteoproliferation (as a repair process) via TNF mediation are critical for AS [1, 4, 5].

It is widely recognized that periodontitis is associated with several systemic conditions including cardiovascular pathology, diabetes mellitus, cancers, as well as immune mediated inflammatory disorders such as rheumatoid arthritis [6-8, 10-12].

Data about the relationship between AS and PD, as well as the potential role of disease activity and inflammatory parameters as predictors of periodontal involvement among AS patients is still controversial [4, 5, 13-19]. While the majority of studies report a higher prevalence of impaired oral health and PD in AS compared to general population [4, 5, 15, 20], certain papers found no association between these two entities [13].

Overall, the rates of PD in AS ranges from 37.5% to 87.8% and is about 25.9 to 71.4% in healthy controls [4, 5, 15, 20], after adjusting for general risk factors for periodontitis such as smoking, obesity, excessive alcohol intake [4, 5, 20].

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Furthermore, a detailed analysis of all parameters measuring periodontal health (e.g. CAL, PPD, POB) identifies important differences in AS and case-control studies [4, 5, 20].

The aim of this report was to assess the relationship between periodontal disease and AS, focusing on the rate and course of periodontitis, factors associated with the severity and the impact of anti-TNF-α treatment on inflammatory status in patients with AS.

Experimental part

Material and method

Prospective observational 24 weeks study in a cohort of 86 consecutive patients aged 18 years or more who meet the 1984 modified New York criteria for AS aiming to assess periodontal disease.

Patients were followed in a single academic rheumatology department and all received TNF inhibitors (adalimumab, infliximab, golimumab, etanercept) based on national recommendations for the use of biologics in active AS sub-optimally controlled by non-steroidal anti-inflammatory drugs.

Periodontal parameters and a complex rheumatologic assessment were done based on the same protocol in all AS patients:

- *Periodontal examination.* Full-mouth periodontal probing using a Williams probe was performed at 4 sites per tooth (mesio-buccal, disto-buccal, mesio-lingual, disto-lingual); probing pocket depth, clinical attachment loss, plaque index (PI), gingival index (GI) and bleeding on probing were measured in all patients.

PPD was defined as the distance from the free gingival margin to the bottom of the sulcus or periodontal pocket, and CAL as the distance from the cement-enamel junction to the bottom of the sulcus or periodontal pocket.

Chronic periodontitis was considered if at least four teeth with a PPD ≥ 5 mm and with CAL ≥ 2 mm at the same time, as recommended by the 1999 Consensus Classiûcation of Periodontal Diseases [9];

-*Standard AS assessme*nts included two disease activity scores, Bath Ankylosing Spondylitis Disease Activity Score, BASDAI, and Ankylosing Spondylitis Disease Activity Score calculated using C reactive protein levels, ASDAS-CRP.

BASDAI is the old subjective activity score for AS, while ASDAS is a new composite index to assess disease activity. The 3 cut-offs for this score are <1.3 between inactive disease and moderate disease activity, <2.1 between moderate disease activity and high disease activity, and >3.5 between high disease activity and very high disease activity.

-*Inflammatory parameters*, erythrocyte sedimentation rate (ESR) analyzed by the Westergren method (mm/hour), and C-reactive protein (CRP) by the classic method (mg/L) were performed in all patients.

Patients with severe aggressive PD requiring professional scaling were excluded from the final analysis, while those presenting with potential risk factors for PD such as diabetes, smoking, excessive alcohol intake and obesity also were not included in the study.

Periodontal evaluation, AS examination and inflammation tests were recorded twice during the study, at week 0 (before the first administration of anti-TNF agents) and at 24 weeks of therapy.

The study protocol was approved by the local ethics committee and patients provided a written informed consent before their enrollment.

Statistical analysis (descriptive, analytical tests) was done in IBM SPSS-19 software, $p<0.05$.

Results and discussions

Baseline data

Demographics, disease duration, inflammatory tests, disease activity scores and periodontal status at baseline are summarized below (table 1).

Periodontal parameters

Overall, we demonstrated impaired oral health in 71 AS (82.55%) patients; 19.76% (17 cases) presented with fewer teeth than normal for age and gender, with an average number of evaluable teeth of 22.8+4.71.

We observed an increased prevalence of sites with dental plaques (34.92%; 22 AS; 30.12+9.87), abnormal

Rheumatologic and periodontal parameters	
AS parameters	
Age (years; mean ± SD)	37.74±18.33
Disease duration (months; mean ± SD)	34.18±17.96
BASDAI (mean ± SD)	6.75±1.29
ASDAS-CRP (mean ± SD)	3.21±1.12
Periodontal status	
Number of missing teeth (mean ± SD)	7.8±3.1
Periodontal disease prevalence (%, n)	73.35 % (63)
Periodontitis severity	
• *Mild (%, n)*	19.04 % (12)
• *Moderate (%, n)*	71.42% (45)
• *Severe (%, n)*	9.52% (6)
Sites with plaque (%, n) (mean±SD)	34.92% (22); 30.12±9.87
Gingival index (mean ± SD)	0.93±0.27
Sites with bleeding on probing (%, n) (mean±SD)	31.39% (27) (12.75±5.31)
Probing pocket depth (mm; mean ± SD)	3.42±0.78
Sites with probing pocket depth≥4 mm (%,n) (mean±SD)	17.55% (15) (7.42±2.35)
Clinical attachment loss (mm; mean ± SD)	2.91±0.92
Sites with clinical attachment loss≥4 mm (%, mean ± SD)	31.39% (27) (5.87±0.23)
Inflammatory parameters	
ESR (mm/h) (mean ± SD)	52.75±12.13
CRP (mg/dL) (mean ± SD)	18.25±5.12

Table 1
AS PATIENTS: BASELINE RHEUMATOLOGIC AND DENTAL CHARACTERISTICS

Table 2

CHANGES IN PERIODONTAL AND RHEUMATOLOGIC MEASUREMENTS AT 24 WEEKS OF TNF INHIBITORS

Characteristics	Week 0	Week 24	P
AS-related parameters			
BASDAI	6.75±1.29	2.89±0.57	<0.05
ASDAS-CRP	3.21±1.12	1.75±0.89	<0.05
Periodontal parameters			
Sites with plaque (%, n) (mean±SD)	34.92% (22); 30.12±9.87	23.25% (20); 27.17±8.15	>0.05
Gingival index (mean ± SD)	0.93±0.27	0.85±0.23	>0.05
Sites with bleeding on probing (%, n) (mean±SD)	31.39% (27); 12.75±5.31	23.39% (20); 8.47±3.26	<0.05
Probing pocket depth (mm; mean ± SD)	3.42±0.78	1.83±0.47	<0.05
Sites with probing pocket depth≥4 mm (%,n) (mean±SD)	17.55% (15); 7.42±2.35	10.46% (9); 4.45±0.37	<0.05
Clinical attachment loss (mm; mean ± SD)	2.91±0.92	1.56±0.29	<0.05
Sites with clinical attachment loss≥4 mm (%, mean ± SD)	31.39% (27); 5.87±0.23	20.93% (18); 4.26±0.25	<0.05
Inflammatory tests			
ESR	52.75±12.13	17.15±9.33	<0.05
CRP	18.25±5.12	7.13±2.64	<0.05

gingival index (0.93+0.27mm) and bleeding on probing (31.39% meaning 27 AS; 12.75±5.31) in our cohort of consecutive active AS. The mean pocket depth was 3.42+0.78mm, while PPD >4mm was reported in 17.55% (15 cases) with a mean value of 12.45±2.9 mm. Clinical attachment loss was noted in 31.39% (27 cases), with a mean of 2.91±0.92 mm.

Chronic periodontitis was demonstrated in 73.35 % (63 cases); about 10% of patients presented with severe aggressive periodontitis requiring scaling and were not taken into account in the final analysis.

Patients with chronic PD featured high inflammatory parameters, with a direct relation between the level of systemic inflammation and the presence and severity of periodontal involvement; thus mean CRP levels were higher in AS and periodontitis as compared to AS without PD (20.15+6.27 mg/dL vs. 12.03 + 4.36 mg/dL, $p<0.05$). In addition, mean ESR was higher in AS with PD as compared to ESR in those without PD (56.12+17.15 mm/h in patients with periodontitis vs. 36.16+7.29 mm/h in those without periodontal disease; $p<0.05$)

CRP levels correlated with the presence and severity of periodontitis ($r=0.82$, $p<0.05$) in studied patients.

AS and inflammatory parameters

The majority of patients were man (83.72 %, 72 cases), in the in third decade (mean age of 31.74+18.33 years) with a mean disease duration of 34.18+17.96 months.

All had active AS, failing to respond to NSAIDs, as we enrolled all patients starting their first biological agent according to the national recommendations; mean BASDAI was 6.75+1.29 (cut-off levels of active AS described before), while mean ASDAS-CRP was 3.21+1.12 (cut off value for active disease described before).

All patients had high levels of inflammation; mean ESR of 52.75 + 12.13mm/h, more than twice the upper normal limit, while mean CRP was 18.25+5.12 mg/dL, up to three times the upper normal limit.

End of study data

Modifications in the periodontal status, AS activity and inflammatory parameters were examined after 24 weeks, following the benefits of TNF inhibitors.

Periodontal status

We demonstrated statistically significant improvement in periodontal status after 24 weeks of treatment with TNF inhibitors ($p<0.05$); no difference among different agents (monoclonal anti-TNF antibodies or soluble anti-TNF receptor) was reported (table 2).

A detailed analysis of all probing parameters found sizeable changes for probing pocket depth and clinical attachment loss ($p<0.05$), with only discrete modification for gingival involvement (gingival index or plaque index) ($p>0.05$) related to TNF blockade.

Thus, mean CAL at 24 weeks was smaller as compared to baseline (1.56±0.29 mm vs. 2.91±0.92 mm, $p<0.05$), while mean PPD featured the same trend (1.83±0.47mm vs. 3.42 ±0.78mm, $p<0.05$). Furthermore, we observed also a decrease in sites with CAL more than 4mm (4.26±0.25 vs. 5.87±0.23' 20.93% vs 31.39%, $p<0.05$) and patients with a PPD more than 4 mm (4.45±0.37 vs. 7.42±2.35; 10.46% vs. 17.55%; $p<0.05$).

Local periodontal treatment was not permitted during the study.

Disease activity and inflammatory tests

After 24 weeks of continuous biological therapy, TNF inhibitors resulted in significant improve in disease activity scores in all cases ($p<0.05$); mean BASDAI decreased to 2.89+0.57, while mean ASDAS-CRP achieved was 1.75+0.89.

Furthermore, ESR and serum concentration of CRP registered the same sizeable response under anti-TNF therapy in all AS ($p<0.05$); mean ESR was 17.15+9.33 mm/h at the end of study, while mean CRP was 7.13+2.64 mg/dL (table 2). Thus we obtained a rapid and consistent change across at 24 weeks of therapy (delta BASDAI of more than -3.89 points, delta ASDAS-CRP of -1.46 points). The same trend was reported irrespective of TNF inhibitor administered, monoclonal anti-TNF antibodies (infliximab, adalimumab or golimumab) or anti-TNF receptor (etanercept).

We performed this cross-sectional observational study taking in mind the potential relationship between PD and AS and the possible favorable impact of TNF inhibitors on the course of both disorders in a cohort of consecutive patients.

We demonstrated compromised oral health among patients diagnosed with AS, particularly a high rate of periodontal disease (73.35%). Abnormal periodontal parameters, meaning increased PPD and CAL values, as well as high levels of gingival involvement as supported by high frequency of sites with plaques and inflammation were reported in such patients.

According to the severity, the majority of AS with PD had mild to moderate periodontal involvement (90.46%), those with severe disease being excluded from the final analyis. Furthermore, we identified positive correlations between the severity of PD, inflammatory parameters (especially CRP) and the activity of the rheumatic condition.

In the second step of the study, the analysis performed after 24 weeks of TNF inhibitor indicated a significantly improved periodontal status in the majority of AS patients, paralleling the improvement of BASDAI and ASDAS-CRP scores. In addition, a significant decrease in inflammatory parameters (ESR and CRP) was registered in all cases, as a good indicator of the efficacy of biologic therapy.

We reported a decline in all parameters reflecting the periodontal pathology (gingival and plaque index, PPD and CAL) suggesting a potential benefit of TNF antagonists in controlling not only systemic, but also local, articular, entheseal and gingival inflammation.

Despite extensive knowledge about the association between chronic periodontitis and systemic diseases, such as immune mediated rheumatic pathology (rheumatoid arthritis), diabetes mellitus, cardiovascular disease [6, 7, 8, 10-12], even adverse pregnancy outcomes, inconsistent data present the correlation between AS and periodontal disease and the impact systemic therapies directed against AS on periodontal inflammation and damage [4, 5].

A systematic review of literature aiming to evaluate the potential association between AS and periodontitis was recently published by Ratz et all, 2105, concluding on significant risk of AS associated with periodontitis [4].

Dissimilarities in reporting the magnitude of impaired periodontal health among different papers are largely based on periodontitis and gingivitis definitions and diagnostic thresholds used (e.g. community periodontal index > 3 or >2, PPD >4 mm or >3 mm, which allow a large proportion of subjects with gingivitis to be subsequently classified as having periodontitis) [4, 5, 15]. However, irrespective of thresholds for periodontitis, different authors [4, 5, 15, 20] demonstrated comparable rate of chronic periodontitis, ranging from 41.7% [4, 5, 15] to 47.92% [4, 5, 20] of the AS patients, significant higher than in controls, 29.2% [4, 5, 15] and 31.25% [4, 5, 20]. Moreover, patients with AS had significant 6.81-fold increased odds ratio (95% CI 1.96 to 23.67) of PD (defined as mean attachment loss >3 mm) compared to controls as reported by Pischon et al, 2010.

Our data in the Romanian cohort of consecutive patients confirm a high prevalence of periodontitis during active AS.

Although various parameters (e.g. disease activity, age, gender, education, smoking, alcohol consumption, body mass index) were proposed as predictors for developing periodontitis during AS, stepwise logistic regression, including AS status, age, gender, education, smoking, alcohol consumption and body mass index, only AS status, age and education remained significant predictors of periodontal disease [4, 5, 15, 20].

Interestingly, Chang et all [13] failed to demonstrate an association between periodontal disease, AS and the use of TNF-á inhibitors in a Korean population. The prevalence of PD was comparable in healthy controls and AS (59% vs. 68%, $p>0.05$), with no significant difference in all probing measurements (PI, BOP, PPD, CAL) between groups. Moreover, only male gender was significantly ($p<0.05$) associated with PD when performing the initial AS assessment; however, other variables including the current use of TNF antagonists was not important ($p>0.05$). Likewise, biological therapy did not affect periodontal treatment outcomes in AS with PD. In conclusion, the prevalence and severity of PD was not increased among AS [13].

This study is not our first experience in evaluating oral health, particularly periodontal disease, in patients with chronic inflammatory rheumatic disorders; we have already published data about rheumatoid arthritis and periodontitis [7, 8], psoriatic arthritis (another disease included in the spondylarthropathies group as AS) and periodontitis [unpublished data], focusing on factors associated with severity and impact of specific biologic therapies on both articular and dental status.

We demonstrated high rate of periodontal disease not only among rheumatoid arthritis, psoriatic arthritis, but also in ankylosing spondylitis, with positive outcomes even after a short course (24 weeks) of TNF inhibitors.

Patients with inflammatory rheumatic pathologies are largely characterized by elevated ESR and CRP; in addition, those presenting with concomitant chronic periodontitis had higher levels of systemic inflammation [4, 5, 7, 8]. We found a robust direct correlation between CRP levels and periodontal health at baseline in our patients, meaning that increased serum CRP concentrations are demonstrated in AS with severe periodontitis. The correlation was maintained throughout the end of the study.

Further studies in larger cohorts of AS patients are recommended to correctly assess the prevalence of periodontitis, to demonstrate predictors of impaired periodontal health and to confirm the dual role of TNF inhibitors on both periodontal and articular status.

In another paper were studied the temporal-mandibular arthrosis and the impact of medication with anti-inflammatory [21].

Conclusions

Patients with AS are at risk to develop periodontal disease, particularly those with high levels of systemic inflammation. Benefits of anti-TNFα therapy in the particular settings of AS patients with periodontal inflammation should be validated through further studies in larger cohorts.

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