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Original Article

Dentistry Section

Periodontal Conditions during Arthritis Therapy with TNF-α Blockers

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ABSTRACT

Introduction: Chronic Periodontitis (CP) and Rheumatoid Arthritis (RA) are both inflammatory diseases, characterised by severe inflammation of the associated tissues. Patients with RA have been reported to have poorer periodontal conditions such as more gingival bleeding, higher probing depth (PD) and Clinical Attachment Level (CAL) or missing teeth. However TNF-α blockers used in the treatment of RA seemed to positively influence the immune response of the periodontium.

Aim: The aim of the present study was to verify if RA-patients under continuous medication with TNF-α blockers had better or worse periodontal health than non-RA-patients with periodontitis.

Materials and Methods: The present case-controlled study included 13 patients with RA and 13 age and sex-matched non-RA periodontitis patients. In the RA-patients, RA-medication and duration of use were registered. In all patients Gingival Bleeding (GBI), Plaque Control Record (PCR), Bleeding on Probing (BOP), Probing Depth (PD), Clinical Attachment Level (CAL) and the number of teeth were recorded. For all patients the severity and extent of periodontitis was recorded respecting the classification system for periodontal diseases as well as serum level of C-Reactive Protein (CRP). Wilcoxon and Chi-square tests were performed for statistical analysis.

Results: RA-patients had significantly less BOP (15.38% vs. 27.23%, p=0.045). RA-patients had a tendency to lower PD-values (2.54 mm vs. 3.15 mm, p=0.068) and fewer sites with PD≥5 mm (6.00 vs. 17.46, p=0.099). Comparing severity and extent of periodontitis RA-patients had significantly better periodontal conditions (p=0.033). No significant influence of the duration of RA-medication was found.

Conclusion: RA-patients treated with TNF-α blockers for more than 12 months have better periodontal health than non-RA-patients with periodontitis. These findings can be explained through the benefits of the TNF-α medication for host immune modulation.

Keywords: Immunomodulating medication, Periodontitis, Rheumatoid arthritis, TNF-α blockers

INTRODUCTION

Chronic periodontitis (CP) is a multi-factorial disease of the periodontium, which can lead to destruction of the alveolar bone and the supporting connective tissue and eventually the loss of tooth [1]. The fifth German oral health study showed that more than 50% of the adult population suffer from a moderate or severe form of periodontitis [2].

Recent literature shows an interaction of CP with age, smoking behaviour, genetic predisposition, socio-economic status and various systemic diseases such as diabetes mellitus, arteriosclerosis, obesity, osteoporosis and rheumatoid arthritis (RA) [1, 3-4].

RA and CP are two inflammatory diseases that occur worldwide. In addition, many immunological processes have been described in which both diseases have similarities; the dysregulated inflammatory reaction is the focus of attention. Autoreactive T cells, natural killer cells, heat shock proteins, autoantibodies, and genetic factors are reported to have an important role in the inflammatory pathway of RA and CP [1, 5].

CP is considered to be an inflammatory disease that causes a dysbiotic proinflammatory shift in the composition of the oral microbiome [6]. Periodontopathogenic bacteria in the dental plaque induce antibody formation. High levels of oral anaerobic bacterial antibodies have been found in the serum and synovial fluid of RA-patients. Bacterial DNA of *Porphyromonas gingivalis, Tannerella forsythia and Prevotella intermedia* has also been identified in RA synovial fluid [7]. *P. gingivalis* as a major pathogen causes dysbiosis and a dysregulated inflammation of periodontitis by modulating the host response. Bacterial DNA and specific antibodies against *P. gingivalis* were concluded to possibly promote tissue destruction in RA [8-9]. *P. gingivalis* also contain the enzyme Peptidyl Arginine Deiminase (PAD). PAD citrullinates fibrinogen and α-enolase, which are major autoantigens in RA [10]. Antibodies against *P. gingivalis* were associated with higher serum antibodies against citrullinated peptide levels in RA-Patients [11-12].

Numerous investigations exhibited an increased prevalence of CP in RA and RA in CP [13-14]. Good evidence was found to support an association with regard to tooth loss, Attachment Level (AL), and erythrocyte sedimentation rate. Moderate evidence was identified based on biochemical markers (CRP and IL-1β). Some evidence for a positive outcome of periodontal treatment on clinical features of RA was noted. However, common risk factors and/or dysregulation of the inflammatory response could explain the association between RA and CP [15].

The etiology of the two diseases differ, but the pathogenic mechanism seemed to be similar. In both diseases proinflammatory cytokines such as IL-1β, IL-6 and TNF-α are increased in Gingival Crevicular Fluid (GCF) and synovial fluid, leading to an inflammation of the soft tissue and bone destruction [16]. TNF-α is the main regulatory cytokine in both RA [17] and CP [5].

Some studies have revealed that TNF-α blockers and IL-6-inhibitors for RA-patients do not suppress signs and symptoms of the diseases, but inhibit the destruction of the bone in RA and CP [18-21]. The medications of the RA-patients, especially with TNF-α blockers, seemed to be effective in improving periodontal health and reducing production of inflammatory cytokines (IL-1β, IL-6 and TNF-α) in GCF. Better periodontal conditions, less plaque and calculus were found in RA-patients than in healthy controls with periodontitis [21].

Nevertheless many studies and an actual review describe poorer periodontal conditions in RA-patients. They found higher rate of GBI, greater PD, greater AL and higher numbers of missing teeth in RA [5, 13, 22-24]. The mean alveolar bone loss was significantly

more severe in RA than in systemically healthy controls. CRP was also associated with the severity of periodontal disease in RA [25].

The aim of the present study was to verify if RA-patients under constant medication with TNF-α blockers have better or worse periodontal conditions according to the age and sex-matched non-RA-patients with periodontitis. The hypothesis is that RA-patients under constant medication with TNF-α blockers do not have more severe periodontitis considering the classification by Armitage [26] than non-RA-patients with periodontitis.

MATERIALS AND METHODS

This cross-sectional epidemiological case-control study was conducted in a private dental practice and two practices of internal medicine in Oldenburg, Germany. The recruitment of the volunteers took place over a period of twenty one months from January 2015 till September 2016. Two groups of volunteers were studied, RA-patients with periodontitis and continuous therapy with TNF-α blockers of three different generations (n=13) and non-RA-patients with periodontitis (n=13). The medication, duration and the dosage of the TNF-α blockers for the RA-patients are given in [Table/Fig-1].

Medication	Active ingredient	Dosage	Number of RA-patients [n=13]	Number of RA-patients [%]
Enbrel®, (Pfizer Inc., New York City, New York, USA)	etanercept	1×50 mg/week	2	15.38
Humira®, (AbbVie Ltd., North Chicago, Illinois, USA)	adalimumab	1×40 mg/2 weeks	5	38.46
Simponi®, (Janssen Biotech Inc., Horsham, Pennsylvania, USA)	golimumab	1×50 mg/month	6	46.15

[Table/Fig-1]: Medication, duration and dosage of TNF-α blockers in the RA-group.

Ethical approval of the study was obtained by the Ethics Commission of the University of Leipzig Medical Faculty (#290/15-ff). A total of 26 volunteers (sixteen females and ten males) gave written and informed consent. Informed consent was obtained before initiation of any study-related procedure.

Patient recruitment: The recruitment of RA-patients was performed in two practices of internal medicine that predominantly treat patients with RA and other rheumatoid diseases. The recruitment of age and sex-matched non-RA-patients with periodontitis as well as all periodontal examinations were performed in a private dental practice (R.S.). RA- and non-RA-patients were included in the study when they met the following criteria:

- patients >35 years and <75 years
- chronic periodontitis

RA-patients had to be diagnosed as RA-patients according to parameters of American Rheumatism Association (ARA) [27]. RA-patients were recruited from a pool of patients who attended the rheumatological practice for routine examination every three months. These patients were under continuous therapy with TNF-α blockers of different generations for at least more than 12 months.

Exclusion criteria were pregnancy or lactation, ongoing systematic periodontal treatment and the use of antibiotics within the last three months, other immunosuppressive disease, diabetes mellitus, infectious diseases (HIV, hepatitis), addictive disorders (alcohol, drugs), tumour disease, and participation in other studies.

Clinical examination: Volunteers were included on the basis of "first come, first examined" after signing written informed consent. Epidemiologic and amnestic data (gender, age, and medication) were recorded.

The clinical variables: Probing Depth (PD), Clinical Attachment Level (CAL), Bleeding On Probing (BOP) were determined in a six-point-measurement per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual) at all existing teeth using a manual periodontal probe (PCP-UNC 15, Hu-Friedy Manufacturing Co., Chicago, IL, USA). In addition, the number of missing teeth, Gingival Bleeding Index (GBI) [28] and Plaque Control Record (PCR) [29] were recorded. All measurements were recorded with a UNC-15 periodontal probe (Hu-Friedy) by a single trained and calibrated examiner (R.S.). Reproducibility of clinical measurements was verified by carrying out double clinical periodontal data recording for PD and AL on volunteers by two independent examiners (R.S. and H.J.). Assessment of mean difference in score (kappa value 0.94) indicated that there was no systematic bias in the measurements. Based on AL and the classification of periodontal disease (Armitage) [26] the periodontitis was classified considering severity and extent of the disease.

For RA, the time point of the initial diagnosis and the current medication were taken from the patient records. For further analysis the RA-group was divided in two subgroups with duration of RA ≤ or >5 years.

Blood samples from both groups were obtained. A single laboratory technician, masked to the groups and the health status, performed CRP assay. Total CRP level was determined by using a quantitative turbidimetric immunoassay (Beckman Coulter AU analyser, Beckman Coulter, Inc. 250 S. Kraemer Blvd., Brea, USA). The blood samples were mixed with R1 buffer (glycine) and R2 latex suspension (coated with anti-CRP-antibody). CRP reacts with anti-CRP-antibodies on the latex particles. The absorption of these aggregates is proportional to the CRP concentration in the sample.

Compliance with Ethical Standards

Ethical approval: Ethic approval of the study was obtained by the Ethics Commission of the University of Leipzig Medical Faculty (#290/15-ff).

Informed consent: Informed consent was obtained by every participant.

STATISTICAL ANALYSIS

All data from the case report form (CRF) were transferred in a data matrix in the spreadsheet program Microsoft Office Excel 2013. The Wilcoxon test was used to analyse differences between the periodontal variables in both groups. The Chi-square-test was used to compare the severity of periodontitis between the groups and association between gender and duration of RA in the two subgroups. A p≤0.05 was considered to be statistically significant. A p-value between 0.05 and 0.1 indicated a tendency towards significance.

RESULTS

Two groups of volunteers were studied. The demographic data and all results of both groups are summarised in [Table/Fig-2]. The mean age of the 26 volunteers was 52.2 years with a range of 37-67 years. There was no significant difference in the number of teeth between both groups (p=0.454). Similarly, there was no significant difference between the groups GBI (p=0.182) and PCR (p=0.150), although the mean values of GBI were much lower than in the non-RA-group with periodontitis. RA-patients had significantly lower BOP (p=0.045) and a tendency to lower PD-values (p=0.068). There was no significant difference in AL between both groups (p=0.134). No significant difference in the number of sites with PD ≥5 mm between both groups was seen (p=0.099), although the RA-group tended to fewer sites than the non-RA group.

Considering severity and extent of periodontitis in accordance to Armitage [26] there was a significant difference between both groups

Variable	RA-patients [mean±SD]	Non RA-patients [mean±SD]	p-value
Age [years]	52.38±7.92	52.31±8.05	0.816[2]
Gender	M 5 (38.5%) F 8 (61.5%)	M 5 (38.5%) F 8 (61.5%)	1[2]
Duration of RA [years]	8.38±8.27	-	-
Number of teeth [n]	25.08±4.27	26.62±2.62	0.454[2]
Gingival bleeding index [%]	19.38±8.20	31.77±20.76	0.182[2]
Plaque control record [%]	38.54±11.81	45.69±14.74	0.150[2]
Bleeding on probing [%]	15.38±8.04	27.23±18.49	**0.045**[2]
Probing depth [mm]	2.54±0.66	3.15±0.90	0.068[2]
Attachment level [mm]	2.85±0.69	3.31±0.75	0.134[2]
Sites with probing depth ≥5 mm [n]	6.00±9.46	17.46±22.21	0.099[2]
CRP [mg/l]	4.29±5.12	3.17±3.17	0.310[2]
Generalised mild chronic periodontitis [n]	0	1 (7.69%)	**0.033**[1]
Generalised mild, localised moderate chronic periodontitis [n]	7 (53.85%)	0	
Generalised mild, localised severe chronic periodontitis [n]	0	0	
Generalised moderate chronic periodontitis [n]	3 (23.08%)	4 (30.77%)	
Generalised moderate, localised severe chronic periodontitis [n]	2 (15.38%)	6 (46.15%)	
Generalised severe chronic periodontitis [n]	1 (7.69%)	2 (15.38%)	

[Table/Fig-2]: Demographic data and periodontal variables of RA-patients and non RA-patients with periodontitis and statistical analysis.
[1]Chi square test; [2]Wilcoxon test

Variable	Duration ≤5 years [mean±SD]	Duration >5 years [mean±SD]	p-value
Age [years]	48.00±7.21	55.13±7.45	0.161[2]
Gender	M 3 (23.08%) F 2 (15.38%)	M 2 (15.38%) F 6 (46.16%)	0.499[1]
Duration of RA-medication [years]	3.20±0.84	11.63±9.26	
Number of teeth [n]	26.60±2.41	24.13±5.03	0.463[2]
Gingival bleeding index [%]	23.00±7.58	17.13±8.20	0.212[2]
Plaque control record [%]	39.00±10.34	38.25±13.33	0.825[2]
Bleeding on probing [%]	18.20±7.50	13.63±8.33	0.340[2]
Probing depth [mm]	2.60±0.89	2.50±0.53	1[2]
Attachment level [mm]	2.80±0.84	2.88±0.64	0.871[2]
Sites with probing depth ≥5 mm [n]	8.00±12.04	4.75±8.12	0.569[2]
CRP [mg/l]	2.32±1.07	3.17±3.17	0.280[2]
Generalised mild chronic periodontitis [n]	0	0	0.748[1]
Generalised mild, localised moderate chronic periodontitis [n]	2 (15.38%)	5 (38.46%)	
Generalised mild, localised severe chronic periodontitis [n]	0	0	
Generalised moderate chronic periodontitis [n]	2 (15.38%)	1 (7.69%)	
Generalised moderate, localised severe chronic periodontitis [n]	1 (7.69%)	1 (7.69%)	
Generalised severe chronic periodontitis [n]	0	1 (7.69%)	

[Table/Fig-3]: Comparison of demographic data and periodontal variables in the RA-group by different disease durations and statistical analysis.
[1]Chi square test; [2]Wilcoxon test

(p=0.033). The proportion of generalised moderate, localised severe periodontitis and generalised severe periodontitis was more than twice as high as in the non-RA-group with periodontitis (61.53% vs. 23.07%). The mean CRP in both groups did not differ significantly (p=0.310).

There were no significant differences between the two RA-subgroups regarding the demographic and clinical periodontal data, duration of RA and mean CRP. The results are given in [Table/Fig-3].

DISCUSSION

The present study verified if RA-patients under constant medication with TNF-α blockers have better or worse periodontal findings than non-RA-patients with periodontitis. There is evidence from the literature that TNF-α blockers seem to reduce periodontal inflammation and bone resorption by suppressing proinflammatory cytokines and restoring the cytokine balance [16]. In conclusion better periodontal health should occur. The use of anti-TNF-α as a therapeutic means of treating a chronic inflammatory disease has been confirmed in RA. To treat periodontal disease immunomodulation occurs via medication with tetracycline/doxycycline [30]. The significant risk of undesirable side-effects by the use of TNF-α medication precludes the use of anti-TNF-α agents in periodontal therapy.

CP is considered as an opportunistic infection. Depending on the pathogenicity of the pathogens and the capacity of the host's immune system, there is either direct tissue damage or an excessive autodestructive inflammatory reaction [4]. Recent literature shows an interaction of CP with age, smoking behaviour, genetic predisposition, socio-economic status and various systemic diseases such as diabetes mellitus, arteriosclerosis, obesity, osteoporosis [1, 3, 31]. Few studies have been carried out on a possible connection between RA and CP; although there have been indications; this is still a controversial issue [5, 14, 22, 32].

Han et al., examined in their review that there is a limited evidence on the effectiveness of anti-TNF-α medications in reducing periodontal inflammation and biomarkers in RA-patients with periodontitis [16]. Two studies reported low mean gingival index scores in RA-patients receiving anti-rheumatic agents [19, 33]. Three studies reported no overall effect of TNF-α medications on BOP in RA [19, 33-34]. Two studies have reported lower levels of TNF-α in gingival crevicular fluid (GCF) and serum of RA-patients receiving TNF-α medication [19, 34]. On the other hand RA-patients with immunomodulating medication presented lower local IL-1β and TNF-α levels as well as less gingival inflammation, based on GI and BOP, than healthy controls with CP [34].

The results of the present study suggest that RA-patients receiving TNF-α blockers exhibited milder periodontal disease, lower BOP (p=0.045) and a tendency to lower PD (p=0.068) compared to non-RA-patients with periodontitis. This occurs also after shorter anti-rheumatic TNF-α medication. RA-patients in both subgroups (duration of RA ≤ or >5 years) did not show any difference. These findings suggest that TNF-α medication may decelerate the destructive processes due to periodontitis. The present results are in agreement with Mayer et al., who revealed that RA-patients receiving anti-TNF-α therapy exhibited lower GCF levels of TNF-α and milder periodontal disease compared to matched patients with RA, who did not receive this therapy [19]. Mirrielees et al., showed that the concentration of IL-1β and TNF-α in GCF was influenced by the intake of immunomodulatory medications [34]. Kobayashi et al., found reduced gingival inflammation and constant plaque levels during a three months administration of the TNF-α medication with adalimumab in RA-patients and stated the beneficial effect of TNF-inhibition on periodontal conditions [18]. Miranda et al., found that the anti-inflammatory treatment of RA also affected periodontal inflammation. They investigated the anti-inflammatory effect of rheumatic medications on inflammatory mediators in sulcus fluid. It was confirmed that patients with

anti-inflammatory rheumatoid arthritis medication had lower levels of inflammatory mediators than control patients [35].

RA-patients who received TNF-α blockers had better periodontal indices (GBI, PD and CAL) compared to patients with RA who got other medication such as MTX, NSAIDs, DMARD. Bleeding indices (BOP) in RA-patients during therapy with anti-TNF-α medication were also reduced [19]. Nilsson et al., showed that gingivitis and periodontitis were associated with high level of circulating TNF-α. Patients with high levels of TNF-α had higher frequency of BOP as well as increased clinical AL and PD compared to those with low levels. This is plausible because TNF-α is related to periodontal inflammation with regard to tissue destruction and vascular reaction in RA-patients [36]. However RA-patients with periodontitis treated with anti-TNF-α medications have lower periodontal inflammation and lower levels of inflammatory cytokines in GCF and saliva [16]. Scher et al., found that RA without medication had worse periodontal findings than those with medication [37]. Kobayashi et al., also revealed that changes in periodontal and serum parameters were different between patients with RA and CP during treatment with and without adalimumab [38].

Among the limitations of this study the low number of patients should be taken into account. A case number analysis and power calculation in the run-up (with an assumed power of 80%) revealed a study population size of 78486.4 participants. The study size (n=26) was calculated assuming a very small effect (r<0.3) due to the lack of preliminary examinations and a power of 40%. The small study population also could be traced back to the fact that narrow inclusion criteria were established in order to reduce as many disruptive factors (e.g. 16 existing teeth, diabetes, antibiotics) as possible. Considering the prevalence of RA (approx. 0.5-1% [39]) it was difficult to recruit suitable patients. Hence, further studies with higher numbers of participants would be useful.

Nevertheless, all TNF-α drugs show excellent efficacy with similar rates of clinical response and prevention of radiographic disease progression in RA [40]. In coincidence with the results of several other studies the present study clearly shows that the TNF-α medication in RA-patients with periodontitis leads to improved periodontal conditions in comparison to age- and sex-matched non-RA-patients with periodontitis.

CONCLUSION

The data show that RA-patients who were treated with TNF-α blockers of three different generations for more than 12 months have lower severity and extent of CP and partially better clinical variables than non-RA patients with chronic periodontitis. However, the interdisciplinary cooperation between rheumatologists and dentists seems to be mandatory.

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