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ORIGINAL ARTICLE

Effects of non-surgical periodontal therapy on periodontal laboratory and clinical data as well as on disease activity in patients with rheumatoid arthritis

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Abstract

Objectives To compare the effect of non-surgical periodontal therapy on clinical and inflammatory parameters in patients with moderate to severe chronic periodontitis (CP) and rheumatoid arthritis (RA) (RA-CP) with that in CP patients without RA.

Material and methods Eighteen patients with RA-CP and 18 systemically healthy patients with CP were treated with scaling and root planing (SRP) within 24 h. At baseline, and at 3 and 6 months after SRP, clinical periodontal parameters, inflammatory markers, and microorganisms in subgingival biofilm were assessed. In addition, disease activity markers of RA (DAS28, CRP, ESR) and specific antibodies (RF) were monitored in the RA-CP group.

Results In both groups, non-surgical therapy yielded to statistically significant improvements in all investigated clinical periodontal variables; in RA patients, a statistically significant decrease in serum-CRP was seen at 3 months. At all time-points, levels of inflammatory markers in GCF were higher in RA-CP than in CP patients. Counts of *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* decreased statistically significantly in CP but not in the RA-CP group. Changes of DAS28 correlated positively with those of *P. gingivalis* and negatively with the plaque index.

Conclusions Within their limits, the present data suggest that (a) non-surgical periodontal therapy improves periodontal conditions in CP patients with and without RA and (b) in patients with RA, eradication of *P. gingivalis* in conjunction with a high level oral hygiene may transiently decrease disease activity of RA.

Clinical relevance In patients with RA and CP, non-surgical periodontal therapy is a relevant modality not only to improve the periodontal condition but also to decrease RA activity.

Keywords Rheumatoid arthritis · Periodontitis · Non-surgical periodontal treatment · Porphyromonas gingivalis · Rheumatoid disease activity

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Introduction

Accumulating evidence suggests a possible relationship between rheumatoid arthritis (RA) and periodontal disease [1–7]. Both RA and periodontitis are chronic inflammatory diseases where inflammation occurs in an area composed of connective tissue [8].

RA affects about 1% of the population and, despite various therapeutic approaches, may still be associated with significant morbidity and mortality [9, 10]. Contrary to periodontal disease, RA is an autoimmune disease characterized by accumulation of an inflammatory infiltrate in the synovial membrane of the joints leading to synovitis and progressive destruction of the joints and resulting in variable degrees of deformities and functional disabilities, accelerated

atherosclerosis, psychological implications, and socioeconomic decline [9]. While its exact etiology remains unknown, genetical and environmental factors (e.g., smoking) have been proved to be risk factors [11, 12]. Disease activity of RA is mostly assessed by determining the Disease Activity Score 28 (DAS28) including C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) [13]. Additionally, rheumatoid factor (RF) [14–16] or antibodies against citrullinated proteins/peptides may also be determined in diagnosing RA, the latter having been indicated to be a superior alternative to RF [17]. RA may be therapied by administration of disease-modifying antirheumatic drugs (DMARDS), including methotrexate (MTX), leflunomide, and sulfasalazine. Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) [18] may also often be indicated, and in cases with remained moderate or high activity, corticoids and/or biological therapy (e.g., TNF inhibitors) [19] may be prescribed.

Chronic periodontitis (CP) is one of the world's most prevalent inflammatory diseases, affecting about 15–30% of the adult population, and is one of the most common causes for tooth loss [20]. CP is initiated by dental plaque biofilm leading to inflammation of the tooth supporting structures (e.g., periodontal ligament, connective tissue, and alveolar bone) leading to bone resorption and, if left untreated, to tooth loss. Several studies suggest a bidirectional relationship between RA and periodontal disease [21–25]; however, findings so far are ambiguous [1]. Recent animal studies support this relationship evidencing that the induction of experimental arthritis in rats led to associated periodontal breakdown and increased cytokine and matrix metalloproteinase (MMP) levels in the periodontal tissue [21, 26]. Moreover, some early studies on self-reported RA together with case-control studies have pointed to a higher incidence of periodontal disease in RA patients and vice versa [25, 27, 28]. However, large epidemiologic studies found only a weak association between the two diseases [29, 30]. Although disease initiation of RA and CP seems to be different, both may be the result of an imbalance between anti-inflammatory and pro-inflammatory cytokines [31] and of a release of MMPs from inflammatory cells [32, 33]. It is suggested that, in addition to the local inflammatory response to the bacteria in subgingival biofilm, the systemic inflammation in RA may booster the development of periodontitis [34]. *Porphyromonas gingivalis*, a gram-negative anaerobic bacterium, is an important etiological agent in chronic periodontal disease [35]. Based on the presence of a unique *P. gingivalis*-peptidylarginine deiminase [36] which citrullinates fibrinogen and α-enolase (major autoantigens in RA) [37], *P. gingivalis* was proposed as the principal link between periodontitis and RA [38].

Furthermore, RA and CP seem to harbor a similar cytokine profile consisting of elevated levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) [39]. IL-1β and TNF-α are important cytokines involved in bone resorption: IL-1β plays an important role in inflammation regulation, acting synergistically with TNF-α [40]. TNF-α is involved in the upregulation of osteoclastogenesis and downregulation of osteoblastogenesis [41].

Some clinical trials suggest a positive influence of non-surgical periodontal treatment on the severity of RA [23, 24, 42–45]. However, evidence regarding the effects of non-surgical periodontal treatment on the clinical, microbiological, and immunological profile in RA patients is scarce since bacteria in subgingival biofilms were not assessed in these studies.

Therefore, the aim of the present study was to compare the effect of non-surgical periodontal treatment on clinical, microbiological, and inflammatory parameters in patients with moderate to severe chronic periodontitis (CP) and rheumatoid arthritis (RA) (RA-CP) with CP patients without RA.

Material and methods

Trial design, patient population, inclusion, and exclusion criteria

In this prospective, case-controlled, clinical intervention trial, the following hypothesis was tested: "non-surgical periodontal treatment improves clinical periodontal, microbiological, and inflammatory variables in CP patients with RA and without RA."

Sample size calculation was based on the data of Biyikoglu et al. [44] considering a reduction of CRP by 50% and calculating an alpha of 0.05 with a power of 95% thus requiring 14 RA patients. Considering possible dropouts, 18 study participants with RA and CP were recruited.

One hundred thirty-five patients from the Clinic of Rheumatology Cluj-Napoca (University of Medicine and Pharmacy "Iuliu Hatieganu," Cluj-Napoca, Romania) with the diagnosis of RA were contacted to participate in this study between 01.05.2012 and 01.05.2013. Sixty-nine RA patients consented to screening and periodontal examination. Out of these, 45 patients were diagnosed with moderate to severe CP and met the inclusion criteria; 18 patients consented to be periodontally treated within the study. Finally, 36 patients were included in the present study: 18 RA patients with CP (RA-CP group) and 18 systemically healthy patients with moderate to severe chronic periodontitis (CP group) recruited at the Dental Clinic of Cluj-Napoca (University "Iuliu Hatieganu," Cluj-Napoca, Romania) (Fig. 1).

All study participants had to fulfill the following inclusion criteria: moderate to severe chronic periodontitis [46]; > 30 years of age; ≥ 10 natural teeth present in the oral cavity; full-mouth plaque scores (FMPS) ≤ 30% [47] after oral hygiene instructions; no other systemic diseases or medications except for RA, which are known to influence periodontal conditions/treatment outcome (e.g., Down syndrome, HIV, diabetes mellitus types 1 and 2); no infectious or heart diseases

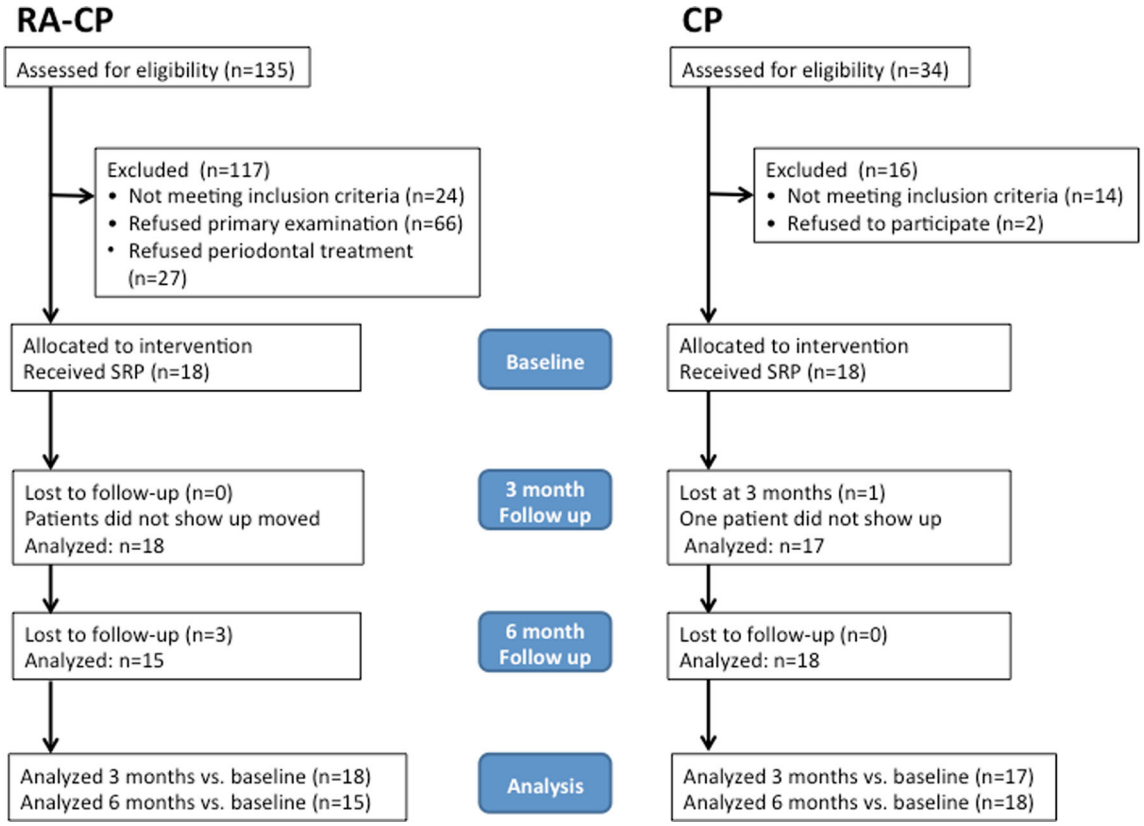

Fig. 1 Flowchart of the study. RA: rheumatoid arthritis; CP: chronic periodontitis; RA-CP: test group, RA patients diagnosed with CP; CP: control group, patients with CP

that need prophylactic administration of antibiotics before dental treatment; no liver disease; and no head and neck radiation therapy. Exclusion criteria were non-surgical periodontal therapy within the previous 12 months, systemic or local use of antibiotics within the previous 3 months, medication with a possible influence on the periodontium (e.g., cyclosporines, phenytoins, calcium channel blockers), pregnancy, or lactation. In the RA group, RA was diagnosed according to the criteria set by the American College of Rheumatology [48, 49]; inclusion criterion was DAS28 $\geq$ 3.2.

The study was conducted according to the Declaration of Helsinki (1964, revision 2008) and approved by the local Ethical Committee of the Faculty of Medicine and Pharmacy, University "Iuliu Hatieganu," Cluj-Napoca (application—approval no. 580/13.04.2012). Informed written consent to participate in the study was obtained from all subjects prior to inclusion in the study. The study was registered in the ISRCTN trial registry (study ID ISRCTN60187959, http://www.isrctn.com/ISRCTN60187959).

Periodontal treatment, GCF/microbial sampling and analysis, and assessment of RA activity

At baseline [i.e., prior to scaling and root planing (SRP)], and at 3 and 6 months after SRP, medical and smoking history, clinical periodontal variables (i.e., FMPS) [47], periodontal pocket depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) were recorded; furthermore, gingival crevicular fluid (GCF) and subgingival plaque were sampled by one calibrated examiner in both patient groups. PD and CAL were measured at six sites per tooth at the nearest millimeter using a manual rigid periodontal probe (PCP UNC-15, Hu-Friedy). The cemento-enamel junction was used as a reference for CAL measurements; if this was modified by a restoration, the margin of the restoration was used as a reference. For RA patients, the rheumatological parameters DAS28, ESR, CRP, and RF were determined at the same time-points by one specialized rheumatologist at the University Clinic of Rheumatology, University of Medicine and Pharmacy "Iuliu Hatieganu."

Oral hygiene instructions and professional prophylaxis sessions were performed until each patient had a FMPS $\leq$ 30%. Thereafter, SRP was performed within 24 h by one experienced periodontist as follows: under local anesthesia, all teeth exhibiting pockets with PD $\geq$ 4 mm were scaled and planed by means of sonic (KaVo SONICflex Scaler, KaVo Dental GmbH, Biberach, Germany) and hand instruments (Gracey curettes, Hu-Friedy, Chicago, IL, USA); treated pockets were then thoroughly rinsed with 0.2% chlorhexidine digluconate solution (Corsodyl®, GlaxoSmithKline, Brentford, London,

UK), and patients were instructed to rinse twice daily for 2 min with a 0.2% chlorhexidine digluconate solution (Corsodyl®, GlaxoSmithKline, Brentford, London, UK) and to brush their teeth with 0.2% chlorhexidine digluconate tooth paste (Elugel®, Pierre Fabre, Paris, France) for 14 days.

Patients were recalled at 3 and 6 months after therapy, when the above-mentioned clinical assessments and samplings were performed. Additionally, supragingival calculus was removed, but residual periodontal pockets, i.e., pockets with PD = 4 mm and BOP positive, or PD ≥ 5 mm, were not re-instrumented.

For GCF and microbial sampling, four deepest sites, one in each quadrant, were selected. These sites were isolated with cotton rolls and air-dried. After careful removal of supragingival plaque with cotton pellets, first a standard paper strip (PerioPaper, Oraflow) was placed at the entrance of the periodontal pocket for 30 s; thereafter, a sterile paper point was inserted for 30 s into the gingival crevice until mild resistance was felt. Both paper strips and points of the same patient from one time-point were pooled into a transportation vial. All oral clinical measurements and periodontal treatment were conducted at the Department of Prosthodontics, Dental Clinic, University of Medicine and Pharmacy "Iuliu Hatieganu."

GCF samples were stored at − 70 °C and microbial samples at − 20 °C until assayed. GCF samples were eluted at 4 °C overnight into 750 μl phosphate-buffered saline, and the host-derived biomarkers IL-1β, IL-10, TNF-α, and MMP-8 were determined by commercially available ELISA kits (R&D Systems Europe Ltd., Abingdon, UK) according to the manufacturer's instruction. The detection levels of the kits were 2 pg/ for IL-1β, IL-10, and TNF-α and 0.1 ng/ml for MMP-8.

Microbial analysis was performed by means of real-time polymerase chain reaction (PCR) to detect the periodontopathogens *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)*, *Porphyromonas gingivalis (P. gingivalis)*, *Tannerella forsythia (T. forsythia)*, and *Treponema denticola (T. denticola)* as described recently [50].

To determine RA activity, DAS28-ESR was assessed by an experienced rheumatologist (BD). The laboratory markers CRP and ESR were determined from peripheral blood samples at baseline, and at 3 and 6 months at the University laboratory ("Iuliu Hatieganu" University, Cluj-Napoca) by the routinely used methods: CRP by means of latex immunoturbidimetry, ESR using the Westergren method, and RF by immunofluorescence.

Intra-examiner reproducibility and statistical analysis

Ten patients with a minimum of 10 teeth and PD ≥ 6 mm on at least one site of a tooth in each quadrant were used for calibration. In order to determine the intra-examiner reproducibility, the examiner assessed PD and CAL on two separate occasions 48 h apart, prior to commencing the study. Calibration was accepted if the two sets of measurements of PD and CAL did not differ by ≥ 1 mm in over 90% of the cases. The mean intra-examiner reliability was 0.78 for PD and 0.71 for CAL (Cohen's kappa analyses).

For statistical analyses, data were introduced into a database by one person (RT) and checked for errors by comparison with the original patients' charts by two additional independent persons. The statistical unit was the patient, and the primary outcome variable was the decrease of CRP in the RA group at 3 months. Secondary variables were changes (Δ) of CRP at 6 months, ESR and DAS28 at 3 and 6 months in the RA-CP group, and BOP, FMPS, PD, CAL, number of sites, PD ≥ 4 mm including their changes (Δ) as well as qualitative and quantitative analysis of microorganisms, and inflammatory markers in GCF at 3 and 6 months for both patient groups. Comparisons within the groups between the various time-points were performed using Wilcoxon signed-rank test. Differences between the two groups at the various time-points were analyzed by means of the Mann-Whitney *U* test. Correlations were calculated by using Spearman test. General linear models (GLM) for analysis of variance and covariance that determine the decrease in disease activity of rheumatoid arthritis were applied. The level of significance was set to $p = 0.05$. Software SPSS 22.0 (IBM Armonk, NY, USA) was used.

Results

Patients

Thirty-six patients (mean age 47.58 ± 11.41 years, 12 male, 24 female) with CP were included in this study. Out of the 36 patients, 18 had RA while 18 were systemically healthy. Most patients ($n = 16$) in the RA group showed a disease duration of > 10 years. All RA patients were treated with DMARDs and NSAIDs and/or corticoids or anticytokine therapy. Demographical data, RA disease duration, and RA treatment are depicted in Table 1. Besides age matching, which proved to be statistically significant between the two treated groups ($p = 0.03$), no statistically significant differences were seen for smoker/non-smoker or the gender distribution.

Non-surgical periodontal therapy was performed between June 2012 and September 2013. All included patients in the present analyses followed rigorously the post-treatment instructions. However, at 6 months, three RA-CP subjects did not comply with the reexamination while in the CP group, all patients completed participation in the study, but for one subject who did not comply with the 3-month recall evaluation (Fig. 1). No adverse effects were registered for any of the patients. A slight but transient increase in tooth hypersensitivity was reported in both patient groups.

Table 1 Demographic data

	Group RA-CP	Group CP
No. of subjects (*n*)		
Included	18	18
3 months	18	17
6 months	15	18
Gender		
Male/female (*n*)	4/14	8/10
Age (years)	51.61 ± 11.04	43.55 ± 10.56
Smoking (*n*)		
Non-smoker	8	12
Former smoker	6	3
Smoker	4	3
RA duration (years)	14.88 ± 5.55	–
RA treatment (*n*/% of patients)		
DMARDS	18 (100%)	–
Anticytokine therapy	3 (16.66%)	–
NSAIDS	13 (72.22%)	–
Corticoids	6 (33.33%)	–

DMARDS disease-modifying antirheumatic drugs, *NSAIDS* non-steroidal anti-inflammatory drugs

Thus, for the comparison baseline, 6 months in the RA-CP group data from 15 patients and in the CP group from 18 patients were available; for the comparison baseline, 3 months in the CP-group data from 17 subjects and in the RA-CP group from 18 subjects were included (Fig. 1). Exclusion of the patients from the baseline data did not result in statistically significant differences (Table S1).

Clinical findings, microbial and inflammatory markers in GCF

Clinical periodontal parameters assessed at baseline and at 3 and 6 months are depicted in Table 2. Except for the number of pockets with PD ≥ 4 mm and the mean PD, none of the evaluated parameters differed statistically significantly at baseline between the two groups ($p > 0.05$). Both variables showed statistically significant reductions in the two patient groups at 3 and 6 months; the difference between the groups remained statistically significant at both time-points. However, considering the procentual reduction of sites with PD ≥ 4 mm, no statistically significant difference was found between the groups. CAL and BOP improved significantly at 3 and 6 months after SRP in both groups with no statistically significant difference between the groups. Both groups had a FMPS at baseline about 0.25 in median, which increased at 3 and 6 months (Table 2).

The microbial analysis has shown that *P. gingivalis* was detectable in both groups at baseline, but only in CP patients did counts of *P. gingivalis* decrease statistically significantly at 3 and 6 months (Table 3). Subsequently, at these time-points, the counts of *P. gingivalis* were statistically significantly lower in the CP group compared to RA-CP patients. At baseline, statistically significantly lower counts of *T. forsythia* and higher counts of *T. denticola* were assessed in the RA-CP group in comparison with the CP group (Table 3). At 3 and 6 months, only CP patients showed a statistically significant reduction of these bacterial counts as compared to baseline; the statistically significant difference between the groups for *T. denticola* was still detectable ($p < 0.05$). *A. actinomycetemcomitans* was detected in 5 of 18 samples of the RA-CP group and 9 of 18 samples of the CP group. Intra- and inter-group differences never reached statistical significance.

At baseline, the levels of IL-1β and MMP-8 were statistically significantly higher in RA-CP patients than in the patients from the CP group; this was maintained for MMP-8 also at 3 and 6 months (Table 3). However, at the follow-ups in both patient groups, no statistically significant changes as compared to baseline were seen for IL-1β and MMP-8. Levels of IL-10 increased statistically significantly ($p = 0.033$) only in the CP-group at 6 months (Table 3).

Marker of disease activity RA-CP patients

In these patients, DAS28, CRP, and ESR were decreased at both follow-ups; however, the only statistically significant reduction ($p = 0.023$) was registered for CRP at 3 months (Table 4).

Spearman correlation between different variables and changes of DAS28 and CRP were performed. Correlations were detected only with changes of DAS28: baseline–3-month changes correlated positively with those of *P. gingivalis* between these time-points ($R = 0.667$, $p = 0.005$). Changes of DAS28 between baseline and 6 months were negatively correlated with BOP at 6 months ($R = -0.557$, $p = 0.031$) and with MMP-8 at 6 months ($R = -0.559$, $p = 0.031$).

Variables with a potential influence were modeled on changes of DAS28 and CRP between baseline and 3 or 6 months. Modeling changes of *P. gingivalis* counts (log10) and changes of GCF IL-1β level between baseline and 3 months and FMPS at 3 months, on response to disease activity of RA (baseline–3-month changes of DAS28) as a continuous variable by GLM, showed a significant influence of these variables ($p = 0.006$). The strongest influence was seen for *P. gingivalis* changes (estimate = 0.318; $p < 0.001$), followed by FMPS at 3 months (estimate = − 0.781; $p = 0.028$) and IL-1β changes between baseline and 3 months (estimate = − 0.024; $p = 0.044$). Different other analyzed models did not result in any statistical significance.

Table 2 Median [interquartile] values of clinical periodontal data at baseline as well as 3 and 6 months after SRP and *p* values for inter-group comparisons (Mann-Whitney *U* test) and for intra-group comparisons with baseline (Wilcoxon test)

Variables	Time-point	Group RA-CP	*p* value vs. baseline	Group CP	*p* value vs. baseline	*p* value RA-CP vs. CP
PD (mm)	Baseline	2.75 [2.50; 3.33]		3.37 [2.95; 3.89]		0.006**
	3 months	2.18 [1.94; 2.41]	0.001**	2.50 [2.23; 2.98]	< 0.001**	0.019*
	6 months	2.21 [2.13; 2.39]	0.001**	2.50 [2.19; 3.07]	< 0.001**	0.020*
Δ PD (mm)	Baseline–3 months	0.55 [0.33; 0.86]		0.82 [0.35; 1.82]		0.191
	Baseline–6 months	0.48 [0.17; 0.83]		0.65 [0.41; 1.42]		0.145
PD ≥ 4 mm (*n*)	Baseline	27.0 [16.0; 43.0]		57.0 [32.0; 76.5]		0.001**
	3 months	5.50 [2.50; 15.8]	< 0.001**	19.0 [15.0; 27.5]	< 0.001	0.001**
	6 months	5.00 [3.00; 14.0]	0.001*	18.5 [13.8; 32.3]	< 0.001	< 0.001**
Δ *n* PD ≥ 4 mm (*n*)	Baseline–3 months	13.5 [8.00; 26.3]		26.0 [19.5; 44.5]		0.009**
	Baseline–6 months	14.0 [7.00; 33.0]		27.5 [18.8; 47.5]		0.048*
Δ *n* PD ≥ 4 mm (%)	Baseline–3 months	67.9 [47.6; 88.1]		61.1 [37.5; 72.9]		0.168
	Baseline–6 months	73.2 [40.0; 92.9]		59.9 [34.5; 74.4]		0.135
CAL (mm)	Baseline	4.11 [3.41; 5.50]		4.07 [3.54; 5.20]		0.628
	3 months	3.75 [2.82; 4.79]	0.010*	3.93 [3.48; 5.15]	0.001**	0.423
	6 months	3.33 [2.85; 4.20]	0.001**	3.92 [3.50; 4.70]	0.043*	0.100
Δ CAL (mm)	Baseline–3 months	0.25 [0.10; 0.68]		0.24 [0.11; 0.68]		0.628
	Baseline–6 months	0.62 [0.17; 0.88]		0.24 [0.09; 0.76]		0.229
BoP (%)	Baseline	47.7 [19.0; 95.8]		61.6 [32.0; 85.8]		0.424
	3 months	14.4 [10.0; 18.5]	0.002**	14.9 [9.37; 22.1]	< 0.001**	0.845
	6 months	13.5 [6.25; 18.1]	0.009**	10.6 [6.20; 13.7]	< 0.001**	0.307
FMPS (%)	Baseline	25.0 [16.7; 27.6]		24.0 [18.0; 30.0]		0.719
	3 months	32.2 [23.4; 72.4]	0.034*	31.1 [23.6; 46.3]	0.005**	0.897
	6 months	34.7 [20.0; 56.0]	0.061	34.0 [26.5; 55.7]	0.017*	0.551

PD periodontal pocket depth, *CAL* clinical attachment level, *FMPS* full-mouth plaque scores, *BoP* bleeding on probing
*$p < 0.05$; **$p < 0.01$

Discussion

The present study has evaluated the effect of periodontal therapy on RA disease activity in association with changes of periodontal parameters, levels of biomarkers in GCF, and counts of bacteria known to be associated with periodontal disease. The outcome of non-surgical periodontal therapy in RA-CP patients was compared with that in systemically healthy CP patients.

The primary outcome variable was the decrease of CRP in RA-CP group at 3 months, based on data of Biyikoglu et al. [44]. Despite the fact that CRP is not a representative marker for RA, we considered it as the main outcome variable and determined it only in RA patients since it represents a marker of systemic inflammatory activity in RA and data suggest a correlation between the CRP levels and the severity of periodontal disease depicted in clinical parameters [51–53]. Our data confirm statistically significant reductions of CRP at 3 months; however, only tendencies of reductions were seen for CRP at 6 months and for DAS28 at 3 and 6 months. Most of the studies report a decrease of DAS28 in RA patients after non-surgical periodontal therapy [24, 43, 44, 54, 55]. All studies that included evaluation of RF failed to show any influence of the periodontal therapy on this marker [23, 42, 44, 54, 56], which is in line with our findings. Contradictory results were reported for changes of ESR and CRP: two studies did not show any changes of these variables [42, 45], whereas Erciyas et al. [55] observed a decrease of ESR and CRP in RA patients with both low and high disease activity. Nonetheless, ESR and CRP are not specific for RA representing measures of inflammation per se, and the CRP decrease at 3 months observed in the present study may depict the consequence of resolving periodontal inflammation. Discrepancies between the studies may be related to different baseline patient settings, by methodological limitations and intercurrent illness [57]. The patients in the present study had been diagnosed and treated for RA for longer than 10 years, still exhibiting moderate to high RA activity (DAS28 ≥ 3.2). Interestingly, disease activity decreased at 6 months from moderate to remission (DAS28 < 2.6) in two patients and from high (DAS28 > 5.1) to moderate in four patients.

Table 3 Median [interquartile] values of microbiological data (*A. actinomycetemcomitans* (*A.a.*), *P. gingivalis*, *T. forsythia*, *T. denticola*) and levels of biomarkers (MMP-8, IL-1β, IL-10) in GCF at baseline as well as 3 and 6 months after SRP and *p* values for inter-group comparisons (Mann-Whitney *U* test) and for intra-group comparisons with baseline (Wilcoxon test)

Variables	Time-point	Group RA-CP	*p* value vs. baseline	Group CP	*p* value vs. baseline	*p* value RA-CP vs. CP
A. actinomycetemcomitans (log10)	Baseline	0.00 [0.00; 2.45]		0.86 [0.00; 4.11]		0.252
	3 months	0.00 [0.00; 0.00]	0.225	0.00 [0.00; 3.16]	0.286	0.224
	6 months	0.00 [0.00; 1.37]	0.917	0.00 [0.00; 1.94]	0.051	0.934
P. gingivalis (log10)	Baseline	6.63 [3.31; 7.31]		5.74 [5.06; 6.26]		0.152
	3 months	5.36 [3.21; 6.60]	0.594	4.19 [0.00; 5.39]	0.004**	0.095
	6 months	6.17 [4.61; 7.49]	0.508	4.38 [0.00; 5.14]	0.006**	0.048*
T. forsythia (log10)	Baseline	6.33 [2.95; 7.22]		7.39 [6.96; 7.61]		0.005**
	3 months	5.75 [3.08; 7.03]	0.955	6.22 [4.09; 6.81]	< 0.001**	0.851
	6 months	6.90 [4.61; 7.49]	0.433	6.72 [0.00; 7.32]	0.001**	0.457
T. denticola (log10)	Baseline	5.84 [4.55; 6.15]		4.85 [3.75; 5.34]		0.047*
	3 months	5.13 [0.00; 6.01]	0.198	3.58 [0.00; 4.54]	0.005**	0.050
	6 months	5.84 [2.71; 6.18]	0.859	4.19 [0.00; 4.75]	0.026**	0.007**
MMP-8 (ng/site)	Baseline	4.89 [3.14; 5.52]		2.50 [1.00; 4.18]		0.017*
	3 months	4.29 [3.10; 5.15]	0.910	1.46 [0.40; 2.65]	0.112	< 0.001**
	6 months	4.23 [3.66; 5.25]	0.388	2.69 [1.31; 4.28]	0.795	0.022
IL-1β (pg/site)	Baseline	21.3 [10.9; 33.3]		6.76 [4.36; 14.4]		0.021*
	3 months	24.0 [7.55; 34.1]	0.510	7.57 [3.76; 24.3]	0.831	0.126
	6 months	18.7 [12.1; 45.0]	0.480	11.7 [6.06; 18.9]	0.233	0.110
IL-10 (pg/site)	Baseline	0.00 [0.00; 0.00]		0.00 [0.00; 0.00]		0.394
	3 months	0.00 [0.00; 0.00]	1.000	0.00 [0.00; 2.84]	0.237	0.096
	6 months	0.00 [0.00; 0.00]	1.000	2.45 [0.00; 8.05]	0.033*	0.006**

Table 4 Median [interquartile] values of markers of rheumatoid arthritis parameters in the RA-CP group at baseline as well as 3 and 6 months after SRP and *p* values for intra-group comparisons with baseline (Wilcoxon test)

Variables	Group RA-CPA	*p* value vs. baseline
DAS28		
Baseline	4.80 [3.90; 5.68]	
3 months	4.70 [3.61; 5.54]	0.199
6 months	4.28 [3.97; 4.65]	0.088
RF		
Baseline	32 [8; 80]	
3 months	32 [8; 125]	0.362
6 months	64 [12; 145]	0.878
CRP		
Baseline	2.40 [1.05; 7.13]	
3 months	1.20 [0.60; 2.40]	0.023*
6 months	1.20 [0.60; 3.70]	0.346
ESR		
Baseline	20.0 [12.8; 48.3]	
3 months	22.0 [16.0; 39.3]	0.722
6 months	20.0 [15.0; 26.0]	0.700

DAS28 disease activity score 28, *RF* rheumatoid factor, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

*$p < 0.05$

Furthermore, we investigated changes of RF, which showed no significant changes at any of the follow-ups compared to baseline (Table 4); this is in line with the current literature, RF being a marker for RA diagnosis [15, 16] that may maintain elevated levels even if RA patients show disease remission [58].

In our study, in 49 of the 69 (65.2%) examined RA patients, a moderate to severe periodontitis was diagnosed being in line with the prevalence reported in other studies. Moderate to severe periodontitis was diagnosed in 63% of a Korean RA cohort [59] and in 58% of an Indian RA cohort [60].

The results of the present study revealed that in both treatment groups, at 3 and 6 months, an overall improvement was obtained for the clinical periodontal parameters PD, CAL, and BOP in comparison to baseline. However, although patients received repeatedly oral hygiene instructions and motivations prior to periodontal therapy, a slight but statistically significant increase in FMPS was observed already at 3 months in both study groups. In general, PD (median and number of sites with PD ≥ 4 mm) was lower in RA-CP than in CP patients. The differences were found at all times, and following, there was a higher decrease in the numbers of sites with PD ≥ 4 mm in the CP group compared to RA-CP patients. Patients in the control group exhibited at baseline significantly more sites with PD ≥

4 mm and higher median PD than those with RA, although there was no statistically significant difference regarding attachment loss between these two groups. This may be due to the anti-inflammatory prolonged RA therapy of the patients in the test group (majority of the patients had been diagnosed and therapied for RA for more than 10 years). Values for PD were lower than in other studies [44, 45] however, in these studies plaque indices were extremely high with initial values of 84% [45] or 100% [44]. Our patients were included only if they reached a FMPS not higher than 30%. As reported in the studies by Biyikoglu et al. [44] and Kurgan et al. [42], changes in periodontal parameters were similar in CP patients with and without RA; in particular, no difference was seen for changes of BOP, PD (mean and % of sites with PD ≥ 4 mm), and CAL. Furthermore, Erciyas et al. [55], comparing periodontal treatment outcomes in patients with low and high disease activity of RA, obtained no difference regarding clinical parameters. Taken together, these data suggest that non-surgical periodontal therapy is equally effective in patients with RA than in systemically healthy ones.

One shortcoming of our study, which may have influenced the comparison between the two groups, was the fact that there were statistically significant differences regarding age, the patients in the RA group being slightly older than those in the control group (Table 1). The reason for this age discrepancy was that younger RA patients that would have matched to the control group refused to comply with the study appointments and therefore were not included in the present study. However, age is a factor controversially discussed in the literature regarding its prognostic value for tooth loss: while some authors showed no significant influence [61, 62], others reported the contrary [63, 64]. Age over 40 years appears to increase the risk for tooth extraction due to periodontal reasons [63].

A further shortcoming of the study is the fact that CRP-serum has been evaluated only in the test and not in the control group. CRP-serum was determined in RA patients within their routine check-up at the Clinic of Rheumatology, and no supplementary blood analysis was needed. For the controls, measuring CRP would have meant supplementary invasive analysis methods (blood samples) just for study purposes and no real benefit for the patients. Therefore, we did not consider determining this parameter in the control group.

GCF pro-inflammatory markers IL-1β and MMP-8 did not change statistically significantly over time in both study groups, which may be related to the statistically significant increase of FMPS in our study patients. Levels of both biomarkers were statistically significantly higher in the RA-CP group than in the CP group at baseline, these differences for MMP-8 being maintained at 3 and 6 months. It has been repeatedly demonstrated that the presence of dental plaque is a major factor that may negatively affect the outcomes of non-surgical periodontal therapy. In the present study, prior to treatment, plaque scores were low and did not differ between the two treatment groups but increased statistically significantly at 3 months. This increase may have hindered the resolution of inflammation and, subsequently, a statistically significant decrease in pro-inflammatory biomarkers. Similar data report on positive correlations between elevated IL-1 beta or MMP 8 levels and plaque [65, 66].

In line with our findings, Kurgan et al. [42] measured higher MMP-8 levels in RA patients with periodontitis than in systemically healthy ones, before and after therapy. However, contrary to our findings, they obtained significant reductions in the RA group 3 months after periodontal treatment compared to baseline. In that study, RA patients exhibiting not only low to high RA activity scores, but also patients in remission (DAS28 < 2.6) were included. Thus, the chance of significantly reducing pro-inflammatory cytokines was probably increased. In our study, levels of the anti-inflammatory cytokine IL-10 increased only in the CP group, being, however, undetectable in RA-CP patients. Therefore, at 6 months, significant elevated levels of IL-10 were found in the GCF of the CP group as compared to RA-CP patients. This is in line with the above argumentation, suggesting that in patients with moderate to severe RA activity, periodontal treatment might not resume significantly the inflammation on GCF level.

Studies investigating the presence of periodontopathogenic bacteria in patients with RA and CP are scarce. However, the few studies that evaluated these bacteria did not find any differences in the prevalence of *P. gingivalis* [4, 67] and the other investigated periodontopathogens [68] between periodontitis patients with and without RA; these findings are in line with our baseline data. Some studies have shown in RA patients antibody responses to *P. gingivalis*, *T. forsythia*, *P. intermedia*, and *A. actinomycetemcomitans* [54, 69]. Intra- and inter-group comparisons in our study indicated no statistically significant differences of *A. actinomycetemcomitans* at none of the timepoints. Nonetheless, prevalence of *A. actinomycetemcomitans* is generally low in chronic periodontitis [70, 71]. In our study, counts of *P. gingivalis*, *T. forsythia*, and *T. denticola* did not change statistically significantly in RA-CP subjects; contrarily, the CP group showed a statistical significant decrease in *P. gingivalis*, *T. forsythia*, and *T. denticola* counts, both at 3 and 6 months. The lack in bacterial reduction in RA subjects might also contribute to the persistent high levels of pro-inflammatory cytokines, maintaining thus inflammation in RA-CP patients. This, in turn, questions the long-term stability of clinical outcomes in RA-CP patients as *P. gingivalis* and *T. denticola* persisted, and since these two bacteria were identified as predictors for progressive attachment loss in periodontitis maintenance patients [72].

Finally, and most importantly, the influence of periodontal variables on changes of CRP and DAS28 was modeled. Changes of DAS28 between baseline and 3 months were correlated with those of *P. gingivalis* and were negatively

influenced by FMPS at 3 months and the change of IL-1β in GCF between baseline and 3 months. The strongest impact in this model had the change in *P. gingivalis* counts, which may support the hypothesis of *P. gingivalis* playing a role in RA disease activity. A recent systematic review performed by our group found higher antibody levels against this species in RA patients than in systemically healthy individuals [73]. The second strongest impact in the model had FMPS at 3 months, which underlines the necessity of good oral hygiene in obtaining a low RA disease activity. However, patients with severe RA may have difficulties in performing adequate oral hygiene. This is supported by Bozkurt et al. [74], who have shown that a high plaque score was the only clinical periodontal parameter that demonstrated statistically significant differences between RA-CP and non-RA-CP patients. Although in our model, the inverse change of IL-1β in GCF had the lowest impact on disease activity score, this influence should not be neglected. We can speculate that patients with decreased DAS28, and following less pain, reduced the intake of NSAID, which might have led to higher IL-1β levels. Certain NSAIDS have been shown to reduce the release of IL-1β [75, 76].

The effects of non-surgical periodontal therapy on disease activity occurred transiently only at 3 months. It may be speculated that these findings might, at least partly, be also due to the increase of the FMPS, which thus represents a limitation of the study. Furthermore, it cannot be excluded that the loss of three patients at 6 months may have also influenced the outcomes.

Conclusions

Chronic periodontitis in RA patients is characterized by moderate PD values, elevated levels of inflammatory biomarkers, and high counts of *P. gingivalis*. Non-surgical periodontal therapy improves clinically periodontal conditions in RA patients as in systemically healthy CP patients. Eradication of *P. gingivalis* combined with a good personal oral hygiene may be beneficial in decreasing disease activity of RA.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (application—approval no. 580/13.04.2012).

Informed consent Informed consent was obtained from all individual participants included in the study.

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