

Effects of nonsurgical periodontal therapy in patients with rheumatoid arthritis: a prospective before and after study

Efectos de la terapia periodontal no quirúrgica en pacientes con artritis reumatoide: estudio prospectivo de antes y después

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Palabras clave:

Artritis reumatoide; periodontitis; proteína C reactiva; factor reumatoide; anticuerpos anti-proteína citrulinada; debridamiento periodontal; disbiosis

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Abstract

Background:

Periodontal therapy has been suggested to have systemic effects. However, studies of periodontal therapy in rheumatoid arthritis patients have produced controversial results.

Aim:

To compare the effects of nonsurgical periodontal therapy on biochemical markers of rheumatoid arthritis and periodontal parameters in patients with and without rheumatoid arthritis.

Methods:

A prospective before-and-after study was conducted that included 21 participants without and 29 participants with rheumatoid arthritis. Periodontal parameters, *Porphyromonas gingivalis* detection, C-reactive protein, rheumatoid factor and anti-citrullinated protein antibodies were measured at baseline and three months after nonsurgical periodontal therapy and the changes were statistically assessed.

Results:

Groups presented statistically significant improvement in periodontal parameters ($p < 0.05$). There was an increase in the counts of *P. gingivalis* in both groups at three months. In addition, there was a reduction in levels of anti-citrullinated protein antibodies and rheumatoid factor in participants with rheumatoid arthritis. In contrast, C-reactive protein levels increased in both groups but were higher in the rheumatoid arthritis group. Periodontal parameters in rheumatoid arthritis participants under disease-modifying antirheumatic drugs presented a slightly higher improvement ($p < 0.05$).

Conclusions:

Nonsurgical periodontal therapy has similar improvements in periodontal parameters in patients with and without rheumatoid arthritis. In addition, nonsurgical periodontal therapy may benefit serum levels of anti-citrullinated protein antibodies and rheumatoid factors in patients with rheumatoid arthritis. NCT04658615.

Conflicts of interest:

Authors declared that they have no conflict of interests.

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Resumen

Antecedentes:

Se ha sugerido que la terapia periodontal tiene efectos sistémicos. Sin embargo, los estudios de la terapia periodontal en pacientes con artritis reumatoide han producido resultados controvertidos.

Objetivo:

Comparar los efectos de la terapia periodontal no quirúrgica sobre los marcadores bioquímicos de la artritis reumatoide y los parámetros periodontales en pacientes con y sin artritis reumatoide. Se realizó un estudio prospectivo de antes y después que incluyó a 21 participantes sin artritis reumatoide y 29 participantes con artritis reumatoide. Se midieron los parámetros periodontales, detección de *Porphyromonas gingivalis*, proteína C reactiva, factor reumatoide y anticuerpos anti-proteína citrulinada al inicio del estudio y tres meses después de la terapia periodontal no quirúrgica y los cambios se evaluaron estadísticamente.

Resultados:

En general, ambos grupos presentaron mejoría estadísticamente significativa en los parámetros periodontales ($p < 0.05$). Hubo un aumento en los recuentos de *P. gingivalis* en ambos grupos a los tres meses. Además, hubo una reducción en los niveles de anticuerpos anti-proteína citrulinada y factor reumatoide en participantes con artritis reumatoide. Por el contrario, los niveles de proteína C reactiva aumentaron en ambos grupos, pero fueron más altos en el grupo de artritis reumatoide. Los parámetros periodontales en los participantes con artritis reumatoide bajo fármacos antirreumáticos modificadores de la enfermedad presentaron una mejoría ligeramente mayor ($p < 0.05$).

Conclusiones:

La terapia periodontal no quirúrgica tiene mejoras similares en los parámetros periodontales en pacientes con y sin artritis reumatoide. Además, la terapia periodontal no quirúrgica puede beneficiar los niveles séricos de anticuerpos anti-proteína citrulinada y factor reumatoide en pacientes con artritis reumatoide. NCT04658615.

Remark

1) Why was this study conducted?

It has been suggested that periodontitis and rheumatoid arthritis are bi-directional and that periodontal therapy has systemic effects. Therefore, this study was carried out to compare the effects of periodontal therapy on biochemical and clinical parameters in patients with and without rheumatoid arthritis.

2) What were the most relevant results of the study?

Periodontal parameters improved regardless of the systemic condition. However, there was a reduction in levels of anti-citrullinated protein antibodies and rheumatoid factor in participants with rheumatoid arthritis after periodontal treatment.

3) What do these results contribute?

Periodontal therapy may positively affect serum levels of anti-citrullinated protein antibodies and rheumatoid factor in patients with rheumatoid arthritis and consequently help improve their disease activity.

Introduction

Periodontitis and rheumatoid arthritis (RA) are inflammatory diseases that lead to connective tissues and bone destruction. The prevalence of severe periodontitis globally has been estimated at around 11% but with the additional sum of moderate and slight periodontitis, the prevalence could rise to nearly 50%^{1,2}. In Colombia, around 60% of the population has periodontitis³. In contrast, recent data indicate that the global prevalence of RA is between 0.40-1%, with a similar prevalence in Colombia (0.52%)^{4,5}. Both diseases are of great interest as they have been found to impact the quality of life of people negatively^{6,7}. In the last decade, evidence has emerged suggesting an association between the two conditions⁸⁻¹⁰.

While periodontitis has a strong microbial etiology, RA results from an autoimmune response. The accumulation of a dysbiotic biofilm around teeth leads to the inflammation of gingival tissues that, without proper control, continue to develop periodontitis in which periodontal attachment tissues and tooth surrounding bone are resorbed. On the other hand, RA results from an accumulation of an autoimmune inflammatory infiltrate in the synovial membrane leading to the continuous destruction of connective and bone tissues of the joints. The etiology of RA is unknown but genetic, environmental factors and smoking have been recognized as significant risk factors, and more recently, dysbiosis of the gut microbiome has been associated as a contributing factor for autoimmune diseases including RA¹¹⁻¹³. In addition, RA affects the joints and contributes to chronic systemic inflammation and, therefore, compromises multiple organs and tissues in the body¹⁴.

Studies have suggested that both conditions share some pathogenic mechanisms. They are characterized by the increased local production of matrix metalloproteinases (MMPs) and proinflammatory cytokines such as IL-1, TNF α , IL-6 and IL-17, which are important inducers of connective tissue and bone resorption. C-reactive protein (CRP), a pentameric protein produced in the liver as a result of chronic inflammation and infection, is elevated in periodontitis and RA^{12,13,15}. Dysbiosis, defined as the imbalance in the normal microbial community, is an important feature in periodontitis and studies suggest that it also plays a role in RA contributing to the onset of chronic inflammation¹¹. These shared molecular and biological mechanisms create a dysregulated inflammatory reaction responsible for the destruction of connective tissues and bone around teeth and joints.

It has been proposed that periodontitis may contribute to the pathogenic effects of arthritis. The link was established through *Porphyromonas gingivalis*, an important pathogen in the dysbiotic biofilm in periodontitis. *P. gingivalis* synthesizes a peptidyl arginine deiminase (PAD) that mediates the citrullination of several proteins such as vimentin, fibrin, and α -enolase. Citrullinated proteins are recognized by anti-citrullinated protein antibodies (ACPAs), which is a relevant characteristic of RA^{13,16,17}. Studies have found that ACPAs are increased in subjects positive for *P. gingivalis* with and without RA^{18,19}. However, *P. gingivalis* affects the production of ACPAs and induces NETs (neutrophil extracellular traps), osteoclastogenesis (prostaglandin E2), and Th17 proinflammatory response that, in a consortium, contribute to bone damage and systemic inflammation²⁰. Such mechanisms are suspected to act in a bidirectional way, meaning that RA may be a risk factor for periodontitis and vice versa.

Nonsurgical periodontal therapy (NSPT) has been shown to have systemic effects. Gaudilliere *et al.*²¹, showed that patients with periodontitis have an exaggerated pro-inflammatory reaction to *P. gingivalis* and a dysfunctional systemic immune response. But more interesting was that the systemic immune dysfunction was temporarily reversed by NSPT²¹. Studies in RA patients suggest that NSPT improves the periodontal and RA condition²². Others found no benefit on clinical parameters of RA and the effects of NSPT on biochemical markers of RA remains controversial^{23,24}. Also, differences in the clinical response after NSPT in patients with and without RA have not been addressed. Therefore, the objective of this study was to compare the effects of nonsurgical periodontal therapy on biochemical markers of RA and periodontal parameters in patients with and without RA.

Materials and Methods

This prospective before-and-after study protocol was reviewed and approved by the institutional review board (Universidad de Antioquia 05-2016) and conducted according to the Declaration of Helsinki of 1975, as revised in 2013. All participants were required to sign an informed consent upon inclusion. Additionally, the study protocol was registered in Clinical Trials (NCT04658615).

Participants and selection criteria

Patients with and without RA were recruited between march 2019 and march 2020 from the dental clinics of the Universidad de Antioquia and Artmédica, respectively. Individuals were included according to the following criteria: age ≥ 18 years old; diagnosis of RA according to the American College of Rheumatology with a disease activity score-28 (DAS28-CRP) ≥ 3.2 and no change in RA medication in the previous 3 months and during the follow-up; at least 15 teeth excluding third molars; interdental sites with loss of periodontal attachment level (PAL) in ≥ 2 non-adjacent teeth²⁵. Patients without RA met the same criteria except for the diagnosis of RA. In addition, individuals were excluded if they reported periodontal treatment or use of antibiotics in the previous three months, diabetes, HIV, liver disease, head and neck radiation therapy, pregnancy, and use of cyclosporine. Smoking, hypertension, and hyperlipidemia medication were not exclusion criteria and were recorded accordingly.

RA participants were under medication, including nonsteroidal anti-inflammatory drugs (NSAIDs), nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs), and corticosteroids. Non-biologic DMARDs included hydroxychloroquine, methotrexate, sulfasalazine and leflunomide. Biologic DMARDs included Adalimumab, Etanercept, Abatacept, Golimumab, Infliximab, Rituximab and Tocilizumab. No changes in the medication during the follow-up period was performed in order to analyze the effects of periodontal treatment. However, once the follow-up was finalized, the treating doctor adjusted or modified the pharmacological therapy according to each case.

Clinical examination, microbiological and serum samples

After participants were screened for inclusion, serum samples were collected for the analysis of high-sensitivity C-reactive protein (hs-CRP; mg/L), rheumatoid factor (RF; U/mL) and anti-citrullinated protein antibodies (ACPAs; U/mL) in a reference laboratory. A complete periodontal chart was completed at six sites per tooth excluding third molars by a single experienced clinician using a calibrated probe (UNC-15, Hu-Friedy Mfg. Co.). An experienced rheumatologist examined RA patients to determine their DAS28-CRP score. Subgingival plaque samples were collected and pooled from the 5 most profound periodontal sites. Detection of *P. gingivalis* was immediately performed using culture techniques and expressed as colony-forming units per mL (CFU/mL) and frequency detection²⁶. All examinations were taken at baseline and repeated three months after the intervention.

Intervention

Nonsurgical periodontal therapy (NSPT) was administered on the following 5 days of inclusion. A single 1-hour session of full-mouth debridement with an ultrasonic device and curettes was carried out in each participant under local anesthesia by an experienced clinician. After NSPT was completed, each patient received oral hygiene instructions and an oral care pack that included a toothbrush and toothpaste (toothbrush Vitis Encias Medium; Toothpaste Vitis Encias; Dentaïd, Colombia).

Outcomes

The primary outcome was the change in C-reactive protein levels measured as the difference between the baseline and 3-month examination. Secondary outcomes included change in RF and ACPAs as well as change in periodontal attachment level (PAL), probing depth (PD) and bleeding on probing (BOP).

Data collection

Demographic, clinical history, as well as medication data for all participants, were collected. Periodontal clinical parameters of PD (mm), PAL (mm) and BOP (%) were recorded at each visit. The stage of periodontitis was established according to the current classification of periodontal diseases²⁵. The clinician who recorded data was not blinded to the condition of the patients.

Statistical analyses

The sample size was calculated to detect a 50 % change in CRP with a power of >80% (alpha 0.05), resulting in 15 participants per group²². Considering possible dropouts, 20 participants were included per group. Randomization was not performed since the purpose was to compare the effects of NSPT in patients with and without RA. The clinical investigator who recorded periodontal parameters was calibrated for repeated measurements before patient inclusion (Kappa value was ≥ 0.80 for PAL and PD).

A per-protocol analysis was carried to analyze the changes in clinical variables. Categorical variables are presented as frequencies (%) and analyzed in contingency tables and X^2 . Kolmogorov-Smirnov test was applied to assess for normality. Continuous variables are presented as the mean and 95% confidence interval (CI). Changes in biochemical markers (CRP, RF, ACPAs) and periodontal parameters (PAL, PD, BOP) are expressed as the delta (Δ) from baseline to 3 months after the intervention. Differences were determined by the Wilcoxon test for paired and Mann Whitney test for unpaired samples. Considering that the main objective of NSPT is to reduce periodontal inflammation and, in consequence, improve the systemic condition, the outcome of interest was defined as the reduction in biochemical markers of RA. This occurrence was cross-tabulated with the study group type, and the relative risk (RR) was calculated. The level of statistical significance was 5% ($p \leq 0.05$).

Results

The recruitment and demographic description of the study participants are presented in Figure 1 and Table 1. Twenty-one (21) patients without RA and 29 patients with RA with a mean age of 52.3 years old participated in the study. The proportion of female participants was higher in both groups, especially in the RA group ($p = 0.04$). The duration of RA was 11.3 years (95% CI: 7.7-14.6). Participants presented similar number teeth, but the stage IV of periodontitis distribution was higher in the group without RA ($p = 0.01$). The distribution of diabetes, hypertension and smoking was not statistically significant between groups. Osteoporosis was more frequent in RA participants.

Changes in periodontal and microbiological parameters at three months after intervention are shown in Table 2. In general, both groups presented statistically significant improvement in periodontal parameters ($p = 0.001$). Participants without RA had more severe periodontitis than participants with RA, and therefore, the reduction observed at three months in BOP, mean PAL and mean PD was higher than RA participants. However, the relative magnitude (%) in reduction was similar between groups (15-20% reduction). There was a more significant increase in the number of sites with PAL 1-2 mm and PD ≤ 3 mm, greater reduction in the number of sites with PAL 3-5 mm and ≥ 5 mm in the group without RA. There was a greater reduction in the number of sites with PD ≥ 4 mm in the group without RA than the RA group. Nonetheless, the relative magnitude (%) in reduction was greater in the participants with RA than the group without RA (42% vs. 20%). The total microbial counts decreased in both groups at 3 months after the intervention. However, there was an increase in the counts and frequency detection of *P. gingivalis* in both groups, but these differences were not statistically significant (Table 2). Participants that were positive for *P. gingivalis* remained positive after NSPT.

Changes in biochemical parameters at three months after intervention are reported in Table 3. There was a mean evident reduction in levels of ACPAs and RF in participants with RA. The

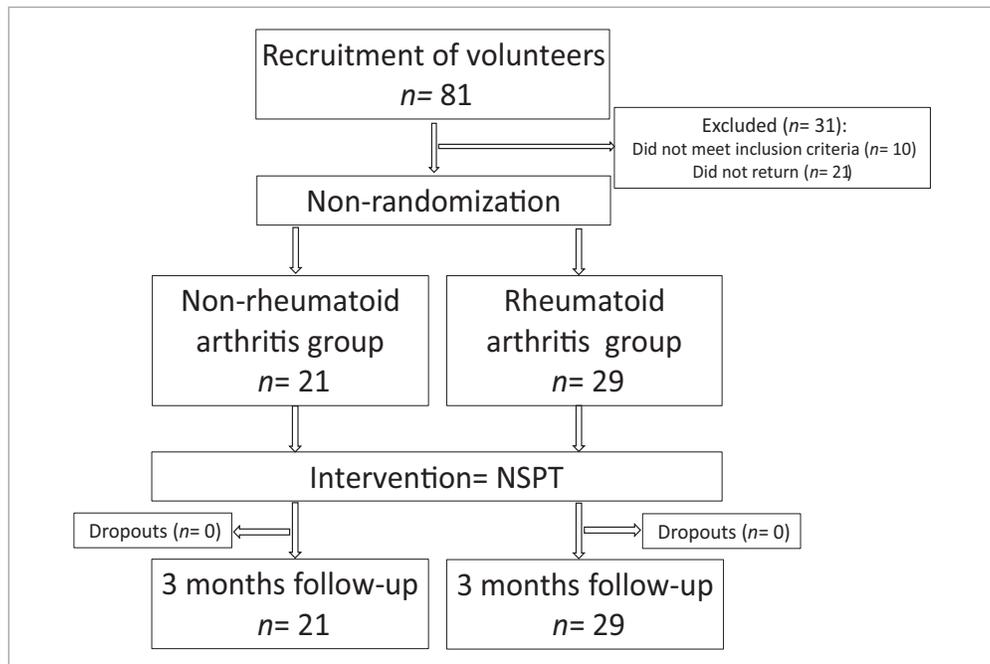


Figure 1. Flowchart of patient inclusion.

levels of RF in patients without RA did not change after NSPT. In contrast, the levels of CRP increased in both groups but were higher in the RA group. This increase's relative magnitude (%) was similar between groups (20-25%). The reduction in CRP levels was more likely to occur in patients without RA.

In contrast, the reduction in levels of ACPAs was more likely in patients with RA ($p = 0.003$). In the same manner, a reduction in levels of RF was more likely in patients with RA ($p = 0.001$) (Table 4). Changes in RF levels in patients without RA were not observed in any patient. This shows that in some patients with RA, NSPT may have beneficial effects on biochemical markers.

Subgroup analysis of RA participants assessed changes in periodontal parameters according to the medication used (Table 5). In general, periodontal parameters in RA participants under DMARD medication presented a slightly higher improvement ($p = 0.003$) except for PD in the non-biologic DMARD group. Nevertheless, these differences were not statistically significant between groups.

Table 1. Demographic description of the study sample

Variable	Without RA (n= 21)	RA (n= 29)	p*
Sex			
Male (%)	10 (47.6%)	6 (20.7%)	0.04
Female (%)	11 (52.4%)	23 (79.3%)	
Mean age (95% CI)	52.3 (47.2-57.3)	52.3 (49.4-55.1)	NS
27-59 years old	17 (80.9%)	20 (68.9%)	NS
>60 years old	4 (19.1%)	9 (31.1%)	NS
RA duration (years); mean (95% CI)	NA	11.3 (7.7-14.6)	NA
Number of teeth present	24.4 ± 2.9	22.6 ± 4.4	NS
Stage of periodontitis n (%)			
I	0	0	0.01
II	0	5 (17.2%)	
III	5 (23.8%)	16 (55.2%)	
IV	16 (76.2%)	8 (27.6%)	
Diabetes	0 (0)	1 (3.4%)	NS
Hypertension	3 (14.3%)	10 (34.5%)	NS
Osteoporosis	0 (0)	8 (27.6%)	0.008
Smoking	0 (0)	1 (3.4%)	NS

* χ^2 . NS: not significant; CI: confidence interval; RA: rheumatoid arthritis; NA: not applicable.

Table 2. Change in periodontal clinical and microbiological parameters from baseline to 3 months.

Variable	Without RA				RA			
	Baseline	3 months	Change (Δ)	<i>p</i> *	Baseline	3 months	Change (Δ)	<i>p</i> *
Mean BOP (95% CI)	55.6 (44.6-66.5)	33.9 (21.9-45.9)	21.6 (15-28.3)	0.001	21.4 (14.6-28.2)	10.4 (7.5-13.2)	11 (5.3-16.8)	0.001
PAL								
Mean PAL (95% CI)	4.4 (4.0-4.8)	3.7 (3.0-4.1)	0.7 (0.4-1.0)	0.001	2.9 (2.4-3.4)	2.6 (2.1-3.0)	0.3 (0.1-0.5)	0.001
n sites PAL 1-2 mm (95% CI)	38.6 (27.4-49.7)	48.4 (35.8-61.0)	-9.8 (-14.9--4.7)	0.002	27.1 (20.3-33.9)	28.2 (21.5-34.8)	-1.1(-2.8-0.7)	0.241
n sites PAL 3-4 mm (95% CI)	45.7 (35.2-56.2)	42.6 (32.7-52.5)	3.1 (-4.4-10.6)	0.780	33.6 (25.6-41.7)	34.9 (26.4-43.4)	-1.2 (-2.8-0.4)	0.127
n sites PAL \geq 5 mm (95% CI)	39.1 (29.2-48.9)	31.8 (22.9-40.7)	7.3 (2.4-12.1)	0.006	16.0 (9.6-22.5)	14.4 (8.4-20.5)	1.6 (-0.2-3.3)	0.095
PD								
Mean PD (95% CI)	4.2 (3.7-4.5)	3.4 (3.0-3.8)	0.7 (0.4-0.9)	0.001	3.0 (2.6-3.3)	2.4 (2.2-2.5)	0.6 (0.3-0.8)	0.001
n sites PD \leq 3 mm (95% CI)	104.4 (91.5-117.4)	112.2 (97.1-127.4)	-7.8 (-17.8-2.2)	0.019	128.9 (117.3-140.5)	131.7 (120.6-142.7)	-2.7 (-4.9- -0.6)	0.006
n sites PD \geq 4 mm (95% CI)	41.3 (30.4-52.3)	33.2 (18.2-48.3)	8.1 (-2.0-18.2)	0.019	7.4 (3.41-11.4)	4.3 (2.0-6.6)	3.1 (0.6-5.6)	0.006
<i>P. gingivalis</i> frequency detection n (%)	9 (50.0)	10 (55.5)	-1 (5.5)	0.077	2 (7.4)	3 (11.1)	-1 (3.7)	0.786
<i>P. gingivalis</i> CFU / mL (95% CI)	2.26 x 10 ⁴ (-2.41 x 10 ⁴ -6.94 x 10 ⁴)	1.40 x 10 ⁵ (-9.46 x 10 ⁴ -3.76 x 10 ⁵)	-1.18 x 10 ⁵ (-3.61 x 10 ⁵ -1.25 x 10 ⁵)	0.204	1.59 x 10 ³ (-1.45 x 10 ³ -4.63 x 10 ³)	8.07 x 10 ³ (-7.12 x 10 ³ -2.32 x 10 ⁴)	-6.48 x 10 ³ (-2.21 x 10 ⁴ -9.15 x 10 ³)	0.500
Total microbial CFU / mL (95% CI)	4.82 x 10 ⁶ (2.11 x 10 ⁶ -7.54 x 10 ⁶)	4.77 x 10 ⁶ (-2.15 x 10 ⁶ -1.17 x 10 ⁷)	5 x 10 ⁴ (-6.83 x 10 ⁶ -6.93 x 10 ⁶)	0.218	2.46 x 10 ⁶ (2.22 x 10 ⁵ -4.71 x 10 ⁶)	1.44 x 10 ⁶ (6.28 x 10 ⁵ -2.26 x 10 ⁶)	1.02 x 10 ⁶ (-1.29 x 10 ⁶ -3.33 x 10 ⁶)	0.284

*Paired Wilcoxon test. CI: confidence interval; RA: rheumatoid arthritis; PAL: periodontal attachment level; PD: probing depth; CFU: colony forming units. Negative values denote an increase.

Table 3. Change in biochemical parameters from baseline to 3 months.

Parameter	Without RA				RA			
	Baseline	3 months	Change (Δ)	<i>P</i> *	Baseline	3 months	Change (Δ)	<i>P</i> *
Mean CRP mg/L (95% CI)	2.2 (1.2-3.1)	2.8 (0.9-4.6)	-0.6 (-2.1-0.9)	0.670	7.2 (03.4-10.9)	9.0 (5.3-12.6)	-1.8 (-7.1-3.3)	0.165
Mean ACPA U/mL (95% CI)	0.8 (0.4-1.1)	0.9 (0.4-1.4)	-0.1 (-0.3-0.1)	0.211	190.5 (80.2-300.8)	118 (65.1-172.5)	71.7 (-23.9-167.3)	0.136
Mean RF U/mL (95% CI)	15	15	0	1.000	213.8 (86.9-340.7)	166.7 (73.3-259)	47.7 (-0.1-107.1)	0.113

*Paired Wilcoxon test. CI: confidence interval; RA: rheumatoid arthritis. Negative values denote an increase.

Table 4. Treatment effect association with biochemical parameters in patients with and without RA

CRP	No-change / Increase	Without RA	RA	Relative Risk	<i>p</i>
		9 (42.9%)	18 (62.1%)		
ACPA	Reduction	12 (57.1%)	11 (37.9%)	7.4 (1.8-30.7)	0.003
	No-change / Increase	18 (85.7%)	13 (44.8%)		
RF	Reduction	3 (14.3%)	16 (55.2%)	0.4 (0.2-0.6)	0.001
	No-change / Increase	21 (100.0%)	12 (41.4%)		
	Reduction	0 (0.0%)	17 (58.6%)		

CI: confidence interval; RA: rheumatoid arthritis; CRP: C-reactive protein; ACPA; anti-citrullinated protein antibodies; RF: rheumatoid factor.

Discussion

This study aimed to compare the effects of NSPT on clinical parameters in patients with and without RA. An improvement in clinical periodontal parameters in both groups, reduction in ACPAs and RF, and increase in CRP in RA participants was observed at three months after the intervention. However, these findings should be interpreted with caution.

Clinical periodontal parameters improved in both groups after NSPT, and this finding was statistically significant within each group and in agreement with other studies^{22,27,28}. Although participants without RA presented higher values in periodontal parameters at baseline as compared to RA participants and appeared to have had a more significant improvement, the relative magnitude of the change was similar between groups. Previous studies have found that periodontitis is more severe in RA patients^{10,29}, but this was not the case of this study and therefore marks a difference. One possible explanation is the chronic use of potent anti-inflammatory medication such as DMARDs, which were exclusive in RA participants of this study. Results from animal studies showed reduced inflammation and bone loss in experimental periodontitis with the administration of chloroquine³⁰. Recent studies in humans reported less progression in periodontal attachment loss in RA patients under DMARD medication^{31,32}.

In addition, RA patients had access to managing protocols for their disease at their treating facility that included changes in daily habits and periodic visits to the doctor and dentist as opposed to patients without RA in this study. This could have influenced their periodontal condition³³. In this matter, subgroup analysis of RA participants' clinical data showed a slightly better improvement in periodontal parameters in patients under biologic and nonbiologic DMARDs. Therefore, the possibility that DMARD medication slowed down the progression of periodontitis in RA participants is plausible and merits further studies in randomized clinical trials.

Previous studies have suggested beneficial effects of NSPT on biochemical markers of RA and eventual improvement of disease activity²². But changes in biochemical markers in RA participants may also be related to the altered immune and inflammatory reaction characteristic of the disease^{12,15}. We found a greater decrease in ACPAs / RF and in contrast, an increase in CRP at three months after NSPT in RA participants but did not reach statistical significance. Furthermore, the response in ACPAs and RF in RA participants was towards reduction despite no change in RA medication during the study. In some patients, the reduction of periodontal inflammation by NSPT may benefit biochemical serum markers. Although periodontal improvements were comparable in participants with and without RA, an improvement in the levels of ACPAs and RF in RA participants could be explained because they had increased levels before NSPT and, therefore, more room for reduction.

Table 5. Change in periodontal parameters from baseline to 3 months according to medication in RA participants.

Parameter	Biologic DMARDs								
	Yes				<i>p</i> *	No			<i>p</i> *
	Baseline	3 months	Change (Δ)			Baseline	3 months	Change (Δ)	
Mean PAL (95% CI)	3.3 (1.6-5.0)	2.8 (1.4-4.1)	0.5 (-0.3-1.4)	0.180	2.8 (2.2-3.3)	2.5 (2.0-3.0)	0.3 (0.1-0.4)	0.002	
Mean PD (95% CI)	3.3 (2.0-4.5)	2.5 (2.1-3.0)	0.7 (-0.2-1.6)	0.109	2.9 (2.5-3.3)	2.3 (2.2-2.5)	0.5 (0.3-0.8)	0.002	
Parameter	Non-biologic DMARDs								
	Yes				<i>p</i> *	No			<i>p</i> *
	Baseline	3 months	Change (Δ)			Baseline	3 months	Change (Δ)	
Mean PAL (95% CI)	2.9 (2.3-3.5)	2.5 (1.9-3.0)	0.4 (0.1-0.6)	0.003	3.1 (2.1-4.1)	2.9 (1.8-3.9)	0.3 (-0.2-0.8)	0.109	
Mean PD (95% CI)	2.9 (2.5-3.3)	2.4 (2.2-2.5)	0.5 (0.2-0.8)	0.003	3.3 (2.4-4.1)	2.0 (2.1-3.2)	0.7 (0.2-1.2)	0.066	

*Paired Wilcoxon test. CI: confidence interval; RA: rheumatoid arthritis; PAL: periodontal attachment level; PD: probing depth; DMARD: disease-modifying antirheumatic drugs.

In contrast to the study by Cosgarea *et al.*²², CRP tended towards increase after NSPT. ACPAs and RF are highly variable parameters in RA and can show a great range of change after initiating treatment with DMARDs in patients with periodontitis³⁴. On the other hand, CRP is an unspecific indicator of inflammation that can be elevated at 24-72 hours after severe tissue damage or infection³⁵. Also, RA patients can have periods of disease remission/relapse and this way, the systemic inflammation will be altered increasing CRP levels³⁶. The results agree with other studies^{22,27,37-39}, but systematic reviews have shown no effect of NSPT on ACPAs and RF, consequently, producing contrasting conclusions^{23,40}. It has been suggested that NSPT has systemic effects by reducing periodontal inflammatory sources²¹. However, the complex immune and systemic inflammatory response in the etiopathogenesis of RA makes this assumption more complicated despite the improvement in clinical parameters observed in our study. In addition, this study was not designed as a randomized clinical trial (RCT) and therefore, this reduction cannot be directly attributed to NSPT. It is more likely that the changes in biochemical parameters in patients with RA are to a certain extent the combined result of the activity of the disease, response to the medication used and NSPT, but this requires further studies.

Some studies have suggested an association between *P. gingivalis* and RA⁴¹. Additionally, periodontal intervention studies have reported an association between the reduction of *P. gingivalis* levels and improvement in RA disease activity⁴². Although NSPT resulted in the reduction of the total microbial counts, the counts of *P. gingivalis* increased at three months after therapy in our study. This may be related to the type of NSPT administered as a one-single session of scaling and root planning may not be sufficient to suppress *P. gingivalis* in severe periodontitis cases effectively. In addition, subgingival samples were taken at three months from remaining periodontal pockets which could still be harboring high counts of the microorganism. It has been shown that *P. gingivalis* is prevalent in sites that do not improve after therapy⁴³. However, no relation between *P. gingivalis* and the change in biochemical parameters of RA were observed in this study. Other researchers^{44,45}, using molecular detection methods, found no significant association between *P. gingivalis* and RA and therefore, the relation between periodontitis and RA remains inconclusive due to high heterogeneity between studies.

The present study has the following shortcomings. First, the study was designed as a before-and-after study since the purpose was to compare the effects of NSPT in patients with and without RA. It can be argued that only RCTs provide the only valid evidence. But the benefits of NSPT in restoring periodontal health have been extensively proven and thus it seemed more reasonable to administer the therapy to all participants⁴⁶. However, sample size calculation and careful selection criteria and clinical measurement of important parameters allowed us to make valid real-world comparisons that are relevant for their periodontal and systemic condition. Second, follow-up time was only three months, and this was determined since participants were scheduled to receive only one session of NSPT and was the expected time to observe for initial clinical changes⁴⁷. A more extended observation period would have only delayed additional periodontal treatment that participants needed for their condition.

Conclusions

Nonsurgical periodontal therapy has similar improvements in periodontal parameters in patients with and without rheumatoid arthritis. In addition, NSPT may help reduce ACPAs and RF serum levels in patients with rheumatoid arthritis.

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