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The effect of anti-tumor necrosis factor-alpha and nonsurgical periodontal therapy in individuals with rheumatoid arthritis

Hatice Yemenoglu¹ , Melek Beder^{1*} , Osman Cüre² , Oğuz Köse¹ , Medeni Arpa³ , Mehtap Atak³ and Semih Alperen Bostan¹

Abstract

Background TNF- α inhibitors (anti-TNF- α) decrease the amount of inflammatory cells, osteoclast formation, and bone loss. The purpose of this study was to investigate the effect of non-surgical periodontal therapy (NSPT) combined with anti-TNF- α on oxidative stress in individuals with RA and periodontitis.

Methods A total of 42 patients with RA and periodontitis who were treated with anti-TNF- α ($n=21$) and not treated with anti-TNF- α ($n=21$) were included in the study. Plaque index (PI), bleeding on probing (BOP), gingival index (GI), clinical attachment loss (CAL), and probing pocket depth (PPD) measurements were measured at baseline, at 3 months, and at 6 months after NSPT, and serum and gingival crevicular fluid (GCF) samples were obtained from the patients. RANKL/OPG, MMP-8, MDA, GSH, and OSI levels were evaluated using ELISA.

Results In both groups, baseline PI, BOP, GI, PPD, and CAL decreased significantly after NSPT ($p < 0.05$). The GCF RANKL/OPG ratio was statistically significantly lower in anti-TNF- α treated patients at baseline and at 6 months post-NSPT ($p < 0.05$), and the serum OSI was significantly higher in anti-TNF- α treated patients at baseline ($p < 0.05$). GCF MMP-8 increased significantly after NSPT in both groups compared with baseline ($p < 0.05$). In those treated with anti-TNF- α , OSI and MDA decreased significantly after NSPT ($p < 0.05$).

Conclusions The data from this study suggest that anti-TNF- α therapy can suppress inflammation and alveolar bone resorption by affecting the RANKL/OPG ratio, MMP-8, and oxidative stress parameters, and thus increase the effectiveness of NSPT.

Trial registration This study was retrospectively registered on ClinicalTrials.gov (NCT06818045), 2025-02-02.

Keywords Anti-TNF- α , Periodontitis, Rheumatoid arthritis

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Background

Periodontitis is a long-standing inflammatory condition triggered by a dysbiotic subgingival microbiota, leading to progressive damage of the hard and soft tissues supporting the teeth [1]. Chronic, low-grade inflammation not only contributes to local periodontal destruction but also poses systemic health risks. A growing body of evidence suggests a link between periodontal disease and systemic conditions such as diabetes, cardiovascular diseases, and rheumatoid arthritis (RA) [2, 3]. RA is a systemic autoimmune disorder with a complex and multifactorial nature. Its etiology remains unclear, but if left untreated, it can cause joint destruction, functional impairment, and a decline in quality of life [4]. Approximately 1% of the global population is affected by RA [5]. Both periodontitis and RA share several risk factors, including age, smoking, obesity, and genetic predisposition [6].

Interestingly, both diseases exhibit overlapping inflammatory pathways, particularly involving elevated levels of pro-inflammatory and bone-resorptive cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β) [7]. Additionally, upregulation of the receptor activator of the nuclear factor kappa B ligand (RANKL) and matrix metalloproteinases (MMPs) pathway promotes immune cell infiltration, osteoclast differentiation, and subsequent tissue degradation [6]. TNF- α plays a central role in enhancing osteoclastogenesis while simultaneously inhibiting osteoblastogenesis in both conditions [8].

The pathogenesis of RA involves numerous factors, among which oxidative stress—due to excessive production of reactive oxygen species (ROS)—plays a critical role [9]. Similar oxidative mechanisms are also implicated in the development and progression of periodontitis [10, 11]. Given the complexity of measuring individual oxidant species, systemic oxidative stress is typically assessed through biomarkers such as total oxidant status (TOS), total antioxidant status (TAS), malondialdehyde (MDA), and glutathione (GSH) [12].

Cumulative evidence points to a bidirectional relationship between RA and periodontitis. Periodontal disease has been associated with the onset and exacerbation of RA, and individuals diagnosed with RA are more likely to exhibit periodontal pathology [13]. Notably, individuals with a history of periodontitis exceeding five years have been reported to carry a 69% higher risk of developing RA compared to periodontally healthy individuals [3]. Furthermore, RA patients with coexisting periodontitis demonstrate significantly elevated disease activity scores (DAS28) compared to those without periodontal involvement [3].

Although no curative treatment exists for RA, current therapeutic strategies offer substantial disease

control. These include lifestyle modifications, analgesics, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs) [6]. According to the European League Against Rheumatism (EULAR), initiation of DMARD therapy is recommended upon diagnosis [14]. DMARDs are classified into conventional synthetic (csDMARDs), biological (bDMARDs), and targeted synthetic (tsDMARDs) categories. csDMARDs include agents such as methotrexate and leflunomide; bDMARDs comprise TNF- α inhibitors (anti-TNF- α), B-cell-depleting therapies, and IL-6 receptor blockers; tsDMARDs encompass Janus kinase (JAK) inhibitors [14].

Given the close interplay between RA and periodontal disease, recent research has investigated the effects of anti-rheumatic therapies on periodontal outcomes. Some studies suggest that RA treatment—particularly with anti-TNF- α agents—not only alleviates joint inflammation but also improves periodontal health [8, 15–19]. However, other findings indicate that such treatments may have minimal or even unfavorable effects on periodontal status [4, 20–24].

Based on these insights, the present study was designed to evaluate whether anti-TNF- α therapy could enhance the clinical efficacy of non-surgical periodontal treatment (NSPT) in individuals diagnosed with both RA and periodontitis. Additionally, the study aimed to assess the combined effect of NSPT and anti-TNF- α agents on oxidative stress. This was accomplished by comparing the levels of MMP-8 and RANKL/osteoprotegerin (OPG) in gingival crevicular fluid (GCF) and serum, as well as serum levels of MDA, GSH, and the oxidative stress index (OSI).

Methods

Study participants

This study was approved by the Non-Invasive Clinical Research Ethics Committee of Recep Tayyip Erdoğan University (Approval No: 2023/213). Written informed consent was obtained from all participants. The study population included volunteers with rheumatoid arthritis (RA) who were under routine follow-up at the Department of Periodontology, Faculty of Dentistry, and the Department of Rheumatology, Faculty of Medicine, Recep Tayyip Erdoğan University, between October 2023 and January 2025. The study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. The diagnosis of RA was established based on the criteria of the American College of Rheumatology [25].

Inclusion criteria were as follows: age between 18 and 65 years, confirmed RA diagnosis [25], diagnosis of stage III or IV, grade C periodontitis [26], and presence of at least 20 natural teeth. Exclusion criteria included

systemic antibiotic use within the past three months, pregnancy or lactation, periodontal treatment within the last six months, presence of diabetes, and active smoking.

Ninety RA patients who presented to our clinic for periodontal treatment were questioned about their medication use ($n = 40$ not receiving anti-TNF- α therapy, $n = 50$ receiving anti-TNF- α therapy) and duration of use, and underwent an oral examination. Twenty-five patients from each group who met the inclusion criteria agreed to participate in the study. After excluding patients who missed the 3rd and 6th-month follow-ups ($n = 8$), the study was completed with 21 participants in each group (Fig. 1).

A total of 42 patients were included and allocated into two groups: Group 1 comprised individuals with RA and periodontitis who were not receiving anti-TNF- α therapy ($n = 21$). At the same time, Group 2 consisted of those with RA and periodontitis under anti-TNF- α treatment for a minimum duration of one year ($n = 21$). Clinical parameters including the number of swollen joints (SJs), tender joints (TJs), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), visual analog scale (VAS), disease activity score 28 (DAS28), medications used, and treatment durations were recorded. DAS28 was calculated using TJs, SJs, ESR, CRP, and VAS, a standard method for assessing RA disease activity [27]. All rheumatologic assessments were conducted by a single rheumatologist (OC).

Periodontal Examination

Periodontal evaluations were carried out by a certified periodontist (MB). The intraclass correlation coefficients (ICC) were 0.995 for clinical attachment loss (CAL) and

0.987 for probing pocket depth (PPD), indicating excellent intra-examiner reliability. Periodontitis diagnosis was made in accordance with the 2017 World Workshop classification [26]. Clinical parameters assessed included the gingival index (GI) [28], plaque index (PI) [29], CAL, PPD, and bleeding on probing (BOP) [30]. Stage III-IV periodontitis was diagnosed in patients presenting with interdental CAL ≥ 5 mm, PPD ≥ 6 mm, history of multiple tooth loss, and deep periodontal lesions extending to the root apex [26].

Sample collection

GCF and serum samples were collected at the Faculty of Dentistry, Recep Tayyip Erdoğan University, between 08:00 and 10:00 a.m., following 15–20 min of rest. For serum collection, 5 mL of venous blood was drawn into anticoagulant-free tubes, centrifuged at 4000 rpm for 10 min, and aliquoted into Eppendorf tubes.

GCF sampling was performed one day after the periodontal examination to minimize contamination from probing-induced bleeding. Samples were obtained from four sites with the deepest periodontal pockets using Periopaper strips (Proflow Inc., Amityville, NY), following removal of supragingival plaque, air-drying, and isolation with cotton rolls. Strips were inserted into the gingival sulcus until slight resistance was felt and left in place for 30 s. GCF volume was measured using a Periotron device (Periotron 8010; Harco Electronics, Winnipeg, Canada). Strips contaminated with saliva or blood were excluded. Accepted strips were placed into Eppendorf tubes containing 200 μ L phosphate-buffered saline (PBS, pH 7.4) and stored at -80°C until analysis.

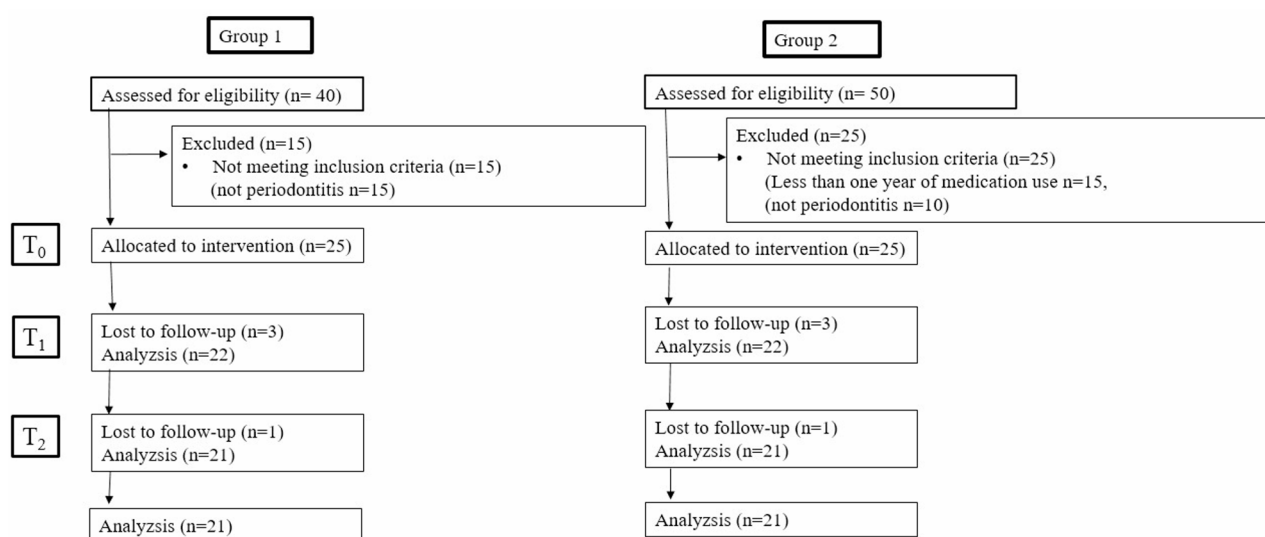


Fig. 1 Flowchart of the study. T0; baseline, T1; 3 months after non-surgical periodontal treatment (NSPT), T2; 6 months after NSPT, RA; rheumatoid arthritis, Group 1; individuals with RA and periodontitis who were not receiving anti-TNF- α therapy, Group 2; individuals with RA and periodontitis under anti-TNF- α treatment for a minimum duration of one year

NSPT was applied after baseline measurements. Clinical parameters and biological samples were re-evaluated at baseline (T0), 3 months (T1), and 6 months (T2) post-therapy.

Biochemical analyses

All biochemical assays were conducted at the Recep Tayyip Erdoğan University Medical Biochemistry Laboratory by two experienced analysts (MA, MA). Levels of RANKL, OPG, and MMP-8 in serum and GCF were determined using ELISA kits from Elabscience (Catalog Nos: E-EL-H1450, E-EL-H5813, E-EL-H1341) according to the manufacturer's protocols. RANKL concentrations were reported in pg/mL, while OPG and MMP-8 were expressed in ng/mL.

Lipid peroxidation was assessed by measuring thiobarbituric acid-reactive substances (TBARS) following the method of Ohkawa et al. [31]. Serum MDA levels were determined via standard curve comparison and expressed in nmol/mL. GSH was quantified using Ellman's reagent [32]. Briefly, 116.6 μ L of 3 M Na_2HPO_4 and 41.7 μ L of DTNB (4 mg DTNB in 10 mL of 1% sodium citrate) were mixed with 41.7 μ L of serum, and absorbance was read at 412 nm. GSH concentrations were calculated using a standard curve ranging from 0.2 to 1 mM and reported in mM [33].

TAS and TOS were measured using commercial kits (Mega Medical Industry and Trade Ltd., Turkey) on the DxC700 Beckman Coulter autoanalyzer. Results were expressed as μ mol Trolox equivalent/L for TAS and μ mol hydrogen peroxide (H_2O_2) equivalent/L for TOS. The oxidative stress index (OSI) was calculated as the ratio of TOS to TAS, using the formula: $\text{OSI} = \text{TOS} (\mu\text{mol H}_2\text{O}_2 \text{ eq./L}) / \text{TAS} (\mu\text{mol Trolox eq./L})$ [34].

Statistical analysis

The sample size for this study was calculated using MMP-8 as the primary outcome variable, with two groups [35]. A priori power analysis using the G*Power (ver.3.1.9.7) software determined a required sample size of 46 participants (23 per group), based on an effect size of 0.8, power of 80%, and alpha error of 5%. Due to drop-out at the 3- and 6-month follow-ups, the final sample consisted of 42 patients (21 per group). Statistical analyses were performed using IBM SPSS Statistics, ver.29 (SPSS Inc., Chicago, USA). Data with normal distribution were presented as mean $\pm$ standard deviation, and non-normally distributed data were shown as median (min–max). Group comparisons were conducted using either the independent samples t-test or Mann–Whitney U test, depending on data distribution. Repeated measures were analyzed using repeated ANOVA with Bonferroni correction or Friedman's test. Categorical variables were compared using Chi-square tests. Correlations between

continuous variables were examined using Spearman's rank correlation coefficient. Statistical significance was set at $p < 0.05$.

Results

The demographic characteristics and RA-related clinical parameters of the study population are summarized in Table 1. Among the 42 participants, 16 were male, and 26 were female. No significant differences were observed between the two groups in terms of sex, age, RF, VAS, DAS28-ESR, CRP, or ESR ($p > 0.05$). However, a significant difference was noted in DAS28-CRP scores ($p < 0.05$).

The inter- and intragroup comparisons of periodontal clinical parameters are presented in Table 2. Between-group analysis revealed that at six months following NSPT, PI was significantly higher in the anti-TNF- α treatment group ($p = 0.006$). At three months post-NSPT, BOP was also significantly elevated in the same group compared to patients not receiving anti-TNF- α therapy ($p = 0.020$). Other periodontal variables showed no statistically significant intergroup differences ($p > 0.05$). Within-group comparisons showed significant reductions in PI, BOP, GI and CAL at both three and six months post-NSPT relative to baseline in both groups ($p < 0.001$). PPD values decreased significantly in the group not receiving anti-TNF- α therapy at 3 and 6 months post-NSPT compared to baseline ($p < 0.05$).

Analysis of GCF parameters demonstrated a significantly lower RANKL/OPG ratio in the anti-TNF- α group at baseline and six months post-NSPT compared to the control group ($p = 0.012$ and $p = 0.017$, respectively), while no significant differences were observed for GCF RANKL, OPG, or MMP-8 levels ($p > 0.05$) (Table 3). In intragroup analysis, GCF MMP-8 levels were significantly increased at both three and six months post-NSPT in both groups ($p < 0.05$).

Regarding serum biomarkers, OSI was significantly higher in the anti-TNF- α group at baseline compared to the control group ($p = 0.003$). No significant intergroup differences were detected for serum levels of RANKL, OPG, RANKL/OPG, MMP-8, MDA, GSH, TAS, or TOS ($p > 0.05$) (Table 3). In the control group, serum MDA levels significantly declined at both follow-up points, while GSH levels decreased at three months but significantly increased by the sixth month ($p < 0.05$). OPG levels increased significantly at month 3 compared to baseline, but decreased significantly at six months compared to three months ($p < 0.05$). A significant increase was observed in RANKL/OPG and TAS levels at 6 months compared to 3 months ($p < 0.05$). In the anti-TNF- α group, serum levels of MDA and OSI significantly decreased at three and six months post-NSPT compared to baseline ($p < 0.05$). GSH decreased significantly at

Table 1 Comparison of demographic data and RA-related parameters by group

Parameters		Group 1 (n = 21)	Group 2 (n = 21)	p
Gender (male/female) (n)		8/13	8/13	1.00
Age (years; mean ± SD)		51 ± 11	57 ± 7	0.059
RF (positive/negative) (n)		10/11	10/11	1.00
VAS (mean ± SD)		5.1 ± 2.72	3.71 ± 2.90	0.060
DAS28CRP (mean ± SD)		2.76 ± 0.83	2.3 ± 0.92	0.049*
DAS28ESR (mean ± SD)		2.98 ± 1.05	2.77 ± 1.54	0.303
CRP (median (min-max))		10 (0.5–39)	4.40 (0.6–26)	0.252
ESR (median (min-max))		13 (2–86)	12 (2–41)	0.820
TJs (n/%)	0 Joint	3/14.3	7/33.3	
	1 Joint	9/42.9	8/38.1	
	2 Joint	4/19	3/14.3	
	3 Joint	4/19	2/9.5	
	4 Joint	0/0	1/4.8	
	5 Joint	1/4.8	0/0	
SJs (n/%)	0 Joint	7/33.3	12/57.1	
	1 Joint	7/33.3	3/14.3	
	2 Joint	6/28.6	5/23.8	
	3 Joint	1/4.8	1/4.8	

Numbers in bold indicate a statistically significant difference

RF rheumatoid factor, VAS visual analog scale, DAS28 disease activity score28, CRP C reactive protein, ESR erythrocyte sedimentation rate, TJs number of tender parts, SJs number of swollen joints, min minimum, max maximum, SD standard deviation, n number, RA rheumatoid arthritis, Group 1 individuals with RA and periodontitis who were not receiving anti-TNF-α therapy, Group 2 individuals with RA and periodontitis under anti-TNF-α treatment for a minimum duration of one year, *, statistically significant at $p < 0.05$

Table 2 Comparison results of periodontal clinical parameters

parameters		Group 1	Group 1 (within-group p value) [#]	Group 2	Group 2 (within-group p value)	p value between groups*
PI (med (min-max))	T0	1.17 (0.98–1.75)	0.004 (T₀-T₁)	1.25 (1–4.3)	0.001 (T₀-T₁)	0.273
	T1	1.05 (0.33–1.22)	1.00 (T ₁ -T ₂)	1.08 (0.16–1.5)	0.741 (T ₁ -T ₂)	0.361
	T2	0.98 (0.2–1.45)	< 0.001 (T₀-T₂)	1.1 (0.5–1.5)	0.033 (T₀-T₂)	0.006
GI (med (min-max))	T0	1.26 (0.87–1.68)	0.001 (T₀-T₁)	1.34 (0.87–3.1)	0.010 (T₀-T₁)	0.378
	T1	1.1 (0.55–1.42)	1.00 (T ₁ -T ₂)	1.16 (0.27–1.62)	1.00 (T ₁ -T ₂)	0.423
	T2	1.02(0.33–1.35)	< 0.001 (T₀-T₂)	1.12 (0.33–1.48)	< 0.001 (T₀-T₂)	0.078
BOP (%; med (min-max))	T0	31.5 (13.33–82)	< 0.001 (T₀-T₁)	36.84 (17.8–85)	0.003 (T₀-T₁)	0.358
	T1	15(3.7–47)	1.00 (T ₁ -T ₂)	22.22 (7.4–60)	1.00 (T ₁ -T ₂)	0.020
	T2	15 (4.54–41.2)	< 0.001 (T₀-T₂)	21.5 (3.84–46)	< 0.001 (T₀-T₂)	0.217
PPD (mm; mean ± SD)	T0	2.61 ± 0.33	< 0.001 (T₀-T₁)	2.54 ± 0.52	0.080 (T ₀ -T ₁)	0.593
	T1	2.32 ± 0.34	1.00 (T ₁ -T ₂)	2.37 ± 0.36	1.00 (T ₁ -T ₂)	0.637
	T2	2.36 ± 0.37	0.018 (T₀-T₂)	2.37 ± 0.32	0.191 (T ₀ -T ₂)	0.912
CAL (mm; mean ± SD)	T0	2.8 ± 0.31	0.005 (T₀-T₁)	2.8 ± 0.49	0.029 (T₀-T₁)	0.997
	T1	2.55 ± 0.35	1.00 (T ₁ -T ₂)	2.6 ± 0.41	1.00 (T ₁ -T ₂)	0.676
	T2	2.54 ± 0.4	0.007 (T₀-T₂)	2.57 ± 0.35	0.019 (T₀-T₂)	0.797

Numbers in bold indicate a statistically significant difference

PI plaque index, GI gingival index, BOP bleeding on probing, PPD probing pocket depth, CAL clinical attachment loss. T0; baseline. T1; 3 months after non-surgical periodontal treatment (NSPT). T2; 6 months after NSPT. med; median. min; minimum. max; maximum. SD; standard deviation. RA; rheumatoid arthritis. Group 1; individuals with RA and periodontitis who were not receiving anti-TNF-α therapy. Group 2; individuals with RA and periodontitis under anti-TNF-α treatment for a minimum duration of one year. *: Independent Sample t Test or Mann Whitney-U Test. #: Generalized Linear Repeated Measures or Friedman test

month 3 compared to baseline ($p < 0.05$), while there was no significant difference at month 6 compared to baseline ($p > 0.05$). TOS levels significantly decreased by the sixth month in this group ($p < 0.05$).

Comparison of changes in periodontal parameters from baseline to six months revealed that the reduction in PI

was significantly greater in the non-anti-TNF-α group ($p < 0.05$) (Table 4). In contrast, the anti-TNF-α group exhibited a significantly greater reduction in serum TOS and OSI levels over the same period ($p < 0.05$) (Table 4).

Correlation analyses between periodontal and biochemical parameters showed that, in the control group,

Table 3 Comparison results of biochemical parameters according to groups

Parameters		Group 1	Group 1 (within-group <i>p</i> value) [#]	Group 2	Group 2 (within-group <i>p</i> value)	<i>p</i> value between groups [*]
RANKL (serum) (pg/mL; median (min-max))	T0	43.63 (8.58-126.66)	> 0.05 (T ₀ -T ₁)	38.06(13.32–98.59)	> 0.05 (T ₀ -T ₁)	0.308
	T1	56.17 (8.63-165.01)	> 0.05 (T ₁ -T ₂)	36.74(17.78-131.98)	> 0.05 (T ₁ -T ₂)	0.489
	T2	53.4 (8.26-220.53)	0.840 (T ₀ -T ₂)	42.66 (10.5-107.98)	> 0.05 (T ₀ -T ₂)	0.127
OPG (serum) (ng/mL; mean ± SD)	T0	1.23 ± 0.48	0.047 (T₀-T₁)	1.38 ± 0.51	> 0.05 (T ₀ -T ₁)	0.329
	T1	1.43 ± 0.44	0.012 (T₁-T₂)	1.44 ± 0.56	0.062 (T ₁ -T ₂)	0.917
	T2	1.13 ± 0.48	0.861 (T ₀ -T ₂)	1.21 ± 0.49	0.192 (T ₀ -T ₂)	0.601
RANKL/OPG (serum) (median (min-max))	T0	47.46 (6.21-174.52)	> 0.05 (T ₀ -T ₁)	30.06 (7.48-442.14)	0.368 (T ₀ -T ₁)	0.061
	T1	39.45 (4.9-127.11)	0.010 (T₁-T₂)	31.89 (9.39-268.54)	0.092 (T ₁ -T ₂)	0.505
	T2	52.87 (6.31-174.46)	0.092 (T ₀ -T ₂)	36.75 (7.16–210.5)	> 0.05 (T ₀ -T ₂)	0.195
MMP-8 (serum) (ng/mL; mean ± SD)	T0	4.75 ± 1.91	> 0.05 (T ₀ -T ₁)	5.6 ± 1.51	0.133 (T ₀ -T ₁)	0.114
	T1	4.75 ± 1.92	> 0.05 (T ₁ -T ₂)	4.99 ± 1.47	0.739 (T ₁ -T ₂)	0.649
	T2	4.64 ± 2.27	> 0.05 (T ₀ -T ₂)	5.41 ± 1.44	> 0.05 (T ₀ -T ₂)	0.197
MDA (serum) (nmol/mL; mean ± SD)	T0	3.46 ± 0.47	< 0.001 (T₀-T₁)	3.32 ± 0.53	< 0.001 (T₀-T₁)	0.365
	T1	2.62 ± 0.37	0.037 (T₁-T₂)	2.71 ± 0.29	0.005 (T₁-T₂)	0.367
	T2	2.4 ± 0.36	< 0.001 (T₀-T₂)	2.43 ± 0.46	< 0.001 (T₀-T₂)	0.816
GSH (serum) (mM; mean ± SD)	T0	0.45 ± 0.08	< 0.001 (T₀-T₁)	0.47 ± 0.11	< 0.001 (T₀-T₁)	0.663
	T1	0.35 ± 0.06	< 0.001 (T₁-T₂)	0.36 ± 0.08	< 0.001 (T₁-T₂)	0.592
	T2	0.46 ± 0.08	> 0.05 (T ₀ -T ₂)	0.47 ± 0.08	> 0.05 (T ₀ -T ₂)	0.909
RANKL (GCF) (pg/mL; (mean ± SD)	T0	14.01 ± 1.99	> 0.05 (T ₀ -T ₁)	13.96 ± 2.35	> 0.05 (T ₀ -T ₁)	0.933
	T1	14.13 ± 2.37	> 0.05 (T ₁ -T ₂)	14.07 ± 3.1	0.605 (T ₁ -T ₂)	0.945
	T2	13.64 ± 1.97	> 0.05 (T ₀ -T ₂)	13.1 ± 1.7	0.470 (T ₀ -T ₂)	0.349
OPG (GCF) (ng/mL) (median (min-max))	T0	0.10 (0.05–0.36)	> 0.05 (T ₀ -T ₁)	0.12(0.06–0.29)	0.368 (T ₀ -T ₁)	0.850
	T1	0.12(0.05–0.29)	> 0.05 (T ₁ -T ₂)	0.12(0.06–0.50)	> 0.05 (T ₁ -T ₂)	0.202
	T2	0.10 (0.06–0.33)	0.840 (T ₀ -T ₂)	0.14(0.05–0.28)	0.269 (T ₀ -T ₂)	0.139
RANKL/OPG (GCF) (median(min-max))	T0	133.2 (48.5-310.6)	> 0.05 (T ₀ -T ₁)	112.1 (43.79-258.17)	0.840 (T ₀ -T ₁)	0.012
	T1	128.6 (43.24–294.6)	> 0.05 (T ₁ -T ₂)	97.75 (35.42–256.5)	0.840 (T ₁ -T ₂)	0.141
	T2	151.89(31.67-215.83)	> 0.05 (T ₀ -T ₂)	93.54(49.32–236.8)	0.092 (T ₀ -T ₂)	0.017
MMP-8 (GCF) (ng/mL; (mean ± SD)	T0	0.57 ± 0.05	0.004 (T₀-T₁)	0.56 ± 0.05	0.002 (T₀-T₁)	0.477
	T1	0.62 ± 0.02	> 0.05 (T ₁ -T ₂)	0.61 ± 0.03	> 0.05 (T ₁ -T ₂)	0.370
	T2	0.61 ± 0.03	0.013 (T₀-T₂)	0.61 ± 0.03	0.001 (T₀-T₂)	1.000
TAS (serum) (median (min-max))	T0	1 (0.98–1.01)	0.651 (T ₀ -T ₁)	1 (0.94–1.02)	> 0.05 (T ₀ -T ₁)	0.285
	T1	1 (0.97–1.01)	0.021 (T₁-T₂)	1 (0.92–1.01)	> 0.05 (T ₁ -T ₂)	0.477
	T2	1 (0.98–1.03)	0.428 (T ₀ -T ₂)	1 (0.96–1.01)	0.840 (T ₀ -T ₂)	0.117
TOS (serum) (median (min-max))	T0	33.29 (10.85-234.55)	0.840 (T ₀ -T ₁)	30.98 (0.69-535.27)	0.840 (T ₀ -T ₁)	0.372
	T1	24.29 (10.44-169.68)	0.651 (T ₁ -T ₂)	36.92 (10.81-676.19)	0.368 (T ₁ -T ₂)	0.274
	T2	28.66 (9.2-286.76)	> 0.05 (T ₀ -T ₂)	28.45 (6.6-152.7)	0.026 (T₀-T₂)	0.715
OSI (serum) (median (min-max))	T0	3.29 (1.09–23.93)	> 0.05 (T ₀ -T ₁)	12.43 (1.74-996.96)	0.016 (T₀-T₁)	0.003
	T1	2.47 (1.04–17.13)	0.368 (T ₁ -T ₂)	3.65 (1.08–68.3)	> 0.05 (T ₁ -T ₂)	0.320
	T2	3.28 (1.32-910.89)	> 0.05 (T ₀ -T ₂)	4.31 (1.09–660)	0.001 (T₀-T₂)	0.697

Numbers in bold indicate a statistically significant difference

GCF gingival crevicular fluid, RANKL nuclear factor kappa-B ligand. OPG osteoprotegerin. MMP-8; matrix metalloproteinase-8; MDA; malondialdehyde. GSH; glutathione. TOS; total oxidant status. TAS; total antioxidant status. OSI; oxidative stress index. T0; baseline. T1; 3 months after non-surgical periodontal treatment (NSPT). T2; 6 months after NSPT. min: minimum. max; maximum. SD; standard deviation. RA; rheumatoid arthritis. Group 1; individuals with RA and periodontitis who were not receiving anti-TNF- α therapy. Group 2; individuals with RA and periodontitis under anti-TNF- α treatment for a minimum duration of one year. *: Independent Sample t Test or Mann Whitney-U Test. #: Generalized Linear Repeated Measures or Friedman test

PI was positively associated with serum MDA ($p < 0.001$); GI correlated positively with both serum MDA ($p < 0.001$) and GSH ($p < 0.05$); BOP showed positive correlations with GCF OPG ($p < 0.05$), serum MDA ($p < 0.001$), and GSH ($p < 0.05$); PPD was negatively correlated with GCF MMP-8 ($p < 0.05$) but positively with serum GSH

($p < 0.05$); and CAL negatively correlated with GCF MMP-8 ($p < 0.05$) (Table 5).

In the anti-TNF- α group, PI exhibited a strong positive correlation with serum MDA ($p < 0.001$) and a negative correlation with TAS ($p < 0.001$). BOP was positively correlated with both GCF RANKL/OPG ($p < 0.05$) and serum MDA ($p < 0.001$), while negatively associated with

Table 4 T0-T2 comparison results of periodontal and biochemical parameters

Parameters	Group 1	Group 2	<i>p</i> *
	T0-T2 difference		
PI (median (min-max))	0.41 (-0.2-1.52)	0.16 (-0.25-3.8)	0.044
GI (median (min-max))	0.32 (-0.15-0.9)	0.2 (-0.48-2.48)	0.642
BOP (%) (median (min-max))	12.88 (-2.8-72.75)	17 (-14.75-53.75)	0.744
PPD (mm) (mean ± SD)	0.25 ± 0.31	0.16 ± 0.45	0.244
CAL (mm) (mean ± SD)	0.26 ± 0.32	0.23 ± 0.41	0.395
RANKL (Serum) (pg/mL) (median (min-max))	-7.54 (-96.71-73.26)	1.35 (-45.66-62.12)	0.163
OPG (Serum) (ng/mL; mean ± SD)	0.1 ± 0.45	0.17 ± 0.35	0.281
RANKL/OPG (GCF) (med (min-max))	-11.91 (-61.76-74.89)	-2.42 (-86.32-231.64)	0.058
MMP-8 (Serum) (ng/mL; mean ± SD)	0.11 ± 2.03	0.19 ± 1.69	0.439
MDA (Serum) (nmol/mL; mean ± SD)	1.06 ± 0.47	0.89 ± 0.6	0.156
GSH (Serum) (mM; mean ± SD)	-0.01 ± 0.08	0 ± 0.12	0.379
RANKL (GCF) (pg/mL; mean ± SD)	0.37 ± 3.04	0.85 ± 2.34	0.285
OPG (GCF) (ng/mL; (median (min-max))	0.01 (-0.22-0.11)	-0.03 (-0.16-0.1)	0.089
RANKL/OPG (Serum) (median (min-max))	-6.56 (-127.05-153.6)	26.8 (-47.66-187.52)	0.099
MMP-8 (GCF) (ng/mL; mean ± SD)	-0.04 ± 0.05	-0.05 ± 0.06	0.271
TAS (Serum) (median (min-max))	0 (-0.04-0.02)	-0.01 (-0.05-0.04)	0.776
TOS (Serum) (median (min-max))	-1.68 (-217.41-112.8)	19.12 (-57.77-382.57)	0.019
OSI (Serum) (median (min-max))	-0.42 (-909.64-11.76)	3.02 (-591-995.5)	0.004

Numbers in bold indicate a statistically significant difference

PI plaque index, GI gingival index, BOP bleeding on probing, PPD probing pocket depth, CAL clinical attachment loss, GCF gingival crevicular fluid, RANKL nuclear factor kappa-B ligand, OPG osteoprotegerin, MMP-8 matrix metalloproteinase-8, MDA malondialdehyde, GSH glutathione, TOS total oxidant status, TAS total antioxidant status, OSI oxidative stress index, T0; baseline, T2; 6 months after nonsurgical periodontal treatment, min: minimum, max; maximum, SD; standard deviation, RA; rheumatoid arthritis, Group 1; individuals with RA and periodontitis who were not receiving anti-TNF- α therapy, Group 2; individuals with RA and periodontitis under anti-TNF- α treatment for a minimum duration of one year. *: Independent Sample t Test or Mann Whitney-U Test

GCF OPG ($p < 0.05$). PPD showed positive correlations with serum MMP-8 ($p < 0.05$) and MDA ($p < 0.05$), and CAL was positively correlated with both serum MMP-8 ($p < 0.05$) and MDA ($p < 0.001$) (Table 6).

Discussion

As far as the current literature indicates, no prior study has comprehensively evaluated how anti-TNF- α therapy influences both clinical and biochemical outcomes following NSPT in patients diagnosed with both RA and periodontitis. The results showed that although baseline values of PI, GI, and BOP were higher in the anti-TNF- α group, all periodontal parameters—including PPD and CAL—showed improvement after NSPT in both groups. Moreover, patients receiving anti-TNF- α therapy demonstrated lower GCF RANKL/OPG ratios and higher OSI levels at baseline, with both parameters significantly decreasing post-treatment. Positive correlations between oxidative stress markers (particularly MDA) and periodontal indices (PI, GI, PPD, CAL) in the anti-TNF- α group raising the possibility that these agents contribute to improved periodontal recovery by affecting inflammatory pathways, bone turnover, and oxidative stress regulation.

To evaluate localized periodontal responses, we utilized GCF sampling, a minimally invasive and site-targeted approach, in parallel with systemic serum analysis

[36]. The study groups were matched for age and sex to eliminate demographic confounding factors.

Interestingly, PI and BOP were significantly higher in the anti-TNF- α group despite the treatment, while other clinical parameters showed no significant intergroup differences in the present study. This contrasts with the findings of Mayer et al., who reported lower GI, BOP, PPD, and CAL values in anti-TNF- α -treated patients. Other studies have reported mixed outcomes, with some showing no significant changes in GI [22], CAL [21–23, 37], or PPD [17, 21–23, 37] post-treatment with anti-TNF- α agents. In contrast, others noted either increases [36], decreases [15, 17] or no significant difference [21, 23] in BOP. Unlike our findings, there were also studies that found an increase in GI [23, 37], a decrease in PI [22, 37] or no significant difference in PI [17, 21, 23] after the use of anti-TNF- α drugs. Such variability may be attributed to differences in oral hygiene behaviors, sample characteristics, and the independent mechanisms governing inflammation and bone loss.

In the present study, we used high-specificity ELISA kits suitable for low-volume samples such as GCF [17, 38, 39]. While no significant differences were found in GCF RANKL or OPG levels, the RANKL/OPG ratio was significantly lower in the anti-TNF- α group at both baseline and six months post-NSPT, in this study. Over time, the rate also decreased in the anti-TNF- α group, although not statistically significant. Although no previous studies

Table 5 Group 1 correlation analyses

Parameters	Serum MMP-8 (ng/ml)	GCF MMP-8 (ng/ml)	Serum OPB (ng/ml)	GCF OPB (ng/ml)	Serum RANKL (pg/ml)	GCF RANKL (pg/ml)	Serum MDA (nmol/mL)	Serum GSH (mM)	PI	GI	BOP(%)	PPD (mm)	CAL (mm)	TAS	TOS	OSI	Serum RANKL/OPG
GCF MMP-8 (ng/ml)	r -0.064	–															
p	0.616																
Serum OPB (ng/ml)	r -0.127	0.068	–														
p	0.322	0.597															
GCF OPB (ng/ml)	r 0.176	-0.057	-0.193	–													
p	0.168	0.660	0.129														
Serum RANKL (pg/ml)	r 0.326**	0.065	0.194	0.091	–												
p	0.009	0.614	0.127	0.477													
GCF RANKL (pg/ml)	r 0.005	-0.149	0.199	-0.095	0.140	–											
p	0.966	0.244	0.118	0.460	0.274												
Serum MDA (nmol/mL)	r 0.166	-0.283*	0.086	0.035	-0.057	0.054	–										
p	0.194	0.025	0.503	0.784	0.655	0.675											
Serum GSH(mM)	r 0.220	-0.173	-0.246	0.037	0.050	-0.061	0.153	–									
p	0.084	0.175	0.052	0.774	0.700	0.633	0.231										
PI	r 0.041	-0.102	0.136	0.091	0.061	0.194	0.431**	0.128	–								
p	0.753	0.427	0.287	0.477	0.636	0.128	0.000	0.316									
GI	r 0.019	-0.152	0.034	0.206	0.084	0.137	0.476**	0.249*	0.638**	–							
p	0.885	0.236	0.791	0.105	0.511	0.284	0.000	0.049	0.000								
BOP (%)	r 0.031	-0.139	0.022	0.318*	-0.027	0.092	0.366**	0.304*	0.537**	0.716**	–						
p	0.810	0.279	0.865	0.011	0.834	0.474	0.003	0.015	0.000	0.000							
PPD (mm)	r 0.083	-0.278*	0.080	0.116	0.099	0.234	0.209	0.253*	0.253*	0.526**	0.373**	–					
p	0.515	0.027	0.532	0.364	0.440	0.065	0.100	0.046	0.045	0.000	0.003						
CAL (mm)	r 0.085	-0.258*	0.080	0.128	0.120	0.224	0.216	0.240	0.267*	0.542**	0.344**	0.971**	–				
p	0.508	0.041	0.533	0.319	0.348	0.078	0.089	0.059	0.035	0.000	0.006	0.000					
Serum TAS	r 0.081	0.113	-0.361**	-0.028	0.093	0.027	-0.165	0.277*	-0.178	0.066	0.011	0.087	0.108	–			
p	0.530	0.377	0.004	0.830	0.470	0.834	0.197	0.028	0.162	0.605	0.933	0.496	0.400				
Serum TOS	r 0.081	0.113	-0.361**	-0.028	0.093	0.027	-0.165	0.277*	-0.178	0.066	0.011	0.087	0.108	-0.002	–		
p	0.530	0.377	0.004	0.830	0.470	0.834	0.197	0.028	0.162	0.605	0.933	0.496	0.400	0.986			
Serum OSI	r 0.339**	0.042	0.062	0.183	0.062	0.179	0.084	0.340**	0.172	0.081	0.220	0.144	0.140	0.068	0.906**	–	
p	0.007	0.745	0.631	0.152	0.628	0.161	0.514	0.006	0.178	0.526	0.083	0.259	0.274	0.595	0.000		
Serum RANKL/OPG	r 0.248*	0.026	0.035	0.130	0.012	0.183	0.065	0.358**	0.091	0.018	0.190	0.074	0.047	0.204	0.020	-0.024	–
p	0.050	0.842	0.785	0.310	0.927	0.151	0.613	0.004	0.476	0.886	0.136	0.567	0.717	0.109	0.879	0.855	
GCF RANKL/OPG	r 0.363**	0.057	-0.314*	0.100	0.819**	0.046	-0.139	0.210	0.057	0.067	-0.027	0.045	0.054	0.058	-0.085	-0.032	-0.070
p	0.003	0.657	0.012	0.435	0.000	0.723	0.276	0.098	0.659	0.600	0.833	0.725	0.672	0.654	0.879	0.805	0.558

Numbers in bold indicate a statistically significant difference

*, $p < 0.05$; **, $p < 0.01$; r , Spearman correlation coefficient, PI plaque index, GI gingival index, BOP bleeding on probing, PPD probing pocket depth, CAL clinical attachment loss, GCF gingival crevicular fluid, RANKL nuclear factor kappa-B ligand, OPG osteoprotegerin, MMP-8 matrix metalloproteinase-8, MDA malondialdehyde, GSH glutathione, TOS total oxidant status, OSI oxidative stress index, RA rheumatoid arthritis, Group 1: individuals with RA and periodontitis who were not receiving anti-TNF- α therapy, Group 2: individuals with RA and periodontitis under anti-TNF- α treatment for a minimum duration of one year

Table 6 Group 2 correlation analyses

Parameters	Serum MMP-8 (ng/ml)	GCF MMP-8 (ng/ml)	Serum OPG (ng/ml)	GCF OPG (ng/ml)	Serum RANKL (pg/ml)	GCF RANKL (pg/ml)	Serum MDA (nmol/mL)	Serum GSH (mM)	PI	GI	BOP (%)	PPD (mm)	CAL (mm)	TAS	TOS	OSI	Serum RANKL/OPG
GCF MMP-8 (ng/ml)	r 0.053	--															
	p 0.677																
Serum OPG (ng/ml)	r -0.131	-0.101	--														
	p 0.305	0.429															
GCF OPG (ng/ml)	r 0.107	-0.002	-0.051	--													
	p 0.404	0.989	0.693														
Serum RANKL (pg/ml)	r -0.313*	0.161	0.090	-0.160	--												
	p 0.013	0.209	0.481	0.209													
GCF RANKL (pg/ml)	r -0.066	-0.145	-0.014	-0.095	0.036	--											
	p 0.609	0.256	0.916	0.459	0.777												
Serum MDA (nmol/mL)	r 0.125	-0.408**	0.271*	-0.239	-0.078	0.129	--										
	p 0.327	0.001	0.032	0.059	0.541	0.315											
Serum GSH (mM)	r -0.069	-0.196	0.017	-0.132	0.193	0.179	0.018	--									
	p 0.589	0.123	0.896	0.303	0.129	0.160	0.888										
PI	r 0.066	-0.086	0.092	-0.135	-0.196	0.083	0.341**	0.082	--								
	p 0.605	0.505	0.472	0.293	0.124	0.520	0.006	0.525									
GI	r 0.055	-0.067	0.199	-0.148	-0.104	0.105	0.369**	-0.105	0.666**	--							
	p 0.669	0.603	0.117	0.246	0.419	0.415	0.003	0.414	0.000								
BOP (%)	r 0.101	-0.129	0.219	-0.258*	-0.111	0.107	0.481**	-0.139	0.623**	0.818**	--						
	p 0.431	0.314	0.085	0.041	0.385	0.404	0.000	0.279	0.000	0.000							
PPD (mm)	r 0.273*	-0.165	-0.040	0.000	-0.141	0.029	0.268*	0.025	0.308*	0.364**	0.393**	--					
	p 0.030	0.197	0.753	0.997	0.270	0.824	0.034	0.843	0.014	0.003	0.001						
CAL (mm)	r 0.276*	-0.163	-0.057	0.047	-0.049	-0.024	0.325**	0.073	0.319*	0.320*	0.350**	0.900**	--				
	p 0.028	0.201	0.656	0.716	0.701	0.855	0.009	0.571	0.011	0.010	0.005	0.000					
TAS	r 0.002	0.198	-0.154	-0.044	0.207	-0.124	-0.330**	-0.050	-0.328**	-0.111	-0.096	0.066	0.069	--			
	p 0.990	0.120	0.228	0.733	0.103	0.334	0.008	0.700	0.009	0.387	0.456	0.606	0.589				
TOS	r 0.022	-0.101	0.182	-0.013	-0.081	0.148	0.375**	0.047	-0.058	-0.129	0.063	-0.037	0.003	-0.289*	--		
	p 0.863	0.433	0.154	0.917	0.530	0.248	0.002	0.713	0.654	0.315	0.621	0.776	0.981	0.022			
OSI	r 0.023	-0.118	0.064	-0.003	-0.131	0.140	0.456**	0.122	0.149	0.013	0.053	0.007	0.078	-0.496**	0.562**	--	
	p 0.858	0.358	0.619	0.983	0.307	0.275	0.000	0.340	0.242	0.921	0.678	0.959	0.545	0.000	0.000		
Serum RANKL/OPG	r -0.151	0.181	-0.438**	-0.116	0.782**	0.052	-0.166	0.171	-0.123	-0.181	-0.236	-0.111	-0.041	0.206	-0.243	-	--
	p 0.237	0.156	0.000	0.367	0.000	0.684	0.194	0.180	0.335	0.157	0.063	0.387	0.748	0.105	0.055	0.146	0.255

Table 6 (continued)

Parameters	Serum MMP-8 (ng/ml)	GCF MMP-8 (ng/ml)	Serum OPG (ng/ml)	GCF OPG (ng/ml)	Serum RANKL (pg/ml)	GCF RANKL (pg/ml)	Serum MDA (nmol/mL)	Serum GSH (mM)	PI	GI	BOP (%)	PPD (mm)	CAL (mm)	TAS	TOS	OSI	Serum RANKL/OPG
GCF RANKL/OPG	r	-0.116	-0.051	0.031	-0.955**	0.150	0.261*	0.190	0.164	0.158	0.266*	-0.006	-0.056	0.013	0.077	0.048	0.121
OPG	p	0.364	0.692	0.807	0.000	0.241	0.039	0.135	0.199	0.217	0.035	0.962	0.663	0.918	0.550	0.708	0.343

Numbers in bold indicate a statistically significant difference

*, $p < 0.05$, **, $p < 0.01$, r Spearman correlation coefficient, PI plaque index, GI gingival index, BOP bleeding on probing, PPD probing pocket depth, CAL clinical attachment loss, GCF gingival crevicular fluid, RANKL nuclear factor kappa-B ligand, OPG osteoprotegerin, MMP-8 matrix metalloproteinase-8, MDA malondialdehyde, GSH glutathione, TOS total antioxidant status, TAS total antioxidant status, OSI oxidative stress index, RA rheumatoid arthritis, Group 1: individuals with RA and periodontitis who were not receiving anti-TNF- α therapy, Group 2: individuals with RA and periodontitis under anti-TNF- α treatment for a minimum duration of one year

have directly assessed this ratio in RA patients receiving anti-TNF- α therapy, several studies have demonstrated its association with alveolar bone loss in periodontal disease [40–42], with post-treatment reductions in the ratio consistent with our findings [40]. There are studies reporting that biomarker changes associated with periodontal disease progression and response to treatment are predominantly more pronounced in oral fluids (GCF, saliva), while serum biomarkers may show weaker or variable correlations [43–45]. Since the effects of the inflammatory response in RA on local periodontal tissues and systemic circulation can occur through different biological mechanisms, this may lead to the fact that GCF and serum biomarker levels do not always show parallel changes. The differences observed in serum and GCF biomarker levels in the present study may also be related to these reasons.

MMP-8, an established marker of tissue degradation, was evaluated in both GCF and serum [46, 47]. Despite its known association with disease severity [46, 47], our study did not reveal significant intergroup differences in MMP-8 levels. In both groups, GCF MMP-8 levels increased significantly post-NSPT, while serum levels showed no significant change. In patients with RA, the inflammatory profile of oral fluids may differ from that of serum and joint fluid. In a study by Arvikar et al. [46], it was reported that the majority of RA patients included in the study received regular dental care, and an inflammatory profile dominated by neutrophil-related mediators such as IL-8 and MMP-8 was observed in saliva and GCF. These mediators were found to be at high levels not only in the presence of periodontitis but also in RA patients with gingivitis or periodontally healthy [46]. These findings suggest that an inflammatory response in gingival tissues may persist in RA patients regardless of periodontal health status. For these reasons, even though improvement in clinical parameters was observed post-NSPT in the present study, the RA-specific neutrophilic inflammatory response may have caused MMP-8 levels to remain high or temporarily increase in GCF. Furthermore, the relatively limited sample size of our study and the analytical sensitivity of the methods used may also have contributed to this variability.

Oxidative stress, a known contributor to RA pathogenesis [48], was assessed using a comprehensive panel of markers, including MDA, GSH, TOS, TAS, and OSI. In some studies, anti-TNF- α therapy has been observed to decrease oxidative stress markers [48, 49]. Serum MDA levels significantly reduced in both groups following NSPT. However, changes in GSH differed between groups: in both groups, GSH decreased in three months and rose again in six months. These divergent trends may reflect different patterns of systemic oxidative response to treatment.

Measurements of TOS and TAS provide broader insight into redox balance [50]. In our study, OSI was significantly higher at baseline in the anti-TNF- α group, and both OSI and TOS levels decreased significantly after NSPT in this group, whereas TAS levels remained stable. In contrast, the untreated group showed an increase in TAS from three to six months, but no significant change in OSI or TOS. These findings suggest that anti-TNF- α therapy may enhance oxidative stress reduction in response to periodontal treatment; this conclusion is supported by the findings of the study by Cacciapaglia et al. [49].

Correlation analyses reinforced these observations. In the anti-TNF- α group, serum MDA positively correlated with PI, BOP, PPD, and CAL, while MMP-8 was linked to PPD and CAL. PI was negatively correlated with TAS, and BOP was inversely correlated with GCF OPG and positively associated with the RANKL/OPG ratio. This pattern reflects the complex interplay between oxidative and inflammatory factors in periodontal tissue dynamics.

Overall, the data did not clearly indicate that anti-TNF- α therapy could increase the effectiveness of NSPT. However, the study has some limitations. These include the small sample size and the loss of participants during the follow-up process. This study should therefore be considered preliminary, and larger, longitudinal clinical trials are needed to further elucidate the therapeutic interactions between RA treatment and periodontal health.

Conclusion

To date, no previous study has simultaneously evaluated the clinical and biochemical impact of anti-TNF- α therapy on NSPT outcomes in individuals with RA and periodontitis, using both GCF and serum levels of RANKL/OPG, MMP-8, MDA, GSH, TOS, TAS, and OSI. Our findings suggest that NSPT is effective in reducing inflammation and tissue destruction in both treatment groups. However, the addition of anti-TNF- α therapy had no significant effect on further enhancing these effects by modulating bone resorption, inflammatory responses, and oxidative stress. To better understand these interactions and optimize therapeutic strategies, future studies with larger sample sizes and extended follow-up periods are essential. We believe the current study provides a foundation for such investigations.

Abbreviations

RA	Rheumatoid Arthritis
TNF- α	Tumor Necrosis Factor-alpha
IL-1 β	Interleukin-1 beta
MMPs	Matrix Metalloproteinases
RANKL	Receptor Activator of the Nuclear factor Kappa B Ligand
ROS	Reactive Oxygen Species
TOS	Total Oxidant Status
TAS	Total Antioxidant Status

MDA	Malondialdehyde
GSH	Glutathione
DAS	Disease Activity Scores
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
DMARDs	Disease-modifying anti-rheumatic drugs
EULAR	According to the European League Against Rheumatism
JAK	Janus Kinase
NSPT	Non-surgical Periodontal Therapy
OPG	Osteoprotegerin
GCF	Gingival Crevicular Fluid
OSI	Oxidative Stress Index
SJs	Swollen Joints
TJs	Tender Joints
ESR	Erythrocyte Sedimentation Rate
CRP	C-reactive Protein
VAS	Visual Analog Scale
ICC	Intraclass Correlation Coefficients
CAL	Clinical Attachment Loss
PPD	Probing Pocket Depth
GI	Gingival Index
BOP	Bleeding on Probing
PBS	Phosphate-buffered Saline
TBARS	Thiobarbituric Acid Reactive Substances
H ₂ O ₂	Hydrogen Peroxide

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Authors' contributions

Planning of the study: HY, MB, OC and OK; Methodology: HY, MB, OC, OK, MA and SAB; Analysis: MA and MA; Evaluation of the results: HY, MB, MA and MA; Research and verification: HY and MB; Visualization: HY, MB; Writing: HY, MB and OK; Review and editing: HY, MB, OC, OK, MA and SAB; All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Non-Invasive Clinical Research Ethics Committee of Recep Tayyip Erdoğan University (Approval No: 2023/213). The study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. The purpose and content of the research were explained to all individuals included in the study and voluntary consent forms were signed.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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