ORIGINAL ARTICLE

Salivary levels of BAFF, TWEAK, and soluble CD163 and salivary arginase activity before and after periodontal treatment

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Abstract

Objective: To monitor salivary B-cell activating factor (BAFF), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), and soluble (s)CD163 levels and arginase activity in periodontitis patients following nonsurgical periodontal treatment.

Background: BAFF, TWEAK, and sCD163 and arginase are associated with activities of B cells and macrophages, which are important regulators of periodontal immune-inflammatory response and healing following treatment. Increased salivary BAFF and sCD163 levels and arginase activity in periodontitis have been demonstrated, but their changes following treatment have not been evaluated before.

Materials and Methods: Forty-four Stage III/IV periodontitis patients and 35 periodontally healthy controls were included in the study. Full-mouth periodontal measurements were recorded and unstimulated saliva was obtained from all participants at baseline. Sample collection and measurements were repeated in periodontitis patients at 2, 6, 12, and 24 weeks following full-mouth scaling and root debridement, whereas controls were only seen at baseline. BAFF, TWEAK, and sCD163 levels were analyzed with bead-based multiplexed immunoassay. Arginase activity was measured with Chinard's method.

Results: BAFF ($p < .001$) and sCD163 ($p = .003$) levels and arginase activity ($p < .015$) were higher in periodontitis patients compared to healthy controls. BAFF levels ($p < .001$) and arginase activity ($p < .001$) of periodontitis patients were reduced at 2 weeks posttreatment and continued to decrease up to 6 ($p = .038$) and 12 weeks ($p = .024$), respectively. The reduction of sCD163 levels became significant ($p = .003$) at 24 weeks posttreatment.

Conclusions: The decrease in salivary BAFF levels 2 weeks after periodontal treatment indicates a change in cell signaling toward limited B-cell activation. Decreasing arginase activity similarly reflects a significant reduction in inflammatory response. The reduction in sCD163 levels that are observed at 24 weeks may reflect a long-standing anti-inflammatory macrophage activation, given their multiple functions in immune response, inflammation, and healing.

1 | INTRODUCTION

Periodontitis is initiated and orchestrated by the interactions between pathogenic biofilm and the host response. Various signaling molecules such as cytokines and chemokines and cell types such as polymorphonuclear leukocytes, macrophages, and lymphocytes are involved in periodontal pathogenesis and healing following periodontal treatment.[1,2] Due to their high plasticity and diverse functional capabilities, macrophages are considered key regulators of the immune-inflammatory response.[3] They are broadly classified as pro-inflammatory M1 and anti-inflammatory, pro-repair M2 phenotypes. The phenotypic switch between macrophage types is considered to mediate inflammation and periodontal tissue loss.[4] Cells of B-lineage are the predominant cell types in periodontitis lesions and, together with the cytokines inducing their differentiation, they drive alveolar bone resorption.[5,6] B-cell activating factor (BAFF), a cytokine of the tumor necrosis factor (TNF) superfamily, induces B-cell proliferation and differentiation and is involved in signal transmission between B cells and monocyte-lineage cells.[7] BAFF is expressed by various cell types, such as macrophages, dendritic cells, B cells, epithelial cells, and T cells.[8] It has been shown that BAFF blockade in mice with periodontitis can shift macrophage polarization toward M2 phenotype by simultaneously inhibiting M1 and inducing M2 macrophages.[9]

M2 macrophages express high levels of CD163, the hemoglobin scavenger receptor, which is a surface marker of monocyte-lineage cells. The soluble form of CD163 (sCD163) is the shedding product of CD163^{+} cells, which occurs due to proteolytic cleavage as a response to inflammatory stimuli.[10] In pathological conditions, CD163 also acts as a scavenger for tumor necrosis factor-like weak inducer of apoptosis (TWEAK), another member of the TNF superfamily.[11] TWEAK is involved in cell proliferation, apoptosis, angiogenesis, and inflammation through several signaling pathways, and there is growing evidence on the role of interactions between TWEAK and its receptors (Fn14, and CD163 as a decoy receptor) in autoimmune diseases.[12] The CD163/TWEAK ratio has been associated with inflammatory conditions such as skin lesions and cardiovascular events.[13] Recently, our group revealed that baseline tissue levels of CD163 and the CD163/TWEAK ratio are associated with pocket healing following nonsurgical treatment.[14]

Arginase (L-arginine amidohydrolase) is an enzyme of the urea cycle hydrolyzing L-arginine to urea and to L-ornithine, a precursor of proline and polyamine, which are essential for cell proliferation and differentiation, collagen synthesis, and wound healing.[15] The number of arginase-expressing macrophages is increased in healing periodontal wounds and arginase is considered a potential marker of inflammation and healing via switching macrophage polarization.[16] Prior research has revealed that salivary arginase activity is increased in periodontitis and decreases following periodontal treatment.[17,18]

Saliva is a complex medium, containing proteins derived from salivary glands, gingival crevicular fluid, serum, microorganisms, etc., which can be related to various diseases, including periodontitis.[19–21] Salivary BAFF and sCD163 levels were found to be increased in periodontitis, but their alterations following periodontal treatment have not been demonstrated before.[22,23] Moreover, although higher gingival crevicular fluid levels of TWEAK were found in periodontitis patients, salivary TWEAK levels in periodontitis patients compared to periodontally healthy individuals and their alterations following treatment have not been investigated.[24] Our hypothesis was that baseline salivary levels of BAFF, sCD163, and TWEAK and salivary arginase activity are elevated in periodontitis and they gradually decrease following treatment. Therefore, this study aimed primarily to observe changes in BAFF, sCD163, and TWEAK levels and salivary arginase activity in individuals with periodontitis after nonsurgical treatment after controlling for smoking. The secondary aim was to compare the aforementioned analytes of periodontitis patients before treatment with those of periodontally healthy participants, again after controlling for smoking.

2 | MATERIALS AND METHODS

2.1 | Participant recruitment

This study was conducted as a continuation of the project, which was registered on clinicaltrials.gov with the number NCT04792372.[14] The study's accordance with the ethical principles of the Helsinki declaration was approved by the Ethics Committee of Biruni University's Medical Faculty, Türkiye (2015-KAEK-43-19-27). All participants were informed about the study protocol and signed written informed consent.

Sample size was determined as part of the main project with a statistical power analysis software (G*Power 3.1, Düsseldorf, Germany). The estimation was based on the difference between two independent means of gingival crevicular fluid TWEAK levels in periodontitis and those in periodontal health as reported before.[14,24] A minimum required sample size of 48 participants in total (smoker periodontitis vs. periodontally healthy and nonsmoker periodontitis vs. periodontally healthy) was calculated ($\alpha = 0.05$; $1 - \beta = 0.95$; $d = 1.594$). Individuals who applied to Biruni University's Faculty of Dentistry, Türkiye between March and August 2021 were initially recruited, reaching 44 periodontitis and 35 periodontally healthy individuals at the end of the study period, which was substantially more participants than calculated due to consideration of potential losses during follow-up and difficulty in predicting healing response. All participants initially received detailed clinical and radiographic examinations. Patients with generalized Stage III/IV Grade C

periodontitis and periodontally healthy subjects with at most 10% full-mouth bleeding on probing score and no sites with pocket depth >3 mm as controls were included in the study.[25] The grade was assigned based on indirect evidence of disease progression (percent bone loss/age) and the impact of smoking. Smokers were chosen among individuals who consumed at least five cigarettes a day. Eligible individuals who have less than 15 teeth, have any systemic disease with potential impact to the inflammatory status or periodontal condition, smoke occasionally (<5 cigarettes/day) or are former smokers, taken any antimicrobial or anti-inflammatory medicine in the previous 3 months, use contraceptives or are pregnant or in lactation were excluded. The periodontitis group of the current study was formed from the same individuals as in our previous publication, while the control group was primarily composed of different individuals.[14]

2.2 | Clinical measurements and periodontal treatment

Full-mouth clinical parameters were measured at six sites of each tooth by a previously calibrated examiner (E.D.; intraclass correlation coefficient = 0.87–0.90) at baseline (T0) in periodontally healthy individuals and at baseline and 2, 6, 12, and 24 weeks following treatment (T0–T4, respectively) in periodontitis patients: plaque index (PI), probing depth (PD), indirect clinical attachment level (CAL) by summing gingival recession and PD, and bleeding on probing (BoP). Periodontitis patients received supragingival scaling and root debridement performed with a piezoelectric scaler (Variosurg™, NSK) and gentle use of hand curettes (American Eagle Instruments). The treatment was conducted by the same clinician (M.Y.) in two consecutive sessions with a 30–60-min break in between. Detailed oral hygiene instructions were then delivered to the patients. Supragingival prophylaxis was repeated and oral hygiene was reinforced at 6, 12, and 24 weeks following treatment. The periodontally healthy control group received oral hygiene instructions after sample collection and periodontal recordings at baseline and they were not followed thereafter.

2.3 | Saliva collection

Unstimulated saliva samples were collected from periodontitis patients at baseline and at 2, 6, 12, and 24 weeks following treatment, and from healthy individuals at baseline, before any clinical measurements or interventions. Participants were asked not to consume any food or beverages for at least 2 h before the sample collection. All saliva samples were collected by passive expectoration in the morning, while the participants were sitting on a dental chair. The samples, which were collected into plastic tubes, were immediately stored at −80°C for a period of approximately 3–15 months and sent to Turku University, Finland in dry ice for the biochemical analyses.

2.4 | Biochemical analysis

Saliva samples were thawed and then centrifuged at 500× g for 10 min at 5°C. The supernatant fractions were used for the biochemical analysis. The levels of sCD163, TWEAK and BAFF were determined using bead-based immunoassay (Luminex xMAP, Luminex Corporation) with commercial kits (Bio-Plex Pro Human Inflammation Panel 1, Bio-Rad Laboratories) according to the manufacturer's instructions. The assays had the following limit of detection (LOD) ranges: sCD163: 1338.7–975916.6 pg/mL; TWEAK: 3.1–6772.8 pg/mL; BAFF: 91.5–200008.9 pg/mL. The samples were analyzed as monoplicates and the results were determined within the linear portions of four-parameter logistic curves. The intra- and inter-assay coefficients of variability reported by the manufacturer were as follows: BAFF, 1.6 and 5.2, respectively; TWEAK, 2.2 and 15.2, respectively; and sCD163, 4.2 and 8.1, respectively. Salivary arginase activity was analyzed by Chinard's method, measuring ornithine levels (IU/mL) produced by the hydrolysis of arginine by arginase.[26]

2.5 | Data analysis

Among the evaluated participants, three in the periodontitis group did not show up in the control session at 24 weeks, while the rest attended all sessions. The missing variables of these participants were handled according to their corresponding observations at 12 weeks. Statistical analysis was performed with statistics software (SPSS 27.0.1.0, IBM). Shapiro–Wilk test and Q–Q plot analysis revealed that the data were not normally distributed. A natural logarithmic transformation was first performed, achieving an approximate distribution of normal and equal error variances. Unadjusted and adjusted for age and smoking, univariate analysis of variance was conducted to compare the baseline variables of healthy and periodontitis subjects. The alterations in clinical and biochemical data of periodontitis patients between T0 and T4 were evaluated with repeated measures analysis of variance, controlling for smoking. In pairwise comparisons, Bonferroni adjusted p values were calculated. The correlations between the analytes and clinical parameters were evaluated with Spearman's rank correlation test. A value of $p < .05$ was considered significant.

3 | RESULTS

3.1 | Study population and clinical variables

Following drop-outs, 44 periodontitis patients (20 males; 18 smokers) and 35 periodontally healthy individuals (10 males; 15 smokers) finalized the study. The demographics and baseline clinical variables of the participants are presented in Table 1. The age of periodontitis patients was significantly higher than that of the periodontally healthy group ($p < .001$). As expected, baseline PI%, PD, CAL, and

TABLE 1 Demographics and baseline clinical measurements.

Demographics and clinical variables	Periodontally healthy (n = 35)	Periodontitis (n = 44)	p
Age (year)	34 (13)	40.5 (17)	**<.001**
Male	10 (28.6%)	20 (45.4%)	.125
Smokers	15 (42.9%)	18 (40.9%)	.862
Full-mouth PI%	8.4 (16.7)	85.4 (24.9)	**<.001**
Full-mouth mean PD	1.6 (0.4)	3.7 (0.7)	**<.001**
Full-mouth mean CAL	1.7 (0.4)	4.0 (0.6)	**<.001**
Full-mouth BoP%	1.9 (2.4)	72.3 (39.3)	**<.001**

Note: Sex and smoking distribution are given as *n* (%). The age and clinical variables are presented as median (interquartile range). *p* values in bold indicate statistically significant difference (<.05).
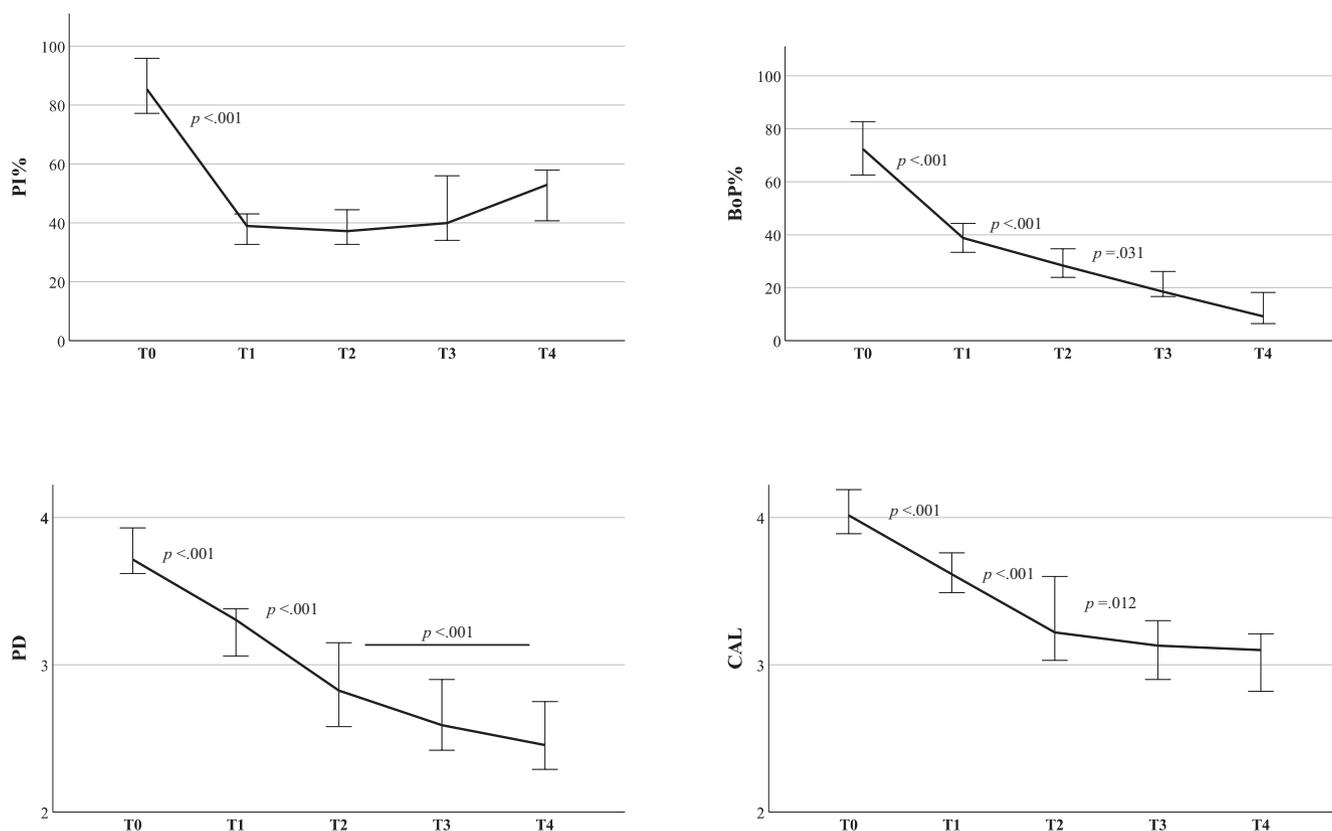

FIGURE 1 Clinical variables of participants with periodontitis at baseline (T0) and at 2 (T1), 6 (T2), 12 (T3), and 24 (T4) weeks following treatment. *p* values, which were calculated using repeated measures analysis of variance after controlling for smoking, adjusted to the Bonferroni correction for multiple comparisons and indicate changes in mean full-mouth periodontal parameters. BoP, bleeding on probing; CAL, clinical attachment level; PD, probing depth; PI, plaque index.

BoP% scores of the periodontally healthy group were lower than those of the periodontitis group (each *p* < .001). PI%, PD, CAL, and BoP% scores of the periodontitis patients significantly decreased following periodontal treatment (Figure 1). In the periodontitis group, the median (minimum–maximum) number of pockets (PPD ≥ 4 mm) of the participants with periodontitis were 74 (21–126) at T0, 52 (17–96) at T1, 31 (5–84) at T2, 20 (3–77) at T3, and 17.5 (0–81) at T4. Number of pockets with PPD ≥ 4 mm significantly decreased at T1 compared to baseline (*p* < .001), at T2 compared to T1 (*p* < .001), and at T4 compared to T2 (*p* = .003). The median (minimum–maximum) number of deep pockets (PPD ≥ 6 mm) was 21 (4–67) at T0, 10 (0–40)

at T1, 5 (0–40) at T2, 3 (0–44) at T3, and 2 (0–39) at T4, respectively. The number of pockets with PPD ≥ 6 mm significantly decreased at T1 compared to baseline (*p* < .001), at T2 compared to T1 (*p* < .001) and at T4 compared to T2 (*p* = .015).

3.2 | Salivary BAFF, TWEAK, and sCD163 levels

BAFF, TWEAK, and sCD163 levels were below the limit of detection (LOD) in 19 (54.35%), 14 (40%), and 24 (68.6%) healthy participants, respectively. BAFF levels were below the LOD in 3 (6.8%), 7 (15.9%),

13 (29.5%), 12 (27.3%), and 14 (31.8%) periodontitis patients at T0–T4, respectively. TWEAK levels were below the LOD in 21 (47.7%), 17 (38.6%), 16 (36.4%), 16 (36.4%), and 17 (38.6%) periodontitis patients at T0–T4, respectively. sCD163 levels were below the LOD in 9 (20.5%), 13 (29.5%), 22 (50%), 16 (36.4%), and 22 (50.0%) periodontitis patients at T0–T4, respectively. The biochemical variables below the LOD were substituted with half of the corresponding lowest LOD.[27] Arginase activity was detected in all samples at all time points.

Baseline salivary levels of BAFF, TWEAK, and sCD163 levels and arginase activity in periodontitis patients and in periodontally healthy individuals are presented in Table 2. BAFF ($F = 54.178$; $p < .001$; adjusted) and sCD163 ($F = 9.110$; $p = .003$; adjusted) levels and arginase activity ($F = 53.842$; $p = .015$; adjusted) were higher in periodontitis patients when compared to healthy participants. TWEAK levels ($p = .678$; adjusted) were similar among groups. BAFF ($p = .221$) and TWEAK ($p = .882$) levels were not affected by smoking. Non-smokers had significantly higher salivary sCD163 levels ($F = 16.861$; $p < .001$) and arginase activity ($F = 7.968$; $p = .006$).

The alterations of the analytes following periodontal treatment are presented in Figure 2. BAFF levels and arginase activity significantly decreased at T1 (both $p < .001$). BAFF levels and arginase activity continued to decrease between T1–T2 ($p = .038$) and T1–T3 ($p = .024$), respectively. sCD163 levels demonstrated significant alteration only at T4 ($p = .003$), while TWEAK levels were similar between T0 and T4. The correlations between the salivary analytes and clinical variables of periodontitis patients are presented in the Table S1.

4 | DISCUSSION

Here we show for the first time that salivary BAFF and sCD163 levels in periodontitis patients decrease following nonsurgical periodontal treatment. In the present study, the statistically significant reduction of BAFF levels and arginase activity occurred first at 2 weeks post-treatment, suggesting a rapid response to treatment, and continued to decrease until 6 and 12 weeks, respectively. On the other hand, the reduction of salivary sCD163 levels became significant later, at 6 months following treatment.

Salivary BAFF and sCD163 levels in periodontitis patients compared to healthy individuals have been investigated in prior research.[22,23] To the best of the authors' knowledge, salivary TWEAK levels of periodontitis patients compared to healthy controls and the alterations of salivary BAFF, sCD163, and TWEAK levels following periodontal treatment have not been evaluated before. As the shifts in arginase activity following treatment have been demonstrated in previous studies,[17,18] we implemented salivary arginase activity into our study as a positive control for macrophage-related immune-inflammatory response.

This study is a continuation of our previous research, where we reported an association between baseline tissue levels of M2 macrophage activity-related CD613, TWEAK, and IL-10 and healing outcomes at 2, 6, and 12 weeks following treatment. These time points were determined based on soft tissue healing and pocket reduction following nonsurgical periodontal treatment: The essential stages of healing are re-epithelization of the junctional epithelium and connective tissue maturation with collagen fiber orientation, which are observed at 2 and 6–8 weeks following treatment, respectively.[28,29] Healing and tissue maturation and the associated pocket depth reduction and attachment gain continue thereafter, with the greatest change being observed at 3 months after the treatment.[30]

A limitation of our study is that only a few participants demonstrated full pocket closure and achieved the gingival health status defined by Chapple et al.[31] This was expected, since only severe periodontitis patients were included in the present study. Moreover, mean plaque scores of periodontitis patients were considerably high throughout the study period, although supragingival prophylaxis and oral hygiene motivation were repeated at 6 and 12 week-control sessions. To note, high plaque scores can also be related to dichotomous plaque assessment, where small quantities of deposits are equally counted with substantial ones. Bleeding on probing scores and attachment levels, on the other hand, continued to improve, suggesting that treatment was generally effective in reducing the inflammation and providing an environment for healing despite insufficient oral hygiene status of some participants. Another point to take into account is that the periodontitis patients in our study were slightly older than periodontally healthy individuals: Although this difference was rather modest, it should be mentioned here since aging undoubtedly has the capacity to affect the immune-inflammatory

TABLE 2 Salivary BAFF, TWEAK, and sCD163 levels and salivary arginase activity of healthy participants and participants with periodontitis at baseline.

Salivary analytes	Periodontally healthy ($n = 35$)	Periodontitis ($n = 44$)	p Unadjusted	Adjusted[a]
BAFF (pg/mL)	45.8 (671.8)	4520 (4098.7)	**<.001**	**<.001**
TWEAK (pg/mL)	21.2 (30.7)	15.0 (30.9)	.614	.678
sCD163 (pg/mL)	669.4 (833.0)	1651.7 (6634.2)	**<.001**	**.003**
Arginase activity (mU/μL)	1.9 (2.0)	24.8 (21.0)	**<.001**	**.015**

Note: The values are presented as median (interquartile range). *p* values in bold indicate statistically significant difference (<.05).
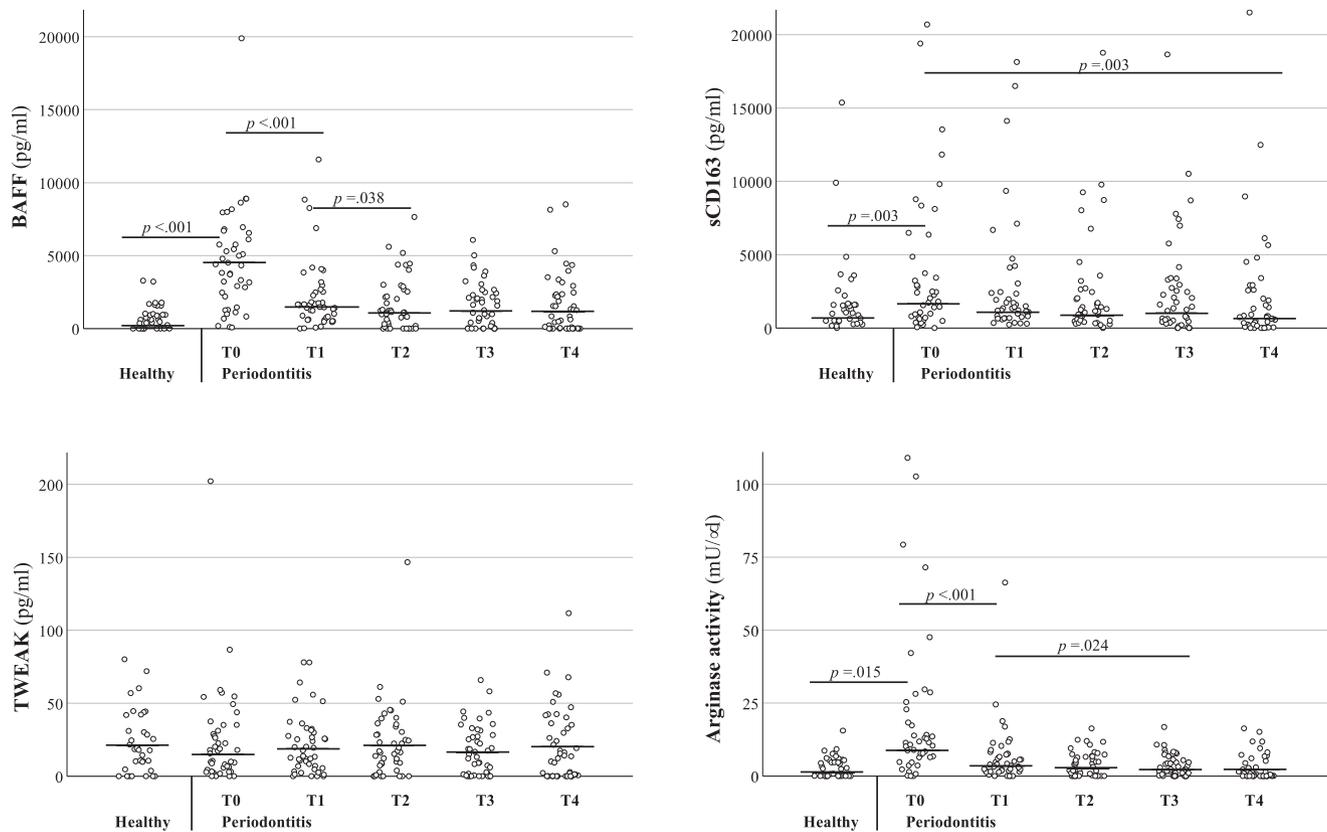[a]Adjusted for age and smoking.

FIGURE 2 Salivary levels of BAFF, sCD163, and TWEAK and salivary arginase activity of periodontally healthy participants at baseline and those of participants with periodontitis at baseline (T0) and at 2 (T1), 6 (T2), 12 (T3), and 24 (T4) weeks following treatment. Outliers are excluded in the scatter-plot graphs to improve the visibility of the data. The horizontal lines represent the medians of the analytes. p values, which were calculated using repeated measures analysis of variance after controlling for smoking, adjusted to the Bonferroni correction for multiple comparisons and indicate changes in median analyte levels.

response.[32] In fact, serum BAFF levels are inversely correlated with age,[33] which shows that the effect of age is possibly negligible in comparison to the substantial increase of salivary BAFF levels in advanced periodontitis patients. On the other hand, sCD163 levels are found to increase with aging and are thought to be linked with inflammatory age-related diseases.[34] In order to overcome the impact of the age difference on our results, an analysis of variance with age adjustment was performed. We should also mention that even though sample collection was standardized, the storage time of the samples varied from 3 to 15 months due to the study design. To the best of the authors' knowledge, there is no direct evidence on the reliability of the proteins analyzed in the present study at varying storage times. However, salivary cytokines have been previously reported to exhibit a high level of stability up to 2 years at −80°C and thus, the storage method and the storage time have no impact on our results, in our opinion.[35,36] One final limitation of our study is that the salivary samples were not tested in replicates, which increases the likelihood of variability in the assay results.

Our study revealed that salivary BAFF levels in periodontitis patients are higher when compared to periodontally healthy individuals, which is in accordance with previous research.[23] BAFF is considered an essential cytokine for alveolar bone loss mediated by B cells, while BAFF levels correlate with B- and plasma cell numbers in periodontal tissues.[5] BAFF expression has been found to be increased in tissue

biopsies obtained from periodontitis lesions.[6] Patients with periodontitis under supportive therapy have significantly higher serum levels of BAFF and these levels are correlated with probing depth and attachment loss.[37] BAFF overexpression has been linked with autoimmune connective tissue diseases such as systemic lupus erythematosus, primary Sjögren's syndrome, and rheumatoid arthritis, and salivary BAFF levels have been found to be correlated with probing depth in patients with primary Sjögren's syndrome.[38,39] Salivary BAFF was also linked to gingivitis and thalassemia major, suggesting that altered lymphocyte activity in thalassemia may be enhanced by gingival inflammation.[40] The elevated baseline salivary BAFF levels in our study, together with the significant posttreatment decrease, support the previous studies suggesting a crucial role for BAFF in periodontal immune response, and indicate that B-cell activation via BAFF is rapidly restricted following treatment. These results were consistent both in smokers and non-smokers, which is in line with prior research demonstrating no significant difference in salivary BAFF levels between smokers and non-smokers.[23]

Soluble CD163 is a biomarker of macrophage activation and inflammation, while several signals such as lipopolysaccharides, oxidative stress, and thrombin can induce CD163 shedding.[10] CD163 is the surface marker of M2 macrophages, which mediate resolution of inflammation, angiogenesis, and wound healing.[41] Periodontitis patients have increased sCD163 levels in their serum and saliva, and gingival

crevicular fluid levels of sCD163 have also been found to increase with gingival inflammation, demonstrating interindividual variations.[22,42] According to our results, salivary sCD163 levels are downregulated following periodontal treatment, which occurs at a slower pace when compared to BAFF. This can be explained by a possible balance between decreased CD163 shedding, which reflects reduced inflammation, and an increasing number of CD163^{+} cells that are involved in wound repair in the posttreatment period. It has been demonstrated in a murine study that BAFF blockade alters macrophage phenotypes.[9] Thus, it can also be speculated that the rapid change in BAFF levels may induce M2 macrophages and therefore CD163 expression.

In the present study, salivary TWEAK levels did not differ between disease and health and demonstrated no significant difference in the posttreatment period. TWEAK is a cytokine with multiple immune regulatory, pro-inflammatory, and pro-angiogenic functions.[43,44] Previous studies showed either higher or lower serum soluble TWEAK levels in periodontitis patients as compared to periodontally healthy individuals.[45–47] In the oral cavity, increased TWEAK levels were reported in gingival crevicular fluid samples of periodontitis patients.[24,48] A significant reduction in gingival crevicular fluid TWEAK levels after periodontal treatment was also demonstrated.[49] Therefore, our results indicate either a noteworthy dilution or proteolytic degradation of TWEAK in saliva or that, considering its multiple functions in inflammation and wound healing, salivary TWEAK levels are balanced in periodontal health, periodontitis, and wound healing.

Macrophages play a primary role in arginine breakdown during wound healing.[50] Arginine is metabolized by M1 macrophages via nitric oxide synthase to nitric oxide and citrulline or by M2 macrophages to ornithine and urea.[51] Yet, salivary arginase may originate both from host cells and oral bacteria, and periodontal pathogens can induce arginase activity in macrophages.[17,52] Indeed, increased arginase expression and bacteria that can metabolize arginine in infected chronic wounds are considered to decrease nitric oxide production, leading to impaired healing.[53] Our results are in accordance with previous studies revealing increased salivary arginase activity in periodontitis patients and a decrease following periodontal treatment.[17,18] Similar to BAFF levels, salivary arginase levels responded to treatment with a rapid decrease both in smokers and non-smokers. Interestingly, baseline arginase activity in smokers was comparably lower, which is contradictory with a previous study where elevated salivary arginase activity was reported in smokers when compared to that in non-smokers, both with and without dental implants.[54] The impact of smoking on salivary arginase activity is possibly altered in periodontitis and can be explained by a suppressed immune-inflammatory response in smoking individuals.[55]

5 | CONCLUSION

Salivary levels of BAFF and sCD163 levels, as well as arginase activity, are elevated in periodontitis and decrease after nonsurgical periodontal treatment, demonstrating significant changes at varying time points. Our results indicate a substantial and rapid reduction of BAFF,

which might be an indicator of restrained B-cell activation. Further research in patients with gingivitis and different severities of periodontitis can reveal if salivary BAFF can be utilized as a biomarker for diagnosing periodontitis and monitoring the healing response.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.