BMC Oral Health

RESEARCH

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Evaluation of thiol/disulfide homeostasis and ischemia modified albumin as potential markers for periodontitis

Bilge Karcı[1*] and Hasan Basri Savas[2]

Abstract

Background The current study aimed to assess the impact of periodontitis on oxidative stress parameters by examining serum total antioxidant capacity (TAS), total oxidant status (TOS), oxidative stress index (OSI), thiol/disulfide homeostasis and ischemia modified albumin (IMA).

Methods The study had 90 participants, categorized into 3 groups: Group 1: Periodontally healthy; Group 2: Stage II Grade B periodontitis; Group 3: Stage III and IV Grade B periodontitis. Demographic and periodontal variables were assessed. The levels of serum TAS, TOS, OSI, IMA, and thiol/disulfide were assessed.

Results No significant differences in sex and age were detected among the groups ($p > 0.05$). When compared to Group 1, all clinical measurements were statistically significantly greater in Group 3 ($p < 0.05$). Statistical analysis revealed no significant differences in serum TAS, TOS, and OSI levels among the groups ($p > 0.05$). The highest serum IMA value was observed in Group 3 ($p = 0.037$), whereas native thiol ($p = 0.00$), total thiol ($p = 0.00$) and disulfide values ($p = 0.023$) were highest in Group 1.

Conclusions These findings indicate that thiol/disulfide homeostasis and IMA could hold promise as a potential biomarker of inflammation in periodontitis.

Keywords Periodontitis, Oxidative stress, Thiol/ disulfide, Ischemia modified albumin

Background

Periodontitis is a chronic inflammatory condition induced by pathogenic bacteria interacting with the host immune system, eliciting a response from neutrophils, the primary defense against microbial assaults; epigenetic bacterial species may possibly be the cause of this reaction cascade [1]. Host cells release reactive oxygen species (ROS) when periodontopathic bacteria stimulate the immune response. Excessive reactive oxygen species production in polymorphonuclear leukocytes is a pathogenic feature of periodontal lesions that adversely affect periodontal tissue via multiple pathways [2]. A disparity between antioxidants and oxidants that favors the oxidants and may cause damage is known as oxidative stress (OS) [3]. Biomarkers employed to assess OS activities include serum total antioxidant status (TAS), oxidative stress index (OSI), total oxidant status (TOS), as well as the recently favored thiol balance and Ischemia Modified Albumin (IMA) [4]. Given the impracticality of identifying individual oxidant molecules and their cumulative

*Correspondence:
Bilge Karcı
bilge0013@hotmail.com
[1]Faculty of Dentistry, Department of Periodontology, Alanya Alaaddin Keykubat University, Alanya, Antalya, Turkey
[2]Faculty of Medicine, Department of Biochemistry, Mardin Artuklu University, Mardin, Turkey

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oxidant effects, assessing a sample's TOS and TAS may be a feasible approach [5, 6].

IMA and thiol balance are new biochemical markers that guide the assessment of antioxidant capacity and OS [7]. A sulfhydryl group is present in the thiol formation. Thiol is accomplished at reducing OS owing to sulfhydryl. When thiol is oxidized, then the disulfide bond is created where there is a large rise in OS. Disulfide bonds can return to the thiol structure if OS is reduced, and antioxidant ability is increased. The dynamic thiol balance is the name given to this cycle [8, 9]. Thiols are extremely strong antioxidants that shield the body from the adverse effects of OS [10].

Chapple noted that the identification of a low molecular weight thiol in gingival crevicular fluid (GCF) serves as a crucial defensive mechanism against detrimental ROS-mediated damage [11]. Nevertheless, findings regarding the correlation between antioxidant levels and periodontitis have been inconsistent. Tayman et al. found significant association between the severity of periodontitis and serum total thiol and disulphide levels, confirming the belief of oxidative stress in the etiology of periodontitis [12]. However, the crucial role of thiol/disulphide homeostasis in the origins of periodontal disease, a recognized chronic inflammatory condition, remains inadequately clarified.

Ischemia is exacerbated by oxidation. The albumin structure is altered because of ischemia and OS. IMA is the N-terminal modified albumin structure [13]. Increased IMA levels are releated to OS-related diseases in the previous. Albumin's metal binding potential reduces during ischemia because of the free radical disruption at the amino terminus (N-terminus) of the metal-binding portion of the protein [14, 15]. The presence of IMA in the serum has been linked with higher values of OS [16].

Several studies have established that IMA is a standard and crucial marker for patients experiencing diverse acute and chronic conditions, including myocardial ischemia, skeletal muscle ischemia, pulmonary embolism, stroke, and chronic diseases associated with vascular complications from type-2 diabetes mellitus [17, 18]. Despite numerous inflammatory diseases showing elevated IMA levels, the connection between IMA and periodontitis remains unclear.

The purpose of the current study was to evaluate IMA and thiol/disulfide balance as OS potential biomarker by comparing healthy people to those with periodontitis.

Methods

Research population

This cross-sectional research was conducted in the Departments of Biochemistry and Periodontology at Alanya Alaaddin Keykubat University. The Ethics Committee of ALKU's Faculty of Medicine approved the study protocol (date: Sept 2019-Feb 2020, Protocol No. 2019/83). Prior to clinical periodontal examinations and serum collection, all individuals in the research were apprised of the objectives and methodologies of study, and written informed consent forms were developed in compliance with the principles of the Helsinki Declaration and distributed.

90 individuals in all were enlisted using the inclusion criteria, and they were then divided into three study groups as follows: Group 1: Periodontally healthy (30 individuals); Group 2: Stage II Grade B periodontitis (30 individuals); Group 3: Stage III, IV Grade B periodontitis (30 individuals).

The exclusion criteria encompassed metabolic disorders (diabetes, hyperlipidemia, hypercholesterolemia, menopause, thyroid abnormalities), rheumatic and coronary illnesses, a history of malignancy, pregnancy, lactation, recent use of anti-inflammatory medications and/or antibiotics within the last three months, periodontal therapy within the last six months, ex-smokers or current smokers and possessing fewer than 10 teeth in the oral cavity [19]. Age and sex were documented as demographic variables.

Periodontal examination

A calibrated examiner (BK) utilized a Williams periodontal probe (Hu-Friedy, Chicago, IL) to obtain clinical periodontal measures. The bleeding on probing percentage (BOP%) [20], plaque index (PI) [21], probing depth (PD), gingival index (GI) [22], and interproximal clinical attachment level (iCAL) were analyzed. Radiographic data was obtained. The periodontally healthy group (control group) includes people bleeding on probing (BOP) < 10% and probing depth (PD) ≤ 4 mm. The consensus report from the 2017 World Workshop established the categorization for the diagnosis of periodontal disease [23].

Blood samples

Prior to periodontal diagnosis, peripheral venous blood samples were obtained from individuals. Centrifugation was used to separate the serum from the cells for ten minutes at 1500 x g and following that kept at -80 °C prior to biochemical analysis.

Laboratory analyses

Serum TAS levels were quantified using Erel's technique [5]. The completely automated technique relies on the bleaching of the distinctive hue of a more stable ABTS (2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic**x**acid) radical cation by antioxidants. The absorbance variation was quantified at 660 nm. The test has an optimal variation of under 3%. The findings are shown in mmol Trolox equivalent per liter (Relassay, Turkey). The analytical

sensitivity was found to be 0.11 Absorbance/Amount, [AX $(mM)^{-1}$] for TAS. Inter-assay coefficent of variation 2.8% and intra-assay coefficent of variation 3.3% for TAS. Samples containing 0.01–4.00 mmol Trolox Equiv. /L can be assayed for TAS.

Serum TOS levels were quantified utilizing the colorimetric technique delineated by Erel [6]. In the procedure, the iron ion-o-dianisidine complex is oxidized by the oxidants in the sample.

Glycerol molecules in the reaction medium, ferric ions in an acidic environment, and xylenol orange coloration. The spectrophotometrically quantifiable color intensity correlates with tthe total number of oxidant molecules in the environment. The data are given in micromolar hydrogen peroxide equivalent per liter (µmol H2O2 equivalent / L) (Relassay, Turkey). Inter-assay coefficent of variation 3.2% and intra-assay coefficent of variation 3.9% for TOS. Samples containing 0.2–80 µmol H202 Equiv. /L can be assayed for TOS. The analytical sensitivity was found to be 0.0076 Absorbance/Amount [AX $(\mu M)^{-1}$]. The OSI is determined by the TOS/TAS ratio [24].

The serum IMA level was assessed using the albumin cobalt binding test methodology. To quantify serum IMA, 95 µl of participant serum is combined with 5 µl of cobalt chloride and incubated for five minutes. The cobalt chloride concentration during incubation is 0.58mmol/L. In the ischemic area, minimal cobalt is linked to albumin. 25 µl of dithiothreitol (final concentration 1.67 mmol/L) remains unbound to albumin after incubation for cobalt determination in the absence of albumin. The measurement was conducted spectrophotometrically at a wavelength ofii500 nm. A calibration curve with five points was constructed within the range ofii5 to 180 U/mL. The sample absorbances were assessed using this calibration curve. IMA levels were computed. The unit for IMA levels was g/L [25]. Coefficients of variation for within-run and between-run assays are < 4% for IMA.

The method of Erel and Neselioglu [26] was employed to measure the concentrations of serum native and total thiols. This process involved utilizing NaBH4 to decrease dynamic disulfide linkages (-S-S-) to functional thiol groups (-SH). Formaldehyde was employed to remove the remaining NaBH4 components from the environment. The sample's total thiol concentration was determined using Ellman's reagent. The ratios were then determined for each research participant after the dynamic disulfide content was computed through the formula (total thiol – native thiol) / 2. Percent coefficient variation (%CV) was 4 ($\overline{X}$ = 29.12 and σX = 1.2) for high levels, 5 ($\overline{X}$ = 16.03 and σX = 0.79) for medium levels and 13 ($\overline{X}$ = 7.15 and σX = 0.98) for low levels for the thiol–disulphide method. The analytical sensitivity was found to be $7.9 \times 10 - 4$ Absorbance/Amount, [A × $(\mu M)^{-1}$] for the thiol–disulphide method. The detection limit, defined as the mean value of zero calibrator + 3 standard deviations (SDs), was 2.8 µM for the thiol–disulphide method.

Table 1 Demographic characteristics of the study groups

		Group 1 (*n* = 30)	Group 2 (*n* = 30)	Group 3 (*n* = 30)
Age (mean ± SD)		40.8 ± 5.3	43.6 ± 4.1	44.3 ± 6.5
Sex	Male	13 (43.3%)	12 (40%)	15 (50%)
	Female	17 (56.7%)	18 (60%)	15 (50%)

Statistical analysis

The study's data underwent statistical analysis utilizing SPSS for Windows Version 22.0. Categorical variables were represented as counts and percentages, whilst continuous variables were analyzed using mean and standard deviation (SD), or median along with minimum and maximum values where applicable. One-way Anova technique was used to examine whether there was a significant difference between serum biomarker values between group 1, group 2 and group 3. For this technique, first of all, Kolmogorov-Smirnov test was used to examine whether the groups showed normal distribution in terms of relevant variables, and Levene test was used to examine whether the variances of the groups were homogeneous. As a result of this examination, it was seen that the data were normally distributed ($p > 0.05$) and the variances were homogeneous ($p > 0.05$). In case of a significant difference between the groups as a result of variance analysis, Duncan, Tukey HSD, Post-Hoc techniques were used to examine which group or groups caused the difference. Three groups, 30 people in each group, a total of 90 people, the significance level was 0.05 and the analysis used was one-way variance analysis, the effect size was 0.75, and the statistical power was calculated with GPower and found to be 0.94. This suggests a strong likelihood that the analysis would identify a disparity between the group means if such a disparity were there.

Results

Clinical and demographic findings

The demographic characteristics and clinical periodontal assessments of the patients are encapsulated in Tables 1 and 2. No significant differences in age and sex were seen among the groups ($p > 0.05$). All clinical parameters were statistically significantly increased in Group 3 relative to Group 1 ($p < 0.05$). Despite the higher PI, GI, and iCAL values in Group 3 in comparison to Group 2, this increase was not statistically significant ($p > 0.05$). A statistically significant difference in PD and BOP (%) values was noted between Group 3 and Group 2, Group 3 and Group 1, and Group 2 and Group 1 ($p < 0.05$).

Table 2 Clinical periodontal parameters of the study groups

	Group 1	Group 2	Group 3	*p*
PI	0,22 ± 0,07	1,92 ± 0,53	2,03 ± 0,24	**< 0,05** (3 – 1,2 – 1)
GI	0,42 ± 0,23	1,65 ± 0,35	1,95 ± 0,50	**< 0,05** (3 – 1,2 – 1)
PD	1,61 ± 0,36	2,24 ± 0,31	3,72 ± 0,81	**< 0,05** (3 – 1,2 – 1,3 – 2)
BOP (%)	8,76 ± 2,50	55,52 ± 1,5	72,49 ± 2,17	**< 0,05** (3 – 1,2 – 1,3 – 2)
iCAL	1,6 ± 0,49	5,21 ± 0,76	5,47 ± 0,83	**< 0,05** (3 – 1,2 – 1)

Values are presented as mean ± SD

P < 0.05; statistically significant difference

Group numbers in parentheses represent groups with statistically significant differences

Laboratory findings

Table 3; Fig. 1 present the mean and SD values for serum TAS, TOS, OSI, IMA, and thiol levels across all groups. No notable variations were detected in serum TAS, TOS, and OSI levels across the groups in the statistical analysis ($p > 0.05$). Serum IMA values were identified as 89.50 ± 13.37 (g/L) in Group 1, 84.75 ± 11.76 (g/L) in Group 2, and 92.84 ± 10.71 (g/L) in Group 3. A statistically significant difference was found between Group 3 and Group 2 ($p = 0.037$), with the highest levels observed in Group 3. Serum native thiol levels were measured as 342.83 ± 45.91 (µmol/L) in Group 1, 272.34 ± 47.76 (µmol/L) in Group 2, and 264.29 ± 54.27 (µmol/L) in Group 3. Groups 2 and 3 had significantly lower values compared to Group 1 ($p = 0.000$). Nevertheless, no significant difference was found among Groups 2 and 3. Serum total thiol levels were recorded as 418.21 ± 62.79 (µmol/L) in Group 1, 340.24 ± 57.62 (µmol/L) in Group 2, and 318.61 ± 68.51 (µmol/L) in Group 3. Groups 2 and 3 showed significantly lower values in comparison to Group 1 ($p = 0.000$), while no statistically significant difference was seen among Groups 2 and 3. Serum disulfide levels were reported as 37.69 ± 16.37 (µmol/L) in Group 1, 33.95 ± 11.27 (µmol/L) in Group 2, and 27.16 ± 15.97 (µmol/L) in Group 3. Group 3 showed significantly lower levels in comparison to Group 1 ($p = 0.023$). No significant difference was identified between Group 1 and Group 2.

Discussion

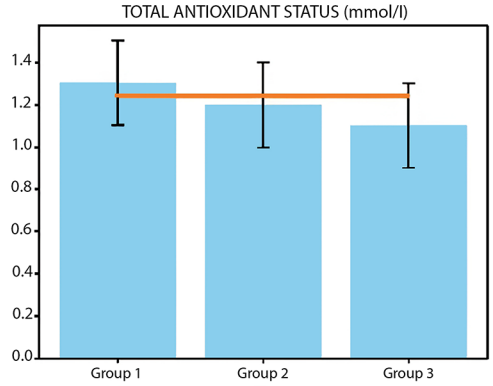
Although an important advancement in our knowledge of the etiopathogenesis of inflammatory periodontal diseases has been made., their diagnosis and classification still rely heavily on traditional clinical methods. Given that periodontal diagnosis is predominantly subjective and retrospective, there is a continuous effort to identify biochemical biomarkers of periodontopathic. Biomarkers measured in serum, GCF or saliva have the potential to provide a more objective diagnosis, assess disease severity, and evaluate the effectiveness of treatments.

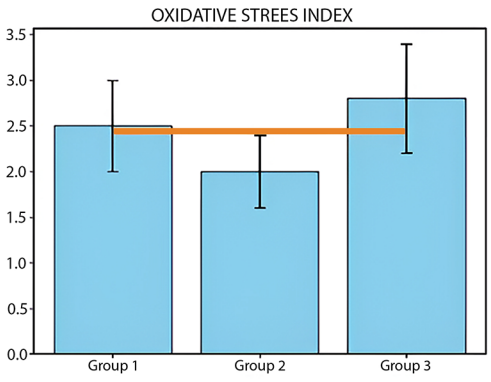
In the present study, we observed that no significant differences were observed in serum TAS, TOS, and OSI values among the groups. However, serum IMA, native thiol, total thiol, and disulfide levels showed significant differences. Native thiol, total thiol, and disulfide levels

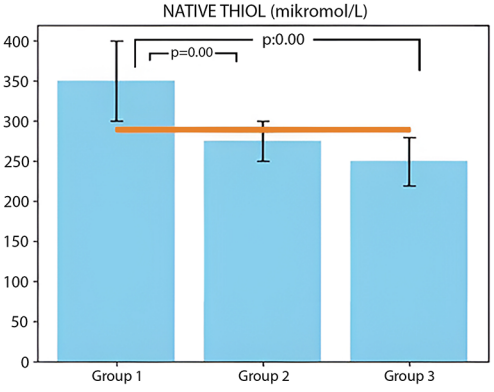
Table 3 Serum TAS, TOS, OSI, IMA and Thiol/disulfide levels

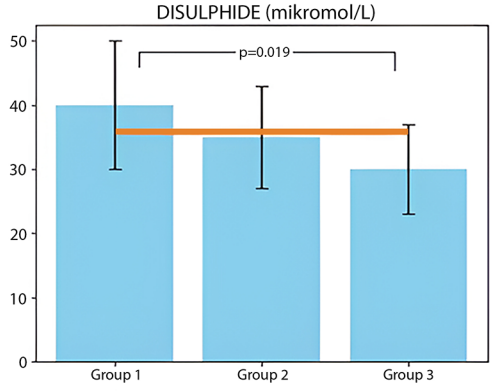
			One way anova			
	Group	**Mean**	**Sd**		***df***	***F***	***p***
TAS (mmol/L)	1	1,3497	,2234	Between group	2	2,367	,1
	2	1,338	,2258	Within Group	87		
	3	1,2314	,246	Total	89		
TOS (µmol/L)	1	3,2675	,2949	Between group	2	0.905	,408
	2	2,5363	1.0378	Within Group	87		
	3	2,8882	1,1684	Total	89		
OSI	1	,2450	,132	Between group	2	1,111	,334
	2	,1940	,0835	Within Group	87		
	3	,2617	,1	Total	89		
IMA (g/L)	1	89,5087	13,3771	Between group	2	**3,440**	**,037***
	2	84,754	11,7681	Within Group	87		
	3	92,842	10,7187	Total	89		
Native Thiol (µmol/L)	1	342,8333	45,9123	Between group	2	**20,659**	**,000***
	2	272,3433	47,7626	Within Group	87		
	3	264,29	54,2755	Total	89		
Total Thiol (µmol/L)	1	418,2167	62,7926	Between group	2	**22,909**	**,000***
	2	340,24	57,6261	Within Group	87		
	3	318,6133	68,514	Total	89		
Disulfide (µmol/L)	1	37,69	16,3791	Between group	2	**3,941**	**,023***
	2	33,95	11,2733	Within Group	87		
	3	27,16	15,9793	Total	89		

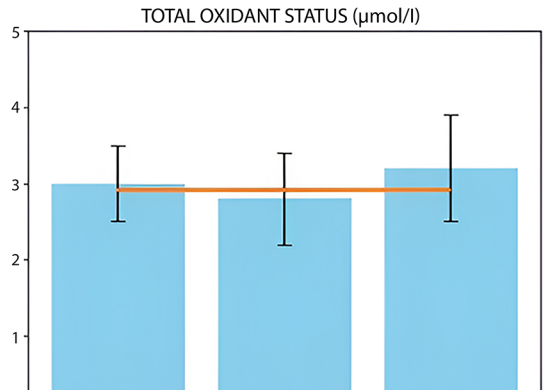
P < 0.05; statistically significant difference

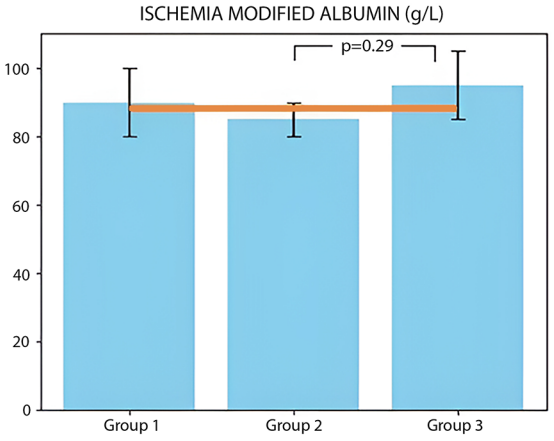












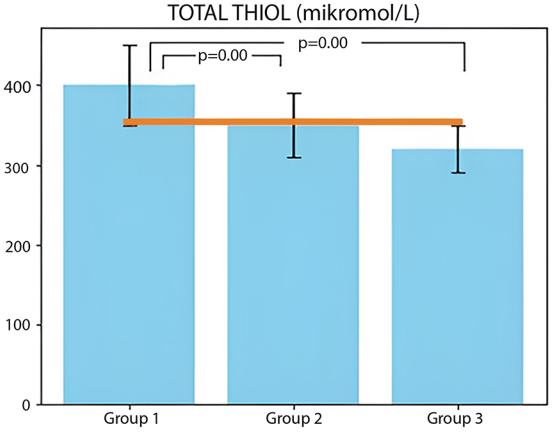


Fig. 1 Serum TAS, TOS, OSI, IMA and Thiol disulfide levels

were greatest in Group 1, whereas IMA levels were greatest in Group 3.

Periodontal pathogens cause mitochondrial dysfunction by overactivating neutrophils. This results in elevated ROS and damaged redox metabolism [27, 28]. Excessive ROS production in the mitochondria and cytosol has been implicated in NLRP3 inflammasome activation. As a result, IL-1β and IL-18 release increases. Thus, an inflammatory response occurs [29].

According to Chen et al., TAS and TOS are more practical indicators compared to measuring individual oxidants and antioxidants separately, as they provide an overall assessment of the oxidative and antioxidative status. These parameters account for the interactions among oxidant and antioxidant molecules and enzymes, making them effective and convenient biomarkers for assessing oxidative damage in periodontal tissues [30].

Numerous studies examining TAS levels in individuals with periodontitis and healthy controls have proposed a wide range of conclusions. Research has revealed that periodontitis is often associated with significantly lower TAS levels [31–33] and higher serum TOS levels [33–35]. However, some studies have demonstrated no significant differences in OS parameters between periodontitis patients and healthy controls [24, 36–38]. In this present research, there was no significant difference in TAS levels between the control and periodontitis groups. Such inconsistencies may stem from disparities in the periodontal health of the populations examined.

According to Erel, TOS is a solid indication of OS and a direct measurement [6]. Researchers found that periodontitis patients had higher serum TOS levels compared to healthy controls [34, 35, 39, 40]. Serum TOS levels were not significantly different in the studies [24, 37, 38]. Results from the present study showing no significant difference in TOS levels between the periodontitis and healthy groups are in accordance with these findings.

OSI is considered a reliable indicator of OS in systemic diseases, offering a novel contribution to existing literature. As a measurement parameter, the TOS/TAS ratio, known as OSI, provides distinct advantages over other methods for assessing oxidant/antioxidant imbalances and OS [6]. Previous research has indicated that OSI values tend to increase in individuals with periodontitis [33, 36], although other studies have found no significant differences [24, 37–39, 41]. There was no significant difference in OSI levels between the control and periodontitis groups in our investigation. These discrepancies may be attributed to methodological variations, including differences in the equipment utilized, the heterogeneity of disease activity, and the sample size of the study groups.

IMA, a modified variant of human serum albumin, is produced under certain conditions, including OS, localized ischemia, and inflammation, although its exact formation mechanism remains undetermined. Existing evidence suggests that IMA levels are elevated in acute and chronic ischemic states, as well as in both systemic and localized inflammatory diseases [13, 42–44]. Since periodontitis is characterized by inflammation, OS, and hypoxia in periodontal tissues, these factors are likely to contribute to IMA production via albumin modification [45]. Consistent with this hypothesis, our findings demonstrated significantly elevated IMA levels in Group 3 periodontitis patients compared to controls, aligning with previous studies that highlight the role of OS in periodontitis pathogenesis [31, 45, 46]. Tayman et al. found that serum IMA values were significantly higher in the periodontitis group than in the control group [47]. These findings are consistent with our study.

The thiol-disulfide balance is a dynamic system that contributes to detoxification, apoptosis, cellular signaling, enzyme activation regulation, transcription, and antioxidant activity. Thiols neutralize free radicals through non-enzymatic mechanisms, thereby mitigating the effects of reactive oxygen species. OS disrupts this balance, favoring disulfide formation, which lowers serum thiol levels and leads to functional disorders [48]. Notably, thiol groups are vital components of the cellular antioxidant defense system, with the formation of disulfide bonds marking an early stage of protein oxidation induced by radicals [49]. Numerous investigations have indicated abnormal thiol/disulfide balance levels in the etiology of chronic conditions, including cardiovascular illnesses, diabetes mellitus, and rheumatoid arthritis [49, 50]. Our analysis revealed markedly reduced thiol and disulfide levels in Group 3 and Group 2 relative to Group 1. These findings align with literature. Karim et al. discovered that thiol concentrations in the periodontitis group were markedly lower than those in the periodontally healthy group in their investigation of gingival crevicular fluid and saliva [51]. These results are consistent with the thiol concentrations we found in our study in serum. No studies have been conducted comparing the thiol-disulfide balance in serum between periodontitis and periodontally healthy individuals.

The multifaceted nature of OS is likely the primary reason for the inability to achieve significant findings in serum samples. Although it is well-established that variables such as dietary habits and living conditions affect OS levels, standardizing these factors within the study groups was not feasible.

The relationship between exercise and oxidative stress depends on the type of exercise, intensity, and duration. Regular moderate-intensity training appears to protect against oxidative stress. In contrast to aerobic exercise, high-intensity training may increase oxidative stress. High carbohydrate intake may promote oxidative stress and inflammatory responses [52].

A potential limitation of this study lies in its cross-sectional design, small sample size, and the challenge of standardizing participants' dietary habits and living conditions, all of which may have influenced the assessment of oxidant/antioxidant status.

The small sample size and the presence of potential confounding factors may limit generalizability. Cross-sectional designs cannot establish causality. Longitudinal studies are needed for this. Single-timepoint sampling may exclude individuals with transient oxidative stress fluctuations, reducing applicability to dynamic disease states. Recruitment from a university clinic may be oversample for individuals with higher health literacy or access to care, skewing results compared to community-based populations.

Conclusion

We have found that no significant differences were observed in serum TAS, TOS, and OSI levels among the groups. However, serum IMA, native thiol, total thiol, and disulfide values showed significant differences. These findings indicate that thiol/disulfide homeostasis and IMA could hold promise as a potential biomarker of inflammation in periodontitis.

- It is recommended to explore the markers in different biological fluids (gingival crevicular fluid or saliva) to assess local and systemic oxidative stress.
- Interventional studies are recommended to assess biomarker changes in response to periodontal therapy.
- Further investigations with longitudinal and larger sample size studies are essential to substantiate these results and to deepen our understanding of thiol/disulfide homeostasis and IMA's role in the pathogenesis of periodontal disease.

Abbreviations

ROS	Reactive oxygen species
OS	Oxidative stress
TAS	Total antioxidant status
TOS	Total oxidant status
OSI	Oxidative stress index
IMA	Ischemia modified albumin
BOP	Bleeding on probing
PI	Plaque index
PD	Probing depth
GI	Gingival index
CAL	Clinical attachment level

Acknowledgements
Not applicable.

Author contributions
Study concept and design: B.K. Data Acquisition: B.K. Analysis and interpretation of data: B.K, H.B.S. Writing - original draft preparation: B.K. Writing - review and editing: B.K, H.B.S. All authors read and approved of the final manuscript.

Funding
This study was supported by scientific research projects (ALKU BAP, grant 2020-06-01-MAP01).

Data availability
All data generated or analyzed during this study are included in this published article & supporting material.

Declarations

Ethics approval and consent to participate
The study was initiated following the approval of the Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Research Ethics Committee (protocol# 2019/83). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee. Informed consent terms were obtained from every individual participant included in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 December 2024 / Accepted: 25 March 2025
Published online: 10 April 2025

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