The Effects of Chronic Periodontitis and Rheumatoid Arthritis on Serum and Gingival Crevicular Fluid Total Antioxidant/Oxidant Status and Oxidative Stress Index

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Background: Chronic periodontitis (CP) and rheumatoid arthritis (RA) appear to share many pathologic features. Oxygen metabolism has an important role in the pathogenesis of both CP and RA. The aim of this study is to evaluate the relationship between these two chronic inflammatory diseases with regard to antioxidant and oxidant status.

Methods: A total of 80 participants were divided into four groups of 20 each: group RA–CP (patients with RA and CP), group RA (periodontally healthy patients with RA), group CP (systemically healthy patients with CP), and group C (periodontally and systemically healthy volunteers) were included in the study. After assessment of periodontal measurements, gingival crevicular fluid (GCF) samples were taken at one incisor, premolar, and molar tooth and stored with serum samples at –80°C for the antioxidant/oxidant assay.

Results: Although all clinical measurements in groups RA–CP and CP were statistically higher compared to those of C and RA groups ($P<0.001$), there were no differences between CP and RA–CP groups ($P>0.05$). GCF total oxidant status (TOS) values of CP and RA–CP groups were higher than those of the RA group ($P<0.05$). GCF oxidative stress index (OSI) values of the RA–CP group were higher than those of the RA group ($P<0.05$). There were no differences among the groups in terms of serum TOS and OSI values ($P>0.05$).

Conclusions: Local OSI values in groups with patients with CP were higher, whereas systemic OSI values showed no difference among the groups. The presence of RA seems not to affect local and systemic OSI values in patients with CP. *J Periodontol 2012;83:773-779.*

KEY WORDS

Antioxidants; arthritis, rheumatoid; chronic periodontitis; gingival crevicular fluid; oxidative stress.

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Chronic periodontitis (CP) is a common disease worldwide that has a bacterial etiology and is characterized by an inflammatory process, resulting in the destruction of the soft- and hard-tissues that support the teeth. Periodontal tissue destruction is mainly caused by an inappropriate host response to pathogenic microorganisms and their products. More specifically, a loss of homeostatic balance among proteolytic enzymes (e.g., neutrophil elastase) and their inhibitors (e.g., α1-antitrypsin) and reactive oxygen species (ROS) and the antioxidant defense systems that protect and repair vital tissue, cell, and molecular components is believed to be responsible.[1]

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of the joints and is characterized by loss of articular cartilage and bone.[2] Although the cause of RA is unknown, exogenous infectious agents; endogenous substances, such as connective tissue proteins; and altered immunoglobulins are suspected factors.[3] Some investigators have focused on oxidative stress in rheumatoid inflammation because phagocytosis triggers a respiratory burst characterized by increased oxygen consumption, increased anaerobic glycolysis, and generation of oxygen radicals.[4] Increased

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oxidative stress in synovial tissue and synovial fluid may be associated with increased disease activity, tissue damage, and bone erosions in RA.[5]

Reports suggest an increased prevalence of diabetes, atherosclerosis, myocardial infarction, and stroke in patients with periodontal disease.[6-8] RA is one of these diseases proposed to have a relationship with CP. Although the etiologies of the two diseases are distinctly separate, animal and clinical studies have shown that pathogenic similarities exist between periodontitis and RA.[3,9] Indeed, several observational studies[9-11] demonstrated a high prevalence of periodontitis in patients with RA compared to the general population. Moreover, the presence of periodontitis in individuals with RA was associated with more active disease manifested by higher acute-phase responses and a higher number of tender and/or swollen joints.

Most recently, Wegner et al.[12] presented a novel model in which *Porphyromonas gingivalis*-mediated citrullination of bacterial and host proteins provides a molecular mechanism for generating antigens that drive the autoimmune response in RA. Hitchon et al.[13] in a genetically predisposed population of Native American patients with RA and their relatives showed that anti-*P. gingivalis* antibodies were associated with anti-citrullinated protein antibodies, suggesting that immune responses to *P. gingivalis* may be involved in breaking immune tolerance to citrullinated antigens.

All living systems require oxygen to oxidize molecules rich in carbon and hydrogen, thus producing the energy needed for life. However, the reduction in molecular oxygen in biologic systems is accompanied by the release of free energy, giving rise to ROS or free radicals (FRs), such as superoxide radical and hydroxyl radical.[14] Under some conditions, overproduction of oxidants or decrease in antioxidants are inevitable. Equilibrium between oxidant and antioxidants shifts in favor of the former, resulting in cell injury and harmful oxidative reactions in organisms. Antioxidants are molecules that prevent these chain reactions that result in many systemic disorders by inactivating ROS. It is well known that FRs/ROS play an important role in inflammation.[15] Previous studies[1,5,14,16,17] have pointed to the role of oxidative stress in the pathogenesis of periodontitis. Similarly, investigators have reported that increase in oxidative stress negatively affects pathology of RA.[4,18-21]

To the best of our knowledge, this was the first study to evaluate the relationship between these two chronic inflammatory diseases with regard to antioxidant and oxidant status.

The aims of this study are to: 1) compare the gingival crevicular fluid (GCF) and serum total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) values of patients with RA, CP, and with RA and CP and 2) clinically investigate to what extent the presence of RA affects the severity of CP.

MATERIALS AND METHODS

Study Groups

Between November 2009 and October 2010, a total of 80 participants (12 males and 68 females; age range: 18 to 80 years) were enrolled. Forty systemically healthy participants were recruited from the Department of Periodontology, Faculty of Dentistry, University of Erciyes, Kayseri, Turkey, and 40 otherwise systemically healthy individuals with RA were recruited from the Rheumatology Department. The study groups (20 each) were: group RA–CP (patients with RA and CP), group RA (periodontally healthy patients with RA), group CP (systemically healthy patients with CP), and group C (periodontally and systemically healthy volunteers). Exclusion criteria were a history of periodontal therapy or the use of antibiotics during the last 3 months before examination, pregnancy or lactation, and smoking. None of the patients participating were periodontally treated prior to this study.

RA was diagnosed according to the American Rheumatism Association.[22] According to the classification, individuals with RA have four of the following seven criteria: 1) morning stiffness; 2) arthritis of three or more joint areas; 3) arthritis of hand joints; 4) symmetric arthritis; 5) rheumatoid nodules; 6) serum rheumatoid factors; and 7) radiographic changes.

The periodontal criteria for RA–CP and CP groups were teeth with attachment loss (AL) ≥4 mm and probing depth (PD) ≥5 mm. The RA and C groups had no AL, PD ≤3 mm and no bleeding on probing (BOP). Written informed consent was obtained from each individual before participation. The study protocol was approved by the Erciyes University, Faculty of Dentistry Ethics Committee.

Clinical Assessments

Assessment of clinical rheumatologic parameters. Disease activity in individuals with RA was assessed by the disease activity score in 28 joints (DAS28). This index ranges from 0 to 10 and includes a 28 tender-and-swollen joint count, the erythrocyte sedimentation rate (millimeters per hour),[23] and the patient's assessment of disease activity measured with a visual analog scale (100 mm).[23]

Periodontal assessments. The periodontal assessment of the participants was performed by the same examiner (CE) on six sites on one incisor, premolar, and molar tooth of each participant and included plaque index (PI),[24] gingival index (GI),[25] BOP, PD, and clinical attachment level (CAL). All clinical parameters were measured with a periodontal probe.§ Bleeding scores were expressed as the percentage of positive sites.

§ Goldman/Fox Williams probe, Hu-Friedy, Chicago, IL.

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Table 1.

Demographic and DAS28 Data of the Study Participants

Groups	C (n = 20)	RA (n = 20)	CP (n = 20)	RA–CP (n = 20)
Age (years; mean ± SD)	40.05 ± 9.8	44.4 ± 15.5	42.85 ± 9.6	46.3 ± 11.7
Range (years)	20 to 55	18 to 80	29 to 61	18 to 64
Male	4	1	4	3
Female	16	19	16	17
Former smoker	2	1	2	2
DAS28 (mean ± SD)	NA	3.15 ± 1.16	NA	3.60 ± 1.01

NA = not applicable.

Collection of Samples

GCF sampling. To avoid irritation, samples were obtained between 8:00 am and 10:00 am 2 days after clinical measurements. The participants were instructed not to eat or drink anything that morning.[16] Individuals were questioned about their protocol adherence before sample collection. GCF samples were taken at six sites on one incisor, premolar, and molar tooth of each participant. Samples from periodontally healthy individuals were collected from mesio-buccal and disto-palatal sites of the test teeth, and from the two deepest pockets of the same teeth in patients with CP. The area was isolated with cotton rolls and slightly air dried; great care was taken to avoid saliva contamination, and plaque was gently removed by a curet. Each paper strip[||] was held for 30 seconds within the sulcus or pocket by the orifice method of Rüdin et al.[26] Any paper contaminated by blood was discarded. The GCF volume of each strip was measured using a precalibrated electronic device,[¶] and all six strips were pooled in glass tubes containing 1 mL of 20 mM Tris-HCl buffer (pH 6.5). Samples were eluted for 30 minutes at room temperature[27] and, after the removal of the paper strips, stored at –80°C until analysis.[28]

Blood sampling. Venous blood was collected from the antecubital fossa and allowed to stand at room temperature for 30 minutes and then centrifuged at 3,500 rpm for 5 minutes. Supernatant serum samples were transferred to microcentrifuge tubes[#] and stored at –80°C until analysis.[28]

Laboratory Assessments

TAS. Serum and GCF TAS levels were determined using a commercially available assay kit.[**29] This method is based on the bleaching of the characteristic color of a more stable 2,2′-azino-bis (3-ethylbenz-thiazoline-6-sulfonic acid) radical cation by antioxidants. The results were expressed in millimoles 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid[††] equivalents per liter.

TOS. Serum and GCF TOS levels were determined using a commercially available assay.[‡‡30] This method is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidative species in acidic medium and the measurement of the ferric ion by xylenol orange. The results were expressed in micromoles of H_2O_2 per liter. The TAS and TOS methods[29,30] are colorimetric and automated, and the precision of this assay is excellent at <3%.

OSI. Percentage ratio of TOS to TAS was accepted as OSI: OSI = [(TOS, millimoles per liter)/(TAS, millimoles 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid[§§] equivalent per liter) × 100].[31]

Statistical Analyses

All data analyses were performed using statistical software.[||||¶¶] Shapiro-Wilks test was used for the normality of the test parameters. For parameters that passed the normality test, comparisons between the four study groups were performed using the one-way analysis of variance. Kruskal-Wallis test was used for parameters that failed the normality test. Tukey's test was used for multiple comparisons of mean groups in one-way analysis of variance that show homogeny variance. Results were considered statistically significant at $P<0.05$.

RESULTS

Individuals in groups were age and sex matched ($P>0.05$) (Table 1). There was no significant difference with respect to former smoking among the groups ($P>0.05$) (Table 1). No statistically significant differences existed among the groups, including patients

|| PerioPaper, Oroflow, Amityville, NY.
¶ Periotron 8000, Oroflow.
# Eppendorf tubes, Interlab, Istanbul, Turkey.
** REL assay diagnostics, Mega Tip, Gaziantep, Turkey.
†† Trolox, Hoffman-LaRoche, Bern, Switzerland.
‡‡ REL assay diagnostics, Mega Tip.
§§ Trolox, Hoffman-LaRoche, Bern, Switzerland.
|||| SPSS v.15.0, IBM, Chicago, IL.
¶¶ SigmaStat 3.5, Systat Software, San Jose, CA.

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with RA (i.e., RA and RA–CP) in terms of DAS28 values (P>0.05) (Table 1).

Periodontal Findings

Clinical periodontal parameter scores (PI, GI, BOP, PD, CAL) including GCF volume were statistically higher in groups of patients with CP (CP and RA–CP) than in the groups of the periodontally healthy individuals (C and RA) (P<0.001). There was no difference between CP and RA–CP groups in any of the parameters above (P>0.05) (Table 2).

Laboratory Findings

GCF findings. No statistically significant difference could be detected between RA and RA–CP groups with regard to GCF TAS values (P>0.05). GCF TAS values of C and CP groups were higher than those of RA and RA–CP groups (P<0.05). GCF TOS values of the RA group were lower than those of C, CP, and RA–CP groups (P<0.05). GCF OSI values of RA–CP and CP groups were higher than the values of RA and C groups (P <0.05) (Table 3). Although, the median and 25% values of GCF TOS in control and RA groups are the same, there is a difference in 75% values which the statistical significance probability stems from.

Serum findings. No difference could be found among the groups in terms of serum TOS and OSI values (P >0.05). However, serum TAS values of the RA group were higher than the RA–CP group (P<0.001). In addition, serum TAS values of controls were also higher than the values of the CP and RA–CP groups (P<0.001) (Table 4).

DISCUSSION

There is an abundance of literature investigating the relationship between RA and periodontitis.[3,9-11] We are not aware of any study that evaluated the relationship between these two chronic inflammatory diseases with regard to local and systemic antioxidant and oxidant status.

RA is a systemic inflammatory disorder with a prevalence of 0.5% to 1.0% in Western populations; it affects females approximately three times more often than males.[32] Our study population primarily consisted of non-smoker females because most of the male patients with RA presenting to the Rheumatology Clinic were smokers, which is representative of the Turkish general population. Because smoking is a risk factor for periodontitis,[33,34] affects RA disease progress,[35] and increases ROS production and oxidative stress,[15,36] smokers were excluded from the study. Seven participants were former smokers, and they were almost equally distributed in the groups.

Periodontitis has a remarkably similar pathobiology to RA.[37] Previous studies[38-40] have reported contradictory findings on the relationship between RA and CP. This may be the result of different RA and periodontal disease classifications and methodology used. Mercado et al.[41] reported a significant association between periodontitis and RA and suggested that this association could be a reflection of a common underlying dysregulation of the inflammatory response in these individuals. Although the design of the current study does not allow us to conclude that there is such an association, we can say that findings did not confirm the hypothesis that, in the coexistence of these two chronic inflammatory conditions, severity of periodontitis increases.

RA often affects the proximal interphalangeal and metacarpophalangeal joints, which may lead to substantial manual disability.[32] Oral hygiene may be impaired in these patients, making them susceptible to plaque accumulation and, consequently, periodontal disease. Pischon et al.[42] suggested that individuals with RA have significantly increased clinical AL compared to controls, and oral hygiene may only partially

Table 2.

Clinical Parameters and GCF Volume of the Study Groups

Parameter	C	RA	CP	RA–CP	P
PI (mean ± SD)	0.358 ± 0.292	0.584 ± 0.246	1.999 ± 0.690*	2.134 ± 0.467*	<0.001
GI (25% to 75%)	0.585 (0.330 to 0.830)	0.670 (0.415 to 0.830)	2.000 (1.915 to 2.170)*	2.000 (1.915 to 2.000)*	<0.001
PD (mm) (25% to 75%)	1.915 (1.670 to 2.330)	1.670 (1.500 to 1.830)	6.170 (5.330 to 6.500)*	5.170 (5.000 to 5.500)*	<0.001
BOP (%) (25% to 75%)	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	100 (100 to 100)*	100 (100 to 100)*	<0.001
CAL (mm) (25% to 75%)	0.015 (0.010 to 0.021)	0.017 (0.011 to 0.024)	6.330 (5.670 to 7.085)*	5.000 (4.585 to 5.500)*	<0.001
GCF volume (µL) (25% to 75%)	0.200 (0.170 to 0.245)	0.255 (0.205 to 0.335)	0.960 (0.835 to 1.050)*	1.180 (1.050 to 1.310)*	<0.001

* P <0.001, significant difference compared to the C and RA groups.

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Table 3.

GCF TAS, TOS, and OSI Values of the Study Groups

Parameter	C	RA	CP	RA–CP	*P*
TAS (25% to 75%)	0.105 (0.070 to 0.145)*	0.0587 (0.023 to 0.073)	0.0875 (0.059 to 0.140)*	0.0525 (0.035 to 0.066)	<0.001
TOS (25% to 75%)	0.010 (0.010 to 0.415)†	0.010 (0.010 to 0.175)	0.285 (0.070 to 0.360)†	0.190 (0.100 to 0.255)†	0.030
OSI (25% to 75%)	0.0155 (0.011 to 0.354)	0.0617 (0.017 to 0.298)	0.386 (0.141 to 0.476)‡	0.337 (0.152 to 0.670)‡	0.023

* $P < 0.001$, significant difference compared to the RA and RA–CP groups.
† $P = 0.030$, significant difference compared to the RA group.
‡ $P = 0.023$, significant difference compared to the C and RA groups.

Table 4.

Serum TAS, TOS, and OSI Values of the Study Groups

Parameter	C	RA	CP	RA–CP	*P*
TAS (25% to 75%)	2.510 (2.170 to 2.725)*	2.385 (2.090 to 2.535)†	1.980 (1.835 to 2.195)	1.805 (1.675 to 2.080)	<0.001
TOS (25% to 75%)	6.935 (5.655 to 8.755)	6.435 (5.695 to 8.650)	7.115 (4.920 to 8.055)	6.595 (4.945 to 8.900)	0.920
OSI (25% to 75%)	0.280 (0.226 to 0.341)	0.280 (0.240 to 0.404)	0.325 (0.262 to 0.407)	0.351 (0.277 to 0.494)	0.245

* Significant difference compared to the CP and RA–CP groups ($P < 0.001$).
† Significant difference compared to the RA–CP group ($P < 0.001$).

account for this association. Absence of a significant difference in terms of PI between CP and RA–CP and RA and C groups indicates that manual disability did not interfere with the oral hygiene measures in our study population. This fact may presumably be explained by the relatively young age of the patients with RA, whose hands were not severely affected yet by the disease.

In this study, the GCF TAS value of the C group is significantly higher than the RA and RA–CP groups, but surprisingly similar to that of the CP group, contradicting the findings of Brock et al.,[16] who stated that GCF antioxidant capacity in patients with CP was lower than that of healthy controls. Results of the current study showed that, in the coexistence of RA and CP, GCF TAS values were lower than those of CP alone. This outcome may be interpreted as RA having a negative impact on GCF TAS values. The serum TAS value in the C group was higher than that of the CP group, which corroborates the findings of Pendyala et al.[43] who reported lower serum antioxidant values in patients with CP compared to healthy controls. Interestingly, there was no significant difference between the C and RA groups in serum TAS values.

There is evidence on the role of oxidative stress in RA pathogenesis. Studies provide evidence for the involvement of FRs/ROS in the pathogenesis of RA.[20,21,44] Oztürk et al.[4] suggested that the antioxidant system is impaired and peroxidation reactions are accelerated in patients with RA. Wruck et al.[18] claimed that oxidative stress is significantly involved in cartilage degradation in experimental arthritis. Seven et al.[19] reported that increased lipid, protein, and DNA oxidation markers and impaired antioxidant status confirm the role of oxidative stress in the pathogenesis of RA. There are also many studies that point to the role of oxidative stress in the pathogenesis of periodontitis.[1,5,14,16,17] Akalın et al.[45] reported that GCF and serum TOS values of the CP group were higher than healthy controls. In our study, interestingly, the GCF TOS value of the C group was higher than the RA group. There was no statistically significant difference among the groups in terms of serum TOS values. Although, the median and 25% values of GCF TOS in control and RA groups are the same, there is a difference in 75% values which the statistical significance probability stems from. We had difficulty in interpreting some of our findings mentioned above when we only used TAS and TOS values. However, we also evaluated the OSI, which is expressed as the percentage ratio of total TOS to TAS. To the best of our knowledge, this is the first report to consider OSI in periodontal issue. We think that the OSI value must be taken into consideration rather than TAS and TOS values because OSI seems to serve as a delicate balance between TAS and TOS.

Findings of the present study clearly demonstrate that presence of the local (GCF) inflammatory condition acted as a principle factor rather than the systemic (serum) inflammatory condition on crevicular fluid OSI values. Moreover, RA seems to affect neither serum nor GCF OSI values in the presence of CP.

The major limitation of our study is the absence of information regarding history of the drug used by the

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patients with RA and its possible effect on masking the severity of disease in patients with periodontitis. Patient profile applied to the Rheumatology Clinic consisted of individuals who have already used non-steroidal anti-inflammatory drugs (NSAIDs) and anti-cytokine drugs given at other centers or were unaware which drugs they used. Mercado et al.[41] and Reichert et al.[46] pointed to the possible effect of NSAIDs on limiting gingival inflammation and periodontal bone loss in patients with RA. Reichert et al.[46] suggested that juvenile patients with RA who were taking NSAIDs had significantly higher PI scores in the presence of decreased values for sulcular bleeding index. Similarly, Pers et al.[47] and Nilsson and Kopp[48] documented that anti-tumor necrosis factor-α therapy may have beneficial effects on periodontal conditions.

Another limitation of our study is that the study population was not balanced with regard to sex, with females being dominant; estrogen acts as an antioxidant,[49] and this may have led to the misinterpretation of antioxidant status of study population, including postmenopausal females, because Baltacioğlu et al.[50] found a decrease in systemic and local antioxidant defense in the postmenopausal patients with CP. However, in our study, mean ages in the groups are similar, discarding such a possible effect of postmenopausal status on antioxidant activity.

CONCLUSIONS

The following major conclusions can be drawn from this study: 1) RA did not show any additional detrimental effect on clinical parameters in patients with CP; 2) GCF OSI values of patients with CP were higher than those of periodontally healthy individuals; 3) RA seems to affect neither serum nor GCF of OSI values in the presence of CP; and 4) because OSI serves as an element of balance, it is likely to be of greater importance to use OSI values than TAS and TOS values. In other words, antioxidant and oxidant status vary dynamically throughout the lifespan of the individual. The important point is whether a balance occurs or not between these two conditions. In this context, it seems logical to use OSI in the interpretation of the study results.

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