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Original Article

Advanced oxidation protein products and monocyte chemoattractant protein-1 in periodontal disease

Periodontal hastalıkta ileri oksidasyon protein ürünleri ve monosit kemoatraktan protein-1

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ABSTRACT

Aim: The aim of the study was to determine gingival crevicular fluid (GCF) levels of advanced oxidation protein product (AOPP) and monocyte chemoattractant protein (MCP)-1 in subjects with periodontal disease and health.

Materials and Methods: A total of 75 non-smokers, including 25 participants with chronic periodontitis (CP), 25 participants with gingivitis (G) and 25 participants with periodontally healthy (H) were included into the present study. The probing depth (PD), clinical attachment level (CAL), plaque index (PI) and gingival index (GI) were recorded. The GCF samples from 4 sites in each individual were collected and GCF AOPP and MCP-1 levels were determined by enzyme-linked immunosorbent assay method.

Results: GCF AOPP and MCP-1 levels were the lowest in the H group; followed by the G group and the highest in the CP group. These differences were statistically significant between G and H groups and between the CP and the other groups ($p < .05$). A statistically positive correlation was detected between GCF AOPP and MCP-1 levels.

Conclusion: GCF AOPP and MCP-1 levels might play a considerable role during periodontal inflammation and an elevated GCF AOPP and MCP-1 levels are suggested as a potential biomarker for periodontal diseases.

Key Words: Advanced oxidation protein products, Gingival crevicular fluid, Monocyte chemoattractant protein, Oxidative stress, Periodontitis

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Öz

Amaç: Çalışmanın amacı periodontal hastalıklı ve sağlıklı bireylerde dişeti oluğu sıvısı (DOS) ileri oksidasyon protein ürünleri (AOPP) ve monosit kemoatraktan protein-1 (MCP)-1seviyelerini belirlemekti.

Gereç ve Yöntemler: 25 kronik periodontitisli (KP), 25 gingivitisli (G) ve 25 periodontal sağlıklı (S) toplam da 75 sigara içmeyen birey çalışmaya dahil edildi. Sondalanabilir cep derinliği (SCD), klinik ataşman seviyesi (KAS), plak indeksi (Pİ) ve gingival indeks (Gİ) kaydedildi. Her bireyde 4 alandan DOS örnekleri toplandı ve DOS AOPP ve MCP-1 seviyeleri enzim bağlı immunosorbent analizi ile belirlendi.

Bulgular: DOS AOPP ve MCP-1 seviyeleri en düşük S grupta; ardından G grubunda ve en yüksek KP grubunda idi. Bu farklılıklar G ve S grupları ile KP ve diğer gruplar arasında istatistiksel olarak anlamlı farklıydı ($p < .05$). DOS AOPP ve MCP-1 seviyeleri arasında pozitif istatistiksel korelasyon bulundu.

Sonuç: Periodontal inflamasyon sırasında DOS AOPP ve MCP-1 seviyeleri önemli bir rol oynayabilir ve artmış DOS AOPP ve MCP-1 seviyeleri, periodontal hastalıklar için potansiyel bir biyolojik belirteç olarak önerilebilir.

Anahtar kelimeler: İleri oksidasyon protein ürünleri, Dişeti oluğu sıvısı, Monosit kemoatraktan protein, Oksidatif stres, Periodontitis

Introduction

Oxidative stress is called serious imbalance between the formation of free radical and antioxidant defense mechanism and leads to the tissue damage. The tissue damages of free radicals include many mechanisms such as protein damage, lipid peroxidation, DNA damage, oxidation of important enzymes and stimulation of proinflammatory cytokines [1].

Advanced oxidation protein product (AOPP) has been identified as a novel marker of oxidant-mediated protein damage, the intensity of oxidative stress, and inflammation. AOPP is defined as the cross-linked protein products containing dytrosine and considered to be a reliable marker for determination of protein damage [2]. AOPP was recognized in uremic patients in 1996 and results from activation of the chloronise oxidants with proteins [3]. It is used as a biomarker in several pathological conditions including diabetes mellitus, rheumatoid arthritis, ulcerative colitis, inflammatory bowel disease [4-7]. Furthermore, it is also suggested that AOPP acts as cytokine-like mediator between neutrophils and monocytes by activating mononuclear phagocytes [2,3]. When the relationship between cell activation markers and AOPP was examined, it was found that there was a close correlation with activation markers of monocytes rather than T and B cells' activation markers [2].

Chemokines are a family of polypeptide that activate different cell types and in relationship with them selectively [8]. Monocyte chemoattractant protein (MCP) - 1 is a possible mediator of completion and activation of monocytes. It is a major chemoattractant for specific subsets of lymphocytes, monocytes and macrophages [9]. MCP - 1 can be released by monocytes, endothelial cells, fibroblasts and T cells. It plays a role in the pathogenesis of various diseases, such as atherosclerosis, diabetes mellitus, idiopathic pulmonary fibrosis, tumors, rheumatoid arthritis, osteoarthritis [10-14]. MCP - 1 is also known to be associated with oral infection with monocyte chemotactic ability [15]. Previously, it has been shown that MCP - 1 expression increased in periodontal tissues [9] and gingival crevicular fluid (GCF) of patients with periodontal diseases [16-18].

To the best of the authors' knowledge, there is no study evaluating AOPP level in GCF of subjects with periodontal disease and health as a biomarker of protein oxidation. Therefore, the aims of our study were 1) to determine GCF AOPP and MCP - 1 levels in periodontal disease and health 2) to examine the possible correlation between the GCF AOPP and MCP - 1 levels. We hypothesized that AOPP may be stimulated by periodontal inflammation and there might be a positive correlation between AOPP and MCP - 1 levels.

Material and Methods

Study population

Seventy-five non-smokers (12 females and 13 males, aged 27 to 66 years [mean age, 42.28 ± 9.00 years]) with chronic periodontitis [CP], 12 females and 13 males, aged 18 to 45 years [mean age, 28.28 ± 7.25 years] with gingivitis [G], and 15 females and 10 males, aged 20 to 54 years [mean age, 31.80 ± 10.16 years] with healthy [H] participants) were selected from

participants referred to the Department of Periodontology, School of Dentistry, Kirikkale University, Kirikkale, Turkey, from May 2014 to January 2015. After all participants were informed about the procedures, they gave written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committe of Kirikkale University. (31.03.2014 Number: 11/04) The study protocol (NCT02848378) was approved by the Institutional Review Board. Each participant who have ≥ 20 teeth was examined clinically and radiographically. Participants having any systemic and bone diseases, bacterial oral infection, immunologic disorders, hepatitis, pregnant and lactating females, former and current smokers, receiving any periodontal treatment in the last 6 months, taking any antibiotics, anti-inflammatory or antioxidants were excluded.

Study groups

Participants were classified into three groups based on their periodontal condition according to criteria proposed by the 1999 International World Workshop for a Classification of Periodontal Disease and Conditions [19]. Participants with CP had moderate to severe alveolar bone loss and clinical attachment level (CAL) ≥ 5 mm and probing depth (PD) ≥ 6 mm in multiple sites of all four quadrants of the mouth but with no evidence of rapid progression. Participants with G had gingival inflammation that was based on the presence of bleeding on probing (BOP) at > 50% of sites in the whole mouth, no clinical and radiographic signs of periodontitis. Participants with healthy periodontium had no sites with PD > 3 mm and CAL > 2 mm, a BOP score of < 15% at the examination, and no alveolar bone loss.

Clinical periodontal parameters

The plaque index (PI) [20], gingival index (GI) [21] from four sites per tooth and the PD and CAL from six sites per tooth using a manual periodontal probe (William's periodontal probe, Hu-Friedy, Chicago, IL) in the whole mouth except third molars were identified. All measurements were performed by a calibrated examiner (MKH). The intraexaminer reliability was high as revealed by an intraclass correlation coefficient of 0.82 and 0.80 for PD and CAL measurements, respectively.

Collection of GCF samples

Four GCF samples including first incisors and canine teeth in H group; single-rooted teeth with the most inflammation in G group and single-rooted teeth with ≥ 4 and < 7 mm PD and ≥ 30% bone loss in CP group were obtained from buccal aspects of the mesial or distal interproximal sites of all teeth. After the samples sites were isolated with cotton rolls and slightly air-dried, the standardized strips (Periopaper, Ora Flow Inc.,Amityville, NY, USA) were used to collect GCF in 30 seconds and volume was measured on a precalibrated device (Periotron 8000, Oraflow Inc., Plainview, NY, USA). Phosphate-buffered saline (500 mL, pH 7.2) was added to each Eppendorf tube containing four paper strips. Then, tubes were vortexed (Vortex, Velp Scientifica, Usmate Velate, Italy) for 1 minute, mixed for 20 minutes with shaking (Biosan Orbital Shaker OS-10, Riga, Latvia), and centrifuged (Mikro 22 R Hettich Centrifugal Machine, Tuttlingen, Germany) for 5 minutes at 5,800 rpm. All samples were stored at -80°C until analysis. GCF AOPP and MCP - 1 levels were measured by enzyme-linked immunosorbent assay (ELISA) (Sun Red Biotechnology Company, Shanghai, China, eBioscience, Inc. San Diego, CA, USA, respectively) using commercial kits according to the manufacturers' instructions.

Statistical analysis

Sample size of 25 has been taken which was found to be adequate to achieve more than 80% power at 0.5 level of significance. The normality of the data distribution was examined using the Shapiro-Wilk test. Non-normally distributed data were expressed as median (IQR). The non-parametric Kruskal-Wallis test was used for comparisons among the study groups for levels of AOPP and MCP - 1. Post hoc two-group comparisons were performed with Bonferroni corrected Mann-Whitney U tests for significant differences. Spearman rank correlation analysis was used to observe any correlation between the GCF AOPP and MCP - 1 levels and P < 0.05 was considered to be statistically significant. All data analyses were performed using a statistical package (SPSS for Windows v.15.0, IBM, Chicago, IL) and software (Minitab 16 Statistical Software, Minitab, State College, PA.) was used for the power analyses.

Results

Demographic and clinical findings

The demographic characteristics and clinical data of the study groups are presented in Table 1. There was no significant difference in gender and age among the study groups (p >.05). PI, PD and CAL scores in the CP group were significantly higher than those of the H and G groups (p <.05). GI score in the H group was significantly lower than the CP and the G groups (p <.05). PI and PD scores were significantly higher in the G group than the H group (p <.05).

Table 1: Demographic Characteristics and Full-Mouth Clinical Parameters of Study Groups

Characteristic	H (n=25)	G (n=25)	CP (n=25)
Age (years; mean±SE)	31.80 ± 10.16	28.28 ± 7.25	42.28 ± 9.00
Sex			
Females	15	12	12
Males	10	13	13
PI	0.16 ± 0.11	1.29 ± 0.27*	1.80 ± 0.27*,**
GI	0.04 ± 0.05	1.75 ± 0.29*	1.79 ± 0.31*
PD (mm)	1.34 ± 0.49	2.17 ± 0.51*	5.71 ± 0.74*,**
CAL (mm)	-	-	6.35 ± 0.70*,**

H= Healthy group; G= Gingivitis group; CP= Chronic periodontitis
*p <0.05, significant difference compared with the H group
**p <0.05, significant difference compared with the G group

Laboratory findings

GCF volume was significantly lower in the the H group than the G and the CP groups and was significantly higher in the CP group than the G group. The total amount of GCF AOPP and MCP - 1 were significantly higher in G and CP groups than the H group.

GCF AOPP and MCP - 1 levels were significantly lower in the G group compared to the CP group (Table 2). The significant positive correlations were found between all clinical parameters and GCF AOPP and MCP - 1 levels. GCF AOPP level was positively correlated with GCF MCP - 1 level (Table 3).

Table2: GCF Volume, the total amount of AOPP and MCP-1 in GCF of Study Groups (Median [IQR])

	H (n=25)	G (n=25)	CP (n=25)	p
GCF Volume (µl)	0.07 ± 0.03	0.38 ± 0.13*	0.48 ± 0.17*,**	<0.05
AOPP (nmol/4 sites)	1.36 ± 0.63	11.11 ± 3.69*	18.70 ± 7.68*,**	<0.05
MCP-1 (pg/4 sites)	0.35 ± 0.23	9.21 ± 5.84*	28.77 ± 11.49*,**	<0.05

H= Healthy group; G= Gingivitis group; CP= Chronic periodontitis; GCF= Gingival crevicular fluid; AOPP= Advanced Oxidation Protein Product;
MCP= Monocyte Chemoattractant Protein
*p <0.05, significant difference compared with the H group
**p <0.05, significant difference compared with the G group

Table 3: Correlations of the gingival crevicular fluid advanced oxidation protein product and monocyte chemoattractant protein-1 levels with clinical parameters

	PI		GI		PD		CAL		MCP-1	
	r	P	r	P	r	P	r	P	r	p
AOPP	0.759	<0.01	0.705	<0.01	0.755	<0.01	0.694	<0.01	0.896	<0.01
MCP-1	0.715	<0.01	0.580	<0.01	0.813	<0.01	0.816	<0.01	-	-

PI= Plaque index; GI= Gingival index; PD= Probing depth; CAL= Clinical attachment level; AOPP= Advanced Oxidation Protein Product; MCP= Monocyte Chemoattractant Protein

Discussion

In this cross-sectional study, we evaluated GCF AOPP level, as a protein damage mechanism's product and GCF MCP - 1 level, as a marker of monocyte function in periodontal disease and health. The data of the present study showed that the levels of AOPP and MCP - 1 in GCF were significantly higher in participants with periodontal disease than periodontally healthy participants and there was a significant positive correlation between GCF AOPP and MCP - 1 levels.

Reactive oxygen species (ROS) act a part in redox-dependent signaling and are necessary for physiological functions. However, excessive generation of ROS and/or reduction of antioxidant defense system against ROS can lead to oxidative stress [1]. Oxidative stress contributes to many diseases and pathologic conditions such as diabetes mellitus [22], cancer [23], chronic renal failure [24], atherosclerotic cardiovascular disease [25], rheumatoid arthritis [26]. Many human studies investigated oxidative stress markers in GCF in periodontitis [27-29].

ROS can cause fragmentation of the peptide chain, alteration of electrical charge of proteins, cross-linking of proteins, and oxidation of specific amino acids and therefore lead to increased susceptibility to proteolysis by degradation by specific proteases [30]. AOPP, as a marker of protein oxidation, is generated during oxidative stress. This product is dependable marker to identify oxidative alteration of proteins. It was shown that in vivo-generated AOPP was able to result in oxidative bursts in neutrophils as well as in monocytes, in this way it was represented to act as inflammatory mediator [31]. Several studies have specified the linkage between AOPP and diabetes mellitus [4,32]. Pan et al. [32] reported a significant increase serum AOPP and protein carbonyl in diabetes mellitus compared with healthy participants. In another study investigating the role of oxidative stress in the pathogenesis of rheumatoid arthritis, it was shown that serum AOPP and the total thiol levels were higher in patients than the control group and protein oxidation has been shown to play an

important role as much as the peroxidation of lipid oxidation in the pathogenesis of rheumatoid arthritis [5]. To the best our knowledge, this is the first study to investigate the AOPP level in GCF in participants with periodontal diseases. In our study, the increment of GCF AOPP level from periodontal health towards periodontal disease supports to use AOPP as a marker of oxidative stress in periodontitis. These results suggest that oxidative protein damage initiates in early stages of periodontal disease and keeps to enhance as the disease progresses and that AOPP is also acceptable marker for determining oxidative stress as a protein damage biomarker in periodontal diseases.

MCP - 1 is a chemokine involved in cell migration during inflammation process. It is secreted from cytokine-activated endothelial cells and vascular smooth muscle cells for the migration of monocytes to inflammation area [18]. Hanazawa et al. [33] evaluated MCP - 1 gen expression in periodontal tissues and monocyte chemotactic activities in GCF in patients with periodontal diseases and they revealed that MCP - 1 gen expression in gingival tissues was significantly higher in patients with chronic periodontitis than periodontally healthy participants and emphasized that MCP - 1 expresssion plays an important role in monocyte infiltration in gingival tissues with periodontal diseases. Yu and Graves [34] examined MCP - 1 expression in chronic inflammed gingival tissues and reported MCP - 1 expression was significantly higher in severe inflamed tissue than moderate and mild inflamed tissues. In a study investigating GCF MCP - 1 level in periodontal health and disease, it was suggested that MCP - 1 level in GCF increased with disease and decreased after periodontal treatment [18]. In an another study, MCP - 1 level in GCF was increased in chronic and aggressive periodontitis compared to periodontally healthy participants [17]. Similarly, in our study, it was shown that MCP - 1 level in GCF was found to be significantly higher in CP and G groups compared to periodontally healthy group. Similarly, these results presented that MCP - 1 level in GCF was parallel to the increase of periodontal clinical parameters and it was determined this increment plays a role in the pathogenesis of periodontal disease.

In this study, we also aimed to examine the possible correlations between AOPP and MCP - 1 levels in GCF and we found that there was a significant positive correlation between AOPP and MCP - 1 levels. In vitro study pointed out MCP - 1 expression at both the protein and mRNA levels was properly increased by AOPP [35]. In rat mesenchymal cells, AOPP can induce MCP - 1 mRNA and protein expression via nuclear factor kappa B activation [36]. A clinical study displayed a relation between AOPP levels and serum markers of monocyte activation [2]. We also found strong positive correlations between the total amount of AOPP and MCP - 1 in GCF. This condition suggests that oxidized proteins may contribute to the inflammatory process that is associated with periodontal inflammation.

Conclusion

The results of our study suggest that a significant protein damage mechanism's product may occur in periodontal disease. GCF AOPP level may be used as a biomarker to detect the protein damage caused by oxidative stress and the potent positive correlation between GCF AOPP and MCP - 1 levels may provide an elucidation for the mechanisms of inflammatory condition in periodontal diseases. Further, longitudinal prospective studies are needed to affirm the findings of our study.

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Declaration of conflicting interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

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