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Original Scientific Paper

THE INFLUENCE OF PERIODONTAL DISEASE TREATMENT ON 8-HYDROXY-DEOXYGUANOSINE CONCENTRATIONS IN SALIVA AND PLASMA OF CHRONIC PERIODONTITIS PATIENTS

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SUMMARY – The 8-hydroxy-deoxyguanosine (8-OHdG) is one of the customary products of oxidized DNA. The purpose of this study was to compare salivary and plasma 8-OHdG concentrations in a group of chronic periodontitis patients to those measured in a group of patients with healthy periodontium, as well as to determine the impact of periodontal therapy on 8-OHdG concentrations in saliva and plasma in chronic periodontitis patients. The study sample comprised of 24 patients with chronic periodontitis and 16 periodontally healthy individuals. Plaque index, gingival index, papilla bleeding index, probing depth and clinical attachment level were indices used to determine patient periodontal status. Salivary and plasma 8-OHdG concentrations were determined by ELISA method. The salivary 8-OHdG concentration was statistically significantly higher in the group of periodontitis patients compared to periodontally healthy subjects. After initial periodontal therapy, the 8-OHdG concentration in saliva was significantly reduced in the periodontitis group (p=0.021). Differences in plasma 8-OHdG concentrations between the two groups did not reach statistical significance and no significant changes were noted in the periodontitis group following initial periodontal therapy. A higher salivary 8-OHdG concentration reflects increased oxidative stress caused by periodontal disease. Initial periodontal therapy may be helpful in reducing salivary 8-OHdG concentrations in chronic periodontitis patients.

Key words: *Deoxyguanosine; Oxidative stress; Periodontal diseases; Saliva; Plasma*

Introduction

Periodontitis is an inflammatory disease that damages the tooth supporting structures and is one of the main causes of tooth loss in adults[1]. While periodontal pathogens are recognized as primary etiologic factors, excessive host response to bacterial challenge has a decisive role in the disease development[2-4]. Growing body of empirical evidence indicates that periodontitis induces excessive reactive oxygen species (ROS) production in periodontal tissue[5-7]. Additionally, some authors speculate that, during phagocytosis of periodontal pathogens, polymorphonuclear leukocytes also produce ROS, which can exacerbate oxidative stress caused by periodontitis[8].

On the other hand, findings yielded by several studies suggest that periodontal infection can adverse-

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ly affect systemic health, leading to coronary heart disease, atherosclerosis, diabetes mellitus, preterm labor, low birth weight delivery, and respiratory diseases[9-12]. Although the processes of periodontal diseases that are believed to increase the risk of developing these systemic diseases are complex and not fully understood, some authors suggest that diffusion of ROS produced by periodontal inflammation into the bloodstream is the contributing factor. Once in the bloodstream, ROS may cause protein, lipid and nucleoside oxidation, resulting in systemic oxidative stress that can cause remote tissue and organ damage[13,14].

One of the customary products of oxidized DNA is the 8-hydroxy-deoxyguanosine (8-OHdG). Findings yielded by several studies indicate that 8-OHdG may serve as an oxidative stress biomarker and can be employed in evaluating oxidative DNA damage resulting from a wide range of diseases such as diabetes mellitus, cancer, neurovegetative diseases, rheumatoid arthritis, coronary artery disease, and liver diseases[15-20]. More recent research also suggests a link between 8-OHdG concentration and chronic periodontitis[21-23].

Extant studies indicate that salivary 8-OHdG concentrations are significantly higher in chronic periodontitis patients than in healthy individuals and that concentration of this marker tends to decrease following periodontal treatment[22-26]. Similarly, it can be postulated that, if periodontitis causes blood oxidative stress, its levels would likely be reduced due to periodontal treatment. However, data regarding the influence of oxidative stress arising from periodontal lesions on the 8-OHdG concentration in systemic circulation currently are limited[22,26,27]. As the data regarding the impact of treatment of periodontal diseases on the 8-OHdG concentrations in systemic circulation are particularly scarce, further investigation is warranted.

The aim of the present study was to determine salivary and plasma 8-OHdG concentrations in periodontally healthy patients and those diagnosed with chronic periodontal diseases, as well as to compare salivary and plasma 8-OHdG concentrations measured before and after periodontitis therapy.

Subjects and Methods

Systemically healthy nonsmokers aged 25-70 years with more than 20 teeth present having received no periodontitis therapy in the past six months were invited to take part in the study. The patients that reported taking antibiotics or anti-inflammatory drugs in the last six months, as well as anti-oxidant or vitamin supplement consumers were excluded from the study. Forty patients that met the study inclusion criteria agreed to participate. Prior to commencing the study, approval was obtained from the local Ethics Committee and all participants provided a written informed consent after verbal and written explanation regarding the nature of the study and treatment they would undergo. All procedures performed in the study involving human participants were in accordance with the Declaration of Helsinki.

Periodontal condition was evaluated through the following indices, measured at the mesial, buccal, distal and lingual surfaces of each tooth: plaque index (PI)[28]; gingival index (GI)[29]; papilla bleeding index (PBI)[30]; probing depth (PD); and clinical attachment level (CAL). Michigan 'O' probe with William's markings was used for this purpose. Saliva and plasma 8-OHdG concentrations were measured to assess oxidative DNA damage.

Samples of unstimulated whole saliva (approximately 2 mL) were obtained from each participant in the morning, prior to any periodontal manipulation, whereby the participants were instructed not to consume any food or drink for 8 hours prior to attending the appointment. All patients rinsed their mouth with water before expectorating saliva into a disposable tube. After centrifugation of collected samples at 3000 g for 10 minutes in the laboratory, the supernatants were transferred to Eppendorf tubes and stored at -80 °C until final analysis.

Blood samples were collected from the fingertip at chairside using tubes coated with EDTA (Kabe Labotechnik, Germany) and transported to the laboratory, where they were immediately centrifuged at 3000 g for 10 minutes, after which the plasma samples were transferred to Eppendorf tubes and stored at -80 °C until final analysis.

Salivary and plasma 8-OHdG concentrations were determined by ELISA (Cell Biolabs OxiSelect™, USA) according to the manufacturer's instructions. The kit has an 8-OHdG detection sensitivity range of 100 pg/mL to 20 ng/mL. All samples were tested in duplicate. The results were expressed in ng/mL.

Table 1. Clinical parameters and 8-OHdG levels in saliva and plasma in the CP and H group at baseline and three months upon periodontal therapy completion

	CP group (baseline)		H group		CP group (after therapy)	
	Mean±SD	Min-max	Mean±SD	Min-max	Mean±SD	Min-max
PI	1.35±0.40	0.50-1.97	0.28±0.33[a]	0.04-0.78	0.29±0.10[b]	0.13-0.61
GI	1.66±0.50	1.15-2.79	0.22±0.39[a]	0.00-0.73	0.34±0.39[b]	0.00-1.22
PBI	1.41±0.59	0.64-3.07	0.20±0.26[ac]	0.00-0.58	0.62±0.33[b]	0.08-1.65
PD (mm)	3.22±0.51	2.57-4.42	1.30±0.29[ac]	1.15-1.65	2.64±0.44[b]	1.95-3.81
CAL (mm)	2.63±1.07	1.76-5.50	0.35±0.62[ac]	0.00-0.59	2.05±0.98[b]	0.59-4.08
8-OHdGs (ng/mL)	0.89±0.42	0.25-1.63	0.67±0.30[d]	0.18-1.03	0.68±0.31[e]	0.25-1.20
8-OHdGp (ng/mL)	0.49±0.18	0.17-0.81	0.44±0.23	0.11-1.00	0.44±0.15	0.20-0.78

CP = chronic periodontitis; H = healthy; SD = standard deviation; PI = plaque index; GI = gingival index; PBI = papilla bleeding index; PD = probing depth; CAL = clinical attachment level; 8-OHdGs = 8-hydroxy-deoxyguanosine in saliva; 8-OHdGp = 8-hydroxy-deoxyguanosine in plasma;
[a]statistically significant difference between CP group and H group at baseline ($p<0.001$);
[b]statistically significant difference in CP group relative to baseline ($p<0.001$);
[c]statistically significant difference between CP group and H group three months upon therapy completion ($p<0.05$);
[d]statistically significant difference between CP and H group at baseline ($p<0.05$);
[e]statistically significant difference in the CP group compared to baseline values ($p<0.05$).

Based on clinical measurements, two groups were formed, comprising of chronic periodontitis patients (CP) and subjects with healthy periodontium (H). The CP group included patients with at least one pocket with PD ≥5 mm and CAL ≥4 mm *per* quadrant, accompanied by positive bleeding on probing. Patients without clinical signs of periodontal diseases formed the control group (group H).

Patients in whom periodontal disease was diagnosed underwent initial therapy, which included intensive hygiene phase, and scaling and root planing within seven days. Scaling and root planing were conducted using periodontal curettes (Gracey Access curettes, Kohler, Austria) and ultrasonic scalers (Mini-Piezon, EMS, Switzerland).

In chronic periodontitis patients, measurements of all periodontal indices were recorded, and saliva and blood sampling and analysis were performed at two time points, i.e. at the beginning of the study and three months after completing the initial treatment. In patients with healthy periodontium, measurements were taken and saliva and blood sampling and analysis were performed only once, at the beginning of the study.

In order to evaluate the particular influence of the GI, PD and CAL on the 8-OHdG levels, patients in the CP group were additionally subdivided as follows: based on the GI scores, the samples were allocated to the subgroups with moderate (Loë-Silness 0.1-2) or severe (Loë-Silness 2.1-3) inflammation; according to PD values, patients were allocated to the subgroups with PD ≥5 mm on more than 20% of sites or PD ≥5 mm on less than 20% of sites; and according to CAL measurements, patients were allocated to the subgroups with CAL ≥3 mm or CAL <3 mm.

Data collected as part of the study were analyzed using the SPSS 16 for Windows statistical package. All values were expressed as mean ± SD. The t test was used to analyze differences in clinical parameters, age, and salivary and plasma 8-OHdG concentrations between the groups. Wilcoxon test was utilized to determine differences in salivary and plasma 8-OHdG levels measured before and after periodontal therapy, as well as for assessing the influence of GI, PD and CAL on the 8-OHdG concentrations before and after treatment. Results were considered significant at $p<0.05$.

Results

The study sample comprised of 40 patients, 24 of them diagnosed with chronic periodontitis (8 male and 16 female, aged 30-70 years, mean age 49.30 years), while the remaining 16 subjects were periodontally healthy and served as controls (6 male and 10 female, aged 27-65 years, mean age 47.28 years). There were no statistically significant differences in age and gender composition of the two groups.

Table 2. Influence of gingival inflammation on 8-OHdG levels in patients with periodontitis at baseline and three months upon periodontal therapy completion

8-OHdG (ng/mL)	Level of gingival inflammation	CP group (baseline) Mean±SD Min-max	CP group (after therapy) Mean±SD Min-max
Saliva	Moderate (n=10)	0.88±0.38 0.25-1.38	0.61±0.35[a] 0.25-1.18
	Severe (n=14)	0.90±0.60 0.37-1.63	0.65±0.52[a] 0.25-1.20
Plasma	Moderate (n=10)	0.49±0.16 0.17-0.80	0.42±0.16 0.28-0.78
	Severe (n=14)	0.50±0.19 0.22-0.81	0.45±0.19 0.20-0.75

CP = chronic periodontitis; 8-OHdG = 8-hydroxy-deoxyguanosine; SD = standard deviation;
[a]statistically significant difference compared with baseline in CP group (p<0.05).

Table 3. Influence of probing depth on 8-OHdG levels in patients with periodontitis at baseline and three months upon periodontal therapy completion

8-OHdG (ng/mL)	Probing depth	CP group (baseline) Mean±SD Min-max	CP group (after therapy) Mean±SD Min-max
Saliva	≥5 mm <20% (n=11)	0.68±0.54 0.25-1.08	0.57±0.40[b] 0.25-1.08
	≥5 mm ≥20% (n=13)	0.98±0.48[a] 0.41-1.63	0.65±0.39[b] 0.26-1.20
Plasma	≥5 mm <20% (n=11)	0.48±0.21 0.17-0.81	0.42±0.15 0.20-0.68
	≥5 mm ≥20% (n=13)	0.50±0.09 0.26-0.58	0.47±0.15 0.28-0.78

CP = chronic periodontitis; 8-OHdG = 8-hydroxy-deoxyguanosine; SD = standard deviation;
[a]statistically significant difference between ≥5 mm ≥20% and ≥5 mm <20% groups at baseline (p<0.05);
[b]statistically significant difference in CP group relative to baseline values (p<0.05).

Table 4. Influence of clinical attachment level on 8-OHdG levels in patients with periodontitis at baseline and three months upon periodontal therapy completion

8-OHdG (ng/mL)	Clinical attachment level	CP group (baseline) Mean±SD Min-max	CP group (after therapy) Mean±SD Min-max
Saliva	<3 mm (n=12)	0.66±0.32 0.25-1.15	0.53±0.22[b] 0.25-0.90
	≥3 mm (n=12)	0.98±0.62[a] 0.41-1.63	0.72±0.45[b] 0.25-1.20
Plasma	<3 mm (n=12)	0.44±0.16 0.17-0.58	0.43±0.16 0.28-0.75
	≥3 mm (n=12)	0.51±0.20 0.26-0.81	0.49±0.18 0.20-0.78

CP = chronic periodontitis; 8-OHdG = 8-hydroxy-deoxyguanosine; SD = standard deviation;
[a]statistically significant difference between CAL ≥3 mm and CAL <3 mm groups at baseline (p<0.05);
[b]statistically significant difference in CP group compared to baseline values (p<0.05).

Clinical periodontal measurements pertaining to the two groups at the beginning of the study and after periodontal disease therapy are presented in Table 1. At the beginning of the study, all periodontal indices were significantly higher in patients with chronic periodontitis compared to healthy controls (p<0.001). Three months after initial therapy, significant reduction in PI, GI, PBI, PD and CAL was noted in the CP group (p<0.001).

The mean 8-OHdG concentrations in saliva and plasma are also shown in Table 1. In the CP group, 8-OHdG concentrations in saliva were significantly higher compared to controls (p=0.024). Salivary concentrations of this marker decreased significantly after periodontal therapy (p=0.021). However, 8-OHdG concentrations in plasma were not significantly higher in the CP group compared to the healthy group (p=0.362). In addition, reduction in plasma 8-OHdG concentrations recorded upon completion of periodontal treatment was not statistically significant (p=0.147).

Our results further indicated that salivary 8-OHdG concentration in the subgroup with PD ≥5 mm ≥20%

was significantly higher compared to the subgroup with PD ≥5 mm <20%. Similarly, 8-OHdG concentration in saliva was significantly higher in patients with CAL ≥3 mm than in the subgroup with CAL <3 mm. However, differences in 8-OHdG concentrations in saliva between patients with severe and moderate gingival inflammation were not statistically significant. Additionally, plasma 8-OHdG concentrations were similar in the subgroups with severe and moderate gingival inflammation. No statistically significant differences in plasma 8-OHdG concentration were recorded between the subgroup with PD ≥5 mm ≥20% and subgroup with PD ≥5 mm <20%, or between patients with CAL ≥3 mm and CAL <3 mm (Tables 2, 3 and 4).

Discussion

Data reported in the majority of published studies on oxidative DNA damage reveal elevated salivary 8-OHdG concentrations in chronic periodontitis patients[24,31,32]. These findings imply that the extent of oxidative burst in periodontitis may cause significant local DNA damage. In a study conducted by Canakci *et al.*[33], salivary 8-OHdG concentration in patients with periodontitis was much higher than in the periodontally healthy group (4.24 ng/mL and 1.26 ng/mL, respectively). Sezer *et al.*[34] also report 3.13 ng/mL and 1.56 ng/mL as 8-OHdG concentrations in saliva of periodontitis patients and healthy controls, respectively. Our results are in line with these findings, as salivary 8-OHdG concentrations in the chronic periodontitis group (0.89 ng/mL) were significantly higher than in the healthy group of patients (0.67 ng/mL). Our results are also in agreement with the approximate values of 8-OHdG reported by Dede *et al.*[21]. Differences in methodology are likely the reason for such a marked discrepancy in salivary 8-OHdG concentrations obtained in various studies. While we used whole unstimulated saliva as did Dede *et al.*[21], Canakci *et al.*[33] and Sezer *et al.*[34] utilized stimulated saliva. In fact, there is presently no consensus on whether oral environment is better represented by stimulated or unstimulated saliva, even though this may influence the 8-OHdG levels measured. Periodontal status of the patients included in different studies could also be a source of differences in reported findings. This assertion is grounded in the research conducted by Takane *et al.*,[24,32] who reported significantly higher 8-OHdG concentrations in saliva of patients who had teeth with poor prognosis compared to patients with no such teeth or with healthy periodontium. These findings thus suggest that increased salivary 8-OHdG levels have a strong relationship with the severity of periodontitis and can potentially serve as an indicator of disease progression.

In this study, we also evaluated the particular influence of GI, PD and CAL on the salivary 8-OHdG levels. Previous studies have shown that salivary 8-OHdG concentrations are directly associated with periodontitis severity[25,32,35,36]. Ibrahem[35], for example, reports on significantly higher 8-OHdG concentrations in saliva of patients with PD >6 mm compared to those with PD <6 mm. We found that patients with PD ≥5 mm on more than 20% of sites also had significantly higher salivary 8-OHdG concentrations compared to those measured in the group with PD ≥5 mm on less than 20% of sites. Additionally, our study showed that 8-OHdG concentration in the subgroup of patients with CAL ≥ 3 mm was significantly higher compared to that obtained for the subgroup of patients with CAL < 3 mm. On the other hand, it seems that the GI level did not exacerbate DNA damage, since we found no significant differences between 8-OHdG concentrations in saliva of patients with severe and moderate gingival inflammation. These results are in line with those reported by Sezer *et al.*[34] and Canakci *et al.*,[33] who noted that 8-OHdG levels in saliva are significantly positively correlated with PD and CAL, but not with GI and PI. Thus, it can be assumed that inflammation alone does not lead to significant elevation of salivary 8-OHdG concentration.

Several studies have shown that salivary 8-OHdG concentrations can decrease after periodontal therapy relative to the baseline[35,37]. Ibrahem[35] reports on a significant reduction in salivary 8-OHdG concentrations in patients with periodontal pockets >6 mm, but not in patients with periodontal pockets <6 mm. In our study, periodontal therapy also led to reduction in 8-OHdG. Decrease in 8-OHdG concentrations that was achieved in patients with PD ≥5 mm at more than 20% of sites was twice as high as that in patients with PD ≥5 mm at less than 20% of sites. Hence, it can be concluded that initial periodontal therapy including mechanical debridement and removal of periodontal pathogens can result in reduction of oxidative stress in the oral cavity.

In our study, plasma 8-OHdG concentrations were measured in patients with CP, as well as in subjects with healthy periodontium, with the aim of ascertaining whether periodontal tissue damage affects circulating oxidative stress. Ekuni *et al.*[7] studied a rat periodontitis model and report higher gingival and plasma 8-OHdG levels relative to controls. The authors conclude that 8-OHdG reflects periodontal health status and serves as a clinical biomarker of oxidative damage in periodontitis. They further indicated that, as cytokines are commonly used as systemic markers of inflammation in periodontitis, it may be clinically useful to detect the 8-OHdG level in addition to the cytokine levels. In the studies on humans, Hendek *et al.*[22] and Onder *et al.*[26] found significant differences in salivary 8-OHdG levels between periodontitis patients and periodontally healthy group, but not for 8-OHdG in serum. In the present study, we found that the periodontitis and control groups had similar 8-OHdG concentrations in plasma. Even though the subgroup with CAL ≥3 mm had higher 8-OHdG concentrations in plasma compared to that with CAL <3 mm, the difference was not statistically significant.

Ekuni *et al*. also report that mechanical stimulation through tooth brushing reduced 8-OHdG levels in plasma in an animal periodontitis model[7]. The authors conclude that reduction in gingival inflammation due to tooth brushing may decrease ROS production and limit transfer of oxidative stress from periodontal lesions to systemic circulation. Our results, however, did not support this conclusion, as no significant differences were noted in the 8-OHdG concentrations in plasma before and after periodontal treatment.

The potential limitations of this study could be a relatively small sample of patients and the fact that we used only one marker of oxidative stress. Therefore, further research is required in order to reach more definitive conclusions about the impact of periodontal disease on systemic oxidative stress.

Within the limitations of the present study, our results suggest that 8-OHdG, a product of DNA oxidation, was elevated in the saliva of CP patients. The level of salivary 8-OHdG could be associated with periodontal disease severity. The results yielded by our study also showed that periodontal therapy was beneficial in reducing oxidative stress, as it resulted in lower salivary 8-OHdG concentrations. There was no elevation in plasma 8-OHdG concentrations in CP patients.

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Sažetak

UTJECAJ PARODONTNE TERAPIJE NA KONCENTRACIJU 8-HIDROKSI-DEOKSIGVANOZINA U SLINI I PLAZMI KOD BOLESNIKA S KRONIČNIM PARODONTITISOM

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8-hidroksi-deoksigvanozin (8-OHdG) je jedan od uobičajenih proizvoda oksidirane DNA. Svrha ove studije bila je usporediti koncentracije 8-OHdG u slini i plazmi u skupini pacijenata s kroničnim parodontitisom i skupini ispitanika sa zdravim parodontom te odrediti utjecaj parodontne terapije na koncentracije 8-OHdG u slini i plazmi kod pacijenata s kroničnim parodontitisom. Uzorak studije činila su 24 pacijenta s kroničnim parodontitisom i 16 osoba sa zdravim parodontom. Indeks plaka, indeks gingive, indeks krvarenja iz papile, dubina sondiranja i razina kliničkoga pričvrstka bili su indeksi koji su primijenjeni za određivanje parodontnog stanja pacijenata. Koncentracije 8-OHdG u slini i plazmi određivane su metodom ELISA. Koncentracija 8-OHdG u slini bila je statistički značajno veća u skupini pacijenata s parodontitisom u usporedbi s ispitanicima sa zdravim parodontom. Nakon inicijalne parodontalne terapije, koncentracija 8-OHdG u slini značajno je smanjena u skupini pacijenata s parodontitisom (p=0,021). Razlike u koncentracijama 8-OHdG u plazmi između dviju skupina nisu dostigle statističku značajnost i nisu uočene značajne promjene u skupini pacijenata s parodontitisom nakon inicijalne parodontalne terapije. Veća koncentracija 8-OHdG u slini odražava povećani oksidacijski stres uzrokovan parodontnom bolešću. Inicijalna parodontna terapija može biti korisna u smanjenju koncentracije 8-OHdG u pacijenata s kroničnim parodontitisom.

Ključne riječi: *Deoksi gvanozin; Oksidacijski stres; Parodontna bolest; Slina; Plazma*