



ASSESSMENT OF CYTOGENETIC DAMAGE TO EXFOLIATED GINGIVAL CELLS IN PATIENTS WITH CHRONIC GENERALIZED PERIODONTITIS

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SUMMARY – The aim of this cross-sectional study was to investigate the occurrence of chromosomal abnormalities through the frequency of micronuclei and other genomic damage markers in patients with chronic generalized periodontitis and without periodontal disease. Micronucleus assay was performed in exfoliated gingival epithelial cells of 35 patients with generalized chronic periodontitis and 30 control subjects with healthy periodontium. Full mouth clinical examination was performed to define periodontal condition. The mean number of cells with micronuclei observed in chronic periodontitis and control groups was 1.8 (± 1.49) and 2.0 (± 1.34), respectively. Differences between the groups were not significant ($p=0.574$). Compared to control subjects, patients with chronic periodontitis showed a significant increase in the number of binucleated cells ($p\leq 0.001$) and number of cells with nucleoplasmic bridges ($p=0.042$). Study results indicated that chronic periodontitis was not associated with higher occurrence of chromosomal damage in gingival cells compared to individuals with healthy periodontium.

Key words: *Periodontitis; Cytotoxicity; Genotoxicity; Gingival cell; Micronucleus assay*

Introduction

Periodontal disease contributes significantly to the global burden of oral disease at high prevalence rates. The World Health Organization estimates that severe periodontal disease is found in 10%-15% of the middle-aged adult world populations¹. Periodontal disease is chronic infection that involves destruction of the tooth-supporting tissue and is considered to be of multifactorial nature where multiple causal risk factors act simultaneously in its onset and progression^{2,3}. There are three main causal risk factors, i.e. microbiology, ge-

netics, and lifestyle such as tobacco use, diet, excessive alcohol consumption, stress, and poor hygiene practices⁴. Numerous microorganisms from dental plaque stimulate host cells to release proinflammatory cytokines that attract polymorphonucleocytes to the site of infection, which then produce proteolytic enzymes and reactive oxygen species (ROS) by oxidative burst. Tissue damage in inflammatory periodontal pathologies can be mediated by ROS and can occur through a number of mechanisms such as protein disruption, lipid peroxidation, induction of proinflammatory cytokines, and DNA damage⁵. It is also well known that inflammatory processes are associated with perpetual cell division, thus enabling the incidence of errors during mitosis and consequently chromosomal damage that, in turn, stimulates apoptosis^{6,7}. By constantly renewing tissues, apoptosis ensures tissue homeostasis; however, its occurrence in increased frequency can be

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an indication of genotoxic effects that are related to the initiation of a malignant transformation process^{6,8,9}.

Cytogenetic biomonitoring has been employed in human health risk studies for several decades in diagnosing and staging disease, as well as to assess the risk of disease occurrence. Such information provides statements concerning the level of risk and further evidence on susceptibility⁹⁻¹¹.

Oral epithelial cells are the preferred target cells for determining early genotoxic events caused by carcinogenic agents that enter the body by inhalation and ingestion, as well as those that are applied for therapeutic benefit within the oral cavity. Micronucleus test in the epithelial cells of the oral cavity is one of the least invasive methods, which can measure systemic DNA damage in humans. Oral epithelium is maintained by continuous renewal of cells by mitosis of mesenchymal cells in the basal layer. Newly produced cells migrate to the surface of the mucosa to replace the desquamated ones. The basal layer contains stem cells that during cell division can manifest genetic damage (breakage or loss of chromosomes) in the form of micronuclei. Micronuclei are formed by condensation of acentric fragments (chromosome fragments lacking the centromere), or lagging whole chromosomes in anaphase of cell division. These chromatin entities will not travel to either of the two poles of the dividing cell^{8,12-14}. Investigation of chromosomal damage in human oral cells (buccal, gingival) by micronucleus assay is a common method used in epidemiological studies, including *in vivo* studies focused on the impact of various dental materials, dietary habits, oral conditions, and a variety of diagnostic and therapeutic procedures on cells^{8,10,15,16}.

The aim of this cross-sectional clinical study was to evaluate the ability of generalized chronic periodontal diseases to induce local genotoxic and cytotoxic damage to gingival cells. The micronucleus assay was used in exfoliated human gingival cells from patients with healthy periodontium and those with chronic periodontitis. The null hypothesis tested was that there would be an increased frequency of cytogenetic endpoints in patients with periodontal diseases.

Subjects and Methods

The study was carried out at the Department of Oral Medicine and Periodontology and Department of Restorative Dental Medicine and Endodontics,

Study of Dental Medicine, University of Split, and approved by the University Ethics Committee (No. 2181-198-03-04-15-0022). All eligible subjects that agreed to participate signed an informed consent form prior to the study procedures.

This study included 35 patients with chronic severe or moderate generalized periodontitis, while control group consisted of 30 healthy adults with healthy periodontium.

Each participant filled out a questionnaire answering questions regarding demographic factors (age, gender), lifestyle factors (smoking, alcohol consumption), personal factors (health status, use of medication, x-ray exposure), and dietary aspects. Individuals who smoked three or more cigarettes *per* day for at least one year were considered to be smokers. Individuals who reported consumption of two or more units of alcohol *per* day were excluded from the study. Patients with systemic illness, oral lesion, history of malignant diseases, previous radio- or chemotherapy and exposure to diagnostic x-rays in the past 3 months were excluded from the study. Patients with removable and fixed prosthodontics and those undergoing orthodontic treatment were also excluded from the study.

Complete clinical periodontal examination was performed using a periodontal probe (PCPUNC-15, Hu-Friedy, Leimen, Germany) and included full mouth plaque score, full mouth bleeding score, clinical attachment level, and pocket probing depth at six sites *per* tooth (disto-buccal, mid-buccal, mesio-buccal, disto-lingual, mesio-lingual, mid-lingual). Full mouth plaque score and full mouth bleeding score were recorded dichotomously after measuring all teeth in the respective quadrant. Chronic periodontitis group consisted of patients with moderate to severe alveolar bone loss and attachment loss of 5 mm or more at multiple sites of all four quadrants of the mouth¹⁷.

Samples of epithelial cells were collected using the swab technique. One hour prior to sampling, study participants were asked to refrain from smoking, eating, and drinking alcohol. After rinsing oral cavity with tap water, oral mucosa swab was obtained by gently brushing the gingival area with a cytologic brush. Cells were immediately smeared onto cleaned microscope slides and then fixed in methanol (80% v/v) at 4 °C for 20 min. Staining was carried out with 5% Giemsa solution for 10 min. Afterwards, the slides were rinsed in distilled water and air-dried. The analysis was

Table 1. Descriptive statistics for independent variables

Variable	Level	n	%	Median	Range
Sex	Female	31	47.7		
	Male	34	52.3		
Age (yrs)				45.95	27-59
Smoking habits	Yes - less than 20 cigarettes/day	25	38.5		
	No	40	47.7		
Alcohol drinking	Yes - less than 7 units/week	31	27.7		
	No	34	52.3		
Meat consumption	Yes - 3 days/week	46	70.7		
	Yes - every day	19	29.3		
Vegetables consumption	Yes - 3 days/week	36	55.4		
	Yes - every day	29	44.6		
Fruits consumption	Yes - 3 days/week	30	46.2		
	Yes - every day	35	53.8		
Coffee drinking	Yes - 3 days/week	13	20.0		
	Yes - every day	52	80.0		
Tea drinking	Yes - every day	26	40.0		
	No	39	60.0		

Table 2. Summary statistics for outcome variables

Nuclear abnormality	Group with chronic periodontitis			Group with healthy periodontium (control)			p
	Mean (\pm SD)	Min	Max	Mean (\pm SD)	Min	Max	
Micronucleated cells	1.80 (\pm 1.49)	0	4	2.00 (\pm 1.34)	0	4	0.574
Karyolytic cells	0.62 (\pm 0.94)	0	4	0.43 (\pm 0.73)	0	2	0.360
Nucleoplasmic bridge	0.20 (\pm 0.42)	0	1	0.03 (\pm 0.18)	0	1	0.042*
Pyknotic cells	0.08 (\pm 0.37)	0	2	0.00 (\pm 0.00)	0	0	0.214
Nuclear buds	0.20 (\pm 0.42)	0	1	0.16 (\pm 0.38)	0	1	0.735
Binucleated cells	4.51 (\pm 1.67)	1	9	2.70 (\pm 1.60)	0	6	\leq0.001*

*p<0.05 compared to control

done under a light microscope with 400 \times magnification, and each micronucleus and other chromatin anomalies were additionally verified under 1000 \times magnification. Two replicate slides were prepared for each subject, and 1000 epithelium cells *per* preparation were scored. Frequencies of chromatin abnormalities other than micronuclei, such as binucleated cells, pyknosis, karyolysis, nuclear buds and nucleoplasmic bridges were also evaluated and classified according to Tolbert *et al.*¹⁸. In order for a micronucleus to be counted as such, it has to meet the following conditions: (a) it must consist of nuclear material; (b) it must be com-

pletely separated from the parent nucleus; (c) it must be less than 1/3 of the diameter of associated nucleus; (d) it must be smooth, oval or round shaped; (e) it must be on the same plane of focus; and (f) it must be of the same color, texture and refraction as the main nucleus. Cells with two nuclei were considered to be binucleated. Nuclear anomalies such as karyolysis (dissolution of the nucleus), nuclear buds (precursors of micronuclei) and nucleoplasmic bridges (nuclei that appear connected by a strain of chromatin), and pyknosis (irreversible condensation of chromatin) were recorded separately^{16,18}.

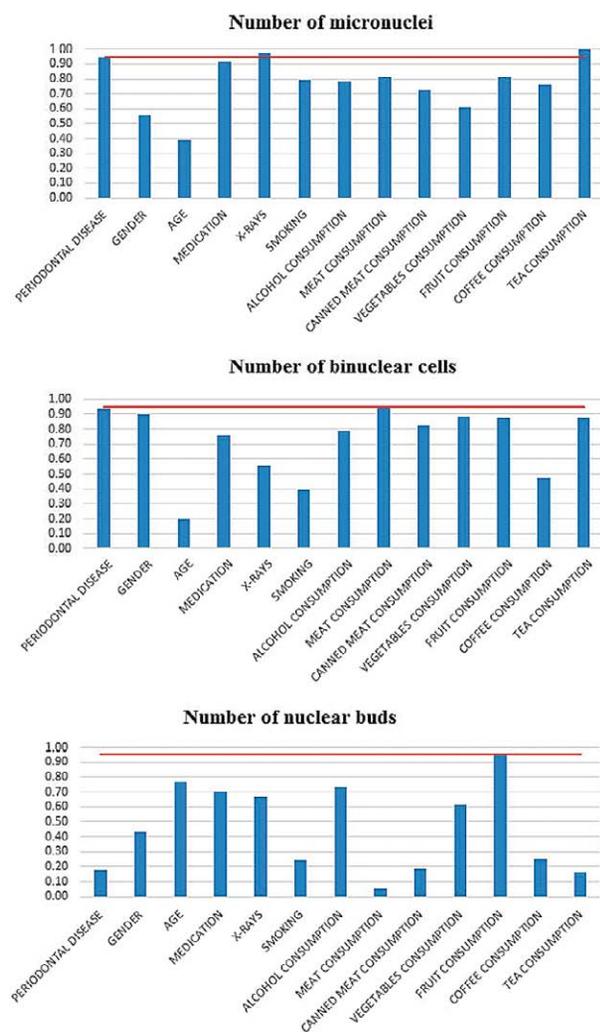


Fig. 1. Multiple regression analysis results.

Significant dependence of measured cytogenetic endpoints (number of micronuclei, binuclear cells, and nuclear buds) on gingival cells, and demographic and lifestyle factors as possible predictors.

Statistical analysis was performed by using SPSS software package (IBM Corp., Armonk, NY, USA). By descriptive statistical analysis, the basic statistical parameters, mean and standard deviation, were determined. Differences in the number of micronuclei and other nuclear anomalies between the groups of subjects were tested by Student's *t*-test. General regression model (GRM) from linear/nonlinear modeling method was used to assess the effect of predictor variables (age, gender, and profession, use of medication, x-ray exposure, dietary habits, periodontal disease, and lifestyle factors) on dependent variables (micronucleus, binucleated cells, nucleoplasmic bridges, nuclear

buds, pyknosis, and karyolysis). The results of GRM were expressed in the form of Pareto charts of *t* values. The level of statistical significance was set at $p \leq 0.05$.

Results

The final study sample consisted of 65 individuals (34 men and 31 women). In accordance with periodontal diagnostic criteria, 35 individuals were classified with chronic generalized severe or moderate periodontitis, and 30 showed no changes in periodontium and were classified as control subjects. Among the subjects with chronic periodontitis, there were 16 men and 19 women, whereas control group consisted of 18 men and 12 women. The mean age (\pm SD) of study groups with and without periodontal disease was 43.77 (\pm 10.24) and 48.10 (\pm 7.58) years, respectively.

A structured questionnaire scheduled for this study was used to collect demographic data and data on the habits such as smoking, alcohol consumption and dietary habits (meat, meat products, fruits, vegetables, tea, and coffee consumption) (Table 1).

Among independent variables, the frequency of tea consumption and x-ray exposure were the variables with a significant effect on the number of cells with micronuclei ($\beta=1.740$, $p \leq 0.001$; $\beta=-1.041$, $p=0.027$) (Fig. 1). The frequency of eating fruits had a significant effect on the number of cells with nuclear buds ($\beta=-0.309$, $p=0.038$) (Fig. 1). The frequency of meat consumption had a significant effect on the occurrence of binucleated cells ($\beta=-1.405$, $p=0.048$) (Fig. 1).

Table 2 shows distribution of the occurrence of micronuclei and other chromatid abnormalities in the groups of individuals with chronic severe or moderate periodontitis and individuals with healthy periodontium. Significant between-group differences were only observed in the number of binucleated cells ($p \leq 0.001$) and number of cells with nucleoplasmic bridges ($p=0.042$).

Discussion

The aim of the present cross-sectional study was assessment of cytogenetic damage in patients with chronic periodontitis in comparison with healthy controls. The investigation was conducted using the micronucleus assay in oral gingival exfoliated cells. The null-hy-

pothesis was only partly confirmed because no correlation was found between any of the cytogenetic endpoints tested and occurrence of chronic periodontal diseases. It was found that only the increase in the number of binucleated cells and nucleoplasmic bridges was significant in participants with chronic periodontitis as compared with healthy control subjects.

Gingival mucosal cells are not keratinized epithelial cells, characterized by a high turnover, which has previously been used for evaluating molecular and biochemical alterations in gingivitis and periodontitis^{19,20}. Periodontal disease is an inflammatory process involving a set of changes that directly affect tissues that hold the teeth. There are few studies that assessed the occurrence of genetic damage associated with periodontal disease^{6,20-26}. Genotoxic damage of periodontal disease was followed by the micronucleus assay in peripheral lymphocytes^{21,24}, gingival^{6,20} and buccal cells^{22,26}, and by sister chromatid exchange method in peripheral blood lymphocytes²⁵.

In this study, the results obtained did not indicate any significant difference in the number of micronuclei between patients with periodontal disease and subjects with healthy periodontium ($p=0.574$). The presence of chronic periodontal disease did not affect the number of karyolytic cells ($p=0.360$), pyknotic cells ($p=0.214$) and nuclear buds ($p=0.735$) either. Only the increase in the number of cells with nucleoplasmic bridges ($p=0.042$) and binucleated cells ($p\leq 0.001$) differed significantly between the study groups. The number of binucleated cells can be correlated to alterations in cell division dynamics and is an indicator of toxic effects on the cell protein structures, particularly the cytoskeleton. The appearance of nucleoplasmic bridges indicates a significant disturbance of the structural integrity of chromosomes^{15,26}. Nucleoplasmic bridges may indicate premature shortening of telomeres due to long-term burdening of the genetic material by chemicals. Telomeres are not replicated as they should, thus being inappropriately finished. Rather, unfinished bare ends of chromosomes are left, which are joined non-homologously and form a bridge between two newly formed nuclear poles. This finding is in agreement with detection of increased binuclear cells. They indicate lagging in cell division, which may be induced by premature telomere shortening and disability of chromosomes to divide between two newly formed cellular poles equally^{12,14}.

The results obtained in this study are in accordance with some previously published studies. D'Agostini *et al.* report that there was no significant elevation of micronucleated and binucleated cells in gingival epithelium related to periodontal disease (gingivitis and periodontitis)²⁰. The authors observed a higher frequency of binucleated cells in periodontitis positive subjects (1.55 ± 0.25) compared to controls (1.31 ± 0.15) but it was not statistically significant. Similar results were obtained by a Brazilian group of authors applying the same methodology⁶. The results obtained in their study did not show a higher frequency of chromosomal damage, as assessed by the occurrence of micronuclei, as a consequence of periodontal disease but they did observe higher occurrence of nuclear alteration indicative of apoptosis (karyorrhexis, pyknosis, and condensed chromatin) in individuals with periodontitis, suggesting the cytotoxic effects associated with an inflammatory process. Avula *et al.* also investigated the frequency of micronuclei in peripheral blood lymphocytes in different forms of periodontitis (generalized aggressive and chronic) in comparison to healthy controls and concluded that there were no differences between the study groups²⁴. Emingil *et al.* used sister chromatid exchange analysis to evaluate cytogenetic damage in periodontitis patients, revealing no differences in tested parameters between periodontitis patients and healthy controls²⁵. However, Bloching *et al.* have described the increased occurrence of micronuclei in individuals with severe periodontitis compared to individuals with moderate periodontitis and those without periodontal disease²². An increased number of micronuclei in buccal exfoliated cells from patients with moderate to severe periodontitis compared to control subjects was also noted by Bastos-Aires *et al.*²⁶. Based on their results, it could be concluded that buccal cells are more sensitive to cytogenetic damage than gingival cells and lymphocytes.

The impact of demographic parameters such as age, gender, lifestyle and diet-related factors (alcohol consumption, meat consumption, etc.) is often not evaluated when the primary focus of the authors is on a certain environmental factor or disease. Among the variables tested in our study, we observed the impact of tea consumption and x-ray exposure on the number of micronucleated cells. In patients who consumed tea on a daily basis, a significantly higher number of micronuclei may have been attributed to high temperature

of consumed tea. Numerous researches have proven that irradiation (x-ray) can cause damage to the cellular system, such as genotoxicity and cytotoxicity, but there also are studies that do not corroborate these claims²⁷. The habit of fruit consumption had a significant negative effect on the number of cells with nuclear buds. Fruits may influence inflammatory and cellular redox processes, which are primarily responsible for the pathogenesis of various chronic diseases²⁸.

In conclusion, based on the results of this study, periodontal disease is not related to the frequency of chromatin damage to gingival cells. Although our study did not confirm the relation of cytogenetic damage in individuals with periodontal disease, further research is recommended. Furthermore, the study suggested that long-term effect of periodontal treatment on the occurrence of chromosomal damage endpoints should be investigated. It would provide correct evaluation of micronuclei as early biomarkers of genomic damage, which may have a prognostic value.

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Sažetak

PROCJENA CITOGENETSKIH OŠTEĆENJA U OLJUŠTENIM GINGIVNIM STANICAMA U BOLESNIKA S KRONIČNIM GENERALIZIRANIM PARODONTITISOM

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Cilj ovog istraživanja bio je ispitati pojavu citogenetskih abnormalnosti kroz učestalost mikronukleusa i drugih genomskih oštećenja u pacijenata s generaliziranim kroničnim parodontitisom i ispitanika s klinički zdravim parodontom. Mikronukleus test je proveden u oljuštenim gingivnim epitelnim stanicama 35 pacijenata s kroničnim generaliziranim parodontitisom i 30 kontrolnih ispitanika sa zdravim parodontom. Svakom ispitaniku je napravljen klinički pregled kako bi se utvrdio parodontološki status. Prosječan broj stanica s mikronukleusom kod pacijenata s kroničnim generaliziranim parodontitisom i kontrolne skupine bio je 1,8 ($\pm 1,49$) i 2,0 ($\pm 1,34$). Razlike među skupinama nisu bile statistički značajne ($p=0,574$). Pacijenti s kroničnim parodontitisom pokazali su značajno povećanje broja binuklearnih stanica ($p\leq 0,001$) i broja stanica s nukleoplazmatskim mostovima ($p=0,042$) u usporedbi s kontrolnom skupinom. Rezultati su pokazali kako kronična parodontna bolest nije povezana s povećanom pojavom kromosomskih oštećenja u gingivnim stanicama u usporedbi s osobama sa zdravim parodontom.

Ključne riječi: *Parodontitis; Citotoksičnost; Genotoksičnost; Gingivne stanice; Mikronukleus test*