Relationship between serum tumor necrosis factor receptor-2 concentration and periodontal destruction in patients with type 2 diabetes: Cross-sectional study

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SUMMARY

Introduction The role of tumor necrosis factor-α (TNFα) is well documented in pathogenesis of chronic periodontitis (CP) and type 2 diabetes (T2D). Considering short half-life of TNFα, tumor necrosis factor receptor-2 ($TNFR_2$) is used as prosperous surrogate marker of TNFα activity.

Objective The aim was to detect $TNFR_2$ serum concentration and correlate it with periodontal destruction in patients with diagnosed T2D and nondiabetics.

Methods The study included 85 patients divided into three groups: T2D + CP (group T2D, n = 34); nondiabetics + CP (Group PD, n = 27); and healthy controls (group HC, n = 24). T2D was diagnosed according to WHO criteria (2013) and periodontitis was diagnosed using International Workshop for a Classification of Periodontal Diseases and Conditions criteria (1999). $TNFR_2$ level was measured by enzyme-linked immunosorbent assay (ELISA).

Results There was no difference in $TNFR_2$ level among the groups (Kruskal–Wallis, p = 0.482). Significant correlation (Pearson's correlation coefficient) was observed between clinical attachment loss (CAL) and $TNFR_2$ concentration in PD group (r_p = -0.460, p = 0.016). In T2D group, correlations were observed between $TNFR_2$ concentration and CAL (r_p = 0.363, p = 0.005) and periodontal inflamed surface area (PISA) (r_p = 0.345, p = 0.046) and periodontal epithelial surface area (PESA) (r_p = 0.578, p = 0.000).

Conclusion Higher concentration of $TNFR_2$ was associated with higher CAL, PESA, and PISA scores in T2D group. Contrary to that, nondiabetics with higher values of CAL exhibited lower concentration of $TNFR_2$, presenting potential protective effect on periodontal destruction. These results imply that diabetes may alter $TNFR_2$ secretion originated from periodontium.

Keywords: chronic periodontitis; $TNFR_2$; TNF-alpha; type 2 diabetes

INTRODUCTION

Plaque-associated periodontal diseases are chronic infectious diseases caused by mixed microbial flora that lead to inflammation and destruction of tooth attachment and ultimately tooth loss [1]. Although bacteria of dental biofilm are considered to be the main etiological factor in periodontitis, it is a well-known fact that a local immune and inflammatory response to bacteria leads to destruction of periodontium [2].

Key mediator of periodontal inflammation is tumor necrosis factor-alpha (TNFα). TNFα is potent proinflammatory cytokine produced by many cells in response to inflammation, infection and injury. TNFα plays a vital role in host defense processes and immune surveillance. However, increased levels of TNFα exhibit harmful effects [3]. TNFα binds two specific TNFRs – $TNFR_1$ and $TNFR_2$. $TNFR_1$ is expressed in most cell types, whereas immune cells constitutively express low levels of $TNFR_2$ [4]. Both receptors exist in two forms – transmembrane and soluble (s). The soluble forms compete with TNFα for TNF binding sites on transmembrane receptors [3]. Therefore, receptors participate in signal transduction, and regulate TNFα bioavailability [5].

Beneficial and pathological signals diverge at receptor levels. Transmembrane TNFα and $TNFR_2$ are responsible mostly for prosurvival signals, while sTNFα and $TNFR_1$ mediate detrimental effect [6]. Since $TNFR_2$ half-life is longer (4 hours) than TNFα half-life (~ 6 min), it exhibits superior sensitivity and reliability when measuring in frozen plasma. Therefore, $TNFR_2$ is used as an effective surrogate marker of TNFα activity.

Type 2 diabetes (T2D) is a metabolic disorder characterized by hyperglycemia, which results from progressive insulin secretory defect on the background of insulin resistance [7]. For 30 years now, periodontitis has been acknowl-

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edged as the sixth chronic complication of diabetes [8]. There is increasing evidence that the relationship between T2D and periodontitis is bidirectional [9]. Roles of TNFα in pancreatic β-cell destruction and insulin resistance have been established [10].

OBJECTIVE

This study was aimed at detecting $TNFR_2$ serum concentration and correlating it with periodontal destruction in type 2 diabetics and nondiabetics.

METHODS

Study population

The study was conducted as a cross-sectional study, approved by the Ethical Committee of the Faculty of Dental Medicine, University of Belgrade (decision No. 36/9 of 20th of February 2013) between March 2013 and January 2014. A total of 85 subjects (41 men and 44 women, 28–68 years of age) were divided into three groups: healthy control (HC) group consisted of 24 healthy volunteers without clinical signs of periodontitis and free of systematic diseases; periodontitis group (PD) consisted of 27 patients with diagnosed chronic periodontitis (CP) and free of systematic diseases (periodontitis patients were referred to Department of Periodontology and Oral Medicine, Faculty of Dental Medicine, University of Belgrade); 34 patients, hospitalized at the Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, with diagnosed T2D and CP comprised the T2D group. All the subjects who participated in the study signed an informed consent.

Inclusion and exclusion criteria

The subjects included in study had more than 14 teeth and body mass index (BMI) of 18–30 kg/m^2. The exclusion criteria were as follows: pregnancy/lactation, presence of a systemic disease except T2D and its chronic complications, injury in the previous six months, systemic antibiotic/immunomodulatory therapy in the previous three months, therapy of periodontitis during 18 months prior to the study, everyday usage of oral antiseptics.

Anamnesis of the patients and clinical examination

Data regarding smoking history, mental stress, physical activity and health status were obtained through clinical chartings and interviews. Patients were classified according to their smoking status as "nonsmoker" and "smoker". Smokers were further classified as "former smoker" (with subgroups consisted of subjects who ceased smoking more or less than five years ago, respectively) or "current smoker" (with subgroups smoking more or less than 10 cigarettes per day, respectively). Pack-years (PPY) were calculated by multiplying duration of smoking in years and the number of cigarettes smoked per day, and then dividing by 20. Patient histories included information about the subjects' everyday mental stress in terms of intensity and frequency. The final score was calculated as the sum of the mentioned measurements, and categorized as low/medium/high stress [11]. Information about the intensity (low, moderate, hard), frequency (never, less/more than 2 times/week) and type (aerobic/anaerobic) of physical exercise was also recorded.

T2D and chronic periodontitis diagnosis

T2D was diagnosed by measuring glycaemia using oral glucose tolerance test (OGTT), as well as glycated hemoglobin (HbA_1c) values [7]. Nondiabetics exhibited normal parameters on OGTT and $HbA_1c < 6.5\%$. The blood sugar regulation was classified as satisfactory ($HbA_1c \geq 7.5\%$) and poor control ($HbA_1c < 7.5\%$).

A full-mouth clinical examination performed at six sites per tooth was done for each tooth in order to asses the following periodontal parameters: Silness–Löe plaque index (PI), dichotomous bleeding on probing (BOP), probing pocket depth (PPD) and clinical attachment loss (CAL). All examinations were performed by two calibrated doctors – one collected the measurements using Williams probe (Hu-Friedy Mfg. Co., LLC, Chicago, IL, USA) and the other recorded the results. Periodontitis was diagnosed if the subject exhibited CAL > 1 mm and PPD > 3 mm at least at three sites in two different quadrants. According to CAL, periodontitis patients were classified into the following three subgroups: patients with mild CP (CAL = 1–2 mm); moderate CP (CAL = 3–4 mm), and severe CP (CAL ≥ 5 mm). Periodontitis was defined as localized/generalized depending on the number of affected sites (more/less than 30%, respectively) [12]. The inflammatory impact from periodontium on general health was calculated using periodontal epithelial surface area (PESA) and periodontal inflamed surface area (PISA) [13]. Calculations were done by using Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheets available at *http://www.parsprototo.info/* using PPD, CAL, recession for PESA, and additionally BOP for PISA on each tooth. Results were presented in mm^2. Patients without clinical signs of periodontitis had PPD < 3 mm and CAL = 0 mm.

Blood sampling and measurements

Venous blood was collected from cubital vein day after periodontal examination, following fasting, in the resting state in the morning, between 7 and 9 a.m., to minimize diurnal variations. Total leukocyte count, plasma concentrations of cholesterol, high and low density lipoproteins, triglycerides, fibrinogen, HbA_1c, sedimentation rate, and fasting plasma glucose (FPG) levels were measured. Sera obtained from blood samples for $TNFR_2$ analysis were immediately frozen at -72°C and stored until use.

The $TNFR_2$ level was measured by the enzyme-linked immunosorbent assay (ELISA) (eBioscience, Human $TNFR_2$ Platinum ELISA, San Diego, CA, USA) as described by the manufacturer. The values were expressed as ng/ml.

Statistical analysis

The sample size calculation using literature based data for $TNFR_2$ level as a reference variable showed that sample size with 25 patients in each group would provide 80% of power and significance level (α) of 5%.

The statistical analysis package SPSS 18.0 (SPSS Statistics for Windows, SPSS, Inc., Chicago, IL, USA) was used. Categorical variables were compared using the chi-square test (χ^2). Numeric data were tested for normal distribution using the Kolmogorov–Smirnov test. For normally distributed data, Student's t-test / One Way ANOVA was used. Non-parametric data were analyzed using the Kruskal–Wallis / Mann–Whitney U-test. Spearman's/Pearson's correlation coefficients were obtained in order to assess the relationship between $TNFR_2$ concentrations and clinical parameters. Linear regression model was used to determine the predictors of $TNFR_2$. Reliability was tested by Cohen's kappa test. The Cohen's kappa score was determined for each periodontal index in order to test intraobserver agreement. Participants with missing data were not included in the study. All reported p-values were two-sided. Differences were considered significant when p-value was <0.05.

RESULTS

Demographic data and clinical measurements

A total of 170 patients were examined. After anamnesis, and clinical and biochemical examinations, 97 were recruited for the study. According to ELISA plate size, we analyzed only 88 samples. Considering that absorbance of three samples were not detectable, results were obtained for 85 patients.

Demographic data and clinical measurements are presented in Table 1. Groups are matched by age and gender. Although the BMIs were 18.0–30.0 kg/m^2, BMI differed between T2D and two other groups. HbA_1c and FPG levels were higher in T2D than in HC and PD groups. The groups were similar by smoking status (χ^2, $p > 0.05$). Regarding T2D management, 19 subjects used oral antidiabetics, 10 were on insulin therapy and five were on combined insulin therapy.

There was a significant difference in the clinical periodontal parameters between the groups (Table 2). Intergroup analysis revealed differences for PI and CAL between all groups (Mann–Whitney U-test, p = 0.000). BOP and PPD did not differ between PD and T2D groups (Bonferroni > 0.05). Number of present teeth was higher in HC than in other groups (Bonferroni, $p < 0.05$). PESA and PISA were similar between T2D and PD groups. The kappa score for clinical parameters were 0.5–0.8, representing very good agreement.

TNFR2 concentrations

There was no difference in $TNFR_2$ concentrations between the groups. Average concentration in HC, PD and T2D groups were respectively 4.8 ± 4.680, 4.9 ± 7.366, and 5.2 ± 9.719, expressed in ng/ml. $TNFR_2$ serum concentration of diabetics with and without complications were 6.22 ± 11.94 and 4.22 ± 5.54 ng/ml, respectively.

Relationship between TNFR2 concentrations and periodontal clinical parameters

A significant correlation was observed between CAL and $TNFR_2$ concentrations in PD and CAL, PESA, PISA, and $TNFR_2$ in T2D groups (Table 3). Difference was not observed between the concentration of $TNFR_2$ and extent of periodontitis neither in T2D (p = 0.674, Mann–Whitney) nor in PD group (p = 0.487, Mann–Whitney).

Relationship between TNFR2 concentrations and biochemical parameters

Pearson's correlation coefficient between $TNFR_2$ concentrations and BMI in all patients (r = 0.025, p = 0,822) and each group were positive but nonsignificant (HC group: r = 0.248, p = 0.248; PD group: r = 0.054, p = 0.79; T2D group: r = 0.067, p = 0.708).

According to the smoking status, there was significant difference between $TNFR_2$ concentrations (smokers: 5.6 ± 3.738 ng/ml; non-smokers: 4.4 ± 8.713 ng/ml; p = 0.02,

Table 1. Group demographic and clinical data

Variable	Group			p-value
	Healthy control	Chronic periodontitis	Type 2 diabetes	
Age	42.0 ± 3.709	44.9 ± 12.494	46.1 ± 7.606	0.078a
Gender (male/female) (N/%)	7 (29.2)/ 17 (70.8)	11 (40.7)/ 16 (59.3)	16 (47.1)/ 18 (52.9)	0.390b
Body Mass Index (kg/m2)	22.5 ± 2.625	24.4 ± 3.189	27.0 ± 2.98	0.000a
HbA_1c [(%) mmol/mol]	4.8 ± 0.637 (29.0 ± 6.696)	4.8 ± 0.639 (29.0 ± 7.062)	8.4 ± 2.013 (68.0 ± 22.414)	0.000c
FPG level (mmol/l)	4.7 ± 0.714	4.9 ± 0.753	9.5 ± 2.605	0.000c
Smokers/nonsmokers [N (%)]	2 (8.3)/ 22 (91.7)	9 (33.3)/ 18 (66.7)	9 (26.5)/ 25 (76.5)	0.096b

Results are presented as mean ± standard deviation (SD). Results for discrete measures are presented as percentage (%).
N – number of patients; HbA_1c – glycated hemoglobin; FPG – fasting plasma glucose
[a] ANOVA
[b] Pearson χ^2
[c] Kruskal–Wallis test

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Table 2. Clinical periodontal parameters

Variable	Group			p-value
	Healthy control	Periodontitis	Type 2 Diabetes	
PI (Silness–Löe)	0.8 ± 0.499	1.5 ± 0.725	2.1 ± 0.815	0.000[a]
BOP (%)	34.8 ± 17.307	59.8 ± 23.646	63.0 ± 29.409	0.000[a]
PPD (mm)	1.9 ± 0.434	2.7 ± 0.544	2.6 ± 0.116	0.048[a]
CAL (mm)	0.0	2.4 ± 1.909	4.1 ± 1.944	0.001[b]
Extent of periodontitis localized/ generalized (%)	N/A	10 (38.5)/ 16 (61.5)	7 (20.6)/ 27 (79.4)	0.128[c]
Number of present teeth	27.3 ± 1.681	21.6 ± 3.974	19.6 ± 3.544	0.000[a]
PESA (mm2)	N/A	1046.2 ± 292.66	976.9 ± 271.84	0.343[d]
PISA (mm2)	N/A	694.7 ± 359.75	720.0 ± 421.79	0.804[d]

Results are presented as mean ± SD. PPD and CAL values presents average of all sites, including affected and unaffected sites.
PI – plaque index; BOP – bleeding on probing; PPD – probing pocket depth; CAL – clinical attachment level; PESA – periodontal epithelial surface area; PISA – periodontal inflamed surface area
[a] One-way ANOVA
[b] Kruskal–Wallis test
[c] Independent samples t-test
[d] Pearson χ^2

Table 3. Pearson's correlation coefficient (r) between periodontal parameters and TNFR2 serum concentrations in periodontitis and type 2 diabetes groups

Group	Clinical parameters		r	p-value
Periodontitis	TNFR2	CAL	-0.46	0.016
		PPD	0.085	0.675
		PESA	-0.357	0.068
		PISA	-0.164	0.414
Type 2 diabetes	TNFR2	CAL	0.363	0.005
		PPD	0.298	0.087
		PESA	0.345	0.046
		PISA	0.578	0.000

PPD – probing pocket depth; CAL – clinical attachment level; PESA – periodontal epithelial surface area; PISA – periodontal inflamed surface area

Kruskal–Wallis) in PD group. In this group, a correlation between PPY and $TNFR_2$ concentrations were observed (r = 0.424, p = 0.028, Spearman's correlation coefficient).

The concentrations of $TNFR_2$ were neither influenced by the levels of self-reported stress (Kruskal–Wallis, p = 0.459) nor by parameters of physical exercise (Kruskal–Wallis, p > 0.05). Spearman's correlation revealed a weak positive but nonsignificant correlation between $TNFR_2$ and HbA_1c concentrations (r = 0.015, p = 0.935), and duration of T2D (r = 0.05, p = 0.781).

In linear regression analysis, none of the parameters (hematological and biochemical data, physical exercise, mental stress, smoking status, clinical periodontal parameters, duration of diabetes) were assessed as univariate predictors.

DISCUSSION

This study investigated serum concentrations of $TNFR_2$ in T2D patients with periodontitis, and compared them with serum $TNFR_2$ levels in nondiabetics with periodontitis and subjects with clinically healthy periodontium. T2D and periodontitis both are chronic inflammatory disorders which share certain pathogenetic mechanisms, have common inflammatory mediators, although they are of different etiological origin. Advanced periodontitis is considered to be a source of inflammatory mediators. On the other hand, low-grade inflammation precedes diabetes. The role of inflammatory mediators derived from chronically inflamed periodontium and its influence on diabetes onset is yet to be determined [14]. Most published studies investigating inflammatory mediators originated from periodontium have been done in systemically healthy subjects. In contrast, studies with diabetic patients did not take into consideration influence of periodontal inflammation, which surely should not be neglected. We did not find differences in $TNFR_2$ serum concentration between the groups. Local production of both receptors is elevated in periodontal pockets > 3 mm, but their levels progressively diverged as the PPD increased, with the $TNFR_2$ level being comparatively lower than $TNFR_1$ [5]. Although local $TNFR_2$ concentration was negatively correlated with PPD and is considered to be protective for periodontal tissues, serum $TNFR_2$ concentrations were not increased after treatment [9]. It is possible that local periodontal production of receptors is not sufficient for a detectable change of serum concentrations. The results of studies dealing with local periodontal production of TNF family are conflicting: although it is almost accepted that diabetes elevates local cytokine production [15], one study showed lower amount of TNFα in gingival crevicular fluid (GCF) in T2D + PD than in PD patients [16]. Elevated concentrations of both receptors are detected in diabetics with complications [17]. In our study we found slightly increased $TNFR_2$ levels in patients with chronic complications of diabetes.

This study tried to determine systemic inflammatory/infectious burden originating from periodontium using PISA and PESA calculation. There is a limited number of studies investigating PISA–T2D relationship, but all are related to HbA_1c level [18]. As mentioned in the Methods section, PESA and PISA are calculated using PPD, CAL, gingival recession, and BOP. As BOP correlates to PI, we took into consideration all clinical periodontal parameters. Statistical correlation was found between CAL and $TNFR_2$ in T2D and PD groups. Significant correlations between PISA/PESA and $TNFR_2$ were observed in diabetics. In PD group, CAL–$TNFR_2$ correlation was negative. This negative correlation is in agreement with the study that

found negative correlation of local $TNFR_2/TNFR_1$ ratio with PPD, and increasing of this ratio after scaling and root planning [9]. It seems that reduction of inflammation leads to increase of local $TNFR_2$ concentration. The same study also measured receptor serum level before and after the treatment and did not show any differences in serum $TNFR_2$ level due to its long-term stable concentration. Also, measuring the serum TNFα and receptors concentration, Ikezawa et al. [5] found decreased ratio of serum $TNFR_2/TNFR_1$ at periodontitis vs. healthy subjects ($p = 0.051$). This finding also supports a protective role of $TNFR_2$ in periodontal tissues. These findings are in correlation with our results supporting the role of $TNFR_2$ in periodontitis. The $TNFR_2$ is directly involved in TNFα signaling pathways and is considered as prosurvival receptor, which suppresses basal osteoclastogenesis [6, 19]. While TNFα and $TNFR_1$ are overexpressed in gingival tissues at periodontitis, $TNFR_2$ is sporadically found in infiltrating monocyte/macrophage cells and gingival fibroblasts, which may be explained as unsuccessful attempt of gingival tissue to neutralize detrimental effects of TNFα [20]. This in agreement with our results, which support the negative correlation between $TNFR_2$ concentration and CAL in nondiabetic periodontitis patients.

In T2D group, we found significant and positive correlation between CAL/PESA/PISA and serum $TNFR_2$ concentration. Our results lead to the assumption which is in agreement with other studies – that diabetes through extended TNFα/receptors expression changes the inflammatory reaction and thereby response to periodontal pathogens [16, 21]. The aforementioned changes in inflammatory response may lead to exaggerated vulnerability to systematic consequences of local infection. TNFα is implicated in insulin resistance mechanism [10], and serum $TNFR_2$ levels and/or adiponectin concentration are good prediction markers of T2D onset [22]. Increased $TNFR_2/TNFR_1$ ratio is associated with insulin resistance [23]. Almost all studies which explored TNFα level in diabetics did not take into consideration periodontal inflammation. Engebretson et al. [14] considered the periodontal status in T2D patients and demonstrated that severity of chronic periodontitis was associated with increased TNFα level in T2D patients and found a positive correlation between the TNFα serum concentration and CAL.

According to some studies, BMI could influence $TNFR_2$ [24]. We did not find correlation between BMI and $TNFR_2$ in total of 85 patients and separately for each group which is in accordance with most of the studies correlating BMI with TNFα and/or its receptors [10, 14, 17].

TNFα and its receptors serum level could be influenced by emotional stress [25], regular exercise [26], and smoking [27]. According to the results of our study, self-reported evaluation of the aforementioned parameters could not be considered to be an independent predictor of $TNFR_2$ concentration. To the best of our knowledge, this is the first study that took into consideration these factors when examining the influence of periodontitis and T2D on cytokine level.

We observed a higher $TNFR_2$ concentration in smokers in the PD group. This group showed a significant correlation between PPY and $TNFR_2$ concentration. Although a relationship between cigarette consumption and TNFα release from macrophages has been reported [27], results about correlation of smoking and $TNFR_2$ serum concentration are still inconsistent [9].

$TNFR_2$ reflects chronic activation of TNFα and has inducible but relatively stable concentration and may act both as an inhibitor and depot of TNFα [9]. It transduces the most prosurvival signals, buffers TNFα [21], and has certain roles in pathogenesis of peridontitis[19, 28] and diabetes [22, 23]. In our study we could not detect any predictors of $TNFR_2$ concentration using regression statistical models.

CONCLUSION

$TNFR_2$ showed negative correlation with periodontal destruction in nondiabetics, but its dysregulated production and function in T2D may affect this correlation and its potential protective effect. Measuring circulating levels of proinflammatory cytokines is more accurate at animal models, because of the strong influence of environmental factors on expression of these cytokines in humans. Larger and more controlled studies, which take into consideration genetic background, are needed to confirm these findings.

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Корелација између концентрације рецептора 2 фактора некрозе тумора у серуму и деструкције пародонцијума код болесника са дијабетес мелитусом тип 2: студија пресека

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КРАТАК САДРЖАЈ

Увод Улога фактора некрозе тумора-алфа (*TNFα*) доказана је у патогенези хроничне пародонтопатије (ХП) и дијабетеса мелитуса типа 2 (ДМ тип 2). С обзиром на то да је полуживот *TNFα* веома кратак, рецептор 2 фактора некрозе тумора ($TNFR_2$) користи се као маркер активности *TNFα*.

Циљ рада Циљ овог рада је одређивање концентрације $TNFR_2$ у серуму и корелирање са параметрима деструкције пародонцијума код здравих и испитаника са дијагностикованим ДМ тип 2.

Методе рада У студију је укључено 85 пацијената подељених у три групе: ДМ тип 2 + ХП (ДМ група, $n = 34$), здрави испитаници + ХП (ПД група, $n = 27$) и здраве контроле (ЗК група, $n = 24$). Дијагноза ДМ тип 2 постављена је на основу критеријума СЗО (2013), док је дијагноза ХП постављена на основу критеријума Интернационалне радионице за класификацију стања и обољења пародонцијума (1999). Концентрација $TNFR_2$ мерена је *ELISA* методом.

Резултати Концентрација серумског $TNFR_2$ није се разликовала међу групама (Краскал–Волис, $p = 0{,}482$). Постоји значајна корелација (Пирсон) између нивоа припојног епитела (НПЕ) и концентрације $TNFR_2$ у ПД групи ($r_p = -0{,}460$, $p = 0{,}016$). У ДМ тип 2 групи, статистички значајна корелација уочена је између концентрације $TNFR_2$ и НПЕ ($r_p = 0{,}363$, $p = 0{,}005$), као и параметара утицаја инфламације из пародонцијума на системско здравље – *PISA* ($r_p = 0{,}345$, $p = 0{,}046$) и *PESA* ($r_p = 0{,}578$, $p = 0{,}000$).

Закључак Код пацијената са дијабетесом веће концентрације $TNFR_2$ одговарају већим вредностима НПЕ, *PESA* и *PISA*. Насупрот томе, код системски здравих испитаника са ХП веће вредности НПЕ су повезане са мањим концентрацијама $TNFR_2$, што би могло говорити о потенцијалној заштитној улози овог цитокина на деструкцију пародонцијума. Резултати говоре да дијабетес може утицати на секрецију $TNFR_2$ из пародонцијума.

Кључне речи: хронична пародонтопатија; $TNFR_2$; *TNFα*; дијабетес мелитус тип 2

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