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# Intima-media thickness and other markers of atherosclerosis in patients with type 2 diabetes and periodontal disease

Edward Franek[1, 2], Joanna Januszkiewicz-Caulier[1], Anna Błach[1], Magdalena Napora[3], Krystyna Jedynasty[1], Tadeusz Budlewski[1], Dariusz Gozdowski[4], Renata Górska[3]

[1]Department of Internal Diseases, Endocrinology and Diabetology, Central Clinical Hospital MSWiA, Warsaw, Poland
[2]Department of Endocrinology, Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
[3]Department of Periodontology, Medical University of Warsaw, Warsaw, Poland
[4]Department of Applied Statistics and Bioinformatics, Warsaw University of Life Sciences, Warsaw, Poland

## Abstract

**Background:** Periodontal disease is an inflammatory process which results in increased cardiovascular risk in patients with type 2 diabetes mellitus (DM2). It is not clear, however, whether periodontal inflammation may be associated with increased markers of atherosclerosis in these patients.

**Aim:** This cross-sectional study aimed to answer the question of whether periodontal disease in DM2 is associated with increased markers and risk factors of atherosclerosis.

**Methods:** One hundred and twenty one patients were included in the study. Sixteen were classified as periodontally healthy (BGI-H), 87 as having gingivitis (BGI-G), and 18 as having periodontitis with moderate bleeding (BGI-P2), according to the new Offenbacher classification. In all patients, intima-media thickness (IMT), pulse wave velocity (PWV), lipids, and C-reactive protein (CRP) were assessed.

**Results:** Patients with periodontitis and gingivitis had a higher IMT value compared to the BGI-H group (0.804 ± 0.112 and 0.772 ± 0.127 *vs* 0.691 ± 0.151 mm, $p < 0.01$ and $p < 0.05$, respectively, odds ratio 5.25 for having IMT ≥ 0.8 mm, 95% CI 1.1; 25). Patients from the BGI-P2 group also had higher blood pressure (BP) compared to the BGI-G and BGI-H groups, and higher CRP compared to the BGI-G group (4.6 ± 2.3 *vs* 3.8 ± 4.8 mg/L, $p < 0.01$). Lipid parameters and PWV were comparable in all the groups.

**Conclusions:** Periodontal inflammation in patients with DM2 seems to be associated with increased IMT and BP, but not with greater arterial stiffness. These results support the hypothesis that periodontal disease may be associated with a vascular pathology.

**Key words**: diabetes, periodontal disease, intima-media thickness, pulse wave velocity

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## INTRODUCTION

Diabetes mellitus (DM), especially when it is not well controlled, is a risk factor for periodontal disease [1]. Conversely, the presence of chronic periodontitis in diabetic patients is associated with worse glycaemic control [2] and the induction of periodontitis in rodents leads to glucose intolerance and diabetes [3]. Therefore, diabetes and periodontal disease may form a vicious circle, mutually enhancing each other's severity.

**Address for correspondence:**
Prof. Edward Franek, Department of Internal Medicine, Endocrinology and Diabetology, Central Clinical Hospital MSWiA, ul. Wołoska 137, 02–507 Warszawa, Poland, tel: +48 22 508 14 05, fax: +48 22 508 14 00, e-mail: Edward.Franek@cskmswia.pl
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Gingivitis and chronic periodontitis are inflammatory diseases of the periodontium. They are associated with local inflammation, which manifests itself as pain and bleeding and slowly leads to the weakening and loosening of periodontal structures, and subsequent loss of teeth. Recent data suggest that bacteria and bacterial products present in dental plaque and crevicular fluid can stimulate immune cells to produce and release a number of inflammatory mediators [4]. They play a role in the local destruction of gingiva and bone, but are also released to the bloodstream, and their serum concentration is regarded as a marker of periodontal disease. This is true in particular for serum C-reactive protein (CRP) concentration, in the general as well as in some specific populations [5–7], but also for other cytokines [8].

According to current knowledge, inflammation is responsible for the development of atherosclerosis. It has been found that markers of inflammation are predictors of cardiovascular (CV) mortality and morbidity in the general population [9, 10]. Therefore, chronic periodontitis-induced, low-grade systemic inflammation may play a specific role in the pathogenesis of atherosclerosis. Bacteria causing periodontal diseases, such as *Porphyromonas gingivalis* and *Treponema denticola*, have also been found in atherosclerotic plaques [11], provoking speculation regarding their direct role in the pathogenesis of atherosclerosis.

Chronic periodontitis (as well as diabetes itself) is associated with an increased risk of CV complications [1]. However, the mechanisms involved are not clear. It may be partially caused by increased left ventricular mass associated with periodontal disease [12–15], as increased left ventricular mass is an independent CV risk factor [16]. It seems possible that atherosclerotic processes may be initiated or accelerated by periodontal disease-associated inflammation and/or bacteria [11].

As not much is known regarding atherosclerosis in diabetic patients with periodontal disease, the aim of this study was to answer the question of whether gingivitis or chronic periodontitis (defined according to the Offenbacher classification) are associated with markers and risk factors of atherosclerosis in patients with type 2 DM.

## METHODS

### *Investigated group*

Type 2 diabetics were recruited from the patients of the Diabetes Outpatient Clinic of the Central Clinical Hospital MSWiA in Warsaw. The study protocol, prepared in accordance with the Declaration of Helsinki of 1973 (with later revisions), was approved by an appropriate Ethics Commission. All subjects included had signed informed consent papers. Former and current smokers, and those with any current acute or chronic infection, were excluded from the study. In order to exclude an infection, all recruited subjects were carefully examined, (including a gynaecological examination in women, urine culture, otorhinolaryngological examination with perinasal sinus radiographs if necessary, and an abdominal and cardiac ultrasound examination). Patients with an other than the periodontitis infection source in the oral cavity, and those with fewer than seven teeth, were also excluded from the study. Because of the low number of patients in the BGI-P1 and BGI-P3 groups (see the Offenbacher classification below), they were also excluded. None of the patients had been treated by a periodontologist before the study.

### *Methods*

Medical history was recorded, including any history of diabetes, hypertension and medication. Weight, height and office blood pressure (BP) were measured. A dental examination was performed by an experienced dentist, using the WHO-621 periodontal probe, in order to assess the subject's periodontal status (periodontal pocket depth and bleeding on probing).

Pocket depth (PD) is the distance from gingival margin to base of pocket in millimetres. In subjects with healthy gingival and junction epithelium, clinical PD should be below 1.5 mm (although histologically no more than 0.5 mm). Deep pockets, however, are not necessarily associated with present active inflammatory process. If gingivitis or periodontitis are present, the probe tip perforates the pocket bottom or injures the pocket epithelium and infiltrates vascular connective tissue, causing bleeding. Therefore, bleeding on probing (BOP) is a widely used criterion to diagnose gingival inflammation. All six surfaces of every tooth are assessed with regard as to whether probing elicits bleeding or not. The BOP is expressed as a percentage of bleeding sites [17].

The patients were classified according to their periodontal status using a new classification, based on the differences in biologic phenotype [18]. In brief, subjects with PD $\leq$ 3 mm and BOP extent scores $<$ 10% were classified as biofilm-gingival interface — healthy (BGI-H). Patients with PD $\leq$ 3 mm and BOP extent score $>$ 10% were classified as biofilm-gingival interface — gingivitis (BGI-G). Patients with PD $\geq$ 4 mm were classified as periodontitis; those with BOP extent scores $<$ 10% as BGI-P1; deep lesion/low bleeding, with BOP extent scores 10–50% as BGI-P2; and deep lesion/moderate bleeding and with BOP extent scores $>$ 50% as BGI-P3-deep lesion/severe bleeding.

Finally, after stomatological and medical examination, 121 patients were included in the study. In all subjects, blood samples were collected after overnight fasting. Serum concentrations of creatinine, lipids and glucose were measured, using standard laboratory methods. Office BP was recorded; the measurements were performed three times, after 15 min of rest, in a seated position. For the assessment of atherosclerosis, two methods were used: intima-media thickness (IMT) was measured, and arterial stiffness was assessed by pulse wave velocity estimation.

The IMT was assessed in common carotid artery. Carotid arteries were examined bilaterally using B-mode ultrasonography, using a 10 MHz linear transducer. All measurements

were performed by the same experienced sonographist. Three recordings were taken from each left and right artery and the mean value was calculated for each side and for all six measurements.

Pulse wave velocity (PWV) was measured by a noninvasive automated device (Sphygmocor®, Atcor Medical), using a high-fidelity applanation tonometer (SPT-304, Millar Instruments), in a standardised manner [19], after at least 15 min of rest. Briefly, PWV was calculated from a pulse transit time between two measurement sites (carotid-radial). Aortic pressure waveform was generated from radial pressure waveform (averaged from sequential radial waveforms derived from a 10-s long measurement period) and aortic BP was computed. Augmentation index (AIx), showing an augmentation of aortal pressure as a percentage of pulse pressure, was also calculated.

Investigators performing the ultrasound and PWV examination were not aware of the periodontal status of the patients.

### *Statistical analysis*

Statistical significance was set at 0.05. Classification according to Offenbacher (see above) was used for group stratification. The differences between more than two groups were assessed by Anova Kruskal-Wallis test and $\chi^2$ Pearson test. The differences between two groups were compared using the U Mann-Whitney test for continuous variables, and a $\chi^2$ test for nominal scale data. A logistic regression model was constructed to investigate the independent influence of age, sex, body mass index (BMI), HbA1c, LDL-cholesterol, CRP and periodontal status on IMT, AIx and PWV. The IMT was regarded as a binary variable; the threshold value of IMT for pathology was adopted at level 0.8 (IMT $\geq$ 0.8 means pathology). All independent variables were also regarded as binary variables; the thresholds were set *a priori* (for HbA1c, LDL-cholesterol and BMI) or according to ROC analysis. The analyses were performed using Statistica 8.0 (StatSoft, Inc.) and Statgraphics 4.1 (Statpoint Technologies, Inc.) statistical packages.

## RESULTS

After the dental examination, patients were divided into three subgroups according to the Offenbacher classification: BGI-H (16 patients), BGI-G (n = 87), and BGI-P2 (n = 18). Basal parameters of the patients from the three groups are summarised in Table 1.

Patients in the examined groups did not differ with regard to age, sex distribution or BMI, nor with regard to renal function or lipid parameters. The number of teeth was the lowest in the BGI-H group, and the highest in the BGI-P2 group. Diabetes duration and the percentage of patients with diabetes complications, as well as fasting serum glucose, were comparable in all the groups. Glycated haemoglobin level, however, was significantly higher in patients with periodontitis compared to periodontally healthy subjects and to the BGI-G group. The percentage of insulin metphormin, sulphonylurea and statin treated patients was similar. The percentage of hypertensive patients and the number of antihypertensive drugs were similar in all the examined groups, but the systolic as well as diastolic BP was significantly higher in patients with deep lesions/moderate bleeding (BGI-P2 group) compared to periodontally healthy subjects and patients with gingivitis (Table 1).

The results regarding surrogate markers of atherosclerosis are also shown in Table 1. The CRP was higher in patients with periodontitis compared to those with gingivitis. The differences between other groups were not significant. The AIx and PWV did not significantly differ between the groups. However, subjects with more advanced periodontal lesions tended to have increased arterial stiffness expressed as PWV. The comparison of IMT values showed that the patients with gingivitis and periodontitis (P2 group) have significantly higher IMT than periodontally healthy subjects (Fig. 1). Patients with gingivitis or periodontitis were more likely to have IMT $\geq$ 0.8 mm (Fig. 2). A positive correlation was found between serum CRP concentration and BMI ($R = 0.30$, $p < 0.001$).

The logistic regression analysis showed that age, CRP and periodontal status exerted a significant effect on IMT. The highest odds ratio (OR) was observed for gingivitis or periodontitis *vs* periodontally healthy (OR = 5.25, 95% CI 1.1; 25). Weaker but significant effects were observed for age and CRP. The OR for patients older than 65 years *vs* younger patients was 2.83 (95% CI 1.13; 7.13) and the OR for CRP higher *vs* lower than 2.5 was 2.44 (1.06; 5.66). For other examined variables, the effects were not significant.

In the regression models used for the evaluation of the effects of the same independent variables on PWV, no independent association has been found, and AIx was independently associated only with BMI and sex (values not shown).

## DISCUSSION

We found that in the subjects with gingivitis and chronic periodontitis with moderate inflammation (the BGI-G and BGI-P2 groups), IMT was higher compared to periodontally healthy subjects. This finding is consistent with studies published previously by us and by others in renal patients [6] and in non-diabetic patients with periodontal disease [20]. It is, however, the first study showing similar results in diabetic patients.

Diabetes itself is associated with high CV risk [21], but many additional 'classical' and 'non-classical' risk factors cumulate in these patients. Periodontitis seems to belong to the latter group. It has been shown that chronic periodontitis is associated with a higher risk of CV and death in the general population [22]. This finding has also been confirmed in type 2 diabetics [23]. Periodontitis may influence the CV risk in different ways. As periodontal pathogens have been found in atherosclerotic plaques [11], it is possible that they may play

**Table 1.** Comparison of demographic, clinical and laboratory parameters between three studied groups

| Parameter | BGI-H (n = 16) | BGI-G (n = 87) | BGI-P2 (n = 18) | P (ANOVA or $\chi^2$ test) |
|---|---|---|---|---|
| Age [years] | 59.3 ± 7.1 | 62.1 ± 7.2 | 60.9 ± 6.4 | NS |
| Body mass index [kg/m$^2$] | 30.9 ± 6.1 | 32.6 ± 5.5 | 34.5 ± 3.9 | NS |
| Males [%] | 43 | 57 | 61 | NS |
| Number of teeth (median) | 20 (10–28) | 18 (7–28) | 15.5 (9–21)$^{***,\#}$ | < 0.01 |
| Duration of diabetes [years] | 9.1 ± 6.3 | 9.6 ± 5.7 | 10.4 ± 6.7 | NS |
| Complications of diabetes (% of patients) | 44 | 31 | 33 | NS |
| Hypertension [%] | 100 | 100 | 94 | NS |
| Systolic blood pressure [mm Hg] | 132 ± 14 | 136 ± 13 | 147 ± 11$^{**,\#\#}$ | < 0.005 |
| Diastolic blood pressure [mm Hg] | 77 ± 7 | 80 ± 7 | 85 ± 6$^{*,\#}$ | < 0.05 |
| Number of antihypertensive drugs (median) | 2 (0–3) | 2 (0–5) | 2 (0–5) | NS |
| Statins (% treated) | 44 | 55 | 50 | NS |
| Insulin (% treated) | 50 | 37 | 61 | NS |
| Metformin (% treated) | 69 | 72 | 89 | NS |
| Sulphonylurea (% treated) | 38 | 46 | 56 | NS |
| HbA1c [%] | 7.0 ± 0.7 | 7.4 ± 1.4 | 8.4 ± 1.5$^{***,\#\#\#}$ | < 0.001 |
| Fasting serum glucose [mg/dL] | 118 ± 16 | 134 ± 40 | 144 ± 40 | NS |
| Serum creatinine [mg/dL] | 0.83 ± 0.24 | 0.86 ± 0.19 | 0.89 ± 0.20 | NS |
| Serum total cholesterol [mg/dL] | 181 ± 32 | 177 ± 35 | 175 ± 32 | NS |
| Serum LDL-cholesterol [mg/dL] | 104 ± 28 | 95.7 ± 31.3 | 82 ± 21.6 | NS |
| Serum HDL-cholesterol [mg/dL] | 52.9 ± 21.2 | 54.2 ± 14.6 | 60.5 ± 21.9 | NS |
| Serum triglycerides [mg/dL] | 124 ± 53 | 136 ± 64 | 169 ± 145 | NS |
| C-reactive protein [mg/L] | 2.7 ± 2.3 | 3.8 ± 4.8 | 4.6 ± 2.3$^{\#\#}$ | < 0.001 |
| Augmentation index | 24.1 ± 10.0 | 25.7 ± 9.7 | 24.7 ± 8.1 | NS |
| Pulse wave velocity | 8.4 ± 1.0 | 8.7 ± 1.1 | 9.0 ± 1.4 | NS |

*p < 0.05, **p < 0.01, ***p < 0.005 compared to periodontally healthy subjects, and #p < 0.05, ##p < 0.01, ###p < 0.005 compared to G group by Mann-Whitney test

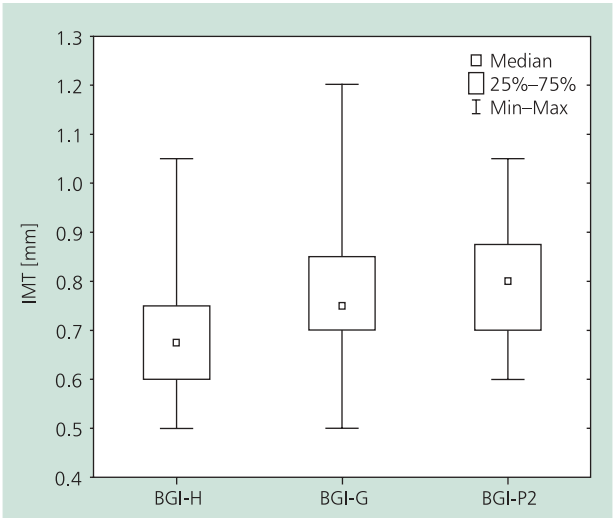


**Figure 1.** Intima-media thickness (IMT) in patients with type 2 diabetes mellitus, according to their periodontal status (BGI-H — healthy periodontium; BGI-G — gingivitis; BGI-P2 — chronic periodontitis); *p < 0.05, **p < 0.01 compared to BGI-H group

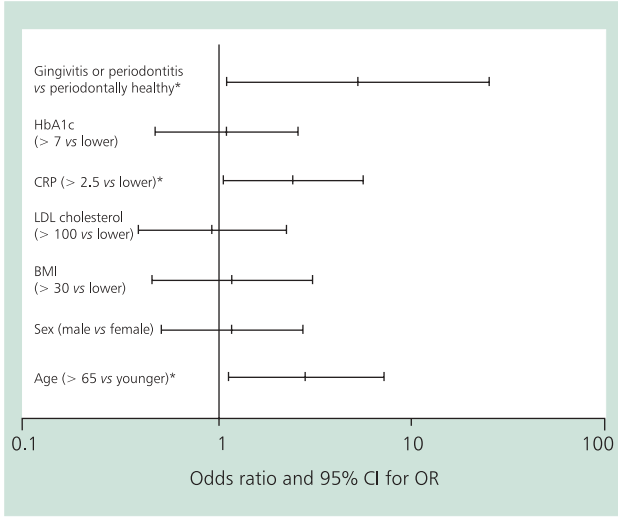


**Figure 2.** Influence of independent variables on intima-media thickness (IMT) — logistic regression analysis results. Odds ratio (OR) over one indicates increased probability of IMT ≥ 0.8 mm; *p < 0.05; CRP — C-reactive protein; BMI — body mass index

a direct role in the process of plaque development. Periodontal disease may be associated with an increase in some CV risk factors, like markers of atherosclerosis: IMT or higher BP [6, 15, 20], and markers of inflammation, such as CRP [6, 13, 14, 24] which is an independent CV risk-factor [25, 26].

An increase of CRP level was found also in this study (Table 1). Although the difference between patients with gingivitis or periodontitis compared to periodontally healthy subjects was not significant, the logistic regression analysis has shown that in a combined gingivitis and periodontitis group, the OR for IMT ≥ 0.8 was 2.44 (Fig. 2). This result is influenced by a relatively broad distribution of CRP values, which suggests that in spite of careful elimination of potential infection, some of the patients may have an occult source of inflammation. Regarding the presence of the positive correlation between serum CRP concentration and BMI, it seems probable that the source of inflammation may be located in the fat tissue. Unfortunately, obesity may nullify the positive effects of periodontal treatment on CRP [27].

It has been shown previously that, at least in some populations, chronic periodontitis is associated with increased systemic BP, which is another CV risk factor [14]. In the large population examined in the NHANES study, hypertension was associated with higher periodontal pocket scores and with more intensive gingival bleeding, although BP in patients with moderate and severe periodontitis was comparable [28]. It is not clear whether it is periodontal inflammation that causes an increased BP, or whether a common pathophysiological pathway exists that links these two diseases. The same is true for the association of periodontal disease and increased IMT. The IMT thickness and arterial stiffness (assessed as PWV or AIx) are important surrogate markers of atherosclerosis. An increase of both of them may be regarded as an independent predictor of coronary heart disease and CV events [29, 30]. Significantly higher IMT and similar non-significant trends of PWV in patients with both gingivitis and periodontitis (i.e. with increased bleeding index regardless of PD) supports the hypothesis that local inflammation of periodontal tissue with subsequent low-grade systemic inflammation may influence the vasculature and result in increased atherosclerotic processes. It is of course unclear whether a pathway exists leading from periodontal disease to atherosclerosis or whether there is rather a common pathway that leads independently to both these conditions from an unknown, common cause. It is also true that no increase of AIx in patients with periodontal disease has been shown in this study. However, it seems that this marker of atherosclerosis is less reliable than the other two [31].

The patients were divided according to the new classification of periodontitis, based on the different severity (and probable duration) of periodontal disease expression, as proposed by Offenbacher et al. [18]. They have been able to show that patients with gingivitis and chronic periodontitis (defined based on two combined parameters: PD and severity of bleeding) differ from periodontally healthy patients with regard to such parameters as mediators of chronic inflammation (like IL-6 or MCP-1), or patterns of periodontal pathogens [8].

Results presented in this study seem to confirm the validity of the new classification. It seems that diabetic patients with different periodontal status according to the Offenbacher classification may also differ phenotypically with regard to important CV parameters, i.e. BP, CRP and IMT.

Periodontitis is the main cause of tooth loss in Western countries. Poland, however, differs from them substantially with regard to the prevalence of caries, which was, and still is, much more frequent, in eastern Europe. In 1987, only about 10% of children in Poland were caries-free, and in 2003 this figure was still only about 20% [32]. It seems then, that caries, not only periodontal disease, may be responsible for tooth loss in the population of Poland. Therefore, the low number of teeth in some patients from the H and G groups does not mean that they were wrongly classified.

This study did not confirm our earlier results [14] that showed an increase of LDL-cholesterol level in hypertensive patients with advanced periodontitis. In fact, an opposite trend existed in the examined diabetic patients. This result may be caused by the fact that a higher percentage of patients with periodontal disease was treated with statins. Anyway, as patients with periodontitis seem to have increased CRP levels, the use of statins in such patients seems to be justified [33].

As with every study, this one has some limitations. A disadvantage of using a new classification is that it may be incomparable to previous results. In most of the papers investigating the relationship between periodontal disease and the CV system, the Community Periodontal Index of Treatment Needs (CPITN) score was used for dental assessment. It is less accurate than a full dental examination with quantitative assessment of dental PD and bleeding index; however, it is not unreliable and is commonly used.

Another limitation is the relatively small study population and subsequently, small number of patients in BGI-H and BGI-P2. Such unequal distribution and lower number of patients in the H and P groups necessitates a cautious interpretation of the results, especially when comparing these two groups.

Additionally, the design of this study does not allow to draw of any causative conclusions. Therefore, longitudinal studies including a greater number of patients will be necessary. In any case, it seems that patients with diabetes should be intensively screened for other CV risk factors and every effort should be made to treat or eliminate these risk factors in order to diminish a probability of future CV incidents. It is not entirely clear whether diabetic patients should undergo an aggressive periodontal treatment. Recent meta-analysis confirmed that such a treatment improves the metabolic control of diabetes [34]. To date, however, there has been no proof that treatment of periodontal disease decreases CV risk.

The strength of this study is that all efforts have been made to exclude patients with infections other than periodontitis. This would seem to be necessary when a study is performed in a small group of patients, but however it is almost never done. Another strength of this study is that it has additionally proven the clinical value of the new classification of Offenbacher.

## CONCLUSIONS

The presented results confirm that the inflammatory process of the periodontal tissue is associated with increased markers of atherosclerosis, and support the hypothesis that it may influence atherosclerotic processes in patients with type 2 diabetes. It seems also that the study confirms the validity of the new Offenbacher classification.

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***Conflict of interest:*** *none declared*

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# Grubość kompleksu błony wewnętrznej i środkowej tętnicy szyjnej i inne markery arteriosklerozy u pacjentów z cukrzycą typu 2 i chorobą przyzębia

Edward Franek[1, 2], Joanna Januszkiewicz-Caulier[1], Anna Błach[1], Magdalena Napora[3], Krystyna Jedynasty[1], Tadeusz Budlewski[1], Dariusz Gozdowski[4], Renata Górska[3]

[1]Klinika Chorób Wewnętrznych, Endokrynologii i Diabetologii, Centralny Szpital Kliniczny MSWiA, Warszawa
[2]Zakład Epigenetyki Człowieka, Instytut Medycyny Doświadczalnej i Klinicznej, Polska Akademia Nauk, Warszawa
[3]Klinika Periodontologii, Warszawski Uniwersytet Medyczny, Warszawa
[4]Katedra Doświadczalnictwa i Bioinformatyki, SGGW, Warszawa

## Streszczenie

**Wstęp:** Choroba przyzębia jest procesem zapalnym, którego skutkiem u chorych na cukrzycę typu 2 jest zwiększone ryzyko sercowo-naczyniowe. Nie jest jednak jasne, w jakim stopniu zapalenie przyzębia powoduje zmiany w zakresie markerów arteriosklerozy u tych pacjentów.

**Cel:** Celem pracy była odpowiedź na pytanie, czy choroba przyzębia u pacjentów z cukrzycą typu 2 wiąże się z pogrubieniem kompleksu błony wewnętrznej i środkowej tętnicy szyjnej (IMT) i zwiększeniem sztywności naczyń.

**Metody:** Do badania włączono 121 chorych. Zgodnie z nową klasyfikacją Offenbachera 16 z nich zakwalifikowano jako periodontologicznie zdrowych (BGI-H), 87 jako pacjentów z zapaleniem dziąseł (*gingivitis*, BGI-G), a 18 jako osoby z zapaleniem przyzębia z krwawieniem średniego stopnia (BGI-P2). U wszystkich chorych oceniano IMT, prędkość fali tętna (PWV), stężenia lipidów i stężenie białka C-reaktywnego (CRP) w surowicy krwi.

**Wyniki:** Chorzy z zapaleniem dziąseł i zapaleniem przyzębia charakteryzowali się większą wartością IMT w porównaniu z pacjentami ze zdrowym przyzębiem (0,804 ± 0,112 i 0,772 ± 0,127 *v.* 0,691 ± 0,151 mm, odpowiednio $p < 0,01$ i $p < 0,05$, iloraz szans dla IMT ≥ 0.8 mm wynosił 5,25; 95% CI 1,1; 25). Pacjenci z grupy BGI-P2 charakteryzowali się także wyższym ciśnieniem tętniczym w porównaniu z grupą BGI-G i BGI-H, a także wyższym stężeniem CRP w surowicy w porównaniu z grupą BGI-G (4,6 ± 2,3 *v.* 3,8 ± 4,8 mg/l; $p < 0,01$). Parametry gospodarki lipidowej i PWV nie różniły się znamiennie między grupami.

**Wnioski:** Zapalenie przyzębia u chorych na cukrzycę typu 2 wiąże się ze zwiększeniem IMT i ciśnienia tętniczego, ale nie ze zwiększoną sztywnością naczyń. Wyniki te wskazują na prawdziwość tezy, że proces zapalny przyzębia może korelować z patologią naczyniową.

**Słowa kluczowe:** cukrzyca, zapalenie przyzębia, grubość kompleksu błony wewnętrznej i środkowej tętnicy szyjnej, prędkość fali tętna

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**Adres do korrespondencji:**
prof. dr hab. n. med. Edward Franek, Klinika Chorób Wewnętrznych, Endokrynologii i Diabetologii, Centralny Szpital Kliniczny MSWiA, ul. Wołoska 137, 02–507 Warszawa, tel: +48 22 508 14 05, faks: +48 22 508 14 00, e-mail: Edward.Franek@cskmswia.pl
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