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Prospective Analysis of the Relationship Between the State of Periodontal Tissues and Changes in Selected Cardiovascular Parameters in Patients with Type 2 Diabetes

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

Background. Periodontitis is considered a risk factor in many systemic diseases, including cardiovascular pathologies and diabetes. Diabetes can also exacerbate early vascular changes, mainly due to the synthesis of advanced glycosylation end-products and oxidative stress. It has not yet been fully explained whether the additional presence of periodontal disease can affect the course of atherosclerosis and left ventricle hypertrophy in diabetic patients.

Objectives. The aim of the study was to assess the relationship between periodontal and cardiovascular diseases and their progression in patients with type 2 diabetes.

Material and Methods. The study included 119 patients diagnosed with type 2 diabetes. Periodontal pocket depth (PD), clinical attachment loss (CAL), plaque index (PI) and bleeding index (BOP) were determined. Basic laboratory tests were performed. The intima-media thickness (IMT) and the left ventricular mass index (LVMI) were determined by means of ultrasonography. After one year the examinations were repeated. The statistical analysis included the 84 patients who took part in both the first and second examinations.

Results. A positive correlation between the number of deep and active periodontal pockets and LVMI value was observed in men. The IMT value correlated with the mean CAL, PI and BOP, while a negative correlation was found between the IMT and the number of deep pockets, as well as between the IMT and the number of retained teeth. A multivariate analysis demonstrated a significant correlation between CAL and both IMT and LVMI change after one year.

Conclusions. A relationship between periodontitis and cardiovascular diseases has been confirmed in diabetic patients. The most significant periodontal parameter in relation to the progression of atherosclerosis and left ventricle hypertrophy was shown to be clinical attachment loss – a measure of the history of periodontal disease during the patient's lifetime (*Adv Clin Exp Med* 2016, 25, 5, 879–886).

Key words: periodontitis, diabetes, atherosclerosis, left ventricular hypertrophy.

Although periodontitis may seem to be nothing but a local infection, confined to the oral cavity, there has been speculation as to whether the inflammation process in periodontal tissues affects the general condition of the body. The “Periodontal Diseases and Human Health: New Directions in Periodontal Medicine” Symposium held in 1997 at Chapel Hill, North Carolina (USA), was a turning point in the field of periodontology. The participants stressed the importance of the development and severity of periodontitis in the course of sys-

temic diseases [1]. The inflammatory response in periodontal tissues is not just a local pathology, but can also affect other body structures and influence the development and course of systemic diseases. A chronic inflammation in the body, including the periodontal tissues, underlies certain cardiovascular disorders, such as atherosclerosis [2, 3].

The basis of all previously described pathomechanisms explaining the relationship between periodontitis and atherosclerosis and its consequences is speculation that oral bacteria, their tox-

ins and released inflammatory mediators penetrate through the periodontal pocket epithelium into the bloodstream. The frequency and severity of bacteremia correlates with the state of the periodontal tissues. Numerous studies confirm the significance of periopathogens in atherosclerotic plaque [4]. Chronic inflammation plays an important role in the mechanisms of the development of atherosclerosis [2, 5, 6]. It may induce the expression of adhesion molecules and the creation of fatty streaks, which constitute a stage in the formation of stable atherosclerotic plaque. Consequently, this may lead to plaque rupture. A particularly high risk of developing arteriosclerosis is observed in the presence of chronic inflammation with concomitant increase in blood pressure [6].

The development and course of cardiovascular diseases are influenced by various risk factors: sex, age, smoking, obesity and increased levels of cholesterol and hypertension. Cigarette smoking is a known risk factor for the development of both atherosclerosis and periodontitis, so just for this reason one can expect an increased incidence of cardiovascular diseases in patients with periodontitis [7].

Although hypertension is not listed among the risk factors for periodontal diseases, patients with hypertension demonstrate elevated levels of proinflammatory mediators [6], including acute phase protein (CRP), TNF- α and IL-6, which also increase in the course of periodontitis. Furthermore, elevated levels of fibrinogen, plasminogen activator inhibitor-1 and platelet-activating factor PAF have been observed in the peripheral blood of patients with periodontitis [2, 5, 8–11].

Periodontitis affects a significant number of patients in developed countries. In a study conducted in the United States by Eke et al. [12], the incidence and severity of periodontitis in the adult population was analyzed on the basis of 2009 and 2010 data from National Health and Nutrition Examination Surveys (NHANES). The periodontal status of 3742 individuals aged 30 years and older was evaluated. Levels of attachment loss and periodontal pocket depth on six surfaces of each tooth (excluding third molars) were assessed. Periodontitis was observed in more than 47% of adults. Mild, moderate and severe forms were found in 8.7%, 30.0% and 8.5%, respectively. Among individuals aged 65 years and older, 64% had moderate or severe periodontitis. With regard to the degree of disease severity, 56% of the study group had 5% or more sites with attachment loss of ≥ 3 mm, and 18% showed 5% or more sites with pocket depth ≥ 4 mm. Periodontitis was more advanced in males, Mexican Americans, adults with less than secondary education,

in those below 100% of the federal poverty level, and in current smokers [12].

Poor periodontal status has also been observed in the Polish society. A nationwide epidemiological study conducted by Górski et al. in 2011 indicated that the periodontal status of Poles aged 35–44 is among the worst in Europe [13]. An epidemiological study conducted on individuals aged 35–44 shows that only 1% of adult Poles had no lesions in their periodontal tissues, whereas 16% of the patients in the study had advanced periodontitis. Only 1% of adult Poles did not require prophylactic and therapeutic procedures, while 12% needed only oral hygiene instructions and plaque removal. About 23% of the patients in the study required oral hygiene instructions and supragingival scaling, while more than 40% needed oral hygiene instructions plus subgingival scaling. Comprehensive treatment of periodontitis was necessary for more than 16% of the patients in the study [13].

In the present day physicians have to face the problem of multiple concomitant systemic diseases and their mutual influence on each other. Due to many common risk factors as well as the widespread prevalence of both diabetes and cardiovascular diseases, these two entities often develop in the same subjects. Diabetes is nowadays generally accepted as a risk factor in periodontal diseases; periodontitis is in fact listed as one of the main complications of diabetes. Most studies on the relationship between periodontal diseases and diabetes excluded patients with other concomitant health issues, such as cardiovascular diseases. Yet in clinical practice it is important to know how concomitant diseases can affect the risk of other pathologies.

The aim of the study was therefore to assess the relationship between the state of the periodontal tissues and selected cardiovascular parameters, as well as the progression of left ventricle hypertrophy and coronary atherosclerosis in patients with type 2 diabetes.

Material and Methods

The study included patients with type 2 diabetes being treated at the Clinical Department of Internal Diseases, Endocrinology and Diabetology at the Central Clinical Hospital of the Ministry of the Interior in Warszawa, Poland. The study was conducted in accordance with the Helsinki Declaration of 1973, updated in 2002, and it was endorsed by Committee for Ethics and Oversight of Research on Humans and Animals of the Central Clinical Hospital of the Ministry of the Interior in Warszawa. The participants were acquainted with

an information form and signed their informed consent.

The study included people with at least seven natural teeth other than third molars. Smokers, patients with an acute or chronic inflammation other than an inflammation of the periodontal tissues, and patients who had undergone periodontal treatment in the previous 12 months were all excluded.

Based on the criteria described above, from among 250 randomly selected type 2 diabetes patients, 119 were included in the study (67 men and 52 women). Their median age was 62 years (range: 39–82 years) and the median duration of type 2 diabetes was eight years (range: 1–27 years).

The examinations were conducted over a two-week period at the aforementioned department. Each patient underwent general medical and periodontal examinations on the same day. The size of the heart chambers was determined, as well as left ventricular mass (LVM) [14].

Left ventricular mass was calculated using the Devereux formula [15]:

$$\text{LVM [g]} = 0.8 \times \{1.04 \times [(IVS + LVEDD + PW)^3 - LVEDD^3]\} + 0.6.$$

The left ventricular mass index (LVMI) was calculated as a quotient of left ventricular mass and body surface area.

Intima-media thickness (IMT), which is an indicator of atherosclerosis severity, was assessed by ultrasound examination of the carotid arteries. The common carotid artery, internal carotid artery and carotid sinus were measured [16]. Systemic arterial pressure was also measured.

The patients underwent basic periodontal measurements using a WHO-612 periodontal probe. The periodontal pocket depth (PD), clinical attachment level (CAL) and bleeding index (BOP, introduced by Ainamo and Bay) were determined on six tooth surfaces (mesial buccal, midline buccal, distal buccal, mesial lingual, midline lingual and distal lingual). O'Leary's plaque index (PI) was rated on four surfaces – mesial, midline buccal, distal and midline lingual – and was expressed as a percentage. The number of retained teeth, the mean of pocket depth and clinical attachment loss, percentage of deep pockets (≥ 4 mm) and percentage of deep pockets with bleeding on probing (so-called active pockets) were all noted. All the patients were instructed on oral hygiene. If periodontitis was diagnosed on the basis of the clinical examination, the patients were advised on the possibilities of periodontal treatment.

After a year the examinations were repeated in the same cycle. Out of the 119 originally examined, 84 individuals (70.6%) reported to the fol-

low-up after one year, including 49 males (58.3%) and 35 females (41.7%). The remaining 35 patients from the initial study group failed to appear for the second examination, including all of the 13 participants who underwent non-surgical periodontal treatment. All the patients remained under diabetes care provided by the Central Clinical Hospital of the Ministry of the Interior in Warszawa.

The statistical analysis included only those patients who participated in both the first and second examinations. The data obtained from 84 individuals were analyzed statistically using PQStat software (PQStat Software, Poznań, Poland). Spearman's rank test was used to assess the correlation between the patients' periodontal state and the degree of left ventricle hypertrophy as well as coronary atherosclerosis.

A multivariate analysis was performed by the backward multiple linear regression method. The multivariate analysis of risk factors for left ventricle hypertrophy and coronary atherosclerosis progression included following parameters:

- independent general variables: age, sex, body mass index (BMI), blood pressure (systolic & diastolic), initial LVMI value, initial IMT value, leukocytes, cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides, C-reactive protein (CRP), glycemia, HbA1c, insulin treatment;

- independent periodontal variables: the number of teeth, the mean pocket depth (PD), number of pockets ≥ 4 mm deep, the mean clinical attachment level (CAL), the plaque index (PI), bleeding on probing (BOP).

The threshold of statistical significance was set at $p < 0.05$ for the univariate analyses and $p < 0.20$ for the multivariate analyses.

Results

Tables 1 and 2 present analyses of the relationship between periodontal parameters and cardiovascular parameters, including the LVMI and the severity of atherosclerosis (assessed by the IMT), in the study group, divided according to gender. No statistically significant correlation was observed between the periodontal parameters and LVMI in the study group as a whole. When the group was divided by sex, a positive correlation between the number of pockets ≥ 4 mm and the number of pockets ≥ 4 mm with bleeding on the one hand, and the LVMI in males on the other hand was observed in the second examination.

The analysis of the relationship between the periodontal parameters and the IMT in the study group as a whole demonstrated an inverse correla-

Table 1. Results of a univariate analysis (Spearman's correlation test) of the correlation between periodontal parameters and the left ventricular mass index in the study group at the first (1) and second (2) examinations

Parameter	LVMI [g/m ²]					
	women		men		total	
	1	2	1	2	1	2
Number of pockets $\geq$ 4 mm	ns.	ns.	ns.	$r = 0.28$ $p < 0.05$	ns.	ns.
Number of pockets $\geq$ 4 mm with bleeding	ns.	ns.	ns.	$r = 0.29$ $p < 0.05$	ns.	ns.

ns. – not statistically significant.

Table 2. Results of a univariate analysis (Spearman's correlation test) of the relationship between periodontal parameters and the IMT value at the first (1) and second (2) examinations

Parameter	IMT [mm]					
	women		men		total	
	1	2	1	2	1	2
Number of teeth	ns.	$r = -0.41$ $p = 0.01$	ns.	ns.	ns.	$r = -0.26$ $p < 0.05$
Number of pockets $\geq$ 4 mm	$r = 0.39$ $p < 0.05$	ns.	ns.	ns.	$r = 0.21$ $p = 0.05$	ns.
Mean CAL [mm]	ns.	$r = 0.38$ $p < 0.05$	ns.	ns.	ns.	$r = 0.24$ $p < 0.05$
PI [%]	ns.	ns.	$r = 0.27$ $p < 0.1$	ns.	$r = 0.19$ $p < 0.1$	ns.
BOP [%]	ns.	ns.	ns.	$r = 0.35$ $p = 0.01$	ns.	$r = 0.25$ $p < 0.05$

ns. – not statistically significant.

tion between the number of retained teeth and the IMT. In the second examination there was a positive correlation between mean clinical attachment loss and the bleeding index on the one hand, and the IMT value on the other hand. The IMT increased as the clinical status of the periodontium worsened. When the group was divided by sex, the females demonstrated an inverse relationship between the number of retained teeth and the IMT value. In the second examination, there was a positive correlation between mean clinical attachment loss and the IMT in females. In males, the second examination showed a statistically significant relationship between the bleeding index and the IMT.

Tables 3 and 4 present the results of the multivariate analysis of potential risk factors for left ventricle hypertrophy and coronary atherosclerosis progression. According to this analysis, the main parameter affecting the pace of LVMI increase was the initial LVMI value, with a negative standardized beta coefficient. The second param-

Table 3. Multivariate analysis of risk factors for left ventricle hypertrophy progression (expressed as LVMI change after one year of observation) in subjects with type 2 diabetes (backward multiple linear regression analysis, $r^2 = 0.53$, $p < 0.001$)

Independent variable	Standardized beta coefficient	p-value
LVMI at the beginning	-0.73	< 0.001
Insulin treatment	-0.19	0.017
Number of teeth	0.24	0.030
IMT	0.18	0.038
Mean CAL	0.21	0.051

eter negatively influencing left ventricle hypertrophy development was insulin treatment. A higher initial IMT value was related to faster LVMI increase. Two periodontal parameters were found to

Table 4. Multivariate analysis of risk factors for coronary artery atherosclerosis progression (expressed as IMT change after one year of observation) in subjects with type 2 diabetes (backward multiple linear regression analysis, $r^2 = 0.34$, $p < 0.001$)

Independent variable	Standardized beta coefficient	p-value
IMT at the beginning	-0.43	< 0.001
Mean CAL	0.25	0.011
BMI	-0.17	0.077
Insulin treatment	0.16	0.092

be independent risk factors for left ventricle hypertrophy: the number of retained teeth and the mean clinical attachment level.

In the second multivariate analysis, related to the progression of atherosclerosis, the initial degree of atherosclerosis proved to be the main independent factor affecting inversely the IMT change. Also, the patients' BMI was negatively correlated with atherosclerosis progression. A positive correlation was observed between insulin treatment and atherosclerosis progression. One of the independent risk factors for atherosclerosis progression was again mean clinical attachment loss.

Discussion

In recent years a relationship between periodontal disease and certain systemic pathologies, such as cardiovascular diseases and diabetes, has been proven by many authors. Still, not much is known about the character of this relationship in the simultaneous presence of two or more systemic diseases.

In the present study the authors have assessed the correlation between the periodontal state and two cardiovascular diseases, as well as their progression, in patients diagnosed with and undergoing treatment for type 2 diabetes. The relationship between cardiovascular pathologies and diabetes is well known – a specific form of coexistence of these problems is the so-called metabolic syndrome. The role of diabetes in the development of vascular complications seems to share similar processes as the accelerating progress of periodontal disease, mainly the production of advanced glycosylation end-products that induce a systemic inflammatory response, collagen cross-linking and oxidative stress [17–19]. Yet the role of oral health in the development of the metabolic syndrome as well as other cardiovascular pathologies in patients with elevated blood glucose has not been clearly explained.

As physiological LVMI values differ for males and females, the univariate analysis of a correlation between periodontal health and left ventricle hypertrophy was performed separately for each gender. Among the women in the study group, no correlation was observed between the patients' periodontal state and left ventricle mass index, while in the men a positive relation was found with the number of deep periodontal pockets (≥ 4 mm) as well as with so-called active periodontal pockets – teeth with PD ≥ 4 mm and the presence of bleeding on probing.

A study by Franek et al. assessed the condition of periodontal tissues using the Offenbacher scale. A higher value of LVMI in patients diagnosed with periodontitis compared to healthy controls was observed [20]. A study by Ganowicz et al. also showed that patients with periodontitis demonstrate more severe left ventricular hypertrophy [21].

In the present research, the study group demonstrated a negative correlation between the number of teeth and the severity of atherosclerosis, observed both in the group as a whole and among the women (Table 2). The numerous missing teeth suggest that the patients included in this study did not pay enough attention to dental prophylaxis and treatment, which led to tooth loss. A low number of retained teeth may indicate past chronic or acute inflammatory processes in the periodontal tissues, including the marginal and periapical periodontium (complications of pulp diseases), which affected the development of atherosclerosis. Similar results were obtained by Paunio et al., who in a group of 1384 males observed that the incidence of coronary heart disease was twice as frequent in individuals with fewer than half their remaining teeth [22]. A study by Desvarieux et al. demonstrated a relationship between the number of missing teeth and presence of atherosclerosis in the carotid artery [23]. Progressive periodontal tissue inflammation and clinical attachment loss lead to loosening and loss of teeth. The presence of inflammatory markers and periopathogens during this process can affect the development of atherosclerotic lesions. A lack of teeth may be a marker of past periodontitis which, during its course, initiated the development of subclinical atherosclerosis. Such a relationship was also confirmed by the results of research by Zaremba et al., in which the authors observed the presence of bacteria typical for periodontitis in atherosclerotic plaque in toothed and edentulous subjects.

The present study found a positive correlation between clinical attachment loss and the severity of atherosclerosis (Table 2). Increased clinical attachment loss indicates advanced periodontal dis-

ease and is a summary indicator of the past course of the disease, because spontaneous regeneration of the attachment is infrequent. Therefore it may be concluded that higher clinical attachment loss means the patient has experienced longer or stronger exposure to the markers of inflammation, bacterial toxins and other compounds released in the course of periodontitis. Similar results were obtained by Franek et al., who observed a positive relationship between periodontal disease and the severity of atherosclerosis [24].

In the present study, a statistically significant correlation ($p < 0.05$) between bleeding gingiva and the thickness of the intima-media complex was observed (Table 2). Bleeding is one of the primary symptoms of current inflammation in the periodontium. In the aforementioned study carried out by Franek et al. on a group of diabetic patients, a higher IMT was observed in the patients with a higher bleeding index on probing [24]. Similarly, in a study by Söder et al., a higher IMT was characteristic of patients with an elevated bleeding index. In that study the authors observed a significantly higher IMT value in patients with gingivitis and periodontitis compared with patients without inflammation within the periodontal tissues [25]. Emingil et al. also demonstrated a correlation between periodontal tissue inflammation and advanced atherosclerotic lesions of the cardiovascular system leading to acute myocardial infarction (AMI); they found a relationship between the bleeding index and a periodontal pocket depth ≥ 4 mm on the one hand and the occurrence of acute myocardial infarction on the other hand [26]. Different results were obtained by Lopez-Jornet et al., who found no statistically significant correlation between the bleeding index and the severity of atherosclerosis (expressed by the IMT), nor between the bleeding index and the presence of atherosclerotic plaque [27].

Cario et al. suggest the presence of subclinical atherosclerosis in patients with periodontitis [28]. A study conducted by Beck et al. also confirmed an association between periodontitis and the thickness of the intima-media complex; the authors observed a higher IMT value in patients with periodontal disease [29].

Research by Ganowicz demonstrated a correlation between the level of oral hygiene and the number of missing teeth, and between the presence of periodontal disease and early signs of atherosclerosis as well as left ventricular hypertrophy [21].

A high plaque index indicates an abundance of bacteria in periodontal pockets. As the authors pointed out in a previous publication, the specific plaque hypothesis asserts that the presence of periopathogens can be expected in bacterial

plaque, so a link may exist between bacteria typical of periodontitis and the progression of atherosclerosis with narrowing of the arteries [30].

The present work confirms that the association between cardiovascular disease and periodontitis also exists in the population additionally burdened with type 2 diabetes. In particular, a correlation between past (CAL) and present (BOP) periodontitis and the severity of atherosclerosis (IMT) was clearly demonstrated. It is noteworthy that this correlation is strong, despite the fact that the patients were undergoing treatment for diabetes.

The awareness of many common risk factors for periodontal and cardiovascular diseases, including diabetes, prompted the authors to perform a multivariate analysis of the parameters assessed. This analysis revealed that among the independent risk factors for both left ventricle hypertrophy and atherosclerosis was the same periodontal parameter: clinical attachment loss, which is an indicator of periodontal history. In the present study no correlation was found between cardiovascular disease progression and blood glucose level or HbA1c level. It should be noted, however, that all the subjects were being treated for diabetes, so these parameters did not fully represent the systemic burden of diabetes at the time of the periodontal and cardiologic examinations.

A few papers by other authors concerning the risk of cardiovascular diseases in patients with diabetes and periodontal diseases have also reported an increased risk of atherosclerosis, measured by increased IMT values and acoustic shadowing, in patients suffering from both diabetes and periodontal diseases. Southerland et al. also observed correlations between atherosclerosis and age, race, sex, heavy smoking, hypertension and LDL cholesterol levels [18]. It is important to note that their study was not prospective in nature, as it only related potential risk factors to the prevailing state of the arterial walls. However, the authors also included groups without diabetes and groups with and without periodontal disease. Comparing all the possibilities, they stated that only diabetic patients with concomitant severe periodontitis present an increased risk of atherosclerosis, as compared to periodontally healthy subjects without diabetes.

The authors concluded that the relationship between periodontitis and cardiovascular diseases observed in patients without concomitant health problems has also been confirmed in diabetic patients. The most significant parameter describing periodontal health in relation to the progression of atherosclerosis and left ventricle hypertrophy has proven to be clinical attachment loss, which can be interpreted as a measure of exposure to periodontal pathogens and inflammatory mediators during the lifetime.

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