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Blood pressure and left ventricular mass in subjects with type 2 diabetes and gingivitis or chronic periodontitis

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Abstract

Introduction: This study aimed to answer the question of whether chronic periodontitis in subjects with type 2 diabetes mellitus is associated with increased left ventricular mass (LVM) and systemic and central blood pressure (CBP).

Material and Methods: One hundred and fifty-five subjects with type 2 diabetes (67 F, 88 M, mean age 61.1 ± 6.9 years, BMI 32.7 ± 5.7 kg/m^2) were divided according to their periodontal status into biofilm–gingival interface – healthy (BGI-H, 14 subjects), BGI-gingivitis (BGI-G, 119 subjects) and BGI-periodontitis (BGI-P, 22 subjects) groups. In all subjects, LVM, systemic and CBP were measured. The LVM index (LVMI) was calculated.

Results: (1) BGI-P and BGI-G subjects, respectively, had higher (mean; 95% CI) LVM (238.6 g; 206.6–267.4 and 222.8 g; 207.0–238.2) *versus* BGI-H subjects (170.3 g; 125.5–217.8).

(2) BGI-P and BGI-G subjects, respectively, had higher (mean; 95% CI) LVM1 (95.2 g/m^2; 82.9–107.4) and 87.8 g/m^2; 81.5–94.1) *versus* BGI-H subjects (63.7 g/m^2; 45.2-62.3).

(3) BGI-P subjects had higher central and systemic systolic and diastolic blood pressure than subjects from BGI-G and BGI-H groups.

Conclusion: In subjects with type 2 diabetes, periodontitis and gingivitis are associated with increased LVM and periodontitis is associated with increased central and systemic blood pressure.

Key words: blood pressure; cardiovascular; diabetes; heart; periodontal disease

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Gingivitis and chronic periodontitis are inflammatory diseases of the tissues surrounding the teeth, called the periodontium. They manifest themselves as pain and bleeding and lead to weakness of the periodontal structures, loosening and eventual loss of teeth. Diabetes (as well as genetic factors, age, smoking and lack of oral cavity hygiene) is a risk factor of gingivitis and periodontitis, and the prevalence of these diseases in subjects with diabetes, especially when glycaemia is not adequately controlled, is higher (Ryan et al. 2003). On the other hand, chronic periodontitis is associated with worse glycaemic control, which may be improved by periodontal treatment (Darre et al. 2008, Taylor & Borgnakke 2008). It has also been proven that induction of periodontitis in rodents results in glucose intolerance and diabetes (Watanabe et al. 2008).

The negative consequences of periodontal disease in patients with diabetes are, however, not limited to the oral cavity and worse glycaemic control. Chronic periodontitis (as well as diabetes itself) is associated with an increased risk of cardiovascular complications (Blaizot et al. 2009). One of the possible explanations for this is that

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bacteria and bacterial toxins present in dental plaque and crevicular fluid stimulate immune cells to release a number of inflammatory mediators (Bodet et al. 2006), which act locally but also pass into the systemic circulation. Their blood levels, in particular serum hs-CRP concentration, are regarded as a marker of periodontal disease in the general population, as well as in patients with renal disease or hypertension (Ebersole et al. 1997, Czerniuk et al. 2006, Franek et al. 2006, Herrera et al. 2007). On the other hand, it is known that inflammation may play an important role in the pathogenesis of atherosclerosis and inflammatory markers (e.g. hs-CRP) predict cardiovascular mortality and morbidity in the general population (Bassuk et al. 2004).

Another explanation for the higher cardiovascular risk in subjects with periodontal disease is that periodontal bacteria play a direct role in atherosclerotic plaque development (Zaremba et al. 2007), and a third possible explanation is an increase in the left ventricular mass (LVM). In non-diabetic subjects, it has been proven that more severe forms of chronic periodontitis are associated with increased LVM. This is true for patients with essential hypertension (Angeli et al. 2003, Franek et al. 2009) and for renal patients (Franek et al. 2005). This has also been shown in a general population (Shimazaki et al. 2004), but no data on patients with diabetes have been published.

The aim of this study was to answer the question of whether chronic periodontitis in subjects with type 2 diabetes mellitus is associated with increased LVM and increased central and peripheral blood pressure.

Material and Methods

Two hundred and fifty subjects with type 2 diabetes were randomly selected from among the patients of the Diabetes Outpatient Clinic of the Central Clinical Hospital MSWiA in Warsaw, Poland, and screened for this study. Only subjects with seven or more teeth were included. Smokers and subjects with any stated acute or chronic infection (including other than periodontitis infection source in the oral cavity) were excluded. In order to exclude an infection, the subjects were carefully examined. A gynaecological examination in women, urine culture, otorhinolaryngological examination with perinasal sinus radiographs, if necessary, abdominal and cardiac ultrasound examinations were performed. Finally, 155 subjects were included in the study.

The study protocol, prepared in accordance with the Declaration of Helsinki of 1973 (as revised in 2002), was approved by the proper Ethics Committee. All included subjects had signed the informed consent.

Medical history was recorded, including a history of diabetes, hypertension, and medication. Weight, height and office blood pressure were measured. In all subjects, blood samples were collected in the morning, after an overnight fast. The serum concentrations of the biochemical parameters examined were measured using standard laboratory methods. Office blood pressure was also recorded; the measurements were performed three times, after 15 min. of rest, in the sitting position.

A dental examination was performed by an experienced dentist, using the WHO-621 periodontal probe. Periodontal status was assessed by assessment of pocket's depth and bleeding on probing (BOP). Pocket depth (PD) was measured as the distance from the gingival margin to the base of the pocket and expressed in millimetres. In subjects with a healthy periodontium, clinical PD should be below 1.5 mm (although histologically a maximum of 0.5 mm). Longstanding inflammation causes loosening of the tooth–epithelium junction and deepening of the PD, which persists even after resolution of the inflammatory process. Thus, deep pockets are not necessarily associated with active inflammation. If it is present, the probe tip perforates the pocket epithelium and infiltrated vascular connective tissue, causing bleeding. Therefore, BOP is a widely used criterion to diagnose active gingival inflammation. Four surfaces of every tooth should be examined, in order to assess whether probing elicits bleeding or not. The BOP extent score, expressed as a percentage of bleeding sites is also called the Bleeding Index (BI).

A new classification of periodontal status was used, which is based on the differences in the biological phenotype (Offenbacher et al. 2007). In brief, subjects with PD $\leqslant$3 mm and BOP extent score $<$10% were classified as BGI-H: biofilm–gingival interface – healthy. Subjects with PD$\leqslant$3 mm and BOP extent score $>$10% were included in a biofilm–gingival interface – gingivitis group (BGI-G). Subjects with PD$\geqslant$4 mm were classified as having chronic periodontitis: with BOP extent score $<$10% as the P1 group (BGI-deep lesion/low bleeding), with BOP extent score 10–50% as P2 (BGI deep lesion/moderate bleeding) and with BOP extent score $>$50% as P3 (BGI-deep lesion/severe bleeding).

Echocardiography was performed by one experienced sonographist, according to the recommendations of the American Society of Echocardiography (Sahn et al. 1978). B-mode presentation was applied in order to exclude endocardial vegetation. M-mode presentation was used in order to calculate the LVM according to the Devereux formula. In brief, each result was calculated as a mean value from three measurements. Results were corrected according to the formula: $LVM_{corrected} = 0.8 \times LVM + 0.6$, and the LVM index (LVMI) was calculated by dividing the corrected $LVM_{corrected}$ by the body surface.

Central blood pressure (CBP) was measured by a noninvasive automated device (Sphygmocor®, Atcor Medical, Sydney, Australia), using a high-fidelity applanation tonometer (SPT-304, Millar Instruments, Houston, TX, USA), in a standardized manner (Laurent et al. 2006). Aortic pressure waveform was generated from radial pressure waveform (averaged from sequential radial waveforms derived from a 10-s-long measurement period) and central (aortic) blood pressure was computed. The examination was performed after at least 15 min. of rest.

Statistical analysis was performed using Statistica software version 8.0 (StatSoft Inc., Tulsa, OK, USA): The classification according to Offenbacher et al. (2007) was used for group stratification. The differences between groups were compared using Tukey's method (which allows for adjustment for multiple comparison) based on ANOVA results for continuous variables, the ANOVA Kruskal–Wallis test for count variables and a χ^2-test for binomial data. The Spearman rank-order test was used to measure the univariate correlations between the variables. Additionally, general linear models (GLM) were applied to examine the effect of potential confounding factors, divided into categorized factors and continuous predictor variables, on LVM, LVMI, aortic systolic (AoSP) and diastolic pressure (AoDP). All the potential confounding factors used in this analysis are presented in Table 3.

Table 1. Comparison of basal parameters in patients with different periodontal status, according to Offenbacher et al. (2007)

Parameters	BGI-H ($n = 14$)	BGI-G ($n = 119$)	BGI-P ($n = 22$)	p (ANOVA or χ^2-test)
Age (years)	58.6 ± 6.5 (39–67)	61.4 ± 7.0 (46–72)	60.3 ± 6.3 (47–71)	NS
BMI (kg/m^2)	30.7 ± 6.3	32.8 ± 5.8	34.2 ± 3.8	NS
Waist circumference (cm)	100 ± 16	106 ± 13	111 ± 10	NS (0.06)
Male sex (%)	50	55	68	NS
Duration of diabetes (years)	11.9 ± 8.5	12.7 ± 7.4	10.8 ± 7.0	NS
Duration of hypertension (years)	15.7 ± 9.8	13.4 ± 7.9	13.9 ± 8.8	NS
Systolic blood pressure (mmHg)	130 ± 14	136 ± 12	145 ± 11[a]	<0.005
Diastolic blood pressure (mmHg)	79 ± 8	79 ± 7	84 ± 7[b]	0.03
Hypertension (%)	93	94	91	NS
Number of antihypertensive drugs*	2 (1–3)	2 (0–5)	2 (0–5)	NS
ACE inhibitors/AT1-R blockers (% treated)	86	73	64	NS
Statins (% treated)	29	39	45	NS
Insulin (% treated)	50	54	68	NS
Metformin (% treated)	71	71	91	NS
Sulphonylurea (% treated)	36	40	59	NS
HbA1c (%)	7.06 ± 0.67	7.56 ± 1.46	8.27 ± 1.57[a]	0.05
Fasting serum glucose (mmol/l)	6.6 ± 0.9	7.5 ± 2.2	7.8 ± 2.3	NS
Serum creatinine (μmol/l)	64.5 ± 10.6	76.0 ± 16.8	78.7 ± 17.7	NS
Serum total cholesterol (mmol/l)	4.7 ± 0.9	4.6 ± 0.9	4.50 ± 0.9	NS
Serum LDL cholesterol (mmol/l)	2.6 ± 0.8	2.5 ± 0.8	2.2 ± 0.6	NS
Serum HDL cholesterol (mmol/l)	1.5 ± 0.6	1.4 ± 0.4	1.5 ± 0.5	NS
Serum triglycerides (mmol/l)	1.3 ± 0.6	1.7 ± 0.9	1.6 ± 0.8	NS
CRP (mg/l)	1.64 ± 1.68	3.06 ± 3.56	3.55 ± 2.78	NS
Periodontal pocket depth (mm)	2.43 ± 0.5	2.56 ± 0.43	4.11 ± 0.41	<0.00001
Bleeding index (%)	7 ± 2	31 ± 15	37 ± 15	<0.00001

Values are shown as mean ± SD or percentage number.

Significant difference at [a]$p < 0.01$, [b]$p < 0.05$, as compared with BGI-H and BGI-G, according Tukey's multiple comparisons.

*Median (with minimal and maximal value).

BGI, biofilm–gingival interface; BGI-H, healthy; BGI-G, gingivitis; BGI-P, chronic periodontitis; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; NS, not significant.

Results

Finally, 155 subjects were included (67 F, 88 M, mean age 61.1 ± 6.9 years, BMI 32.7 ± 5.7 kg/m^2). After a dental examination, they had to be divided into five subgroups, according to the Offenbacher classification. However, in the examined group, there was no single subject who could be included in the P1 group (deep lesion/low bleeding). Therefore, all the included subjects were divided into only four groups: BGI-H (14 subjects), BGI-G (119 subjects), P2 (18 subjects) and P3 (four subjects). Because of the small number of subjects in the latter group, groups P2 and P3 were analysed together, as the BGI-P group (22 subjects).

The basal parameters of the subjects from all groups are shown in Table 1. Subjects with no periodontal disease did not differ significantly from those with gingivitis or periodontitis with regard to the sex distribution, age, BMI, duration of hypertension and diabetes, antihypertensive and antidiabetic treatment. The fasting serum glucose concentration (as well as serum CRP, creatinine and lipids) was comparable in the examined groups, but long-term glucose control, measured as the HBA1c level, was worse in the BGI-P group. Systemic (systolic and diastolic) blood pressure was also higher in the latter group (Table 1).

The comparison of LVM, LVMI and CBP between the groups with different periodontal status is shown in Table 2. Subjects with chronic periodontitis and those with gingivitis had higher LVM as well as LVMI than those with a healthy periodontium, whereas the differences between BGI-G and BGI-P groups were not significant. Central systolic and diastolic blood pressure was higher in subjects with chronic periodontitis as compared with those with gingivitis and with a healthy periodontium, whereas it was similar in the latter two groups.

From many univariate correlations performed, one is to be mentioned. A significant correlation was found between serum CRP concentration and BI ($R = 0.19$, $p = 0.03$) in subjects with gingivitis or periodontitis, but not in periodontally healthy ones.

In Table 3, the multivariate (GLM) analysis is shown. For clarity, only p-values are shown. As can be seen in the constructed models, LVM, LVMI, AoSP and AoDP were all significantly independently associated with the Offenbacher periodontal disease score.

Discussion

It was found that LVM as well as LVMI were higher in subjects with type 2 diabetes and concomitant gingivitis or chronic periodontitis as compared with periodontally healthy ones. This finding is consistent with previous studies published by us and others: in a sample from the general population (Shimazaki et al. 2004), in renal patients (Franek et al. 2005, 2006) and in patients with essential hypertension (Angeli et al. 2003, Franek et al. 2009). In those studies, advanced or severe periodontitis was defined as Community Periodontal Index of Treatment Needs (CPITN) score of 3–4. This is the first study showing similar results in subjects with diabetes that applies the new empirical,

Table 2. Comparison of examined parameters in patients with different periodontal status, according to Offenbacher et al. (2007) score, using GLM analysis

Parameters	BGI-H ($n = 14$)	BGI-G ($n = 119$)	BGI-P ($n = 22$)	p-value (GLM)
LVM (g)	170.3 (125.5; 217.8)	222.8 (207.0; 238.2)[a]	238.6 (206.6; 267.4)[a]	0.044
LVMI (g/m^2)	63.7 (45.2; 82.3)	87.8 (81.5; 94.1)[a]	95.2b (82.9; 107.4)[a]	0.016
Aortic systolic pressure (mmHg)	116.2 (106.5; 125.9)	124.2 (121.0; 127.3)	131.8 (125.7; 137.9)[a,b]	0.011
Aortic diastolic pressure (mmHg)	76.1 (70.9; 81.3)	79.9 (78.2; 81.6)	84.6b (81.3; 87.8)[a,b]	0.006
Aortic pulse pressure (mmHg)	42.3 (34.0; 50.6)	45.8 (43.2; 48.5)	48.3 (43.1; 53.6)	NS
PWV (m/s)	8.31 (7.48; 9.14)	8.54 (8.26; 8.83)	8.72 (8.17; 9.27)	NS

Values are shown as adjusted means and 95% confidence intervals.
[a]$p < 0.05$ as compared with BGI-H.
[b]$p < 0.05$ as compared with BGI-G, according Tukey's multiple comparisons based on GLM analysis.
BGI, biofilm–gingival interface; BGI-H, healthy; BGI-G, gingivitis; BGI-P, chronic periodontitis; LVM, left ventricular mass; LVMI, left ventricular mass index; PWV, pulse wave velocity; NS, not significant; GLM, general linear model.

Table 3. Influence of independent variables (only p-values given) on left ventricular mass (LVM), left ventricular mass index (LVMI), aortic systolic pressure (AoSP) and aortic diastolic pressure (AoDP) – general linear model analysis (GLM)

	LVM	LVMI	AoSP	AoDP
Categorized factors				
Insulin treatment	0.003	0.001	0.229	0.221
ACE/sartan treatment	0.013	0.006	0.072	0.047
Sex	0.086	0.752	0.332	0.405
Offenbacher	0.044	0.016	0.011	0.006
ACE/sartan × sex	0.047	0.031	0.739	0.218
Insulin × ACE/sartan	0.277	0.344	0.315	0.288
Continuous predictor variables				
Antihypertensive therapy duration	0.481	0.250	0.317	0.078
Number of antihypertensive drugs	0.967	0.811	0.525	0.854
Age	0.627	0.216	0.208	0.963
BMI	0.075	0.552	0.741	0.090
Systolic blood pressure	0.448	0.303	NI	NI
Diastolic blood pressure	0.653	0.441	NI	NI
Body surface	0.428	NI	NI	NI
Serum creatinine concentration	NI	NI	0.548	0.692

NI, variable not included into model; BMI, body mass index.

based on phenotype, classification of periodontal disease (Offenbacher et al. 2007), for the comparison of LVM and blood pressure in subjects with different periodontal statuses. It seems that this classification, combining the assessment of pockets' depth and bleeding in one score, may better reflect the biology of the BGI. The relevance of the Offenbacher classification for diabetes in terms of association between the periodontal score and ''cardiovascular'' phenotype seems to be confirmed in this study.

Diabetes itself and its poor metabolic control is associated with a high cardiovascular risk (Selvin et al. 2004), which is additionally increased because of many ''classic'' risk factors. Age, gender, smoking, hypertension, high serum cholesterol and triglyceride levels are probably the most important of them all. Additionally, many ''non-classic'', emerging risk factors may be present in these subjects. For example, it was shown that chronic periodontitis is associated with a higher risk of cardiovascular events and death in the general population (Janket et al. 2003). This finding was also confirmed in patients with type 2 diabetes. A longitudinal study performed in native Americans from the Gila River Indian community has shown that periodontitis is associated with a higher risk of cardiovascular events and death (Saremi et al. 2005). Thus, it seems that periodontal disease could indeed be regarded as an emerging cardiovascular risk factor (Blaizot et al. 2009). However, a link is not clear. As periodontal pathogens were found in atherosclerotic plaques (Zaremba et al. 2007), it is possible that bacteria such as *Porphyromonas gingivalis* may play a direct role in plaque formation. The systemic inflammation caused by periodontitis may also be associated with atherosclerosis and atherothrombosis, which is the direct cause of a cardiovascular event.

Additionally, atherosclerosis causes arterial stiffness and plays a role in the pathogenesis of hypertension. Increased blood pressure does increase cardiovascular risk, and on the other hand, even a small decrease of blood pressure improves the cardiovascular prognosis. For example, in the UKPDS study, each 10 mmHg increase in systolic blood pressure resulted in a 15% increase in deaths (Adler et al. 2000), and in a newer study, systolic blood pressure reduction of only about 7 mmHg was associated with a 14% reduction of total and an 18% reduction of cardiovascular mortality (Patel et al. 2007). Therefore, even an apparently small blood pressure increase or decrease may have a significant clinical impact. An even greater impact can of course be expected if the difference of 15 mmHg is set, as between the BGI-H and the BGI-P groups in this study (see Table 1 for systemic and Table 2 for CBP).

Another explanation for periodontitis-associated cardiovascular risk may be an increased LVM. The potential mechanisms responsible for this increase have not been fully elucidated; it seems that an increase of peripheral (Shimazaki et al. 2004) or central (Franek et al. 2009) blood pressure may be associated with greater LVM in these subjects. The results of this study confirm that periodontal disease is associated with greater LVM also in patients with type 2 diabetes. It is not clear, however, whether it is a cause–effect relationship. Hypothetically, the longstanding inflammation (confirmed by advanced periodontal changes with deep periodontal pockets) may play a

role in the development of atherosclerosis, resulting in increased blood pressure, increased afterload and eventually in increased LVM.

The fact that systemic and CBP was higher in subjects with chronic periodontitis than in those with gingivitis and with healthy periodontium, whereas it was comparable in the latter two groups (Table 2), suggests that it is indeed a longstanding inflammatory process rather than active inflammation that may cause vascular stiffness and influence blood pressure. On the other hand, LVM and LVMI are higher not only in subjects with chronic periodontits but also in those with gingivitis (Table 2), suggesting that LVM may increase even in those subjects with periodontal disease in whom blood pressure is comparable with those of periodontally healthy subjects, and that factor(s) other than blood pressure may exist, linking periodontal disease and LVM. This is consistent with at least some previous studies. The association of periodontal disease with higher blood pressure was confirmed in the general population (Shimazaki et al. 2004, Holmlund et al. 2006), although not in renal patients (Franek et al. 2005, 2006). In hypertensive patients with advanced periodontitis, central, but not systemic blood pressure is increased (Franek et al. 2009). Unfortunately, the design and power of this and previous studies is not sufficient and a future prospective study would be needed to prove or refute the above-mentioned possible cause–effect relationship.

Regardless of the underlying mechanisms, an increase of LVM is an independent cardiovascular risk factor (Schillaci et al. 2000). Thus, although there are no prospective studies regarding this issue, either in subjects with or in subjects without diabetes, it seems quite possible that at least part of the increased cardiovascular risk associated with periodontal disease may be attributed to increased LVM.

As in our earlier studies (e.g. Blach et al. 2009, Franek et al. 2009), all efforts were made to exclude all subjects with infections other than gingivitis or periodontitis (as it is possible that the presence of infection may influence the results, especially the inflammatory parameters, like CRP). However, relatively high CRP values were found in some subjects, especially from BGI-G and BGI-P groups. As a positive correlation was found between CRP and the BI in subjects with periodontal disease, it seems that high CRP concentrations may be caused by an oral inflammatory process.

Some subjects had a low number of teeth. Poland differs from the developed countries with regard to the prevalence of caries, which is much more frequent in Eastern Europe. In 1987, only about 10% of children in Poland were caries-free, and in 2003, it was still only about 20% (Emerich & Adamowicz-Klepalska 2007). Caries, and not periodontal disease, is the main reason for teeth loss in Poland. Therefore, a low number of teeth in some subjects with a healthy periodontium or gingivitis does not mean that they are wrongly classified.

A limitation of the study is that the results obtained using a new empirical classification of periodontal disease are only partially comparable with the results based on the CPITN score used in earlier research projects. Therefore, only a general comparison can be made. The limitation of the new classification is that subjects with rapidly progressive or early-onset forms are not represented; however, it does not seem that the population examined may include such subjects. Furthermore, the study population is relatively small. Among the 155 subjects, there were no subjects who could be classified as P1 (deep lesion/low bleeding) and only four subjects classified as P3 (deep lesion/severe bleeding). The low number of P3 subjects does not allow us to draw any reliable conclusions regarding this particular group, which theoretically should be characterized by the worst results. Additionally, the cross-sectional design of the study does not allow us to assess the cause–effect relationship between the parameters examined, and only associations can be confirmed.

In conclusion, observations in this study in subjects with type 2 diabetes confirm earlier results suggesting that periodontal disease (periodontitis and gingivitis) is associated with increased LVM and that periodontitis (but not gingivitis) is associated with higher central and systemic blood pressure. Unfortunately, this study cannot prove the connection resulting from periodontitis through local and systemic inflammation to atherosclerosis, increased blood pressure and, subsequently, to an increase of the LVM. A prospective study should be performed to explore this issue.

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Clinical Relevance

Scientific rationale for the study: While periodontitis may increase cardiovascular risk in people with diabetes, the mechanisms involved are unclear.

Principal findings: This study found that periodontitis and gingivitis are associated with increased LVM and that periodontitis is associated with increased systemic and CBP.

Practical implications: Increased BP and LVM may partially explain the increased cardiovascular risk in diabetics with periodontal disease. More research is needed to confirm these findings.