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Doppler Ultrasound Detection of Preclinical Changes in Foot Arteries in Early Stage of Type 2 Diabetes

Jolanta Leoniuk[1ABCDEFG], Adam Łukasiewicz[1ACDEF], Małgorzata Szorc[2ABDF], Izabela Sackiewicz[1BCEF], Jacek Janica[1BD], Urszula Łebkowska[1ACDEFG]

[1] Department of Radiology, Medical University of Białystok, Białystok, Poland
[2] Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Białystok, Białystok, Poland

Author's address: Jolanta Leoniuk, Department of Radiology, Medical University of Białystok, Sklodowskiej-Curie 24A Str., 15-276 Białystok, Poland, e-mail: monachjola@wp.pl

Summary

Background: There are few reports regarding the changes within the vessels in the initial stage of type 2 diabetes. The aim of this study was to estimate the hemodynamic and morphological parameters in foot arteries in type 2 diabetes subjects and to compare these parameters to those obtained in a control group of healthy volunteers.

Material/Methods: Ultrasound B-mode, color Doppler and pulse wave Doppler imaging of foot arteries was conducted in 37 diabetic patients and 36 non-diabetic subjects to determine their morphological (total vascular diameter and flow lumen diameter) and functional parameters (spectral analysis).

Results: In diabetic patients, the overall vascular diameter and wall thickness were statistically significantly larger when compared to the control group in the right dorsalis pedis artery ($P=0.01$; $P=0.001$), left dorsalis pedis artery ($P=0.007$; $P=0.006$), right posterior tibial artery ($P=0.005$; $P=0.0005$), and left posterior tibial artery ($P=0.007$; $P=0.0002$). No significant differences were observed in both groups in flow lumen diameters and blood flow parameters (PSV, EDV, PI, RI). In the diabetic group, the level of HbA1c positively correlated with flow resistance index in the right dorsalis pedis artery ($r=0.38$; $P=0.02$), right posterior tibial artery ($r=0.38$; $P=0.02$) and left posterior tibial artery ($r=0.42$; $P=0.009$). The pulsatility index within the dorsalis pedis artery decreased with increased trophic skin changes ($r=-0.431$, $P=0.009$).

Conclusions: In the diabetic group, overall artery diameters larger than and flow lumina comparable to the control group suggest vessel wall thickening occurring in the early stage of diabetes. Doppler flow parameters are comparable in both groups. In the diabetic group, the level of HbA1c positively correlated with flow resistance index and negative correlation was observed between the intensity of trophic skin changes and the pulsatility index.

MeSH Keywords: **Diabetes Mellitus, Type 2 – ultrasonography • Peripheral Arterial Disease – ultrasonography • Ultrasonography, Doppler, Color**

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Background

The increase in the incidence of type 2 diabetes is associated with sedentary lifestyle and obesity. Due to the associated risks, particularly the risk of early mortality, type 2 diabetes has been recognized as one of the most serious health problems in the world today [1,2]. The global number of diabetic patients in the year 2000 was 171 million individuals; the number is expected to grow to 366 million in the year 2030 [3].

Atherosclerosis is one of the most serious complications of type 2 diabetes [4]. Early onset of atherosclerosis in type 2 diabetes with its typical diffuse location in small peripheral vessels leads to increased stiffness of these vessels. In addition, clinical presentation may be affected by calcifications

Figure 1. (**A**) Measuring the diameter of the vessel in ultrasound B-mode examinations. (**B**) Measuring the diameter of flow canal in a color Doppler imaging.

of arterial intima media, commonly observed in diabetic patients [5]. Following techniques are used in diagnostics of lower limb arteries: pulse measurements, ankle-brachial index (ABI), being the primary measure in clinical diagnostics, Doppler flow imaging, conventional and subtraction arteriography, angio-CT and angio-MR. Ultrasonographic methods are valuable, noninvasive tools that may be used multiple times to assess the stage of the disease and patient's qualification for treatment, as well as to monitor the results of treatment procedures. In the available literature, ultrasound assessment was performed most commonly in patients with diabetes accompanied by advanced atherosclerotic lesions and extensive clinical symptoms. No reports are available with regard to the assessment of foot arteries in patients in Fontaine stage I disease.

The aim of the study was to estimate the hemodynamic and morphological parameters in foot arteries: dorsalis pedis artery (DPA) and posterior tibial artery (PTA) in patients with type 2 diabetes by means of ultrasound imaging and to compare the results to those obtained in a control group.

Material and Methods

The study included 37 patients with type 2 diabetes, aged 30 to 72 years – mean of 59.5±10.27 years, including 29 women and 8 men. The selection criterion consisted in the clinical assessment of lower limb ischemia stage – patients included in the study group suffered from type 2 diabetes at Fontaine stage I, i.e. without clinical symptoms or with discrete symptoms of lower limb ischemia (tingling, numbness, increased sensitivity to cold in the feet). The control group consisted of 36 subjects aged 31 to 74 years – mean of 56.81±9.27, including 29 women and 9 man with normal carbohydrate and lipid metabolism, without symptoms of lower limb ischemia. Normal carbohydrate and lipid metabolism was defined as normal fasting blood glucose level, family history free of diabetes, normal cholesterol level, normal blood pressure values and, in addition, no history of smoking. Glycated hemoglobin level (HbA1c) was determined and presence of trophic skin lesions within shanks and feet (thinning, desquamation) was assessed in the study group. Both groups were assessed for hypertension and smoking. Ankle-brachial index (ABI) was calculated in each group to assess limb ischemia. Normal range was established at 0.9–1.15. ABI assessments were performed after a 10-minute adaptation in supine position using blind Doppler technique (Echo Sounder Hadeco) by calculating the ratio of the systolic pressure at the arm level to the systolic pressure at the ankle level of both sides. The higher value of ankle-level pressure was used for calculations. In 4 cases within the study group, ABI could not be determined for technical reason (arm circumference higher than the manometer cuff length).

Doppler examinations were performed using a Siemens Elegra apparatus equipped with a linear head with the mean frequency of 7.5 MHz (range 4–9 MHz). Examinations were conducted in supine position with the limb bent at the knee at the angle of ca. 90°. Following ultrasound assessments of vessels were performed:

- B-mode assessment to evaluate the external diameter of vessel (Figure 1A) and vessel wall thickness;
- color Doppler imaging to evaluate the diameter of color vessel flow (Figure 1B);
- Spectral Doppler imaging to evaluate the flow spectrum and blood flow parameters, i.e. peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI) and resistance index (RI).

Measurements were conducted in both lower limbs, in dorsalis pedis artery at the level of the neck of the ankle bone and posterior tibial artery at the level of medial malleolus. A total of 148 and 144 vascular segments were assessed in the study group and the control group, respectively. The study included patients without hemodynamically significant stenoses in arteries proximal to the arteries examined in the study.

The obtained results were subjected to statistical analysis using Statistica 9 (StatSoft Inc., Tulsa, OK, USA) and SPSS 13.0 (Chicago, IL, USA) software packages. For normally distributed variables assessed by Shapiro-Wilk's test, comparisons between groups were conducted using the Student's t-test, while the Mann-Whitney's U-test was used for variables of non-normal distribution. For the purpose of calculations, statistical significance level was defined as $p<0.05$. The study conduct was subject to approval of the Bioethics Committee

Table 1. Characteristics of the study group and the control.

	Patients with diabetes (n=37) Mean ±SD (mm)	Control group (n=36) Mean ±SD (mm)	P
Age (years)	59.46±10.27	56.81±9.27	NS
Hypertension	25	0	–
Trophic changes	9	0	–
BMI (kg/m^2)	31.38±7.01	23.41±1.60	0.00001
HbA1c (%)	7.03±1.12	–	–
ABI right	1.07±0.12	1.08±0.08	NS
ABI left	1.1±0.16	1.09±0.09	NS

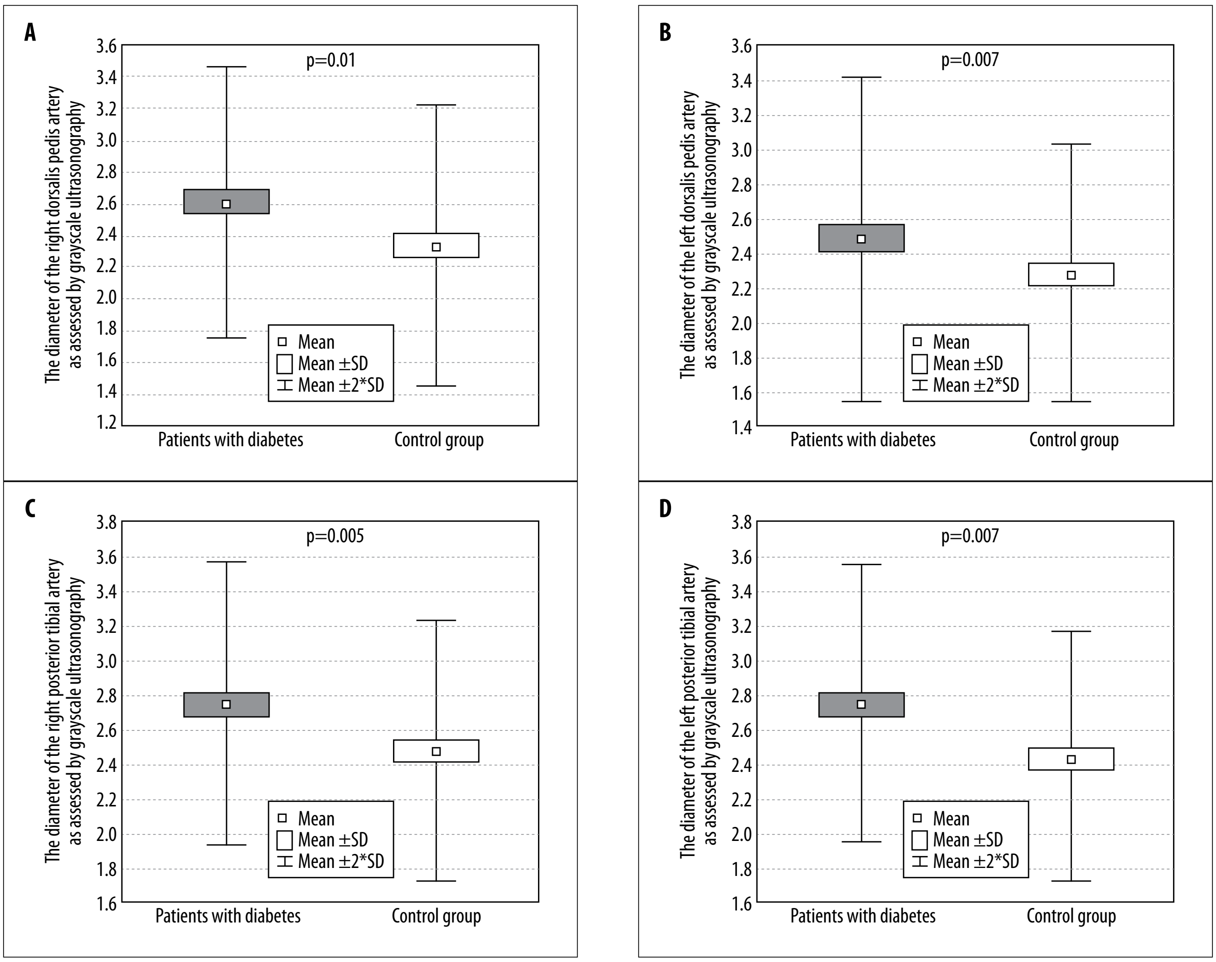

Figure 2. Ultrasound B-mode assessment of the diameter of the dorsalis pedis artery right (**A**) and left (**B**) and posterior tibial artery right (**C**) and left (**D**).

Results

There were no significant differences in age between the study group and the control group. Mean body mass indices in the study group of diabetic patients were significantly higher than in the control group (Table 1). Mean HbA1c level in diabetic patients was 7.03±1.12%. The parameter was not determined in the control group. In the group of diabetic patients, arterial hypertension was diagnosed in 25/37 patients while the presence of skin changes (thinning and desquamation) was observed in 9.37 cases. No hypertension or trophic changes were observed in the control group. In diabetic patients, mean ABI was 1.07±0.12 and 1.1±0.16 for the right and the left side, respectively. ABI values in the control group were not significantly different from that in the study group (Table 1).

Table 2. Assessment of the diameter of vessels in ultrasound B-mode examinations, the diameter of flow lumen assessed in color Doppler imaging and the thickness of the vessel wall.

		Patients with diabetes (n=37) Mean ±SD (mm)	Control group (n=36) Mean ±SD (mm)	P
DPAR (mm)	B-mode vessel diameter	2.61±0.43	2.34±0.44	0.01
	Flow lumen diameter in color Doppler imaging	2.06±0.36	2.00±0.44	NS
	Wall thickness	0.55±0.30	0.34±0.25	0.001
PTAR (mm)	B-mode vessel diameter	2.75±0.42	2.48±0.38	0.005
	Flow lumen diameter in color Doppler imaging	2.22±0.43	2.14±0.36	NS
	Wall thickness	0.60±0.36	0.34±0.24	0.0005
DPAL (mm)	B-mode vessel diameter	2.49±0.47	2.28±0.38	0.007
	Flow lumen diameter in color Doppler imaging	1.89±0.42	1.94±0.35	NS
	Wall thickness	0.49±0.29	0.33±0.18	0.006
PTAL (mm)	B-mode vessel diameter	2.75±0.41	2.45±0.36	0.007
	Flow lumen diameter in color Doppler imaging	2.17±0.41	2.12±0.34	NS
	Wall thickness	0.56±0.29	0.33±0.2	0.0002

DPAR/DPAL – dorsalis pedis artery right /left. PTAR/PTAL – posterior tibial artery right/left.

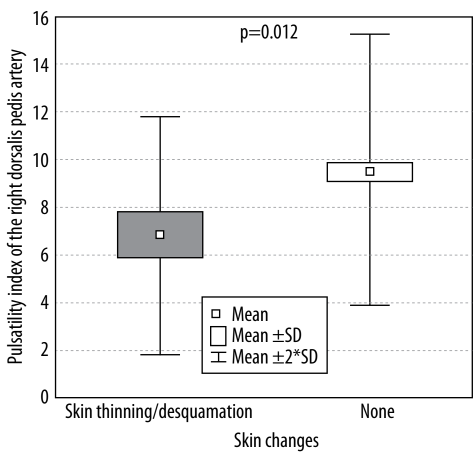

Figure 3. Pulsatility index of the right dorsalis pedis arteries assessment depending on the presence or absence of trophic skin changes.

Statistically higher values of overall vessel diameter as well as the wall thickness of all vessels as compared to the study group were observed in grayscale ultrasound with no statistically significant differences in the lumen diameter (Figure 2, Table 2).

A change to biphasic spectral character was observed in 41/148 of arteries in diabetic patients (27.7%), while a change to monophasic character was observed only in 4/148 cases (2.7%) (Figure 3, Table 3).

No statistical differences were demonstrated between the groups in terms of blood flow parameters (PSV, EDV, PI, RI) as assessed by spectral Doppler imaging. Positive correlation was demonstrated in the study group between the HbA1c level and RI for the right dorsalis pedis artery (r=0.38; *P*=0.02), right posterior tibial artery (r=0.38; *P*=0.02) and left posterior tibial artery (r=0.42; *P*=0.009).

PI values observed in the group of patients with trophic skin changes within shanks were lower than in the group without skin lesions and were statistically different in case of the right dorsalis pedis artery. Negative correlation was demonstrated between PI and the presence of skin changes. In case of the right dorsalis pedis artery, the difference was statistically significant (r=–0.431, *P*=0.009) (Figure 3).

Discussion

WHO predicts a continuous increase in the population of diabetic patients from 300 million individuals in 2025 [6,7] to 366 million in 2030 [8]. The etiology of numerous complications of diabetes commonly includes micro- and macroangiopathy changes. The best way to avoid such changes is to maintain appropriate metabolic control. Glycated hemoglobin level is one of the indicators of diabetes control. According to the 2008 recommendations of the American Diabetes Association, correct diabetes control is characterized by HbA1c levels of <7.0% [8]. According to the Polish Diabetological Association the value should be ≤7.0% [9]. HbA1c levels in the study group were within the range acceptable in diabetes treatment and amounted to the average of 7.03±1.12%, demonstrating relatively good diabetes control.

Table 3. Types of spectral waveform in calf and foot arteries.

	Triphasic		Biphasic		Monophasic	
	Patients with diabetes n=37	Control group n=36	Patients with diabetes n=37	Control group n=36	Patients with diabetes n=37	Control group n=36
DPAR	17	36	19	0	1	0
PTAR	25	36	11	0	1	0
DPAL	30	36	6	0	1	0
PTAL	31	36	5	0	1	0
Total	103	144	41	0	4	0

DPAR/DPAL – dorsalis pedis artery right /left. PTAR/PTAL – posterior tibial artery right/left.

Chronic hyperglycemia as measured by the HbA1c level is a risk factor predisposing to diabetes-related angiopathies [10]. The UKPDS study [11,12] demonstrated a linear correlation between the percentage content of glycated hemoglobin and diabetes-related deaths and micro- and macroangiopathy type complications. Despite the fact that mean HbA1c levels oscillated around normal values, a relationship was observed between the value of this parameter and the flow resistance index (RI): in all examined vessels, increase in HbA1c was associated with an increase in flow resistance as measured by RI. This might suggest changes occurring within vessel walls (wall stiffening), affecting the flow parameters and manifested by gradual increase in the flow resistance [13]. Zhang et al. also observed elevated resistance in both groups of diabetic patients as compared to the control group ($P<0.001$). RI values were also significantly higher in group 2 with the diabetes duration of >5 years 1 compared to group 1 with diabetes duration of <5 years ($P<0.01$) [14]. The assessment of vessels was carried out using two common, noninvasive examination methods: the ankle-brachial index measurement and ultrasound evaluation (grayscale ultrasound, color Doppler and spectral Doppler imaging).

Doppler ultrasound scans provide information on the direction and character of blood flow spectrum. The flow in the lower limb arteries is of high-resistance character. In diabetic patients, the correct triphasic flow spectrum was observed in 103/148 of examined artery segments (69.6%), biphasic flow was observed in 41/148 artery segments (27.7%), while monophasic flow was observed only in 4 vessels (2.7%) (Table 3). Biphasic flow spectrum was most common in the right dorsalis pedis artery. Shahhen et al. demonstrated triphasic flow in as little as 38% of vessels and monophasic flow in as much as 21% of vessels in patients wit advanced diabetes associated with intermittent claudication [15]. As suggested by the presented own results and the literature, Doppler flow parameters are not sensitive markers of changes occurring in the natural history of diabetes at early stages. In many cases of advanced diabetes with diabetic foot symptoms, Doppler flow parameters in femoral arteries, popliteal arteries and crural arteries are within normal ranges and become altered only within the distal segments of foot arteries. In the assessment of flow parameters (PSV, EDV, RI, PI) significant correlations were observed for the pulsatility index – lower values were significantly more common in the subgroup of patients with trophic skin changes. Janssen et al. demonstrated that the pulsatility index is a better marker in noninvasive assessment of limb ischemia in diabetic patients that the ankle-brachial index [16].

The development of atherosclerosis in the course of diabetes consists in the process of vessel wall remodeling. At the early stage of atherosclerosis, remodeling allows to maintain the flow lumen as it consists in centrifugal thickening of vessel wall with increase in overall vessel diameter (outward remodeling) [17]. In a more advanced stage of atherosclerosis, the wall undergoes centripetal hypertrophy, leading to stenosis of the flow lumen (inward remodeling) [18]. Pathophysiology of vessel remodeling was first described by Galgov [19]. The type and size of remodeling depends on the production of vascular epithelial growth factor, proteases and cellular adhesion molecules as a response to the changes in blood flow. The outward remodeling of the vessel wall is a compensatory mechanism that allows to maintain a non-narrowed flow lumen while being an early marker of atherosclerotic lesions. In our study, we demonstrated statistically higher overall diameters of arteries (including vessel walls) in grayscale ultrasound in diabetic patients compared to the control group. No significant differences were observed between both groups in relation to the measurements of the flow lumen diameter using color Doppler ultrasound imaging. This discrepancy may lead to suspicion that the increase in the overall vessel diameter is due to the thickening of the vessel walls. This is confirmed by a statistically significantly higher thickness of walls in all the examined vessels in the study group compared to the control group (Table 2).

The type and stage of vessel wall remodeling in diabetic patients is affected numerous factors, including hyperglycemia, as long-term exposure to elevated blood glucose levels stimulates vascular wall remodeling [20]. HbA1c level is an indicator of good glycemic control. In our study, HbA1c values oscillated around the good glycemic control threshold, and this was the probable reason why statistically significant relationships between HbA1c levels and examined vessel wall thickness could not be demonstrated.

Another factor of established impact on vessel wall remodeling is hypertension – it was demonstrated that hypertension in type 2 diabetes patients caused outward remodeling walls, increasing their thickness while maintaining or increasing the vessel lumen [20,21]. In the study group, hypertension was observed in most, i.e. 37/37 diabetic patients (65%), while no cases of hypertension were observed in the control group.

Using a 10 MHz probe, Zhang et al. demonstrated a statistically significant reduction in arterial diameter and increase in the flow resistance (RI) within the thumb arteries in a group of diabetic patients [14]. Diabetic patients in the study were divided into two groups depending on their disease duration: group 1 with diabetes duration of <5 years and group 2 with diabetes duration of >5 years. Both groups of diabetic patients had significantly lower diameters of arterioles of the distal phalanx of the right thumb as compared to the control group ($P<0.001$) [14]. Due to the difficulties in detecting the flow signals in tiny vessels, the authors made use of a novel technique of quality Doppler profiles (QDP) developed by combining the power spectrum intensities at all depths along the ultrasound beam.

Contrary results, i.e. the increase in the diameter of the examined vessels as obtained in our study may be due to the larger caliber of the foot vessels and changes occurring within the vessel walls, with predominance of outward remodeling. The reduction in the diameter of arterioles of the distal thumb phalanx is suggestive rather of inward wall thickening, which might be characteristic for small peripheral arteries.

Intravascular ultrasound examinations (IVUS) making use of high frequency (20–50 MHz) allow for precise measurements of vessel wall thickness. Currently, the applicability of this method is restricted by its invasive character and limited mostly to the assessment of coronary vessels. Using IVUS in a group of diabetic patients, Reddy et al. demonstrated a significantly higher positive remodeling of coronary arterial walls as compared to the control group of patients without diabetes [22].

Currently available linear probes for vascular assessments are characterized by a wide range of available frequencies (2–18 MHz), facilitating high resolution imaging of superficial structures. However, selection of highest frequencies and highest definition leads to reduction of the maximum beam penetration depth (e.g. down 38 mm for the frequency of 15.7 MHz) and the reduction in the range of flow rates being measured.

Color Doppler imaging of blood flow was helpful in the assessment of vessel lumen diameter. The enhancement of the color-coded flow signal was selected so as not to exceed the vessel wall. The power Doppler technique is another method that might help in the assessment of the flow lumen; of non-Doppler technique, such possibility is also offered by coded B-flow imaging. B-flow imaging (BFI) is characterized by higher spatial and temporal resolution than Doppler imaging, thus allowing for better visualization of the vessel wall. Limitations of the method include disturbance in flow signals in the areas of calcified plaques and calcifications within the vessel walls and difficulties in the assessment of the lumen and the wall at high pulsation of the vessel [23,24]. Similar as in other ultrasound flow assessment methods, the sensitivity of the technique is decreased with depth. B-flow imaging technique is free of typical artifacts such as color blooming or aliasing [25].

Conclusions

1. A significantly higher overall diameter of arteries in diabetic patients as compared to the control group with comparable flow lumen diameters in both groups suggests vessel wall thickening as an early symptom of diabetes-related changes.
2. Doppler flow parameters assessed in patients at the early stage of diabetes are not significantly different from those observed in healthy individuals.
3. HbA1c level in the group of diabetic patients is positively correlated with the resistance index (RI).
4. Pulsatility index (PI) was demonstrated to drop as the intensity of trophic skin changes increased.

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