ORIGINAL STUDY

Факторы, ассоциированные с патологическим сердечно-лодыжечным сосудистым индексом, у пациентов с сахарным диабетом 2 типа и предиабетом

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Цель: *изучить факторы, ассоциированные с патологическим сердечно-лодыжечным сосудистым индексом, у пациентов с нарушениями углеводного обмена (НУО).*

Материалы и методы*. Одномоментное исследование проведено в рамках многоцентрового эпидемиологического исследования «Эпидемиология сердечно-сосудистых заболеваний и их факторов риска в регионах РФ» (ЭССЕ-РФ). Объектом исследования явилась случайная популяционная выборка мужского и женского взрослого населения в возрасте 25–64 лет Кемеровской области. Стандартный протокол исследования ЭССЕ-РФ расширен определением сердечно-лодыжечного сосудистого индекса (CAVI) на аппарате VaSeraVS-1000 (Fukuda Denshi, Япония). В несколько этапов была сформирована выборка из 1619 человек, из которой выделены пациенты с НУО: сахарным диабетом (СД) 1 и 2 типа, нарушением гликемии натощак (НГН), нарушением толерантности к глюкозе (НТГ) – всего 318 человек, из которых исключены пациенты с СД 1 типа (СД1), с лодыжечно-плечевым индексом (ЛПИ) менее 0,9, с неизвестным значением CAVI. Окончательная выборка – 282 пациента с СД 2 типа (СД2) и предиабетом (НГН, НТГ) разделены на две группы: I (n=41) – патологический CAVI (≥9,0), II (n=241) – нормальный CAVI (<9,0).*

Результаты*. В популяционной выборке с нарушениями углеводного обмена патологический CAVI (≥9,0) выявлен у 14,5% обследованных. При однофакторном регрессионном анализе с патологическим CAVI ассоциировались увеличение возраста, длительности курения, инсульт в анамнезе, наличие артериальной гипертензии (АГ), корригируемый инсулином СД2, висцеральное ожирение, повышение частоты сердечных сокращений (ЧСС), систолическое и диастолическое артериальное давление (САД и ДАД), снижение скорости клубочковой фильтрации (СКФ). При многофакторном анализе сохранили свою значимость возраст (ОШ 1,077 на каждый год жизни, p=0,012), САД (ОШ 1,024 при увеличении на каждый мм рт. ст., p=0,007), ЧСС (ОШ 1,027 на каждый удар в минуту, p=0,033), СКФ CKD-EPI (ОШ 1,506, при снижении на каждые 5 мл/мин/1,73 м^2, p=0,002), корригируемый инсулином СД2 (ОШ 10,238, p=0,031).*

Заключение. *Выявлены предикторы патологического CAVI у больных диабетом и предиабетом. Оценка CAVI в данной когорте позволяет выделить пациентов с повышенным риском сердечно-сосудистых осложнений.*

Ключевые слова*: патологический сердечно-лодыжечный сосудистый индекс; сахарный диабет; предиабет; факторы сердечно-сосудистого риска*

Factors associated with abnormal heart-ankle vascular index in patients with type 2 diabetes and prediabetes

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Aim*. To identify the prevalence of abnormal cardio-ankle vascular index (CAVI) in patients with impaired glucose metabolism (IGM) and factors associated with CAVI.*

Materials and methods*. The study was conducted within the 'Epidemiology of Cardiovascular Diseases and their Risk Factors in Regions of the Russian Federation' (ESSE-RF) study, a cross-sectional, multicenter trial. The random sample of adults, males and females aged 25–64 years, from Kemerovo region was included in this investigation of CAVI. CAVI was measured using the VaSeraVS-1000 vascular screening system (Japan). A total of 318 people with diabetes mellitus (DM) type 1 or 2, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) were identified in the sample of 1,619 patients with IGM. Two patients with type 1 diabetes, 29 patients with ankle-brachial index (ABI) <0.9 and 5 patients with unknown CAVI were excluded from the analysis. The final sample of 282 patients with DM2 or prediabetes (IFG and IGT) was divided into the following two groups: 41 patients with CAVI ≥9.0 (pathological CAVI) and 241 patients with CAVI <9.0 (normal CAVI).*

Results*. Pathological CAVI was detected in 14.5% of patients with DM2 or prediabetes. In univariate logistic regression, pathological CAVI was associated with increase in age, greater duration of smoking, previous stroke, presence of arterial hypertension (AH), receiving insulin therapy for DM2, visceral obesity, increased heart rate (HR), systolic and diastolic blood pressure (SBP*

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and DBP) and decreased glomerular filtration rate (GFR). In multivariate analysis, age [odds ratio (OR) =1.077, p=0.012], SBP (OR=1.024, p=0.007), HR (OR=1.027, p=0.033), CKD-EPI GFR (OR=1.506, p=0.002) and insulin therapy for DM2 (OR=10.238, p=0.031) retained their significance.

***Conclusion**. The predictors of pathological CAVI in patients with DM2 or prediabetes were identified. Evaluation of CAVI in this cohort allowed the identification of patients with increased risk of cardiovascular complications.*

***Keywords**: abnormal cardio-ankle vascular index; diabetes; prediabetes; factors of cardiovascular risk*

Background

Cardiovascular diseases are the major cause of mortality in patients with diabetes mellitus (DM) [1]. For adequate prevention of cardiovascular complications, it is necessary to identify their early precursors. One of the markers of cardiovascular diseases is increased arterial stiffness [2, 3]. Pulse wave velocity, a traditionally used parameter for measurement of this marker, has the following limitations: 1) lack of standardization and 2) dependence on the operator and blood pressure (BP) levels. In recent years, a new parameter, cardio-ankle vascular index (CAVI), which does not exhibit any of the aforementioned disadvantages, has been used to assess the arterial stiffness. Studies have demonstrated that CAVI increases in patients with the following risk factors of cardiovascular diseases: 1) hypertension [4], 2) dyslipidaemia [5], 3) smoking [6], 4) low physical activity [7] and 5) DM [8, 9]. A relationship exists between CAVI and the prevalence of both peripheral [10] and coronary [11, 12] atherosclerosis as well as prognostic values in some categories of patients with coronary artery disease [10, 13]. It is impossible to exclude CAVI values in various conditions including impaired glucose metabolism (IGM). Therefore, a relevant reason exists for studying CAVI in diabetic patients, primarily for detection of asymptomatic cardiovascular diseases. The above data were primarily obtained from Asian populations; therefore, it is important to note that regional differences in CAVI values exist in healthy individuals [14].

Aim

We aimed to examine the factors associated with abnormal CAVI values of patients with type 2 diabetes mellitus (T2DM) and prediabetes in a population-based 'Epidemiology of Cardiovascular Diseases and their Risk Factors in Regions of the Russian Federation' (ESSE-RF) study in one of the regions of Western Siberia, Russia.

Materials and methods

This study was conducted within the epidemiological multicenter trial ESSE-RF, wherein CAVI values of patients in the Kemerovo region were specifically investigated. The study population comprised a randomized group of adult males and females (age 25–64 years) from the Kemerovo region. A cross-sectional epidemiological trial was performed from March to October, 2013. The preparation of study sample, which involved three phases including serial sampling of municipal medical institutions, medical sites and households, has been mentioned in the study protocol. Of the 2000 people who were asked to participate in this study, 1628 were enrolled (81.4%). Of those enrolled, 1619 fulfilled all study criteria. The study was approved by the Independent Local Ethics Committee of the Research Institute for Complex Issues of Cardiovascular Diseases protocol from meeting No. 61 dated 6 February 2013. Each participant received written informed consent form for study participation. Population examination, according to the cardiac screening program, was conducted during the morning. Physical examination included measurement of BP, heart rate (HR) and anthropometric indicators; a resting 12-lead electrocardiography (ECG) and blood sampling for biochemical laboratory tests. All measurements were performed by staff qualified in cardiac epidemiological research methods.

BP measurements were performed on the right hand of each study participant, adopting a sitting position after a 5 min rest period, using an automatic sphygmomanometer. BP was measured twice with an interval of 2–3 min. The mean value of the two measurements was used for analysis. Arterial Hypertension (AH) was determined as BP of 140/90 mm Hg and higher or BP < 140/90 mm Hg during antihypertensive therapy. Height and weight measurements were performed using a stadiometer with an accuracy of 1 cm and floor electronic medical balance with an accuracy of 100 g. Each examined person removed their shoes and outerwear. Obesity was defined as a body mass index (BMI) ≥ 30 kg/m2, calculated according to the formula: weight in kg/height in m2 (Quetelet index). Waist circumference (WC) and the hip circumference (HC) were also measured for all study participants. Visceral obesity was determined by a WC ≥ 80 cm in women and 94 cm in men [15]. Participants who smoked ≥ one cigarette or more per day were considered to be chronic smokers. IGM was determined according to the diagnostic criteria of DM and other glycaemic disorders [16].

Blood sampling in examined persons was performed via vein puncture after 12-h fasting. All laboratory procedures were strictly standardized and performed using the same equipment and equipment-specific reagents in clinical laboratories. Glomerular filtration rate (GFR) was calculated on the basis of serum creatinine using the Modification of Diet in Renal Disease Study (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas.

The cardiac screening program included a standard questionnaire comprising the following 12 modules: 1) socio-demographic data of responders; 2) dietary habits; 3) physical activity; 4) smoking; 5) alcohol consumption; 6) health, attitude to health and quality of life; 7) sleep; 8) economic

conditions and performance; 9) stress; 10) anxiety and depression; 11) data on medical referrals and disability and 12) medical history of diseases: angina, myocardial infarction, hypertension, diabetes etc.

Standard research protocol ESSE-RF included specific measurements of peripheral arterial stiffness using a VaSeraVS-1000 vascular screening system (Fukuda Denshi, Japan) to obtain automatic CAVI values. The calculation of this parameter was performed using a plethysmogram on four extremities, an ECG and a phonocardiogram using a special algorithm for calculations.

The study design is shown in Figure 1. From a sample of 1619 people, 318 participants with IGM were isolated on the basis of the following: DM type 1 and 2, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Two patients with type 1 diabetes, 29 patients with values of Ankle-Brachial Index (ABI) < 0.9 and 5 patients with unknown CAVI were excluded from the study to avoid a distortion of CAVI values. The final sample, divided into the following two groups, included 282 patients with type 2 diabetes and prediabetes (IFG, IGT): I (n = 41) participants with CAVI ≥ 9.0 (pathological CAVI) and II (n = 241) participants with CAVI < 9.0 (normal CAVI).

Data was analysed using the standard software package StatSoft STATISTICA v.8.0. Distribution of quantitative data was performed using the Shapiro–Wilk test. Because distribution of all quantitative traits varied, they are presented as medians and quartiles (25th and 75th percentile). Mann–Whitney test and $\chi 2$ test were used for comparisons between groups. Fisher exact test with Yates' correction was used for a small number of observations. Logistic regression analysis was performed to assess the association of a binary trait with one or more quantitative or qualitative characteristics. Multivariate regression analysis included variables which have values of the statistical significance test in the univariate analysis was less than 0.1. Previously an identification of possible correlations between the presumed predictors was conducted, and multiple regression models based on identified correlations were constructed. A p value = 0.05 was considered to be significant.

Results

Clinical and anamnestic characteristics of patients are displayed in Table. 1. The majority of patients with IGM in Group I and II were females (73.2% and 65.2%, respectively, p = 0.314). Patients in the group with pathological CAVI were older (p < 0.001) and had a longer history of smoking (p = 0.013).

The majority of patients with IGM in both groups had T2DM (85.4% in Group I and 85.9% in Group II, p = 0.929, Table. 1). T2DM with insulin dependency was significantly more frequent in the group with pathological CAVI (p < 0.001). Patients in both groups displayed the same prevalence of kidney diseases, coronary artery disease and incidence of myocardial infarction.

A larger number of patients in Group I than those in Group II suffered a stroke (12.2% and 2.9% respectively, p = 0.006) and previously had AH (61.0% and 38.2%, respectively, p = 0.006).

Patients in both groups had similar anthropometric parameters (BMI, WC and HP; Table 2). High prevalence of obesity (BMI ≥ 30 kg/m2) existed for both groups (51.2 % in Group I and 57.7% in Group II, p = 0.436). Visceral obesity with a WC ≥ 80 cm in women and 94 cm in men was detected significantly more often in individuals with pathological CAVI (95.1% vs. 80.4%, respectively, p = 0.034).

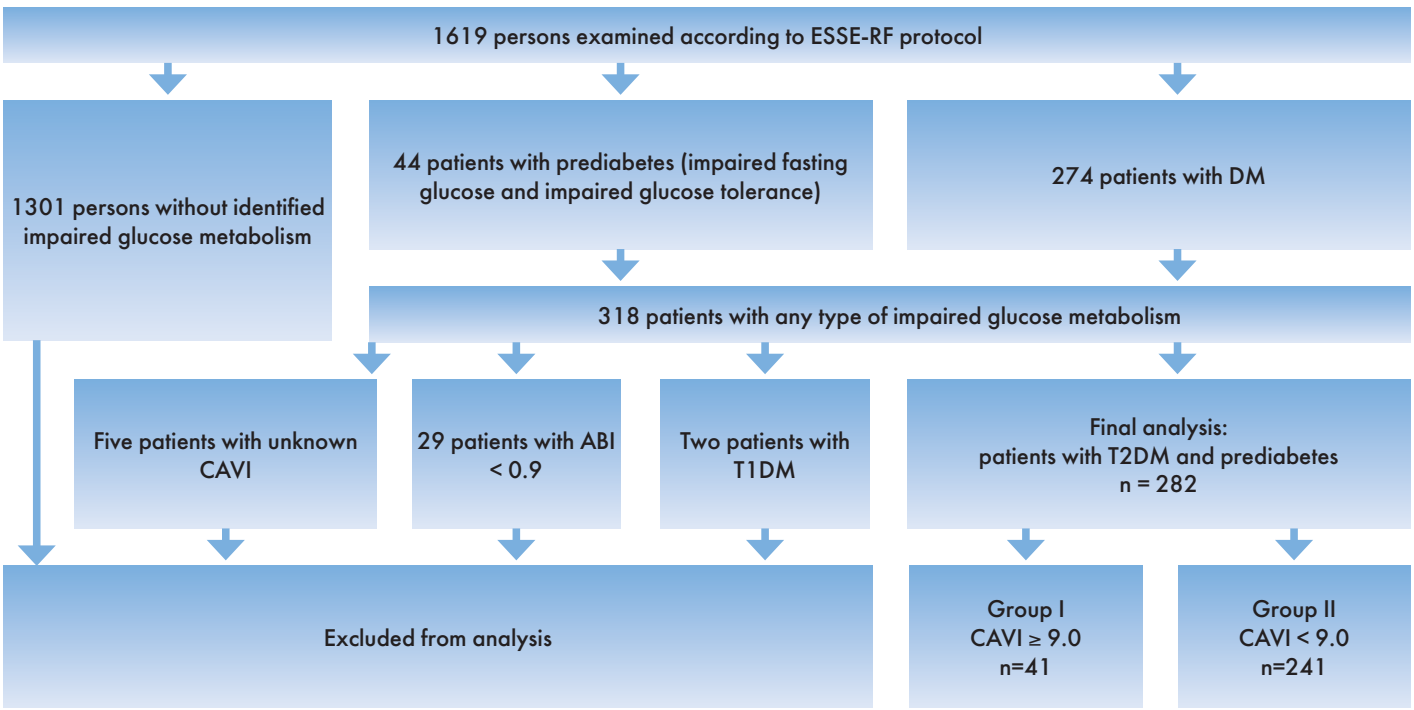

Figure 1. Study design
Abbreviations: DM, diabetes mellitus; CAVI, cardio-ankle vascular index; ABI, ankle-brachial index

Table 1

General Data and Social Status of Patients with Impaired Glucose Metabolism (n = 282)			
Parameter	Group I Pathological CAVI (≥9.0) n = 41	Group II Normal CAVI (<9.0) n = 241	P
Female, n (%)	30 (73.2)	157 (65.2)	0.314
Age, years, Me (LQ; UQ)	59.0 (54.0; 63.0)	54.0 (47.0; 59.0)	<0.001
Smoking, n (%)	4 (9.8)	54 (22.4)	0.064
Smoking history, years, Me (LQ;UQ)	42.5 (35.5; 44.5)	32.8 (24.0; 41.0)	0.013
Presence of diagnosed diseases			
Coronary artery disease, n (%)	6 (14.6)	33 (13.7)	0.871
Prior myocardial infarction, n (%)	0 (0)	5 (2.1)	0.352
Prior stroke, n (%)	5 (12.2)	7 (2.9)	0.006
Arterial hypertension, n (%)	25 (61.0)	92 (38.2)	0.006
Type 2 diabetes mellitus, n (%)	35 (85.4)	207 (85.9)	0.929
Type 2 diabetes mellitus type 2, insulin dependent, n (%)	3 (7.3)	1 (0.4)	<0.001
Kidney disease, n (%)	18 (43.9)	82 (34.0)	0.222
Family history of cardiovascular disease, n (%)	25 (61.0)	169 (70.1)	0.242

Table 2

Anthropometric Characteristics and Volumetric Sphygmographic Parameters in Groups (VaSera VS-1000)			
Parameter	Group I Pathological CAVI (≥9.0) n = 41	Group II Normal CAVI (<9.0) n = 241	P
Anthropometric characteristics			
Height, cm	165.0 [156.5; 170.5]	165.0 [159.0; 172.0]	0.210
Body weight, kg	81.2 [74.5; 94.7]	88.5 [159.0; 172.0]	0.305
BMI, kg/m2	30.2 [26.7; 35.4]	31.3 [26.8; 36.4]	0.757
BMI≥30 kg/m2, n (%)	21 (51.2)	138 (57.7)	0.436
WC, cm	101.0 [90.0; 109.0]	101.0 [90.0; 110.0]	0.866
HC, cm	107.0 [103.0; 120.0]	109.0 [102.5; 117.0]	0.930
Visceral obesity (≥80 cm in women and ≥94 cm in men), n (%)	39 [95.1]	193 [80.4]	0.034
Volumetric sphygmographic parameters			
SBP—hand, mm Hg	157.0 [142.0; 169.0]	143.1 [128.0; 153.0]	<0.001
DBP—hand, mm Hg	94.0 [89.0; 103.0]	89.0 [80.0; 95.0]	<0.001
HR, beats/min	73.0 [66.0; 82.0]	66.0 [60.0; 74.0]	<0.001
CAVI	9.6 [9.3; 10.8]	7.3 [6.6; 8.0]	<0.001
ABI	1.09 [1.02–1.15]	1.13 [1.05; 1.2]	0.899

Note: data are presented as median [Q25; Q75].
Abbreviations: BMI, body mass index; WC, waist circumference; HC, hip circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CAVI, cardio-ankle vascular index; ABI, ankle-brachial index.

Comparison of volumetric sphygmographic parameters (Table 2) shows that systolic blood pressure (SBP) in both groups corresponded to AH parameters, while the median SBP in individuals with pathological CAVI was significantly higher than in those with normal CAVI (157.0 mm Hg and 143.1 mm Hg, respectively; $p < 0.001$). Median diastolic blood pressure (DBP) was also significantly higher in Group I (94.0 mm Hg and 89.0 mm Hg, respectively, $p < 0.001$). ABI values were similar for both groups ($p = 0.899$). CAVI values were higher in Group I ($p < 0.001$). Median HR was significantly higher in Group I (66.0 and 73.0 bpm in Group I and II, respectively; $p < 0.001$).

Blood chemistry tests revealed no differences between groups regarding the following lipid profile parameters: glucose and uric acid ($p > 0.05$, Table 3). The median GFR calculated according to CKD-EPI formula was significantly lower in patients with pathological CAVI ($p < 0.001$), although within the reference range for both groups. The median creatinine and MDRD GFR values were similar for both groups ($p > 0.05$).

Logistic regression was used for analysis of factors associated with pathological CAVI in the entire sample of patients with IGM (Table 4). According to univariate analysis, pathological CAVI was associated with increased age, smoking history, prior stroke, hypertension, insulin-dependent T2DM, visceral obesity, increased HR, SBP and DBP, a decrease in GFR CKD-EPI and MDRD.

According to multivariate analysis age (OR 1.077 per each year of life, 95% CI 1.016–1.142, $p = 0.012$), SBP (OR 1.024 with increase for every mm Hg, 95% CI 1.006–1.042, p =

Table 3

Laboratory Parameters in Group I and II Patients with Impaired Glucose Metabolism

Parameter	Group I Pathological CAVI (≥9.0) n = 41	Group II Normal CAVI (<9.0) n = 241	P
Tot. cholesterol, mmol/l	5.8 [4.9; 6.2]	5.4 [4.7; 6.2]	0.244
HDL cholesterol, mmol/l	1.6 [1.4; 1.8]	1.6 [1.3; 1.9]	0.880
LDL cholesterol, mmol/l	3.9 [3.2; 4.5]	3.6 [3.0; 4.2]	0.091
Triglycerides, mmol/l	1.3 [0.9; 1.7]	1.4 [0.95; 1.9]	0.484
Glucose, mmol/l	6.4 [5.1; 6.6]	5.8 [5.1; 6.7]	0.701
Creatinine, μmol/l	76.4 [62.1; 78.2]	69.75 [64.5; 72.6]	0.998
GFR CKD-EPI, ml/min/1.73 m2	93.1 [89.8; 95.6]	97.1 [92.8; 102.6]	0.000
GFR MDRD, ml/min/1.73 m2	83.3 [77.5; 96.3]	89.0 [80.7; 100.6]	0.097
Uric acid, μmol/l	0.3 [0.3; 0.4]	0.3 [0.3; 0.4]	0.694

Note: data are presented as median [Q25; Q75].
Abbreviations: HDL cholesterol, cholesterol high-density lipoproteins; LDL cholesterol, cholesterol low-density lipoproteins; GFR, glomerular filtration rate

0.007), HR (OR 1.027 with increase for every beat per minute, 95% CI 1.002–1.051, p = 0.033) retained their significance regardless of gender, stroke and MDRD GFR (see Table. 4).

The decrease in GFR CKD-EPI for every 5 ml/min/1.73 m2 was associated with 1.5 times increased likelihood of pathological CAVI (OR 1.506, 95% CI 1.165–1.949, p = 0.002), regardless of gender, visceral obesity and prior stroke. In patients with insulin-dependent T2DM, the likelihood of high CAVI detection was increased more than 10 times (OR 10.238, 95% CI 1.016–98.677, p = 0.031). Adjustment for age were made, regardless of gender, presence of hypertension and smoking history.

Discussion

The present study demonstrates that in a population-based sample, pathological CAVI values (≥9.0) were present in 14.5% of patients with IGM. Independent factors associated with pathological CAVIs in this cohort of patients were age, increased SBP and HR, decreased GFR and dependence on insulin therapy.

Previous studies have obtained contradictory data concerning a relationship between various factors and pathological CAVI values in patients with diabetes [8, 9, 17, 18, 19]. Perhaps, only the association of CAVI deterioration with increasing age of patients is not divisive among researchers [8, 9, 19]. In the study performed by Tian G. et al. [19], the only independent predictor of increase in CAVI in patients with DM was patient age, whereas in the other studies, it was noted that CAVI was dependent on the following factors: dyslipidaemia [17], BP [19] and the degree of IGM control [9, 19]. Shimizu Y. et al. [17] observed increased arterial stiffness (CAVI ≥ 8.0) in diabetic patients with high values of triglycerides/high density lipoproteins ratio (HR 2.57; 95% CI 1.32–5.02), but not in patients with low values of this ratio (HR 1.17; 95% CI 0.52–2.63) [17]. A correlation between CAVI values and total cholesterol (r = 0.101; p < 0.05) was also noted [20]. Unlike data revealed in this study, other studies revealed no association between lipid profiles and CAVIs [9, 19]. Some Spanish authors [19] also observed the same positive correlation between CAVI values and blood pressure as that observed in the present study; however, a correlation was not observed in a Japanese population [9]. A positive correlation between CAVI and BP differences, obtained from measurements on hand, existed in one study involving patients with DM (r = 0.240; p = 0.0005). A multiple linear regression analysis revealing differences in BP, obtained from hand measurement, was an independent determinant of the increase in CAVI (β = 0.213; p = 0.0011) [18]. These data suggest that asymptomatic atherosclerosis existed in these patients; therefore, it is necessary to consider the relationship between CAVI and BMI in DM separately. Other completed studies have not revealed any relationship between CAVI and obesity [9] or any negative correlations between CAVI and body mass index or waist circumference [19]. The univariate logistic regression analysis in the present study revealed a relationship between pathological CAVI and visceral obesity, but not between pathological CAVI and BMI. Apparently, this phenomenon can be explained by the phenotypic obesity differences and BMI increases due to the presence of subcutaneous fat; however, these factors are not necessarily associated with poor cardiovascular prognoses [21]. The presence of visceral obesity, demonstrated by increased WC measurements, is not a not a satisfactory parameter to evaluate metabolism [21, 22].

A level of IGM control, specific for this group of patients, may indicate a relationship between CAVI values and other clinical and laboratory parameters in patients with DM. Thus, an independent association of CAVI with the postprandial glycaemia [23, 24] and glycated hemoglobin levels (HbA1c) is noted [9, 19]. In addition, the reduction of HbA1c levels due to glycaemic control was significantly correlated with an improvement in CAVI values [9]. Relevant literature has mentioned the influence of various long-term medications on CAVI value decrease [23, 24, 25].

During 12 months of treatment with acarbose, a decrease occurred both in the postprandial glucose and HbA1c levels as well as some asymptomatic inflammation serum markers (hs-CRP, PTX3, MMP-2 and MMP-9). In addition, there was a significant decrease in CAVI, and the multivariate analysis showed that decreased blood glucose levels, PTX3 expression and MT1-MMP are independent predictors of favourable

Table 4

Factors Associated with Pathological CAVI in Patients with Impaired Glucose Metabolism (n = 282)		
Parameters	OR (95% CI)	P
Univariate analysis		
Age (with increase for every 1 year)	1.111 (1.050–1.176)	<0.001
T2DM, insulin dependent	18.947 (1.902–87.783)	0.006
Prior stroke	4.695 (1.408–15.658)	0.018
Arterial hypertension	2.528 (1.278–4.999)	0.006
Visceral obesity (WC ≥ 80 cm in women and ≥ 94 cm in men)	3.088 (1.001–10.495)	0.038
Smoking history (with increase for every 1 year)	1.093 (1.008–1.185)	0.009
HR (with increase for every 1 beat per minute)	1.037 (1.014–1.061)	0.001
SBP (with increase for every 1 mm Hg)	1.035 (1.018–1.0511)	<0.001
DBP (with increase for every 1 mm Hg)	1.058 (1.029–1.090)	<0.001
CKD-EPI GFR with decrease per 5 ml/min/1.73 m2	1.590 (1.240–2.037)	<0.001
MDRD GFR with decrease per 5 ml/min/1.73 m2	1.131 (1.011–1.265)	0.028
Multivariate analysis		
Model 1, regardless of sex, prior stroke, MDRD GFR, p < 0.001 for the model		
Age (with increase per every 1 year)	1.077 (1.016–1.142)	0.012
HR (with increase for every 1 beat per minute)	1.027 (1.002–1.051)	0.033
SBP (with increase for every 1 mm Hg)	1.024 (1.006–1.042)	0.007
Model 2, regardless of gender, visceral obesity, prior stroke, p < 0.001 for the model		
CKD-EPI GFR (with decrease per 5 ml/min/1.73 m2)	1.506 (1.165–1.949)	0.002
HR (with increase for every 1 beat per minute)	1.032 (1.008–1.056)	0.009
Model 3, regardless of gender, smoking history, arterial hypertension, p < 0.001 for the model		
Age (with increase for every 1 year)	1.094 (1.031–1.160)	0.003
T2DM, insulin-dependent	10.238 (1.016–98.677)	0.031

Note: WC, waist circumference; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; GFR, glomerular filtration rate

CAVI changes [23]. Changes in treatment regimens of patients with diabetes may further impact the improvement in vascular stiffness. Thus, 3 months after replacing premixed human insulin (30/70) with biphasic insulin aspart (30/70) a significant decrease in CAVI (from 9.77 ± 1.11 to 9.35 ± 1.17; $p < 0.005$) was noted, along with a significant negative correlation between change in CAVIs and the concentration of 1,5-anhydro-D-glucitol (1,5-AG), a marker of postprandial hyperglycaemia ($r = -0.393$; $p < 0.05$). The reduction of arterial stiffness may also be associated with improved post-prandial glucose levels [24]. Comparison of the two groups of patients with DM, including one group receiving glimepiride for 6 months and the other receiving glibenclamide, revealed a significant decrease in CAVI values in only the glimepiride group (from 9.4 ± 1.4 to 8.9 ± 0.8; $p < 0.05$). The concentration of urine 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, was decreased in the glimepiride group and increased in the glibenclamide group. Changes in the two groups significantly differed (-1.5 ± 3.5 vs +1.8 ± 3.6; $p = 0.009$). The change in the concentration of 8-OHdG served as a significant independent predictor of the CAVI change among all examined patients. Researchers concluded that the improvement of CAVI values during glimepiride therapy may be mediated by a reduction both in the oxidative stress and insulin resistance [25].

An important aspect of the CAVI evaluation in patients with DM is its association with the presence of subclinical signs of both peripheral and coronary artery atherosclerosis. Atherosclerotic plaques in carotid arteries, therefore, were found more frequently in diabetic patients with pathological CAVI than in those with normal CAVIs (89% and 67%, respectively ($p < 0.001$). In addition, it was observed that a significant correlation between CAVI and the thickness of the intima-media complex exists ($r =$ in 0.288; $p < 0.001$) [26]. According to the multiple linear regression analysis, an independent positive association between CAVI values and the marker of asymptomatic atherosclerosis mentioned above exists in the European population ($\beta = 0.29$; 95% CI 0.09–0.48; $p < 0.01$ [19]. The presence of pathological CAVI also correlated with the presence of diabetic polyneuropathy (HR 1.36; 95% CI 1.13–1.65; $p = 0.001$) [26] for target organ lesions in diabetic patients [19]. According to multislice computed tomography (MSCT) of the coronary arteries in asymptomatic patients with IGM, CAVI is also an independent predictor of increased in calcium scores and the severity of coronary artery stenosis [11]. Age, gender, presence of hypertension, diabetes and dyslipidaemia, along with a CAVI of ≥8.0 was associated with severe calcification of the coronary arteries (calcification index of ≥300 Agatston units) and with the presence of significant coronary artery stenosis (OR 3.143; 95% CI 1.004–9.842; $p = 0.049$) [11]. Additionally, a sample of T2DM patients demonstrated a positive correlation between, CAVI and calcium scores in coronary arteries ($r = 0.303$, $p < 0.0001$) [12].

Clinical significance of CAVI measurements in patients with DM primarily consists of patients demonstrating

subclinical manifestations of peripheral and coronary atherosclerosis according to this measurement method. In addition, the follow-up CAVI evaluation in patients with DM allows assessing the efficacy of therapeutic interventions focused on IGM control (already mentioned) and on pharmaceutical treatment of concomitant pathology [27, 28]. For example, it was shown that a decrease in CAVI, accompanied by a significant reduction of the LDL-CL level occurred in diabetic patients with increased LDL-CL levels after a 6-month treatment regimen of ezetimibe [27]. A significant decrease in CAVI existed for the olmesartan group as opposed to the amlodipine group when treating diabetic patients with hypertension, although the decrease in BP measurements for these groups was comparable [28]. Special studies concerning the effect of risk factors' correction on the CAVI value in patients with DM were not conducted; however, the positive effect of lifestyle modification [29], physical exercises, weight loss [30] and smoking cessation [6] on this parameter is well-known in other examined cohorts.

Conclusion

In a population-based sample, pathological CAVIs (≥ 9.0) were revealed in 14.5% of patients with IGM. Independent factors associated with abnormal CAVI values in this study cohort were age (OR 1.094; p = 0.003), increase in SBP (OR 1.024; p = 0.007), heart rate (OR 1.027; p = 0.033), reduced CKD-EPI glomerular filtration rate (OR 1.094; p = 0.003) and dependence on insulin therapy (OR 10.238; p = 0.031). Evaluation of CAVI in patients with diabetes is helpful for identifying patients with subclinical manifestations of atherosclerosis, as well as for follow-up efficacy assessment of hypoglycaemic therapy, pharmacological correction of risk factors and for preventive measures.

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