ULTRASOUND MEASUREMENT OF PERIPHERAL ENDOTHELIAL DYSFUNCTION IN TYPE 2 DIABETIC PATIENTS: CORRELATION WITH RISK FACTORS

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Abstract

The purpose of the study was to assess the endothelial dysfunction (ED) in type 2 diabetic patients ultrasonographicaly and estimate the correlation of ED with glycemia and other cardio-metabolic risk factors. 171 patient (age 60,0 + 8,5 years) with diagnosed type 2 diabetes and coronary artery disease (CAD) were randomly included in a cross sectional study. B-mode ultrasound system with a linear transducer of 7.5 MHz was used for evaluation of flow-mediated vasodilation in brachial artery (FMV). FMV was presented as a change of brachial artery diameter at rest and after limb ischemia, previously provoked by cuff inflation.

Peripheral ED was found in 77,2% (132 patients). Multivariate logistic regression model defined: age (OR 1,071, 95% CI 1,003 1,143) and plasma cholesterol (OR 4,083 95%CI 1,080 17,017) as determinants for ED. Linear multivariate analysis presented duration of diabetes (Beta 0,173, Sig 0,024), and glycemia (Beta 0,132, Sig 0,044) to be associated independently with FMV value. Estimated factors influencing FMV, might be potential therapeutic targets for presented endothelial dysfunction in type 2 diabetic patients with coronary artery disease.

KEY WORDS: endothelial dysfunction, ultrasound, type 2 diabetes,

Introduction

Endothelial dysfunction (ED) is a functional marker of atherosclerosis. ED presented as peripheral impaired endothelial-dependent vasodilation (FMV) has been established in type 2 diabetes (T2D) patients (pts) (1,2). Degree of endothelial impairment in type 2 diabetic subjects correlates with increased plasma levels of glucose and lipid and inflammatory markers: Total cholesterol, HDL, LDL Cholesterol, CRP and fibrinogen (3-5). Enderle suggested that other risk factors than hyperglycemia are more responsible for ED in T2D patients (6). Previous studies addressed that endothelial function in T2D patients could be normalized with correction of hyperlipidemia and arterial hypertension with statins and ACE inhibitors (7,8). Because of high prevalent diabetic dislipidemia and arterial hypertension it still remains unclear how type 2 diabetes acts on endothelial function. We hypothesized that ED in T2D could correlate with glycemia. We'll want to assess whether the value of flow mediated vasodilation (FMV) correlates with continuous values of cardiometabolic risk factors: plasma lipids, blood pressure, body mass index and waist when glycemia was adjusted in a model.

Materials and Methods

Study population

171 patient (age 60,0 + 8,5 years) were randomly included in a cross sectional study. All of them were with diagnosed type 2 diabetes and coronary artery disease. Diabetes mellitus type 2 was defined by the criteria of International Diabetes Federation. Coronary artery disease in our study was defined as symptomatic coronary artery disease, confirmed by coronary angiography. The study excluded patients with primary hiperlipidemia, established kidney failure, anemia and recent diabetic ketoacidosis. Patients were taking following drugs: acetil salicylic acid (94,1% of patients), statins (85,9%). 58,2% of patients were treated with insulin and rest of them (42,2% with oral antidiabetics). 78,4% of patients (134) were treated with antihypertensive drugs: 66,7% with ACE inhibitors, 12,3% with AT blockers, 15,2% with Ca antagonists and 66,7% were taken Beta blockers. 74 patients (or 43,3%) were smokers All patients signed written agreement for inclusion in the study. The study was conducted according to the Helsinki declaration for clinical studies.

Study protocol

B-mode ultrasound system with a linear transducer 7.5 MHz (HP Agilent S 4500, Phillips Corp.) was used for evaluation of peripheral impaired endothelial-dependent vasodilation in brachial artery. Lumen diameter was defined as distance between media-adventitia interfaces of far and near wall. Brachial artery diameters were measured at rest and after realising of limb ischemia, provoked by cuff inflation. Value of flow-mediated vasodilation (FMV) was presented as: [(post reactive diameter – baseline diameter) / baseline diastolic diameter). Percentage value up to 10% was defined as ED. FMV was assessed in the morning, after overnight fasting. Patients were in a supine position (9-11). Drugs were withdrawn 24 hours before investigation. Observer was blinded for patients' data. All patients were evaluated for the following parameters: age, duration of diabetes, used drugs, risk factors for coronary artery disease: arterial hypertension, hyperlipidemia, and metabolic syndrome's components: low HDL, hypertriglyceridemia, obesity and systolic pressure. Blood pressure was measured with a standard sphygmomanometer in a sitting position and presented as a mean value of two readings (in mmHg). Arterial hypertension was defined as a systolic blood pressure >/= 130 mmHg, or/and diastolic pressure >/= 85 mmHg, or as antihypertensive drugs used. Anthropometric measurements were made with patient wearing lightweight clothing and no shoes. Weight was presented in kilograms (kg) and Body mass index (BMI) in kg/m2. Waist and hip circumferences were measured by a plastic tape meter at the level of the umbilicus and of the major trohanter. The following standard laboratories were performed in the evaluated patients: Enzymatic methods for assessment of: total cholesterol, in the presence cholesterol oxidizes, triglycerides, in the presence of glicerokinase and HDL fraction with direct method. LDL fraction was evaluated with Friedewald formula. Non-HDL cholesterol was determinate as a value of total cholesterol minus HDL cholesterol. According to ATP III criteria: hipertriglyceridemia was defined as value of triglycerides >/= 1,7 mmol/L and low HDL as value of < 1,03 mmol/L. Obesity was defined as BMI > 30 kg/m2.

Statistical analysis

SPSS 10 packet for statistical analysis was used. Data were expressed as mean ± SD. The significance of

the variables in the multivariate logistic regression model was assessed by the Wald $\chi 2$ test and CIs. Two models were built. Multivariate logistic regression analyses were conducted to identify variables predictive for FMV after smoking and metabolic syndrome's components: hypo HDL-emia, hypertriglyceridemia, increased BMI and waist, and arterial hypertension, as well, were put in a model. Linear multivariate analysis was built to in order to assess whether the value of flow mediated vasodilation (FMV) correlates with continuous values of risk factors: glycemia, total cholesterol, HDL-, LDL- and non-HDL-cholesterol, body mass index, waist and diabetes duration. Models were adjusted for age.

Results

The average age of the study population was 60,0 + 8,5 years. Mean diabetes duration was 8,5 + 6,1 years. 64 patients were women and 107 were men. In Table 1. are presented basic characteristics of pts.

Variables	Mean values	Std deviation
Systolic pressure (mmHg)	143,9	19,6
Diastolic pressure	86,1	9,2
Weight (kg)	82,9	13,4
High (cm)	169,4	7,5
Waist	96,9	8,0
BMI (kg/m^2)	28,7	4,0
Glycemia (mmol/L)	8,5	2,4
Total cholesterol (mmol/L)	5,4	1,4
HDL	1,0	0,4
Non HDL	4,3	1,4
LDL	3,3	0,9
Triglycerides	2,0	1,0

TABLE 1. Basic characteristics of study population

Ultrasound measured peripheral ED was found in 77,2% (or 132 pts). Most of the pts with ED presented relative values of FMV between 0,060-0,090 , as shown in Figure 1.

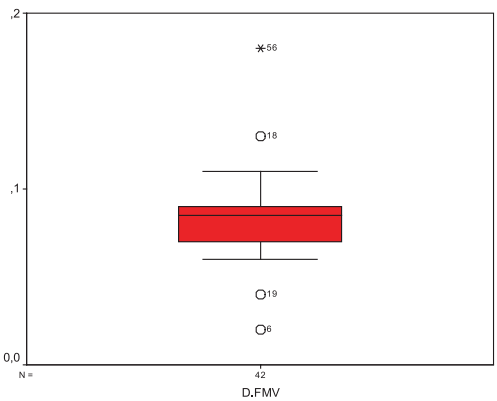

FIGURE 1. Distribution of FMV values

Gender differences and smoking differences in FMV values were not found (dFMV in men was 0,1251 vs. relative value of 0,09094 in women; dFMV in smokers was 0,1158 vs. value of 0,1097 in non-smokers) . Multivariate logistic regression model defined: age (OR 1,071, 95% CI 1,003 1,143) and plasma total cholesterol (OR 4,083 95%CI 1,080 17,017) as independent factors for ED (Table 2). Linear multivariate analysis presented duration of diabetes (Beta 0,173, Sig 0,024), and glycemia (Beta 0,132, Sig 0,044) to be associated independently with relative change of FMV value (Table 3).

Variables	B	Std. Error	Beta	T	Sig
Constant	0,473	0,121		3,920	0,000
DM.duration (years)	1,139E-02	0,005	0,173	2,280	**0,024**
Glycemia (mmol/L)	2,242E-02	0,013	0,132	1,740	**0,044**

TABLE 3. Multiple linear regression analysis for predictors of FMV value

Discussion

Endothelial dysfunction (ED) has been presented in type 2 diabetic population, previously. Almost 80% of our investigated patients presented endothelial dysfunction. Most of previous papers regarding FMV in diabetic patients were studied with an indepenendent vascular dilatation method after nitrate administration. Only few ones studied FMV, as measurement of endothelium dependent post reactive hyperaemia. Our results of change of brachial diameter are comparable with these ones (12). ED reflects the presence and extent of atherosclerosis. Therefore it is not be surprising that CAD risk factors are related to ED (13-15). Presence of ED correlates with plasma total cholesterol level according to our data. MRFIT study presented relationship between low HDL and diabetic atherosclerosis and prognosis of these patients (11). Cholesterol has been presented as one of the major risk factor for large artery disease, and its imbalance is in relationship with enhanced brachial reactivity. Other explanation is that presence of ED is due to the control of risk factors. Plasma total cholesterol level in type 2 diabetic patients, usually is uncontrolled. No association was found between ED and blood pressure, which could be explained with proper treatment of arterial hypertension. The process of aging of arteries makes those stiff and with low vasodilatative reactivity because of the enzymatic and mechanical differences. Presence of diabetes might impair endothelial function additionally (16).

Variables	B	S.E.	Wald	Df	Sig.	Exp(B)	95% CI Exp(B)	
							Lower	Upper
Age	0,068	0,033	4,199	1	0,040	1,071	1,003	1,143
Cholesterol	1,407	0,728	3,732	1	0,053	4,083	0,980	17,017
Non.HDL	-1,346	0,656	4,210	1	0,040	0,260	0,072	0,941
Constant	10,309	22,525	0,209	1	0,647	30001,		

TABLE 2. Multivariate logistic regression analysis for independent factors for ED

Diabetes duration has been presented as independent risk factor for development of large artery disease in type 2 diabetic pts, previously (17). ED is also determinate by diabetes duration, according own results. Value of glycemia of 1 mmol/L is responsible for 13% change of FMV, by our data. The relative change of endothelial impairment correlates with hyperglycemia (18). In vivo studies revealed that hyperglycemia affects multiple mechanisms that exchange oxidation, thrombosis and inflammation (19). Clinical studies are less comprehensive (12). None of these articles found independent relation between continuous value of glycemia and FMV. Our results approve thesis that endothelial dysfunction is in correlation with glycemia. Endothelial dysfunction in type 2 diabetes represents the cumulative effects of risk factors: hyperglycemia and cardio-metabolic risk factors on the vessels (20). Diabetic pts with more than one of risk factors presented severe atherosclerosis angiographicaly and a high risk for future vascular events (21-22). Our results contribute and raise the point whether assessment of endothelial dysfunction in type 2 diabetes can be used as a therapeutic target and consequently in a risk stratification of these patients.

Study limitation

This study does not have a large population group. Underestimation and overestimation of lumen diameter couldn't be excluded. It relates to several factors, as first, time of second measurement of lumen diameter after cuff deflation, and as second location of cuff. Using beat-to-beat analysis may lead to more precise estimation of FMV of brachial artery.

Conclusion

Ultrasound measurement found peripheral ED in 77,2% of pts with type 2 diabetes and coronary artery disease. Risk factors for ED in type 2 diabetes are same as those ones for large artery disease. Our study defined age, duration of diabetes and risk factors: glycemia and plasma total cholesterol, for determinants of ED. Estimated factors that influence FMV: glycemia and cholesterol, might be potential therapeutic targets for presented endothelial dysfunction in type 2 diabetic patients with coronary artery disease.

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