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RISK FACTORS FOR DEVELOPMENT OF PERIPHERAL AND CAROTID ARTERY DISEASE AMONG TYPE 2 DIABETIC PATIENTS

Bosevski M., Georgievska-Ismail Lj., Tosev S., Borozanov V.

University Cardiology Clinic, Medical Faculty, Skopje, Macedonia

A b s t r a c t: The study was aimed to define the risk factors for development of peripheral arterial (PAD) and carotid artery disease (CARD) among type 2 diabetic patients (T2D).

The study population consisted of 30 patients diagnosed with type 2 diabetes and absent vascular disease. the mean age of the study population was 53.3 $\pm$ 7.3 years. 60% of patients were women and 40% of them men.

Patients were followed up for three years for development of peripheral and carotid artery disease. Peripheral arterial disease (PAD) was defined by ankle-brachial index < 0.9 or > 1.3. Carotid arterial disease was defined if carotid plaque or stenosis (> 50%) presented. We built a multivariable logistic regression analysis to define the factors of development of vascular disease and a multiple linear regression analysis to identify the factors associated independently with numerous values of carotid IMT and ABI.

Development of PAD and CARD were registered in 43.8% of patients. Progression of carotid IMT was found in 62.5 % of pts. Progression of PAD was predicted by HDL – cholesterol and urea, systolic blood pressure and diabetes duration. Progression of carotid IMT was determinate with: BMI, weight, diastolic blood pressure and age.

Our study defined risk factors that independently influence the development of PAD and CARD in pts with T2D. This data has clinical usefulness in the improvement of prevention and in optimizing the treatment of type 2 diabetic patients.

Key words: peripheral arterial disease, ankle-brachial index, carotid plaque, carotid stenosis, IMT, type 2 diabetes.

Introduction

The patients had type 2 diabetes were referred for a high incidence of progression of peripheral arterial (PAD) and carotid artery disease (CARD). Previous studies revealed that the incidence of progression of new PAD was at 2.1% estimated over a year, and a worsening of ankle-brachial indexes in 40% of this population over a period of 3 years. [1] Age, systolic blood pressure, lipid profiles, diabetes duration, smoking and albuminuria were defined as predictors for PAD progression in type 2 diabetic (T2D) pts. [2] DECODE and UKPDS referred for hyperglycaemia as an independent factor for the occurrence of diabetic vascular disease. Interventional studies on carotid atherosclerosis in T2D pts showed that only reduction in blood pressure and blood lipids in these pts could stop its progression (SECURE, PREVENT, LIPID, ACAPS). [3] Reduction of blood pressure by a 5 mmHg leads to a regression of carotid IMT by 0.01 mm/year, according to Wang's meta-analysis. [4]

Despite all investigations on the progression of carotid and peripheral atherosclerosis in T2D patients, drugs to stop their progression could not be found. The determination of predictors for the progression of PAD and CARD in T2D is still current.

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Patients and methods

The study population consisted of 30 patients with diagnosed type 2 diabetes. The absence of coronary artery disease was defined by electrocardiography and exercise stress test, and peripheral and carotid artery disease by vascular ultrasound.

The mean age of the study population was 53.3 $\pm$ 7.3 years. 60% of patients were women and 40% of them were men.

Pts were followed-up for three years for development of peripheral and carotid artery disease by *vascular ultrasound.*

Peripheral arterial disease (PAD) was defined by ankle-brachial index < 0.9 or > 1.3. Carotid arterial disease was defined if carotid plaque or stenosis (> 50%) presented.

Evaluation for carotid artery disease was done by ultrasound system HP Agilent S4500. Carotid IMT was measured by B-mode ultrasound using a linear transducer (7.5–10 MHz) and presented as a mean value of three measurements

from both sides. Carotid IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans, with the first line representing the lumen-intimal interface and the second line representing the collagen-containing upper layer of the adventitia. IMT with a value equal to or great than 0.8 mm was defined as increased IMT. Plaque was defined as a localized thickening lesion (=/> 1.1mm). In each longitudinal projection, the site with the greatest thickness (including plaque) was detected along the vessel from the common carotid artery to the internal carotid artery. the observer was blind to the patients' risk factors.

Continuous Doppler was used for determination of the lowest and median value of the ankle-brachial index (ratio of ankle to brachial pressure). There was nointer-observer disagreement with regard to ultrasound interpretation, as reported previously.

Physical examination of was done on pts regarding their blood pressure, weight, height, waist and body mass index (BMI). 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 (HTA) 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 the patient wearing lightweight clothing and no shoes. Weight was presented in kilograms (kg) and body mass index (BMI) in kg/m^2. Waist and hip circumferences were measured using a plastic tape-measureat the level of the umbilicus and of the major trohanter. According ATP III criteria: hipertriglyceridaemia was defined as a value of triglycerides >/= 1.7 mmol/L and a low HDL as a value of < 1.03 mmol/L. Obesity was defined as BMI > 30 kg/m2 and increased weight as BMI > 25 and < 29.9 kg/m2. Waist circumferences > 88 cm in women and > 102 cm in men was defined as abdominal obesity.

Biochemical enzymatic methods with a spectrophotometre at 30^0C were used for determination of total cholesterol, HDL-cholesterol and triglycerides. LDL was determined with the Friedewald formula. Enzymatic-photometric methods with glucose dehydrogenase were used for the determination of fasting glycemia.

A multivariable logistic regression analysis was built to define the factors of development of vascular disease. Multiple linear regression analysis was done to identify the factors associated independently with numerous values of carotid IMT and ABI.

The study was conducted according to the Helsinki declaration for clinical studies.

Results

A high prevalence of metabolic risk factors was found in the patients (Table 1). Arterial hypertension and dyslipidaemia were found in 90% of patients. Obesity was found in 40%, and increased weight in 43.3% of the patients. Hypertriglyceridaemia was found in 80%, and low HDL cholesterol in 26.7% of patients.

Table 1 – Табела 1

Basic characteristics of study population
Основни карактеристики на испитуваната популација

Characteristics	No. of pts (%)
HTA	27 (90%)
Dyslipidaemia	27 (90%)
Physical inactivity	3 (10%)
Microvascular complications	4 (13,3%)
Increased weight	13(43,3%)
Obesity	12 (40%)

The population had a mean diabetes duration of 7.5 years and the mean value of glycemia was 8.47 $\pm$ 2.20 mmol/L (Table 2). Higher mean values of systolic, diastolic blood pressure, BMI, plasma cholesterol, LDL – cholesterol and triglycerides were noticed.

Table 2 – Табела 2

Characteristics of study population
Карактеристики на испитуваната популација

	Min	Max.	Mean	Std. Dev.
DM.duration	1,00	15,00	7,53	3,36
Syst.TA	120,00	190,00	149,17	16,19
Diast.TA	80,00	110,00	88,67	6,69
Weight	50,00	116,00	80,93	14,37
BMI	20,00	45,00	30,15	5,49
Waist	49,00	138,00	94,70	14,16
Chol	4,10	8,90	5,99	1,16
HDL	0,60	2,10	1,08	0,29
Non HDL	3,10	7,50	4,95	1,11

LDL	2,20	6,30	3,66	0,84
Tr	0,90	4,60	2,27	,91
Glycaemia	5,50	13,60	8,47	2,20

Legend: Syst (Diast) TA = systolic (diastolic) TA, Chol = total cholesterol, Tr = triglycerides

66.7% of pts received Aspirin, and 73.3% of them statins. Almost 36.7 % were on insulin therapy, and 56.7% on oral antidiabetic therapy.

The patients were followed up for three years for the onset of PAD and CARD. PAD was defined as a pathological value of ABI (< 0.9, or > 1.3). CARD was defined as the occurrence of carotid plaque or stenosis.

In 43.8% of pts the development of PAD was noticed. All patients had asymptomatic PAD. the occurrence of carotid plaque was noticed in 43.8%. the progression of carotid IMT was defined in 62.5% of patients.

In the multivariate logistic regression analysis for development of PAD obesity and creatinin were entered, but none revealed an independent value. After Insulin was put in the model, it revealed with predictive value (Table 3).

Table 3 – Табела 3

Predictors for PAD progression
Прeдскажувачи на прогресијата на ПАБ

Varijables	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.IEXP (B)	
							Lower	Upper
Obesity	1,828	1,616	1,279	1	,258	6,219	,262	147,731
Creatinine	-,297	,160	3,437	1	,064	,743	,542	1,017
Insulin	-2,996	1,351	4,917	1	,027	,050	,004	,706
Constant	1,609	1,095	2,158	1	,142	4,999		

The multiple linear regression analysis was done after variables with continuous values were put in the model (Table 4). A minimal value of ABI (ABImin) was associated with HDL-cholesterol and urea and a mean value of ABI (ABIx) with diabetes duration. the difference in ABI value between the beginning and end (dABI) was independently associated with systolic blood pressure, and its difference in value over a year with HDL-cholesterol.

A maximal value of carotid IMT (IMTm) was predicted with BMI, a first mean value with (IMTx) with diastolic blood pressure. Change in the value of IMTx was predicted with age, weight and BMI (Table 4).

Plot figures presented diabetes duration with the lowest residual value for dABIx, and BMI for dIMTx. Because of this, these parameters were presented as the most important factors for the progression of peripheral and carotid atherosclerosis (Figure 1 and 2).

Table 4 – Табле 4

Multiple linear regression analysis for dABI and dIMT
Мултипна линеарна регресиона анализа за dABI и dIMT

Model		B	Std. Error	Beta	t	Sig
ABI min	Constant	-,666	,357		-1,864	0,121
	HDL	1,312	,201	**1,206**	6,538	**0,001**
	Urea	0,130	,036	**0,674**	3,656	**0,015**
dABIm	Constant	-,189	,096		-1,969	0,120
	HDL	,657	,020	**1,220**	32,581	0,000
	Urea	4,849E-02	,004	**0,507**	13,182	0,000
	Syst.TA	-2,850E-03	,001	**-0,149**	-4,918	**0,008**
dABIx/y	Constant	-6,176E-02	,070		-,886	0,410
	HDL	,197	,063	**0,788**	3,135	**0,020**
dABIx	Constant	,171	,026		6,690	0,001
	DM.duration	-1,612E-02	,004	**-0,867**	-4,260	**0,005**
IMTm	Constant	2,042	,401		5,093	0,002
	BMI	-3,452E-02	,014	**-0,709**	-2,466	**0,049**
IMTx	Constant	-1,513	,925		-1,636	0,153
	Diast.TA	2,710E-02	,010	**0,726**	2,585	**0,041**
dIMTx	Constant	-,890	,157		-5,665	0,002
	Weight	8,956E-03	,001	**1,200**	7,541	**0,001**
	Age	4,801E-03	,002	**0,490**	3,079	**0,028**
dIMTx/y	Constant	-,214	,018		-11,871	0,000
	Weight	4,259E-03	,000	**1,139**	12,082	0,000
	BMI	-3,804E-03	,001	**-0,478**	-5,480	**0,005**

Legend: Syst (Diast) TA = systolic(diastolic) TA, dABIx/y (dIMTx/y) = change of mean ABI (IMT) per year.

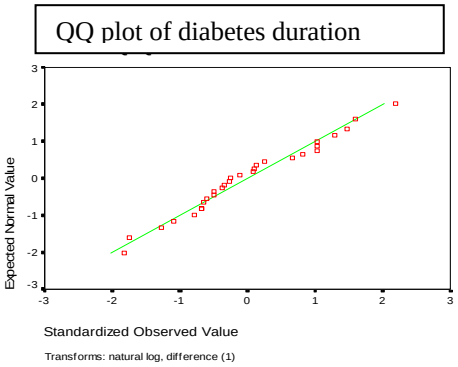

Figure 1 – Distribution of dABIx according to diabetes duration

Слика 1 – Распределба на вредностите на dABIx според времетраењето на дијабетот

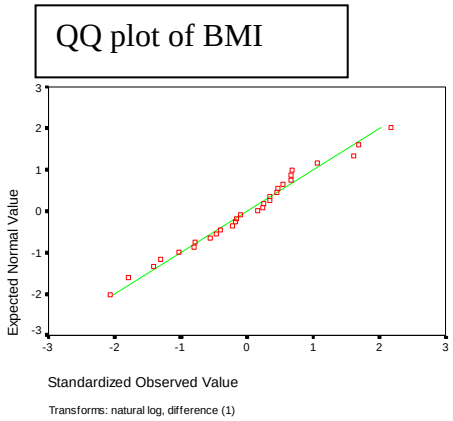

Figure 2 – Distribution of dIMTx according to BMI

Слика 2 – Распределба на вредностите на dIMTx според BMI

Discussion

Previous studies have not shown a difference in prevalence in risk factors of arterial disease with type 2 diabetic population if PAD whether was present or not. [5] Diabetes duration, glycaemic control, age, smoking, albuminuria, arterial hypertension and dyslipidaemia have been recognized as risk factors for the occurrence of PAD in the diabetic population. [6, 7]

Lipid profile and arterial hypertension were revealed as factors for the progression of ABI, according our results. In the type 2 diabetic populations

there was a low rate of mortality, risk factors from metabolic group have greater importance. Among pts with PAD and T2DM and excessive risk smoking and albuminiria were of a greater importance. [8]

Insulin administration is an independent factor for the development of PAD. The role of Insulin is prophylactic in the development of arterial disease in diabetic pts. Its use defined those pts with poor glyco-metabolic control that explained its independent role. [9, 10]

The maximal value of carotid IMT was determined with BMI, and mean IMT with diastolic blood pressure, according to multiple linear analyses. In the early phase of atherosclerosis, the influence of arterial hypertension is dominant. That is the explanation for the independent role of diastolic blood pressure in the sclerosis process in vessels. [11, 12] EVA and CAPS studies revealed BMI as representing metabolic disturbances in T2DM and as an independent factor for the progression of carotid atherosclerosis. [13, 14] The same studies presented age as a factor influencing carotid progression. This was confirmed by our results on the population with T2DM.

The results of the study have limitations because of the number of pts enrolled in the study.

Conclusions

Our data presented development of PAB and CARB in 43.8% of pts. the rogression of PAB is determinate with HDL–cholesterol and urea, systolic blood pressure and diabetes duration, and progression of carotid IMT with: BMI, weight, diastolic blood pressure, age and endothelial dysfunction. These results might prove helpful in the prevention of pts with type 2 diabetes.

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Р е з и м е

ФАКТОРИ НА РИЗИК ЗА РАЗВОЈ НА ПЕРИФЕРНА И КАРОТИДНА АРТЕРИСКА БОЛЕСТ КАЈ ПАЦИЕНТИ СО ТИП 2 ДИЈАБЕТ

Бошевски М., Георгиевска-Исмаил Љ., Тошев С., Борозанов В.

Универзитетска клиника за кардиологија, Медицински факултет, Скопје, Р. Македонија

Студијата имаше за цел дефинирање на факторите на ризик за развој на периферна и каротидна артериска болест кај пациентите со тип 2 дијабет.

Испитуваната популација ја сочинуваа 30 пациенти со дијагностициран тип 2 дијабет и отсутна васкуларна болест. Средната возраст на испитаниците беше 53,3 $\pm$ 7,3 години, 60% беа жени, а 40% мажи.

Пациентите беа следени три години во однос на развој на периферна и каротидна артериска болест. Периферната артериска болест (ПАБ) беше дефинирана како вредност на глуждно-надлактен индекс (АБИ) < 0,9 или > 1,3. Каротидната артериска болест (КАРБ) беше дефинирана како каротидна плака и стенози > 50%. Беа изведени мултиваријантни логистички регресиони анализи за дефинирање на фактори на развој на васкуларна болест и мултипни линеарни анализи за одредување на фактори што независно ја одредуваат нумеричката вредност на АБИ и дебелината на интима-медијата (ИМТ).

Развојот на ПАБ и КАРБ беше регистриран кај 43,8% од пациентите. Прогресијата на каротидната ИМТ беше најдена кај 62,5% од пациентите. Прогресијата на ПАБ беше претскажана со HDL – холестеролот, уреата, систолниот крвен притисок и времетраењето на дијабетот. Прогресијата на каротидната ИМТ беше предодредена со: БМИ, тежината, дијастолниот крвен притисок и возраста.

Студијата ги дефинира факторите на ризик што влијаат независно на развојот на ПАБ и КАРБ во популацијата со тип 2 дијабет. Овие наоди имаат клиничко значење во однос на подобрувањето на превенцијата и оптимизирањето на лекувањето на овие пациенти.

Corresponding Author:

Bosevski M.,
University Cardiology Clinic,
Medical Faculty,
1000 Skopje, R. Macedonia
Tel. 389 2 3147918, 389 2 3132373

E-mail: marijanbosevski@yahoo.com