

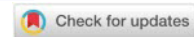
DEVELOPMENT OF OCCLUSIVE ARTERIAL DISEASE OF LOWER EXTREMITIES IN PATIENTS WITH DIABETES MELITUS TYPE 2 IN CORRELATION WITH HBA1C LEVEL AND INDEPENDENT RISK FACTOR

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Abstract: In clinical practice, the development of peripheral artery complications in the lower extremities is a significant issue among patients with type 2 diabetes. The progression of stenotic-occlusive disease can be predicted based on the SCORE risk factor assessment and HbA_{1c} levels. Color Doppler findings are crucial for evaluating hemodynamic flow in the arteries of the lower extremities.

Aim: To determine HbA_{1c} levels in patients with stenotic-occlusive disease of the lower extremities, correlate risk factor scores and HbA_{1c} levels in the progression of stenotic-occlusive disease, and assess the significance of elevated HbA_{1c} levels in relation to the clinical grade of stenotic-occlusive disease.

Patient and methods: The study included 113 patients with type 2 diabetes (52.1%) and 104 non-diabetic patients (47.9%) as the control group, making a total of 217 participants. Both groups were classified as high-risk due to the presence of independent risk factors such as hyperlipidemia, smoking, obesity, and arterial hypertension. When the cumulative SCORE risk factor for the total group of participants (n=217) was analyzed, the results indicated a high level of risk with statistical significance, p<0.0001.

Results: Patients with predominantly occlusive changes in the type 2 diabetes group had HbA_{1c} values of 8.25%, which was significantly higher compared to those with stenotic changes, whose HbA_{1c} values were 7.3% (p=0.002). According to the SCORE tables, a value >5% indicates high risk for developing cardiovascular disease, while a SCORE value of 7% was identified as a predictor for disease progression in patients with type 2 diabetes, with high significance (p=0.0001). In the non-diabetic group, lower values of peak systolic velocity (PSV) in the superficial femoral artery (p=0.051) were observed. In the type 2 diabetes group, PSV values in the profunda femoral artery were lower (p=0.053), while significantly lower PSV values were recorded in the anterior tibial artery (p=0.008). Occlusive disease of the lower extremity arteries was present in 89.6% of cases in the type 2 diabetes group, with 90 patients affected, which was significantly higher compared to stenotic disease (p<0.0001).

Conclusion: Subjects in the DM2T group with dominant occlusive changes had significantly higher HbA_{1c} values compared to the HbA_{1c} group with dominant stenotic changes p<0,002. The risk factor score for the examined group, DM2T, was 7% (SCORE of high cardiovascular risk), and in the control group, non-diabetics, it was 8%, and both groups are high risk. HbA_{1c} can be a predictor for the development of occlusions on the arteries of the lower extremities in subjects with DM2T.4. DM2T group subjects with occlusive changes had high HbA_{1c} values, ≥8.25.

Keywords: diabetes mellitus type 2, SCORE, HbA_{1c}, lower extremities, complications of stenotic-occlusive disease

Field: Medical sciences and Health

1. INTRODUCTION

Macrovascular diabetic angiopathy is a chronic complication of diabetes on the main arterial blood vessels with the terminal consequence regarding a flow reduction at the level of the main arteries. The process of atherosclerosis is central pathological mechanism in the development of macrovascular diabetic angiopathy, which in this type of diabetic angiopathy has a clear and proven basis in the so-called "accelerated atherosclerosis" (Hense, 2003). Accelerated atherosclerosis in diabetics is associated with diabetes and other risk factors: arterial hypertension, smoking, hyperlipoproteinemia, obesity (Creager, 2009). Diabetes mellitus per se significantly increases the risk in development of cardiovascular disease (Laing, 2003). In Europe, the SCORE table (Systematic Coronary Risk Evaluation) is used to determine the total 10-year cardiovascular risk. Higher values of hemoglobin HbA_{1c} indicate poor regulation of diabetes and increase the risk of micro- and macrovascular complications, including occlusive disease of the arteries of the lower extremities (Viigimaa, 2020). Color Doppler echosonography is used to evaluate the hemodynamic changes in the arteries, which is essential for the hemodynamic assessment of stenotic-occlusive disease. We believe that the combination of these clinical variables; glycohemoglobin

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HbA1c, five clinical variables that are included in the SCORE risk tables, with hemodynamic diagnostics (Color Doppler echosonography), could have a clear prediction of the development and complications of stenotic-occlusive disease in people with diabetes mellitus type 2. Furthermore, increased level of glycohemoglobin HbA1c, with increased risk factors and verified hemodynamic diagnostics (using Color Doppler echosonography), they can determine the gradation of stenotic-occlusive disease and indicate the risk of developing further complications (Rehman, 2023).

2. PATIENT AND METHODS

The research included 217 patients with atherosclerotic stenotic-occlusive disease of the main arteries of the lower extremities treated at the Clinic for Vascular Diseases and the Clinic for Endocrinology, Diabetes and Metabolic Diseases of Clinical Center Sarajevo University. Research group was composed of 113 patients with arterial atherosclerotic stenotic-occlusive disease and diabetes mellitus type 2. Control group included 104 patients, non-diabetics, with arterial atherosclerotic stenotic-occlusive disease. Inclusion criteria: patients with type 2 diabetes, age between 40-65 years, both sexes, patients with symptomatic stenotic-occlusive disease of the lower extremities, with clinical stage FII-IV. Exclusion criteria: patients with clinical stage FI, patients with cardiac decompensation, oncology patients, on corticosteroid therapy and intervention (PTA) and surgery on blood vessels.

Methods

At the reception for each patient, anamnestic data, age and sex, duration of diabetes mellitus, as well as the previous quality of glycemic regulation were taken. Clinical examination: Standard clinical examination, after the anamnesis a physical examination. The subjects were subjected to multiple measurements of blood pressure, ECG, body mass index (BMI) was determined, laboratory results were taken. The score of multiple risk factors was determined - SCORE table of high risk.

Diagnostic procedures - Color Doppler of the main arteries of the lower extremities, Arteriography of the lower extremities - DSA according to Seldinger, CT-angiography.

Procedures planned according to research objectives: Comparison of clinical findings in two groups, clinical stage and type of stenotic-occlusive disease of the lower extremities, comparison of Color Doppler hemodynamic parameters: highest systolic flow velocity (PSV) according to the following reference values: a.tib.ant. - 35 cm/s, a.tib.post. - 50 cm/s, a.poplitea - 60 cm/s, a.profunda fem. - 90 cm/s, a.fem.superfit - 90 cm/s, a.fem.superfit - 90 cm/s, a.iliaca ext.- 110 cm/s

Comparison of arteriographic findings in two groups of subjects: a) stenotic changes, b) occlusive changes.

Determination of the clinical stage of the disease according to the Fontaine classification (II to IV), the score of risk factors according to the SCORE table.

Statistic analysis

For the statistical analysis of the obtained data, the software package SPSS for Windows (version 19.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excell (version 11. Microsoft Corporation, Redmond, WA, USA) was used. We analyzed the nominal and ordinal variables in the research χ^2 test. For continuous variables in the study, we first analyzed the symmetry of their distribution using the Kolmogorov-Smirnov test. Since the distribution of continuous variables deviated statistically significantly ($p < 0.05$) from a symmetrical (Gaussian) distribution, we used the median and interquartile range (rank) to display the mean value and the measure of dispersion, and for their comparison non-parametric tests (Mann-Whitney U test, Kruskal-Wallis test). Using binary logistic regression, we examined the impact of individual variables on the prediction of binary: occlusion of arteries (1-Yes; 0-No), that is, we examined the chance of occlusion. The reliability of the testing model was tested by the Hosmer&Lemeshow test, the usability of the model was tested by the Cox&SnellR2 and NagelkerkeR2 tests. For the limit of statistical significance, we took the value $\alpha = 0.05$. We made decisions about accepting or rejecting hypotheses in the respective tests according to the p value of the statistical test ($p \geq \alpha$ hypothesis is accepted, $p < \alpha$ hypothesis is rejected).

3. RESULTS

A total of 217 subjects were included in the study, of which 113 (52.1%) patients with diabetes mellitus type 2 (hereinafter referred to as DM2T) and 104 (47.9%) non-diabetic patients. Both groups had more male than female pts. The gender structure among subjects with DM2T and non-diabetics was uniform, $p = 0.149$. Age structure in both groups were equal, the differences in age between the groups were not statistically significant, $p = 0.511$. More than half were smokers in both groups. The difference in the

percentage of smokers between two groups was statistically significant, non-diabetics vs. DM2T, $p=0.001$. The dominant proportion of subjects in both groups had hypertension, which was significant, $p<0.01$. A larger proportion of subjects in both groups was not in the obese category, $p=0.137$. Hyperlipidemia as a risk factor dominated in both groups of subjects, without statistical difference between groups, $p=0.076$. Subjects in the F II clinical stage were equally represented in both groups, there was a numerical difference of -12, however, statistically, the difference was insignificant, $p<0.18$. Subjects in the F III clinical stage were significantly more represented in the group of non-diabetics, statistically significant, $p<0.01$. Subjects in the F IV clinical stage were more significantly represented in the DM2T group, statistically highly significant, $p<0.001$ (Table 1).

Table 1. Distribution of stenotic-occlusive disease - clinical stage of the disease.

Clinical stage Fontaine (F) stage	Groups of patients		P (Mann-Whitney test)
	DM2T (N-113)	Non-diabetic (N-104)	
F II (intermittent claudication)	43	55	No.diff N-12 $P<0,18$
F III (ischemic, pain at rest)	19	29	$P<0,01$
F IV (terminal ischemia, gangrene)	51	20	$P<0,001$

Source: Author Balić Š.at. all. (2024)“ Development of occlusive arterial disease of lower extremities in patients with diabetes melitus type 2 in correlation with HbA1c levels and independent risk factor“

Average PSV flow rates through a. iliaca externa ($p=0.188$), a. femoris communis ($p= 0.812$), a. poplitea ($p= 0.383$), a. tibialis posterior ($p= 0.236$) did not statistically differ between groups. Average flow velocities through a. femoris superficialis were lower in subjects from the non-diabetic group, $p=0.051$. Average PSV flow rates through a. femoris profunda were significantly lower in subjects with DM2T, $p=0.053$. Average PSV flow rates through a.tibialis anterior were statistically significantly different between groups, $p=0.008$ (Table 2)

Table 2. The average values of the highest systolic flow velocity (PSV) of the main arteries of the lower extremities are shown.

	Groups of pateints		P(Mann-Whitney test)
	DM2T *Mediana (25ti-75ti percentil)	Non-diabetic*Mediana (25ti-75ti percentil)	
a.iliaca externa	87,0(68,5-109,0)	97,0(87,0-105,5)	0,188
a.femoris communis	82,0(60,0-98,0)	85,5(8,0-95,5)	0,812
a.femoris superficialis	47,0(31,0-80,0)	35,0(31,0-48,0)	0,051
a.profunda femoris	28,0(23,0-43,0)	39,5(27,7-51,3)	0,053
a.poplitea	28,0(24,0-45,0)	33,0(25,0-37,3)	0,383
a.tibialis posterior	20,0(14,0-31,0)	23,0(15,0-29,0)	0,312
a.tibialis anterior	16,0(11,0-23,0)	24,0(12,0-32,0)	0,008

Source: Author Balić Š.at. all. (2024)“ Development of occlusive arterial disease of lower extremities in patients with diabetes melitus type 2 in correlation with HbA1c levels and independent risk factor “

In the DM2T group, $n=113$, there were more subjects with occlusive changes on the arteries 90 (79.6%) compared to subjects with stenosis 23 (20.4%), the difference was highly significant, $p <0.001$. 4 out of 5 subjects with DM2T had manifested occlusions, while every fifth had stenoses on the blood vessels (Table 3). The average values of HbA1c were statistically significantly different between the groups with occlusive changes vs. stenotic changes. Subjects with dominant occlusive changes had

higher average HbA1c values of 8.25% (7.37-9.4), compared to the HbA1c values of the group with dominant stenotic changes, 7.3% (6.9-7.7), statistically significant, $p < 0.002$ (Table 3). Average cholesterol values do not differ statistically between the group with occlusive changes vs. stenotic changes, $p = 0.972$. Average values of HDL-cholesterol did not differ statistically between the group with occlusive changes vs. stenotic changes, $p = 0.126$. Average values of LDL-cholesterol did not differ statistically between the group with occlusive changes vs. stenotic changes, $p = 0.985$, the values were equalized. The average values of the risk factor score did not differ statistically between the groups with occlusive changes vs. stenotic changes, $p = 0.791$ (table 3).

Table 3. Values of HbA1c, Cholesterol, HDL-cholesterol, LDL-cholesterol, risk factor score, in subjects with DM2T

	DM2T N (113)		
	Subjects with predominant occlusive changes	Subjects with predominate stenotic changes	P (MannWhitnay test)
	90,0 (79,6%)	23(20,4%)	
*HbA1c %	8,25(7,37-9,4)	7,3(6,9-7,7)	0,002
*Holesterol mmol/L	4,4(3,55-4,92)	4,2(3,6-4,9)	0,972
*HDL mmol/L	0,91(0,71-1,01)	0,96(0,96-1,1)	0,126
*LDL mmol/L	2,7(2,2-3,17)	2,4(1,7-2,7)	0,985
Skor rizikofaktora %	7,0(3,75-10,25)	8,0(3,0-12,0)	0,791

* average values are presented as medians and ranks (25th and 75th percentiles)

Source: Author Balić Š.at. all. (2024)“ Development of occlusive arterial disease of lower extremities in patients with diabetes melitus type 2 in correlation with HbA1c levels and independent risk factor “

Binary logistic regression was used to examine the predictive significance of HbA1c and the risk factor proximity to the possibility of developing occlusion in relation to stenosis of the arteries of the lower extremities in subjects with DM2T (n=113). The result of the Hosmer&Lemeshow test $\chi^2=11.55$, $p=0.152$, showed the claim that the model for predicting occlusion was good. The usability of the model according to Cox&Snell was $R^2=0.386$ and Nagelkerke $R^2=0.535$, that is, the model explained between 38.6% and 53.5% of the variance (Table 4). HbA1c can be a predictor for the development of occlusions on the arteries of the lower extremities in subjects with DM2T, $p=0.006$, $EXP(B)=0.546$. If the HbA1c values increase by 1%, the chance of developing occlusion on the lower extremities increases by 45% in our sample, $n=113$, while in the population of such subjects the chance of occlusion ranges between 64 and 16% (Table 4). The values of the risk factor score in our sample are in the area of high cardiovascular risk, for occlusions the risk score was 7.0%, for stenoses 8%. However, the difference between the score values, in a predictive sense, did not show a statistically significant prediction for the development of occlusion, in relation to the development of stenosis, in DM2T, $p=0.635$, which is shown in (Table 4).

Table 4. Predictive significance of HbA1c and near risk factors for the development of occlusion in DM2T

Model	B	S.E.	Wald	df	P	Exp(B)	95,0% 95.0% int. confidence for EXP(B)		
							Lower limit	Lower limit	
DM2T N=113	HbA1c%	-,606	,220	7,582	1	,006	0,546	,36	,84
	Risk factor score%	-,025	,053	,225	1	,635	,975	,880	1,081
	Constant	3,630	1,793	4,098	1	,043	37,715		

B: unstandardized coefficient; SE: standard error; Wald: standardized coefficient; df: number of degrees of freedom; EXP(B): chance quotient; p: significance

Source: Author Balić Š.at. all. (2024)“ Development of occlusive arterial disease of lower extremities in patients with diabetes melitus type 2 in correlation with HbA1c levels and independent risk factor “

4. DISSCUSION

Stenotic-occlusive disease of the arteries of the lower extremities is one of the most common complications of atherosclerosis. Arterial stenotic-occlusive disease leads to a reduction in blood flow and has different clinical stages, and the most severe stage is a critical reduction of hemodynamic flow with tissue ischemia or gangrene. (Myers, 2014) In our work, we observed that patients with type 2 diabetes had a terminal clinical stage diseases (F IV), which indicates that DM2T is an independent risk factor for cardiovascular diseases and that diabetics are at a higher risk compared to non-diabetics. The UKPDS (United Kingdom Prospective Diabetes Study) monitored the role of hyperglycemia in the development of stenotic-occlusive disease in type 2 diabetes (DM2T), taking into account other potential risk factors. In the results of the study, poor glycemic control, which was assessed through HbA1c, was associated with an increased risk of developing stenotic-occlusive disease, independent of other risk factors, including age, increased blood pressure, reduced HDL-cholesterol, smoking, pre-existing cardiovascular disease (Jude, 2010; Cardoso 2020). These data shows that the mesured flows in both groups of patients in all arteries of the lower extremities are significantly lower compared to the reference values. This shows that risk factors such as diabetes, arterial hypertension, smoking, hyperlipoproteinemia significantly affect the development of stenotic-occlusive disease (Faselis, 2020). Eraso et al. (2014) conclude that risk factors impact development of atherosclerosis in diabetics, that risk factros multiply the effect of one on the other, that they accelerate the process of atherosclerosis, and that those patients who, in addition to diabetic angiopathy, also have coronary ischemic disease and cerebrovascular disease. In our research, in the group of subjects with DM2T, the number of patients with stenosis was n=23 (20.4%), and with occlusion n=90 (89.6%), which indicates a high percentage of atherosclerotic changes of the occlusion type on main arteries of the lower extremities. Subjects with dominant occlusive changes have higher average values of HbA1c 8.25% (7.37-9.4%) compared to HbA1c values of the group with dominant stenotic changes 7.3(6.9-7.7)%. Average values HbA1c are statistically significantly different between the examined groups, p=0.002. In both groups, Hba1c values were above 7%, which represents a risk for the development of stenotic-occlusive disease, while in patients with dominantly occlusive changes, HbA1c is significantly higher compared to patients with dominantly stenotic changes. In our research, HbA1c can be a predictor for the development of occlusions on the arteries of the lower extremities in diabetics with DM2T, p=0.006, EXP(B)=0.546. If HbA1c values increase by 1%, the chance of developing occlusion on the lower extremities increases by 45% in our sample, n=113, while in the population of such subjects the chance of occlusion ranges between 64 and 16% (Paladino, 2020). Scicali R. et al. (2016) concluded that peripheral arterial disease is a frequent cardiovascular complication in DM2T. The risk of developing peripheral arterial disease is much higher in patients with diabetes, and the disease is more severe and progresses faster than in non-diabetics. In addition, the presence of peripheral arterial disease is a strong marker of increased cardiovascular risk (Perk, 2012).

The UKPDS study demonstrated that a 1% reduction in HbA1c reduced the risk of peripheral arterial disease by 43%, myocardial infarction by 14%, cerebrovascular insult by 12%, diabetes-related mortality by 21% and microvascular disease by 37% (Ryden, 2007). Subjects with occlusive changes have average values of the risk factor score SCORE=7.0 %(3.75-10.25), and on average they are lower than the average values of the risk score of the group with stenotic changes SCORE=8.0 %(3.0-12 ,0). The average values of the risk factor scores do not differ statistically between the examined groups, p=0.791. In patients with dominantly stenotic and dominantly occlusive changes, the risk factor score was high, given that a SCORE >5% is considered a high cardiovascular risk (AHA/ACF, 2011).

5. CONCLUSION

Subjects in the DM2T group with dominant occlusive changes had significantly higher HbA1c values compared to the HbA1c group with dominant stenotic changes. The risk factor score for the DM2T group, was 7% (SCORE of high cardiovascular risk), and in the control group, non-diabetics, it was 8%, and both groups are high risk groups. Hight level of HbA1c can be a predictor for the development of occlusions on the arteries of the lower extremities in subjects with DM2T. Subjects in the DM2T group with occlusive changes had high HbA1c values, ≥8.25. In the hemodynamic clinical parameter, the highest systolic velocity (PSV-peak systolic velocity) on the arteries of the lower extremities was significantly lower compared to normal PSV values, in both groups. PSV values of a. femoris profunda and a. tibialis ant. were significantly lower in the DM2T group.

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