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GLYCOSYLATED HEMOGLOBIN AS A PREDICTOR FOR THE OCCURRENCE OF MACROANGIOPATHIC COMPLICATIONS IN DIABETIC PATIENTS FROM BIHOR COUNTY

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Abstract

Background and Aims: *Prospective studies showed that long-term hemoglobin A1c (HbA1c) levels correlate directly with the risk of developing and progression of diabetic complications. The aim of the study was to evaluate the correlation between metabolic control and HbA1c variability with macrovascular complications and assess the role of HbA1c as an independent predictive factor for the occurrence of macrovascular complications in diabetic patients from Bihor County, Romania.* ***Material and method****: The study was conducted for a 5 years period (2007-2011) and included 321 diabetic patients with no evidence of macroangipathic complications. During the follow-up all the major vascular events were recorded.* ***Results****: At the end of the study a total of 85 chronic macrovascular complications were reported. Distribution plots show significantly higher incidence of vascular complications in patients in the group with poor glycemic control. Multivariate analysis showed that HbA1c can be considered an independent predictor of atherosclerotic complications as well as atherosclerotic complications risk score. The variability of HbA1C was not an independent predictor for macroangiopathic complications (p=0.78).* ***Conclusions:*** *Overall glycemic control was the most important factor in the progression of atherosclerosis but we could not rule out that glycemic variability might play a role in the development of complications in type 2 diabetes mellitus (T2DM) patients.*

key words: *glycosylated hemoglobin, type 2 diabetes*

Background and Aims

For almost 50 years it was observed that a decrease of chronic diabetes complications or a delay of their appearance can be achieved by optimal control of blood glucose [1]. A number of studies conducted in the late 70s confirmed for the first time the usefulness of measuring hemoglobin A1c (HbA1c) as an effective method for the monitoring of glucose control in patients with both type 1 (T1DM) and type 2 diabetes mellitus (T2DM) [1]. Moreover, the concept that HbA1c may reflect with accuracy

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blood glucose levels was certified. In addition, the temporal relationship between the decrease in HbA1c and improvement of the metabolic control was established [2].

Although the association between diabetes and the risk of atherosclerosis was confirmed by many longitudinal studies conducted so far, sometimes these studies omitted adjustment for some of the traditional risk factors for atherosclerotic disease such as smoking, obesity or lack of exercise [3-6]. It is therefore not surprising that after such adjustments, the risk of macrovascular complications in diabetic patients decreased by 2-3% [7-9].

The main objective of this study was to evaluate the correlation between metabolic control and HbA1c variability with macrovascular complications and assess the role of HbA1c as an independent predictive factor for the occurrence of vascular complications in diabetic patients from Bihor County, Romania. Another aim of the study was to determine the influence of antidiabetic treatment used in these patients (diet only, oral agents and / or insulin) on the onset of these complications.

Material and method

We conducted a prospective study over a period of 5 years (2007-2011). The study included patients with newly diagnosed T2DM and no evidence of micro or macro-angiopathic complications at the time of diagnosis. We initially assessed a number of 470 T2DM patients selected from the database of the County Center for Diabetes, Nutrition and Metabolic Diseases Oradea, Bihor. All the patients included signed an informed consent form for participation in the study.

Anthropometric measurements were performed (weight, height, abdominal circumference) and the body mass index (BMI) was calculated. The neuropathy sensitivity test for feet, peripheral pulse palpation, ophthalmoscopic examination and lower limb arterial Doppler exam were done. Systolic and diastolic blood pressure were measured and also the heart rate.

The following laboratory tests were done: glycemia, HbA1c, glycosuria, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), urea, uric acid, serum creatinine, proteinuria, urine test summary. The family history of diabetes and the smoking status as well as the type of medication used for the glycemic control were recorded.

After the examinations of medical history and after the tests listed above were done, 103 patients were excluded due to the presence of micro and macroangiopathic complications.

For the patients remaining in the study, a standard electrocardiogram and an exercise test were performed in order to exclude silent ischemic heart disease. A total of 26 patients with positive exercise test were excluded so that the study group finally included a number of 341 diabetic patients. Until the end of the follow-up period a total of 20 patients were excluded due to withdrawal of consent. This is why at the end of the study data from 321 diabetic patients were analyzed.

During the follow-up all the major vascular events were recorded. Blood glucose levels were determined weekly at home by study participants and HbA1c was assessed every 3 months. Blood pressure, heart rate, body weight, BMI, glycosuria, total cholesterol and triglycerides were repeated every 6 months. Cardiologic, neurologic and ophthalmologic examinations were repeated every 6 months.

The 5 years risk for vascular events was calculated at the inclusion using the Framingham risk equation that includes factors like age, gender, smoking, diabetes, value for systolic blood pressure, total cholesterol and HDL-cholesterol value [10].

Statistical analysis

Statistical analysis was performed after the end of follow-up when patients were divided into two groups: patients with optimal control of blood glucose reflected by an HbA1c < 7% and diabetic patients with poor control of blood glucose defined as HbA1c ≥ 7%. Statistical analysis was done using STATISTICA 8.0 software. The statistical tests used were t test to compare continuous variables, chi-square test and multiple linear regression.

Results

At the end of follow-up a total of 162 patients presented mean values of HbA1c <7%, interpreted as an optimal control of blood glucose (group O) while 159 patients had a suboptimal control of blood glucose defined by mean values of HbA1c ≥ 7% (group NO).

To analyze the effect of HbA1c variability in predicting macrovascular complications, a standard deviation of ±1.00% from baseline values to the end of follow-up was considered to be significant.

The characteristics of the patients included in the study are listed in Table 1.

There were no statistically significant differences between the 2 groups regarding sex or conventional risk factors for atherosclerosis such as smoking, obesity, dyslipidemia.

At inclusion, the 5 years risk score for vascular events calculated with Framingham score showed no statistically significant differences between the two groups: 11.00% ± 6.46% in patients from NO group versus 10.28% ± 5.91% in patients in the group O, p = 0.32).

Uni-variate analysis using suboptimal control of blood glucose values as the dependent variable and conventional risk factors for atherosclerosis showed that obesity is positively correlated with suboptimal glycemic control (p = 0.02).

Table 1. Characteristics of the patients included in the study.

	Group O HbA1c < 7% n=162	Group NO HbA1c≥ 7% n=159	P
	Mean ± SD N (%)	Mean ±SD N (%)	
Age	63.84±8.89	59.53±9.64	0.01
Sex (F)	74 (52.48%)	62 (42.65%)	
Systolic blood pressure (SBP)	148.73± 19.52	142.01±17.24	0.002
Diastolic blood pressure (DBP)	86.90±10.41	84.34±10.63	0.04
Glycemia	114.55± 35.63	100.96±20.94	0.0004
HbA1c value	6.70±0.30	8.07±0.79	0.002
Triglycerides	138.46 ± 31.35	140.78±37.86	0.57
Total cholesterol	212.90 ±48.13	221.66±44.50	0.11
HDL-C	40.40± 9.17	40.42±10.06	0.98
LDL-C	144.80± 50.07	153.08±46.50	0.14
Heart rate	85.97± 8.30	73.60±6.88	<0.0001
Family history of diabetes mellitus	45 (27.78%)	54 (33.95%)	0.09
Dy Dyslipidemia	58 (35.80%)	67 (42.13%)	0.48
Smoking	36 (22.22%)	49 (30.81%)	0.22
Obesity	82 (50.62%)	72 (45.28%)	0.16

Systolic and diastolic blood pressure levels were significantly higher among patients in the NO group compared with patients in group O. The same statistically significant difference was observed for heart rate.

Regarding diabetes therapy at the inclusion into the study, it was noted that of the 321 patients included in the analysis 123 (3.31%) were on oral antidiabetic drugs (OAD) therapy, 108 (41.12%) were on insulin therapy alone and

90 (20.56%) used a combined therapy with insulin and OAD. HbA1c values depending on the type of medication administered varied widely. The lowest values of HbA1c were recorded in the group of patients with combined treatment insulin and OAD treatment, while the highest in the group of patients with OAD only.

At the end of the study a total of 85 chronic macrovascular complications were reported: 60 (70.6%) occurring in patients with ineffective control of blood glucose and 25 (29.4%) in patients with optimal blood glucose control, as shown in Table 2.

There were 4 deaths (4,7%) consecutive to major vascular events (stroke or myocardial infarction), 8 patients (9.4%) suffered a stroke and 10 patients (11.8%) had acute myocardial infarction. Distribution plots show significantly higher incidence of vascular complications in patients in group NO (chi-square =13.60, p=0.0002).

Table 2. Macrovascular complications registered during the study.

Group	**PAD**	**AP**	**stroke**	**death**	**arterial hypertension**	**acute MI**	**silent ischemia**	Total
Group NO	5	7	6	3	21	7	11	***60 (70.6%)***
Group O	2	3	2	1	5	3	9	***25 (29.4%)***
TOTAL n (%)	7 (8.2%)	10 (11.8%)	8 (9.4%)	4 (4.7%)	26 (30.6%)	10 (11.8%)	20 (23.5%)	***85***
Chi-square (NO vs. O)							13.60	
level of significance (NO vs. O)							P = 0.0002	
contingency coefficient (NO vs. O)							0.371	

PAD - peripheral artery disease, AP - angina pectoris, MI - myocardial infarction

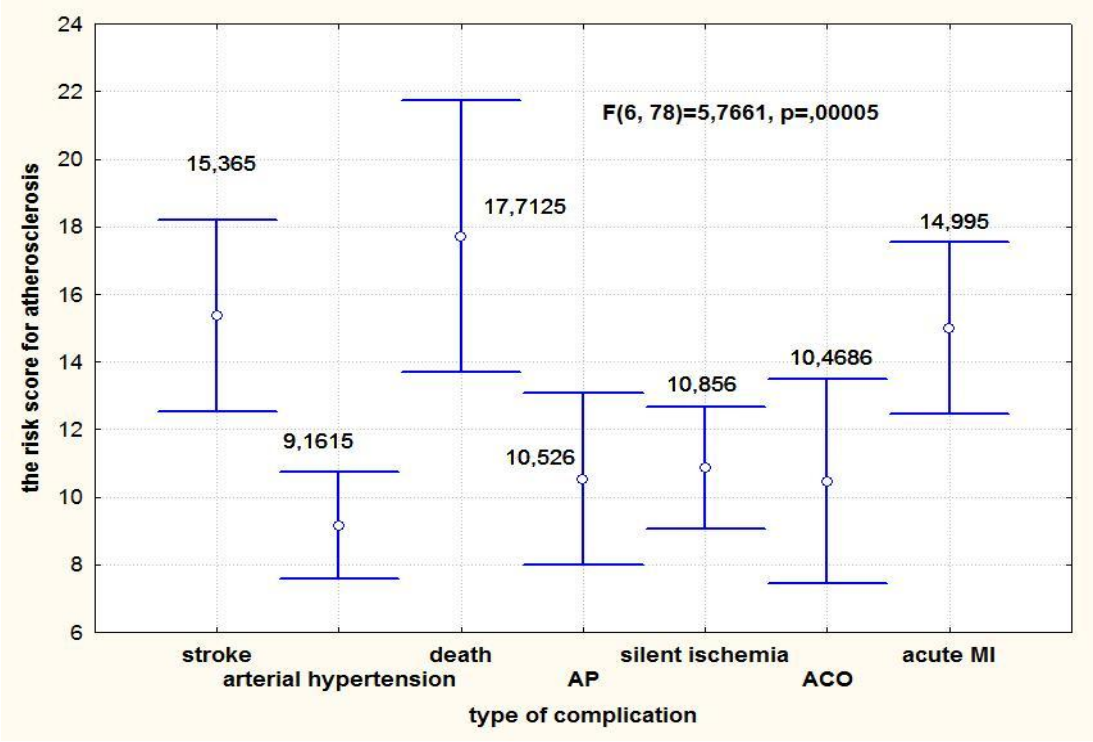

Figure 1. *Risk score for atherosclerosis at 5 years using the Framingham calculator according to the type of macrovascular complication.*

It was noted that the risk of developing macrovascular complications is 3.45 times higher in patients in the NO group versus patients in group O (estimated relative risk =

3.45; 95% confidence interval 1.85 to 5.52 , p = 0.0001).

The average age of patients who developed macrovascular complications in the NO group was 55.92 ± 10.55 years compared with 66.65 ± 9.97 years for group O (p <0.05).

The highest number of complications (n = 42; 49.41%) were recorded in the group of patients treated only with OAD and lowest among patients treated with insulin in combination with OADs (n =20; 23.52%), concordant with the better glycemic control as reflected by the HbA1c values.

The atherosclerosis risk score calculated with the Framingham equation according to the type of macrovascular complication occurred during follow-up period demonstrated significant differences between groups. The highest score was recorded in patients who died, those with stroke and those who have suffered an acute myocardial infarction as shown in Figure 1.

Multivariate analysis using the presence of macrovascular complications as the dependent variable and cardiovascular risk factors and cardiovascular risk score as independent variables showed that HbA1c can be considered an independent predictor of atherosclerotic complications as well as atherosclerosis risk score (beta = 0.26; p <0.0001, respectively beta = 0.61, p <0.0001). The variability of HbA1C was not an independent predictor for macroangiopathic complications (p=0.78).

Discussions

Several trials have shown the importance of HbA1c in assessing the risk for the development of diabetes chronic complications [11-15].

The Veterans Affairs Diabetes Trial (VADT) evaluated the effect of intensive treatment of diabetes mellitus on cardiovascular complications. The target value for HbA1c was below 7% in T2DM patients with a high cardiovascular risk, inadequately controlled despite of maximum oral therapy or of insulin therapy, while the treatment for dyslipidemia and arterial hypertension was intensified in both groups. The results showed that the cardiovascular events were less frequent in the intensive treatment group (25.9% as compared with 29.3%) and the rate of this events was directly associated with the duration of diabetes in the intensive treatment group [16].

Our study suggested that long-term glycemic variability, as measured by HbA1c variability, had no significant influence on the progression of atherosclerosis in patients with T2DM. Therefore, we conclude that HbA1C variability has no influence on the development of vascular complications in patients with T2DM. Compared to the variability of HbA1c, glycemic control as expressed by HbA1c itself has proven to be a stronger predictor in determining progression of carotid atherosclerosis in patients with T2DM [8].

In our study, glycemic status was found to be a more important factor than HbA1c variability in influencing the progression of atherosclerosis in patients with T2DM. This finding indicates that blood sugar control plays a role in reducing the progression of atherosclerosis in T2DM patients.

Global anti-diabetic strategy should aim primarily at improving glycemic control in order to decrease the long-term risk of chronic complications.

Conclusions

In our study, overall glycemic control was the most important predictor for the development of diabetes complications. Thus, the risk of macroangiopathic complications was 3.45 times higher in patients with uncontrolled glucose levels compared with patients with optimal blood glucose values (estimated relative risk = 3.45; 95% confidence interval 1.85 to 5.52; p = 0.0001).

Although overall glycemic control was the most important factor in the progression of atherosclerosis, we could not rule out that glycemic variability might play a role in the development of complications in T2DM patients.

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