Correlation of Glycemic Control Parameters in Non-Diabetic Persons with Cardiovascular Risk Scores - Results from a Cross- Sectional Study

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To assess the correlation between main parameters of glycemic control and cardiovascular risk scores in non-diabetic persons. Risk scores were calculated by using the University of Edinburgh Risk Calculator. Risk scores are used to estimate the probability of cardiovascular disease in individuals who have not already developed major atherosclerotic disease. We correlated the results of these scores with the parameters that describes the glycaemic profile: preprandial glicaemia, HbA1c and 1 hour and 2 h post-prandial glycaemia, determined during Oral Glucose Tolerance Test (OGTT).Both fasting glycaemia and HbA1c significantly correlated with cardiovascular risk scores calculated for a period of 10 years. The recorded post-prandial glycaemic values at 1h and 2h after glucose loading didn't significantly correlate with calculated scores, in the study group. The observed correlations underline the importance of glycaemia in the pathogenesis of cardiovascular diseases.

Keywords glycaemia, glycated hemoglobin HbA1c, cardiovascular risk

It is well known that glucose level in blood is correlated with early atherosclerosis, affecting all vessels, especially big arteries [1, 2].

Many studies have shown that cardiovascular disease, the leading cause of morbidity and mortality in individuals with diabetes, is induced by abnormalities in glucose metabolism [2-4]. It was demonstrated that both fasting and post-prandial hyperglycemia have been associated with cardiovascular risk, in diabetic persons[5].

Fasting plasma glucose (FPG) has been considered the standard parameter in diagnosing diabetes. Hemoglobin A1c ($HbA1_C$) offers an alternative to diagnostic criterion [2] on the basis of the relationship between $HbA1_C$ and microvascular complications. $HbA1_C$ and fasting plasma glucose measure differing aspects of glucose metabolism; $A1_C$ measures chronic glycemia (during the previous 2–3 months), offering an alternative diagnostic criterion, while FPG reflects hepatic glucose output at the time of sampling. Elevated values of $A1_C$ > 5.5% predict significantly increased risk for coronary heart disease and stroke, whereas FPG of 100–126 mg/dl does not [6- 8].

Risk calculators estimates a 2-4 times higher cardiovascular risk in diabetic patients compared with the non-diabetic population. Framingham Study and the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study Group developed a fatal CVD risk equation incorporating glucose tolerance status and fasting plasma glucose [5, 9]. Postprandial hyperglycemia has been associated with increased oxidative stress, inflammation, endothelial dysfunction, decreased fibrinolysis, plaque instability, and cardiac events [1].

Some studies suggested that the cardiovascular risk is positively correlated with vascular stiffness, which is induced by postprandial hyperglycemia [10]. Li et al. have shown that pulse wave velocity is increased in subjects with impared glucose tolerance (IGT) or newly diagnosed diabetes comparative with subjects with normal glucose tolerance or isolated impaired fasting glucose [11].

Other studies underlined the correlation of fasting and post meal plasma glucose level to increased HbA1c levels, in type 2 diabetic patients, which increases the cardiovascular risk [12-14].

Aryangat et al, in a recent study, concluded that post-prandial glycemia, but not fasting plasma glycemia, correlated with chronic micro and macroangiopathy and cardiovascular complications in type 2 diabetics [15].

The aim of the study was to find a correlation between main parameters of glycemic control, in non-diabetic persons, and cardiovascular risk scores.

Experimental part

Material and method

We performed a cross-sectional study in 350 patients, with urban and rural environment of origin. There were excluded 12.1% of patients because they had positive medical history for stroke or myocardial infarctus. There were assessed the traditional risk factors for cardiovascular disease.

Risk scores were calculated by using the University of Edinburgh Risk Calculator. Risk scores are for estimating the probability of cardiovascular disease for individuals who have not already developed major atherosclerotic disease (table 1).

The calculator may produce risk scores based on the following calculations: Framingham, Joint British Societies (JBS) / British National Formulary (BNF), ASSIGN[16].

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CHD*	Coronary heart disease.
MI*	Myocardial infarction.
STROKE*	Stroke.
CVD*	Cardiovascular disease.
CHD_DEATH*	Death from coronary heart disease.
CVD_DEATH*	Death from cardiovascular disease.
BNF*	BNF/JBS2 calculation of cardiovascular disease.
ASSIGN**	Cardiovascular disease.

Table 1
CARDIOVASCULAR OUTCOMES (16)

** Calculated using Framingham equation; ** Calculated using ASSIGN equation*

We used descriptive statistic method to calculate the average and standard deviation of assessed parameters.

Time period to calculate risk over can be varied between 4 and 12 years for any of the Framingham calculations, but is fixed at 10 years for the BNF or ASSIGN scores. The main parameters we used were: age, gender, smoking, number of cigarettes/day, family history of diabetes, Scottish Index of Multiple Deprivation (SIMD) which was considered as value of 20, systolic arterial blood pressure, total cholesterol and HDL-cholesterol (mmol/L).

We used the Edinburgh Risk Calculator to determine the probability of developing a myocardial infarctus, cerebral stroke and death in next 10 years [17].

We correlated the results of these scores with the parameters describing glycaemic profile: preprandial glicaemia, HbA1c and 1 hour and 2 h post-prandial glycaemia, determined during Oral Glucose Tolerance Test (OGTT).

Categories of increased risk for diabetes (ADA 2015-cited by [7]):

Fasting plasma glucose (FPG): 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) = Impaired Fasting Glucose (IFG) or

2-h after glucose in the 75-g OGTT: 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) = Impaired Glucose Tolerance (IGT) or

$HbA1_C$ =5.7–6.4% (39–46 mmol/mol).

In normal adults, hemoglobin usually contains hemoglobin A (HbA), which represents ~97% of the total, HbA2 (~2.5%), and HbF (~0.5% - fetal hemoglobin). HbA is made up of four polypeptide chains, two α and two β chains. There are three minor heme proteins, termed HbA1a, HbA1b, and HbA1c on the basis of their elution. HbA1c is used to refer to a specific molecular form in patients with diabetes compared with healthy individuals [18]. HbA1c has a hexose attached covalently to the NH_2-terminal valine residue of the β-chain of HbA. Glycation is the nonenzymatic attachment of a sugar to amino groups of proteins. HbA1c was defined by the International Union of Pure and Applied Chemistry as the fraction of the β-chains of hemoglobin that has a stable hexose adduct on the NH_2-terminal amino acid valine[19, 20].

Results and discussions

In the study group of 350 patients, there was a predominance of females (61.84%). The average value of age was 54.75 ± 16.25 years. The majority of the subjects in the study were non-smokers, representing 74.22 % of studied population.

The average value of fasting glycaemia in whole studied population was 5.95 ± 1.74 mmol/dL (normal value).

In our study group the average value of 1h post-prandial glycaemia in OGTT was 9.83 ± 2.44 mmol/dL, and 2h post-prandial glycaemia was 6.81 ± 2.10 mmol/dL. The average value of Hb A1c in study group was 5.79 ± 0.88%.

A percentage of 5 % of the subjects had previous diagnosis of diabetes mellitus, without significant differences between male and female; they were excluded after performing the analysis. Arterial hypertension, previously diagnosed, was present in 35.63% of the subjects; the average value of systolic blood pressure was 129.11 mmHg.

In our study group, both fasting glycaemia and HbA1c significantly correlated with cardiovascular risk scores calculated for a period of 10 years. The recorded post-prandial glycaemic values at 1h and 2h after glucose loading didn't significantly correlate with calculated scores, in the study group.

There are numerous epidemiologic studies that shown that fasting glucose and A1among persons with and those without diabetes are associated with elevated risk for cardiovascular disease [21-23]. Observational studies have suggested that the relationship among A1c, CVD, and

Table 2
DESCRIPTIVE STATISTICS

	Mean	Std. Deviation
CHD	7.81	7.29
MI	3.82	4.80
STROKE	2.45	2.85
CVD	12.85	11.61
CHD_DEATH	1.89	2.86
CVD_DEATH	3.40	5.02
BNF	10.27	9.79
ASSIGN	12.75	12.79
Preprandial glycaemia (mmol/l)	5.95	1.74
Glycaemia. 1h pp (mmol/l)	9.83	2.44
Glycaemia 2h pp(mmol/l)	6.81	2.10
Hb A1c (%)	5.79	.88
Systolic_bp (mmHg)	129.11	23.33
Total_chol (mmol/l)	4.64	.98
HDL_chol (mmol/l)	1.19	.19

		fasting	1h post-prandial	2h post-prandial	HbA1c
CHD	Pearson Correlation	.178**	.063	.039	.165**
	Sig. (2-tailed)	.005	.336	.554	.009
MI	Pearson Correlation	.196**	.044	.046	.175**
	Sig. (2-tailed)	.002	.500	.482	.005
STROKE	Pearson Correlation	.211**	.113	.051	.226**
	Sig. (2-tailed)	.001	.083	.440	.000
CVD	Pearson Correlation	.196**	.086	.052	.195**
	Sig. (2-tailed)	.002	.188	.423	.002
CHD_DEATH	Pearson Correlation	.174**	.029	.016	.168**
	Sig. (2-tailed)	.006	.657	.806	.008
CVD_DEATH	Pearson Correlation	.102	.025	-.011	.119
	Sig. (2-tailed)	.105	.701	.868	.060
CVD_DEATH	Pearson Correlation	.102	.025	-.011	.119
	Sig. (2-tailed)	.105	.701	.868	.060
BNF	Pearson Correlation	.194**	.079	.044	.189**
	Sig. (2-tailed)	.002	.224	.506	.003
ASSIGN	Pearson Correlation	.150*	.072	.011	.182**
	Sig. (2-tailed)	.017	.268	.865	.004

Table 3
ASSOCIATIONS BETWEEN CARDIOVASCULAR RISK AND GLYCEMIC VALUES

mortality may be U-shaped (24, 25).Myocardial damage associated to glycaemic abnormalities appears to begin before a diabetes diagnosis and may require a highly sensitive assay to detect it. Cardiovascular risk increases with long-term exposure to hyperglycemia. Although impaired fasting glucose is a risk factor for heart failure, but the risk is only elevated among persons who subsequently develop diabetes.(26). Minimizing the variability of glycaemia, which seems to be the most dangerous, may offer a good protection against atherosclerotic disease [26, 27].

Conclusions

In this study, the significant correlations between fasting glycaemia and HbA1c with cardiovascular risk scores may explain the appearance of macroangiopathic complications before the moment of clinical diagnosis of diabetes mellitus.

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