Relationship between HbA1c levels and coronary artery severity in nondiabetic acute coronary syndrome patients

Diyabeti olmayan akut koroner sendromlu hastalarda HbA1c düzeyi ile koroner arter hastalığı ciddiyeti arasındaki ilişki

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ABSTRACT

Objectives: In this study, we aimed to investigate the relationship between HbA1c levels and the severity of coronary artery stenosis in patients with acute coronary syndrome (ACS) without diabetes mellitus.

Study design: In this study, we included 65 patients (11 females, mean age: 57±11.42 years; 54 males, mean age: 54.56±8.51 years) who were diagnosed as acute myocardial infarction without diabetes mellitus. During hospitalization, fasting blood glucose, postprandial blood glucose and HbA1C were measured in each patient. Gensini score was used to assess the severity of coronary artery disease.

Results: Twenty patients (30.8%) had hypertension, 15 (23.1%) had impaired fasting glucose, 10 (15.3%) had combined impaired fasting and postprandial glucose, 28 had a low HDL cholesterol (45%), and 30 (46%) had abdominal obesity. Coronary angiography revealed one-vessel disease in 13 patients (20%), and two- and three-vessel disease in 52 patients (80%). There were no significant differences in terms of high-sensitive C-reactive protein (hs-CRP), total cholesterol, fasting glucose, and postprandial glucose (0.068, 0.974, 0.178, 0.677, respectively). There was no significant relation between the Gensini score and HbA1c levels (p=0.299), but there was a significant relation between the Gensini score and obesity (p=0.024).

Conclusion: In our study, no significant relationship could be determined between the Gensini score and HbA1C, fasting and postprandial blood glucose levels, lipid profile, and hs-CRP levels in patients with nondiabetic ACSs.

ÖZET

Amaç: Bu çalışmada, diyabeti olmayan akut koroner sendromlu (AKS) hastalarda koroner arter hastalığının ciddiyeti ile serum HbA1c düzeyleri arasındaki ilişkiyi araştırmaya çalıştık.

Çalışma planı: Çalışmaya diabetes mellitusu olmayan akut miyokart enfarktüsü tanısı konan toplam 65 hasta (11 kadın, ortalama yaş 57±11.42 yıl; 54 erkek, ortalama yaş 54.56±8.51 yıl) alındı. Hastanede yatışları sırasında bütün hastalarda açlık ve tokluk kan şekeri, HbA1c ölçümü yapıldı. Koroner arter hastalığının ciddiyeti Gensini skorlaması ile değerlendirildi.

Bulgular: Hastaların 20'sinde (%30.8) hipertansiyon, 15'inde (%23.1) bozulmuş açlık glukozu, 10'unda (%15.3) birlikte bozulmuş açlık ve tokluk glukozu, 28'inde (%45) HDL kolesterol ve 30'unda (%46) abdominal obezite vardı. Koroner anjiyografiyle tek damar hastalığı hastaların 13'ünde (%20), iki ve üç damar hastalığı 52'sinde (%80) tespit edildi. Yüksek duyarlıklı C-reaktif protein (hs-CRP), total kolesterol, açlık kan şekeri ve tokluk kan şekeri açısından anlamlı farklılık yoktu (sırasıyla, 0.068, 0.974, 0.178, 0.977). Gensini skoru ile HbA1c düzeyleri arasında anlamlı korelasyon saptanmadı (p=0.299), fakat Gensini skoru ve obezite arasında anlamlı bir ilişki vardı (p=0.024).

Sonuç: Bu çalışmada, diyabeti olmayan AKS'li hastalarda anjiyografik Gensini skoru ile HbA1c düzeyi, serum açlık ve tokluk glukoz düzeyleri, lipit profili ve hs-CRP düzeyleri arasında anlamlı bir ilişki saptanmadı.

Received: November 14, 2012 *Accepted:* February 27, 2013

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Glycosylated hemoglobin (HbA1c) is an established marker of long-term glycemic control in patients with diabetes mellitus (DM), and elevated HbA1c levels are associated with an increased risk for future microvascular and macrovascular disease.[1] HbA1c can be assessed in the non-fasted state and has higher reproducibility than fasting glucose.[2] There is consistent evidence that optimal glycemic control (defined as HbA1c ≤7%) results in a lower incidence of microvascular complications in both type 1 and type 2 DM.[3] Moreover, a recent report found that elevated HbA1c levels are also predictive for cardiovascular disease and mortality in patients without DM.[4]

Gensini suggested a scoring system, which allocates a numerical value for the degree of stenosis in a coronary artery, and this provides a detailed assessment of coronary artery disease (CAD) and does not ignore even very trivial lesions in coronary arteries.[5]

Some data demonstrated a significant positive correlation between HbA1c and coronary angiographic scores, indicating it as a marker of extensive coronary arterial disease.[6]

In this study, we aimed to investigate the relationship between HbA1c levels and the severity of coronary artery stenosis in patients with nondiabetic acute coronary syndrome.

PATIENTS AND METHODS

Patients diagnosed as non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI) without DM between December 2010 and October 2011were included in the study. Patients with known diabetes, oral antidiabetic medication and/or insulin usage history were excluded from the study. Patients with fasting glucose ≥126 mg/dl and/or postprandial blood glucose ≥200 mg/dl during hospitalization were excluded because of the possibility of newly diagnosed diabetes.

Fasting blood glucose, postprandial blood glucose, lipid profile (low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, triglycerides, total cholesterol), high-sensitive C-reactive protein (hs-CRP), and renal and liver function tests were measured in each patient during hospitalization in the first 48 hours of admission. Serum HbA1c levels were assessed by affinity chromatography method.

Coronary angiography was performed using the Judkins technique. Angiographic CAD was defined as a stenotic lesion of at least 50% in one or more major coronary arteries or in the main coronary artery. The coronary angiograms were reviewed by two physicians to assess the Gensini score. The severity of CAD was scored as 1 for 1-25% narrowing, 2 for 26-50%, 4 for 51-75%, 8 for 76-90%, 16 for 91-99%, and 32 for a completely occluded artery. The score is then multiplied by a factor according to the importance of the coronary artery. The multiplication factor is 5 for a left main stem (LMS) lesion, 2.5 for proximal left anterior descending artery (LAD) and proximal circumflex artery (Cx) lesions, 1.5 for a mid-LAD lesion, and 1 for distal LAD, mid/distal Cx and right coronary artery lesions. The multiplication factor for any other branch is 0.5.

Abbreviations:

CAD	*Coronary artery disease*
Cx	*Cumflex artery*
DM	*Diabetes mellitus*
HbA1c	*Glycosylated hemoglobin*
HDL	*High density lipoprotein*
hs-CRP	*High-sensitive C-reactive protein*
LAD	*Left anterior descending*
MetS	*Metabolic syndrome*
UKPDS	*The United Kingdom Prospective Diabetes Study*

The study protocol was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained from all patients before enrolment.

Statistical analysis

In all analyses, IBM SPSS (Statistical Package for the Social Sciences) for Windows 20.0 statistical software package was used. Kolmogorov-Smirnov test was done to test distribution of the variables. Quantitative variables with a normal distribution were specified as the mean ± standard deviation, and those with non-normal distribution were specified with median (minimum and maximum); categorical variables were specified with number and percentage values. For comparisons between groups, for numeric variables with normal distribution, Student-t test was used, and for non-normally distributed variables, Mann-Whitney U test was used. For comparison of categorical data, chi-square and Fisher's chi-square tests were used. To examine the relationship between the Gensini score and continuous variables, parametric (Pearson) correlations for normally distributed variables and non-parametric (Spearman) correlation analysis for non-normally distributed variables were used.

A p value of less than 0.05 ($p<0.05$) was considered as indicating statistical significance.

RESULTS

A total of 71 patients were included in our study. Six patients were excluded from the study (due to a new diagnosis of diabetes in 4 patients, and due to elevation in troponin thought to be associated with MI for any other reason in 2 patients). After exclusions, a total of 65 patients were evaluated. Clinical and demographic data of the subjects are shown in Table 1. Twenty patients (30.8%) had hypertension,

Table 1. Demographic and clinical characteristics of the study population

	n	%	Mean±SD
Age (years) (n=65)			
Female			57±11.42
Male			54.56±8.51
Gender (n=65)			
Male	54	83.1	
Myocardial infarction (n=65)			
STEMI	41	63.1	
NSTEMI	24	36.9	
Hypertension (n=65)			
+	20	30.8	
–	45	69.2	
Smoking (n=65)			
+	48	73.8	
–	17	26.2	
Coronary artery disease (n=65)			
+	5	7.7	
–	60	92.3	
One-vessel disease (n=65)	13	20	
Two- and three-vessel disease (n=65)	52	80	
Fasting glucose (mg/dl) (n=65)			94.05±13.10
Normal	50	76.9	
Impaired fasting glucose	15	23.1	
Postprandial glucose (mg/dl) (n=65)			142.89±2.27
Normal	29	44.6	
Impaired glucose tolerance	36	55.4	
Obesity (n=65)	30	46.1	
Metabolic syndrome (n=65)	10	15.3	
Total cholesterol (mg/dl) (n=65)			178.28±34.40
HDL cholesterol (mg/dl) (n=65)			38.34±14.44
LDL cholesterol (mg/dl) (n=65)			107.32±35.09
Triglyceride (mg/dl) (n=65)			161.26±101.69
HbA1c (n=65)			5.88±0.58
hs-CRP (mg/L) (n=65)			12.40±13.14
Gensini score (value) (n=65)			43.69±21.80

NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; HDL: High density lipoprotein; LDL: Low density lipoprotein; hs-CRP: High-sensitive C-reactive protein.

Table 2. Relationship between MI subgroups and variables

	Myocardial infarction						*p*
	STEMI (n=41, 63%)			NSTEMI (n=24, 37%)			
	n	%	Mean±SD	n	%	Mean±SD	
Gensini score (value)			46.55±22.53			38.81±19.99	0.169
HbA1C		5.77			5.71		0.822
hs-CRP (mg/L)	9.85			9.85			0.068
Total cholesterol (mg/dl)			178.17±35.03			178.46±34.05	0.974
HDL cholesterol (mg/dl)	36			39			0.307
LDL cholesterol (mg/dl)			108.96±33.76			104.5±37.83	0.624
Triglyceride (mg/dl)	140			148.5			0.844
Fasting glucose (mg/dl)	95			89			0.178
Postprandial glucose (mg/dl)			143.90±23.38			141.17±28.66	0.677
Age (years)			54.07±9.65			56.58±7.76	0.282
Metabolic syndrome	3	5		7	10		0.060
Obesity	10	15.3		20	30.7		0.046
Gender							
Male	34	52		20	31		0.966
Female	7	11		4	6		
Smoking							
+	33	51		15	23		0.111
–	8	12		9	14		
Hypertension							
+	10	15.4		10	15.4		0.145
–	31	48		14	21.2		
Previous CAD							
+	2	3		3	4. 6		0.266
–	39	60		21	32.4		

STEMI: ST elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; hs-CRP: High-sensitive C-reactive protein; HDL: High density lipoprotein; LDL: Low density lipoprotein; CAD: Coronary artery disease.

15 (23.1%) had impaired fasting glucose, 10 (15.3%) had combined impaired fasting and postprandial glucose, 28 had a low HDL cholesterol (45%), and 30 (46%) had abdominal obesity. Metabolic syndrome (MetS) was detected in 10 patients (15.3%).

Coronary angiography revealed one-vessel disease in 13 patients (20%), and two- and three-vessel disease in 52 patients (80%). The mean Gensini score was 43.69±21.80. Scatter diagram of the Gensini score is shown in Figure 1.

The relationship of MI subtypes and clinical and demographical variables is shown in Table 2. There was a significant difference in term of obesity (p=0.046).

The relationship between Gensini score and metabolic variables is shown in Table 3. There was no significant relation between the Gensini score and HbA1c levels (p=0.299), but there was a significant relation between the Gensini score and obesity (p=0.024). There was no significant correlation between Gensini score and glycemic variables. Figure 2 demonstrates the correlation analysis of the relationship between Gensini score and HbA1c levels.

Table 3. Relationship between Gensini score and metabolic variables

	r	p
HbA1C	-0.131	0.299
hs-CRP	0.094	0.454
Postprandial glucose	-0.151	0.231
Fasting glucose	0.06	0.633
Type of MI	-0.154	0.221
Metabolic syndrome	-0.186	0.189
Obesity	-0.322	0.044

hs-CRP: High-sensitive C-reactive protein; MI: Myocardial infarction.

DISCUSSION

Coronary heart disease (CHD) is the main cause of morbidity and mortality in developed countries, and the prevalence is increasing in developing countries. HbA1c is a useful index of glucose intolerance and hyperglycemia, even when fasting glucose concentrations are normal.[7,8] Data on the prognostic role of HbA1c in patients with acute MI are still controversial.[9,10] Lazzeri et al.[11] showed that patients with HbA1c levels higher than 6.5% did not show a higher infarct size (as indicated by troponin I and left ventricular ejection fraction) or a more critical illness. Saleem et al.[12] demonstrated that HbA1C is an independent factor influencing the severity of CAD. The United Kingdom Prospective Diabetes Study (UKPDS) showed a 25% relative risk reduction in microvascular complications with intensive blood glucose control, by keeping HbA1c <7%, but no significant effect of lowering blood glucose on cardiovascular complications.[13] However, the UKPDS-35 revealed that every 1% reduction in baseline HbA1c levels decreased the incidence of MI by 5%.[14] Khaw et al.[15,16] demonstrated that an increase in HbA1C of 1% was associated with a relative risk for death from any cause of 1.24 and 1.28 in men and women, respectively.

An elevated HbA1c level is predictive of the prevalence of cardiovascular disease and mortality in patients without DM, independent of the fasting glucose value.[6]

In this study, we evaluated the relation between the severity of coronary atherosclerosis and HbA1c levels in non-diabetic patients. No relation could be demonstrated between HbA1c and extent of coronary involvement assessed by Gensini score. Although previous studies demonstrated that HbA1c values are associated with coronary lesion complexity and that this association is also observed in non-diabetic patients,[17] our investigation could not demonstrate this association. In our study, type of MI was also not associated with HbA1c levels.

Gerstein et al.[18] showed that the relationship between HbA1c and atherosclerosis is similar in different ethnic groups and cannot be accounted for by

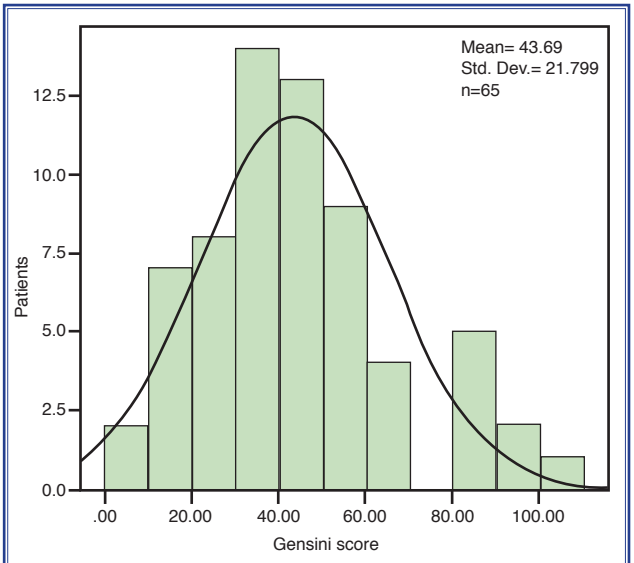

Figure 1. The scatter diagram of the Gensini score.

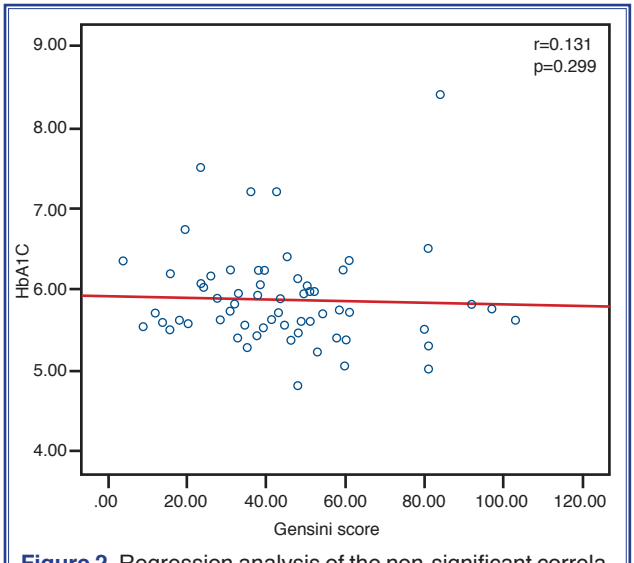

Figure 2. Regression analysis of the non-significant correlation between the Gensini score and HbA1c levels.

differences in abdominal obesity, dyslipidemia, free fatty acids, insulin secretion, or insulin resistance. Yan et al.[19] demonstrated that the extent of CAD did not differ significantly among subjects with normal glucose tolerance, impaired fasting glucose, or impaired glucose tolerance.

Ertek et al.[20] revealed that no single MetS component or gender had a significant relationship with coronary artery severity. In our study, we revealed a significant relation between obesity and coronary artery severity, but there were no relationship between MetS and coronary artery severity.

An important limitation of our study is the low number of study patients. In addition, the number of female patients was low, which may be a reason for the lack of a significant relation between glycemic variables and the Gensini score. Diabetes seems to be a more important risk factor in female than male patients. Therefore, the lack of a significant relation between Gensini score and glycemic variables in a group comprised mainly of non-diabetic male patients suggests that the contribution of impaired glucose metabolism to the progression of atherosclerosis is not as important as the other risk factors.

In conclusion, in our study, no significant relationship could be determined between the Gensini score and HbA1C, fasting and postprandial blood glucose levels, lipid profile, or hs-CRP levels in non-diabetic acute coronary syndrome patients.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Acute coronary syndrome; coronary artery disease; hemoglobin A, glycosylated; myocardial infarction.

Anahtar sözcükler: Akut koroner sendrom; koroner arter hastalığı; hemoglobin A, glikosil; miyokart enfarktüsü.