Relation Between Glycosylated Hemoglobin (Hemoglobin A1c) and Aortic Stiffness in Patients with Type 2 Diabetes

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ABSTRACT

Introduction: Type 2 diabetes mellitus (DM) is a major risk factor for cardiovascular diseases and is responsible for the increase in cardiovascular mortality. Chronic hyperglycemia is related to accelerated atherosclerosis. In this study, we tried to demonstrate the relation between glycosylated hemoglobin (HbA1c) level, which is a marker of long-standing hyperglycemia, and aortic stiffness, which is a marker of cardiovascular disease.

Patients and Methods: In total, 100 patients with type 2 DM were included in this study. Patients were divided into three groups according to the HbA1c level (group 1 HbA1c ≤ 6, group 2 HbA1c between 6 and 7, and group 3 HbA1c ≥ 7).

Results: Significant correlation was found between aortic distensibility and HbA1c level (r= 0.283, p= 0.004). Moreover, aortic distensibility was also correlated with the duration of DM (r= –0.172, p= 0.05) and age (r= -0.27, p= 0.006). Significant correlation was determined between aortic strain and fasting blood glucose level, HbA1c level, and the duration of DM (r= –0.265, p= 0.008; r= 0.279, p= 0.005; and r= –0.14, p= 0.03, respectively).

Conclusion: In this study, we showed that aortic stiffness was increased in patients with type 2 DM who have high blood fasting glucose and HbA1c levels. Our study also showed that the duration of DM was related to aortic stiffness. Echocardiographic non-invasive evaluation of aortic stiffness may be helpful in the estimation of cardiovascular risk in patients with DM.

Key Words: Aortic stiffness; diabetes mellitus

Tip 2 Diabetes Mellituslu Hastalarda Glikolize Hemoglobin (Hemoglobin A1c) ile Aortik Sertlik Arasındaki İlişki

ÖZET

Giriş: Tip 2 diabetes mellitus (DM) kardiyovasküler hastalıklar için major risk faktörüdür ve DM'li hastalar artmış kardiyovasküler mortalite ve morbiditeye sahiplerdir. Kronik hiperglisemi ile ilişkili olan birçok mekanizma bu hızlanmış aterosklerozdan sorumlu tutulmaktadır. Bu çalışmada amaç DM'li hastalarda uzun dönem glisemik kontrolün belirteci olan HbA1c seviyesi ile kardiyovasküler hastalıkların belirteci olan aortik sertlik arasındaki ilişkiyi saptamaktır.

Hastalar ve Yöntem: Çalışmamıza kliniğimize başvuran Tip 2 DM'li 100 hasta alındı. Hastalar HbA1c değerlerine göre üç gruba ayrıldı.

Bulgular: Gruplar arasında açlık kan şekerleri, DM süresi ve oral antidiyabetik ya da insülin kullanımında istatistiksel olarak anlamlı şekilde farklı bulundu. Aortik esneyebilirlik ve HbA1c düzeyi arasında önemli ilişki bulundu (r= 0.283; p= 0.004). Bunun yanı sıra, DM süresi (r= -0.172; p= 0.05) açlık kan şekeri (r= 0.292; p= 0.003) ve hasta yaşı ile (r= -0.27; p= 0.006) aortik esneyebilirlik arasında da istatistiksel anlama ulaşan korelasyon tespit edildi. Bunun yanında aortik gerilim ile açlık kan şekeri, HbA1c, DM süresi arasında (sırasıyla; r= -0.265; p= 0.008, r= 0.279; p= 0.005 ve r= -0.14; p= 0.03) anlamlı korelasyon bulundu.

Sonuç: Bu çalışmada, yüksek açlık kan şekeri ve HbA1c düzeyine sahip tip 2 diyabet hastalarında aortik sertliğin arttığını gösterdik. Aynı zamanda çalışmamız diyabetin süresi ile aortik sertliğin ilişkili olduğunu göstermiştir. Ekokardiyografiyle noninvaziv yöntem olarak ölçülen aortik elastisite parametreleri hastalığın erken döneminde kardiyovasküler riski tahmin etmede ve önlemede faydalı olabilir.

Anahtar Kelimeler: Aortik sertlik; diabetes mellitus

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Submitted: 04.06.2016
Accepted: 24.11.2016

INTRODUCTION

Diabetes mellitus (DM) is the one the major independent risk factor for the development of coronary artery disease[1]. Mortality due to cardiovascular complications is increased by 2-3 fold in patients with diabetes[2]. It is well known that chronic hyperglycemia is related to microvascular complications, but its relation with macrovascular complications has not been exactly shown[3,4].

DM increases arterial stiffness by making changes in the arterial wall[5]. Previous studies revealed that arterial stiffness was increased in patients with diabetes[6]. Monier et al. showed that arterial stiffness was increased in patients with insulin dependent DM[7]. In the Atherosclerosis Risk in Communities (ARIC) study, it was found that carotid arterial stiffness was correlated with the blood glucose level[8].

Glycosylated hemoglobin (HbA1c) level is directly related to the blood glucose level and it reflects the blood glucose level in the past 3 months. In previous studies, it was shown that the HbA1c level might be a marker of cardiovascular morbidity and mortality in patients with diabetes[9,10].

In this study, we investigated the relationship between blood glucose level and arterial stiffness in patients with type 2 DM.

PATIENTS and METHODS

Characteristics of the Study

In total, 100 patients with type 2 DM admitted to our outpatient clinic between January 2010 and March 2010 were prospectively included in this study. American Diabetes Association criteria were used for the diagnosis of diabetes[11]. All participants were informed about the study and their consents were obtained. Patients who satisfied exclusion criteria provided below were excluded from the study. All demographical and clinical characteristics of the patients were noted. Patients in the study were divided into three groups according to their HbA1c level (group 1 HbA1c ≤ 6, group 2 HbA1c between 6 and 7, and group 3 HbA1c ≥ 7). Biochemical parameters [blood glucose, urea, creatinine, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride], HbA1c level, and full blood count were evaluated after 12 h of fasting.

Exclusion criteria were recent acute coronary syndrome, severe valvular disease, peripheral artery disease, severe heart failure, severe hepatic and renal disease, oral anticoagulation usage, acute and chronic infection, and hematological diseases.

Transthoracic Echocardiographic Examination

All patients underwent transthoracic echocardiographic examination using the vivid 7 Dimension (General Electric) echocardiography device with a 2.5-3.5 MHz transducer. All echocardiographic examinations were performed by the same operator who was blinded with respect to the groups of patients. The ejection fraction and left ventricular end systolic and diastolic diameters were noted. Systolic and diastolic diameters of the ascending aorta were measured with M-mode echocardiography 3 cm above the aortic valve. The aortic systolic diameter was measured when the aortic valve was fully open, whereas the diastolic diameter was measured according to the peak of the QRS tracings (Figure 1). Five consecutive measurements were made and their average was calculated.

Aortic strain and distensibility were calculated from the echocardiography-derived aortic diameters and clinical blood pressure. The aortic pulse pressure was calculated by subtracting the diastolic aortic pressure from the systolic aortic pressure. Aortic strain and distensibility were used as aortic elasticity parameters. The formulas used to calculate the above mentioned parameters were as follows[12].

Pulse pressure (mmHg): systolic blood pressure-diastolic blood pressure

Aortic strain (%) = (aortic systolic diameter-diastolic diameter) × 100/diastolic diameter

Distensibility (cm^2/dyn) = (2 × aortic strain)/(systolic pressure-diastolic pressure)

Statistical Analysis

All data were evaluated by Statistical Package for social Sciences for Windows (SPSS, version 10, SPSS Inc. Chicago, Illinois, USA). Parametric data were expressed as mean ± standard deviation and qualitative data were expressed as numbers and percentages. Distribution of the variables was assessed by Kolmogorov-Smirnov test. The Kruskal-Wallis test was used to assess correlations between nonparametric data. Parameters which were significantly different between the groups were assessed by the Bonferroni-corrected Mann-Whitney U test (statistical significance $p< 0.017$). Categorical variables were evaluated by Chi-square test. The Spearman rho test was used for the evaluation of numerical variables.

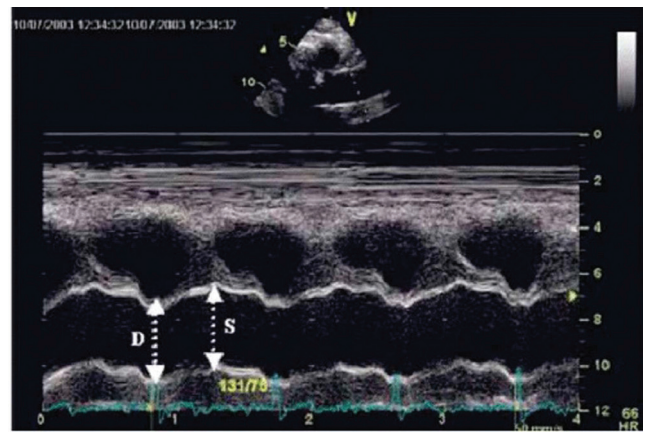

Figure 1. Measurement of systolic and diastolic diameters of the ascending aorta using transthoracic M-mode echocardiography.

RESULTS

The study population (100 patients) was composed of 41 male (41%) and 59 female (59%) patients. Sixty-eight patients (68%) had hypertension, 79 patients (79%) had hyperlipidemia, 47 (47%) patients had a family history of coronary artery disease, and 12 (12%) patients were cigarette smoker. Groups 1, 2, and 3 were composed of 15, 31, and 54 patients, respectively. Demographical and clinical characteristics of the patients are demonstrated in Table 1 and Table 2. There was no statistical difference with respect to age, family history, hypertension, total cholesterol, LDL, HDL, triglyceride, and body mass index between groups.

Fasting blood glucose level, duration of diabetes, and use of oral anti-diabetic medication or insulin were statistically significantly different between groups. The fasting blood glucose level was significantly higher in group 3 than in the

Table 1. Clinical and laboratory findings of all three groups

		HbA1c level			
	All patients (n= 100)	**I (n= 15)**	**II (n= 31)**	**III (n= 54)**	**p value***
Sex					
Male, n (%)	41 (41)	6 (40.0)	11 (35.5)	24 (44.4)	0.719
Female, n (%)	59 (59)	9 (60.0)	20 (64.5)	30 (55.6)	
Hypertension, n (%)	68 (68)	7 (46.7)	24 (77.4)	37 (68.5)	0.110
Hyperlipidemia, n (%)	79 (79)	9 (60.0)	27 (87.1)	43 (79.6)	0.105
Family history, n (%)	47 (47)	9 (60.0)	16 (51.6)	22 (40.7)	0.344
Smoking, n (%)	12 (12)	3 (20.0)	3 (9.7)	6 (12.0)	0.575
CAD history, n (%)	48 (48)	8 (53.3)	13 (41.9)	27 (50.0)	0.700
Treatment					
OAD, n (%)	79 (79)	15 (100.0)	29 (93.5)	35 (64.8)	**0.001**
Insulin, n (%)	21 (21)	0 (0)^{A}	2 (6.5)^{A}	19 (35.2)^{B}	

HbA1c: Glycosylated hemoglobin, CAD: Coronary artery disease, OAD: Oral antidiabetics.
$^{A, B}$A and B show statistical difference according to Bonferroni-corrected Mann-Whitney U test.
*Statistical significance (p< 0.05).

Table 2. Clinical and laboratory findings of the patients

	HbA1c level			
	I (n= 15) Median (min-max)	**II (n= 31) Median (min-max)**	**III (n= 54) Median (min-max)**	**p value***
Age (year)	52.8 (39-72)	57.8 (45-72)	58.4 (39-80)	0.217
Duration of HT (year)	2.4 (0-10)	4.5 (0-20)	5.1 (0-20)	0.188
Duration of DM (year)	3.9 (1-7)^{A}	5.6 (1-30)^{A}	8.0 (1-20)^{B}	**0.009**
T.chol (mg/dL)	181.6 (114-236)	191.8 (111-297)	193.6 (115-280)	0.558
LDL (mg/dL)	104.0 (62-176)	115.5 (47-191)	115.4 (55-183)	0.409
HDL (mg/dL)	47.6 (28-101)	45.6 (30-74)	40.5 (24-62)	0.174
Triglyceride (mg/dL)	150.0 (75-266)	157.7 (68-324)	194.0 (56-8639)	0.305
hsCRP	2.27 (0-6)	2.14 (0-11)	12.8 (0-529)	0.343
BMI (kg/m^2)	26.8 (23-35.5)	30.3 (28.2-39.4)	30.78 (28.8-38.6)	0.365
FBG (mg/dL)	117.5 (89-155)^{A}	135.5 (94-223)^{A}	209.9 (101-412)^{B}	**< 0.001**

FBG: Fasting blood glucose, DM: Diabetes mellitus, HbA1c: Glycosylated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, T.chol: Total cholesterol, BMI: Body mass index, hsCRP: High-sensitivity C-reactive protein.
$^{A, B}$ A and B show statistical difference according to Bonferroni-corrected Mann-Whitney U test.
* Statistical significance (p< 0.05).

Table 3. Echocardiographic and blood pressure parameters of the patients

	Group I	Group II	Group III	p*
Aortic systolic diameter (cm)	3.56 (3.0-4.5)	3.59 (3.0-4.5	3.58 (2.7-4.8)	0.918
Aortic diastolic diameter (cm)	3.29 (2.8-3.9)	3.38 (2.8-4.2)	3.42 (2.6-4.7)	0.585
Aortic systolic–diastolic diameter (cm)	0.27 (0.11-0.60)^{A}	0.21 (0.04-0.62)^{A}	0.15 (0.06-0.40)^{B}	**0.001**
Systolic blood pressure (mmHg)	133 (92-190)	129 (100-156)	132 (95-188)	0.759
Diastolic blood pressure (mmHg)	80 (60-110)	79 (50-113)	79 (43-103)	0.898
Pulse pressure (mmHg)	54 (24-90)	49 (26-75)	53 (25-88)	0.558
Aortic distensibility ($cm^2/dyn/10^3$)	2.48 (0.92-5.74)^{A}	1.93 (0.39-4.1)^{A}	1.45 (0.33-4.26)^{B}	**0.002**
Aortic strain (%)	7.48 (2.69-13.3)^{A}	6.0 (1.33-16.6)^{A}	4.54 (1.4-11.0)^{B}	**0.001**

$^{A, B}$A and B show statistical difference according to Bonferroni-corrected Mann-Whitney U test.
* Statistical significance (p< 0.05).

other groups after Bonferroni-corrected Mann-Whitney U test evaluation (p< 0.001). The duration of DM was significantly longer in group 3 (p= 0.009). The use of oral anti-diabetic medication was significantly higher in groups 1 and 2, while the use of insulin treatment was higher in group 3 (p= 0.001). Aortic systolic and diastolic diameters, systolic and diastolic blood pressure, and pulse pressure were not statistically different between groups (Table 3). Change in the aortic systolic-diastolic diameter, aortic strain, and aortic distensibility were significantly different between groups (p< 0.001). Change in the aortic systolic–diastolic diameter, aortic strain, and aortic distensibility were similar (r= –0.265, p= 0.008; r= 0.279, p= 0.005, and r= –0.148, p= 0.03, respectively) between groups 1 and 2, whereas they were significantly lower in group 3 (p < 0.001). Statistically significant correlation was found between HbA1c and aortic distensibility (r= 0.283, p= 0.004) (Figure 2) and also between aortic distensibility and the duration of DM (r= –0.172, p= 0.05), fasting blood glucose level (r= –0.292, p= 0.003), patient age (r= –0.27, p= 0.006), respectively (Table 4). Moreover, aortic strain was significantly correlated with fasting blood glucose level, HbA1c level, and the duration of DM (Figure 3).

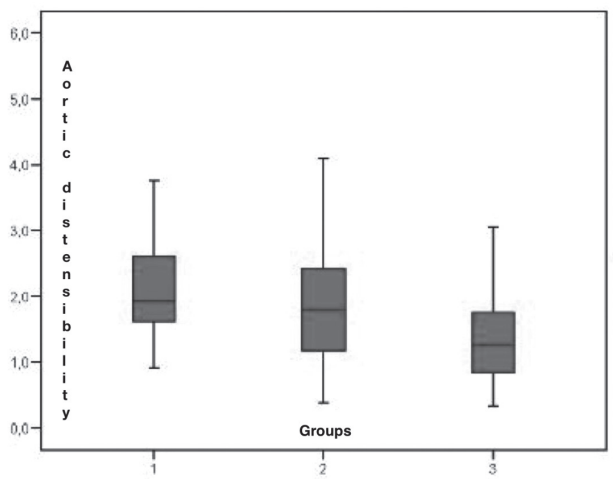

Figure 2. Relation between the HbA1c level and aortic distensibility.

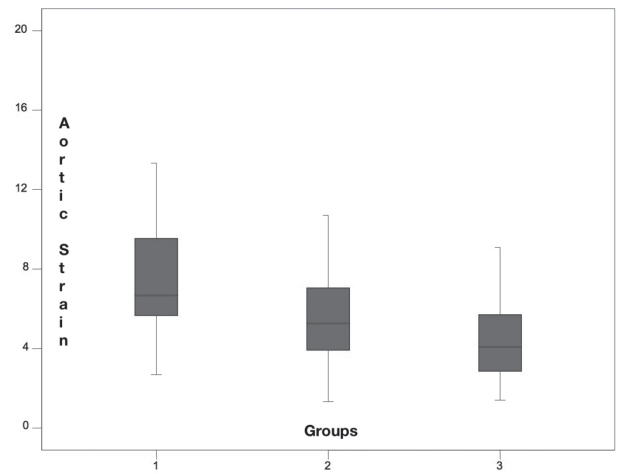

Figure 3. Relation between the HbA1c level and aortic strain.

Table 4. The relation between aortic stiffness parameters and demographical characteristics of the patients

	Aortic distensibility		Aortic strain	
	r value	p value*	r value	p value*
Age	**–0.271**	**0.006**	0.183	0.69
Duration of DM	–0.172	0.05	**–0.148**	0.03
HT	0.51	0.613	0.47	0.645
FBG	**–0.292**	**0.003**	**–0.265**	**0.008**
T. chol	0.30	0.768	0.27	0.79
LDL	0.54	0.591	0.21	0.834
HDL	0.142	0.16	0.115	0.253
Triglyceride	–0.23	0.224	–0.104	0.301
BMI	0.30	0.77	0.09	0.32
HsCRP	–0.150	0.136	–0.163	0.106
HbA1c	**0.283**	**0.004**	**0.279**	**0.005**

FBG: Fasting blood glucose, DM: Diabetes mellitus, HbA1c: Glycosylated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, T.chol: Total cholesterol, BMI: Body mass index, hsCRP: High-sensitivity C-reactive protein.
* Statistical significance (p< 0.05).

DISCUSSION

DM is a major risk factor for coronary artery disease and stroke[13]. Patients with type 2 DM have a 2-4 fold increased risk for cardiovascular diseases. Eighty percent of patients die because of atherosclerosis[14]. On the other hand, this ratio is only 30% in non-diabetic population.

The duration and severity of hyperglycemia are important risk factors for microvascular complications of diabetes[15]. However, the relation between macrovascular complications and the duration and severity of diabetes has not been shown clearly[16,17].

Arterial stiffness is an important marker of cardiovascular mortality and morbidity. Increase in arterial stiffness leads to decrease in coronary arterial filling during diastole by increasing the oxygen consumption and afterload of the myocardium. In previous studies, the authors showed that aortic elasticity parameters could be evaluated directly by color tissue Doppler[18-20].

Echocardiography-derived aortic strain and distensibility are non-invasive parameters in the evaluation of arterial stiffness[21]. Sen et al. investigated a new echocardiographic parameter of aortic stiffness termed as aortic propagation velocity in patients with coronary artery disease in their study. They found that aortic strain, distensibility, and propagation velocity were significantly lower in the coronary artery disease group than in the non-coronary artery disease group[22]. In some studies, it was shown that arterial stiffness was increased in patients with diabetes[19,21,23]. DM increases the stiffness by accumulating glycosylated end products on the arterial wall[24]. Thickening of intima and media layers because of the microvascular degenerative effect of DM leads to a decrease in arterial walland this causes an increase in arterial stiffness[25]. DM also impairs endothelial functions; therefore, this endothelial-derived relaxation is disturbed[26]. The degree of change in the endothelial function and aortic wall elasticity depends on the duration of DM[27,28]. In a study performed by Toutouzas et al., they showed that aortic elasticity decreased as the duration of DM increased. In the same study, they also found that aortic elasticity was negatively correlated with blood fasting glucose levels[19]. In our study, we found that aortic strain and distensibility were lower in group 3 than in groups 1 and 2 because of an increase in aortic stiffness. This means that HbA1c, which is a marker of long-term blood glucose level, is positively correlated with aortic stiffness. Long-term increase in the blood glucose level leads to a decrease in aortic elasticity and increase in aortic stiffness. Our study also showed that the duration of DM was related to aortic stiffness.

Arterial stiffness particularly increases in the proximal arteries as the patients age increases[15]. Age is an independent risk factor for arterial stiffness. In our study, we found that age was significantly related to aortic stiffness.

Another risk factor for arterial stiffness is the blood cholesterol level. High blood cholesterol level induces atheromatous plaque collection and atherosclerotic changes in the arterial wall. Tomochika et al. showed that compared with the control group, aortic stiffness was statistically significantly increased in the familial hypercholesterolemia group. They also demonstrated that aortic stiffness was correlated with pretreatment blood cholesterol level[29]. In our study, we did not observed a statistically significant correlation between the blood cholesterol level and aortic stiffness within groups. This might be due to the fact that total cholesterol, LDL, and triglyceride levels in our study were not as high as those in other studies.

Guray et al. found that the C-reactive protein level was correlated with aortic stiffness in patients with metabolic syndrome[30]. In our study, we did not find any relation between the C-reactive protein level and aortic stiffness in patients with type 2 DM. The reason might be that our patients only had diabetes and the difference in their systolic–diastolic blood pressure was not so high.

In our study, we evaluated many risk factors affecting arterial stiffness together. Results of our study showed that optimum control of hyperglycemia may lead to improvement in aortic elasticity parameters.

CONCLUSION

Aortic stiffness was increased in patients with type 2 DM who have high blood fasting glucose and HbA1c levels. The duration of DM was related to aortic stiffness. Elasticity parameters, which are determined by echocardiography, may be helpful in the estimation of cardiovascular risk in patients with type 2 DM.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: EK, TŞ
Analysis/Interpretation: TŞ, EK
Data Acquisition: EK
Writing: TŞ, EK
Critical Revision: ST, SG
Final Approval: All of authors

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