Tip 2 Diyabetes Mellitus'lu Hastalarda Glikolize Hemoglobin (Hemoglobin A1c) ile Aortik Sertlik Arasındaki İlişki

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ABSTRACT

Introduction: Type 2 diabetes mellitus is a major risk factor for cardiovascular diseases and responsible for increase in cardiovascular mortality. Chronic hyperglycemia is related with 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.

Materials and Method: A hundred patients with type 2 diabetes mellitus were included in the study. Patients divided into 3 groups according to HbA1c level (Group 1 HbA1c ≤ 6, group 2 HbA1c between 6-7 and group 3 HbA1c ≥ 7).

Results: Statistically significant difference was found between groups according to blood glucose level, duration of diabetes and oral anti-diabetics and insulin therapy. 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 (respectively r=-0.265; p= 0.008, r= 0.279; p=0.005 and r=-0.14; p= 0.03).

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

Keywords: Aortic stiffness, diabetes mellitus

Relation Between Glycosylated Hemoglobin (Hemoglobin A1c) and Aortic Stiffness In Type 2 Diabetic Patients

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ÖZET

Giriş: Tip 2 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 Metod: Çalışmamıza kliniğimize başvuran Tip 2 DM'lu 100 hasta alındı. Hastalar HbA1c değerlerine göre 3 gruba ayrıldı.

Bulgular: Gruplar arasında açlık kan şekerleri, DM süresi ve oral antidiyabetik yada insülin kullanımında istatistiksel olarak anlamlı şekilde farklı bulundu. Aortik esneyebilirlik ve HBA!C 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 şekerive HbA1c düzeyine sahip tip 2 diyabet hastalarında aortik sertliğin arttığını gösterdik. aynı zamanda çalışmamız diyabetin süresi ile aortik sertliğin ilişkili olduğunu göstermiştir. Ekokardiyografiyle noninvaziv metod 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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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 2 to 3 fold in diabetic patients (**2**). It is well known that chronic hyperglycemia is related with microvascular complications but its relation with macrovascular complications has not been exactly shown (**3,4**).

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

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

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

PATIENTS AND METHODS

The characteristics of the study

A hundred patients with type 2 diabetes mellitus admitted to our outpatient clinics between January 2010 and March 2010 were included prospectively in this study. American Diabetes Association criteria were used for the diagnosis of the diabetes (**11**). All participants were informed about the study and their consents were obtained. Patients who had exclusion criteria 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 glycosylated hemoglobin (HbA1c) level (Group 1 HbA1c ≤ 6, group 2 HbA1c between 6-7 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 hours starvation.

Exclusion criteria were **r**ecent 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 haematological diseases.

Transthoracic echocardiographic examination

All patients underwent transthoracic echocardiographic examination by vivid 7 Dimension (General Electric) echocardiography device with a 2.5-3.5 MHz transducer. All echocardiographic examinations were performed by same operator who was blind for groups of the patients. Ejection fraction, left ventricular end

systolic and end diastolic diameters were noted. The 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 peak of the QRS tracings (**figure 1**). Five consecutive measurements were made and their average was calculated.

Aortic strain and aortic distensibility were calculated from the echocardiography-derived aortic diameters and the clinical blood pressure. Aortic pulse pressure was calculated by subtracting diastolic aortic pressure from 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 (mm hg): systolic blood pressure – diastolic blood pressure
Aortic strain (%) = (aortic systolic diameter - diastolic diameter) x 100 / diastolic diameter
Distensibility (cm^2/dyn) = (2 x aortic strain) / (systolic pressure - diastolic pressure)

Statistical analysis

All data were evaluated by the SPSS (Statistical for social Sciences for Windows, version 10, SPSS Inc. ,Chicago , Illinois, USA). Parametric data were expressed as mean ± standard deviation and qualitative data as numbers and percentages. Distribution of the variables was assessed by Kolmogorov Smirnov test. Kruskal Wallis test was used to assess the correlations between nonparametric data. Parameters which were significantly different between groups were assessed by the Bonferroni-corrected Mann Whitney U–test (statistical significance p<0,017) .Categorical variables were evaluated by chi-square test. Spearman rho test was used for the evaluation for the numerical variables.

RESULTS

Study population (100 patients) was composed of 41 male (%41), 59 female (%59) patients. 68 patients (%68) had hypertension, 79 patients (%79) had hyperlipidemia, 47 (%47) patients had family history of coronary artery disease and 12 (%12) patients were cigarette smoker. Group 1, group 2 and group 3 were composed of 15, 31 and 54 patients respectively. Demographical and clinical characteristics of the patients were demonstrated in **table 1** and **table 2**. There was no statistical difference according to age, family history, hypertension, total cholesterol, LDL, HDL, triglyceride and body mass index between groups.

Fasting blood glucose level, duration of diabetes, use of oral anti-diabetic medication or insulin were statistically significantly different between groups. Blood fasting glucose level was significantly higher in group 3 than the other groups after Bonferroni-corrected Mann Whitney U test evaluation (p<0.001). Duration of DM was significantly longer in group 3 (p= 0.009). The use of oral anti-diabetic medication was significantly higher in group 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 the groups (**table 3**). Systolic-diastolic aortic diameter change, aortic strain and aortic distensibility were significantly different between the groups (p<0.001). Systolic-diastolic aortic

diameter change, 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 group 1 and group 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 duration of DM (r=-0.172; p= 0.05), fasting blood glucose (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, HbA1c level and duration of DM (**figure 3**).

DISCUSSION

Diabetes mellitus is a major risk factor for coronary artery disease and stroke (**13**). Type 2 diabetic patients have 2 to 4 fold increased risk for cardiovascular diseases. Eighty percent of patients dies due to atherosclerosis (**14**). On the other hand, this ratio is only % 30 in non-diabetic population.

Duration and severity of hyperglycemia are the important risk factors for microvascular complications of diabetes (**15**). However, it has not been clearly shown the relation between macrovascular complications and the duration and severity of the diabetes (**16,17**).

Arterial stiffness is 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 myocardium. In previous studies, the authors showed that aortic elasticity parameters could be evaluated directly by color tissue Doppler (18**,19,20**)

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 named aortic propagation velocity in patients with coronary artery disease in their study. They found that aortic strain, aortic distensibility and aortic propagation velocity were significantly lower in the coronary artery disease group compared to the non-coronary artery disease group (**22**). In some studies, it was shown that arterial stiffness was increased in diabetic patients (**19,21,23**). DM increases stiffness by accumulating glycosylated end products on the arterial wall (**24**). Thickening of intima and media layers due to microvascular degenerative effect of DM leads to decrease in elasticity of the arterial wall which causes increase in arterial stiffness (**25**). DM also impairs endothelial functions as a result of this endothelial derived relaxation is disturbed (**26**). The degree of change in endothelial function and aortic wall elasticity depends on duration of the 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 (**19**). In our study, we found that aortic strain and distensibility were lower in group 3 than group 1 and 2 due to 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 blood glucose level leads to decrease in aortic elasticity and increase in aortic stiffness. Our study also showed that duration of DM was related with aortic stiffness.

Arterial stiffness increases especially in proximal arteries as the patient gets older (**15**). Age is an independent risk factor for arterial stiffness. In our study, we found that age was significantly related with aortic stiffness.

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

Guray et al found that C-reactive protein was correlated with aortic stiffness in patients with metabolic syndrome (**30**). In our study, we did not found any relation between C-reactive protein level and aortic stiffness in type 2 diabetic patients. The reason might be that our patients were only diabetic and their systolic-diastolic blood pressure difference 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 type 2 diabetic patients who have high blood fasting glucose and high HbA1c level. The duration of DM was related with aortic stiffness. Elasticity parameters which are determined by echocardiography may be helpful in the estimation of cardiovascular risk in type 2 diabetic patients.

LEGENDS OF THE FIGURES

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

Figure 2: The relation between HbA1c level and aortic distensibility

Figure 3: The relation between HbA1c level and aortic strain

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Table 1: Clinical and laboratory findings of all three groups

		All patients n: 100	HbA1c level 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 and B show statistical difference according to Bonferroni-corrected Mann Whitney U test.*

* *Statistical significance (p<0.05)*

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Table 2: Clinical and laboratory findings of the patients

	HbA1c level			
	I	II	III	
	n: 15	n: 31	n: 54	P value
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
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 and B show statistical difference according to Bonferroni-corrected Mann Whitney U test.*
* *Statistical significance ($p<0.05$)*

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Table 3: Echocardiographic and blood pressure parameters of the patients

	Grup I	Grup II	Grup III	p value
Aort systolic diameter (cm)	3.56 (3.0-4.5)	3.59 (3.0-4.5)	3.58 (2.7-4.8)	0.918
Aort 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 and B show statistical difference according to Bonferroni-corrected Mann Whitney U test.*

* *Statistical significance ($p<0.05$)*

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 ($p<0.05$)

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