Relationship between HbA_{1c} and coronary flow rate in patients with type 2 diabetes mellitus and angiographically normal coronary arteries

Anjiyografik olarak normal koroner arteri olan tip 2 diyabetli hastalarda HbA_{1c} ile koroner akım hızı arasındaki ilişki

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Objectives: We examined the relationship between glycosylated hemoglobin (HbA_{1c}) level and coronary flow rate in patients with type 2 diabetes mellitus (DM) and angiographically normal coronary arteries.

Study design: The study included 54 consecutive patients (36 males, 18 females; age range 37 to 72 years) with type 2 DM, whose coronary arteries were found normal on coronary angiography. All patients underwent echocardiography and plasma HbA_{1c} levels were measured before coronary angiography. To determine slow coronary flow (SCF), coronary flow rates of the left anterior descending (LAD), circumflex (Cx), and right coronary (RCA) arteries were assessed using the TIMI frame count (TFC) method.

Results: None of the patients had echocardiographic abnormalities. The mean HbA_{1c} level was 7.4±2.0%, and the mean TFCs were 34.3±6.5, 22.4±3.5, and 20.4±2.2 for the LAD, Cx, and RCA, respectively. HbA_{1c} levels were <7% in 26 patients, and ≥7% in 28 patients. Thirty-eight patients (70.4%) were found to have SCF in at least one coronary artery. TIMI frame counts of all three coronary arteries were significantly greater in patients in whom HbA_{1c} was ≥7% (p<0.001). TIMI frame counts showed significant correlations with the HbA_{1c} level (LAD: r=0.782; Cx: r=0.707; RCA: r=0.515; p<0.001 for all). The mean HbA_{1c} level was significantly higher in patients with SCF compared to patients without SCF (7.8±1.9% *vs.* 5.6±0.9%; p<0.001). The incidence of SCF was significantly greater in patients with HbA_{1c} ≥7.0% than those with HbA_{1c} <7.0% (96.4% *vs.* 61.5%; p=0.004). Increased HbA_{1c} (≥7%) significantly increased the risk for SCF in at least one coronary artery (OR=16.875; 95% CI 1.972-144.38).

Conclusion: Our findings suggest that there is a strong correlation between the HbA_{1c} level and coronary flow rate.

Key words: Blood flow velocity; coronary circulation; diabetes mellitus, type 2/complications; endothelium, vascular; hemoglobin A, glycosylated; hyperglycemia/complications.

Amaç: Bu çalışmada, tip 2 diabetes mellitus (DM) tanılı ve anjiyografide koroner arterleri normal bulunan hastalarda glikosile hemoglobin (HbA_{1c}) düzeyi ile koroner akım hızı arasındaki ilişki incelendi.

Çalışma planı: Çalışmaya tip 2 DM tanısı olan ve koroner arter hastalığını şüphesiyle yapılan anjiyografide koroner arterleri normal bulunan 54 ardışık hasta (36 erkek, 18 kadın; yaş aralığı 37-72) alındı. Koroner anjiyografiden önce tüm hastalar ekokardiyografi ile incelendi ve plazma HbA_{1c} düzeyleri ölçüldü. Yavaş koroner akım (YKA) tayini için, sol ön inen (LAD), sirkumfleks (Cx) ve sağ koroner (RCA) arterlerin akım hızları TIMI kare sayısı (TKS) yöntemiyle hesaplandı.

Bulgular: Ekokardiyografide hiçbir hastada anormallik görülmedi. Tüm grupta ortalama HbA_{1c} değeri %7.4±2.0 ve ortalama TKS değerleri LAD için 34.3±6.5, Cx için 22.4±3.5, RCA için 20.4±2.2 bulundu. HbA_{1c} değeri 26 hastada <%7, 28 hastada ≥%7 idi. Otuz sekiz hastada (%70.4) en az bir koroner arterde YKA saptandı. Üç koroner arterde de TKS değerleri HbA_{1c} değeri ≥%7 olan hastalarda anlamlı derecede yüksek bulundu (p<0.001). HbA_{1c} düzeyleri ile TKS değerleri arasında anlamlı pozitif ilişki saptandı (LAD: r=0.782; Cx: r=0.707; RCA: r=0.515; tümü için p<0.001). Yavaş koroner akım görülen hastalarda ortalama HbA_{1c} değeri, koroner akımı normal hastalara göre anlamlı derecede yüksek bulundu (%7.8±1.9 ve %5.6±0.9; p<0.001). Benzer şekilde, HbA_{1c} değeri ≥%7 olan hastalarda YKA oranı da anlamlı derecede yüksekti (%96.4 ve %61.5; p=0.004). Yüksek HbA_{1c} düzeylerinin (≥%7) en az bir koroner arterde YKA görülme riskini anlamlı derecede artırdığı görüldü (OO=16.875; %95 GA 1.972-144.38).

Sonuç: Bulgularımız HbA_{1c} ile koroner arterlerin akım hızları arasında kuvvetli bir ilişki olduğunu göstermektedir.

Anahtar sözcükler: Kan akım hızı; koroner dolaşım; diabetes mellitus, tip 2/komplikasyon; endotel, vasküler; hemoglobin A, glikosile; hiperglisemi/komplikasyon.

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Diabetes mellitus (DM) is known to yield micro- and macrovascular complications via two common mechanisms: hyperglycemia and hyperinsulinemia. Several studies have shown that hyperinsulinemia is an independent risk factor for ischemic heart disease and also a good predictor of mortality from coronary heart disease in healthy individuals.[1-3] Besides, hyperglycemia is known to be associated with early and accelerated atherosclerosis. Although there have been decreases in microvascular complications with improvements in glycemic control,[4] this has not been so firmly established in macrovascular disease. Plasma hemoglobin A1c (HbA_{1c}) reflects mean ambient fasting and postprandial glycaemia over a 2-3 month period. Elevated HbA_{1c} levels (≥7%) are associated with a higher incidence of micro- and macrovascular complications in patients with type 1 and type 2 diabetes mellitus.[5] On the other hand, lower HbA_{1c} levels were found to be associated with reduction in the incidence of macrovascular complications in patients with DM, though this did not reach statistical significance.[6,7] Slow coronary flow (SCF) is a clinical entity in which there is normal coronary anatomy with increased microvascular resistance. Histopathological studies have demonstrated loss of luminary diameter, capillary and endothelial damage in these patients.[8,9] Some investigators also showed that vascular endothelial injury was present in patients with SCF.[10]

The purpose of this study was to investigate the relationship between HbA_{1c} levels and coronary flow rate determined by the TIMI frame count (TFC) method[11] in diabetic patients who were diagnosed to have normal coronary arteries at coronary angiography.

PATIENTS AND METHODS

Patient group. The study included 54 consecutive patients (36 males, 18 females; age range 37 to 72 years) with type 2 DM, who underwent coronary angiography, between March 2005 and August 2007, for clinical symptoms or electrocardiographic findings suggestive of coronary artery disease, and were found to have normal coronary arteries. All the patients were diagnosed according to the World Heart Organization criteria for DM.[12] All participants gave written informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of our medical school.

All patients underwent echocardiography for determination of left ventricular dimension, function, and mass.

Exclusion criteria were cardiomyopathies, severe valvular diseases, chronic renal disease[13] and, to avoid possible confounding effects of lipid modifying drugs, treatment for familial hyperlipidemia. Height and weight were measured using a standardized protocol. Body mass index was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Hypertension was defined as blood pressure greater than 140/90 mmHg or being on treatment with antihypertensive medications. Current smokers were accepted as smokers. Clinical data on age, presence of hypertension and smoking, positive family history, and laboratory data were also verified from the patients' files.

Blood samples. For each participant, blood samples for HbA_{1c} were collected after an overnight fasting and analyzed on the same day.

Diagnosis of normal coronary arteries. Selective coronary angiography was performed through the femoral artery under local anesthesia (2% lidocaine) and with the use of nonionic contrast media (Iohexol 350), using standard multiangulated angiographic techniques.[14] Angiograms were assessed visually by an experienced angiographer for the diagnosis of normal coronary arteries.

Evaluation of coronary flow rate. TIMI frame count provides quantifiable and valuable information about blood flow rate within a given coronary artery.[11] Angiographies of all the patients were evaluated and their TFCs were calculated for the left anterior descending coronary artery (LAD), circumflex artery (Cx), and right coronary artery (RCA) by two independent observers who were blinded to HbA_{1c} levels. Any disagreement was resolved by a third observer. The distal reference points were the terminal bifurcations of the LAD and Cx, and the first side-branch of the posterolateral artery in the RCA. The first frame and the last frame were accepted as the point at which the radiopaque material first appeared through the ostium of the coronary artery and the most distal appearance of the radiopaque material, respectively. TIMI frame count for each artery was estimated by subtracting the first frame from the last frame. Normal values for TFC of the LAD, Cx, and RCA were taken as 36.2±2.6, 22.2±4.1, and 20.4±3.0, respectively, after multiplying the TFC of the LAD by 0.7 to obtain the corrected TFC.[15] The patients who had TFCs greater than the predicted normal values were assessed to have SCF.

Statistical methods. The results were expressed as mean ± standard deviation (SD) and percentages. In-

Table 1. Baseline characteristics of the two groups based on the HbA1c values

	HbA_{1c} <7% (n=26)			HbA_{1c} ≥7% (n=28)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			49.9±7.1			51.9±6.4	0.286
Sex							0.798
Male	13	50.0		13	46.4		
Female	13	50.0		15	53.6		
Hypertension	17	65.4		18	64.3		0.934
Smoking	14	53.9		16	57.1		0.812
Body mass index (kg/m^2)			30.4±0.1			31.5±0.1	0.74
Total cholesterol (mg/dl)			227±13			225±14	0.785
LDL cholesterol (mg/dl)			113±14			110±14	0.538
HDL cholesterol (mg/dl)			37±8			37±7	0.924
Triglyceride (mg/dl)			153±12			153±13	0.948
Hemoglobin A1c (%)			5.7±0.8			9.0±1.3	**0.000**
TIMI frame count							
Left anterior descending			29.2±3.0			39.0±5.1	**<0.001**
Circumflex			20.1±2.5			24.6±2.7	**<0.001**
Right coronary artery			19.3±2.3			21.5±1.5	**<0.001**

dependent samples t-test was used to compare parametric data after testing for normality distribution using the Levene test. Categorical data were compared with the chi-square test. Correlations between HbA_{1c} and SCF were assessed by the Spearman's rank correlation coefficient. All statistical tests were performed with the SPSS computing program (for Windows, version 15.0). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

The mean age was 52.8±7.6 years in females and 52.1±8.7 years in males. None of the patients had echocardiographic abnormalities in terms of systolic or diastolic function, left ventricular mass, and dimensions. The mean HbA_{1c} level was 7.4±2.0%, and the mean TFCs were 34.3±6.5, 22.4±3.5, and 20.4±2.2 for the LAD, Cx, and RCA, respectively. Of 54 patients with type 2 DM, 38 patients (70.4%) were found to have SCF in at least one coronary artery.

Baseline characteristics of the patients divided into two groups based on the levels of HbA_{1c} (HbA_{1c} <7% and HbA_{1c} ≥7%) are given in Table 1. There were no significant differences between the two groups with respect to clinical characteristics other than the HbA_{1c} levels (Table 1). TIMI frame counts of all three coronary arteries were significantly greater in patients having HbA_{1c} ≥7% (p<0.001, Table 1).

TIMI frame counts of the LAD, Cx, and RCA showed significant correlations with the HbA_{1c} level (LAD: r=0.782, p<0.001; Cx: r=0.707, p<0.001; RCA: r=0.515, p<0.001, Fig. 1).

The mean HbA_{1c} values were found as 7.8±1.9% and 5.6±0.9% in patients with and without SCF, respectively, indicating a significant difference (p<0.001). This significant difference was independent from gender and sex.

The incidence of SCF in patients having an HbA_{1c} value of ≥7.0% was significantly greater than those having an HbA_{1c} value of <7.0% (96.4% *vs*. 61.5%; p=0.004). Having an HbA_{1c} value of ≥7% significantly increased the risk for SCF in at least one coronary artery (OR=16.875; 95% CI 1.972-144.38).

DISCUSSION

In the present study, we examined the relationship between HbA_{1c} and SCF. Our study was conducted in patients with type 2 DM, who were admitted to our clinic with classical angina complaints and were found to have normal coronary arteries at angiography. We found a statistically significant positive correlation between HbA_{1c} and TFCs of all three coronary arteries examined, suggesting that as the glycemic control worsens, coronary flow becomes slower. Chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of various organs especially the heart and blood vessels.[5,16,17] Increased glucose levels result in increased oxidative stress and protein glycation of vessel walls, accelerating the atherosclerotic process.[17] Fontbonne et al.[2] clearly demonstrated that hyperinsulinemia was a predictor of coronary heart disease mortality in a healthy population. Several studies have shown that insulin has a regulatory effect on coronary vasoreactivity in healthy individuals.

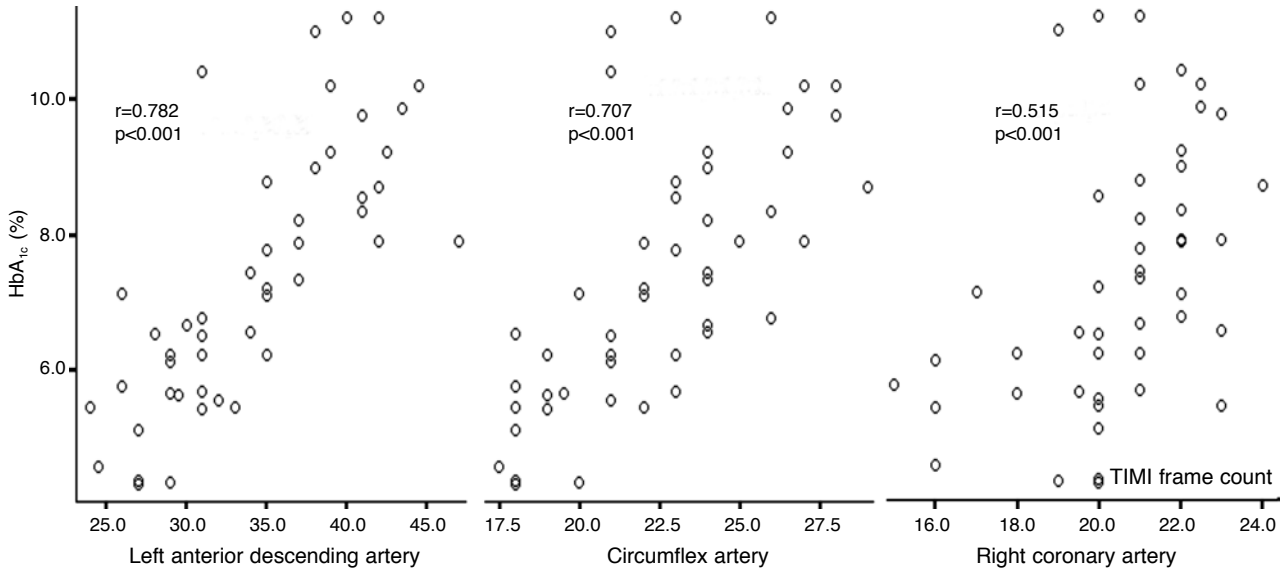

Figure 1. Correlations between HbA_{1C} and TIMI frame counts of the three coronary arteries.

Rogers et al.[18] showed that glucose-insulin-potassium infusion increased coronary sinus blood flow. Laine et al.[19] showed that insulin was capable of modulating coronary vasoreactivity in healthy subjects through acting as a vasoactive peptide in peripheral and myocardial vasculature. Considering the established finding that SCF causes anginal symptoms,[20] the complaints of the patients should be approached in the context of glycemic control. Our findings indicate that a more intensive therapy and also a more intensive approach are needed for diabetic patients with poorly controlled serum glucose.

Diabetes is one of the most important causes of atherosclerosis.[21] It has been clearly demonstrated that inflammation plays an important role in the initiation, development, and evolution of atherosclerosis, suggesting that atherosclerosis is an inflammatory disease.[22,23] Inflammation has been reported to be a major contributing factor in many cardiovascular events, involving in various clinical settings of coronary artery disease.[24,25] A strong relationship has been found between inflammation and SCF.[10,26] Turhan et al.[26] found significantly higher serum ICAM-1, VCAM-1, and E-selectin levels in patients with SCF compared to control subjects with normal coronary flow. They concluded that SCF was an indicator of endothelial activation and inflammation. Hemoglobin A_{1c} is also a strong inflammatory marker.[27] Our study showed a strong relationship between SCF and high HbA_{1c} levels. Advanced glycation end-products (AGE) play a major role in the mechanism of plaque formation and rupture. The underlying reason for increased AGE in serum is mostly poor glycemic control.[28] These end-products show their effects mainly by increasing oxidative stress in the arterial wall and impairing endothelial functions.[16,29,30] It has been demonstrated that both extensive atherosclerosis and endothelial dysfunction may alter coronary flow rate.[8,11] Most of the diabetic patients presenting with chest pain and other symptoms are found to have obstructive lesions on coronary angiography, requiring emergency revascularization. However, a considerable number of diabetic patients with complaints of classic angina have angiographically normal epicardial coronary arteries.[30] Bax et al.[31] showed that these patients had uncontrolled serum glucose levels. Coronary angiography shows obstructive plaques only at the luminal level, it is not helpful in assessing periluminal atherosclerosis, which is the bigger part of the iceberg.[20,32] Pekdemir et al.[32] found that increased intravascular resistance was a result of diffuse atherosclerotic disease demonstrated by intravascular ultrasound.

Our study was limited by its relatively small sample size, simply because it was not easy to find diabetic patients with normal coronary arteries. As the small sample size decreases statistical power for equivalence testing, negative results may simply be due to chance. Besides, coronary angiography is a weak diagnostic tool for the assessment of atherosclerosis, which may potentially involve many parts of the arterial wall. We believe that intravascular ultrasonography (IVUS) would increase the impact of our findings, because it offers better resolution for the radial extension of involvement of the arterial wall.

In conclusion, a strong positive correlation exists between HbA_{1c} and coronary flow rate. Higher HbA_{1c} levels are related to SCF in diabetic patients with normal coronary arteries. This relationship should be taken into consideration in diabetic patients with SCF as an indicator of atherosclerotic involvement.

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