Relationship between Hba1c levels and the severity of coronary artery disease in diabetic patients

Diyabetik hastalarda Hba1c düzeyleri ile koroner arter hastalığı ciddiyeti arasındaki ilişki

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Abstract

Background: Diabetes Mellitus (DM) is one of the most important risk factors for coronary artery disease (CAD). The hemoglobin A1c (HbA1c) is used for evaluating glycemic control in DM patients. It was shown in some studies that; HbA1c levels may be related to cardiovascular risk and all cause mortality in the general population with or without DM. We aimed to examine the relationship between HbA1c level and severity of CAD in diabetic patients.

Methods: One hundred and eleven consecutive diabetic patients who underwent coronary angiography in our clinics were included in the study. The extent of CAD in each patient was calculated via Gensini score. The correlation between the HbA1c level and Gensini score was evaluated.

Results: The mean values of HbA1c and Gensini scores were found to be 7.39 ± 2.06, and 42.02 ± 32.70, respectively. There was also a significant positive linear correlation between the HbA1c and Gensini scores (r=0.762, p<0.001). The patients were grouped according to HbA1c levels (HbA1c ≤7%; Group 1 and HbA1c >7%; Group 2). Gensini scores were found to be significantly higher in Group 2 than Group 1 (p<0.001). HbA1c levels were significantly positively correlated with Gensini scores in both 2 groups (r=0.534, r=0.658, p<0.001 for both, respectively). Significant independent association between the increased Gensini score and Hba1c was found in linear regression analysis (p<0.001).

Conclusion: This study showed the relation between HbA1c levels and the severity of CAD in patients with type 2 DM. By this way, the importance of appropriate glycemic control has been emphasized in diabetic patients.

Key words: Diabetes mellitus, Gensini score, Coronary artery disease, Hemoglobin A1c.

Özet

Amaç: Diabetes Mellitus (DM), koroner arter hastalığı (KAH) için önemli risk faktörlerinden biridir. Hemoglobin A1c (HbA1c), DM hastalarında glisemik kontrolü değerlendirmekte kullanılır. Bazı çalışmalarda, HbA1c düzeyleri ile kardiyovasküler risk ve tüm nedenlere bağlı mortalite arasında, diyabetik veya diyabetik olmayan genel populasyonda ilişki gösterilmiştir. Biz diyabetik hastalarda, HbA1c düzeyi KAH ciddiyeti arasındaki ilişkiyi incelemeyi amaçladık.

Materyal ve metod: Kliniğimizde koroner anjiyografi (KAG) yapılan 111 ardışık diabetik hasta çalışmaya alındı. Her hastada KAH yaygınlığı Gensini skoru ile hesaplandı. HbA1c düzeyi ve Gensini skoru arasında korelasyon değerlendirildi.

Bulgular: HbA1c ve Gensini skorları ortalama değerleri sırasıyla 7.39 ± 2.06 ve 42.02 ± 32.70 bulunmuştur. Aynı zamanda, HbA1c ve Gensini skorları arasında anlamlı pozitif lineer bir ilişki bulundu (r = 0.762, p <0.001). Hastalar HbA1c seviyelerine göre gruplandırıldı (HbA1c ≤7%; Grup 1 ve HbA1c >7%; Grup 2). Gensini skoru Grup 2'de Grup 1'e göre anlamlı olarak yüksek bulunmuştur(p <0.001). HbA1c düzeyleri ile Gensini skorları arasında her iki grupta da pozitif korelasyon saptandı (sırasıyla, r = 0.534, r = 0.658, her ikisi için p <0.001). Lineer regresyon analizinde, artan Gensini skoru ile HbA1c düzeyleri arasında anlamlı bağımsız ilişki tespit edildi (p <0,001).

Sonuç: Bu çalışmada tip 2 Diyabeti olan hastalarda HbA1c düzeyleri ile KAH ciddiyeti arasındaki ilişki gösterilmiştir. Bu sayede, diyabetik hastalarda, uygun glisemik kontrolün önemi vurgulanmıştır.

Anahtar kelimeler: Diabetes mellitus, Gensini skoru, Koroner arter hastalığı, Hemoglobin A1c.

Introduction

Coronary artery disease (CAD) is one of the most common causes of mortality and morbidity in the whole world. Diabetes Mellitus (DM) is one of the most important major risk factors for CAD (1). CAD risk is increased 2 or 3 folds in patients with DM when compared to the normal population (2). Frequency of morbidity and mortality of CAD associated with DM was positively correlated with impaired plasma glucose regulation (3-5). Studies showed that elevated plasma glucose levels negatively affect the severity of atherosclerosis and cardiac remodeling process in all populations regardless of whether DM existing or not. It's known that good glycemic control reduces the frequency and progression of atherosclerotic diseases in patients with DM (5-8). Hemoglobin A1c (HbA1c), which is used for monitoring the regulation of plasma glucose levels of diabetic patients, now becomes one of the diagnostic criteria for DM (9). There is a significant association between HbA1c levels and atherosclerosis even in non-diabetic populations with CAD and even in HbA1c level of normal reference range (10, 11). Several studies revealed an association between HbA1c levels and severity of peripheral artery disease and the number of affected coronary arteries in CAD (5, 12, 13). Some studies showed that the severity of coronary artery disease is related with mortality and morbidity (10-13). Several scoring systems are being used to determine the severity of coronary artery disease. Gensini scoring system is one of these systems which are most commonly used for this purpose (14). There are some studies in the literature to evaluate the relation between severity scores and HbA1c levels in patients with acute coronary syndrome (15, 16). But, to our knowledge, there are no studies in literature, evaluating the association between HbA1c levels and severity scores in patients with stable coronary artery disease and type 2 DM (T2DM).

In the present study, we aimed to investigate the association between HbA1c levels and severity of coronary disease, which has been determined by Gensini scoring system in diabetic patients with stable coronary artery disease.

Materials and methods

Patients

One hundred and eleven consecutive T2DM patients who were referred to our institution for angiography were retrospectively evaluated. Hypertension was defined as systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90 mmHg, and hyperlipidemia was diagnosed according to guideline of the National Cholesterol Education Program (ATP III). T2DM was diagnosed using the American Diabetes Association criteria (9). Renal insufficiency was defined as estimated glomerular filtration rate (eGFR) to be < 60 (ml/min/1.73 m2). eGFR value was calculated by modification of diet in renal disease study group equation (17). Subjects with a history of coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, prior myocardial infarction, type 1 DM, renal or hepatic insufficiency, and patients with acute coronary syndrome were excluded from the study. The study was approved by the ethics committee of our institute, and the procedures were in accordance with the institutional guidelines.

Coronary Angiography

Coronary angiography was performed by standard Judkins techniques via femoral, brachial or radial approach. Two experienced cardiologists who were blinded to study analyzed the angiographic records. Angiography results were divided into Group A (≥50% obstruction in ≥1 coronary artery) and Group B (<50% obstruction in coronary artery). Gensini scoring system evaluates the severity of CAD. A score of 1 indicates 1-25%, 2 indicates 26-50%, 4 indicates 51-71%, 8 indicates 76-90, and 16 indicates 91-99% narrowing in the lumen of coronary artery and a score of 32 indicates completely occluded artery. The Gensini score multiplied with a factor which is associated to the importance of coronary artery. The factor is 5 for left main system lesions, 2.5 for proximal left anterior descending artery and proximal circumflex artery lesions, 1 for distal left anterior descending artery, mid/distal circumflex artery and right coronary artery lesions and 0.5 for lesions in any other artery branches (14).

Biochemical Investigations

Medical records of the patients were screened retrospectively for the biochemical data. Creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin, and glucose levels of patients were recorded. HbA1c measurement was performed by an immunoturbidimetric assay. For the purpose of this study, patients were divided into 2 groups based on the glycostylated hemoglobin results: Group 1 (HbA1c ≤7%) and Group 2 (HbA1c >7%).

Statistical analysis

All statistical analyses were performed using the SPSS software package 15.0 (SPSS Inc, Chicago, IL, USA). Data are presented as frequencies and percentages for categorical variables and mean ± SD or median for continuous variables, unless otherwise indicated. Distribution of continuous variables was evaluated with one-sample Kolmogorov Smirnov test. Differences between two groups were assessed using the Chi-square test for categorical variables and unpaired t-test for normally distributed continuous variables. Because Gensini, triglycerides, GGT and creatinine values were not normally distributed, between-group differences were assessed by the Mann-Whitney U-test. Correlation between continuous variables was determined by Pearson correlation coefficients. Binary logistic regression analysis was performed to identify the independent predictors of CAD severity. To establish independent determinants of HbA1c, multivariate stepwise linear regression analysis was made with HbA1c as dependent variable and covariates for glucose, age, blood pressure, cholesterol, triglycerides, blood urea nitrogen, creatinine, uric acid, and GGT. A value of $p<0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics

The sample of this study included 111 type 2 diabetic patients with age ranging from 32 to 82 (58.45 ± 9.48 year) [54 males (46.2%) and 57 females (53.8%)]. Baseline characteristics of the patients are shown in Table 1. The Gensini score ranged from 3.5 to 133 with a mean of 42.02 ± 32.70 as shown in Figure 1.

HbA1c Levels

A statistically significant positive correlation between Gensini scores and HbA1c levels were found. ($p<0.001$, $r=0.762$). Patients were grouped into group 1 and 2 according to the HbA1c level (HbA1c ≤7% or > 7%). Group 1 included 58 patients, (22 males and 36 females) and group 2 included 53 patients (32 males and 21 females) HbA1c levels were significantly positively correlated with Gensini scores in both 2 groups ($r=0.534$, $r=0.658$, $p<0.001$ for both, respectively) (Figure 2).

Table 1 shows the basic clinical and demographical specialties of the groups. There were significant differences found between the two groups as regards HbA1c, fasting glucose, HDL, Ejection fraction (EF) and Gensini (Table 1). Men and women did not differ significantly with regard to these parameters and correlations ($p>0.05$).

Gensini scores were significantly higher in group 2 than group 1 ($p<0.001$) (Figure 2). Linear multivariate regression analysis shown that high HbA1c levels are independent predictors of severe CAD (OR: 2.394, 95% for CI 1.596 to 3.591, $p<0.001$). Linear regression analysis was performed to show the significant independent association between the increased HbA1c and Gensini among patients (Table 2).

Discussion

The main findings of this study are; 1) A significant positive linear correlation between the HbA1c and Gensini score, 2) HbA1c to be a predictor of extensive coronary artery disease in stabile coronary artery disease with type 2 DM, 3) HbA1c ≥7% was found to be an independent predictor for CAD in logistic regression analysis.

DM is one of the major risk factors for CAD (1). Development of CAD in diabetic patients should be contributed by insulin resistance which is caused by impaired plasma glucose regulation and by the conditions related to insulin resistance such as dyslipidemia, inflammation and hypercoagulability (18). Previous studies revealed the association of HbA1c levels and number of affected coronary arteries in patients with acute coronary syndrome (5, 16). There was a similar association between HbA1c levels and peripheral artery diseases and transplanted coronary artery diseases (12, 13). Moreover, this association was regardless of whether there was the diagnosis of DM. It is not surprising such an association for HbA1c regardless of DM, when we take into account the effects of acute dysglycemia in the infarct area in patients with acute myocardial infarction (19) as chronic hyperglycemia has been identified as a risk factor for diabetic complications leading to accelerated atherosclerosis (20). Our results were similar to literature and revealed a statistically significant positive correlation between HbA1c levels and severity of coronary involvement in type 2 diabetic patients with stable coronary artery disease. Also, regression analyses revealed HbA1c levels to be an independent marker predicting CAD and its severity. Positive correlation between HbA1c and Gensini scores were noted even within group 1 (HbA1c ≤7%) and within group 2 (HbA1c >7%) separately. Gensini scores were found to be significantly different in these 2 groups.

HbA1c is a reliable marker for the assessment of increased glycosylation (9). It is a more valuable marker than fasting plasma glucose for the assessment of the risk of cardiovascular disease and mortality (10). HbA1c levels in patients with CAD predict the increased mortality in both short and long term (15). In United Kingdom Prospective Diabetes Study (UKPDS), every 1 percent increase in HbA1c was reported to be associated with mortality of any cause with a relative risk 1.24 for men and 1.28 for women (21).

An important proportion of patients with CAD are in stable condition. Various scoring systems and biological markers are being used to predict stable CAD patients without performing an angiography. DM is also a risk factor beside age and sex in scoring systems predicting CAD (22-24). Coronary angiography is still gold standard for the diagnosis of CAD. But coronary angiography is an invasive and expensive procedure with various risks and complications (25). Therefore, many researches are being carried out for a marker with high sensitivity to predict stable CAD patients. Our study showed that HbA1c may be a sensitive marker of severity of coronary involvement in stable CAD patients with T2DM.

Because of its asymptomatic nature, patients do not pay enough attention to stable CAD. Previous studies reported insufficiency in both in the diagnosis and in the treatment of stable CAD (26). Stable CAD is an important risk for community health. The neuropathy due to type 2 DM may cause asymptomatic cardiac events such as silent ischemia, acute coronary syndrome and sudden cardiac death. That's why we recommend that physicians to pay more attention to patients with higher HbA1c levels. And we think that HbA1c should be used as a marker of evaluation of this condition.

Limitations

This was a retrospective study, and the sample size was relatively small; thus some subgroup comparisons may have lacked power to detect significant differences for selecting variables. Also, another limitation of our study is that, drug use of most of the patients as antidiabetic, antihypertensive etc. could not be reached completely from the medical records.

Conclusions

This study showed the relation between HbA1c levels and the severity of coronary artery disease in patients with T2DM. By this way, the importance of appropriate glycemic control has been emphasized in diabetic patients.

Table 1: Anthropometrical, angiographic findings and clinical characteristics of groups

Variable	Group 1 (n=58)	Group 2 (n=53)	P value
Age (years)	55.77 ± 9.02	57.81 ± 6.74	0.179
Gender, Male/Female [n (%)]	22/36 (37.9/62.1)	32/21 (60.3/39.6)	**0.001**
Duration of diabetes mellitus (years)	7.70 ± 5.59	6.98 ± 5.74	0.510
Gensini score	24.51 ± 15.67	61.18 ± 35.72	**<0.001**
HbA1c (%)	6.02 ± 0.92	9.16 ± 1.55	**0.011**
Hypertension [n(%)]	25 (43.1)	27 (50.9)	0.413
Smoking [n(%)]	30 (51.7)	25 (47.2)	0.706
Fasting glucose (mg/dl)	134.03 ± 45.9	165.79 ± 53.91	**<0.001**
LDL (mg/dl)	122.28 ± 39.95	116.19 ± 38.99	0.450
HDL (mg/dl)	43.49 ± 13.04	38.48 ± 10.45	**0.040**
BMI (kg/m^2)	27.25 ± 4.28	28.06 ± 4.38	0.352
Hemoglobin (g/dL)	14.26 ± 2.01	13.58 ± 1.84	0.067
Creatinine (mg/dl)	1.02 ± 0.24	1.03 ± 0.07	0.061
Ejection fraction (%)	56.43 ± 10.53	52.75 ± 7.70	**0.037**

Values are presented mea n±SD or proportions/percentages. BMI; Body mass index, HDL; High density lipoprotein, LDL; Low density lipoprotein.

Table 2: Linear regression analysis showing the significant independent association between the increased HbA1c and Gensini scores.

	Beta	Std. Error	Sig.
(Constant)		-0.528	0.601
HbA1c	0.657	6.878	**<0.001**
Age	0.140	1.118	0.270
Gender	0.339	1.937	0.060
Duration of diabetes mellitus	0.357	3.908	0.056
Hypertension	-0.194	-1.616	0.114
Smoking	0.137	1.349	0.185
Fasting glucose	0.164	1.867	0.069
TC	-0.201	-0.234	0.816
LDL (mg/dl)	0.077	0.112	0.912
HDL(mg/dl)	0.335	1.116	0.271
Triglyceride	0.236	0.909	0.369
Waist circumference	0.082	0.535	0.595
Hemoglobin	0.055	0.537	0.594
Ejection fraction (%)	-0.073	-0.647	0.522

TC; Total cholesterol, LDL; Low density lipoprotein, HDL; High density lipoprotein

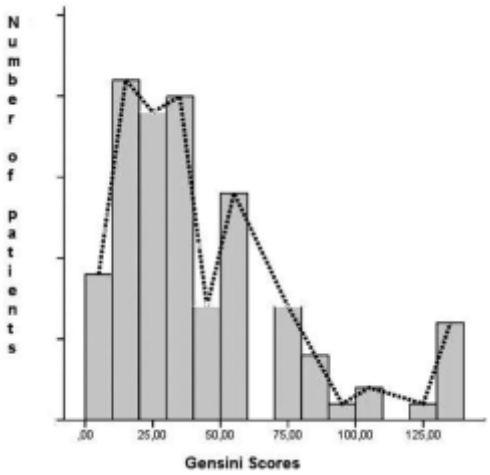

Figure 1: *The Gensini scores of patients.*

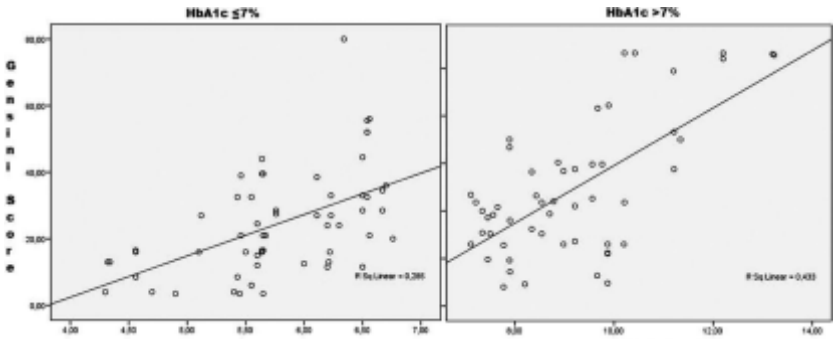

Figure 2: *HbA1c levels were significantly correlated with Gensini scores in both groups. Also, a significant difference was found between the groups in terms of Gensini scores (p<0.001).*

Yazarlarla ilgili bildirilmesi gereken konular (Conflict of interest statement) : Yok (None)

References

1. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339: 229-34.
2. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 1998; 316: 823-8.
3. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999; 22: 233-40.
4. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-12.
5. Ravipati G, Aronow WS, Ahn C, Sujata K, Saulle LN, Weiss MB. Association of hemoglobin A(1c) level with the severity of coronary artery disease in patients with diabetes mellitus. Am J Cardiol 2006; 97: 968-9.
6. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977-86.
7. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NRet al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004; 21; 141: 421-31.
8. Berry C, Noble S, Grégoire JC, Ibrahim R, Levesquie S, Lavoie MA, et al. Glycaemic status influences the nature and severity of coronary artery disease. Diabetologia 2010; 53: 652-8.
9. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2012; 35: S64-71
10. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010; 362: 800-11.
11. Sharma TK, Parchwani H, Kaushik GG, Shankar V, Dahiya K, Ghalaut VS, et al. HbA(1c) levels in cardiovascular diseased patients without diabetes in a developing country. Clin Lab 2011; 57(: 517-22.
12. Aronow WS, Ahn C, Weiss MB, Babu S. Relation of increased hemoglobin A(1c) levels to severity of peripheral arterial disease in patients with diabetes mellitus. Am J Cardiol 2007; 99: 1468-9.
13. Kato T, Chan MC, Gao SZ, Schroeder JS, Yokota M, Murohara T, et al. Glucose intolerance, as reflected by hemoglobin A1c level, is associated with the incidence and severity of transplant coronary artery disease. J Am Coll Cardiol 2004; 43: 1034-41.
14. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983; 51: 606.
15. Liu Y, Yang YM, Zhu J, Tan HQ, Liang Y, Li JD. Prognostic significance of hemoglobin A1c level in patients hospitalized with coronary artery disease. A systematic review and meta-analysis. Cardiovasc Diabetol 2011; 10: 98.
16. Saleem T, Mohammad KH, Abdel-Fattah MM, Abbasi AH. Association of glycosylated haemoglobin level and diabetes mellitus duration with the severity of coronary artery disease. Diab Vasc Dis Res 2008; 5: 184-9.
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461-70.
18. Bansilal S, Farkouh ME, Fuster V. Role of insulin resistance and hyperglycemia in the development of atherosclerosis. Am J Cardiol 2007; 99: 6B-14B.
19. Mather AN, Crean A, Abidin N, Worthy G, Ball SG, Plein S, et al. Relationship of dysglycemia to acute myocardial infarct size and cardiovascular outcome as determined by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2010; 12: 61.
20. Laakso L , Lehto S . Epidemiology of macrovascular disease in diabetes. Diabetes Rev 1997; 5: 294–315
21. United Kingdom Prospective Diabetes Study (UKPDS) group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131): 837-53.
22. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 2010; 32: 1316–30.
23. Morise AP, Haddad WJ, Beckner D. Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. Am J Med 1997; 102: 350–6.
24. Pryor DB, Shaw L, McCants CB, Lee KL, Mark DB, Harrell FE Jr, et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. Ann Intern Med 1993; 118: 81–90.
25. Fernandes MR, Silva GV, Caixeta A, Rati M, de Sousa e Silva NA, Perin EC. Assessing intermediate coronary lesions: angiographic prediction of lesion severity on intravascular ultrasound. J Invasive Cardiol 2007; 19: 412-6.
26. Maron DJ, Boden WE, Spertus JA, Hartigan PM, Mancini GB, Sedlis SP, et al; COURAGE Trial Research Group. Impact of metabolic syndrome and diabetes on prognosis and outcomes with early percutaneous coronary intervention in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial. J Am Coll Cardiol 2011; 58: 131-7.