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Glycated haemoglobin is correlated with the severity of coronary artery disease independently of traditional risk factors in young patients

Korelacja odsetka hemoglobiny glikowanej z ciężkością choroby wieńcowej występująca u młodych osób niezależnie od tradycyjnych czynników ryzyka

S. Selim Ayhan[1], Mehmet Tosun[2], Serkan Ozturk[1], Aytekin Alcelik[3], Mehmet Fatih Ozlu[1], Alim Erdem[1], Kemalettin Erdem[4], Fatma Hizal Erdem[5], Mehmet Yazici[1]

[1]Department of Cardiology, Izzet Baysal Medical Faculty, Bolu, Turkey
[2]Department of Biochemistry, Izzet Baysal Medical Faculty, Bolu, Turkey
[3]Department of Internal Medicine, Izzet Baysal Medical Faculty, Bolu, Turkey
[4]Department of Cardiovascular Surgery, Izzet Baysal Medical Faculty, Bolu, Turkey
[5]Department of Cardiology, Numune Hospital, Sivas, Turkey

Abstract

Introduction: In this study, we aimed to investigate the relationship between glycated haemoglobin (HbA_{1c}) levels and the severity of coronary artery disease (CAD) in < 40 years old patients.

Material and methods: The study population consisted of 211 premature coronary atherosclerotic patients (pCAP) (aged 36.4 ± 2.5 years) and 160 control subjects (36.4 ± 2.4 years). The severity of CAD was evaluated by the Gensini scoring system. HbA_{1c} levels and the other basic biochemical parameters were analysed, and relations with severity of CAD were evaluated.

Results: There were statistically significant differences in serum HbA_{1c} levels between the two groups (pCAP = 6.1 ± 1.8%, control = 4.7 ± 1.2%, $p < 0.001$). HbA_{1c} levels significantly positively correlated with the Gensini score in pCAP ($r = 0.662$, $p < 0.001$). In linear multivariate regression analysis (including age, sex, HbA_{1c}, smoking, diabetes mellitus and hypertension as dependent parameters), only HbA_{1c} was found to be an independent risk factor for the presence of severe CAD (Beta = 0.374, $p < 0.001$). In ROC curve analysis, the optimal cut-off value of HbA_{1c} to predict severe CAD was 6.52%, with 74.4% sensitivity and 75.1% specificity (area under the curve 0.781, 95% confidence interval 0.661 to 0.901, $p < 0.001$).

Conclusions: HbA_{1c} levels were found to be correlated with the Gensini score in pCAP with and without diabetes. In this respect, glucose metabolism abnormalities, indicated by HbA_{1c}, may play an important role in premature CAD. **(Endokrynol Pol 2012; 63 (5): 367–371)**

Key words: *glycated haemoglobin, premature coronary artery disease, Gensini score*

Streszczenie

Wstęp: Niniejsze badanie przeprowadzono w celu oceny zależności między odsetkiem hemoglobiny glikowanej (HbA_{1c}) a ciężkością choroby wieńcowej (CAD) u chorych w wieku < 40 lat.

Materiał i metody: Badana populacja składała się z 211 chorych z przedwczesną miażdżycą tętnic wieńcowych (pCAP) (w wieku 36,4 ± 2,5 roku) i 160 osób stanowiących grupę kontrolną (36,4 ± 2,4 roku). Ciężkość CAD określano na podstawie wartości wskaźnika Gensiniego. Przeanalizowano odsetek HbA_{1c} oraz inne wyjściowe parametry biochemiczne i oceniono ich zależności z ciężkością CAD.

Wyniki: Stwierdzono statystycznie istotne różnice między grupami w zakresie stężeń HbA_{1c} w surowicy (pCAP = 6,1 ± 1,8%, grupa kontrolna = 4,7 ± 1,2%; $p < 0,001$). Wartości HbA_{1c} były istotnie skorelowane z wartościami wskaźnika Gensiniego u chorych z pCAP ($r = 0,662$; $p < 0,001$). W wieloczynnikowej analizie regresji liniowej (w której uwzględniono wiek, płeć, stężenie HbA_{1c}, palenie tytoniu, cukrzycę i nadciśnienie tętnicze jako zmienne zależne) jedynie stężenie HbA_{1c} okazało się niezależnym czynnikiem ryzyka wskazującym na występowanie ciężkiej CAD (Beta = 0,374; $p < 0,001$). Jak wykazano w analizie krzywych ROC, optymalny punkt odcięcia wartości HbA_{1c} pozwalający prognozować ciężką CAD wynosi 6,52%, przy czułości metody 74,4% i swoistości 75,1% (pole pod krzywą 0,781, 95-proc. przedział ufności 0,661–0,901; $p < 0,001$).

Wnioski: U osób z pCAP, zarówno chorych na cukrzycę, jak i bez tej choroby, stwierdzono korelacje między wartościami HbA_{1c} i wskaźnikiem Gensiniego. Jak wynika z powyższych obserwacji, zaburzenia metabolizmu glukozy, których wyznacznikiem jest odsetek HbA_{1c}, mogą odgrywać ważną rolę w rozwoju przedwczesnej CAD. **(Endokrynol Pol 2012; 63 (5): 367–371)**

Słowa kluczowe: *hemoglobina glikowana, przedwczesna choroba wieńcowa, wskaźnik Gensiniego*

Aytekin Alcelik, Abant Izzet Baysal University, Medical Faculty, Department of Internal Medicine, Bolu, Turkey, tel.: +90 374 253 4618, fax: +90 374 253 4615, e-mail: aytekinalcelik@yahoo.com

Introduction

Although the age limits are not defined, the term premature or early atherosclerosis is often used to describe atherosclerosis that develops before 40–50 years of age [1–3]. The main known risk factors for the development of early atherosclerosis are diabetes mellitus (DM), dyslipidaemia, cigarette smoking, and a family history [4–6]. Chronic hyperglycaemia has also been identified as a risk factor for diabetic complications leading to accelerated atherosclerosis [7]. Some studies have shown that elevated plasma glucose levels negatively affect the severity of atherosclerosis and cardiac remodelling in all populations, regardless of the presence of DM [4, 8–10].

Glycated haemoglobin (HbA_{1c}) has been used to monitor the plasma glycaemic status of diabetic patients, and is currently used to diagnose DM [11]. Studies show that HbA_{1c} is more useful than fasting plasma glucose levels for assessing coronary artery disease (CAD) risk and mortality [12]. HbA_{1c} levels indicate both short- and long-term increased mortality risks in patients with CAD [13]. There is a significant relationship between HbA_{1c} levels and atherosclerosis, even in non-diabetic populations and even in people with normal HbA_{1c} levels [12, 14]. Some studies have found a relationship between the severity of CAD and HbA_{1c} levels in patients with acute coronary syndrome [13–15].

To the best of our knowledge, however, no study has evaluated the association between HbA_{1c} levels and the severity of CAD in patients with premature atherosclerosis.

Therefore, this study investigated the relationship between HbA_{1c} levels and the severity of premature coronary artery disease.

Material and methods

Study population

This study was designed retrospectively: 211 premature coronary atherosclerotic patients (pCAP) (36.4 ± 2.5 years) and 160 control subjects (36.4 ± 2.4 years) selected from patients who had undergone coronary angiography at Abant Izzet Baysal University School of Medicine Hospital and Sivas Numune Hospital between January 2010 and December 2011, were included in the study. The control group consisted of age-matched and sex-matched individuals who were selected in a consecutive manner from the catheterized patients during the same study period and who proved to have normal coronary angiograms. Demographic parameters, risk factors for atherosclerosis and past medical history were recorded for all patients.

Hypertension (HT) was considered to be present if the systolic pressure was greater than 140 mm Hg and/or diastolic pressure was greater than 90 mm Hg. Diabetes mellitus was defined as having fasting blood glucose higher than 126 mg/dL or second hour postprandial blood glucose higher than 200 mg/dL, together with previously diagnosed patients using antidiabetic therapy. Cigarette smoking was defined as the use of more than ten cigarettes a day at the time of diagnosis. Subjects with a history of percutaneous transluminal coronary angioplasty, acute myocardial infarction, alcohol intake more than 30 g/day, having transaminases exceeding three times the upper reference range, antioxidant drug use, renal or hepatic insufficiency and type 1 DM were excluded from the study. The indication for coronary angiography was either the presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischaemia, in all groups. The study protocol was approved by the local ethics committee.

Coronary angiography

Coronary angiography was performed by Judkin's technique. Two experienced cardiologists analysed the angiographic results. All angiograms were evaluated by Gensini scoring system in terms of severity of coronary stenosis [16]. 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; a score of 32 indicates a totally occluded artery. The Gensini score is multiplied by a factor which is associated with the functional importance of the coronary artery depending on the myocardial region supplied by that coronary segment. This 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. Angiography results were divided into mild CAD (Gensini score ≤ 20), and severe CAD (Gensini score > 20).

Biochemical investigations

Blood samples were obtained after overnight fasting. HbA_{1c} measurement was made using the immunoturbidimetry method. Analysis of transaminases, creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), gamma-glutamyltransferase (GGT), haemoglobin, and glucose were made using standard methods.

Statistical analysis

All statistical analyses were performed using the SPSS software package 15.0 (SPSS Inc, Chicago, IL, USA).

Table I. *Clinical and laboratory parameters of the study groups*
Tabela I. *Parametry kliniczne i laboratoryjne w badanych grupach*

Parameter	CAD group (n = 211)	Control group (n = 160)	p value
Male (%)	67.8	62.5	0.291
Age (years)	36.4 ± 2.5	36.4 ± 2.4	0.997
Hypertension (%)	37.0	29.4	0.126
Diabetes mellitus (%)	50.2	40.0	**0.050**
Smokers (%)	54.0	53.8	0.958
HbA_{1c} (%)	6.1 ± 1.8	4.7 ± 1.2	**0.001**
Statin use (%)	6.4	5.9	0.180
Haemoglobin [g/dL]	13.2 ± 1.5	13.24 ± 1.32	0.832
Total cholesterol [mg/dL]	177.5 ± 33.7	178.4 ± 34.5	0.346
LDL cholesterol [mg/dL]	105.4 ± 24.2	103.0 ± 24.6	0.218
HDL cholesterol [mg/dL]	44.2 ± 11.4	44.3 ± 10.6	0.829
Triglycerides [mg/dL]	129.2 ± 33.8	132.3 ± 34.7	0.812
Creatinine [mg/dL]	0.8 ± 0.1	0.8 ± 0.1	0.244
AST [U/L]	22.5 ± 6.6	21.9 ± 6.4	0.852
ALT [U/L]	23.0 ± 5.6	22.8 ± 5.8	0.813
GGT [U/L]	37.8 ± 13.0	36.8 ± 9.0	0.418

CAD — coronary artery disease; LDL — low-density lipoprotein; HDL — high-density lipoprotein; ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGT — g-glutamyl transferase

Data is presented as frequencies and percentages for categorical variables and mean ± SD or median for continuous variables, unless otherwise indicated. The groups were compared using the Student's t-test for the continuous variables and the chi-square test for the categorical variables. Correlation between continuous variables was determined by Pearson correlation coefficients. Linear multivariate logistic regression analysis was performed to identify the independent predictors of severe CAD. A value of $p < 0.05$ was considered statistically significant.

Results

The study population consisted of 211 premature coronary atherosclerotic patients (pCAP) and 160 controls. The main clinical characteristics of the study populations are shown in Table I. Laboratory characteristics of patients were not statistically different. There were strong statistically significant differences in serum HbA_{1c} levels between the two groups (pCAP = 6.1 ± ± 1.8%, control = 4.7 ± 1.2%, $p < 0.001$). There were mildly statistically significant differences between the groups with respect to DM ($p = 0.05$). HbA_{1c} levels significantly positively correlated with the Gensini score in pCAP ($r = 0.662$, $p < 0.001$) (Fig. 1).

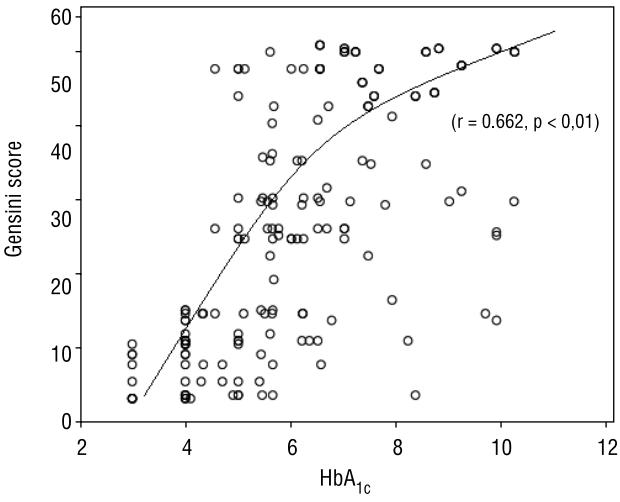

Figure 1. *Correlation of HbA_{1c} levels and Gensini score in Group 1*
Rycina 1. *Korelacje między odsetkiem HbA_{1c} i wskaźnikiem Gensiniego w grupie 1*

In the whole study population, 170 patients had DM (106 patients premature coronary atherosclerotic patients, 64 control patients). HbA_{1c} levels were significantly higher in diabetic pCAP (7.1 ± 1.4%, 5.3 ± ± 1.4%, $p < 0.001$). There were no significant differences in sex, HT, family history, creatinine levels, or

smoking between diabetic subgroups except age (36.6 ± 5.3, 35.2 ± 5.1, p = 0.042).

In subgroup analyses of pCAP, 97 patients had mild CAD (Gensini score ≤ 20), and 114 patients had severe CAD (Gensini score > 20). There were no significant differences in age, HT, family history, creatinine levels, or smoking between mild and severe CAD, except DM. HbA_{1c} levels were statistically different between groups (7.0 ± 1.4%, 4.7 ± 1.4%, p < 0.001). HbA_{1c} levels significantly positively correlated with the Gensini score in mild CAD and severe CAD patients (r = 0.347, p = 0.002, r = 0.377, p < 0.001, respectively).

In linear multivariate regression analysis (including age, sex, HbA_{1c} levels, smoking, DM and hypertension as dependent parameters), only HbA_{1c} was found to be an independent risk factor for the presence of severe CAD (Beta = 0.374, p < 0.001).

In ROC curve analysis, the optimal cut-off value of HbA_{1c} to predict severe CAD was 6.52%, with 74.4% sensitivity and 75.1% specificity (area under the curve 0.781, 95% confidence interval 0.661 to 0.901, p < 0.001; Fig. 2).

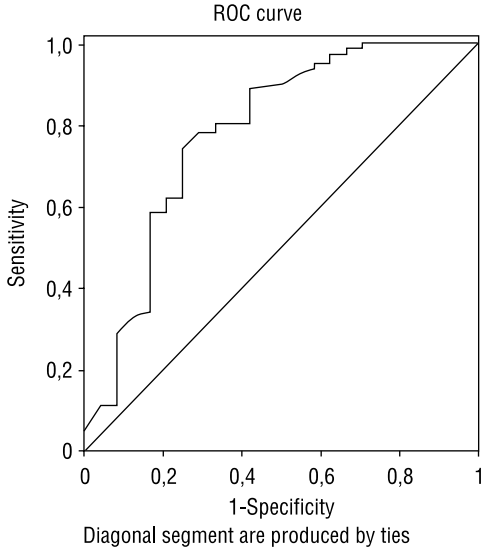

Figure 2. *ROC curve analysis, the optimal cut-off value of HbA_{1c} to predict severe CAD*

Rycina 2. *Analiza krzywych ROC, optymalne punkty odcięcia wartości HbA_{1c} do prognozowania ciężkiej CAD*

Discussion

Glucose metabolism disorders play an important role in the pathophysiology of atherosclerosis [17]. HbA_{1c} is usually used to evaluate the effectiveness of diabetes therapy. Recently, it has also been used to diagnose DM [18]. In this study, we investigated the relationship between HbA_{1c} levels and the severity of CAD in patients younger than 40 years. Our main finding was a significant correlation between the Gensini score and HbA_{1c} levels in premature CAD patients with or without DM. In addition, the HbA_{1c} levels were the only independent predictor of severe CAD (Gensini score > 20). To the best of our knowledge, the relationship between HbA_{1c} levels and the severity of CAD in premature coronary atherosclerotic patients has not previously been reported.

Atherosclerosis affects the coronary arteries of diabetic patients more severely and diffusely than those of non-diabetics [8–10]. Berry et al. found that fasting blood glucose, HbA_{1c}, and presence of diabetes were associated with the severity and progression of coronary atherosclerosis. They concluded that better glycaemic control favourably influences CAD in patients with abnormal glucose tolerance or diabetes [8]. Ravipati et al. showed that the HbA_{1c} level increased significantly with the number of arteries with CAD in diabetics [9]. Similarly, we found that HbA_{1c} levels were correlated with the severity of coronary atherosclerosis in both diabetic and non-diabetic patients.

In a recent trial, Selvin et al. reported that HbA_{1c} was a marker of cardiovascular risk in non-diabetics [12]. They followed 11,092 patients to identify adults at risk for diabetes or cardiovascular disease. HbA_{1c} was more strongly associated with the risks of cardiovascular disease and death from any cause than fasting glucose levels. They also reported that HbA_{1c} was equally associated with the diabetes risk compared to the fasting glucose levels. We did not assess the prognostic importance of HbA_{1c} in our study, and evaluated only patients younger than 40 years. Their study revealed the importance of glucose metabolism abnormalities in the atherosclerotic process, even in non-diabetics. Similarly, we found a correlation between the severity of coronary atherosclerosis and HbA_{1c} levels in premature CAD patients, regardless of the presence of DM.

In a recent meta-analysis, Liu et al. reported that elevated HbA_{1c} levels were an independent risk factor for mortality [13]. In subgroup analyses, they found that an elevated HbA_{1c} level predicted a higher mortality risk in non-diabetics, while they did not detect an increased mortality risk in diabetics. Two reasons for their conflicting findings between patients with and without diabetes were drug use and risk factor control. In other words, diabetic patients were tightly controlled in terms of risk factors such as dyslipidaemia and hypertension. In contrast, we evaluated premature CAD patients in a cross-sectional manner. We also suggest that HbA_{1c} has a high sensitivity and specificity for predicting severe CAD.

In another study, Mi et al. evaluated glycaemic variability and HbA_{1c} as risk factors for CAD in newly diagnosed diabetics [19]. They found that HbA_{1c} and glycaemic variability were associated with the presence and severity of CAD in patients with newly-diagnosed DM. They also evaluated CAD severity using the Gensini score, similarly to us. However, their population was older than ours, as we only evaluated patients younger than 40 years.

In conclusion, HbA_{1c} levels predict the severity of coronary atherosclerosis in patients younger than 40 years. In this respect, our findings demonstrate the importance of maintaining an optimal HbA_{1c} level for increased cardiovascular atherosclerosis, not only in diabetics, but also in non-diabetics.

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