Glycosylated Haemoglobin A1c as An Independent Marker Predicting Coronary Artery Disease in Non-diabetic Patient Population in Primary Healthcare in Turkey: A crosssectional study

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Research article

Keywords: non-diabetic, HbA1c, coronary artery disease, primary care

DOI: https://doi.org/10.21203/rs.3.rs-35447/v1

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Abstract

**Background:** In our role as a preventive physician, there is a need for cheap and accessible biochemical markers that will allow the determination of the risk of coronary artery disease. We aimed to research the value of glycosylated haemoglobin (HbA1c) in the prediction of coronary artery disease.

**Methods:** Patients aged between thirty and ninety years who were admitted to outpatient clinic of Cardiology department in a university hospital between January 2016 and June 2018 for angiography for various reasons were retrospectively screened. Patients with known diabetes or patients with HbA1c of 6.5 or above were excluded from the study. Comparative HbA1c data were obtained according to the stenosis groups and statistical significance was sought. Logistic regression analysis was used to investigate the risk factors affecting stenosis positivity.

**Results:** A total of 247 patients were identified, 120 patients without any stenosis in any coronary artery, 56 patients with > 50% stenosis in one coronary artery, and 71 patients with > 50% stenosis in more than one coronary artery. There was a statistically significant difference between HbA1c measurements according to the degree of stenosis (p = 0.001 and p <0.01, respectively). The odd ratio for HbA1c was 6.260 (95% CI: 3,160-12,401). According to the stenosis positivity, the cut off point for HbA1c was found to be 5.6 and above. In the regression analysis, HbA1c was an independent risk factor for coronary artery disease. One unit increase in HbA1c measurements increases the risk of stenosis positive to 12.424 times (95% CI: 5,990-25,767).

**Conclusions:** The study showed HbA1c can be used as an independent marker in determining the probability and severity of coronary artery disease in non-diabetic individuals and as an useful marker in primary care predicting coronary artery disease (CAD).

Background

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality worldwide (1). In terms of CAD, the basis of preventive medicine is to provide healthier and longer life span with lower costs. For this reason, there is a need for biochemical markers that will enable the determination of the risk of CAD in preventive medicine.

Glycosylated haemoglobin A1c (HbA1c) is a marker of 3-month blood sugar levels. Long-term high blood sugar levels have been shown to pose a risk of cardiovascular disease (2). The studies have shown that high HbA1c value in diabetes patients leads to an increase in overall mortality and cardiovascular disease mortality (3,4). In addition, it has been shown that HbA1c may be a marker for determining the severity of cardiovascular disease in patients with diabetes (5).

Several studies have examined the relationship between HbA1c and CAD. However, while some of these studies were performed on diabetic patients, significant relationships were not found when independent risk factors were removed (5,6).
The aim of this study was to find a laboratory criterion that can be used to diagnose CAD early in subjects with pre-diabetes which can be applied widely even in outpatient conditions. In this context, we aimed to question whether HbA1c molecule may be an independent predictor of CAD.

Methods

The study was done among 247 patients without type 2 diabetes mellitus (T2DM) who were admitted to outpatient clinic of Cardiology department from January 2016 to June 2018 in a university hospital. The non-diabetic patients with HbA1c value below 6.5% who underwent elective coronary angiography (CAG) with various indications were included in the study. The age range of participants was 30-90 years.

The study group was divided into groups according to stenosis degrees yielded from elective angiograms that showed 1) a stenosis of 50% or more in only one of the main branches of the left main coronary artery or left anterior descending artery or left circumflex artery or right main coronary artery and coronary vascular system, 2) more than 50% stenosis in more than one coronary arteries and 3) the patients with normal coronary vessels.

In addition to obtaining HbA1c results of all patients included in the study, other biochemical tests performed before angiography including high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG), liver function tests (AST, ALT), electrolytes (Na, K, Ca). Daemographic characteristics and known chronic diseases were investigated by face-to-face interview.

Patients with diabetes mellitus (DM), with anti-diabetic medication for any reason, whom having active infection, haemoglinopathy, myocardial infarction with active ST elevation and giving a history of coronary bypass surgery (CABG) were excluded.

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was used for statistical analysis. While evaluating the study data, Student t Test was used for comparison of two groups of variables showing normal distribution in the comparison of descriptive statistical methods as well as quantitative data. One-way Anova Test and Bonferroni Test were used for comparison of groups with normal distribution of three and more; Kruskal Wallis test and Bonferroni-Dunn test were used for comparisons between groups of three and above, which were not normally distributed. Logistic regression analysis (Backward Stepwise) was used to investigate the risk factors affecting stenosis positivity. Pearson chi-square test and Fisher-Freeman-Halton test were used to compare the qualitative data. Significance was set at p <0.05.

Results

The study was conducted with a total of 247 cases whose 41.7% (n = 103) were women. The ages of the patients ranged from 33 to 87 years with a mean age of 59.96 ± 10.89 years. CAG results showed that stenosis was lower than 50% in 48.6% (n = 120), higher than 50% in single coronary vascular and 28.7% (22.7%). n = 71) greater than 50% in multiple coronary vascular. In 48.6% (n = 120) of the cases, stenosis
was (-) and in 51.4% (n = 127), stenosis was (+). Stenosis degrees according to descriptive characteristics are shown in Table 1.

**Table 1**: Evaluation of degree of stenosis according to descriptive characteristics.

|                  | Degree of stenosis | p          |
|------------------|--------------------|------------|
|                  | <50 (n=120)        | Single >50 (n=56) | Multiple >50 (n=71) |
| Age (year)       | Min-Max (Median)   | 33-87 (56,5) | 35-87 (60) | 40-85 (63) | a0,003** |
|                  | Ort±Ss             | 57,73±9,97 | 60,70±10,98 | 63,14±11,56 |
| Sex; n (%)       | Female             | 64 (62,1) | 22 (21,4) | 17 (16,5) | b0,001** |
|                  | Male               | 56 (38,9) | 34 (23,6) | 54 (37,5) |
| HT; n (%)        | No                 | 53 (52,5) | 20 (19,8) | 28 (27,7) | b0,545 |
|                  | Yes                | 67 (45,8) | 36 (24,7) | 43 (29,5) |
| CAD; n (%)       | No                 | 101 (58,7) | 35 (20,4) | 36 (20,9) | b0,001** |
|                  | Yes                | 19 (25,3) | 21 (28,0) | 35 (46,7) |
| Hypotroids; n (%)| No                 | 108 (47,4) | 50 (21,9) | 70 (30,7) | c0,043* |
|                  | Yes                | 12 (63,2) | 6 (31,6)  | 1 (5,2)  |
| COPD/Asthma; n (%)| No              | 115 (49,1) | 51 (21,8) | 68 (29,1) | c0,412 |
|                  | Yes                | 5 (38,5)  | 5 (38,5)  | 3 (23,0)  |
| Habit; n (%)     | No                 | 82 (51,3) | 33 (20,6) | 45 (28,1) | b0,457 |
|                  | Yes                | 38 (43,7) | 23 (26,4) | 26 (29,9) |

aOneway ANOVA Test  
bPearson Chi-Square Test  
cFisher Freeman Halton Test  
*p<0,05  **p<0,01

In the study, HbA1c measurements ranged from 4.48 to 6.49 (5.70±0.54) in whole study group and were lower than 5.69 among 44.5% (n=110) of the cases however, it were between 5.7 and 6.5 in 55.5% (n=137) (Table 2).

**Table 2**: Evaluation of HbA1c measurements according to the degree of stenosis.
Stenosis (+) ratio was found to be significantly higher in cases with HbA1c level of 5.7-6.5 than those with HbA1c level of <5.69 (p = 0.001; p < 0.01). HbA1c level 5.7-6.5 increases the risk of stenosis 6,260 times. The odd ratio for HbA1c was 6.260 (95% CI: 3,160-12,401). (Table 3)

Table 3: Evaluation of HbA1c levels according to stenosis positivity in patients without CAD (n = 172).

| Stenosis Situation | b \( p \) | ODDS Ratio | %95 CI |
|-------------------|---------|-------------|-------|
| Stenosis (-)      | n (%)   | n (%)       |       |
| HbA1c (%)         | <5,69   | 67 (79.8)   | 17 (20.2) | \( 0,001 \)** | 6,260 | 3,160-12,401 |
|                   | 5,7-6,5 | 34 (38.6)   | 54 (61.4) |

\( ^b \) Pearson Chi-Square Test \( **p<0,01 \)

According to the stenosis positivity, the cut off point for HbA1c was found to be 5.6 and above. HbA1c for cutoff value of 5.6; sensitivity 91.55%; specificity 61.39%; positive predictive value was 62.50% and negative predictive value was 91.18%. In the obtained ROC curve, 80.9% standard error was 3.2% (Figure 1).

A statistically significant correlation was found between the presence of stenosis and the cut-off value of HbA1c level 5.6 (\( p = 0.001; p < 0.01 \)). The risk of stenosis is 17,222 times higher in cases with HbA1c level of 5.6 and above. The odds ratio for HbA1c is 17,222 (95% CI: 6,814-43,530).
The variables included in the study were included in logistic regression analysis, to assess the end of study; Age, sex, habit (smoking and alcohol) and HbA1c measurements, which are among the risk factors that affect stenosis positivity, are a significant model. The explanatory coefficient of the model is 74.9%. One unit increase in HbA1c measurements increases the risk of stenosis positive to 13,177 times (95% CI: 6,283-27,634). In conclusion, age, sex, habit and HbA1c are independent risk factors.

**Discussion**

HbA1c is one of the recommended parameters in follow-up of diabetic patients, showing a mean plasma glucose value of 3 months. HbA1c level is an important risk indicator for microvascular complications of diabetes, but it is not yet clear whether to use it as a risk indicator for macrovascular complications (7).

The relationship between HbA1c and coronary artery disease has been tried to be clarified in many studies over the years and a certain number of data accumulation has been achieved. Although there is no significant relationship between HbA1c and coronary artery disease in some studies, the general opinion is that there is a significant relationship between these two. In our study, as in previous studies, there was a strong relationship between HbA1c level and coronary artery disease in non-diabetic patients and HbA1c could be used as a predictor in predicting coronary atherosclerosis.

In a study in the literature done with 292 patients, it was aimed to correlate the severity of coronary artery disease with HbA1c value but did not find a significant relationship between gene expression score and HbA1c. In this study, it is stated that HbA1c cannot be used as an independent marker for CAD severity (8). However, in another study, it was showed that HbA1c level correlated positively with gene expression score in diabetic and non-diabetic population (r = 0.662, p <0.001) (9). In a prospective study in India, a syntax score was used for the severity of coronary artery disease, with similar results. There was a high correlation between HbA1c levels and severity of coronary artery disease, number of diseased vessels and increased syntax score in the non-diabetic population (R=0.429; p <0.001) (10).

Due to the inconsistency of many studies, in a published meta-analysis of 27 prospective studies in Western societies, 9 of which contributed to the relationship between HbA1c and CAD. As a result, RR: 1.20 (95% CI: 1.10-1.31) for non-diabetic coronary artery disease was reported for each 1% increase in HbA1c. In the same meta-analysis, it was reported that fasting and post-loading glucose rates were significantly associated with CAD risk in non-diabetic patients, but HbA1c's relationship with CAD risk was slightly stronger (11). In our study, a statistically significant difference was found between coronary artery disease and severity and HbA1c measurements (p = 0.001; p <0.01).

In a randomized double-blind case-control study in women, patients were followed for a mean of 7 years, and the risk of coronary artery disease was 2.25 (95% CI: 1.59-3.18) in patients with a HbA1c concentration of 5.5% in the non-diabetic population. However, HbA1c levels are associated with several other traditional cardiovascular risk factors, and in precisely adjusted models, the predictive value of HbA1c has weakened and RR has become insignificant (6). In a prospective study conducted in 93 patients, the relationship between the severity of coronary artery disease and HbA1c levels was evaluated
by logistic regression analysis and high levels of HbA1c were independent predictors of severe atherosclerosis (OR: 1.975; 95% CI: 1.101-3.542, p = 0.022). In our study, age, gender, hypertension, hypothyroidism, hyperlipidemia, smoking habit and HbA1c were evaluated by logistic regression analysis and significant correlation was found between HbA1c and coronary artery disease. One unit increase in HbA1c measurements increased the risk of coronary artery disease to 13,177 times (95% CI: 6,283-27,634).

In a study conducted, the optimal cut-off value for the prediction of HbA1c in severe ROC curve was 74.4% sensitivity and 75.1% specificity and 6.52% (9). In another study, 299 patients and Gensini score were used to determine the severity of CAD and a significant relationship was found between HbA1c.(p = 0.038). The ideal cut-off value of HbA1c for the formation of coronary artery disease was found to be 5.6% (sensitivity: 60.5%, specificity: 52%) (13). In a study with 411 patients in recent years, based on the ROC curve, the cut-off value of HbA1c between patients with and without coronary atherosclerosis was found to be 5.45% (82.8% sensitivity and 62.7% specificity) (14). In our study, ROC analysis was used and HbA1c cut-off value was 91.55% sensitivity and 61.39% specificity was 5.6% in determining atherosclerotic patients. We also showed that the increase in HbA1c value was also related to the number of diseased vessels.

The lower limit required to diagnose prediabetes with HbA1c is 5.7 in the world. The results of our study show that the risk of coronary disease for HbA1c increases significantly at values of 5.6 and above. The risk of stenosis is 17,222 times higher in cases with HbA1c level 5.6 and above. Therefore, it is thought that the regulation of the diagnosis of prediabetic patients defined as risky group as 5.6 or more in the next years will provide an advantage in the diagnosis of risky patients in preventive medicine.

The inconsistencies between HbA1c and coronary artery disease correlations in our examples may be due to the fact that the studies were in different ethnic groups, different study methods, different scoring systems in CAD grading, and different HbA1c measurement techniques. There is a need for a larger number of studies that take these conditions into account in order to conclusively prove that HbA1c can be used as a predictor of coronary artery disease in patients without diabetes.

Some limitations of our study need to be addressed and the results should be used more carefully for other ethnic groups as they are performed only in a population limited to Turkish patients. In addition, our study is a relatively small scale study from a single center.

**Conclusions**

In our study, we demonstrated that HbA1c can be used as an independent marker in determining the severity of coronary artery disease in non-diabetic individuals. We think that this result can give an idea in preventive medicine in terms of which patients are at risk or should be taken into preventive healthcare procedures. As a result of this study, we planned to offer to family doctors to check HbA1c levels among their bound population in primary care and to consider a cardiological examination to people with
increased risk. In this way, we think that we can slow down the course of CAD and prevent worse outcomes.

**Abbreviations**

Coronary artery disease (CAD)

Glycosylated haemoglobin A1c (HbA1c)

Type 2 diabetes mellitus (T2DM)

Coronary angiography (CAG)

High density lipoprotein (HDL)

Low density lipoprotein (LDL)

Triglyceride (TG)

Diabetes mellitus (DM)

Coronary bypass surgery (CABG)

**Declarations**

Ethics approval Ethical approval was taken from the Institutional Review Board (IRB) at Bezmialem Vakif University, Istanbul, Turkey prior to the commencement of the study with reference number 15/175 on 10/07/2018.

Consent to participate Not applicable. No informed consent was available since the study was done retrospectively.

Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

Funding None.

Authors’ contributions AO designed the study, drafted the manuscript. YK collected the data, performed the statistical analysis, Authors read and approved the final manuscript.

Acknowledgements None

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**Figures**

**Figure 1**

ROC curve