Glycosylated Haemoglobin Level and Severity of Coronary Artery Disease

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Abstract

Diabetes mellitus (DM) is known to cause microvascular and possibly macrovascular complications. This study was designed to evaluate the association between glycosylated hemoglobin (HbA1c) level and the severity of coronary artery disease. 100 diabetic Patients scheduled for cardiac catheterizations were enrolled in this study. The severity of CAD was assessed using the Gensini score. Hypertension was present in 66 patients, dyslipidemia in 43 patients, obesity in 35 patients, and family history of IHD was present in 29 patients, 39 patients were smokers. The mean Gensini score was 55±14 and the mean HbA1c was 11.3±4.2%. There was a significant positive correlation between Gensini score and HbA1c, also between Gensini score and both duration of DM and age. We can conclude that there was a positive correlation between glycosylated hemoglobin of patients, severity of CAD, age and duration of diabetes.

Key Words: Glycosylated haemoglobin – Severity – Coronary artery disease.

Introduction

MOST of the mortality in patients with diabetes mellitus is due to atherosclerotic disease (DM) [1]. While previous effort was focused on the prevention and treatment of microvascular disease complications of diabetes Cardiovascular disease (CVD) remains the principal morbidity and driver of mortality in the setting of diabetes, most commonly in the form of coronary heart disease (CHD), also in the risk for cerebrovascular disease, peripheral vascular disease, and heart failure are associated with diabetes. For these reasons, efforts to mitigate the risk of CVD in diabetes remain a global public health imperative. More recent observations from clinical trials showed that diabetic patients have a higher prevalence of coronary heart disease (CAD) with an increased number of fatal coronary events due to a higher incidence of plaque rupture and superimposed thrombosis in diffusely diseased coronary arteries. Additionally, diabetic patients develop complications more frequently after myocardial infarction (MI) and have double the in-hospital and six-month mortality compared to non-diabetic patients [1].

In the United Kingdom Prospective Diabetic Study (UKPDS), deaths from cardiovascular events were 70 times more common than deaths from microvascular complications. The UKPDS3 demonstrated that intensive glucose control, by keeping the HbA1c <7%, helped to reduce microvascular complications; the reduction in risk of MI was of borderline significance. Other studies suggest that coronary artery disease and HbA1c are predictors of cardiovascular mortality [2].

The American Diabetes Association in its recent position statement stated that lowering HbA1c may be associated with reduction of microvascular, neuropathic and possibly macrovascular complications of diabetes mellitus. They suggested that more studies should be done to establish the relationship between HbA1c and macrovascular complications [3].

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in people with impaired renal function and ESRD [4,5].

There seems to be no threshold level at which this increase in risk starts, as even minor increases in albumin: Creatinine ratio are associated with higher mortality rates. Cross-sectional studies of both diabetic and non-diabetic patients have shown...
microalbuminuria to be associated with coronary heart disease and peripheral vascular disease. In addition, it is also a sensitive index of generalized microvascular disease and a marker for multiorgan damage [6,7].

**Patients and Methods**

Hundred patients previously diagnosed as having type 2 diabetes mellitus (52 male and 48 female) admitted to the National Heart Institute and Ain Shams University for elective coronary angiography from February 2011 till March 2012 were enrolled in our study, their age group ranged between 31 and 70 years (the mean age of 55±14).

Patients should be previously diagnosed to have diabetes mellitus according to American Diabetes Association Diagnostic Criteria for Diabetes Mellitus [8]. Importantly, new to the diagnostic criteria in 2010, a glycosylated hemoglobin (HBA1c) level 6.5% has been added. Patients should be previously diagnosed to have ischemic heart disease either by history of recurrent attacks of typical chest pain, previous unstable angina or myocardial infarction, ECG different criteria of ischemia or ECHO showing regional wall motion abnormalities.

Patient with Alcohol, lead, opiate toxicity, Splenectomy and Uremia should be excluded due to increased level of HbA1c.

All patients were subjected to detailed medical history with stress on risk factors of coronary artery disease, exclusion criteria and detailed physical examination. 12 lead ECG that obtained from all patients while in the supine position. All ECGs were recorded at a paper speed of 25mm/s with 1mV/cm standardization, Random blood sugar and HbA1c measurement on admission.

Two to three milliliter of whole blood in EDTA tube were collected from the patient and transferred to the laboratory in ice box. Samples are known to be stable for one week in refrigerator in 2-8cc. by quantitative colorimetric determination of glycohemoglobin in samples using Teco Glycohemoglobin kits. The apparatus is dimension RXL band produced by Siemens Health care Diagnostics.

The diagnostic coronary angiography was performed via right femoral artery using Seldenger’s technique after giving xylocaine for local anesthesia, with JL 6 French sheaths and C3.5, C4 to visualize the right system. Views were taken in the right oblique with caudal and cranial angulations, in left oblique with cranial and caudal (spider) angulations, lateral projections and additional projection when needed, all images were recorded digitally [9]. Assessment of the severity of coronary artery disease had been done by using Gensini score [10]. Gensini score grades narrowing of the lumen of the coronary artery and scores it with numerical values with the following method: 1 for 1-25% narrowing, 2 for 26-50% narrowing, 4 for 51-75%, and 8 for 76-90%, 16 for 91-99%, and 32 for a completely occluded artery. This score is then multiplied by a factor according to the importance of the coronary artery as follows: The multiplication factor is 5 for a left main stem (LMS) lesion, 2.5 for proximal left anterior descending artery (LAD) and proximal circumflex artery (CX) lesions, 1.5 for a mid-LAD lesion, 1 for distal LAD, mid/distal CX and right coronary artery lesions and 0.5 for any other branch.

Data were statistically described in terms of mean±standard deviation (±SD), frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student $t$-test for independent samples. For comparing categorical data, Chi square ($\chi^2$) test was performed. Correlation between various variables was done using Spearman rank correlation equation for non-normal variables. $p$-values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

**Results**

Study was conducted on 100 diabetic patients admitted to the National Heart Institute and Ain Shams University, who were planned for elective coronary angiography. They included 52 males (52%), 48 females (48%).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>52 (52%)</td>
<td>48 (48%)</td>
</tr>
</tbody>
</table>

The age of our patients ranged between 31 and 70 year with mean age 55±SD14.
In our study hypertension was present in 66 patients, dyslipidemia in 43 patients, smoking in 39 patients, and family history of IHD was present in 29 patients and 35 patients were obese Fig. (2).

The average Gensini score of our studied population was $53\pm35.5$. Gensini score was variably distributed among patients, 24 patients had Gensini score (0-20), 18 had score (21-40), 21 had score (41-60), 9 had score (61-80), 19 had score (81-100) while 6 patients have Gensini score of (101-120) and 3 patients had score of (121-140) Fig. (3).

HbA1c was also variably distributed among patients. HbA1c between (4-6) was found in 4 patients, between (6-8) in 26, between (8-10) in 25, between (10-12) in 18, between (12-14) in 14, between (14-16) in 5, between (16-18) in 5, between (18-20) in 1, between (20-22) in 1 and between (22-24) in 1 patients Fig. (4).

There was a statistically significant positive correlation between HbA1c levels & Gensini scores. With increasing HbA1c values there was an increase in Gensini score Fig. (5).
There was a statistically significant positive correlation between duration of diabetes & Gensini scores. With increasing duration of diabetes there was an increase in Gensini score Fig. (6).

There was a statistically significant positive correlation between age & Gensini scores. With increasing age there was an increase in Gensini score Fig. (7).

![Graph](image1)

Fig. (6): Correlation of Gensini score and duration of diabetes ($p$-value <0.01).

There was statistically significant difference between obese and non-obese patients regarding HBA1c levels (13.4±3.7 versus 9.1±4.2, $p$-value =0.003) while there was no statistically significant difference between males and females patients, hypertensives and non-hypertensives, dyslipidemic and non-dyslipidemic, smokers and non-smokers and patients with positive and negative family history of IHD regarding their HBA1c levels ($p$-value >0.05) (Table 2).

![Graph](image2)

Fig. (7): Correlation of Gensini score and age ($p$-value <0.016).

<table>
<thead>
<tr>
<th>HBA1c Mean±SD</th>
<th>$p$-value</th>
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<tbody>
<tr>
<td>Male 10.3±1.5</td>
<td>Female 9.2±1.1</td>
</tr>
<tr>
<td>Hypertensive 10.0±1.3</td>
<td>Non-hypertensive 9.2±1.1</td>
</tr>
<tr>
<td>Dyslipidemic 9.3±2.2</td>
<td>Non-dyslipidemic 9.1±1.1</td>
</tr>
<tr>
<td>Smoker 8.1±1.1</td>
<td>Non-smoker 8.3±1.2</td>
</tr>
<tr>
<td>Obese 13±3.7</td>
<td>Non-obese 9.1±4.2</td>
</tr>
<tr>
<td>FH 8.6±2.9</td>
<td>No FH 8.4±2.7</td>
</tr>
</tbody>
</table>

Table (2): Showing difference between patients groups regarding their HBA1c level.

**Discussion**

Diabetes mellitus is a disease due to insufficient production of insulin or by the failure to respond appropriately to insulin, resulting in hyperglycemia. Importantly new to the old diagnostic criteria of diabetes mellitus in 2010 [7], a glycosylated hemoglobin (HBA1c) level 6.5% has been added by the American Diabetes Association.

Cardiovascular disease (CVD) remains the principal morbidity and driver of mortality in the setting of diabetes most commonly in the form of coronary heart disease (CHD), but also in the incremental risk associated with diabetes for cerebrovascular disease, peripheral vascular disease, and heart failure. For these reasons, continual efforts toward mitigating the risk of CVD in diabetes remain a global public health imperative [11,12]. In recent years, considerable investigative interest has been directed at evaluation of association of HbA1c as a reflection of diabetes control and microalbuminuria as a reflection of microvascular complications of diabetes with the severity of coronary artery disease.

The prevalence of diabetes in Egypt is 11.4% of total Egyptian population in 2011 according to international Diabetes Federation, so Egypt is considered one of the top 10 ranking of prevalence of diabetes in the world [8,13]. In the United Kingdom Prospective Diabetic Study (UKPDS), deaths from cardiovascular events were 70 times more common than deaths from microvascular complications. The UKPDS3 demonstrated that intensive glucose control, by keeping the HbA1c <7%, helped to reduce microvascular complications; the reduction in risk of MI was of borderline significance.
Other studies suggested that CAD and HbA1c level are predictors of cardiovascular mortality [2].

In our study we found a statistically significant positive correlation between HbA1c levels & GENSINI scores. With increasing HbA1c values there is an increase in GENSINI score.

Our results are in agreement with Gautham Ravipati [14], Tahir Salem et al., [15], Guo L. et al., [16], Gong Su et al., [17] and Zhou Fang et al., [18], who found a positive correlation between severity of CAD and HbA1c.

The American Diabetes Association in its recent position statement stated that lowering HbA1c may be associated with reduction of microvascular, neuropathic and possibly macrovascular complications of diabetes mellitus. They suggested that more studies should be done to establish the relationship between HbA1c and macrovascular complications [5].

Gautham Ravipati [14] in 2006 studied the association of HbA1c level with the severity of CAD in 315 diabetic patients who underwent coronary angiography because of chest pain and stated that hemoglobin A1C level significantly increased with the increasing number of diseased arteries. The present data could partly explain the mechanism of increased vascular atherosclerosis by the long-term poor control of glucose levels in patients with DM. These data indicate the importance of maintaining optimal HbA1c level in patients with DM.

This agreed with the finding of Tahir Salem et al., [15] who studied one hundred and ten diabetic patients with acute MI aiming to test if there is association of HbA1c level and diabetes mellitus duration with the severity of coronary artery disease and concluded that there was a positive significant correlation between Gensini score and HbA1c ($r=0.427, p<0.001$), and that HbA1c was an independent factor influencing the severity of coronary artery disease.

Our finding was matched with data published by Gong Su et al., [17] who studied the association of glycemic variability and the presence and severity of CAD in 252 patients with type 2 diabetes and reported that Gensini score closely correlated with HbA1c level ($p=0.022$) and because of this the effects of glycemic excursions on vascular complications should not be neglected in diabetes.

The concordance between our results and the previously mentioned studies may be explained by many facts. The first is that our patients were diabetics or prediabetics as in the previous studies. Second, all were known to have IHD and were hospitalized because of ACS, or for elective coronary angiography, and third, all the studied population whether in our study or the previous studies were age and sex matched.

All these studies including the current one could be explained by the pathobiologic attribution of hyperglycemia to CVD risk, although this remains poorly understood; but given the clear associations between severity of hyperglycemia and CVD risk in both type 1 and type 2 diabetes (sharing hyperglycemia as the common pathophyslogic disturbance), hyperglycemia is likely to directly influence atherosclerosis development, progression, and instability. The principal vascular perturbations linked to hyperglycemia include endothelial dysfunction, vascular effects of advanced glycation end products, adverse effects of circulating free fatty acids, and increased systemic inflammation [19].

On the contrary to our results and the previous studies Guido Schnyder et al., [20] studied the association of HbA1c with the severity of CAD in 631 patients (148 diabetic patients and 483 non diabetic patients) and he discovered that the severity of CAD was not associated with HbA1c level. This discordance may be attributed to the inclusion of non-diabetic patients representing the major cohort of the study in contrast to our patients who all were diabetics; also the difference of the sample size between our study and this study may be a contributing factor.

S. Ertek et al., [21] concluded that there is no association between CAD and HbA1c in 184 patients. Again a result that is divergent from ours. This can be explained by that the Gensini score of the patients were divided into two groups on the basis of Gensini to mild CAD (Gensini score >20) and severe CAD (Gensini score <20). And also because of inclusion of large number of non-diabetic patients (96 patient) representing 52% of the total study population.

Our results showed that there is a statistically significant positive correlation between duration of diabetes & GENSINI scores the result which is matched with all of the following studies:

In year 2005 Tugrul Norgaz et al., [22] studied the relation of retinopathy to the severity and extent of CAD in patients with type 2 diabetes mellitus in Sixty-nine patients undergoing coronary angiog-
raphy for suspected CAD. The extent of CAD was scored from coronary angiograms using the severity score, and they found that there was a significant positive correlation between CAD severity score and duration of diabetes mellitus.

This correlation and finding was supported by Tahir Salem et al., [18] who concluded that there is a positive correlation between severity of CAD and duration of diabetes mellitus ($p=0.004$).

Our finding was confirmed by data published in year 2010 in a study by Guo L. et al., [16] where Spearman’s correlation analysis was performed with Gensini score as dependent variable and all risk factors as independent variables. This analysis showed that Gensini score was significantly positively correlated with duration of diabetes mellitus.

The similarity of our results to these studies may be attributed to that all the studied patients were diabetics and known to have ischemic heart disease, also the severity of CAD was assessed by Gensini score in all these patients. The relation between CAD and duration of diabetes can also be explained by the prolonged effect of hyperglycemia on atherosclerosis development, progression and endothelial dysfunction as we mentioned before [23].

In our study we found a statistically significant positive correlation between age & GENSINI score, GENSINI score is higher in older patients. This relation was also demonstrated by Guo L. et al., [16] who studied the association between HbA1c and CAD and reported a positive correlation between age and CAD severity.

As previously mentioned, the mean age of the studied patients was 53±35 years denoting a higher incidence of development of CAD among older patients; this finding was confirmed by Zhou Fang et al., [18] who studied 415 diabetic and pre diabetic patients who were scheduled for coronary angiography for suspected myocardial ischemia using the Gensini scoring system and reported that there is a positive correlation between age and Gensini score.

The increase of severity of CAD with aging could be explained by increasing incidence of atherosclerosis in older people in addition of increasing incidence of the other risk factors of IHD. The Hallmarks of cardiovascular aging include progressive increases in systolic blood pressure, pulse pressure, pulse wave velocity, and left ventricular mass and increased incidence of CAD and atrial fibrillation [24,25].

Age-related changes are due to increases in fibrinogen, coagulation factors (V, VIII and IX, XIIa), and von Willebrand factor. Also platelet phospholipid content is altered and platelet activity is increased with increased binding of platelet-derived growth factor to the arterial wall in older compared with younger individuals. Increased levels of plasminogen activator inhibitor (PAI-1) are seen with aging, especially during stress, resulting in impaired fibrinolysis. Circulating prothrombotic inflammatory cytokines, especially interleukin-6, also increases with age and may play a role in the pathogenesis of ACS. All these changes also potentiate development of atherosclerosis [25].

**Conclusion:**

On evaluating the relation of HbA1c and CAD, with increasing HbA1c values there is an increase in Gensini score. Also, with increasing duration of diabetes there is an increase in Gensini score, as well as, Gensini score is higher in older patients.

**References**


