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Impact of Glycated Hemoglobin Level on Severity of Coronary Artery Disease in Non-Diabetic Patients

Abstract

Background: Glycated hemoglobin values reflect two to three months average endogenous exposure to glucose including postprandial spikes in blood glucose level and have low intra-individual variability particularly in non-diabetic patients. Elevated hemoglobin A1C is regarded as an independent risk factor for CAD in patients with or without DM. The purpose of this study is to determine the correlation between the level of Glycated hemoglobin (HbA1c), and the severity of coronary artery disease in non-diabetic patients.

Study design and methods: The study included four hundred and eight patients referred to coronary angiography in two tertiary centers. All patients were subjected to complete medical history, physical examination and full labs including HbA1c. Transthoracic echocardiogram and coronary angiography were done and the Gensini score was calculated. Normally distributed continuous variables will be represented as mean ± SD, or as the percentage of the sample. Comparison between high and low risk groups was done using two-tailed unpaired student t test for continuous variables and the Pearson's chi-square test for categorical variables.

Results: two hundred and ninety two patients (71.6%) high risk group and 28.4% were low risk group. High risk group had HbA1c (HbA1c 5.7 – 6.4%) mg% with mean HbA1c of 6.1 ± 0.3. The mean Gensini score was 39.9 ± 34.9. The level of HbA1c was positively correlated with Gensini score (r=0.243, P<0.05,) and RWMSI (r=0.103, p=0.038) and negatively correlated with LVEF(r= -0.146, p=0.003).

Keywords: Non-diabetic patients; Coronary artery disease; Cardiovascular diseases; Glycated hemoglobin

Research Article

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Noureldin Sahal[1]*, Azza Farrag[1] , Waleed Ammar[1] and Ahmed hegab[2]

[1]Department of Cardiovascular Medicine, Kasr Alainy Hospital, Cairo University, Egypt
[2]National Heart Institute, Egypt

***Corresponding author:** Noureldin Sahal, Department of Cardiovascular Medicine, Kasr Alainy Hospital, Cairo University, Egypt, Tel: 20115674449; Email: nursamhoon@hotmail.com

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Abbreviations: 2-H OGTT: 2 Hours Oral Glucose Tolerance Test; ACC: American College of Cardiology; ACR: Albumin-to-Creatinine Ratio; ACS: Acute Coronary Syndrome; ADA: American Diabetes Association; ADAG: A1C-Derived Average Glucose; ALL: Average Length Lesion; ARIC: Atherosclerosis Risk in Communities; AUC: Area Under the Curve; BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; CGM: Continuous Glucose Monitoring; CI: Confidence Interval; CKD: Chronic Kidney Disease; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; DBP: Diastolic Blood Pressure; DCCT: The Diabetes Control and Complications Trial; DM: Diabetes Mellitus; eAG: Estimated Average Glucose; Echo Echocardiography; EEM: External Elastic Membrane; EF: Ejection Fraction; EPIC: European Prospective Investigation of Cancer; FBG: Fasting Plasma Glucose; FBS: Fasting Blood Glucose; FDR: First Degree Relative; FRS: Framingham Risk Score; GFR: Glomular Filtration Rate; HbA1c: Glycated Haemoglobin; HbF: Fetal Haemoglobin; HbS: Hemoglobin S; HDL: High-Density Lipoprotein; HOPE: Heart Outcomes Prevention Evaluation; HPFS: Health Professionals Follow-Up Study; HR: Hazard Ratios; Hs-CRP: High Sensitivity C-Reactive Protein; HTN: Hypertension; IDL: Intermediate-Density Lipoprotein; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; IMT: Intima Media Thickness; IVUS: Intravascular Ultrasound; JNC: Joint of National Committee; LAD: Left Anterior Descending Artery; LCX: Left Circumflex Artery; LDL: Low-Density Lipoprotein; LV: Left Ventricle; LVEF: Left Ventricular Ejection Fraction; MDCT: Multi-Detector Computed Tomography; MI: Myocardial Infarction; MRI: Magnetic Resonance Imaging; MVD: Multivessel Disease; N: Number; NDR: National Diabetes Register; NEFAs: Nonesterified Fatty Acids; NGSP: National Glycohemoglobin Standardization Program; NHANES: National Health and Nutrition Examination Survey; NHS: Nurses' Health Study; NSTEMI: Non ST Segment Elevation Myocardial Infarction; NWAHS: The North West Adelaide Health Study; OGTT: Oral Glucose Tolerance Test; OHAs: Oral Hypoglycemic Agents; OR: Odds Ratio; P: P-Value; PAI-1: Plasminogen Activator Inhibitor; pCAP: Premature Coronary Atherosclerotic Patients; PCI: Percutaneous Coronary Intervention; PTCA: Percutaneous Transluminal Coronary Angioplasty; PWV: Pulse Wave Velocity; RCA: Right Coronary Artery; RR: Remodeling Ratio; RWMSI: Regional Wall Motion Score Index; SBP: Systolic Blood Pressure; SD: Standard Deviation; SDR: Second Degree Relative; SI: System International; SPSS: Statistical Package for the Social Sciences; STEMI: ST Segment Elevation Myocardial Infarction; SYNTAX: Synergy Between PCI With TAXUS™ and Cardiac Surgery; TC: Total Cholesterol; TG: Triglyceride; US: United State; VLDL: Very-Low-Density Lipoprotein; WC: Waist Circumference; WHO: World Health Organization; Whtr: Waist Height Ratio

Aim of the work

The aim of this work was to assess the relationship between the level of HbA1c and the severity of CAD, assessed by the Gensini score, among non-diabetic patients referred to coronary angiography as indicated clinically.

Introduction

Among the known risk factors for cardiovascular disease, diabetes mellitus (DM) ranks as one of the most potent. The excess risk for cardiovascular disease is two to eight folds higher in patients with diabetes mellitus compared to non diabetic individuals of similar age, sex and ethnicity [1,2]. It has also been recognized that high normal fasting blood glucose and increasing hemoglobin A1C levels in individuals without diabetes mellitus are risk factors for cardiovascular events and subclinical atherosclerosis [3,4].

Glycated hemoglobin values reflect two to three months average endogenous exposure to glucose including postprandial spikes in blood glucose level and have low intra-individual variability particularly in non-diabetic patients [5,6]. New clinical practice recommendation from the American Diabetes Association advocates the use of hemoglobin A1c in diagnosis of diabetes mellitus largely on the basis of the established association between Glycated hemoglobin and microvascular disease [7-9].

Elevated hemoglobin A1C is regarded as an independent risk factor for Coronary artery disease (CAD) in patients with or without DM, whereas levels of hemoglobin A1c less than 7% deemed appropriate for reducing risk of vascular complications [10]. The level of hemoglobin A1c has been correlated with number of vessels significantly diseased at time of coronary angiography [11,12]. Moreover, it has been found that the prevalence of elevated hemoglobin A1c levels in patients undergoing coronary artery bypass grafting is high [13]. Thus; the level of hemoglobin A1c may be correlated with the severity of coronary artery disease innon diabetic individuals.

Study Design and Population

This is a prospective study that included four hundred and eight patients referred to coronary angiography in two tertiary centers (Cairo University Hospitals and National Heart Institute) within a period of three months from January 2013 to April 2013. Patients who were referred to elective coronary angiography as indicated clinically were included in the study. The patients were subjected to complete medical history taking with special emphasis on:

a. History of other risk factors for coronary artery disease including: Hypertension and received medications, smoking status and family history of CAD.

Physical examination was performed by the treating physician with special emphasis on:

a. Identifying patients with hypertension. The diagnosis of hypertension is based on the JNC Seventh Report on Detection, Evaluation and Treatment of High Blood Pressure [14].

b. Identifying the presence of obesity by measuring waist circumference and body mass index. The diagnosis of obesity is based on the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults [15].

Blood samples were taken at the time of admission for HbA1c, serum Creatinine, FPG levels and lipid profile in addition to routine measurements. Samples for FPG and serum Creatinine were taken after eight hours fasting. HbA1c was measured by TECO-diagnostic-USA which is not affected by anemia or renal problems and results reported as percentage of total hemoglobin.

Exclusion criteria

i. Diabetic patients.

ii. Patient not known diabetic but FBS more than 126mg/dl.

iii. Patient with HbA1c more than 6.5%.

iv. Normal Coronary angiography.

A transthoracic echocardiogram study was done to every patient to identify the estimated ejection fraction, regional wall motion abnormalities, cardiac chambers dimensions and associated valvular lesions as per American Society of Echocardiography guidelines and recommendations [16]. Regional wall motion score index (RWMSI) was calculated. The echocardiographic machines used were Philips iE33 xMATRIX and GE Vivid 7.

Coronary angiography was performed by the femoral or radial approach in all subjects by Judkins technique. Images were recorded in multiple projections for left and right coronary arteries on a digital system. The coronary angiograms were done and reviewed by 2 cardiologists who were blinded for the characteristics of the patients during the interpretation; the difference in assessment was solved by consensus. The severity of CAD was assessed by using the Gensini score [17]. It is a scoring system which allocates a numerical value for the degree of stenosis in a coronary artery and a multiplication factor that depends on which coronary artery is involved and where the stenosis is located in the coronary artery.

This scoring system has been used in several studies to establish a correlation between the severity of CAD and other factors. It grades narrowing of the lumen of the coronary artery and scores it as:

a. 1 for 1-25% narrowing.

b. 2 for 26-50% narrowing.

c. 4 for 51-75% narrowing.

d. 8 for 76-90% narrowing.

e. 16 for 91-99% narrowing.

f. 32 for a completely occluded artery.

The score is then multiplied by a factor according to the importance of the coronary artery as follows:

a) Left main stem lesion is 5.

b) Proximal LAD and proximal LCX is 2.5.

c) Mid LAD lesion is 1.5.

d) Distal LAD, mid and distal LCX and RCA lesions is 1. Any branch is 0.5.

Data Collection

Data were collected regarding number of variables concurrently with hospital admission by the treating physicians and filled in prepared sheets.

These variables were:

Personal data

Name , age and gender.

Clinical data

Risk factors for CAD

Hypertension: History including duration of illness and medications received if present. Patients who were recently discovered to be hypertensive on presentation were reported as being hypertensive. The diagnosis of hypertension was based on the JNC Seventh Report on Detection, Evaluation and Treatment of High Blood Pressure [14].

Dyslipidemia: Based on the lipid profile of the patient .

Smoking status: The patients were classified into two groups: Current smoker (who currently smoker or quit before less than five years) and non- smoker (who never smoke or quit smoking more than five years).

Family history of CAD: The family history define as a myocardial infarction (MI) or death from CAD in a first degree relative (ie, parent or sibling) prior to age 50 (males) or 60 (females) [18].

Clinical diagnosis and the reason for coronary angiography

a. Unstable angina pectoris.

b. Non ST segment elevation MI.

c. ST segment elevation MI.

Obesity: Weight, height and waist circumference were measured (the waist circumference is measured at a level midway between the lowest rib and the iliac crest) [19]. Body mass index was calculated (fatness is most commonly assessed by body mass index (BMI) which is calculated by dividing an individual's weight measured in kilogram's by their height in meters squared). The patients were classified as obese or non-obese according to the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults [15].

Echocardiographic data

The estimated left ventricular ejection fraction and RWMSI were reported.

Laboratory data

a) FPG.

b) HbA1c.

c) Total Cholesterol Level (TC).

d) Triglycerides (TG).

e) LDL-C.

f) HDL-C.

g) Serum Creatinine.

Angiographic data

Severity of CAD as assessed by Gensini score.

Statistical Analysis

The study population was stratified into high risk group (HbA1c 5.7 – 6.4%) (n= 292) and a low risk group (HbA1c <5.7%) (n= 116). Continuous variables are expressed as means ± SD, whereas categorical variables are presented as absolute values and percentages. Differences between the two groups regarding continuous variables were analyzed by the unpaired Student's t test or non-parametric Mann-Whitney U test. Categorical variables were compared using Pearson Chi Square test of Fisher's Exact test, as appropriate. Pearson's correlation coefficients were used to evaluate the relationship between HbA1c and Gensini score.

Logistic regression analysis was used to determine which of cardiovascular risk factors were the significant variables associated with severe coronary atherosclerosis (Gensini >30). The following variables were included into the model: age, gender, hypertension, BMI, WC, HbA1c, TC and HDL-C. The sensitivity and specificity of HbA1c values in predicting severe coronary atherosclerosis was determined by constructing Receiver Operating Characteristic (ROC) curves. The sensitivity / specificity cut-off points were reported as percentages with corresponding 95% confidence intervals. Two-tailed p value <0.05 was considered significant. All statistical analyses were done using SPSSS version 16.0 software for windows (SPSS Inc. Chicago, IL).

Discussion

HbA1c reflects the average blood glucose concentrationsover the preceding 2–3 months. There are advantagesof HbA1c testing compared with plasma glucose. The measurementof HbA1c is well standardized, and the biologicvariability is less, and does not require fasting. Inaddition, it is relatively unaffected by acute changes in glucose levels. In this study we examined the correlation between Glycosylated hemoglobin level among non- diabetic patients referred to coronary angiography and the severity of CAD by means of Gensini score.

The studied group included 408 patients referred to coronary angiography as indicated clinically over a period of three months. We excluded normal coronary angiograms and diabetics individuals (fasting glucose > 126mg/dl, Hba1c >6.5 and history

of diabetes). The study population was stratified into high risk group (HbA1c 5.7 – 6.4%) (n= 292) and a low risk group (HbA1c <5.7%) (n= 116). High risk group represented 71.6%of the whole group. Both Groups had comparable age and gender distribution, obesity parameters and laboratory results except for the clinical presentations, FH, BMI, FPG, HbA1c and serum Creatinine. Also there is a significant difference between two groups regarding LVEF, RWMSI and Gensini score.

We demonstrated that the level of HbA1c is positively correlated with the severity of CAD. The level of HbA1c was positively correlated with the Gensini score (r=0.243, P<0.05) among the whole studied population. Khaw et al. [20] has also reported on the associationbetween HbA1c levels and major cardiovascular eventsand mortality. They reported that increasing levels ofHbA1c is associated with all-cause and cardiovascular mortality. An increase of 1% in HbA1c was associatedwith a 28% increase (p<0.002) in the risk of death, independent of traditional cardiovascular risk factors. Interestingly, the association between increasing HbA1clevels and death persisted (hazard ratio 1.46; p=0.05)after individuals with DM and those with a HbA1c levelabove 7% were excluded from the analysis, suggesting arole of HbA1c assessment in risk stratification andprediction among individuals without DM. This was further supported by the results of Santos et al. [21] meta-analysis of prospective cohorts. We didn't follow up patients to trace the incidence of cardiovascular mortality but all patients referred to coronary angiography had an acute coronary syndrome, i.e. cardiovascular event.

Eeg-Olofsson et al. [22] conducted a study to analyze the association between HbA1c and CVD in patients with type 2 diabetes in the Swedish National Diabetes Registry (NDR). This observational study included 18,334 patients (age 30-79 years, previous CVD in 18%, baseline HbA1c 5.0-10.9%) who were followed for 6 years (mean5.6 years) from 1997/1998 until 2003. Adjusted 6-year event rates increased with higher baseline or updated mean HbA1c with no J-shaped risk curves, in all patients and also when sub-grouping by shorter (mean 3 years) or longer (mean 14 years) diabetes duration, by presence or absence of previous CVD, orby treatment with oral hypoglycemic agents (OHAs) or insulin. Risk reductions of 20% for CAD and 16% for CVD (P < 0.001) were found in patients with abaseline mean HbA1c level of 6.5%, compared to those with a mean level of 7.5%. HbA1c was not associated with non-CVD mortality. This observational study showed progressively increasing risks of CAD, CVD and total mortality with higher HbA1c, and no risk increase at lowHbA1c levels even with longer diabetes duration, previous CVD or treatment with either insulin or OHAs. Patients achieving HbA1c <7% showed benefits for risk reduction. Our study didn't include such a large number of patients being not a registry, but we included just non-diabetic patients and we were specifically targeting the CAD severity rather than the prevalence. The level of HbA1c measured was a single reading at time of presentation not a mean value over years.

Several studies were conducted to demonstrate the correlation between the level of HbA1c and the severity of CAD in non-diabetic patients. Study in the Sanjay Gandhi Postgraduate Institute of Medical Sciences Lucknow [23]. India was done in 2011 and showed HbA1c in Non-diabetic Patients is an Independent Predictor of Coronary Artery Disease and its Severity: The total number of the screened patients is 1897 and 756 are excluded, the number of non-diabetic patients is 1141. The patients with CAD is 905.

The conclusion of this study showed that in non-diabetic patients, higher HbA1c levels are significantly associated with CAD. This association is graded, continuous and is independent of conventional major cardiovascular risk factors. Elevated HbA1c is also strongly correlated with disease severity and higher SYNTAX score and HbA1c is a surrogate marker for chronic dysglycemia and could be utilized as an independent predictor of CAD and its severityeven in non-diabetic subjects.

Comparing this study to our study which includes 408 patients during just three months while this study includes 905 patients during one year, the other most important thing they defined significant of CAD as > 50% diameter in any vessel > 1.5 mm and the use of SYNTAX score which is an angiographic tool grading the complexity of coronary artery disease and obtain evidence based guidelines for selecting the optimal technique of revascularization (CABGor PCI) [24] not for assessing severity of CAD as Gensini score. In our study we estimated the severity of CAD in greater detail by using the Gensini score. Gensini [17] suggested a scoring system which allocates anumerical value for the degree of stenosis in a coronary artery and a multiplication factor that depends on which coronary artery is involved and where the stenosis is locatedin the coronary artery. This provides a detailed assessment of CAD and does not ignore even very triviallesions in coronary arteries. Many other studies have used this scoring system to establish a correlation between the severity of CAD and other factors such as serum sodium level [25], renal impairment [26] and impaired glucosetolerance [27]. In the Study in the Sanjay Gandhi Postgraduate Institute of Medical Sciences Lucknow they divided the patients into four groups according to HbA1c (HbA1c < 5.5, HbA1c 5.5-5.8, HbA1c 5.8-6.1, HbA1c >6.1). In our study the study population was stratified into high risk group (HbA1c 5.7 – 6.4%) and a low risk group (HbA1c <5.7%) according to ADA.

In Ravipatiet al. [11] study, coronary angiography was performed for 152 men and 163 women with DM (mean age 55 ± 8 years) because of chest pain. The mean HbA1c level was 6.66 ± 0.58% in 132 patients with 0-vessel CAD, 8.00 ± 0.84% in 40 patients with 1-vessel CAD, 8.83 ± 1.45% in 76 patients with 2-vessel CAD, and 10.40 ± 2.28% in 67 patients with 3- or 4-vessel CAD. There wasa significant increasing trend of HbA1c levels over the increasing number ofvessels with CAD (p<0.0001). In our study we were more detailed regarding assessment of the CAD using the Gensini score. The increasing number of diseased vessel does not reflect the severity of the lesions and in turn does not reflect the atherosclerotic burden. Moreover, patients without CAD represented 42% of the studied group but in our study we did not include patients with normal coronary angiograms.

In a recent study conducted by Department of Cardiology, Ankara Penal Institution Campus State Hospital, Ankara published in July 2013 [28], 65 patients were included (11 females, mean

age: 57±11.42 years; 54 males, mean age: 54.56±8.51 years) who were diagnosed as acute myocardial infarction without diabetes mellitus. During hospitalization, fasting blood glucose, postprandial blood glucose and HbA1C were measured in each patient. Gensini score was used to assess the severity of coronary artery disease. Twenty patients (30.8%) had hypertension, 15 (23.1%) had impaired fasting glucose, 10 (15.3%) had combined impaired fasting and postprandial glucose, 28 had a low HDL cholesterol (45%), and 30 (46%) had abdominal obesity. Coronary angiography revealed one-vessel disease in 13 patients (20%), and two- and three-vessel disease in 52 patients (80%). There were no significant differences in terms of high-sensitive C-reactive protein (hs-CRP), total cholesterol, fasting glucose, and postprandial glucose (0.068, 0.974, 0.178, and 0.677, respectively). There was no significant relation between the Gensini score and HbA1c levels (p=0.299), but there was a significant relation between the Gensini score and obesity(p=0.024). So this study concluded that, no significant relationship could be determined between the Gensini score and HbA1C, fasting and postprandial blood glucose levels, lipid profile, and hs-CRP levels in patients with non-diabetic ACSs. However these results could be explained by small number of patients studied.

In our study, we included a larger number of patients (328 patients vs. 78 patients) and this might have an influence on their conflicting results, and the clinical presentations for coronary angiography were variable (not only acute myocardial infarction). We reclassified the studied group into high and low risk groups (based on HbA1c level) to demonstrate if there are statistical differences among two groups. What is also unique to our study is the use of different parameters of obesity including waist circumference, BMI and waist height ratio to identify correlations with the HbA1c level. RWMSI and serum Creatinine were first to be used as studied variables. They subdivided the CAD into single, two and three vessel disease and measure (hs-CRP), in our study we subdivided CAD according to Gensini score < 30 or > 30 and take all CAD starting Gensini from 1 to 192 to evaluate accurately CAD. So that study showed only there was a significant relation between the Gensini score and obesity (p=0.024) in MI,but in our study we showed the level of HbA1c to be positively correlated with Gensini score (r= 0.243, P< 0.000) and RWMSI (r=0.103, p=0.038) and negatively correlated with LVEF(r=- 0.146, p= 0.003). ***Patients with Gensini score >30 has higher values of HbA1c, Gensini > 30 the HbA1c = 6 ± 0.51 and Gensini <30 the HbA1c = 5.7 5± 0.54 (p < 0.05, CI = 95%).***

Santos-Oliveira et al. [21] investigated 16 datasets (nine for total cardiovascular events and seven for death) from five papers with 44, 158 patients (44% men) over 404, 899 patient-years of follow-up. There were 1, 366 cardiovascular deaths (3.1%;3.37/1,000 person-years) and 2, 142 cardiovascular events (4.9%; 5.29/1,000 person-years). The overall meta-analytic β coefficients were 0.720 (95% CI 0.307–1.133) and 0.757(95% CI 0.382–1.132) for cardiac death and events respectively. Compared with the baseline value of 4.27%, HbA1c level of 5% was associated with a relative riskfor cardiovascular death of 1.13 (95% CI 1.05–1.21), a 6%value with 1.34 (95% CI 1.13–1.58), and a 7% HbA1cwith relative risk 1.58 (95% CI 1.22–2.06). Results for totalcardiovascular events were similar. Thus HbA1c was significantly associated with cardiovascular events anddeaths in persons without diabetes.

Rivera et al. [29] even studied the association between increasing levels of HbA1c in a symptomatic individuals without DM and coronary plaque characteristics. The final study population consisted of 906 individuals without DM (mean age: 49±9 years, 62% males); 19 and 9% of the population had any and two or more segments with coronary plaque, respectively. Unadjusted analysis showed a positive association between increasing levels of HbA1c and the number of coronary segments with any (p< 0.001) and with mixed coronary plaques (p<0.0001). The association persisted even when traditional risk factors were taken into account. No significant relationship was found between increasing HbA1c levels and the burden of non-calcified or calcified plaque. Thus increasing levels of HbA1c in a symptomatic individuals with out DM were associated with the presence of coronary atherosclerosis, but more specifically with the presence and burden of mixed coronary plaques. Our study included a fewer number of patients (408 patients). They were symptomatic and indicated for coronary angiography and not multi-detector computed tomography (MDCT). We did not demonstrate the number of plaques involved or the complexity of the atherosclerotic plaques, rather, we assessed the severity of the lesions

In our study, we found that there is significant correlation between the level of HbA1c and Gensini score (r=0.243, P<0.000). Moreover, high risk patients (HbA1c between 5.7% and 6.4%) had lower LVEF and higher RWMSI adding to their risk profile inspite of having comparable gender distribution and laboratory findings as those with lower HbA1c levels. This could be explained by increased prevalence of STEMI in the high risk group.

These results suggest that HbA1c in non-diabetic patients may be an indicator of metabolic alterations that could develop into cardiovascular events, including disease-specific mortality. There was no significant correlation between the level of HbA1c and total cholesterol, LDL, triglycerides and HDL levels. But there was significant correlation with Gensini score and total cholesterol (r = 0.098, p=0.048), LDL(r = 0.108, p=0.029) and HDL(r = 0.131, p=0.008).

The correlation between Gensini score and FPG was insignificant (r = 0.088, *p*<0.076). In Yu Kataoka et al. [30] study, FPG was a significant predictor of ALL > 20 mm by univariate analysis, which showed the impact of FPG level at time of presentation for coronary angiography and the severity of CAD. However, the prognostic value of FPG in non-diabetic adults was inferior to HbA1c level for identifying adults at risk for diabetes or CVD [9]. HbA1c remained associated with CVD and death even after accounted for baseline FPG levels; in contrast, FPG was not significantly associated after adjustment for the HbA1c value.

Gensini score was also positively correlated with RWMSI (r = 0.272, p<0.05) and negatively correlated with LVEF (r = -0.240, p<0.05). To our knowledge, this is the first study to demonstrate these correlations. The above mentioned studies assessed the severity of CAD and its correlation with HbA1c didn't include echocardiographic data among the studied variables in non-

diabetic patients. Loeblein et al. [31] retrieved the data of 140 consecutive patients who under went CABG between 1/2008-10/2008 to study the association between cardiovascular risk factors [age, BMI, total cholesterol, HDL, LDL, TGs, Hb1Ac, hypertension, positive family history for CVD and history of smoking] and syntax score, EF and BNP level. There was no association between Syntax score and cardiovascular risk factors. There was also no association between Syntax score and EF and between Syntax score and BNP. In our study, we found a significant correlation between the level of HbA1c and LVEF (r=-0.146, p=0.003) and RWMSI (r=0.103, p=0.038). In contrst to H. Lobleinet al. [31], we used the Gensini score and not the Syntax score and the results were conflicting regarding the correlation with EF. This might be due to the fact that Syntax score is a tool currently used in angiographic grading the complexity of CAD in order to select the optimal technique of revascularization rather assessment of the severity of CAD.

Impact of HbA1c in patients with ACS

The study group was divided into two subgroups, the first group was STEMI group and the other one was the patients without STEMI which include (NSTEMI and unstable angina). Patients with STEMI about 126 which were 30.9% from total study group. The second group was 282 patients which is 69.1%. In STEMI group the HbA1c showed only significant correlation with RWMSI (r=0.183, P=0.04) and no correlation between HbA1c and EF (-0.114, p=0.206) or Gensini score (r=0.090, p=0.318). In this group the Gensini score showed negative correlation with EF (r=-0.208, p=0.020) and positive correlation with RWMSI (r=0.243, p=0.006). The second group showed the HbA1c significantly correlated negatively with EF (r=-0.221, p=<0.000) and positively with Gensini score (r=0.326, p<0.000) and non-significant correlation with RWMSI (0.063, P=0.290). In this group the Gensini score showed significant negative correlation with EF (r=-0.270, p<0.000), and positive significant correlation with RWMSI (r=0.242, P=<0.000).

In Ankara Penal Institution Campus State Hospital, Ankara published in July 2013 [28], they included 65 patients (11 females, mean age: 57±11.42 years; 54 males, mean age: 54.56±8.51 years) who were diagnosed as acute myocardial infarction without diabetes mellitus. So this study concluded that, no significant relationship could be determined between the Gensini score and HbA1C(p=0.299), fasting and postprandial blood glucose levels, lipid profile, and hs-CRP levels in patients with non-diabetic ACSs, but showed only there was a significant relation between the Gensini score and obesity (p=0.024). STEMI groupin our study showed significant correlation between HbA1c and RWMSI (r=0.183, P=0.04) and no correlation between HbA1c and EF (-0.114, p=0.206) or Gensini score (r=0.090, p=0.318). But the second group showed the HbA1c significantly correlated negatively with EF (r=-0.221, p=<0.000) and positively with Gensini score (r=0.326, p<0.000) and non-significant correlation with RWMSI (0.063, P=0.290). In STEMI group no significant correlation between Gensini and EF and this is explained by the adverse effect of STEMI that affect EF regardless severity of CAD. However in the second group there was strong relation between Gensini score and EF.

In observational study [32] for impact of admission glycemia and glycosylated hemoglobin A1c on long-term clinical outcomes of non-diabetic patients with acute coronary syndrome, 452 consecutive non-diabetic patients with ACS who underwent PCI between January 1997 and December 2006. The patients were assigned to four groups according to the median values of admission glucose and HbA1c. The primary endpoint comprising a composite of all-cause death and non-fatal MI was compared among the four groups. The primary endpoint occurred in 13.3% of the participants during a median follow-up period of 4.7 years. The cumulative incidence rate of primary endpoint significantly differed among the groups (p=0.048). Multivariable Cox regression analysis showed that the combination of elevated admission glucose and HbA1c was independently associated with long-term clinical outcomes. So this study concluded that combined admission glucose and HbA1c values were independently associated with clinical outcomes in non-diabetic patients with ACS treated with PCI.In our study we assessed the severity of CAD and the clinical outcome, in this study follow up the patients for 4.7 years for primary end point. The two studies searched in HbA1c in non-diabetic patients with ACS.

A systematic review and meta-analysis study [33], regarding prognostic significance of hemoglobin A1Clevel in patients hospitalized with coronary artery disease was conducted in which systematic search of electronic databases (PubMed, EMBASE, OVID, Web of Science, and The Cochrane Library) for studies published from 1970 to May 2011. Cohort, case-control studies, andrandomized controlled trials that examined the effect of HbA1c on all-cause mortality were included. Twenty studies met final inclusion criteria (total n = 13, 224). From the pooled analyses, elevated HbA1c level was significantly associated with increased short-term (OR 2.32, 95% CI, 1.61 to 3.35) and long-term (OR 1.54, 95% CI, 1.23 to 1.94) mortality risk. Subgroup analyses suggested elevated HbA1c level predicted higher mortality risk in patients without diabetes (OR 1.84, 95% CI, 1.51 to 2.24). In contrast, in patients with diabetes, elevated HbA1c level was not associated with increased risk of mortality (OR 0.95, 95% CI, 0.70 to 1.28). In a risk-adjusted sensitivity analyses, elevated HbA1c was also associated with a significantly high risk of adjusted mortality in patients without diabetes (adjusted OR 1.49, 95% CI, 1.24 to 1.79), but had a borderline effect in patients with diabetes (adjusted OR 1.05, 95% CI, 1.00 to 1.11).The study concluded that elevated HbA1c level is an independent risk factor for mortality in CAD patients without diabetes, but not in patients with established diabetes. Prospective studies should further investigate whether glycemic control might improve outcomes in CAD patients without previously diagnosed diabetes. The most studies searched in the HbA1c in non-diabetic patients and adverse outcome, but our study and little other studies searched in HbA1c in the non-diabetic and severity of the CAD. It is worth noting that most studies regarding HbA1c in non-diabetic evaluated its impact on outcome, however limited studies including ours, studied correlation between HbA1c and severity of CAD.

Conclusion and Recommendations

HbA1c level is a useful marker and has a prognostic value to predict the severity of CAD among non-diabetic patients. It may

be used as a cardiac marker in risk stratification of non-diabetic patients presenting with acute coronary syndrome and indicated for coronary angiography. Transthoracic echocardiography including estimation of LVEF and RWMSI should be used routinely prior to coronary angiography and may be used as predictors of severity of CAD. Therapeutic strategy to specifically lower the HbA1c level in non-diabetics still remain uncertain, randomized controlled clinical trials need to be done in this direction [33-199].

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