Relation between HbA1c Levels and the Severity of Coronary Artery Disease in Patients with Acute Coronary Syndrome

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Abstract: Background: One of the major risk factors of coronary artery disease is diabetes mellitus. It is well known that the risk of coronary heart disease is higher in patients with type 2 diabetes than in patients without diabetes and that man with diabetes has a worse survival from coronary heart disease than do those without diabetes. **Aim of the study:** This study aimed to evaluate the relation between HbA1c levels and the severity of coronary artery disease in patients with acute coronary syndrome. **Patients and Methods:** A prospective study was conducted in the Emergency and Cardiology Department of Tanta University Hospitals. Our study was carried out upon (120) patients of both sex. They were selected from patients presented with acute coronary syndrome. Patients were classified into two groups based on HbA1c level at time of admission. **Group I:** Patients with HbA1c < 5.7%. **Group II:** patients with HbA1c ≥ 5.7%. **Results:** The results indicated that there is positive significant relation between HbA1c with acute coronary syndrome, while no significant relationship found between the other factors including age, gender, obesity, family history, smoking and hypertension with ACS. **Conclusions:** In non-diabetic patients, higher glycated hemoglobin levels are significantly associated with coronary artery disease. This association is continuous, graded and independent of conventional major cardiovascular risk factors.

1. Introduction:

Acute coronary syndrome (ACS) is the umbrella term for the clinical signs and symptoms of myocardial ischemia: unstable angina, ST-segment elevation myocardial infarction and non ST-segment elevation myocardial infarction[1].

Coronary artery disease leads to the interruption of blood flow to cardiac muscle when the arteries are obstructed by plaque[2].

Admission high blood glucose levels in patients with acute coronary syndrome (ACS) are common and are associated with an increased risk of death[3].

Multiple studies have expanded the relationship between dysglycemia and adverse cardiovascular outcomes by demonstrating that even milder abnormalities of glucose control (below the diagnostic threshold of diabetes mellitus) are associated with increased cardiovascular risk[4].

The mechanisms might include severe coronary endothelial dysfunction because of increased oxidative stress caused by high glucose, increased platelet adhesion that promotes venous thrombosis, and enhanced inflammatory responses, which cause the progression of atherosclerosis or vascular injury[5].

Furthermore, poor glycemic control may lead to an increased formation of advanced glycation end products, which may cause severe vascular damage[6].

The type 2 diabetes mellitus (DM) population has a higher risk of cardiovascular disease (CVD) and shows poorer outcomes than does the general population[7].

Hemoglobin A1c (HbA1c) has several advantages, including greater convenience, because fasting is not required, and as a long-term marker of glycemic control, it is less influenced than plasma glucose by acute stress and illness[8].

It is possible that intensive glycemic control instituted earlier in the disease process, such as those with newly diagnosed diabetes mellitus, may result in improved outcomes[9].

Ethics of the study

An approval from Ethical Committee was obtained. An informed written consent was taken from each patient after explanation of benefits and risks. Privacy of all patients data was secured. There was a code number for every patient file that included all investigations.

2. Patients and Methods

This study was carried out in duration of one year. It was conducted upon total number 120 persons in Tanta University Hospitals classified into two groups. Inclusion criteria: Patient presented by recent acute coronary syndrome, Patients not known to be diabetic before. Exclusion criteria: History of drugs that alter HbA1c as dapsone and ribavirin, Renal failure or nephrotic syndrome, Hemoglobinopathies, Pregnancy.

Patients were classified into two groups based on HbA1c level at time of admission. The median value of 5.7% has been set as the cutoff point for this grouping each group of sixty (60) patients.

All patients were subjected to the following: An informed consent was taken from all participants, History taking, Age, Sex, Risk factors: Hypertension (HTN), Smoking, Obesity, Past medical history of prior MI, PCI or CABG, Past history of renal disease.

Routine laboratory investigations including HbA1c, Serum cardiac biomarkers, CBC, RBS, Serum urea and creatinine and Virology.

Clinical Examination: Vital signs: heart rate, blood pressure, General examination on the abdomen, chest, head, neck, both the upper and lower limbs, Local cardiac examination, twelve leads surface ECG, echocardiography, diagnostic Coronary Angiography, Complexity of coronary lesion was assessed by SYNTAX score.

Statistical analysis

Data were analyzed using Statistical presentation and analysis of the present study was conducted, using the mean, standard Deviation, paired t-test, Chi-square and analysis of variance [ANOVA] tests by *SPSS V17*.

3. Results

This prospective study was carried out in duration of one year. It was conducted upon total number 120 persons in Tanta University Hospitals classified into:

➤ **Group I:** Sixty patients with HbA1c < 5.7%.
➤ **Group II (Control group):** Sixty patients with HbA1c ≥ 5.7%.

Table (I): Demographic data of the studied groups

Characteristics	n=(120)	(%)
Age Range Mean± S.D	**28-81** **56.2 ± 11.6**	
Gender Male Female	84 36	**70** **30**
Hypertension	64	**53.5**
Smoking	56	**46.7**
Obesity	36	**30**
Family history	12	**10**

Multivariate analysis technique is used for assessing multiple significant variables including age, sex, hypertension, smoking, obesity and family history in relation to HbA1c.

Table (II): Correlation between syntax score and HbA1c level**:**

SYNTAX	Glycated hemoglobin	
	<5.7%	≥5.7%
Range	2-20	6-34
Mean	11.1	16.71
±SD	4.28	6.53
f. test	4.528	
p. value	0.017*	

There is positive significant correlation between SYNTAX score and HbA1c level.

In patients with ≥5.7% SYNTAX score ranged from (6-34) with p value 0.017*.

Table (III): Multivariate analysis of coronary artery disease:

	Multivariate analysis	
	OR (95% CI)	P value
Gender (male)	0.743 (0.272-2.026)	0.561
Hypertension	0.997 (0.974-1.021)	0.822
Obesity	2.807 (0.620-12.710)	0.180
Smoking	0.972 (0.924-1.023)	0.275
Age	1.50 (0.9-2.48)	0.12
Family history	0.877 (0.616-1.247)	0.464
HbA1c%	1.975 (1.101-3.542)	0.022*

Multivariate analysis technique is used for assessing multiple significant variables including age, gender, hypertension, obesity, smoking, family history and glycated hemoglobin level in relation to acute coronary syndrome (ACS). The results indicated that there is positive significant relation between HbA1c with acute coronary syndrome, while no significant relationship found between the other factors including age, gender, obesity, family history, smoking and hypertension with ACS.

4. Discussion

One of the major risk factors of coronary artery disease is diabetes mellitus. It is well known, in fact, that the risk of coronary heart disease is 2 to 6-fold higher in patients with type 2 diabetes than in patients without diabetes and that man with diabetes has a worse survival from coronary heart disease than do those without diabetes[10]. Patients with diabetes but without prior myocardial infarction have for some years been considered to have the same risk of coronary heart disease events as patients without diabetes but with a prior myocardial infarction, as

recently aknowledged by the recommended treatment goals for lipoprotein therapy[11].

The results of the Rancho- Bernardo Study showed that level of glycated hemoglobin (HbAlc) is a better predictor of CHD and ischemic heart disease mortality than is fasting or post-load glycemia[12]. Selvin et al., also demonstrated in participants of the Atherosclerosis Risk In Communities (ARIC) study who did not have a history of diabetes that glycated hemoglobin was also a strong predictor of future diabetes, cardiovascular disease, and all-cause mortality[13].

It was found that the association of glycated hemoglobin with mortality is independent of fasting glucose but not vice versa. This finding suggests that glycated hemoglobin may be superior to fasting glucose in the prediction of mortality[13].

So, in our study we decided to correlate the glycated hemoglobin with the coronary artery disease presence and severity proven by coronary angiography.

The study population was stratified into the following HbAlctertiles: 1st < 5.7% (n=60), 2nd ≥ 5.7% (n=60). We found that there is positive significant relationship between glycated hemoglobin level and coronary artery disease severity (P value = 0.001).

Our results are in agreement with Rivera et al. who studied relation between HbAlc and CAD in 1043 asymptomatic Korean individuals without DM who underwent 64-slice cardiac computed tomography angiography as part of a health screening evaluation and found that increasing levels of HbAlc in asymptomatic individuals without diabetes are associated with the presence of coronary atherosclerosis[14].

Similar results were also obtained by Ashraf H. et al., who enrolled 299 consecutive non-diabetic individuals undergoing coronary angiography for suspected ischemia and studied the association between glycated hemoglobin (HbAlc) and angiographically proven coronary artery disease (CAD) and its severity in nondiabetic individuals. They found that with increasing HbAlc levels, there was a significant increase in the prevalence of CAD and number of vessels involved. In multivariate analysis, HbAlc emerged as an independent predictor of significant CAD (OR: 2.8, 95% CI: 1.3–6.2, p = 0.009)[15].

Verdoia M. et al., also evaluated the relationship between HbAlc and CAD in a consecutive cohort of patients without diabetes mellitus undergoing coronary angiography and found that HbAlc, but not fasting glycemia, was significantly associated with the prevalence of CAD (adjusted OR:1.51, 95% CI:1.15, 1.97, p:0.002)[16].

Conflicting results were obtained by Doerr et al., who compared HbAlc with Oral Glucose Tolerance (OGT) for early detection of silent diabetes, presence and progression of angiographically CAD in routine catheterization laboratory patients. They found no correlation between HbAlc levels and angiographically proven presence or progression of CAD[17].

In, this study, we found a positive relationship between glycated hemoglobin level and the CAD presence proved by coronary angiography. Higher percentage of patients with coronary artery disease were present in the higher glycated hemoglobin group.

Sasso et al. also found that glucose parameters, especially post load glycemia and HbAlc levels, in patients with different atherosclerotic damage are not equally distributed but are significantly higher in those with more severe disease. Like other metabolic variables such as serum cholesterol, the glycemic milieu may also correlate with the cardiovascular risk according to a linear model[18].

In a study by Selvin et al., after 15 years follow up of more than 11000 participants, it was suggested that levels of glycated hemoglobin (HbA1c) values in normal range without DM can identify people at higher risk of coronary artery disease (CAD), stroke and death[13].

Selvin et al. demonstrated in the study named the Atherosclerosis Risk in Communities study (ARIC) that in the participants who did not have a history of diabetes that glycated hemoglobin (HbA1c) was also a strong predictor of future diabetes, cardiovascular disease, and all-cause mortality[13]. In this community-based cohort of middle-aged white and black subjects, the predictive value of glycated hemoglobin (HbA1c) was superior to fasting glucose[13].

Khaw et al., have also studied the association between glycated hemoglobin (HbA1c) levels and major cardiovascular events and mortality. They reported increasing levels of glycated hemoglobin (HbA1c) are associated with all-cause and cardiovascular mortality. An increase of 1% in glycated hemoglobin (HbA1c) was associated with a 28% increase (P<0.002) in the risk of death, independent of other traditional cardiovascular risk factors. Interestingly, the association between increasing glycated hemoglobin (HbA1c) levels and death persisted (hazard ratio 1.46; P=0.05) after individuals with DM and those with a glycated hemoglobin (HbA1c) level above 7% were excluded from the analysis, suggesting a role of glycated hemoglobin (HbA1c) assessment in risk stratification and prediction among individuals without DM[19].

So, in non-diabetic population, glycated hemoglobin (HbA1c) is a better predictor of cardiovascular disease and coronary artery disease

(CAD) related mortality than other glycemic variables[13]. Although, much published data proved the relationship of elevated glycated hemoglobin and incidence of coronary artery disease, intervention studies were needed to demonstrate that lowering glycated hemoglobin would reduce the risk of cardiovascular morbidity and mortality[20].

This study was designed as a prevalence study and hence does not attempt to offer a pathogenic explanation for the relationship between glucose metabolism and CHD in non-diabetic patients.

Conclusions and Recommendations:

Coronary artery disease is a leading cause of death word wide. In addition to the other classic risk factors of CAD (smoking, male, sex, obesity and hypertension), diabetes is recognized as an important risk factor for coronary artery disease[21].

A body of information is now available suggests the need of careful consideration not only of diabetes, but also of other disturbances of glucose metabolism, such as impaired glucose tolerance and impaired fasting glucose, that have emerged as an important risk factor for cardiovascular disease mortality. Moreover, several prospective studies have shown a significant correlation between glycemic variables and morbidity from coronary heart disease in patients with normal glucose tolerance[22].

HbA1c level was the glycemic variable having the higher correlation with CHD.

At this study we aimed at correlating glycated hemoglobin level with the severity of coronary artery disease in non-diabetic patients presented with acute coronary syndrome.

History taken from all patients including (age, sex, obesity, family history, previous revascularization). Clinical examination done for all patients, twelve leaded ECG for diagnosis of acute coronary syndrome and echocardiography also done for all patients. Blood sample taken from all patients and sent to the laboratory for analysis (glycated hemoglobin level, serum cardiac biomarkers, complete blood picture, serum urea and creatinine, virology). The study population was classified into two groups according to glycated hemoglobin level. Significant coronary artery disease was defined as more than 50% diameter stenosis in any major vessel disease.

We found positive significant correlation between glycated hemoglobin level in non-diabetics and coronary artery disease. Our analysis suggest that HbA1c level is a marker for important pathological processes related to elevated glucose levels, we found positive significant correlation between glycated hemoglobin level and coronary artery disease in non-diabetic patients. In non-diabetic patients, higher glycated hemoglobin levels are significantly associated with coronary artery disease.

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