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RESEARCH ARTICLE

The Relation between Glycated Hemoglobin and Severity of Coronary Artery Disease in Non-Diabetic Patients with acute coronary syndrome.

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Abstract

This study aimed to assess the relationship between HbA1c level and the severity of coronary artery disease (CAD) among non-diabetic patients. *Methods:* One hundred patients with acute coronary syndrome (ACS) who referred to coronary angiography were included. According to American Diabetes Association (ADA7) patients were classified into high risk group (HbA1c 5.7 – 6.4%) or low risk group (HbA1c <5.7%). The severity of CAD was assessed by Gensini score which allocates a numerical value for the degree of coronary stenosis and a multiplication factor that depends on lesion location. *Results:* The level of HbA1c was positively correlated with Gensini score ($r=0.35$, $P<0.05$). However HbA1c has no significant correlation with either RWMSI ($r= -0.09$, $p>0.05$) or LVEF ($r= -0.04$, $p>0.05$). *Conclusion:* Among non-diabetic patients, higher HbA1c is significantly correlated with the severity of CAD. HbA1c level has a prognostic value to predict the severity of CAD among non-diabetic patients.

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Introduction:-

Diabetes mellitus (DM) is considered one of the most potent risk factors for cardiovascular diseases. The excess risk for cardiovascular disease is two to eight folds higher in patients with diabetes mellitus compared to non-diabetics of similar age, sex and ethnicity (1). High normal fasting blood glucose plus increased hemoglobin A1c (HbA1c) levels in non diabetics considered as potent risk factors for cardiovascular events(2). 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 (3). New clinical practice recommendation from the American Diabetes Association (ADA) advocates the use of HbA1c in diagnosis of diabetes mellitus largely on the basis of the established association between Glycated hemoglobin and microvascular disease (4). Levels of HbA1c less than 7% deemed appropriate for reducing risk of vascular complications(5). Predictive value of HbA1c for coronary artery disease (CAD) severity and cardiovascular mortality in non diabetics had been widely studied since 2004. Many previous trials found that elevated HbA1c levels are correlated with CAD severity indicating it as a marker of extensive coronary arterial disease (6).

In contrast, other studies found no relationship between HbA1c levels and the severity of CAD in nondiabetics with acute coronary syndrome. We aimed in current study to investigate this relationship using Gensini scoring system. In 1983, Gensini et al suggested a scoring system, which depends on a numerical value for the degree of coronary

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artery stenosis, and this provides a detailed assessment of CAD and does not ignore even very trivial lesions in coronary arteries (7)

Patients and methods:-

This prospective study included 100 non diabetic patients who referred for doing coronary angiography within three months of acute coronary syndrome (unstable angina, Non ST segment elevation MI or ST segment elevation MI). The study conducted in Cath lab of Benha University Hospitals from March 2015 to June 2015.

Diabetic patients or non diabetic patients with fasting blood sugar > 126mg/dl or HbA1c more than 6.5% were excluded from the study.

Included patients were subjected to complete medical history taking and physical examination with special emphasis on history of other risk factors as hypertension, smoking or family history of CAD.

For all patients; 12 lead ECG, cardiac enzymes (troponin T and CK-MB), fasting blood sugar, HbA1c, lipid profile and serum creatinine were done.

Transthoracic echocardiogram study was performed after admission to identify the estimated ejection fraction (EF), regional wall motion abnormalities and associated valvular lesions.

Regional wall motion score index (RWMSI) was calculated as the sum of wall motion scores divide by the number of the segments (normal = 1, hypokinesis = 2, akinesis = 3, dyskinesis = 4, and aneurysm = 5). American Society of Echocardiography guidelines and recommendations were applied (8).

Coronary angiography was performed using femoral or radial approaches. The severity of CAD was assessed by using the Gensini score (7). 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. (Table 1)

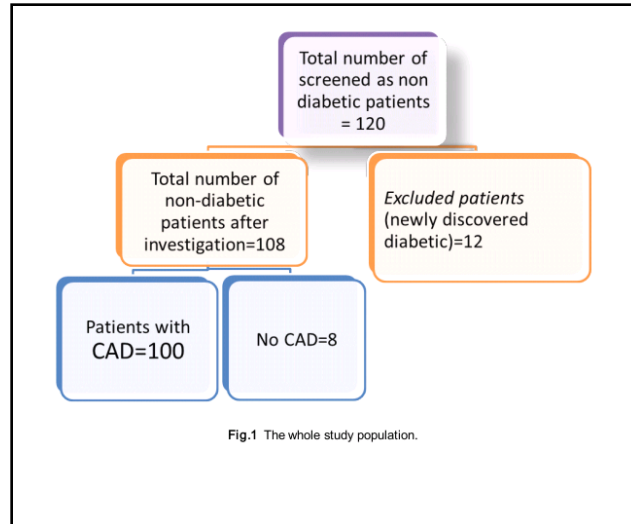
Table 1: Gensini score

% of stenosis	Score
25% stenosis	1
26-50% stenosis	2
51-75% stenosis	4
76-90% stenosis	8
91-99% stenosis	16
Totally occluded artery	32
The score is then multiplied by a factor according to the importance of the coronary artery as follows:	
Left main stem lesion	5
Proximal LAD and proximal LCX	2.5
Mid LAD lesion	1.5
Distal LAD, mid and distal LCX and RCA lesions	1
Any branch	0.5

The Gensini score is expressed as the sum of the scores for the all coronary arteries.

Results:-

Among total number of 120 screened patients as non diabetics, 12 patients were excluded as fasting blood sugar > 126mg/dl or HbA1c more than 6.5%, 8 patients were excluded because no evidence of CAD (figure 1).



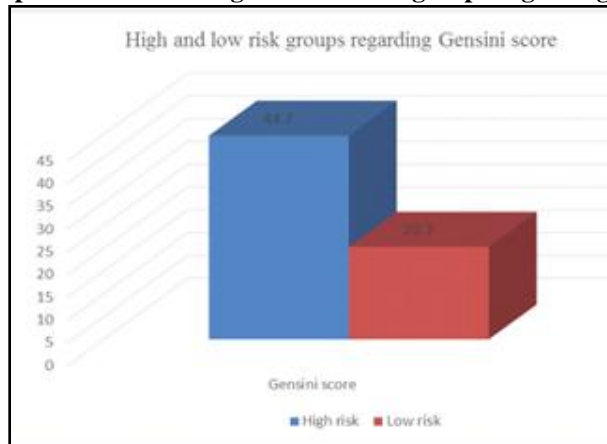
Among 100 patients included, male gender pre dominated (83%). Most of patients were overweight with mean BMI = 29.7 ± 4.9 . The most common cause of performing coronary angiography was unstable angina (45%). The Gensini score ranged from (1 to 168) with a mean of 38.3 ± 34.9 . Seventy four patients were in high risk group with (HbA1c 5.7 – 6.4%) while only 26 patients were in low risk group with (HbA1c <5.7%). Other data of both groups were comparable and shown in (Table 2).

Table 2: Demographic, clinical, laboratory & echocardiographic data of both groups:

Variables	High risk(n=74)74%	Low risk (n=26)26%	<i>p</i>
Age	54.6 ± 7.7	52.7 ± 12.4	>0.05
Male	62 (83.8%)	21 (80.38%)	
Hypertension	26 (35.1%)	11 (42.3%)	
Smoking	56 (75.7%)	17 (65.4%)	
Family history	20 (27%)	4 (15.4%)	
BMI	29.9 ± 4.9	29.3 ± 5.1	
Weight	102.3 ± 11.5	102.04 ± 13.2	
Unstable angina (%)	28 (37.8%)	17 (65.4%)	<0.05
NSTEMI (%)	19 (25.7%)	5 (19.2%)	
STEMI (%)	27 (36.5%)	4 (15.4%)	
FBG(mg/dl)	95.3 ± 16.8	92.4 ± 12.4	>0.05
TC(mg/dl)	189.3 ± 39.4	187.7 ± 4.5	>0.05
TGs(mg/dl)	145.2 ± 66.1	151.3 ± 64.4	>0.05
LDL(mg/dl)	122.4 ± 33.6	119.9 ± 44.2	>0.05
HDL(mg/dl)	36.1 ± 6.1	36.3 ± 4.7	>0.05
Creatinine(mg/dl)	1.03 ± 0.25	1.05 ± 0.28	>0.05
LVEF	55.4 ± 8.6	56.9 ± 10.4	>0.05
RWMSI	1.15 ± 0.2	1.18 ± 0.3	>0.05
Gensini score	44.7 ± 37.2	20.3 ± 17.8	<0.05

Gensini score was found to be significantly higher in the high risk group (Fig 2).

Figure 2: Comparison between high and low risk groups regarding Gensini score.



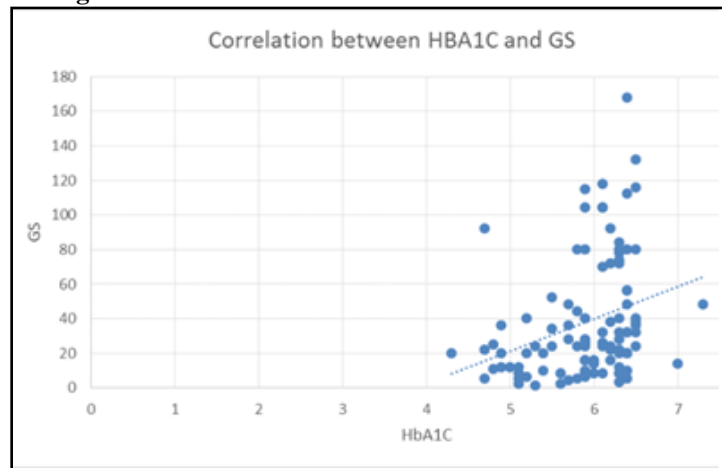
Correlation between HbA1c and Gensini score, LVEF and RWMSI:

Using Pearson’s correlation coefficients, the level of HbA1c was strongly correlated with Gensini score ($r=0.35$, $P<0.05$) while HbA1c was weakly correlated with either RWMSI ($r= -0.09$, $p>0.05$) or LVEF ($r= -0.04$, $p>0.05$) (Table 3) (Figure 3).

Table 3: Correlation between HbA1c and Gensini score,LVEF and RWMSI

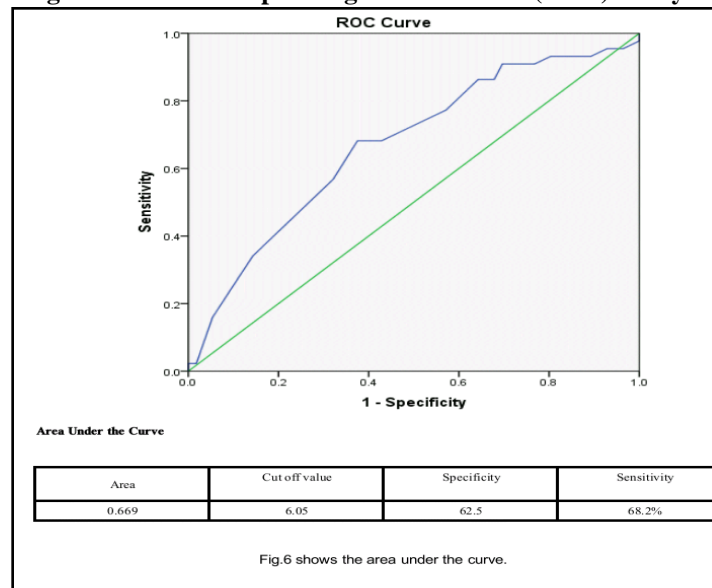
		Gensini score	LVEF	RWMSI
HbA1c	Correlation coefficient	0.35	-0.04	-0.09
	Sig. (2-tailed)	<0.05	.>0.05	>0.05
	N	100	100	100

Figure 3: Correlation between HbA1c and Gensini score



Receiver Operating Characteristic (ROC) Analysis

The sensitivity of HbA1c in predicting severe coronary atherosclerosis (Gensini >30) was 68.2% while the specificity was 62.5% with a cut-off value of 6.05% (figure 4).

Figure 4: Receiver Operating Characteristic (ROC) Analysis**Discussion:-**

HbA1c is an established marker of long-term glycemic control in patients with DM. Elevated HbA1c levels associated with an increased risk for future microvascular & macrovascular disease in diabetics (9). There is consistent evidence that optimal glycemic control (defined as HbA1c $\leq 7\%$) results in a lower incidence of cardiovascular complications in both type 1 and type 2 DM (10).

In non diabetic patients, the predictive value of HbA1c for CAD severity was observed in previous trials since 2004. In the trial of Khaw et al, patients with HbA1c concentrations less than 5% had the lowest rates of cardiovascular disease and mortality. An increase in HbA1c of 1% was associated with a relative risk for death from any cause of 1.24 (95% CI, 1.14 to 1.34; $P < 0.001$) (11).

In 2010, Selvin et al found that elevated HbA1c levels are predictive for cardiovascular events and mortality. Their results showed 20 to 30% increase in mortality and cardiovascular events with any increase in HbA1c level of 1% point (6).

Rivera et al studied the association between increasing levels of HbA1c and coronary plaque characteristics in asymptomatic individuals who diagnosed as non diabetics. Unadjusted analysis showed a positive association between increasing levels of HbA1c and the number of coronary segments ($p < 0.0001$). The association persisted even when traditional risk factors were taken into account (12).

Recently in 2014, Anping et al conducted a study to investigate relationship between HbA1c level and CAD severity in non-diabetic patients. Multivariate regression analyses showed that HbA1c strongly associated with the severity of CAD after adjustment for other traditional risk factors as well as fasting blood glucose (13).

The current study aimed to assess the correlation between HbA1c level among non- diabetics who underwent coronary angiography and the severity of CAD. The novelty of current trial, that we used the Gensini score to assess CAD severity. We concomitantly evaluated the relationship between HbA1c level and CAD severity including clinical scenario severity and the number of coronary artery stenosis. Consistent with previous studies, our results demonstrated that Gensini score was found to be significantly higher in the high risk group (figure 2). HbA1c is positively correlated with the severity of CAD ($r=0.35$, $P < 0.05$). (Table 3) (Figure 3) The sensitivity and specificity of HbA1c in predicting severe coronary atherosclerosis (Gensini > 30) was high (figure 4).

There were different mechanisms might explain the correlation between level of HbA1c and CAD severity even in non diabetics. Increased HbA1c level could reflect more generation of advanced glycosylation end-product, which

might subsequently attached to vessel wall causing endothelial dysfunction and oxidative stress promotion (14). On the other hand, the binding of advanced glycosylation end-product might also result in inflammatory cytokines such as CRP over-production (15). Increased CRP level has been found significantly associated with the instability of plaque (16). Finally, increased advanced glycosylation end-product could interfere with endogenous fibrinolytic system which might result in higher risk of coronary artery stenosis (17).

In contrast to the results of previous trials, Ahmet G et al in 2013 showed no significant relationship between HbA1c level and CAD severity ($p=0.299$) in 65 non diabetic patients with acute myocardial infarction. They concluded that the extent of CAD did not differ significantly among subjects with normal glucose tolerance, impaired fasting glucose, or impaired glucose tolerance (18). To overcome this debate, Future clinical randomized studies are warranted to investigate whether reduced HbA1c level will reduce the severity of CAD or not.

Limitations:-

Small number of the patients, No clinical follow up, the study does not show impact of fasting blood sugar or postprandial blood sugar on severity of CAD.

Conclusion:-

Current study demonstrated that higher HbA1c is significantly associated with the CAD severity among non-diabetic patients. 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.

Conflict of interest:-

The authors declare no conflict of interests.

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