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RELATIONSHIP OF GLYCATED HEMOGLOBIN WITH SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS WITH NON-ST ELEVATION MYOCARDIAL INFARCTION

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Contribution

MSJ conceived, designed and wrote manuscript. SAH and SN did data collection. SBK did critical review and final approval of manuscript. All authors contributed equally.

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ABSTRACT

Objective: To determine the association between HbA1c levels and angiographic severity of CAD in patients with NSTEMI.

Methodology: This cross-sectional study was conducted in Lady Reading Hospital, Peshawar from 3rd March, 2016 to 23rd July, 2016. All patients with history of typical chest pain of cardiac origin and positive hs-Trop T value presenting to cardiology unit with non ST elevation MI on ECG who underwent angiography were included in the study. A complete history, physical examination, lab investigations and ECG with echocardiography were done to fulfill the inclusion and exclusion criteria. HbA1c levels were determined for all patients and were categorized into 5 groups. All patients underwent coronary angiography and were categorized into 4 groups, i.e., none, mild, moderate and severe CAD. Association between HbA1c levels and CAD was determined by using Chi-Square test.

Results: A total of 100 patients were included with a mean age of 56.04±9.24 years. Of these, 70% were males and 68% were diagnosed diabetics. Mean HbA1c level was 7.0±1.3% with 61% patients having higher HbA1c levels, 21% patients had HbA1c in normal range,18% in pre-diabetic range, 17% in diabetic range with good control, 31% in diabetic range with satisfactory control and 13% in diabetic range with poor control. About 27% patients had no CAD while mild, moderate and severe CAD was present in 31%, 28% and 14% respectively. By using Chi- Square test, association between HbA1c and CAD was calculated to be 141.96 ($p \leq 0.001$). Increased levels of HbA1c also increased the PORs of CAD by 2.44 times ($p \leq 0.001$).

Conclusion: HbA1c is strongly associated with severity of CAD. It proved to be an independent risk factor for CAD and had a prognostic significance in predicting severity of CAD.

Key Words: HbA1c, Coronary Artery Disease, NSTEMI.

INTRODUCTION

Diabetes mellitus (DM), a major risk factor for CAD increases mortality by 3 to 4 folds among patients of same age and demographic characteristics as compared to non-diabetics.[1] Factors like hypertension, NAFLD, insulin resistance and deranged lipid profile with DM constitute metabolic syndrome, an independent risk factor for CAD.[2] Angiopathy resulting from hyperglycemia seems to be a primary cause of CAD among these patients.[3] HbA1c levels provide a better overview of blood sugar levels over three months span including FBS, postprandial RBS and occasional spikes and has low intrapersonal variability.[4] Because of close association of HbA1c with microvascular disease, ADA has recommended HbA1c as a tool for diagnosing DM.[5] Apart from diagnosis, HbA1c has been implicated to monitor glucose control and complications related to hyperglycemia.[6-8] However, several recent trials have failed to show that lowering HbA1c may decrease the prevalence of complications related to DM.[9-12] Since 2004, extensive work has been done on HbA1c and its predictive value on CAD. Studies have shown that HbA1c levels of <7% reduces the microvascular complications.[13] Trials have shown extensive association between HbA1c and CAD among non-diabetics.[14] On the contrary, studies failed to develop association between CAD and HbA1c levels among patients with STEMI.[15] However, studies regarding the positive relationship between HbA1c and mortality among patients with STEMI are available.[16] To the best of our knowledge, this study is the pioneer in evaluating the relationship between HbA1c and severity of CAD among patients with NSTEMI irrespective of their diabetic status.

METHODOLOGY

This cross-sectional study was conducted from 3rd March, 2016 to 23rd July, 2016 at Cardiology unit, Lady Reading Hospital Peshawar by using non-probability consecutive sampling. All patients presenting with typical chest pain of cardiac origin with a positive hs-Trop T and no changes in ECG were included in the study. Patients who refused to take part in the study or refused to undergo coronary angiography or were too sick to benefit from coronary interventions due to concomitant illnesses were excluded from the study. Also patients with previous history of STEMI, NSTEMI, angioplasty or bypass surgery, congenital heart disease, cardiomyopathy, heart failure, CKD, CLD, anemia, malignancies were excluded from the study. All included patients underwent detailed history taking followed by complete physical exam and lab testing. Blood samples were collected by trained staff soon after admission for hs-Trop T levels, HbA1c levels, serum creatinine, random blood sugar and lipid profile and were sent for analysis to the hospital laboratory. A 12 lead ECG along with transthoracic echo was performed for all the included patients. Echo based assessment for RWMA and ejection fraction was done. Patients were categorized into 5 groups on the basis of HbA1c levels i.e., <5.8%: Normal, 5.8-6.4%: Pre-diabetic, 6.4-<7%: Diabetes with good control, 7-8.4%: Diabetes with satisfactory control and >8.4%: Diabetes with poor control. All patients were subjected to coronary angiography under Axiom Artis Siemens 2005 machine by experienced interventional cardiologists. Patients were classified into 4 groups on the basis of number of vessels having >70% stenosis and caliber of >1.5mm. Patients having SVD, DVD, TVD with greater than 70% stenosis were categorized into mild, moderate and severe CAD respectively and those with no vessel involvement were labelled as none CAD. All the above mentioned data was recorded in a pre-designed proforma. Mean±SD was calculated for continuous variables while categorical variables were recorded as frequency and percentages. Association between HbA1c and CAD was determined by Chi-Square test with $p \leq 0.05$ as significant. Association of HbA1c and CAD with various risk factors for CAD was calculated by Chi-Square test with $p \leq 0.05$ as significant. Logistic regression model used to predict POR of CAD with increasing HbA1c levels.

RESULTS

A total of 150 patients were initially enrolled in this study, 12 patients refused to participate in the study, 31 refused to undergo coronary angiography, 7 patients had concomitant illnesses and were excluded from the study. Finally, 100 patients were included with a mean age of 56.04±9.2 years, of which 70% were male and 68% of the patients were diabetic. Mean HbA1c level was 7.0±1.3 and 61% of patients had an HbA1c level of >6.4%, 21% patients had HbA1c in normal range, 18% in prediabetic range, 17% in diabetic range with good control, 31% in diabetics with satisfactory control and 13% in diabetics with poor control. 27% patients had no CAD while mild, moderate and severe CAD was present in 31%, 28% and 14% respectively. Baseline characteristics of all enrolled patients are given in table 1.

Table 1: Demographic Variables of Study Population (n=100)

Variable	Mean±SD	Frequency (percentage)
History		
Age (years)	56.04±9.24	
Gender(male)		70%
Diabetes mellitus		68%
Hypertension		49%
Smoking		54%
Family hx of cad		26%
Examination		
SBP (mm Hg)	130±32.49	↑ (58%)
BMI (kg/m^2)	25.97±6.36	↑ (48%)
Weight (Kg)	69.24±16.11	
Height (cm)	163.74±9.30	
Waist hip ratio	0.8 1±0.11	↑ (61 %)
Investigations		
hs -TROP T (iu)	778.4±752.8	
EF %	56.36±10.4	↓ (29%)
S. creatinine (mg/dl)	0.98±0.45	↑ (20%)
HBA1C gm %	7.0±1.3	↑ (61%)
Categories		
NDM(<5.8%)		21%
PRE-DM(5.8-6.4%)		18%
DM-GC(6.4-<7%)		17%
DM SC(78.4%)		31%
DM PC(>8.4%)		13%
TGs (mg/dl)	174.59±51.07	↑ (47%)
Cholesterol (mg/dl)	197.05±25.51	↑ (35%)
LDL (mg/dl)	121.41±24.84	↑ (49%)
HDL (mg/dl)	40.03±5.31	↓ (13%)
CAD		73%
Mild CAD		31%
Moderate CAD		28%
Severe CAD		14%

SBP=systolic blood pressure. BMI=body mass index. EF=ejection fraction. NDM=none diabetes mellitus. PRE-DM= pre diabetes mellitus. DM- GC=diabetes mellitus with good control. DM-SC=diabetes mellitus with satisfactory control. DM-PC= diabetes mellitus with poor control. LDL= low density lipoproteins. HDL=high density lipoproteins. CAD=coronary artery disease↑Raised.↓Decreased.

Assosiation between HbA1c and CAD was calculated by using Chi-Square test with a value of 141.96 ($p \leq 0.001$). Association of various other risk factors for CAD with HbA1c as well as CAD had been done in this study. Results were quite unpredictable as in our NSTEMI population, only DM was strongly correlated with both HbA1c as well as CAD. Rest of the variables were neither statistically correlated with HbA1c levels nor to CAD (Table 2).

By using logistic regression model, we calculated the POR for CAD with higher levels of HbA1c showing that HbA1c increased the POR for CAD by 2.44 times (Table 3).

Table 2: Association of Various Risk Factors with HbA1c and CAD (n=100)

Variable	HBA1C		CAD	
	x^2-value	Sig:	x^2-value	Sig:
Age	0.164	0.102	0.128	0.204
Sex	8.17	0.08	16.04	0.95
DM	59.42	0.001	24.5	0.01
HTN	3.63	0.45	0.333	0.564
Smoking	2.39	0.66	0.483	0.487
LDL	0.017	0.87	0.002	0.987
TG	0.07	0.44	0.077	0.448
Cholesterol	0.05	0.59	0.045	0.655
BMI	0.07	0.44	0.167	0.09
WHR	0.08	0.36	0.123	0.22

DM=diabetes mellitus, HTN=hypertension. LDL=low density lipoproteins. TG= triglycerides. BMI= body mass index. WHR=waist hip ratio.

Table 3: Logistic Regression Model Showing POR of CAD with HbA1c (n=100)

Variable			CAD		
	POR	Exp(B)	wald:	df	Sig:
HbA1c(<5.8)	0.61	1 .3 4	11.7	1	0.000
HbA1c(5.86.4)	1.1 1	3 .98	10.6	1	0.000
Hb A1c(>6.4%)	2.44	11.50	20.59	1	0.000

DISCUSSION

Increase in cardiovascular events is associated with 1% increase in HbA1c levels.[15] Rivera et al reported a very strong association glycated hemoglobin had been used as a measure of blood glucose control because of its low intra-person variability. International experts Committee had recommended the diagnostic HbA1c cut-off value as 6.5% for DM.[17] Irrespective of diagnostic role, studies showed the prognostic value of HbA1c in micro and macro vascular between higher levels of HbA1c and diseased coronary artery segments among asymptomatic non-diabetic individuals.[19] Anping et al reported a strong association between HbA1c levels and severity of CAD even after multi-variate adjustment among non-diabetics.[20] In a recent study published in 2015, Ghaffari et al proved a strong association mortality.[3] Recent interest had been focused around between HbA1c and severity of CAD measured by Calliff's.[17] Association of HbA1c with severity of CAD. Khawetal reported in their study that HbA1c level of <5% are associated with low cardiovascular mortality and with every 1% increase in HbA1c level, all-cause mortality increased by 1.24t imes.[18] Selvin et al in 2010 demonstrated a 10-30% core. However, they failed to demonstrate relationship between HbA1c levels and CAD on number of vessels involved.[17]

Our study is the pioneer to assess the relationship between HbA1c levels and severity of CAD on the basis of vessel Involvement in patients of NSTEMI, irrespective of diabetic status. We found that higher levels of HbA1c were strongly associated with severity of CAD having a Chi-Square value of 141.96 with $p \leq 0.001$. We also demonstrated that with increasing levels of HbA1c, the angiography based severity of CAD and number of vessels involved increases as shown in figure 1. We also studied various comorbid conditions along with risk factors for their associations with HbA1c and CAD individually and found that only DM is associated with both. Rest of the variables in our population were neither associated with CAD nor affected HbA1c levels. We also calculated the POR for CAD with higher levels of HbA1C and demonstrated that HbA1c increases the PORs by 2.44 times. Another benefit of our study was that we determined the association in both diabetics and non-diabetics and it came out to be significant.

A variety of mechanisms had been proposed for association between HbA1c and severity of CAD. One was increased HbA1c levels promoted the end products of glycosylation which by attaching to vessel wall promoted endothelial dysfunction and oxidative stress.[21] Also, it resulted in CRP overproduction causing angiopathies.[22] Finally, endogenous fibrinolytic system got corrupted by glycosylation end products resulting in CAD.[23]

LIMITATIONS

Our study also had a few limitations including small sample size, single center study, no follow-up and did not show the effect of FBS or postprandial sugar spike on CAD severity.

CONCLUSION

HbA1C is strongly associated with severity of CAD irrespective of diabetic status. It showed to be a useful marker with prognostic significance for prediction of CAD. It should be used as a cardiac marker in risk stratification of severity of CAD. Those with high levels of glycated hemoglobin should undergo invasive testing for CAD.

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