Original Article

Association of Haemoglobin A1c Level with the Severity of Coronary Artery Disease in Non-diabetic Patients with Non-ST-Segment Elevation Myocardial Infarction

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Abstract:

Background: In nondiabetic patients with non-ST-segment–elevation myocardial infarction, hyperglycemia may be associated with adverse outcome.

Objective: To find out the association between HbA1c levels and the severity of coronary artery disease in non-diabetic patients with non-ST-segment elevation myocardial infarction

Methods: This cross sectional analytical study was carried out at the National Institute of Cardiovascular Diseases (NICVD), Dhaka, during the period from July, 2012 to May, 2013. This study was done with an aim to find out the association between the HbA1c level and the angiographic severity of coronary artery disease in patients with non-ST- elevation myocardial infarction without diabetes mellitus. A total of 170 patients with NSTEMI without diabetes mellitus who agreed to undergo coronary angiography were included in the study. Eighty five patients were selected having HbA1c <5.7% (Group I) and 85 patients were selected having HbA1c ranging from 5.7% to 6.4% (Group II). Severity of the Coronary Artery Disease (CAD) was assessed by angiographic vessel score, and Gensini score.

Results: The mean age of the studied patients was 51.0±9.0 years ranging from 30 to 80 years and male to female ratio was 4.5:1. The incidence of hypertension and level of RBS were significantly higher in group II than group I. The HbA1c level increased in accordance with the vessel score increment. There was a significant difference of the mean value of HbA1c among the vessel involvement groups. In this study mild CAD (scored"36) was significantly higher in group I and moderate to severe CAD (score>36) was significantly higher in group II according to Gensini score. This study showed a positive correlation between HbA1c and vessel score (r=0.47, p=0.01) and also between HbA1c and Gensini score (r=0.41, p=0.01).

Conclusion: Elevated HbA1c levels in non-diabetic non-ST- elevation myocardial infarction patients are associated with the severity of coronary artery disease.

Keywords: Haemoglobin A1c, non-ST-segment elevation myocardial infarction and non-diabetic

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Introduction:

At the beginning of the 20th century, cardiovascular disease (CVD) accounted for less than 10.0% of all deaths worldwide[1]. At the beginning of the 21th century, CVD accounts for nearly half of all deaths in the developed world and 25.0% in the developing world.[1]

In 2008, age standardized all cause mortality rate in Bangladesh was 1210 per 100,000 population, among them mortality due to non-communicable disease was 702 per 100,000 population. Mortality rate due to cardiovascular and respiratory disease were 421 and 97 per 100,000 population respectively.[2]

Diabetes is an independent risk factor of developing coronary artery disease. Much published data support the conclusion that diabetes puts people at very high risk of coronary artery disease. Diabetic patients face an 11% increased risk of mortality from ischemic heart disease.[3]

According to American Diabetic Association[4], it is reasonable to consider an individuals with an HbA1c level, ranges from 5.7 to 6.4% having high risk of future diabetes and it may be referred to as pre-diabetes. This pre-diabetic group should be informed of their increased risk for diabetes as well as CAD.[4]

O'Sullivan et al.[5] found that the HbA1c was associated with CVD and mortality. This association has also recently been extended to non-diabetic subjects as the relationship of CVD with glycaemia is believed to be a continuum without a threshold effect.

Selvin et al.[6] stated that classical cardiovascular risk factors such as smoking, hypertension, and hypercholesterolemia do not account for the excess risk of cardiovascular morbidity and mortality in patients with elevated HbA1c levels. In non-diabetic patients whose HbA1c level exceeded 4.6%; an increase in HbA1c of 1.0% point increased the relative risk of coronary artery disease to 2.36%. However, if the HbA1c level was not greater than 4.6%; an increase of HbA1c level was not associated with CAD risk.

In a study by Selvin et al.[7] after 15 years follow-up of more than 11000 participants, suggested that HbA1c values in normal range without diabetes can identify people at higher risk of CAD, stroke and death.

Sherif, et al.[8] found a statistically significant positive correlation between HbA1c levels and Gensini scores. Garg et al.[9] and Ikeda et al.[10] also showed that higher HbA1c levels are significantly associated with coronary artery disease. Elevated HbA1c level is also strongly correlated with disease severity and higher SYNTAX score[10]. The aim of this study was to see the association of HbA1c with the severity of coronary artery disease in non-diabetic patients with non-ST-segment elevation myocardial infarction.

Method:

This cross-sectional study was conducted in the Department of Cardiology, National Institute of Cardiovascular Diseases and Hospital, Dhaka from July 2012 to June 2013 over a period of one year. A total of 170 patients with NSTEMI without diabetes mellitus underwent coronary angiography in NICVD were selected as study population. Eighty five patients were selected having HbA1c <5.7% (Group I) and 85 patients were selected having HbA1c ranging from 5.7% to 6.4% (Group II)[4]. Patients with acute ST elevation myocardial infarction, valvular congenital heart disease, prior PCI or CABG were excluded from this study.

Informed written consent was taken from each patient before enrollment. Non- ST-elevation MI was confirmed by ESC guideline 2011. Meticulous history and detailed clinical examination were carried out and recorded in patient's data collection sheet. Demographic data, such as, age, sex, height, weight, waist hip ratio were noted. Troponin I, lipid profile, random blood sugar, and echocardiographic ejection fraction were recorded. 12 lead resting ECG will be done. Two to three milliliters of whole blood in EDTA tube was collected from the patient and transferred to the laboratory in ice box. Samples are kept for one week in refrigerator at $2\text{-}8^0$ C. Haemoglobin A1c measurement was done by non-porous ion-exchange high performance liquid chromatography (HPLC) performed on Tosoh G7 HPLC Glycohaemoglobin Analyzer. Angiographic severity of CAD was assessed by Vessel score and Gensini score. Interpretation of coronary angiogram was reviewed by at least two cardiologists who were unaware about this study. All the information was noted in the preformed data sheet. Data were presented as frequency with percentage for categorical variables and as mean with standard deviation for quantitative variables. Categorical variables were analyzed by Chi-Square test. Quantitative variables were analyzed by unpaired t-test or ANOVA. Correlation between HbA1c level and angiographic severity was measured by Pearson's and Spearman's correlation test. P value less than 0.05 was considered as statistically significant. Statistical analyses were performed with SPSS, version 12.0 (SPSS Inc).

Results:

In this study, 85 patients of NSTEMI with HbA1c level < 5.7% were considered as group I and 85 patients of NSTEMI with elevated HbA1c level (e" 5.7% - 6.4%) were considered as group II.

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Table-I
Demographic profile of the study population (N =170)

Age (year)	Group I n (%)	Group II n (%)	Total n (%)	p value
≤40	13 (15.3)	14 (16.5)	27 (15.9)	
41 – 50	34 (40.0)	26 (30.6)	60 (35.3)	
51 – 60	27 (31.8)	36 (42.4)	63 (37.1)	
> 60	11 (12.9)	9 (10.6)	20 (11.8)	
Mean ± SD	50.8±9.0	51.1±9.0	51.0±9.0	0.810^{ns}
Gender				
Male	68 (80.0%)	71 (83.5%)	139 (81.8)	
Female	17 (20.0%)	14 (16.5%)	31 (18.2)	

The mean age of the studied patients was 51.0±9.0 years ranging from 30 to 80 years and male to female ratio was 4.5:1. No significant difference was found between two groups in terms of age and sex distribution.

Table-II
Comparison of the study patients according to cardiovascular risk factors (N=170)

Risk factors	Group In (%)	Group IIn (%)	p value
Smoking	66 (77.6)	68 (80.0)	0.700
Chewing tobacco	34 (40.0)	37 (43.5)	0.640
Hypertension	43 (50.6)	57 (67.1)	0.062
Dyslipidaemia	48 (56.5)	50 (58.8)	0.750
Family history of CAD	22 (25.9)	24 (28.2)	

Smoking, chewing tobacco, hypertension, dyslipidaemia and family history of the patients were higher in the group II than the group I. But there was no significant difference between two groups except hypertension.

Table-III
Comparison of the study patients according to biochemical parameters (N=170)

Biochemical parameters	Group I Mean ± SD	Group II Mean ± SD	P value
Total Cholesterol (mg/dl)	197.8±35.9	209.2±43.5	0.100
Triglyceride (mg/dl)	145.1±34.7	151.9±37.5	0.080
LDL cholesterol (mg/dl)	116.7±23.0	121.0±26.5	0.110
HDL cholesterol (mg/dl)	40.0±4.8	37.9±5.2	0.070
Creatinine (mg/dl)	1.04±0.20	1.24±0.33	0.090
RBS (mmol/L)	6.2±1.2	7.1±1.4	0.010
Troponin I (ng/ml)	13.0±9.3	14.2±10.2	0.240

All components of lipid profile, serum cratinine and troponin I were found higher in group II than group I but not statistically significant (p>0.05). RBS was found significantly higher in group II than group I (p<0.05).

Table-IV
Comparision of the study patients according to vessel score (N=170)

Vessel score	Group I n (%)	Group II n (%)	P value
Score- 0	17(20.0)	6(7.1)	0.01^{s}
Score- 1	42(49.4%)	22(25.9%)	0.001^{s}
Score- 2	19(22.4%)	28(32.9%)	0.04^{s}
Score- 3	7(8.2%)	29(34.1%)	0.001^{s}

According to vessel score, zero (0)- vessel score and 1- vessel score were significantly higher in group I, whereas 2-vessel score and 3- vessel score were significantly higher in group II.

Table-V
*Association between HbA1c and number of vessels involved (N=170)*

Vessel score	HbA1c in %		P value
	Mean	SD	
No vessel involvement (n=23)	5.27	0.59	
Single (n=64)	5.47	0.54	0.001^s
Double (n=47)	5.81	0.47	
Triple (n=36)	6.05	0.57	

The mean HbA1c level was increased in proportion with the number of vessel involved which reflect the significant association between HbA1c % and vessel score of the study patients (p=0.001).

Table-VI
Distribution of the study patients according to Gensini score (N=170)

| Gensini Score	Group I n (%)	Group II n (%)	P value
Mild (CAD d+36)	66 (77.6)	39 (45.9)	0.001
Moderate to severe (CAD >36)	19 (22.4)	45 (54.1)	

Moderate to severe Gensini score was significantly higher in group II (p=0.001).
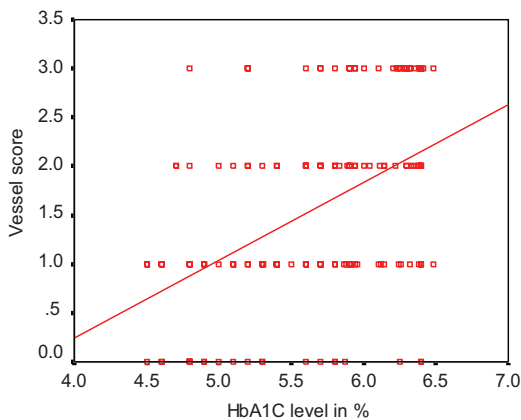
Spearman's correlation r (rho)= 0.47 p= 0.01

Fig.-1: *Correlation between HbA1c level (in percentage) and severity of coronary artery disease according to vessel score*

The figure shows that there is a positive correlation between HbA1c and coronary artery disease severity in terms of vessel score (r=0.47; p=0.01).
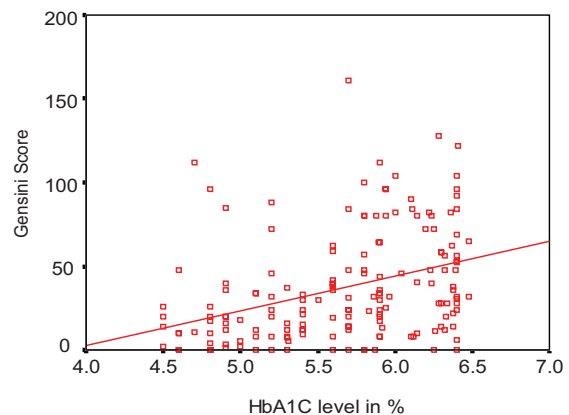
Pearson's correlation r (rho)=0.41 p=0.01

Fig.-2: *Corellation between HbA1c level (in percentage) and severity of coronary artery disease according to Gensini score*

The figure shows that there is a positive correlation between HbA1c and coronary artery disease severity in terms of Gensini score (r=0.41; p=0.01).

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Discussion:

The mean age of the studied patients was 51.0±9.0 years ranging from 30 to 80 years. Hung et al.[11], showed that the mean age of their study population was 51.5 ±13.2 years which was similar to the present study. Sherif, et al.[8] found the mean age of his study subjects was 55.2±7.6 years. Male female ratio was 4.5:1. Male female ratio was found 5.9:1 and 4.95:1 in study done by Khan[12] and Uddin[13] respectively.

The distribution of common risk factors for coronary artery disease in the present study revealed that the most common risk factor was smoking which was present in 66 patients (77.6 %) in group I and 68 patients (80.0 %) in group II but the difference between the two groups was not statistically significant (p=0.70) whereas hypertension was found 43(50.6%) and 57(67.1%) and respectively having statistically significant differnce between two group (p=0.02). Among other risk factors, tobacco use, dyslipidaemia and family history of premature CAD were 40.0%, 56.5% and 25.9% patients in group I and 43.5%, 58.8%, and 28.2% patients in group II respectively with no significant (p>0.05) difference between the study groups. Khan, et al.[12] found that smoking was the highest prevalent risk factor. Rivera, et al.[14], found that individuals with higher HbA1c level were more likely to have a higher prevalence of hypertension and smoking. He found that hypertension was present 47% in patients with HbA1c level 5.5-5.8% and 71% in patients with HbA1c level e"5.9% which was reached a significant difference (p <0.0 So these findings of the present study are similar to the findings of the study done by Rivera, et al[14].

 The mean HbA1c level with normal angiographic findings was 5.27±0.59%, with single vessel was 5.47±0.54%, with double vessel was 5.81±0.47% and with triple vessel disease was 6.05±0.57%. So the HbA1c level was increased in proportion with the number of vessel involved by CAD and the differences were statistically significant (p=0.001). Timmer et al.[15] found association of higher HbA1c level with multivessel coronary disease (e"2 vessel involvement). Ravipati et al.[16] found that the mean HbA1c level was 6.66±0.58% in patients with 0-vessel coronary artery disease (CAD), 8.00 ± 0.84% in patients with 1-vessel CAD, 8.83 ±1.45% in patients with 2-vessel CAD, and 10.40±2.28% in patients with 3- 4-vessel CAD. There was significant increasing trend of hemoglobin A1c levels over the increasing number of vessels with CAD (p <0.0001). Results differ as because only diabetic patients were enrolled in their study. Konstantinou et al.[17] also found association of HbA1c with number of vessel involved.

In this study, the mild Gensini score (d"36) was found in 77.6% and in 45.9% patients in group I and group II respectively whereas moderate to severe (>36) was found in 22.4% patients in group I and 54.1% patients in group II respectively. Moderate to severe Gensini score was significantly higher in group II which was statistically significant (p= 0.001).

Ayhan, et al.[18] found significantly higher level of HbA1c in severe CAD than mild CAD in terms of Gensini score (4.7±1.2% vs 6.0±1.4%, p<0.001). This finding is consistent with this study but differ in value as because this study only includes premature CAD patients and no history of CAD. Sherif et al.[8] found that increased HbA1c level was significantly associated with increased Gensini score. Kataoka et al.[19] found that HbAc level of preclinical DM patient was 6.1±0.9% and impaired glucose tolerant patients was 5.5±0.4%. Gensini score was significantly higher (>36) in preclinical group of patient than IGT group. This result also supports present study.

In this study there was a positive correlation between HbA1c and coronary artery disease severity in terms of vessel score and Gensini score (r=0.47 and r=0.41 respectively, p= 0.01 and 0.01). Konstantinou, et al.[16] found in their study that the stenosis score were independently associated with HbA1c level (r=0.58, p<0.001). Ayhan et al.[17] found that HbA1c levels positively correlated with the Gensini score in coronary atherosclerotic patients (r=0.662; p=0.001). In subgroup analyses of CAD patients, HbA1c levels positively correlated with the Gensini score in mild and severe CAD patients also (r=0.347, p=0.002, r=0.337, p<0.001, respectively). Shu-hua, et al.[20] revealed that Gensini score was closely related to HbA1c level (r=0.201, p=0.001). Statistically significant positive correlation (p<0.001) was also found in study done by Sherif, et al.[8].

Conclusion:

The present study concluded that the elevated HbA1c levels in non-diabetic individuals with non-ST- elevation myocardial infarction patients are associated with the severity of coronary artery disease. This simple HbA1c level measurement could be utilized as an independent predictor of coronary artery disease and its severity in non-diabetic subjects. Early screening may help to maintain an optimal HbA1c level, therefore aggressive treatment in early stage glycometabolic disorder may prevent more severe coronary artery disease.

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