

Prognostic Significance of Glycosylated Hemoglobin Level in Prediabetic and Newly Diagnosed Diabetic Patients with Acute Coronary syndrome: A Multi-Ethnic Population Study in Saudi Arabia

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Abstract

Background: DM is a slowly progressive disease that takes many years to progress from prediabetic to diabetic state. We aimed at finding prognostic significance of varying glycosylated hemoglobin level in prediabetic and newly diagnosed diabetic patients with acute coronary syndrome (ACS) in a multi-ethnic population in Saudi Arabia.

Results: The study evaluated 927 patients presented ACS and no history of DM before. Newly diagnosed DM group showed Significant prevalence of hypertension (p value 0.01) with more prevalence of hypertension in Arabic patients (p value 0.005). New diabetic patients represent statistically significant rise in number of patients having multivessel diseases, slow / no reflow complications or bifurcation lesions (p value 0.031, 0.045, and 0.05) respectively. Hospital stay was significantly higher in this group with mean value of 3.38 ± 3.1 (p value < 0.046). Receiver operating characteristic (ROC) curve for HbA1c showed area under the curve was 0.759, and 0.764 with sensitivity 77.2% and 82% and specificity 74.9% and 77% using a cutoff value > 6.08 % and 8% for prediction of dyslipidemia in prediabetic and diabetic groups, respectively.

Conclusion: we identified that HbA1c has a good sensitivity and specificity for prediction of dyslipidemia in prediabetics and newly diagnosed diabetics patients presented with ACS, but it failed to predict dyslipidemia in non-diabetics. The present study showed that high HbA1c level in admission in newly diagnosed diabetic's patients presented by ACS is a potential prognostic factor for multiverses disease and bifurcation lesions.

Keywords: HbA1; Glycosylated Hemoglobin; Acute Coronary Syndrome; Diabetes Mellitus; Dyslipidemia

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Introduction

Previous studies conducted in Saudi population showed a high percentage of DM with prevalence of 23.7% to 25.4% among adult population in Saudi Arabia [1]. Diabetes Mellitus (DM) is irreversible disease once established. It is a slowly progressive disease that takes many years to progress from prediabetic to diabetic state [2]. Prediabetes or impaired glucose tolerance (IGT) is a state where the blood glucose level is above the normal but below the diagnostic threshold of diabetes mellitus. One study showed that the prediabetic stage can start even from the age of 20 years and above [3]. In the same context, two Saudi studies showed cases of prediabetes with age between 20-44. prediabetic prevalence was 25.5% with strong association with age > 45 years [4,5]. Glycated hemoglobin (HbA1c) is a product of non-enzymatic attachment of hexose molecule to the amino terminal valine residue of β -chain of hemoglobin and it is a marker for the

average plasma glucose level of previous 2-3 months [6]. Taking into consideration classical risk factors for coronary artery diseases (CAD), elevated HbA1c is one of the independent risk factors for CAD. It was reported that each 1% rise in absolute HbA1c value in the diabetic population leads to 18% increased risk of CVD. This positive correlation between HbA1c and CVD has been established in nondiabetic cases, even within the normal range of HbA1c [7,8].

Poor glycaemic control in DM is a common secondary cause of hyperlipidemia [9]. The abnormal lipid parameters in DM are due to increased free fatty acid secondary to insulin resistance [10,11]. According to American Heart Association, 68% of patients of > 65 years with diabetes die due to heart diseases [12]. Many studies have compared and correlated FBG, PPBG and HbA1c with lipid profile in T2DM patients [9]. But few studies are done in prediabetic and newly discovered diabetic patients in this regard.



This study was planned to find out prognostic significance of varying glycosylated hemoglobin level on lipid profile in prediabetic and newly discovered diabetic patients with acute coronary syndrome in a multi-ethnic population in Saudi Arabia.

Methods

The study evaluated 927 patients presented with acute Coronary syndrome (ACS) and no history of DM before. The study was approved by the institutional ethics committee and all patients provided informed consent. We included adult patient ≥ 18 years old and less than 75 years with clinical symptoms of unstable angina (UA), ST segment elevation (STEMI) and non-ST segment elevation (NSTEMI) myocardial infarction according to third universal definition of myocardial infarction [13].

Detailed history, systemic examination and 12 leads ECG were performed for all the participants. Venous blood samples were collected and analyzed for blood glucose level, HbA1c, and lipid profile and cardiac enzymes just after the arrival of the patients to the emergency room. Patients were classified into three groups based on history and HbA1c levels at the time of admission. HbA1c level of 5.7- $<6.5\%$ was used to define prediabetes, while DM is $\geq 6.5\%$, according to the American Diabetes Association 2016 (14).

Body mass index (BMI) was measured as weight in kilograms divided by height in meters squared (kg/m^2) for all participant being studied. Normal BMI is less than $25 \text{ kg}/\text{m}^2$, overweight is considered when BMI is more than $25 \text{ kg}/\text{m}^2$ and less than 30, and obese if BMI more than $30 \text{ kg}/\text{m}^2$ (15). Contrast induced nephropathy was defined as absolute increase in serum creatinine $\geq 25\%$ or $\geq 0.5 \text{ mg}/\text{dl}$ from baseline at 48 hours after administration of contrast media in the absence of an alternative etiology.

The study excluded patients presented with renal, liver disorders or malignancy, patients with history of IHD or stroke, haemoglobinopathies, hemolytic anemia, chronic malaria, or severe iron deficiency anemia, patients with late presentation MI (longer than 48 hrs. between first symptom and admission) or patients already on anti-lipidemic drugs.

Data Collection

Data was collected and tabulated. Statistical package for social

sciences (SPSS) version 25.0 for windows (IBM Corp., Armonk, NY, USA). Data are presented as the Mean \pm standard deviation (SD), frequency, and percentage. Categorical variables were compared using the chi-square (χ^2). Continuous variables were compared by one-way ANOVA test with Tukey's test post hoc test to detect differences between subgroups. $P < 0.05$ was considered statistically significant. Correlations between parameters were determined by the Pearson correlation coefficient. Independent variables were determined by multivariate analysis.

Results

Total 927 patients from different ethnicity were included in the study. Patients were categorized into three groups according to HbA1c level. Number of patients included in non-diabetic, prediabetic and newly discovered diabetes groups were 234, 359 and 334 patients, respectively. Baseline clinical characteristics and demographic data were non-significant between groups except for hypertension where newly discovered DM group showed significant difference with (p value 0.01) as shown in table 1. Sub analysis of different ethnic population showed more prevalence of hypertension in Arabic patients with newly diagnosed DM at admission (p value 0.005). Newly discovered diabetic patients showed significantly higher values of triglycerides with mean values of 2.14 ± 2.60 (p value < 0.05). As regard to left ventricular EF the analysis showed significant difference among studied groups (f (2,580) = 3465, p value < 0.032). Post hoc tests showed prediabetics and newly diagnosed diabetics differed significantly compared to non-diabetic group. Comparison of GFR and post coronary intervention creatinine among studied groups showed no statistically significant difference in the studied groups (Table 2). Comparing lipid profile in different ethnic population did not show any significant differences (Table 3).

Group of new diabetic patients with HbA1c $\geq 6.5\%$ represent statistically significant rise in number of patients having multivessel diseases, slow flow, no reflow complications or bifurcation lesions. Hospital stay was significantly higher in this group with mean value of 3.38 ± 3.1 (p value < 0.046) (Table 4). Multivariate analysis of patients with HbA1c $\geq 6.5\%$ identified that HbA1c and increased age were independent predictors for multivessel disease (OR=2.64 (P=0.001) and OR=1.2 (P=0.03), for HbA1c and age, respectively) and bifurcation (OR=1.8 (P=0.01) and OR=1.02 (P=0.04), for HbA1c and age, respectively).

Table 1: Comparison of baseline clinical characteristics and demographic data for all studied groups. UA = Unstable Angina, STEMI = ST segment elevation myocardial infarction, Non-STEMI = Non-ST segment elevation myocardial infarction.

Parameter		Nondiabetic HbA1c < 5.7	Pre diabetic HbA1c 5.7 $< 6.5\%$	Newly discovered DM HbA1c $\geq 6.5\%$	P value
Patients Number (%)		234 (25.2)	359 (40.9)	334 (38.08)	
UA		19(2%)	48(5.1%)	44(4.7%)	0.9
STEMI		110(11.8%)	170(18.3%)	136(14.6%)	0.4
NON-STEMI		105(11.3%)	141(15.2%)	154(16.6%)	0.53
Gender n (%)	Male	167(18%)	314(33.9%)	269(29%)	0.15
	Female	67(7.2%)	45(4%)	65(7%)	0.71
Ethinity n (%)	Arabic	111(12%)	212(22.9%)	193(20.8%)	> 0.05
	African	10(1%)	10(1%)	15(1.6%)	
	Indian continent	73(7.8%)	112(12.1%)	115(12.4%)	
	Asian continent	40(4.3%)	25(2.7%)	11(1.2%)	
Age in years (mean \pm SD)		55.2 \pm 10	56 \pm 11.5	58.3 \pm 10.9	0.4
Body mass index (kg/m^2)		19 \pm 2.7	28.5 \pm 2.8	28.4 \pm 2.8	0.12
Smokingn (%)		76	119	105	0.11
Family history of CAD n (%)		18	30	27	0.59
Hypertension n (%)		103	173	219	0.005*



Table 2: Comparison of Ejection fraction and laboratory results between studied groups.

Parameter	Non-diabetic HbA1c < 5.7	Pre-diabetic HbA1c 5.7- <6.5%	Newly discovered DM HbA1c ≥ 6.5%	P value
Left Ventricular EF (%)	57.07±13.2	47.5±13.3	47.58±12.3	0.03*
Platelets	257.7±81.4	267.2±81.9	265.7±72.3	0.45
Cholesterol (MEAN ± SD) MMOL/L	4.54±1.24	4.57±1.15	4.57±1.29	0.94
Triglycerides (MEAN ± SD) MMOL/L	1.72±1.27	1.86±1.16	2.14±2.60	0.05*
LDL (MEAN ± SD) MMOL/L	3.02±1.04	3.08±1.02	3.30±1.6	0.72
HDL (MEAN ± SD) MMOL/L	1.04±0.33	1.08±0.73	1.17±0.95	0.81
Troponin	33.56±27.22	52.15±25.75	54.40±28.20	0.35
Total CPK	832.82±	1020.95±	940.41±	0.68
HB A1C (%)	5.31±0.38	6.07±1.03	8.96±2.15	0.001*
Pre PCI-Creatinine (UMOL/L)	80.2±53	70.7±72	98.8±43.6	0.8
Post PCI Creatinine (UMOL/L)	102.5±65	110±64	103.6±76	0.5
GFR ML/MIN/1.73M ²	102.8±37.4	103.4±40.8	98.5±72.6	0.5

Where: EF= ejection fraction, LDL = low density lipoprotein, HDL = High density lipoprotein, CPK = Creatinine phosphokinase, GFR = glomerular filtration rate. * = significant P value.

Table 3: Comparison of lipid profile in different ethnic population.

Parameters	Non-diabetic HbA1c < 5.7		Pre-diabetic HbA1c 5.7- <6.5%		Newly discovered DM HbA1c ≥ 6.5%	
	R	P value	R	P value	R	P value
Cholesterol (mmol/L)	0.035	0.35	0.31	0.05*	0.45	0.04*
Triglycerides (mmol/L)	0.037	0.53	0.59	0.02*	0.53	0.035*
LDL (mmol/L)	0.017	0.78	0.09	0.32	0.002	0.98
HDL (mmol/L)	0.043	0.48	0.06	0.49	0.014	0.82
Troponin	0.05	0.63	0.16	0.14	0.04	0.56
CPK	0.08	0.41	0.024	0.80	0.04	0.59
Platelet	0.09	0.31	0.057	0.54	0.06	0.33
Post PCI creatinine (umol/L)	0.04	0.71	0.11	0.08	0.12	0.09

Table 4: Comparison of cardiac catheterization data between studied groups.

Parameter	Arabic	African	Indian continent	Asian continent	P value
Cholesterol (Mean ± SD) mmol/L	4.4±1.27	4.6±1.04	4.8±1.4	4.4±0.9	0.08
Triglycerides (Mean ± SD) mmol/L	1.7±1.27	1.5±0.86	2±1.2	1.5±0.79	0.45
LDL (Mean ± SD) mmol/L	3.1±1.6	2.9±0.86	3.1±1.11	3.02±0.88	0.99
HDL (Mean ± SD) mmol/L	1.13±0.9	1.09±0.39	0.97±0.23	1.08±0.21	0.87

Table 5: Comparison of lipid profile, cardiac markers, platelets and creatinine with HbA1c in different studied groups.

Parameter	Non-diabetic HbA1c < 5.7	Pre-diabetic HbA1c 5.7- <6.5%	Newly discovered DM HbA1c ≥ 6.5%	P value
Single vessel diseased n (%)	152(16.3%)	194(20.9%)	163(17.5%)	0.07
Two vessels diseased n (%)	54(5.8%)	94(10.1%)	74(7.9%)	0.09
Multivessel disease n (%)	28(3%)	71(7.6%)	97(10.4%)	0.031*
Slow Flow/ No reflow n (%)	9	25(3%)	43(3%)	0.045*
Emergency CABG	0	3(0.3%)	7(0.7%)	0.61
Bifurcation lesion	9(0.9%)	28(3%)	38(4%)	0.05*
Hospital stay (days)	2.7±2.4	3.0±2.8	3.48±3.1	0.046*

The correlation between lipid profile, cardiac markers, platelets and creatinine with HbA1c in different studied groups were analyzed. HbA1c showed significant positive correlation with total cholesterol and triglycerides only in pre-diabetic and newly diagnosed DM as shown in table 5. An elevated HbA1c level was not correlated with a higher incidence of contrast induced nephropathy in all groups.

In prediabetic group, receiver operating characteristic (ROC) curve for HbA1c showed area under the curve was 0.759, with sensitivity 77.2% and specificity 74.9%, using HbA1c cutoff value > 6.08% for prediction of dyslipidemia (Figure 1). In newly diagnosed diabetic patients, receiver operating characteristic (ROC) curve for HbA1c showed area under the curve was 0.764, with sensitivity 82% and specificity 77%, using a cutoff value > 8% for prediction of dyslipidemia (Figure 2).

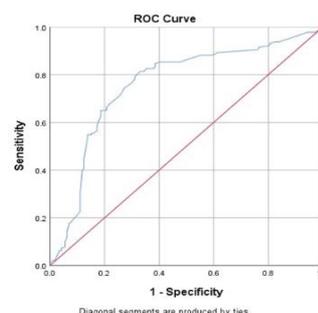


Figure 1: Receiver operating characteristic (ROC) curve for HbA1c showed area under the curve was 0.759, with sensitivity 77.2% and specificity 74.9%, using HbA1c cutoff value > 6.08% for prediction of dyslipidemia in prediabetic group for dyslipidemia.

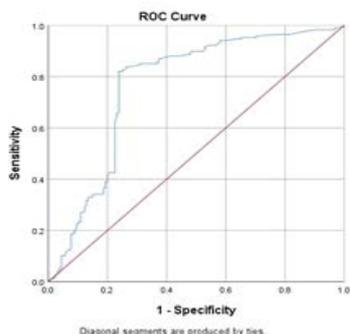


Figure 2: Receiver operating characteristic (ROC) curve for HbA1c showed area under the curve was 0.764, with sensitivity 82% and specificity 77%, using a cutoff value > 8% for prediction of dyslipidemia in newly diagnosed diabetes group.

Discussion

Previous epidemiologic studies have proved greater risk for cardiovascular disease (CVD) among persons with diabetes (16-19). Mansour et al., showed that overall prevalence of DM in Saudi adult population is 23.7%. Incidence of DM among Saudis living in urban areas was 25.5% compared to rural Saudis of 19.5% ($p < 0.00001$). They reported that a considerable number of diabetic patients 1116 (27.9%) were unaware of having DM [2]. There is a strong association between decrease in HbA1c levels in diabetic patients and reduction of the risk of CVD [20,21]. It is estimated that a 0.2% decrease in the HbA1c level could reduce the risk of developing CVD by 10% [7].

The purpose of this study was to evaluate the prognostic value of HbA1c in nondiabetic patients presenting with ACS. Totally, 927 patients presented with ACS from different ethnicity were included. Baseline clinical characteristics and demographic data were non-significant between groups except for hypertension which was significant in newly diagnosed DM group (p value 0.01). Taking into consideration, that DM takes many years to progress from prediabetic to diabetic state, prevalence of hypertension (HTN) in this group is consistent with literature where HTN incidence is more than 50% of patients with (DM) and plays a crucial role in both micro and macrovascular disease in DM [22].

The poor outcomes of patients with newly diagnosed diabetes, although they presented with the same baseline characteristics as patients without diabetes, guide the evidence that metabolic abnormalities contribute to their adverse outcomes [23]. A recent study has found that within new-onset coronary artery disease, the increased cardiovascular risk with prediabetic patients is largely driven by the coexistence of HTN rather than prediabetes alone [24]. Our study showed the prevalence of HTN among Arabic population with newly diagnosed diabetes is higher than that of other ethnicities. It was reported that between Arabic countries, the prevalence of HTN ranged from 16.3% to 44% [25]. A community-based study conducted in Saudi Arabia on 17,230 subjects showed the prevalence of hypertension was 26.1% in crude terms [26].

In the present study, the left ventricular EF was significantly lower in both newly diagnosed diabetics and prediabetics with (p value < 0.032) compared to non-diabetic group. These 2 groups of patients also represent statistically significant rise in number of patients having multivessel diseases, slow flow, no reflow complications or bifurcation lesions and longer hospital stay with p values 0.31, 0.45, 0.05 and 0.046, respectively. Multivariate analysis of patients with HbA1c $\geq 6.5\%$ identified that HbA1c and increased age were independent predictors

for multivessel disease (OR=2.64 ($P=0.001$) and OR=1.2 ($P=0.03$), for HbA1c and age, respectively) and bifurcation lesions (OR=1.8 ($P=0.01$) and OR=1.02 ($P=0.04$), for HbA1c and age, respectively). These findings are consistent with previous studies which proved that hyperglycemia is associated with higher rate of TIMI 0\1 and lower rate of complete revascularization. Chronic hyperglycemia affects platelets function and endothelial function, stimulates inflammation, and result in enhancement of oxidative stress, activation of platelet glycoproteins with abrupt changes in aggregability. It is worth mentioning that hyperglycemia per se in STEMI leads to impaired coronary flow on presentation and after primary coronary intervention [27,28]. All these mechanisms lead to increasing infarct size and reduction of ventricular function [29].

HbA1c showed significant positive correlation with total cholesterol and triglycerides only in pre-diabetic and newly diagnosed DM. lipid profile did not show any significant difference in different ethnic population which strongly indicates that lipid profile was correlated to diabetic state in our study population who share same life style in Saudi Arabia and not related to ethnicity [30]. Al-Kaabba AF, et al. (2012) and colleague showed high prevalence of dyslipidemia among Saudis. He reported high incidence of hypertriglyceridemia affecting 44% of studied population [30] which necessitate to reach the prediabetic population early and evaluate their lipid profile.

Positive correlation of HbA1c level with TC and TG in diabetic patients has been proved in many studies before (31-33). receiver operating characteristic (ROC) curve for HbA1c in our study showed area under the curve was 0.759, with sensitivity 77.2% and specificity 74.9%, using a cutoff value > 6.08% for prediction of dyslipidemia in prediabetics and area under the curve was 0.764, with sensitivity 82% and specificity 77%, using a cutoff value > 8% for prediction of dyslipidemia for newly diagnosed diabetics. On the contrary, this was discordant with Singh et al., who reported no significant difference in total cholesterol, triglyceride in prediabetic individuals with HbA1c between 5.7%-6.4% but this study was conducted on small population of 50 patients without ACS [34].

There is a strong association between HbA1c and subsequent diabetes. In a systematic review analyzed 16 cohort studies included 44,203 individuals with a follow-up interval range between 2.8 and 12 years, the 5-year incidence of developing DM in prediabetics with an HbA1c between 5.5-6.0% was ranging between 9% to 25%. An HbA1c range of 6.0-6.5% had a 5-year incidence of developing diabetes between 25% and 50% and a relative risk 20 times higher compared with an HbA1c of 5.0% [35]. Early recognition of prediabetic people with positive family history will give them the early benefit from lifestyle intervention [36].

This study has several limitations. It was a single center experience and it was conducted on population presented with ACS so conclusions for elective groups with other presentations are needed. Finally follow up over long periods of time is needed.

Conclusion

Our study has identified that HbA1c has a good sensitivity and specificity for prediction of dyslipidemia in prediabetics and newly diagnosed diabetics patients presented with ACS, but it failed to predict dyslipidemia in non-diabetics. Early diagnosis of dyslipidemia can be used as a preventive measure. The present study showed that high HbA1c level in admission in newly diagnosed diabetic's patients presented by ACS is a potential prognostic factor for multivessels disease



and bifurcation lesions. These findings may provide useful information in the therapeutic strategies for this special patient population.

Abbreviations

ACS: Acute coronary syndrome

CVD: cardiovascular disease

DM: Diabetes mellitus

HbA1c: Glycosylated Hemoglobin

HTN: Hypertension

IGT: impaired glucose tolerance

NSTEMI: Non-ST segment elevation myocardial infarction

ROC: Receiver operating characteristic

STEMI: ST segment elevation myocardial infarction

TC: Total cholesterol

TG: Triglycerides

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