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Research Article

Glycated Hemoglobin Level as a predictor of Severity of Coronary Artery Disease in Non-Diabetic Patients

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Abstract

Background: An elevated level of glycated hemoglobin (HbA1c) has been shown to be associated with increased risk of cardiovascular outcomes and all-cause mortality in patients without Type 2 Diabetes Mellitus (T2DM). The pathophysiology underlying this association is not clear but may be related to the development of severe and complex Coronary Artery Disease (CAD). We have evaluated the relation between HbA1c level and severity of CAD angiographically in non-diabetic patients with chronic stable angina.

Study Design and Methods: The study involved patients without T2DM with symptoms of chronic stable angina referred for conventional coronary angiography and found to have CAD defined as 50% reduction in luminal diameter by visual assessment of epicardial coronary arteries (≥50% obstruction in ≥1 coronary artery). Admission serum was analyzed for HbA1c from each participant. Invasive coronary angiography was performed and CAD severity was determined according to the anatomical SYNTAX score, derived using an online calculator.

Results: The study population consisted of 322 patients with a mean age of 54.4 ± 9.2 years; (68% males). Mean HbA1c level was 5.47% ± 1.07 and was divided into 4 quartiles: < 4.8% (n=62, 19.25%), 4.8 to 5.3% (n=99, 30.74%), 5.4-5.8% (n=84, 26.1%) and 5.9-6.5% (n=77, 24.0%). Higher HbA1c groups were associated with more CAD severity as assessed by mean SYNTAX score: HbA1c < 4.8%, SYNTAX score 12.6 ± 9.2; HbA1c 4.8 to 5.3%, SYNTAX score 12.9 ± 9.3; HbA1c 5.4%-5.8%, SYNTAX score 17.14 ± 11.2; HbA1c 5.9-6.5%, SYNTAX score 22.8 ± 12.7, p-value<0.001). Higher HbA1c was also associated with SYNTAX scores above 22, Left Main Stem (LMS)/Triple Vessel Disease (TVD) and increased in mean number of diseased vessel. The increase in HbA1c % level was positively correlated with SYNTAX score (r=0.594, p< 0.001). Multivariate logistic regression analysis showed that HbA1c level was an independent predictor of severity of CAD.

Conclusion: Our study has demonstrated a striking relationship between HbA1c and CAD severity in an incremental consistent pattern in non-diabetic subjects. These findings may implicate the role of chronic dysglycemia in the CAD disease progression and complexity in CAD patients without T2DM.

Keywords: Non-diabetic patients; Coronary artery disease (CAD); CAD risk factor; Glycated hemoglobin (HbA1c%).

Introduction

Type 2 Diabetes Mellitus (T2DM) is an established risk factor for cardiovascular disease, and patients with T2DM has two to eightfold higher risk of cardiovascular disease compared to patients without T2DM [1,2]. More recently, pre-diabetes has been recognized as an important cardiovascular risk factor with reports of associations between impaired glucose tolerance and elevated fasting glucose with macrovascular complications and mortality [3-5] as well as with increased carotid intima-media thickness and carotid plaque [6,7]. High normal fasting blood glucose and increased glycated hemoglobin levels were also recognized as risk factors for cardiovascular events and subclinical atherosclerosis in non-diabetic patients [8,9].The mechanisms of vascular damage by hyperglycemia is not fully understood but the prevailing theories include endothelial dysfunction, oxidative

stress, inflammatory response and also hyperinsulinemia and insulin resistance [10,11].

Glycated hemoglobin (HbA1c) is an indicator of the average blood glucose concentration over the preceding 2 to 3 months that is recommended by clinical practice guidelines for the diagnosis of T2DM and assessment of long-term control of DM [12]. HbA1c has also been used to help diagnose pre-diabetes [13]. An increased association has been reported between HbA1c and mortality from all-causes and cardiovascular outcomes in subjects without known T2DM [14]. This association with cardiovascular outcomes is not fully understood but may be related to the development of severe and complex Coronary Artery Disease (CAD). There has only a limited number of studies that have examined the extent of angiographic findings and the level of HbA1c in patients without T2DM and these had only focused on individuals with pre-diabetes and patients admitted with acute coronary syndromes that can cause stress-induced hyperglycemia [15-17].

The purpose of this study is to evaluate the relation between HbA1c level and severity of CAD angiographically in non-diabetic patients with chronic stable angina.

Methods

Patients with probable chronic coronary syndrome and planned conventional coronary angiography and/or angioplasty were consecutively selected for this study. The participants had no T2DM with no known history of diabetes and/or HbA1c level less than 6.5%. Patients were categorized as pre-diabetics if they had HbA1c: 5.7-6.4%.

All participants provided written informed consent for the study that was approved by the local ethics committee and they fulfilled the inclusion and exclusion criteria shown below:

Inclusion Criteria

Non-diabetes patients (no previous history of diabetes and HbA1c level less than 6.5%) with proven CAD on invasive coronary angiography were included in the study and CAD was defined as 50% reduction in luminal diameter by visual assessment of epicardial coronary arteries (≥50% obstruction in ≥1 coronary artery).

Exclusion Criteria

- Patients with history of diabetes or HbA1c level greater than 6.5%.
- Patients with <50% reduction in luminal diameter of epicardial coronary arteries on angiography.
- History of prior revascularization via Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG).
- Patients with hemoglobinopathies, anemia or history of recent blood transfusion.

Angiographic Assessment

Details of the coronary angiographic findings were reported and SYNTAX score were calculated using professional website tool: http://www.syntaxscore.com/

Statistical Analysis

The analysis was carried out using SPSS Version 24. Severity of coronary artery disease was assessed using SYNTAX score. The number of coronary vessels diseased, LMS/TVD and SYNTAX score > 22. Non- diabetic patients were divided into four quartiles according to their HbA1c values.

Data was presented as frequencies (n) and percentages (%) for categorical variables and mean ± standard deviation (SD) for continuous variables. Differences between groups were assessed by using the chi-square and ANOVA. Correlation between continuous variables (SYNTAX score and HbA1c%) was determined by Pearson correlation coefficients. Linear regression analysis was performed to evaluate association between severity of CAD and HbA1c levels. Multivariate logistic regression was used to identify independent predictors of severity of CAD. P values <0.05 were considered statistically significant.

Results

In this study, a total of 322 patients were included in the analysis. Mean age were 54.44 ± 9.17 years (min 27, max 88). 68% (n=219) were males vs. 32% (n=103) females. Based on their HbA1c levels, patients were graded into four groups (quartiles): less than 4.8%, 4.8 to 5.3%, 5.4-5.8% and 5.9-6.5%. The rates of distribution for each group were 19.25 % (n=62), 30.74% (n=99), 26.1% (n=84), 24% (n=77) respectively. CAD severity was expressed as anatomical SYNTAX score and number of diseased vessels. Both SYNTAX score and number of diseased vessels as a measure of lesion complexity were compared to each HbA1C interquartile utilizing ANOVA test which showed significant differences among different HbA1c groups. Table 1 shows the relationship between HbA1c by quartiles and clinical characteristics.

Characteristic	HbA1c interquartile				*p-value
	<4.8% (n=62)	4.8-5.3% (n=99)	5.4-5.8% (n=84)	5.9-6.5% (n=77)	
Age (mean ± SD)	48.63±12,21	51.18±10.08	53.48±9.87	54.14±11.13	0.01
Gender					
M	51(82.2%)	74(75%)	49(58%)	45(58.5%)	0.002
F	11(17.8%)	25(25%)	35(42%)	32(41.5%)	
BMI mean	27.1±2.8	26.75±3.11	27.18±4.81	26.06±3.5	0.22
e-GFR mean ml/mint	71.41±11.34	69.17±15.94	70.61±19.71	67.13±20.03	0.463
Hypertension	36(58%)	62(62.6%)	55(65%)	52(67.5%)	0.68
Smoking	10(16%)	14(14%)	16(19%)	18(23.3%)	0.43
*Differences between groups were calculated using the one-way ANOVA					

Table 1: Relationship between HbA1c by quartiles and Clinical Characteristics.

Arranged in a graded pattern, higher HbA1c groups were associated with CAD severity as measured by higher mean SYNTAX score with increased HbA1c levels (12.6±9.2, 12.9±9.3, 17.14±11.2, 22.8±12.7; p-value 0.000, by ANOVA), higher rates of SYNTAX score above 22, LMS/TVD and increased mean number of diseased vessel (Table 2).

Lesion Profile	HbA1c				
	<4.8% (n=62)	**4.8-5.3% (n=99)**	**5.4-5.8% (n=84)**	**5.9-6.5% (n=77)**	**P-value**
SYNTAX score					
SYNTAX, Mean±SD	12.6±9.2	12.9±9.3	17.14±11.2	22.8±12.7	<0.001
SYNTAX score >22	13(21%)	22(22.2%)	25(30%)	30(39%)	0.048
Number of diseased vessel (mean ± SD)	1.4±1.5	1.4±1.1	1.6±1.2	2.01±1.3	0.007
LMS and/or triple vessel disease	6(9.7%)	8(8.1%)	15(17.8%)	18(23.4%)	0.018
Chronic total Occlusions	5(8%)	7(7.1%)	7(8.3%)	9	0.74
*Differences between groups were calculated using the one-way ANOVA					

Table 2: Angiographic Findings among different HbA1c% groups.

Linear regression analysis showed that an increase in HbA1c % level was positively correlated with SYNTAX score at a Pearson's linear correlation coefficient of (r=0.594, p< 0.001). Multivariate logistic regression was used to show HbA1c level as independent predictor of severity of CAD (Table 3).

3VD and/or LMS involvement, SYNTAX >22	Unstandardized Coefficients		Standardized Coefficients	P-value
	B	Std. Error	Exp (B)	
Constant	-3.11	0.68		0.000
HbA1c%> 5.3	1.48	0.19	3.9	0.000
Smoking	0.21	0.22	2.15	0.5
HT	0.40	0.13	1.5	0.71
Dyslipidemias	0.61	0.31	1.8	0.13
Age >60y	0.30	0.29	1.4	0.41
Male	0.11	0.26	1.1	0.10

Table 3: Multivariate analysis in non-diabetes, HbA1c >5.3% was found as an independent predictor of severity of CAD.

Compared to non-diabetics, all parameters of angiographic CAD were more severe in pre-diabetic patients. See Table 4.

Angiographic Profile	Non-diabetics (HbA1c% <5.7) n=161	Pre-diabetics (HbA1c%≥5.7-6.4) N=161	p-value
SYNTAX score (mean ± SD)	13.61±9.16	17.95±11.62	0.0003
SYNTAX score >22	26(17.8%)	64(36.4%)	0.0002
Left main and/or triple vessel disease	14(9.6%)	33(18.8%)	0.02
No. of diseased vessels	1.27±1.4	1.73±1.1	0.0011

Table 4: Angiographic profile among non-diabetics (HbA1c% <5.7) vs. Pre-diabetic subgroups.

Discussion

The results from this study indicate that, there was a positive linear correlation between HbA1c% level and severity of angiographic CAD using SYNTAX score as a measure of CAD lesion complexity in non-diabetics and pre-diabetics. Also when graded according to four interquartile groups according to HbA1c% levels, higher glycated Hb groups were associated with higher rates of more severe diseased vessel manifested by SYNTAX score >22, LMS and/or three vessel disease, and number of diseased vessels. When multivariate logistic regression analysis was used to identify independent predictor of LMS/TVD, we found that HbA1c% > 5.3% was the only independent variable out of conventional risk factors. Similarly, when non-diabetics were compared with individuals whose HbA1c% level lies within the pre-diabetic range, all angiographic parameters showed more severe disease in pre-diabetics. These results support the notion that HbA1c% can be used as an independent predictor of CAD severity in addition to the conventional risk factors.

Our findings are supported by previous observations which have reported that HbA1c is related to CAD severity as assessed by both SYNTAX or Gensini scoring [14,17,18]. Our findings extend these observations to the population here in the Middle East. In our study, we found that the CAD severity was particularly worse in the 3rd and 4th quartile in the pre-diabetes range based on the HbA1c range of 5.6 to 6.4%. It is also worth noting that in this cohort, almost half of the patients were pre-diabetic that is in keeping with the reports of pre-diabetes in the region.

Although we did not assess the prognostic value of HbA1c in our population cohort, our findings of more severe CAD may have prognostic implications. There is supportive evidence for this. In a meta-analysis on 44,158 patients without T2DM, Santos-Oliveira, et al. [19] showed an incremental risk for cardiovascular deaths with increments in HbA1c. Compared with the baseline value of 4.27%, HbA1c level of 5% was associated with a relative risk for cardiovascular death of 1.13 (95% CI 1.05–1.21), a 6% value with 1.34 (95% CI 1.13–1.58), and a 7% HbA1c with relative risk of 1.58 (95% CI 1.22–2.06). Another meta-analysis by Liu [20], included 7 studies comprising 5,944 non-diabetic patients for the subgroup analysis of mortality, also showed an increased long-term mortality in non-diabetic patients with elevated HbA1c levels. Lastly a more recent meta-analysis by Geng, et al. [21] examining 20 studies involving 22,428 patients concluded that in non-diabetic patients with CAD, a high HbA1c level was associated with a higher rate of long-term death (odds ratio 1.76, 95% confidence interval 1.44–2.16, P<.001), and myocardial infarction (MI, odds ratio 1.69, 95% confidence interval 1.07–2.67, P=.026).

The finding of a striking relationship between HbA1c and the complexity of angiographic findings provide the growing evidence of the role of hyperglycaemia even in the non-diabetic individuals in the pathogeneisis of coronary artery disease. Although multiple metabolic abnormalities that characterize T2DM are involved in the progression of atherosclerosis in patients with T2DM, our data provides additional support to the notion that prolonged exposure to hyperglycemia and insulin resistance clustering with other cardiovascular risk factors such as obesity, arterial hypertension, and dyslipidemia play crucial roles. This is a subject of intense research that has shown that major biochemical pathways maybe involved in atherosclerosis in diabetic atherosclerosis including overproduction of reactive oxygen species, increased formation of advanced glycation end-products and activation of the AGEs-receptor for AGE axis, polyol and hexosamine flux, protein kinase C activation, and chronic vascular inflammation. Clearly, further research is needed to explore these mechanisms in at risk individual who have no T2DM but have abnormal HbA1c or pre-diabetes.

With respect to potential clinical application, the findings of our study together with others [19-21] may suggest that measuring HbA1c may be considered as be useful to help assess cardiovascular risk in on-diabetic patients along with other conventional cardiovascular risk factors [22,23].

Conclusion

In conclusion, we have shown that an elevated HbA1clevel is strongly correlated with CAD severity and higher SYNTAX scores especially in the pre-diabetes range of HbA1c. Our findings support the notion that HbA1c could be used as an independent predictor of CAD severity even in non-diabetics.

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