CORRELATION BETWEEN GLYCOSYLATED HbA1c LEVEL AND SEVERITY OF CORONARY ATHEROSCLEROSIS IN NON-DIABETICS

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ABSTRACT

Background: *Glycosylated hemoglobin A1C (HbA1c) has been widely recognized as a marker for predicting the severity of diabetes mellitus (DM) and several cardiovascular diseases. However, whether HbA1c could predict presence and severity of coronary artery stenosis in non diabetic patients remains largely unknown.* ***Aim of the work:*** *To study glycosylated hemoglobin level (HbA1c) as an index of presence and severity of coronary artery disease in non-diabetic patients.* ***Methods:*** *We enrolled 100 non diabetic patients underwent coronary angiography for evaluation of chest pain. Patients were included if they had no history of prior revascularization or diabetes mellitus and had fasting blood glucose < 126 mg/dl (7.0 mmol/l) and HbA1c < 6.5% (47mmol/mol). The severity of the CAD was also evaluated using the Gensini score. Serum HbA1c, lipid profile, resting ECG, Echo Doppler and HOLTER monitoring were measured. The patients were classified into two groups by tertiles of baseline HbA1c level (low group (nondiabetics) <5.7%, n = 55 ; high group (prediabetics) between 5.7 and 6.3%, n = 45). The relationships between the plasma HbA1c and presence and severity of CAD and early clinical outcomes were evaluated.* ***Results:*** *There were a statistically significant correlation between the level of plasma HbA1C and angiographic characteristics (P <0.001), statistically significant correlation between the level of plasma HbA1C and total silent ischemic episodes detected by Holter monitoring (P =0.04) and statistically insignificant correlation between the level of plasma HbA1C and myocardial systolic function measured by EF % (P =0.5*) ***Conclusion:*** *High. HbA1C level was an independent predictor of the presence of CAD after adjusting for conventional risk factors of CAD (AUC = 0.8).*

Key words: *HbAIc, coronary stenosis, non-diabetic*

INTRODUCTION

Coronary artery disease (CAD) is a worldwide health epidemic (Valentin Fuster et al., 2008). Atherosclerosis, with its complications, is the leading cause of mortality and morbidity in the developed world. Fortunately, much evidence has emerged over the last decade suggesting that the progression of atherosclerosis can be slowed or even reversed in many people with appropriate lifestyle and drug interventions (Eric J Topol, 2007)

Glucose metabolism disorders play an important role in the pathophysiology of atherosclerosis (Libby P. 2000). HbA1c is a more stable, accurate parameter of glucose homeostasis than fasting glycemia ; An International Expert Committee Report (IECR) recommends using the HbA1c assay as the preferred method for diabetes diagnosis and suggests the diagnosis if the HbA1c level is ≥6.5% (Selvin E et al 2004) There is consistent evidence that optimal glycemic control (defined as HbA1c ≤7%) results in a lower incidence of micro vascular complications in both type 1 and type 2 DM (Stamler J et al., 1993)

Glycosylated hemoglobin A1C (HbA1c) has been widely recognized as a marker for predicting the severity of diabetes mellitus (DM) and several cardiovascular diseases. However, whether HbA1c could predict presence and severity of coronary artery stenosis in non-diabetic patients remains largely unknown (Hong et al., 2014)

AIM OF THE WORK

To study HbA1c level as an index of presence and severity of coronary artery disease in non-diabetic patients.

PATIENTS AND METHODS

Between September 2014 and June 2016, we prospectively enrolled 100 consecutive non diabetic patients (33 males and 67 females) with group ranged between 32 and 72 years. They presented by chest pain and referred for invasive coronary angiography at Fayoum university hospital. The protocol of this study was approved by the hospital ethics committee. The informed consent was obtained from all participants.

EXCLUSION CRITERIA

- Patients with type 1 or 2 DM (DM was diagnosed according to the 2014 American Diabetes Association (ADA) guidelines of diabetes care as fasting plasma glucose (FPG) ≥126 mg/dL,2-hour PG during an OGTT ≥200 mg/dL, HbA1c level ≥6.5% or patients with classical symptoms of hyperglycemia with random blood sugar ≥200 mg/dL, or under the active treatment with insulin or oral hypoglycemic agents)
- Patients with prior coronary revascularization.

- Patient with hemoglobinopathies (sickle cell anemia, G6PD deficiency, autoimmune hemolytic anemia).
- Patients with chronic liver failure.
- Patients with chronic kidney disease on regular Hemodialysis.
- Patients with anemia (iron, folic acid, and vitamin B12 deficiency)
- Patients with familial hyperlipidemias.

All patients included in this study were subjected to:

- Detailed history and complete general and cardiological examinations.
- Laboratory investigations : CBC, Complete lipid profile, fasting and 2 hours postprandial blood glucose level (Fasting is defined as no caloric intake for at least 8 h)
- HbA1C measurement: Venous blood samples were obtained from each patient at baseline on admission. HbA1c levels were measured using ion exchange HPLC technique using Bio-Rad Variant II Dual kits
- 12 lead surface ECG
- Transthoracic echocardiography Using Siemens Acuson CV 70 machine in the traditional views (parasternal long, parasternal short, apical 4 chambers and apical 2 chambers). LV end diastolic diameter (LVEDD) and LV end systolic diameter (LVESD) were measured and the LV EF was calculated using, M-mode and biplane modified Simpson's rule. LA size was assessed by M-mode or 2D anteroposterior (AP) LA linear dimension which was obtained from the parasternal long-axis view. LA volume may also be measured using Simpson's rule. Conventional pulsed wave Doppler echocardiography was used to evaluate trans-mitral LV filling velocities. Peak early diastolic flow velocity (E), peak late diastolic velocities (A), and the ratio of E/A were determined.
- 24 hour Holter ECG monitoring: using Impressario Spacelabs Holter for assessment of ST diversion and > 1 mm ST diversion in two consecutive leads was considered significant.The number of episodes of silent ischemia, total silent ischemic duration, episodes of manifest ischemia and total manifest ischemic burden were determined after asking the patient about the episodes and duration of anginal pain.
- Invasive coronary angiography: The diagnostic procedure was performed via right femoral artery using Seldinger's technique after giving xylocaine for local anesthesia, with JL 6French sheaths and C3.5, C4 to visualize the left system. And JR F6 and C3, C4 to visualize the right system. Views were taken in the right oblique with caudal and cranial angulations, in left oblique with cranial and caudal (spider) angulations, lateral projections and additional projection when needed, all images were recorded digitally. Assessment of the severity of coronary artery disease using Gensini score as showed in the figure below. Gensini score was used to grade the degree of narrowing of coronary artery and score it with numerical values : 1 for 1–25% narrowing, 2 for 26–50% narrowing, 4 for 51–75%, 8 for 76–90%, 16 for 91–99%, and 32 for totally occluded artery. This score was then multiplied by a factor

according to the importance of the coronary artery: 5 for a left main (LM) lesion; 2.5 for proximal left anterior descending artery (LAD) and proximal circumflex artery (CX) lesions, 1.5 for a mid-LAD lesion, 1 for distal LAD, proximal/mid / distal OM and right coronary artery lesions, and 0.5 for any other branch. Correlation between HbA1c level and coronary atherosclerosis degree graded by Gensini score was done.

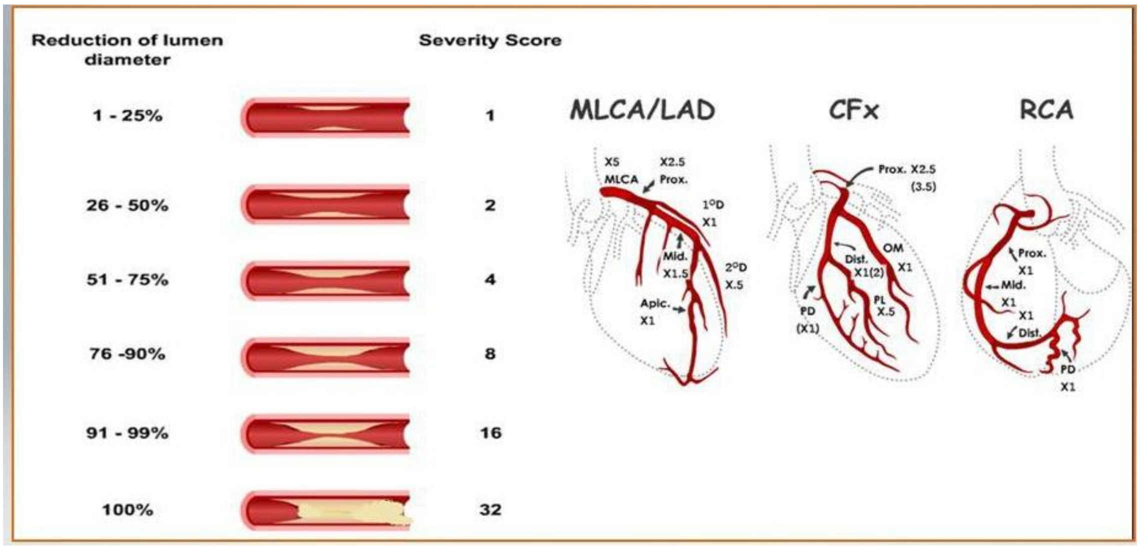

Figure 1. *Gensini score assessment (Sullivan RD et al., 1990)*

STATISTICAL ANALYSIS

Data was collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 under windows 7. Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data, and inferential statistic test. For quantitative parametric data: In-depended student t-Test used to compare measures of two independent groups of quantitative data. For quantitative non-parametric data Mann-Whitney test in comparing two independent groups. For qualitative data: Chi square test to compare two of more than two qualitative groups. Bivariate Pearson correlation test to test association between variables. Multiple linear regressions to test association between quantitative dependent and in-dependent variables and detection of risk factors. The level P ≤ 0.05 was considered the cut-off value for significance.

RESULTS

HbA1c for predicting the extent of CAD

Table 1. *Correlation between the level of Gensini score and total silent ischemic duration through the nondiabetic and pre-diabetic group*

Variables	Non-diabetic (n=55)		Pre-diabetic (n=45)		p-value	Sig.
	Mean	SD	Mean	SD		
Gensini	19.7	12.2	**74.7**	28.6	**<0.001**	**HS**
Total Silent ischemic duration	1.7	2.2	**12.7**	9.5	**0.03**	**S**

Table 2. *Correlation between the level of HbA1c with Gensini score and total silent ischemic duration in the study group*

Variables	HbA1c %		
	r	p-value	Sig.
Gensini	**0.77**	**<0.001**	**HS**
Total silent ischemic duration	**0.55**	**0.04**	**S**

There were a statistically significant correlation between the level of plasma HbA1C and angiographic characteristics (P <0.001). The statistical analysis showed that the plasma HbA1C level was an independent predictor of the presence of CAD after adjusting for conventional risk factors of CAD (AUC = 0.8).

The correlation between HbA1c and extent of coronary artery disease determined by Gensini score after coronary angiography is linear in the non-diabetic group but as the HbA1c reaches the prediabetic level, it reaches a plateau and the risk remains very high independent of the absolute level of HbA1c (P <0.001 for the difference between extent of CAD between the non-diabetic and prediabetic group) .As shown in Figure 1 and 2 and Table 1,2.

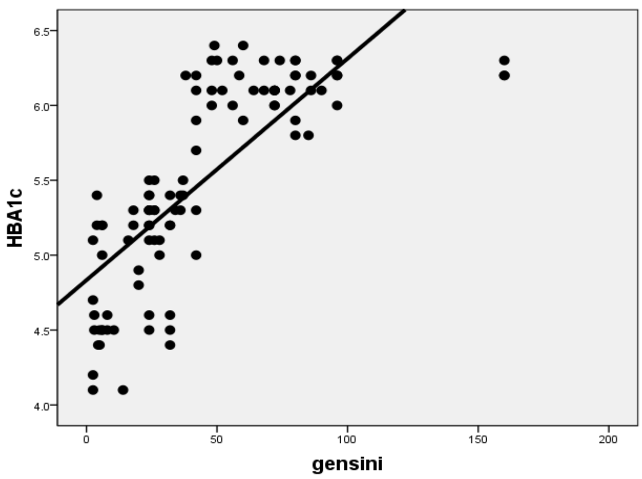

Figure 2. *Correlation between HbA1c and extent of coronary artery disease determined by Gensini score*

Sensitivity and specificity test for HbA1c with illustrates probability of being true positive is (80.6%) more than being false positive when repeat test 100 times with sensitivity (100%) and specificity (80.6%) at cut off value (4.95) when considering cardiac disease at Gensini level 20. As shown in figure 3

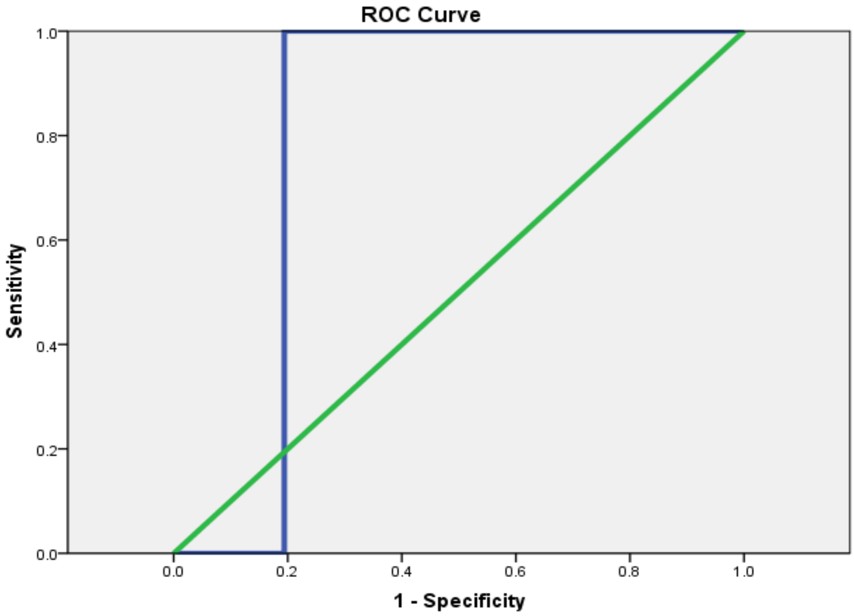

Figure 3. *Sensitivity and specificity test for HbA1c for predicting coronary artery disease determined by Gensini score*

Table 3. *Percentiles of HbA1C and Gensini level among study group*

Variables	Percentiles						
	5th	10th	25th	50th	75th	90th	95th
HBA1c	4.4	4.5	5.1	5.4	6.1	6.3	6.3
Gensini	3	5	21	36	72	86	96

HbA1c for predicting the extent of CAD in non-diabetic group

There were a statistically significant correlation between the level of plasma HbA1C and angiographic characteristics (P <0.001). The statistical analysis showed that the plasma HbA1C level was an independent predictor of the presence of CAD after adjusting for conventional risk factors of CAD. The correlation is linear as the level of HbA1c level increased, the extent of CAD detected by Gensini score increase.As shown in figure 3

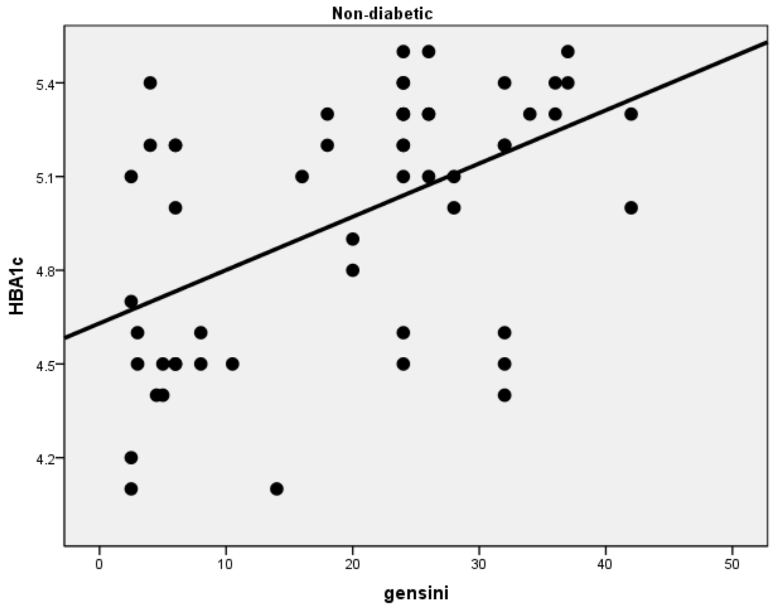

Figure 4. *Correlation between HbA1c and extent of coronary artery disease determined by Gensini score in non-diabetic group*

HbA1c for predicting the extent of CAD in prediabetic group

There were a statistically insignificant correlation between the level of plasma HbA1C in this group and angiographic characteristics (P = 0.3) although the risk of CAD is very high if compared with the non-diabetic group (P <0.001)

HbA1c for predicting silent ischemia

There were a statistically significant correlation between the level of plasma HbA1C and total silent ischemic episodes detected by Holter monitoring (P =0.04). As shown in figure 5

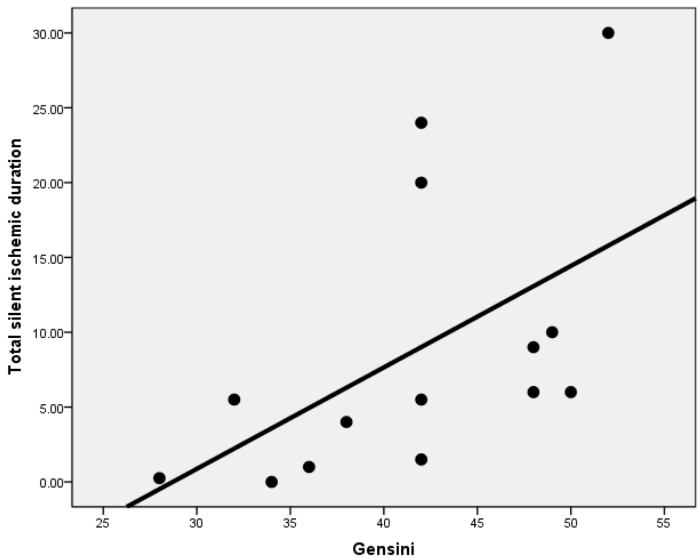

Figure 5. *Correlation between the level of plasma HbA1C and total silent ischemic episodes*

HbA1c for predicting systolic function

There were a statistically insignificant correlation between the level of plasma HbA1C and myocardial systolic function measured by EF % (P =0.5)

Table 4. *Correlation between the level of plasma HbA1C and Gensini score with EF %*

Variables	EF %		
	r	p-value	Sig.
Whole group			
Gensini	0.02	0.9	NS
HbA1c %	-0.06	0.5	NS
Non-diabetic group			
Gensini	-0.06	0.7	NS
HbA1c %	0.02	0.8	NS
Diabetic group			
Gensini	-0.13	0.4	NS
HbA1c %	0.16	0.3	NS

DISCUSSION

CAD is responsible for about one-third or more of all deaths in individuals over age 35 (Rosamond W et al., 2008). Risk factors that make it more likely for a person to develop coronary heart disease have been identified through many scientific studies. Managing the controllable risk factors especially DM can decrease an individual's chances of having CAD (Nichols M et al., 2014)

We assessed 100 non-diabetic patients by invasive coronary angiography to uncover the relation between elevated HbA1c level and CAD in non-diabetics and to assess the correlation between the HbA1c level and the severity of coronary artery disease in non-diabetics. Our study revealed highly significant relation between HbA1c level and coronary artery disease in non-diabetics. Furthermore, there were significant positive correlation between HbA1c level and extent of CAD calculated by Gensini scoring system.

Our results came in agreement with study of Nobutaka et. al. which enrolled 638 non diabetic patients underwent their first coronary angiography and concluded that higher HbA1c is an independent predictor of the prevalence of complex coronary lesions (217).

In addition, Verdoia et. al., assessed 1703 non-diabetic patients by coronary angiography and reported significant coronary artery disease defined as at least one coronary stenosis >50%, and concluded that among non-diabetic patients, higher HbA1c even within the normal range is significantly associated with the risk of CAD.

Furthermore, Liu et. al. 2011 demonstrated that elevated HbA1c level is an independent risk factor for mortality in CAD non-diabetic patients, but not in diabetic patients.

Our results agreed also with the results of Ashraf et. al., 2013 which stated that In non-diabetic subjects, HbA1c could be utilized for risk stratification of CAD and its severity, independent of traditional cardiovascular risk factors, insulin resistance and inflammatory markers.

On the other hand, Ertem et al, reported no significant correlation between HbA1C, fasting and postprandial blood glucose levels, lipid profile, or hs-CRP levels in non-diabetic acute coronary syndrome patients and severity of CAD Gensini score and. These finding can be explained by enrollment of patients with acute coronary syndrome with critical coronary artery lesions and high Gensini score ; consequently, all the patients whether have high HbA1c level or not will have high Gensini score (Ahmet G et al., 2013).

Our result found higher total silent ischemic episodes duration in pre-diabetics than normoglycemic patients. Silent ischemia refers to non-manifested ischemic episodes. Asymptomatic ischemia is the most common manifestation of coronary heart disease. We detect attacks of silent ischemia by performing 24 hours Holter ECG to 16 patients and detection of ST diversion episodes. By taking brief history of the patient and the symptoms of him and its time, we detect the attacks of silent ischemia and its duration. This finding could be explained by the autonomic neuropathy of the heart and increasing anginal pain threshold are found in pre-diabetics as well as the diabetics.

We found that there is no significant correlation between the left ventricular systolic function and either HbA1c or Gensini score in the study group. This may be explained by the fact that we didn't exclude the patients with acute coronary syndromes due to ST elevation MI which may give high Gensini score due to total arterial occlusion and the LV systolic function may be preserved yet as the patient may come early or due to myocardial preconditioning, On the other hand we didn't also exclude patients with previous old MI who may experienced MI then the artery recanalized after some time with low Gensini score on coronary angiography and reduced LV systolic function due to the myocardial damage due to MI.

CONCLUSION

High HbA1C level was an independent predictor of the presence of CAD after adjusting for conventional risk factors of CAD (AUC = 0.8).

Conflicts of interest: *None*

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