Association Of Glycosylated Haemoglobin Level And Microalbuminuria With The Severity Of Coronary Artery Disease

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Abstract: Background: Diabetes mellitus usually associated with higher risk of micro vascular and macrovascular complication especially CAD. Our studies were aimed to examine correlation between HbAIc (severity of DM) and micro albuminuria to severity of CAD assessed by coronary angiography using Gensini score. **Methodology:** 100 diabetic patients (type 2 diabetes) admitted for coronary angiography and diagnosed by criteria to had DM and CAD excluded from our study pts with macroalbuminuria or having condition which increase albumin in urine or have causes that may increase or decrease HbAlC. All pts will be subjected to full medical history physical examination 12 lead ECG, urine analysis for presence of albumin and measurement of HbAIc using quantitative colorimetric determination of glycol hemoglobin in samples by dimension RXL band "Siemens", detection of microalbuminuria by detection of albumin and creatinine level in the spot urine spelimens by Bayer DCA 2000 and analyzer system "Siemens" and coronary angiography with assessment of severity of CAD using Gensini score. **Results:** A total of 100 diabetic patients with age ranging from 39 to 70 yrs, 58 males and 42 females, Gensini score was 50±39.4 and HbAIc level was 10±3.4 and microabluminuria were present in 22 patients, Gensini score showed statistically significant higher values in patients with microalbumin (73.1±40 vs 43.6±30.6 y, $P < 0.001$), there were statistically significant positive correlation between HbAIc levels Gensini scores (P values < 0.001) another positive correlation were found between Gengini score and increasing duration of diabetes and increasing in age (P value 0.011 & 0.017 respectively) HBA1C values were significantly higher in pts with microalbuminuria vs pts without (12+4.3 vs 9.8+3.7, P value 0.017) lastly HbAIc levels were statistically significant higher in obese pts vs non obese (12+4.7 vs 9.4+3.2, P value = 0.002). **Conclusion:** Severity of CAD represented by Gensini Score was higher in pts with HbAIc, age, long duration DM, obesity and microalbuminuria.

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Key words: Coronary artery, microalbuminuria , Gensini score, Diabetes Mellitus.

1. Introduction

Much attention historically has focused on the prevention and treatment of microvascular disease complications of diabetes (i.e., retinopathy, nephropathy, and neuropathy), cardiovascular disease (CVD) remains the principal morbidity and driver of mortality in the setting of diabetes, most commonly in the form of coronary heart disease (CHD), together with the incremental risk associated with diabetes for cerebrovascular disease, peripheral vascular disease, and heart failure. For these reasons, continual efforts toward mitigating the risk of CVD in diabetes remain a global public health imperative ***(1)***.

Whereas older studies have suggested a diabetes-associated CVD risk similar to that observed among non diabetic patients with a prior myocardial infarction (MI) that is, a "coronary disease equivalent".

Recent observations from clinical trials showed that diabetic patients have a higher prevalence of coronary artery disease (CAD) with an increased number of fatal coronary events due to a higher incidence of plaque rupture and superimposed thrombosis in diffusely diseased coronary arteries additionally Diabetic patients develop complications more frequently after myocardial infarction (MI) and have double the in-hospital and six-month mortality compared to non-diabetic patients ***(1)***.

In the United Kingdom Prospective Diabetic Study (UKPDS), deaths from cardiovascular events were 70 times more common than deaths from microvascular complications. The UKPDS3 demonstrated that intensive glucose control, by keeping the HbA1c < 7%, helped to reduce microvascular complications; the reduction in risk of MI was of borderline significance. Other studies suggest that coronary artery disease and HbA1c are predictors of cardiovascular mortality ***(2-4)***.

The American Diabetes Association in its recent position statement stated that lowering HbA1c may be associated with reduction of microvascular, neuropathic and possibly macrovascular complications of diabetes mellitus. They suggested that more studies should be done to establish the relationship between HbA1c and macrovascular complications ***(5)***.

Individuals with diabetes-associated nephropathy typically have long periods of excessive albuminuria with gradual reductions in creatinine clearance as they approach end stage. There is a graded increase in risk for cardiovascular and total mortality with incremental increases in urine albumin:creatinine ratio (ACR) among high-risk individuals with hypertension and diabetes ***(6-8)*** .

Aim of Work:

The aim of our study was:

1. To examine the correlation between the control of diabetes mellitus as assessed by HbA1c and the severity of coronary artery disease as assessed by coronary angiogram, using the Gensini score.
2. To confirm the relation between microalbuminuria and the severity of coronary artery disease.

2. Patients and Methods:

Between January 2011 and July 2011, 100 patients previously diagnosed as having type 2 diabetes mellitus (58 male and 42 female) and admitted to the Critical Care Department Cairo University for elective coronary angiography were enrolled in our study.

Inclusion criteria:

Patients included in our study were fulfilling the following criteria on admission: Patients previously diagnosed to have diabetes mellitus according to American Diabetes Association Diagnostic Criteria for Diabetes Mellitus 2010 (9). Patients who previously diagnosed to have ischemic heart disease either by:- History of recurrent attacks of typical chest pain ,previous unstable angina or myocardial infarction, ECG different criteria of ischemia and ECHO showing regional wall motion abnormalities

Exclusion criteria:

Patients with previous coronary artery bypass graft (CABG), Patients with previous PCI and stenting, Patients with macroalbuminuria which is defined as albumin to creatinine ratio > 300 mcg / mg in a spot urine collection, Patients with factors that increase urinary albumin excretion,

a) Congestive heart failure. b) Urinary tract infection. c) Vaginal discharge. d) Fever.

Patients with the following because of decreased level HbA1c,

a) Shortened life span of RBC (Hemolytic anaemia, congenital spherocytosis, acute or chronic blood loss, Sickle cell disease, Hemoglobinopathies). b) Pregnancy, c) Ingestion of large amounts >1gm/day of vitamin C or E, d) After blood transfusion.

Patient with the following because of increased level of HbA1c.

a) Alcohol, lead, opiate toxicity, b) Splenectomy, c) Ureaemia.

Study design:

All patients were subjected to the following:

Detailed medical history with stress on risk factors of coronary artery disease & exclusion criteria, Detailed physical examination, 12 lead ECG, A 12-lead surface ECG was obtained from all patients while in the supine position. All ECGs were recorded at a paper speed of 25 mm/s with 1 mV/cm standardization, Random blood sugar and HbA_1C measurement on admission.

- **HbA1c measurement:**

Sample collection: two to three milliliters of whole blood in EDTA tube were collected from the patient and transferred to the laboratory in ice box. Samples are known to be stable for one week in refrigerator at 2-8^{o}C.

Methods:

By quantitative colorimetric determination of glycohemoglobin in samples using Teco-Glycohemoglobin kits procedures No. 0350. The apparatus is dimension RXL band produced by Siemens health care diagnostics.

- Routine urine analysis searching for pus cells and albumin.

Laboratory assay of urine albumin excretion in a morning spot urine collection The urinary albumin (microgram-per liter)/creatinine (milligram per liter) ratio (ACR) was used as a measure of albumin excretion

Albuminuria measurement:

Methods: Albumin and creatinine levels in the spot urine specimens were measured in a single rapid (7 min) assay format using colorimetric method using Spectrum Diagnostic kits

The apparatus is Bayer DCA 2000 & analyzer system (quantitative result interpretation) which is produced by Siemens health care diagnostic.

Coronary angiogram:

The diagnostic procedure was performed via right femoral artery using Seldenger's technique after

giving xylocaine for local anathesia, 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 **(10)**.

Assessment of the severity of coronary artery disease using Gensini score **(11)**.

Gensini score grades narrowing of the lumen of the coronary artery and scores it with numerical values with the following method:-

- 1 for 1–25% narrowing
- 2 for 26–50% narrowing
- 4 for 51–75%
- 8 for 76–90%
- 16 for 91–99%
- 32 for a completely occluded artery.

The statistical methods:

Data were statistically described in terms of mean ± standard deviation (± SD), frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Correlation between various variables was done using Spearman rank correlation equation for non-normal variables. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results:

Our study was conducted on 100 diabetic patients.

Demographic analysis:

A total of 100 patients were enrolled in our study. Their ages ranged between 39 and 70 years (mean age 55.2+7.2 years). They included 58 males (58%), 42 females (42%).

Risk factors for Coronary Artery Disease (CAD):

In our study hypertension was present in 70 patients, dyslipidemia in 48, obesity in 32, family history of IHD was present in 36 and 36 patients were smokers.

Gensini score:

Our results showed that the average Gensini score of our studied population was 50±39.4.

Table (1): Gensini score in the study population

Parameters	Mean	Std. Deviation
Gensini score	50	39.4

Gensini score was variably distributed among patients, twenty six patients have Gensini score between (0-20), 16 have it between (21-40), 24 between (41-60), 6 between (61-80) , 22 between (81-100), while only 4 patients have Gensini score between (101-120) and 2 patients between (121-140) as shown in the figure (1).

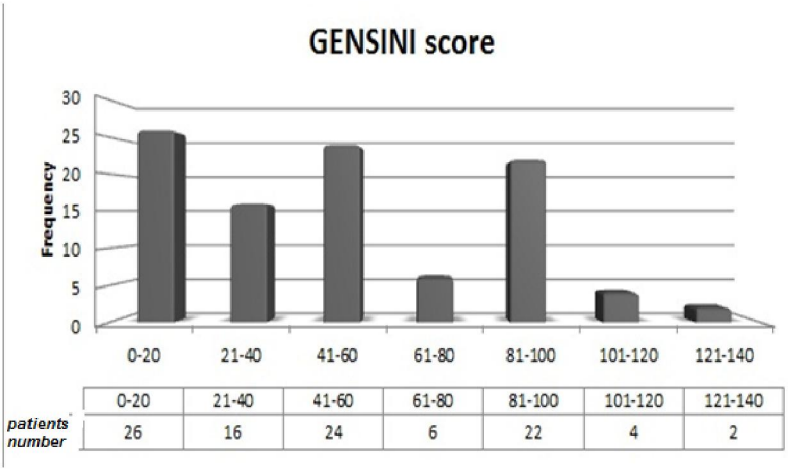

Figure (1): Gensini score for patients involved in the study

HbA1c:

Our study population showed average HbA1c level of 10.3±3.9. HbA1c also was variably distributed among patients. HbA1c between (4-6) was found in 5 patients, between (6-8) in 28, between (8-10) in 22 , between (10-12) in 20 , between (12-14) in 11 , between (14-16) in 6 , between (16-18) in 3, between

(18-20) in 2 , between (20-22) in one patient and between (22-24) in 2 patients.

Microalbuminuria

Microalbuminuria was present in 22 patients of the studied population as shown in figure (2).

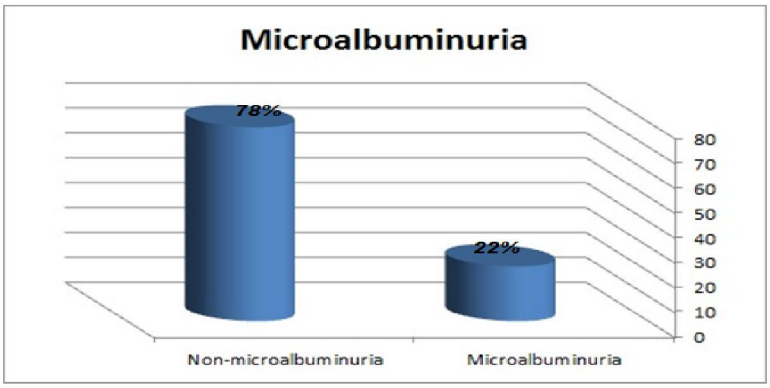

Figure (2): Microalbuminuria in the subjects involved in the study

Correlations:

I- Gensini score and correlations with other variables:

(1) Gensini score and microalbuminuria:

There was statistically significant difference between patients with versus those without microalbumnuria regarding their Gensini scores. Patients with microalbuminuria had higher Gensini scores compared to those with no microalbuminuria, (73.1±40 versus 43.6±30.6, P value <0.001), as shown in table (2) and figure (3)

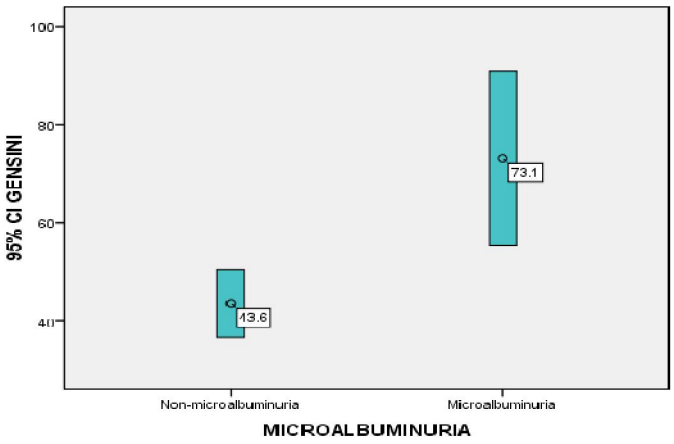

Figure (3): Correlation of Gensini score and microalbuminuria

Table (2): correlation of Gensini score and microalbuminuria

		Mean	SD	P value
GENSINI	Microalbuminuria	73.1	40	<0.001
	No microalbuminuria	43.6	30.6	

(2) Gensini score and HbA1C level

There was a statistically significant positive correlation between HbA1c levels & Gensini scores. With increasing HbA1c values there is an increase in Gensini score (P value <0.001), as shown in figure (4).

(3) Gensini score and duration of diabetes:

There is a statistically significant positive correlation between duration of diabetes & Gensini scores. With increasing duration of diabetes there is an increase in Gensini score with (P value 0.011), as shown in figure (5).

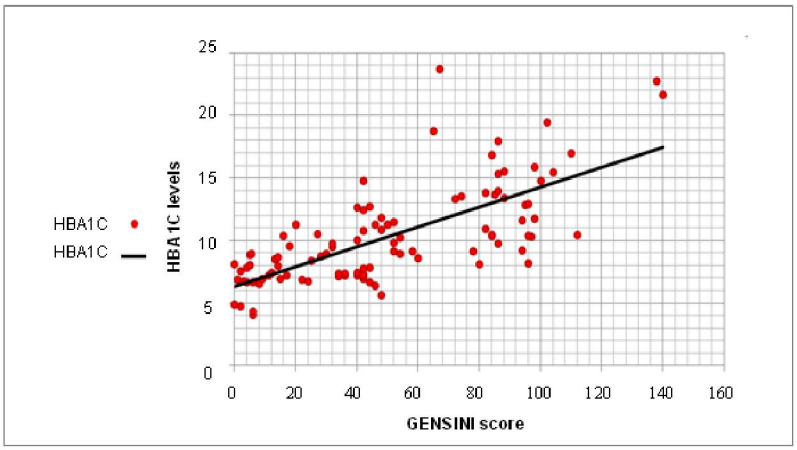

Figure (4): Correlation of Gensini score and HBA1C

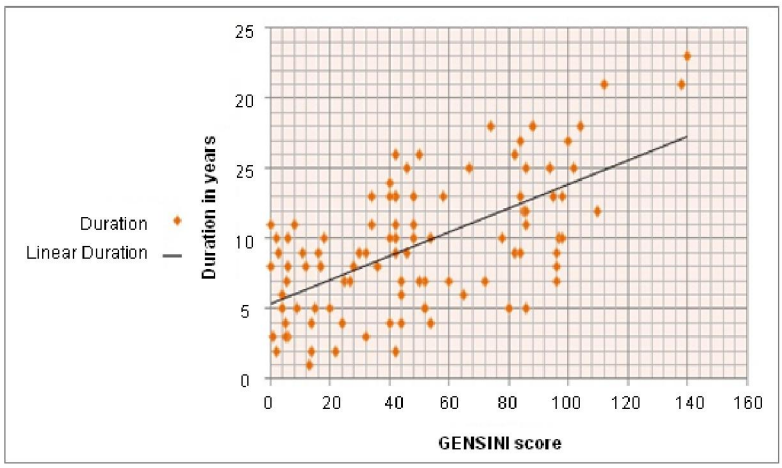

Figure (5): Correlation of Gensini score and duration of diabetes

(4) Gensini score and age:

There is a statistically significant positive correlation between age & Gensini scores (P value 0.017), as shown in figure (6) Gensini score is higher in older patients.

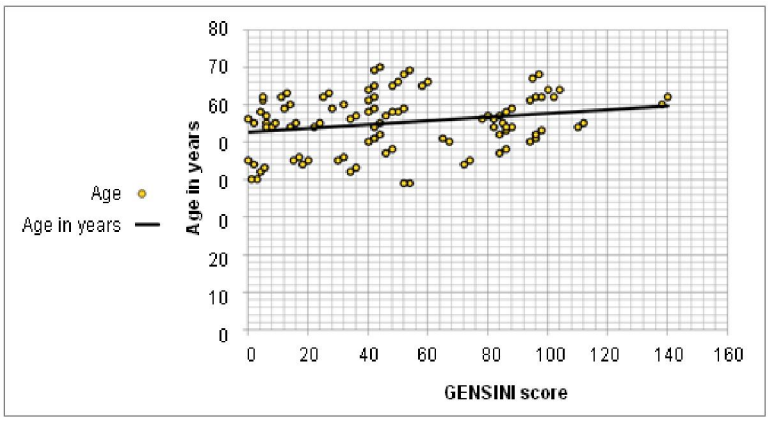

Figure (6): Correlation of Gensini score and age

HbA1c and correlation with other variables:

(1) HbA1C and microalbumnuria

There was statistically significant difference between patients with versus those without microalbuminuria regarding their HbA1c levels. Patients with microalbuminuria have HbA1c level 12±4.3, while patients with no microalbuminuria the level was 9.8±3.7, (*P* value 0.017).as shown in figure (7).

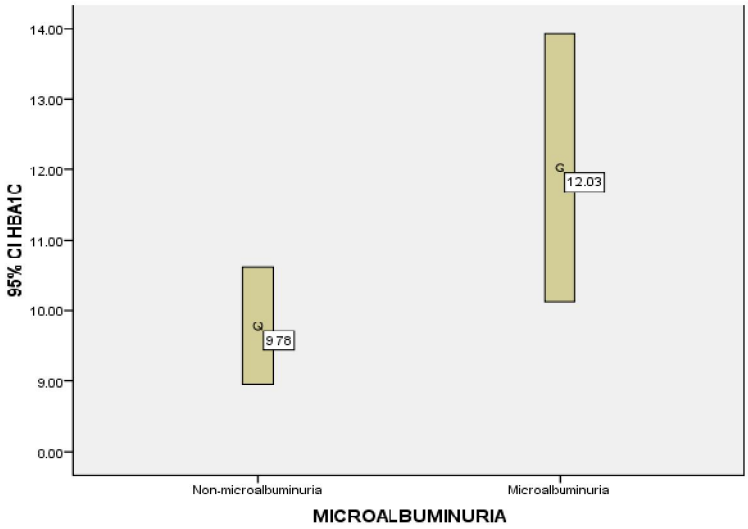

Figure (7): Correlation between HbA1C and microalbuminuria

(1) HbA1C and obesity

There was statistically significant difference between obese versus non obese patients regarding their HbA1c levels. In obese patients HbA1c level was 12±4.7, while in non obese patients HbA1c was 9.4±3.2, (P value 0.002).as shown in figure (8).

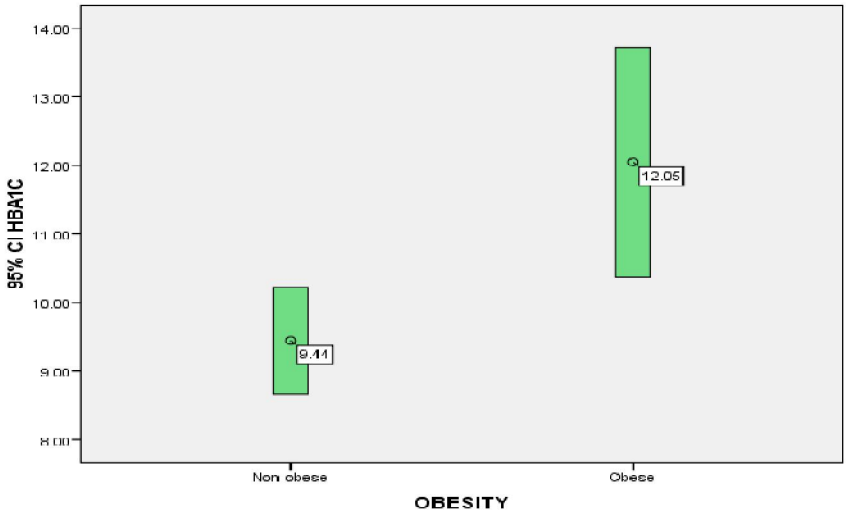

Figure (8): Correlation of HbA1C and obesity

(2) HbA1c and other variables

There is no significant correlation between HbA1c and age, sex, hypertension, smoking, dyslipidemia or family history of IHD as shown in table (3)

Table (3): Correlation of HbA1c and other variables

	Mean	Std. Deviation	HbA1C
GENSINI	50.1	34.9	<0.001
MICROALBUMINURIA	1.2	.4	0.017
AGE	55.2	7.6	0.172
SEX	-	-	0.305
HTN	-	-	0.1
SMOKING	-	-	0.228
DYSLIPIDEMIA	-	-	0.179
OBESITY	-	-	0.002
F.H	-	-	0.287

4. Discussion:

It's worth saying that we noticed most of the studies over the past few years on the association of HbA1c and microalbiminuria with severity of CAD were Chinese studies, we explained this with the relatively larger burden of diabetes in China which contain 21 million diabetic patients so it is considered to be one of the top 10 ranking of the absolute numbers of diabetic patients all over the world.[12]

The prevalence of diabetes in Egypt is 11.4% of total Egyptian population in 2011 according to International Diabetes Federation, so Egypt is considered one of the top 10 ranking of prevalence of diabetes in the world.[13]

From the previously mentioned facts we found that the correlation between control of diabetes as assessed by HbA1c and CAD, and also the relation of microvascular and macrovascular complications of diabetes is very important and worth's studying as recommended by the American Diabetes Association[5] especially in a country which considered to be number nine in the prevalence of diabetes in the world.

1- Regarding to correlation between severity of CAD and microalbuminuria in our study we found statistically significant higher severity of CAD in pts with microalbuminuria ($P < 0.001$).

This matched with Onur et al., [14] studied the relationship between microalbuminuria and the presence and extent of coronary atherosclerosis in four hundred and two patients and found a positive correlation between microalbuminuria and extent of CAD both in the diabetic and non-diabetic patients and concluded that Microalbuminuria is an independent predictor for the presence ($P < .001$) and severity of CAD ($P < .001$, $\beta = .563$).

Also our results goes hand in hand with the data published by Defilippis[15] in ***2010*** who conducted the MESA study (Multi Ethenic Study of Atherosclerosis) which is a prospective cohort study of 5.666 participants free of clinical cardiovascular disease and macroalbuminuria at entry. At baseline, individuals with Microalbuminuria were more likely to have "coronary artery calcification score" CAC > 0 compared with those without Microalbuminuria (62% vs. 48%, $p < 0.0001$).During a mean follow-up of 2.4 ± 0.8 years, those with Microalbuminuria and no CAC at baseline were more likely to develop CAC (relative risk: 2.05, 95% confidence interval: 1.41 to 3.02,$p < 0.0001$) as compared with those without Microalbuminuria in demographic-adjusted analyses.

Guo[16] and **Rein**[17] also concluded that there was a positive correlation between severity of CAD and microalbuminuria and that this association was significant in the subgroup of patients with type 2 diabetes ($P = 0.045$) and in those without diabetes ($P = 0.023$) .

We can explain our results and the other similar studies by clarifying that Microalbuminuria may reflect a generalized defect in vascular permeability and a concomitant atherosclerotic milieu[18] and that there is a strong relationship between microvascular (diabetic nephropathy) and macrovascular (coronary artery disease) complications of diabetes.

Some other studies have shown that the association of microalbuminuria with CAD is independent of hypertension, diabetes and renal function.[19] The mechanism where by microalbuminuria accelerates atherosclerosis and produce. Abnormal vasodilatation [20], endothelial dysfunction[21-22], inflammation, insulin resistance abnormal coagulation all of these factors could be involved [23-24].

(2) Regarding to correlation between severity of CAD and HbA1c

In our study we found a statistically significant positive correlation between HbA1c levels & GENSINI scores. With increasing HbA1c values there is an increase in GENSINI score (P value <0.001).

In the United Kingdom Prospective Diabetic Study (UKPDS), deaths from cardiovascular events were 70 times more common than deaths from microvascular complications. The UKPDS3

demonstrated that intensive glucose control, by keeping the HbA1c < 7%, helped to reduce microvascular complications; the reduction in risk of MI was of borderline significance. Other studies suggested that CAD and HbA1c level are predictors of cardiovascular mortality[2-4].

Our results are in agreement with **Vinita[25], Gong[26]** and **Zhou[27]**, who found a positive correlation between severity of CAD and HbA1c.

Vinita[25] conducted a prospective study in 2011 on the impact of HbA1c on the severity of CAD, presentation and incidence of complications in 92 patients with DM and concluded that the incidence of acute cardiac states (unstable angina and acute myocardial infarction), complications (heart failure, accelerated hypertension and dilated cardiomyopathy) and severity of CAD were higher in patients with poor glycemic control (HbA1c > 7%) compared with those with(HbA1c < 7%).

Gong*[26]* studied the association of glycemic variability and the presence and severity of CAD in 252 patients with type 2 diabetes and reported that Gensini score closely correlated with HbA1c level (p = 0.022) and because of this the effects of glycemic excursions on vascular complications should not be neglected in diabetes.

In 2011 **Zhou**[27] studied the association of NT-pro BNP and other multiple biomarkers including HbAIC with the severity of CAD in 415 patients using the Gensini scoring system and reported that Gensini scores increased with increasing HbA1c level.

All these studies including ours results could be explained by the pathobiologic attribution of hyperglycemia to CVD risk, although this remains poorly understood; but given the clear associations between severity of hyperglycemia and CVD risk in both type 1 and type 2 diabetes (sharing hyperglycemia as the common pathophysiologic disturbance), hyperglycemia is likely to directly influence atherosclerosis development, progression, and instability. The principal vascular perturbations linked to hyperglycemia include endothelial dysfunction, vascular effects of advanced glycation end products, adverse effects of circulating free fatty acids, and increased systemic inflammation.[18]

Ertek *et al.* [28]concluded that there is no association between CAD and HbA1c in 184 patients. Result that is divergent from ours. This can be explained by that the Gensini score of the patients of **Ertek** were not normally distributed and the patients were divided into two groups on the basis of Gensini to mild CAD (Gensini score < 20) and severe CAD (Gensini score > 20). And also because of inclusion of large number of non diabetic patients (96 patient) representing 52% of the total study population.

3- Regarding the correlation between severity of CAD and duration of diabetes mellitus:

Our results showed that there is a statistically significant positive correlation between duration of diabetes & GENSINI scores (P value 0.011).

Our finding was confirmed by data published in year 2010 in a study by **Guo *et al.*[16]** where Spearman's correlation analysis was performed with Gensini score as dependent variable and all risk factors as independent variables. This analysis showed that Gensini score was significantly positively correlated with duration of diabetes mellitus.

The relation between CAD and duration of diabetes can also be explained by the prolonged effect of hyperglycemia on atherosclerosis development, progression and endothelial dysfunction as we mentioned before.[18]

4- Regarding the correlation between severity of CAD and age of patients:

In our study we found a statistically significant positive correlation between age & GENSINI scores (P value 0.017), GENSINI score is higher in older patients.as shown in figure (8)

This relation was also demonstrated by **Guo *et al.*[16]**

The mean age of the studied patients was 55.2± 7.6 years denoting a higher incidence of development of CAD among older patients; this finding was confirmed by **Zhou *et al.*[27]** who studied 415 diabetic and pre diabetic patients who were scheduled for coronary angiography for suspected myocardial ischemia using the Gensini scoring system and reported that there is a positive correlation between age and Gensini score.

This agrees with the finding of **Yuqian *et al.*[29]** who studied the correlation of Severity of CAD with the serum levels of Adipocyte Fatty Acid-Binding Protein (A-FABP). The extent and severity of CAD were assessed by the coronary atherosclerosis index (CAI), and they noticed that there was a significant correlation between increasing age and severity of CAD.

The increase of severity of CAD with aging could be explained by increasing incidence of atherosclerosis in older people in addition of increasing incidence of the other risk factors of IHD.

Age-related changes are due to increases in fibrinogen, coagulation factors (V, VIII and IX, XIIa), and Von-Willebrand factor. Also platelet phospholipid content is altered and platelet activity is increased with increased binding of platelet-derived growth factor to the arterial wall in older compared

with younger individuals. Increased levels of plasminogen activator inhibitor (PAI-1) are seen with aging, especially during stress, resulting in impaired fibrinolysis. Circulating prothrombotic inflammatory cytokines, especially interleukin-6, also increases with age and may play a role in the pathogenesis of ACS. All these changes also potentiate development of atherosclerosis.[30]

5. Conclusion:

Uncontrolled DM (high HbAIc) and long standing DM together with older age in diabetic patients and presence of microalbunimuia were associated with higher Gensini score (severe CAD)

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