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CT CORONARY ARTERY CALCIUM SCORING IN TYPE 2 DIABETES MELLITUS PATIENTS AS AN EARLY PREDICTIVE RISKFOR ISCHEMIC HEART DISEASE

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ABSTRACT : Diabetes Mellitus is an important coronary heart disease risk factor.Most of the morbidity and mortality in this high-risk condition are caused by accelerated atherosclerosis. Several studies hadapproved that subclinical atherosclerosis which measured by coronary artery calcium which progress to future cardiovascular disease.Computed tomography easily identified the coronary calcium because the roentgen graphic attenuation of calcium is much higher as compared with that of the surrounding tissues. The aim of this study is to evaluate Computed Tomographic Calcium scoring in Type 2Diabetes Mellitus patients as a predictive risk of future ischemic heart disease. A case-control study was conducted at Ibn-Alnafees teaching Hospital and Baqubah Teaching Hospital, the study extended for 6 months from April till October 2017. The study included 132patients, 92 male patients and 40 female patients. All patients underwent a proper history taking and through physical examination and were sent for the biochemical investigations. Electrocardiogram done for all patient. Treadmill test and Echo study done for those Electrocardiography was not giving exclusive diagnosis. CT coronary artery calcium score and CTAngiography was done for all patient diagnosed as coronary artery disease. There is a strong correlation between type 2 DM, coronary artery calcium and lipid profile in patient with ischemic heart disease. The study for Coronary Artery Disease patients shows a significant increase of Calcium score which is approved by non-contrast CTAngiography& then confirmed this strong correlation by contrast CTAngiography that shows the luminal arterial defects in diabetic patients group.

Key words **:** CT coronary artery, calcium score.

INTRODUCTION

Diabetes is a chronic illness that affects about 8.3% of the adult population or 382 million people worldwide (Shaw J E *et al*, 2010). Type 2 diabetes mellitus (T2DM) accounts for more than 90% of new cases of diabetes (Mahkalela N *et al*, 2015). T2DM pathophysiology involves as many as seven organs and tissues, including the pancreas, liver, skeletal muscle, adipose tissue, brain, gastrointestinal tract, and kidney (DeFronzo R A, 2009). It is well known that reduced sensitivity to insulin which include both impaired insulin-mediated glucose disposal or insulin resistance in liver, muscle, and adipose tissue, together with a progressive decline in pancreatic β-cell function that leads to impaired insulin secretion and eventually resulting in hyperglycemia, the hallmark feature of T2DM (Fonseca V A, 2009).

Increased plasma concentrations of free fatty acids (FFAs) lead todecline insulin secretion in patients at risk for development of T2DM[5]. Elevated FFAs in β-cells leads to increased oxidative stress and apoptosis (Unger R H and Zhou Y T, 2001).

Adipocytes are resistant to the antilipolytic effect of insulin in patients withT2DM, resulting in elevation of circulating FFAs. Chronic elevation in FFAs stimulate many factors that plays a role in the development of diabetic complications, these include gluconeogenesis, induce hepatic and muscle insulin resistance, and impair insulin secretion (Bays H *et al,* 2004). In T2DMthese lipid-induced changes are part of a sequence of changes induced by excess FFAs, termed lipotoxicity (Unger R H and Zhou Y T, 2001). Excessive amounts of inflammatory and atherogenic cytokines are produced by dysfunctional adipose tissue that can induce insulin resistance which result in inadequately secrete insulin-sensitizing

adipocytokines (Bays H *et al,* 2004).

In Diabetes Mellitus pathogenesis of microvascular and neuropathic complications is complex and not well understood[8].Long term complications are commonly divided into microvascular and macrovascular effects, the microvascular complicationsare caused by damage to small arterioles and capillaries due to glycosylation and oxidation of cell wall proteins. These changes cause the nephropathy, retinopathy and autonomic and peripheral neuropathy commonly seen in diabetic patients. Macrovasculardisease include coronary artery, cerebrovascular and peripheral vascular disease (Rahman S *et al,* 2007). It is well known that Diabetes Mellitus is a coronary heart disease risk equivalent. The associated high overall mortality is largely due to increased cardiovascular deaths (Grundy S M *et al,* 1999). In diabetic patientsmost of the morbidity and mortality are caused by accelerated atherosclerosis which characterized by increased amounts of connective tissue, glycoproteins, and calcified plaque in the blood vessels (Wagenknecht L E *et al,* 2001). Imaging by computed tomography (CT) reveals that diabetic patients have extensive calcification of their vascular beds (Hoff J A *et al,* 2003). Many studies have shown that subclinical atherosclerosis when measured by coronary artery calcium (CAC), will give an idea about future cardiovascular disease (CVD) events and death, independent of conventional risk factors (Detrano R *et al,* 2008). Patients with diabetes mellitus are more likely to have ischemic heart disease, acute coronary syndrome or even sudden silent death.silent ischemia might be due to autonomic neuropathy with involvement of the cardiac sensory innervations, (Otero F *et al,* 2010). In the diabetic patients Angina usually has an atypical presentation. According to studies,Angina occurs with a frequency that varies between 20% and 44%. The site of pain can be at the mandible angle, neck or epigastrium, and it also can be associated with vomiting (Señor B V *et al,* 2007).

CT easily identified the coronary calcium because the roentgen graphic attenuation of calcium is much higher compared with that of the surrounding tissues (Kachelriess M and Kalender W A, 1998). Histologic studies have shown that a CT tissue density of greater than or equal to 130 HU is highly correlated with calcified coronary plaques (Kachelriess M and Kalender W A, 1998). The extent of coronary calcium correlates with the overall atherosclerotic plaque burden (i.e., presence of calcific and non-calcific atherosclerosis), although the calcific plaques constitute only 20% of the total coronary plaque burden (O'Rourke R A *et al*, 2000). So, the presence of coronary calcium is evidence of the presence of coronary atherosclerosis (Hecht H S, Narula J, 2012).

Aim of study

To study the value of CT coronary artery calcium scoring in Type 2 diabetes mellitus patients as a predictive risk for future development of ischemic heart disease.

MATERIALS AND METHODS

A case-control study was conducted at Ibn Al-nafees Teaching Hospital and Baqubah Teaching Hospital, the study extended for 6 months from January till October 2018.

The study included 122patients who visited the internal and cardiac clinic at Ibn Al-nafis Teaching Hospital and Baqubah Teaching Hospital, (72 patients from Ibn Al-nafis Hospital and 60 patients from Baqubah Hospital),with 96 (72%) of them were patients with ischemic heart disease (IHD), and 36 (28%) of them were control group (with no history of IHD). Regarding the patients group, 68 (70.8%) of them were male patients, 50 (73.5%) of male group were diabetic, while the female 28 constitute (29.2%) of the patients group and 18 (64.2%) of them were diabetic. Regarding the controlgroup, 24 (66.6%) of them were male, 9 (37.5%) of male group were diabetic, while the female 12constitute (33.4%) of the control group, 4 (33.4%) of the female group were diabetic. They were selected according to the clinical signs and symptoms (all patients selected were suffering from chest pain), whether they had a history of diabetes or risk factors or without. Then they divided in

Table 1 : Distribution of studied cases and control group according to gender and glycemic status

Total number 132	Cases 96	Male 68	dm	50
			no dm	18
		Female 28	dm	18
			no dm	10
	Control 36	Male 24	dm	9
			no dm	15
		Female 12	dm	4
			no dm	8

Table 2 association between CT angiography results and different studied variables

		CTangiography				SIG
		Abnormal		Normal		
		Count	Row N %	Count	Row N %	
Group	Cases	78	81.3%	18	18.8%	0.001
	Control	12	33.3%	24	66.7%	
Calcium score	High risk	68	97.1%	2	2.9%	0.001
	Low risk	22	35.5%	40	64.5%	
Diabetes	Yes	72	88.9%	9	11.1%	0.001
	No	18	35.3%	33	64.7%	
Gender	Male	66	71.7%	26	28.3%	0.183
	Female	24	60.0%	16	40.0%	
Age	<55 year	9	25.0%	27	75.0%	0.001
	>55 year	81	84.4%	15	15.6%	
Weight status	Normal	15	33.3%	30	66.7%	0.001
	Obese	75	86.2%	12	13.8%	
Smoking	Smoker	58	89.2%	7	10.8%	0.001
	Non smoker	32	47.8%	35	52.2%	
Blood pressure	Hypertensive	66	88.0%	9	12.0%	0.001
	Normotensive	24	42.1%	33	57.9%	
T.cholesterol	Increase	64	90.1%	7	9.9%	0.001
	Normal	26	42.6%	35	57.4%	
TG	Increase	65	84.4%	12	15.6%	0.001
	Normal	25	45.5%	30	54.5%	
HDL	Decrease	65	84.4%	12	15.6%	0.001
	Normal	25	45.5%	30	54.5%	
LDL	Increase	69	89.6%	8	10.4%	0.001
	Normal	21	38.2%	34	61.8%	
VLDL	Increase	69	89.6%	8	10.4%	0.001
	Normal	21	38.2%	34	61.8%	

to two groups the control group and patient group. Blood tests were conducted as well as Electrocardiography (ECG) done for all participants. The selected participants suffering from chest pain and IHD was expected (central chest pain, discomfort or breathlessness, precipitated by exertion or other forms of stress, relieved by rest)) [36]. Subjected to present study and these selected participants were divided into many groups according to the risk factors. It is worth to be mentioned that those patients were suffering from many risk factors and rearranged in groups according to the risk factor taken.

All patients underwent a case history questionnaire and were sent for the biochemical investigations. Electrocardiography(ECG) done for all patient, treadmill test(TMT)and Echocardiographic study done for those ECG was not giving exclusive diagnosis. CT coronary artery calcium score and CT angiography was done for all patient diagnosed as Coronary artery disease.

The exclusion criteria:were a history of coronary artery bypass graft and/or prior stent placement,Inability to sustain a breath holds for at least 15 to 20 seconds, cardiac arrhythmias**.** valvular lesion, patient with history of renal impairment and patient with history of any allergic reaction to contrast agent.

A premade questionnaire was filled by the researcher through interview. The questionnaire included sociodemographicdata and patient was send for biochemical investigations (Fasting blood sugar, lipid profile). Determination of total cholesterol (TC) (fasting patient).Determination of high-density lipoprotein (HDL) (fasting patient). Determination of Triglycerides (TGs) (fasting patient). Determination of LDL and Determination of serum VLDL: calculated as follows: VLDL= TG/5.CT coronary angiography was performed

with a 64-slice scanner with retrospective ECG gating. Before Multi-Slice CT angiography, a non-contrast CT was acquired to measure calcium score according to the Agatston method. Slice thickness was 0.3- 0.5 mm. Calcium score was categorized in to two categories[37]:the first: low risk (less or equal to 100) (0:very low, 0-10:low, 11-100 moderate) the second: high risk (more than 100) (101-400:moderately high, more than 400 :very high) for coronary artery calcifications.

The result of CT Angiography was divided in to (normal and abnormal or diseased arteries). On the day of the test the patient must not take caffeine (no coffee, tea, caffeinated soft drinks or chocolate) and must not smoke. It is recommended that the patients arrive 30 minutes prior to their appointment. If the pulse rate is high, advice to take a tablet (Beta-blocker) to lower the heart rate. CT Coronary Artery Calcium Scoring is performed just like a normal CT scan. It takes about 10 – 15 minutes.. The CT scanner assesses the heart beat and calculates when it wants to take the scans.

Plaque characteristic

For coronary CT analysis, plaques were defined as a structures of >Imm within and or adjacent to vessel lumen and plaque types were classified into calcified (plaque consisting of only calcium), noncalcified or soft plaque (plaque that was calcium free), and multiple plaques (more than one plaque in the same patient).

Statistical analysis

Data were introduced in to personal computer, IBM SPSS V. 23 were used in statistical management of the collected data. Descriptive statistics were displayed using

Table 3 : The correlations between sociodemographics and lipid profile variables and CAC.

		Group	DM	Sex	Age	WT	smoking	HT	Tchol	TG	HDL	LDL	VLDL	Ca	CT
Group	CC	1	.318**	.040	-.083	-.134	.161	.119	.149	.138	.138	.138	.138	.208*	.458**
	P	.	.000	.646	.342	.126	.065	.175	.088	.115	.115	.115	.115	.017	.000
Dm	CC		1	.086	-.667**	-.742**	.657**	.753**	.794**	.686**	.529**	.686**	.813**	.687**	.560**
	P		.	.326	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000
Gender	CC			1	-.003	-.047	.320**	-.042	.083	.078	.078	.078	.078	.073	.116
	P				.969	.589	.000	.630	.343	.374	.374	.374	.374	.405	.186
Age	CC				1	.851**	-.603**	-.702**	-.661**	-.587**	-.449**	-.587**	-.725**	-.617**	-.568**
	P					.000	.000	.000	.000	.000	.000	.000	.000	.000	.000
WT	CC					1	-.708**	-.760**	-.776**	-.689**	-.494**	-.689**	-.786**	-.668**	-.538**
	P						.000	.000	.000	.000	.000	.000	.000	.000	.000
Smoking	CC						1	.736**	.822**	.740**	.433**	.740**	.740**	.745**	.445**
	P							.000	.000	.000	.000	.000	.000	.000	.000
HT	CC							1	.910**	.876**	.597**	.876**	.876**	.834**	.488**
	P								.000	.000	.000	.000	.000	.000	.000
	N								132	132	132	132	132	132	132
Tchol	CC								1	.912**	.604**	.912**	.912**	.833**	.509**
	Sig.									.000	.000	.000	.000	.000	.000
TG	CC									1	.564**	.875**	.875**	.775**	.412**
	Sig.										.000	.000	.000	.000	.000
HDL	CC										1	.564**	.595**	.590**	.412**
	Sig.											.000	.000	.000	.000
LDL	CC											1.	.875**	.775**	.544**
	Sig.												.000	.000	.000
VLDL	CC												1	.775**	.544**
	Sig.													.000	.000
Ca	CC													1	.661**
	P														.000
CTA	CC														1
	P														

tables. Analytic statistics were presented through usage of Spearman correlation.P.V. < 0.005 was considered as significant level marker.

RESULTS AND DISCUSSION

This cross sectional study included 122 persons, with 96 (72%) of them were patients with IHD, and 36 (28%) of them were control group (with no history of IHD). Regarding the patients group, 68 (70.8%) of them were male patients, 50 (73.5%) of male group were diabetic, while the female constitute (29.2%) of the patients group and 18 (64.2%) of them were diabetic. Regarding the control group, 24 (66.6%) of them were male, 9 (37.5%) of male group were diabetic, while the female constitute (33.4%) of the control group, 4 (33.4%) of the female group were diabetic as shown in table (1)**.**

Table 2 shows the association between different studied variables and CTA. It revealed that significant differences were found between age, weight, smoking, HT, DM, lipid profile (TC, TG, HDL, LDL, VLDL) and CAC that are represented by p – value.

Table 3 shows the correlations between sociodemographics and lipid profile variables and CAC. In regarding the correlations between age, CAC, Hypertension (HT)and TC there is strong correlations between them.In regarding the correlations weight, CAC, age, HT and TC. In regarding the correlations between smoking, CAC, age, HT, TC and TG there is strong correlations between them. And the same correlation present related to the HT. In regarding the correlations between DM,CAC, lipid profile (TC,HDL, VLDL) there is strong correlations between them.and lastly there is no correlation between gender and CAC.

Logistic regression showed in table (4) explain that lower age is protective against abnormal finding in CTA outcome, while high Calcium score shows risk factors for abnormal finding of CTA when we neutralized

In regard to the age distribution and sex, the coronary calcium score is highly associated withelderly age group, that is agree with study of Lloyd-Jones D2009 (Lloyd-Jones D *et al,* 2009) they found that there is marked increase in the incidence and prevalence of coronary calcifications with increasing age.

In our study there is no gender differences in occurrence of coronaryartery calcification which detected by CT calcium score,that is not agree with the study of Hoff JA.(2001) (Hoff J A *et al,* 2001) they said that There is gender differences in occurrence of coronary calcium support the association of CAC with coronary atherosclerosis and underline the importance of age- and gender-specific reference points for CAC scoring (Hoff J A *et al,* 2001).

With respect to the weight,there is strong relation to the calcium score, there is a link between calcium score and obesity or over weight that is agree with the study of Marsh, J.(2003) (Julian B Marsh M D, 2003).

Regarding lipid profile, from our study we can conclude that correlation between lipid parameters, weight and calcium score for the patients strongly significant correlation. That is consider the most important step for forming the atherosclerosis that predisposing for CAD. This fact in our study was improved and agree with study done by the journal of the clinical endocrinology and metabolism through Molly C. Carr and John D. Brunzell (Molly C Carr *et al,* 1992) they said that, The changes in lipid metabolism seen with abdominal fat accumulation have been well characterized and include hyper

Table 4 : Binary logistic regression showed effect of each independent studied variable on the result of ctangio after neutralization of other variables effects

	B	S.E.	Sig.	Exp (B)	95% C.I.for EXP(B)	
					Lower	Upper
Age	-2.239	1.064	.035	.107	.013	.859
Weight	-.534	1.215	.660	.586	.054	6.340
Smoking	-1.894	1.384	.171	.151	.010	2.270
Hypertension	-3.433	3.647	.347	.032	.000	41.058
T .cholesterol	1.921	3.418	.574	6.829	.008	5543.830
TG	-42.480	16833.323	.998	.000	.000	.
HDL	.657	.802	.413	1.929	.401	9.292
LDL	22.109	11936.557	.999	3997380018.852	.000	.
VLDL	19.379	11869.261	.999	260801305.371	.000	.
Calcium score	6.420	1.701	.000	614.132	21.907	17216.340
Constant	-.639	3.177	.841	.528		

triglyceridemia, reduced HDL cholesterol, and increased numbers of small, dense LDL particles

Concerning hypertension, from our study we can conclude that correlation between hypertension and calcium score for the patients strongly significant correlation. this fact in our study was improved and agree with study done by Framingham Heart Study, (Vasan R S *et al,* 2001) they said that, even high-normal blood pressure (defined as a systolic blood pressure of 130-139 mm Hg, diastolic blood pressure of 85-89 mm Hg, or both) increased the risk of cardiovascular disease 2-fold, as compared with healthy individuals (Vasan R S *et al,* 2001).

With reference to diabetes mellitus in our study,we conclude that there is strong correlation between calcium score, age and the lipid profile in diabetic patient. Numerous cross-sectional studies have documented that patients with diabetes have a higher prevalence and extent of coronary calcium than non diabetic patients (Raggi P *et al*).

Recent study suggested that CAC scoring may be superior to established cardiovascular risk factors for predicting silent myocardial ischemia and short term cardiovascular outcomes among stable, uncomplicated type 2 diabetic patients (Philip Greenl *et al,* 2007). Patients with diabetes are consideredto be in the highest risk categoryaccording to the Adult Treatment Panel III guidelines (Raggi P *et al,* 2004).

Therefore, there is a clear clinical need to detect CAD at an early stage in DM patients who are at risk of both fatal and non-fatal cardiac events before the onset of symptoms (Daniele Andreini1 *et al,* 2010).

As for smoking, in our study we noticed that there is strong correlation of the VLDL, TC, and calcium score,that is explain how the smoking have strong influence on the CAD by playing important role in deposition of the Ca^{++} in the coronary arteries and through strong correlation with VLDL, our results agree with study done in CHEST journal / 131 / 5 / MAY, 2007 (Dilyara G. Yanbaeva and Mieke A, 2007) which said that,Endothelial dysfunction is mainly caused by diminished production or availability of NO. It has been demonstrated that the serum concentration of nitrate and nitrite, metabolic end-products of NO, is significantly decreased in smokers relative to that in nonsmokers.

With regard to the coronary computed tomographic angiography, our study a prove there is moderate significant correlation in between CAC and CTA measurement and this goes with what had been found by Philip Greenland (2007) (Philip Greenl *et al,* 2007) which said that the Electron-beam computedtomography (EBCT) and multi-detector computed tomography (MDCT) are theprimary fast CT methods for CAC measurement at this time.

CONCLUSION

The physiological study for CAD patients shows a significant increase of Calcium score which is predicted by non-contrast CTA & then confirmed this strong correlation by contrast CTA that shows the luminal arterial defects in diabetic patients group. Lipid profile shows significant correlation with the Calcium score in CAD patient's also strong correlation with each other that explains the mechanism of the atherosclerosis process.

DECLARATIONS

Conflict of Interest: There are no known conflicts of interest, financial or otherwise for the author of this manuscript which would interfere with the integrity of this research.

Statement of Ethics

Informed consent was obtained from all patients for being included in the study. Ethical approval was obtained from the institutional ethical and scientific committee before commencing this study

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