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Impact of Diabetes Duration on The Extent and Severity of Coronary Atheroma Burden in Type 2 Diabetic Patients: Evaluation by Coronary CT Angiography

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ABSTRACT

Aim of the work: this study aimed to explore the association between diabetes duration on both the extent and severity of coronary atheroma burden using coronary computed tomography angiography (CCTA) in type 2 diabetic patients.

Patients and methods: we analyzed 105 symptomatic type 2 diabetic patients without known CAD who underwent CCTA from August 2016 to June 2017. Patients were categorized into two groups according to the duration of diabetes: < 10 years, and ≥ 10 years. Stenosis by CCTA was scored as none (0%), non-obstructive (1–49%), or obstructive (≥50%) for each coronary artery segment. For these patients, we compared the prevalence, extent, and severity of CAD, including coronary artery calcium score (CACS), atheroma burden obstructive score (ABOS), segment involvement score (SIS), segment stenosis score (SSS) and syntax score.

Results: patients with longer duration of type 2 diabetes possessed higher rates of obstructive CAD. Patients with longer duration of diabetes also manifested greater degree of CACS, ABOS, SIS, SSS and syntax score ($P < 0.001$ for all).

Conclusion: in symptomatic type 2 diabetic patients, longer diabetes duration was associated with a higher prevalence, extent, and severity of CAD so, increased risk of developing atherosclerotic cardiovascular disease including major events as myocardial infarction or even sudden cardiac death.

INTRODUCTION

Reducing atherosclerotic cardiovascular disease (ASCVD) burden in diabetes mellitus (DM) is a major clinical imperative that should be prioritized to reduce premature death, improve quality of life and lessen individual and economic burdens of associated morbidities, decreased work productivity, and high cost of medical care [1]. Atherosclerotic cardiovascular disease remains the principal cause of death and disability among patients with diabetes mellitus, especially in those with type 2 diabetes mellitus in whom it typically occurs 14.6 years earlier [2], with greater severity, and with more diffuse distribution than in individuals without diabetes mellitus [3]. Furthermore, about two-thirds of deaths in people with diabetes mellitus are attributable to cardiovascular disease: of these, ≈ 40% are from ischemic heart disease, 15% from other forms of heart disease, principally congestive heart failure, and ≈10% from stroke. Among those with diabetes mellitus, excess risks of death from any cause and of ASCVD mortality are particularly prominent in those with younger age, higher burden of glycaemia, and greater renal complications, in comparison with those without [4]. Although the incidences of diabetes mellitus–related complications including cardiovascular disease have decreased over the past 2 decades, patients with diabetes mellitus continue to have significantly increased risk for vascular complications in comparison with individuals without diabetes mellitus [5]. An estimated 382 million people worldwide have diabetes mellitus and this number is expected to reach 592 million by the year 2035 [6]. Key manifestations of ASCVD in diabetes mellitus included advanced atherosclerosis manifest as coronary artery disease (CAD), ischemic stroke, peripheral vascular disease, and heart failure. Understanding the mechanisms, strategies for and challenges with managing ASCVD and heart failure risk in diabetes mellitus, as well as the potential cardiovascular risks and benefits of glucose-lowering drugs, is important for managing cardiovascular disease in diabetes mellitus [1]. Coronary computed tomography angiography (CCTA) has emerged as a non-invasive imaging modality for the detection or exclusion of CAD, with prior studies observing a high prevalence of CAD in asymptomatic type 2 diabetic patients using CCTA that is associated with worsened outcomes [7]. A

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study had investigated the association of diabetes duration and CAD prognosis in the pre-CCTA era, these outcome-based analyses lacked information regarding the prevalence, extent and severity of CAD. Prior CCTA study had examined CAD findings and prognosis in type 2 diabetic patients, but had limitations of single-center study and small cohorts of diabetic patients [8].

The confirm registry clearly demonstrated that diabetic patients had a higher prevalence, extent and severity of CAD compared with matched non-diabetics, but also had a limitation of the lack of information on the longitudinal nature of the diabetic process on CAD burden and prognosis [9].This study aimed to explore the association between diabetes duration on both the extent and severity of coronary atheroma burden using coronary computed tomography angiography (CCTA) in type 2 diabetic patients.

PATIENTS and METHODS

Patients population

105 selected patients diagnosed with type 2 DM were prospectively recruited from Cardiac Department at Ain Shams University and Kobri El kobba Military Hospital outpatient clinics complaining of typical chest pain suggestive of CAD. Assessment of coronary atheroma burden was done by Multidetector Computed Tomography (MDCT) Coronary Angiography from August 2016 to June 2017 and patients were categorized into two groups according to the duration of diabetes: < 10 years and ≥10 years.

Exclusion criteria

1. Refusal to sign an informed consent.
2. Respiratory failure.
3. Decompensated heart failure.
4. Any rhythm other than sinus rhythm.
5. Hypersensitivity to iodinated contrast agent.
6. Impaired renal function (serum creatinine ≥ 1.5 mg/dl).
7. Type 1 DM.
8. Hyperthyroidism.
9. Morbid obesity with body mass index (BMI ≥ 30).
10. Claustrophobic patients.
11. Previous coronary stenting or CABG.

METHODS

- Informed consents were obtained from all patients.
- ECGs were done for all patients to exclude arrhythmias.
- Full history taking including the following:
  - Age
  - Gender
  - Diabetes mellitus
  - Hypertension
  - Hyperlipidemia
  - Smoking
- Physical examination including vital data, weight and height.
- The following laboratory investigations were done for all patients: serum creatinine, & lipid profile.
- **Obesity**

Weight status was measured using Body Mass Index (BMI). BMI uses a simple calculation based on the ratio of someone's height & weight (BMI = Kg/m^2). Overweight is defined as a BMI between 25.0 & 29.9; and a BMI of 30 or higher is considered obese. In this study patients of BMI ≥ 30.0 were considered obese and were excluded from the study [10].

- **Duration of DM:**

The diagnosis of type 2 diabetes mellitus was made using the 2010 criteria of the American Diabetes Association. According to this definition, subjects with fasting glucose ≥126 mg/dL, glycated haemoglobin (HbA1C) ≥ 6.5% or ≥ 48 mmol/mol, and/or post-challenge glucose (glucose at 2 hours after a 75 gm oral glucose load) ≥200 mg/dL were diagnosed with diabetes**.** Patients with a self-reported or documented history of type 2 diabetes mellitus, or treatment with oral hypoglycemic agents were also considered to be diabetics. Diabetes onset was defined as the point in time when any of the above criteria were first met. The information on diabetes onset in patients with known type 2 diabetes was obtained at the time of the patients' interviews [11].

- **Coronary CT Angiography:**
  - **Scan protocol:**

CCTA was performed with a dual-source CT (DSCT) (Siemens Healthcare) scan. Heart rates of all patients were determined 1 hour before examinations. If heart rate was ≥ 65 bpm, the patient was orally administered 40–80 mg of oral beta

blocker propranolol hydrochloride (Inderal at 40 mg/tablet) except those with contraindications to beta-blockers. A 0.5 mg sublingual dose of nitroglycerin was administered just before the scan. In each patient 60 mL of iodinated contrast mixed with 60 mL of saline solution was injected. Contrast material administration was controlled by test bolus in the ascending aorta. The scan delay was 12 s. Images were reconstructed immediately after completing the scan to identify motion-free coronary artery images. The reconstructed CT image data were transferred to a computer workstation for post-processing, including axial, multiplanar reformat, maximum intensity projection, and short-axis, cross-sectional views. In all individuals, irrespective of the image quality, every arterial segment was scored in an intent-to-diagnose fashion [12].

- **CCTA Analysis:**

The severity of luminal diameter stenosis was scored as none (0% luminal stenosis), non-obstructive (plaques with a lumen narrowing < 50%), or obstructive (plaques with maximum stenosis ≥ 50%). Diagnosis of CAD was made based on the maximum intra-luminal stenosis in any of the segments of the major epicardial coronary arteries at the ≥ 50% stenosis threshold. Obstructive CAD in the diagonal branches, obtuse marginal branches, and posterolateral branches was considered to be part of the left anterior descending (LAD) artery, left circumflex (LCX) artery, and right coronary artery (RCA) system, respectively. Depending on the coronary artery dominance, the posterior descending artery was considered to be part of the RCA or LCX system [12]. For each patient, the number of diseased vessels was calculated through the assignation of one, two, three, or LM coronary artery vessels. The extent and severity of CAD burden were measured by several coronary CT angiographic scores, including coronary artery calcium score (CACS), atheroma burden obstructive score (ABOS), segment involvement score (SIS), segment stenosis score (SSS) and syntax score [13, 14].

Coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU. An overall Agatston score was recorded for each patient [15].

The ABOS was defined as the number of plaques with ≥ 50% stenosis in the entire coronary artery tree. **The SIS** was calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis within each segment (minimum = 0; maximum = 16). **The SSS** was used as a measure of the overall coronary artery plaque extent. To determine the SSS, each individual coronary segment was graded as having no to severe plaque (i.e. scores from 0 to 3) based on the extent of the obstruction of the coronary luminal diameter. Then, the extent scores of all 16 individual segments were summed to yield a total score ranging from 0 to 48.

The Syntax score was derived from the summation of the individual scores for each separate lesion defined as ≥50% luminal obstruction in vessels ≥ 1.5 mm. The syntax scores were calculated for all previous patients using dedicated software [12, 14].

The study was approved by the Ethics Board of Ain Shams University.

- **Statistical analysis**

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 23. Data was summarized using mean, standard deviation (SD), median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests [16]. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 [17]. P-values less than 0.05 were considered as statistically significant.

RESULTS

Descriptive analysis

Demographic and clinical data

Baseline characteristics of the study group are shown in **Table 1**. Patients were categorized into two groups according to diabetes duration**.** Group 1was consisted of 54 patients with DM duration < 10 years and group 2 consisted of 51 patients with diabetes duration ≥ 10 years. When baseline characteristics were examined, those with a longer duration of diabetes were older (P < 0.001), more likely to be smokers (P = 0.005), and more likely to have history of dyslipidemia (P < 0.001).

Sex and history of hypertension didn't differ significantly between the two study groups

Table 1: characteristics of the studied population			
	Group 1 N=54	**Group 2 N=51**	**P Value**
Age, years	48.87 ± 8.5	58.63±8.03	< 0.001
Male (%)	46 (85.2%)	45 (88.2%)	0.646
Smoking (%)	39 (72.2%)	23 (45.1%)	0.005
Hypertension (%)	24 (44.4%)	14 (27.5%)	0.070
Dyslipidemia (%)	16 (29.6%)	34 (66.7%)	< 0.001

Data are given as mean ± SD or number (%).

✓ **CCTA findings**

Number of affected vessels:

About 40.7% of patients with duration of DM < 10 years (**Group 1)** showed normal coronaries, 42.6% of patients had only single coronary vessel affected, 13% of patients had two vessels affected, and 3.7% of patients had three vessels or left main affected, irrespective of degree of obstruction. On the other hand, 9.8% of patients with duration of DM ≥ 10 years (**Group 2)** showed normal coronaries, 17.6% of patients had only single coronary vessel affected, 27.5% of patients had two vessels affected, and 45.1% of patients had three vessels or left main affected, with variable degrees of obstruction. Different variables of affected coronaries are shown in **Table 2**.

Table 2: different variables of the affected coronaries					
	Group 1 N=54		**Group 2 N=51**		**P Value**
	Count	**%**	**Count**	**%**	
Normal Coronaries	22	40.7%	5	9.8%	< 0.001
Single vessel disease	23	42.6%	9	17.6%	0.006
Two vessels disease	7	13%	14	27.5%	0.064
3 vessels or left main	2	3.7%	23	45.1%	< 0.001

✓ **CCTA scores**

Statistical analysis of the two groups regarding different CCTA scores is shown in **Table 3.** Statistical comparison between the two groups revealed that there was a significant increase in CACS, ABOS, SIS, SSS and Syntax score in favor of patients of group 2 (P < 0.001 for all).

Table 3: different variables of CCTA scores			
CCTA score	**Group 1 N=54**	**Group 2 N=51**	**P value**
CACS	17.16 + 34.44	132.1 + 118.2	< 0.001
ABOS	0.59 + 0.79	2.65 + 1.99	< 0.001
SIS	0.89 + 0.98	3.47 + 2.08	< 0.001
SSS	1.69 + 2.1	7.73 + 5.52	< 0.001
Syntax score	3.52 + 4.16	13.76 + 8.81	< 0.001

Data are given as mean ± SD or n (%).

Atheroma burden and degree of coronary obstruction:

Atheroma burden and degree of coronary obstruction as detected by MDCT is shown in **Table 5.**

Table 5: Atheroma burden & degree of coronary obstruction						
Coronary artery and obstruction degree		Group 1 (N=54)		Group 2 (N=51)		P value
		Count	%	Count	%	
LM obstruction	0%	54	100.0%	47	92.2%	0.052
	1-49%	0	.0%	4	7.8%	
	>=50%	0	.0%	0	.0%	
LAD obstruction Proximal	0%	40	74.1%	21	41.2%	0.001
	1-49%	6	11.1%	7	13.7%	
	>=50%	8	14.8%	23	45.1%	
LAD obstruction Mid	0%	42	77.8%	17	33.3%	< 0.001
	1-49%	3	5.6%	3	5.9%	
	>=50%	9	16.7%	31	60.8%	
LAD obstruction Distal	0%	54	100.0%	44	86.3%	0.005
	1-49%	0	.0%	1	2.0%	
	>=50%	0	.0%	6	11.8%	
LCX obstruction Proximal	0%	53	98.1%	43	84.3%	0.010
	1-49%	1	1.9%	2	3.9%	
	>=50%	0	.0%	6	11.8%	
LCX obstruction Mid	0%	46	85.2%	29	56.9%	0.002
	1-49%	3	5.6%	4	7.8%	
	>=50%	5	9.3%	18	35.3%	
LCX obstruction Distal	0%	53	98.1%	47	92.2%	0.052
	1-49%	1	1.9%	0	.0%	
	>=50%	0	.0%	4	7.8%	
RCA obstruction Proximal	0%	48	88.9%	28	54.9%	< 0.001
	1-49%	2	3.7%	10	19.6%	
	>=50%	4	7.4%	13	25.5%	
RCA obstruction Mid	0%	49	90.7%	31	60.8%	0.001
	1-49%	1	1.9%	7	13.7%	
	>=50%	4	7.4%	13	25.5%	

Table 5 (continues): Atheroma burden & degree of coronary obstruction						
Coronary artery and obstruction degree		Group 1 (N=54)		Group 2 (N=51)		P value
		Count	%	Count	%	
RCA obstruction Distal	0%	*54*	*100.0%*	*40*	*78.4%*	*< 0.001*
	1-49%	*0*	*.0%*	*3*	*5.9%*	
	>=50%	*0*	*.0%*	*8*	*15.7%*	

DISCUSSION

In this prospective two-center study we observed an obvious increase in prevalence, extent, and severity of CAD by CCTA in symptomatic type 2 diabetic patients with diabetes duration ≥ 10 years. Also we observed an obvious increase in prevalence of left main trunk, multi-vessel and obstructive lesions in patients with type 2 diabetes duration ≥ 10 years. On comparing our two study groups, we found that there was a significant difference between both study groups as regards CACS by Agatston method (17.16 + 34.44) for group 1 versus (132.1 + 118.2) for group 2. There was also a significant difference regarding ABOS (0.59 + 0.79) for group 1 versus (2.65 + 1.99) for group 2, SIS (0.89 + 0.98) for group 1 versus (3.47 + 2.08) for group 2, SSS (1.69 + 2.1) for group 1 versus (7.73 + 5.52) for group 2 and Syntax score (3.52 + 4.16) for group 1 versus (13.76 + 8.81) for group 2 **(P < 0.001 for all).**

Results regarding prevalence, extent and severity of CAD in our study agreed with results of the study that was done by **Kim *et al.*** [12]**.** This was a two-center study in which 993 asymptomatic type 2 diabetic patients without known CAD were enrolled in. Patients were divided into three groups according to diabetes duration: < 5 years, 5-10 years and ≥ 10 years. Extent & severity of CAD as well as long term clinical outcome was investigated. Our study differs than this study in methods where patients enrolled had symptoms suggestive of CAD without known CAD, as well as Syntax score was added, which has been reported as an independent predictor of major adverse cardiac events in all individuals with a varying extent of CAD.

Arevious study showed that diabetes duration was directly associated with adverse cardiovascular events. The Framingham Heart Study reported a 1.38-fold increased risk for CAD and a 1.86-fold higher risk for cardiovascular death for each 10-year increase in diabetes duration [18]**.**

In the Verona Diabetes study, ischemic heart disease was the single largest cause of cardiovascular deaths in men, and the death rate rose with increasing duration of diabetes [19]**.** Moreover, a study showed that only diabetes with duration of 10 years was a coronary heart disease risk equivalent q[20]**.** Also, in agreement with our results **Park *et al.*** [21] noticed clinical risk factors for significant CAD in asymptomatic type 2 diabetic patients using CCTA. They noted that duration of diabetes was one of the most significant risk factors for developing significant CAD. A study done by **Mukund *et al.*** [22] was performed to assess angiographic changes in type 2 diabetic patients with variable diabetes duration, it showed that there was a significant structural changes in the coronary arteries among the patients with 5–10 years of diabetes when compared to those with less than 5 years of diabetic duration. Also, in agreement with our results **Lindsey *et al.*** [23] studied the association between diabetes duration and coronary plaque burden which were detected by intravascular ultrasound and they noticed that longer duration of diabetes ≥ 10 years was associated with more significant coronary plaque burden than patients with diabetes duration < 10 years.

Tavars *et al* [24] used different noninvasive imaging techniques, in order to screen for asymptomatic coronary artery disease in patients with type 2 diabetes mellitus. Impact of diabetes duration was clearly found to be significant regarding the presence of CAD, a result which is accordance with our study.

A more recent study done by **Bertoluci *et al.*** [25] classified patients with diabetes duration more than 10 years, as a higher risk category for developing CAD. Another study was done by **Shimabukuro *et al.*** [26]. They realized the risk stratification of coronary artery disease in asymptomatic diabetic subjects using MDCT, showed an increase in the prevalence and severity of asymptomatic CAD in patients with longer duration of diabetes. For determination of coronary luminal stenosis severity, the present study employed the use of CCTA, a non-invasive technique that lowers the threshold for evaluation of symptomatic individuals and that offers the added diagnostic ability to directly visualize coronary stenosis. In this regard, our study advances the mechanistic understanding of these prior pivotal studies and suggests a prognostic importance of CAD extent and severity by non-invasive CCTA to identify asymptomatic diabetic individuals who have greater cardiovascular risk **(Achenbach *et al.*** [27]**.** The use of CCTA has been generally endorsed only for symptomatic low-to-intermediate-risk patients by professional societal guidance documents[28]**.** Results of the present study demonstrated an importance of diabetes duration for the detection of CAD severity and risk, and suggest the potential benefit of CAD evaluation in a selected group of diabetic individuals with longer duration of disease. There are extensive evidences suggesting that autonomic dysfunction is associated with silent myocardial ischaemia in diabetic patients, a finding that may mask clinical symptoms associated with the increased CAD extent and severity making screening

of asymptomatic patients with long standing diabetes duration necessary [29].

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