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Incidence of Subclinical Atherosclerosis in Asymptomatic Patients with Metabolic Syndrome: The Potential of Multi-Slice Computed Tomography Coronary Angiography

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Introduction

The approximate prevalence of the metabolic syndrome in patients with coronary heart disease was about 50%, with a prevalence of 37% in patients with premature coronary artery disease (age 45 or less), particularly in women [1]. Metabolic syndrome is a combination of medical disorders that, when occurring together, increase the risk of developing cardiovascular disease and diabetes [2].

Sixty-four-slice computed tomography has emerged as a promising modality to evaluate coronary artery disease that shown to have sensitivity and specificity in the range of 95% for the detection of hemodynamically relevant stenosis, which is higher than those associated with stress myocardial perfusion imaging. The aim of this study was to study the prevalence of coronary plaques detected by 64-slice CT in asymptomatic patients with metabolic syndrome [3].

Methodology

This was a prospective cohort study conducted in the MSCT (multi-slice computerized tomography) unit in National heart institute under the supervision of the Cardiology department of the Menofia faculty of medicine. After approval of the ethical committee and obtaining informed consent from patients, 30 adult patients, (age more than 18 years) of both genders, referred to MSCT coronary angiography in National Heart Institute from January 2012 to January 2013 were included in this study. All cases were in sinus rhythm with heart rate less than 70 beat/ min, had normal ECG, were able to sleep flat and hold their breath for 15 seconds. Exclusion criteria include patients with clinical or radiological evidence of macrovascular atherosclerotic disease (stroke, carotid disease or peripheral arterial disease), atrial fibrillation, renal impairment (serum creatinine more than 1.4mg/dl), B blocker intolerance (as bronchial asthma), pregnant female, acute coronary syndrome or documented coronary artery disease (previous MI, PCI or CABG), those who underwent diagnostic coronary angiography, patients with more than mild valvular disease, end stage renal or hepatic impairment, history of stent placemat or coronary artery bypass surgery, known allergic reaction, and a calcium score .

All patients had full history taken, clinical examination, electrocardiography analysis, laboratory investigation, echocardiographic study, and CT data acquisition and post-processing done. A comprehensive history was taken from every patient including their medical treatment if possible with emphasis the age, gender, history of hypertension, family history of cardiovascular disease, history of diabetes, drug history and history of acute coronary disease. Also a Complete general and cardiac examination stressing on Heart rate, arterial blood pressure, Waist circumference measured (:more than or equal 102cm in men or 88 cm in women) or body mass index more than or equal 30 kg/m2.A standard resting 12-lead surface ECG was done to all patients. Laboratory investigations including fasting and 2 hours post-prandial blood sugar level, blood urea, serum creatinine, cholesterol, triglycerides, HDL and LDL were measured. Echocardiography was performed using echocardiographic machine General Electric vivid 3 equipped with 2.5 and 3.5 MHz probes to detect SWMA .2D echo images were obtained in the PLAX, PSAX, A4Ch, and A2ch to assess SWMA. And a Color flow Doppler was done to exclude more than mild valvular regurgitation. Also a standard M-mode measurements of left ventricular end-diastolic dimension, end-systolic dimension, fractional shortening and ejection fraction were recorded. Moreover a pulsed-wave Doppler echocardiography was performed by measuring mitral inflow velocity in the apical four-chamber view with the sampling window placed at the mitral leaflet tips.

For each case, prospectively ECG gated scan [4] without the use of contrast was done from the aortic bulb to the tip of the heart with a 64-section CT scanner (Siemens 64-section dual source CT scanner) at a single breath-hold and at slice thickness of 3mm Based on previous EBCT studies [5]. A medium sharp reconstruction filter kernel without edge enhancement was chosen in order to provide moderate image noise [6].

Images were collected and processed via Syngo® software to assess calcium in all coronary vessels and to calculate calcium score by agataston score system [7]. Any structure which had densities of 130 Hounsfield units (HU) or more and having an area of 1 mm2 or more was segmented as calcified focus and those foci overlying the anatomic site of coronary arteries were considered to represent calcified plaques. In each segmented calcified focus, based on its peak density, a density score of 1 through 4 was assigned. The stratified density scores 1, 2, 3 and 4 represented the highest densities 130-199 HU, 200-299 HU, 300-399 HU and ≥ 400 HU, respectively. The most important determining factors in calculating calcium score of each plaque were the measured area of each calcified plaque and its density. The total Agatston score (AS) of each individual was calculated by summing the scores of every calcified focus through all of the coronary arteries (8).

After calcium score assessment, those with calcium score >1000 were excluded from the study. The rest of patients were scanned with a dual source 64-section CT scanner (Siemens 64-section dual source CT). The scanning range covered the entire heart from the level of aortic bulb to the tip of the heart. CT data sets that were synchronized to the ECG data were retrospectively reconstructed from 20% to 80% of the R-R interval in 5% steps for each patient.

The adaptive cardiac volume approach was used for image reconstruction; this approach automatically switches between one- and two-segment reconstructions depending on the patient's heart rate. Images were reconstructed with a section thickness of 0.5 mm. The field of view was adjusted to encompass the heart exactly (mean field of view, 154 mm± 17; range, 129–180 mm). All coronary segments were studied at 75% and 40% of cardiac cycle, with selective reconstruction of the improperly visualized coronary segments at different phases of cardiac cycle.

After patient and ECG information was removed, all reconstructed images were transferred to a dedicated workstation (Syngo®),where Axial images, multi-planar coronal, sagittal and curved MPR images were collected and processed to assess all coronary segments (course, patency and luminal study).

CT was successfully performed in all patients without complications. The CT protocol was well tolerated by all patients, and all were able to hold their breath during data acquisition. For data analysis, coronary segments with a diameter of at least 1.5 mm at their origin were included. The cutoff point was set at 1.5 mm because the spatial resolution of 64-section CT was considered insufficient for accurate evaluation of smaller-diameter vessels. Diameters were measured with an electronic caliper tool. The right coronary artery (RCA) was defined to include segments 1–4, the left main (LM) and left anterior descending (LAD) arteries were defined to include segments 5–10, and the left circumflex (LCX) artery was defined to include segments 11–15.

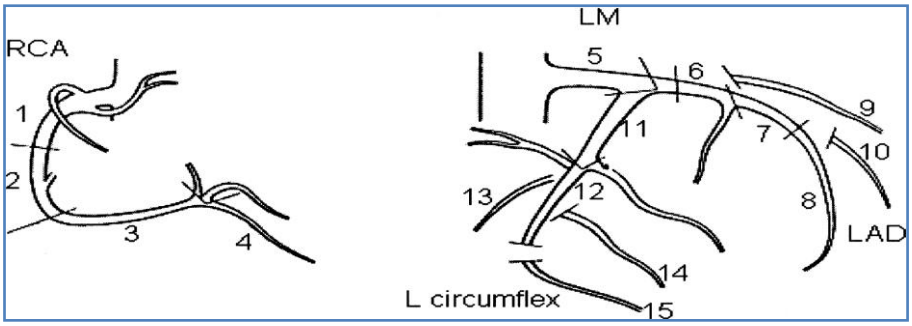

Figure 1: Diagram of the coronary segment analysis.

Statistical Analysis

The data were collected, then it was coded and fed to the computer statistical software system (SPSS) version 15 (statistical package for the social science, Chicago, IL) for statistical analysis. Numerical data were presented as mean, SD and prevalence. Chi-square test was for non-parametric variables. Paired student's t-test was done for the parametric variables. $P < 0.05$ will be considered significant with a confidence interval of 95%. While the $p<0.0001$ will be considered highly significant. Logistic regression was used to determine the association of the components of Mts according to different criteria with of cardiovascular risk. Multivariate analyses were performed to adjust for all components of metabolic syndrome in the same criteria, including age, sex, LDL, cholesterol, and smoking. Logistic regression analysis was done to find the r, and p values for combinations in relation to calcium score, number of vessel diseased and number of segment affected. The results were considered statistically significant if the p-value was less than 0.05

Results

Fifty cases diagnosed as metabolic syndrome came to MSCT unit in national heart institute. Twenty patients were excluded (5 patients had a past history of cerebrovascular stoke, 3 patients suffered AF, 4 patient had renal impairment, 6 patients had history of angina and 2 patients had more than mild vulvular disease). Thirty patients (16 males and 14 females) were included to this prospective cohort study from January 2012 to January 2013.

Mean age of the study group was 52±8, Male predominance 53%, with mean BMI 29±3, and mean waist circumference 101±12 cm, 63% were diabetic patients, 77% were hypertensive, 37% were smokers, and 37% had a family history of CVD. Triglycerides were elevated in 67% and HDL was low in 63%. No patient in the study group was alcoholic (Table 1).

The laboratory parameters for the study group was measured with a mean fasting blood sugar 126±26mg/dl, Triglycerides 115±24mg/dl, HDL 45±10mg/dl, total cholesterol 186±28 mg/dl and LDL 120±19 mg/dl (Table 2).

Table 1: Clinical characteristics of the study group.

Demographic data	**Mean ± SD**
Age (years)	52±8
Sex Male Female	 16 (53%) 14 (47%)
BMI (Kg/m^2)	29±3
Waist circumference (cm)	101 ±12
DM (%)	63%
Hypertension (%)	77%
Smoking (%)	37%
High triglycerides (%)	67%
Low HDL cholesterol (%)	63%
Family history of CVD (%)	37%

BMI: body mass index, DM: Diabetes mellitus, CVD: cardiovascular disease.

Table 2: Laboratory values for the study group

Laboratory values	Mean ± SD	range
Blood sugar mg/dl	126±26	87-167
Triglycerides mg/dl	115±24	84-162
HDL mg/dl	45±10	34-63
Total cholesterol	186±28	148-223
LDL mg/dl	120±19	93-145

HDL: high density lipoprotein, LDL: low density lipoprotein.

Calcium score: The mean calcium score was 61±100 for the study population. Calcium score was zero in 12 case (40%), whereas13 case (43.3%) had above zero till 100, 5 cases (16.7%) had a calcium score above 100 (Table 3).

Eleven cases (37%) had normal vessels, 12 cases (40%) had one vessel disease, and 4 cases (13%) had two vessels disease, while 3 cases (10%) had 3 vessels disease. The mean number of vessel disease was 1±1, (Table 3), (Figure 2). There was a significant relation between calcium score and number of vessels involved ($p<0.0001$), Figure (3).

Table 3: MSCT parameters

CT parameters	Mean ± SD	range
Calcium score	61±100	0-378.20
Number of vessel disease	1±1	0-3
Number of segments disease	2±2	0-7

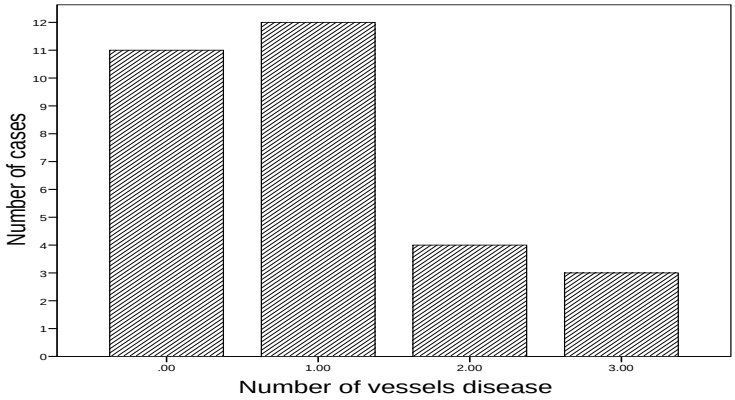

Figure 2: Bar chart presents the number of cases with number of vessels disease

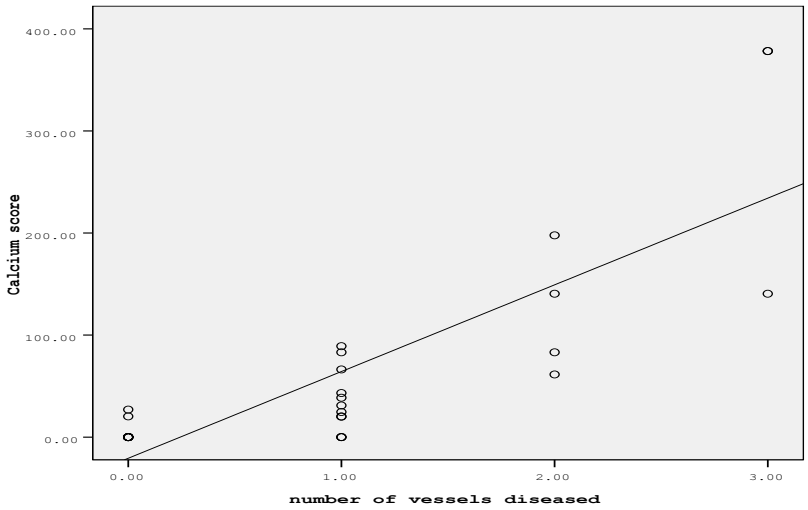

Figure 3: Simple line presents Calcium score (HU) in relation to the number of vessels diseased

Eleven cases (37%) were with normal segments, 8 cases (27%) had one segment diseased, 5 cases (17%) had two segments diseased, 2 cases (7%) had 3 segments diseased, a case (3%) had 4 segments diseased, 2 cases (7%) had 6 segments diseased, and a case (3%) had 7 segments diseased. The mean number of segments disease was 2±2, (Table 3), (Figure 4). There was a significant relation between calcium score and number of segments diseased ($p<0.004$), (Figure 5).

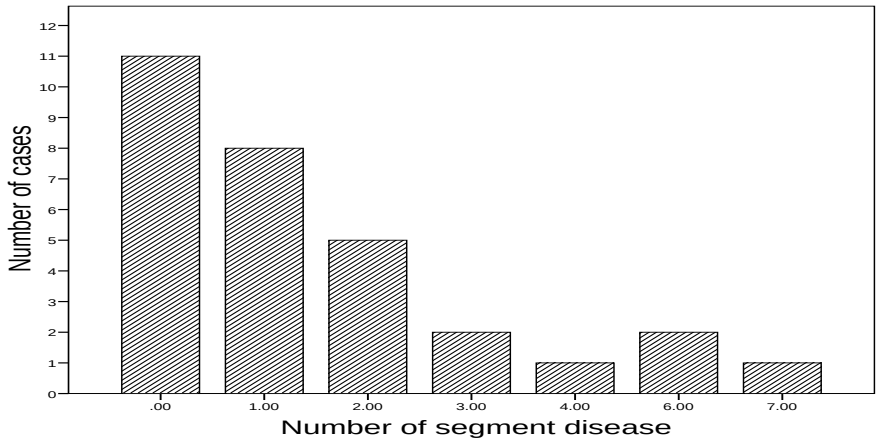

Figure 4: Bar chart presents the number of cases with number of segment diseased

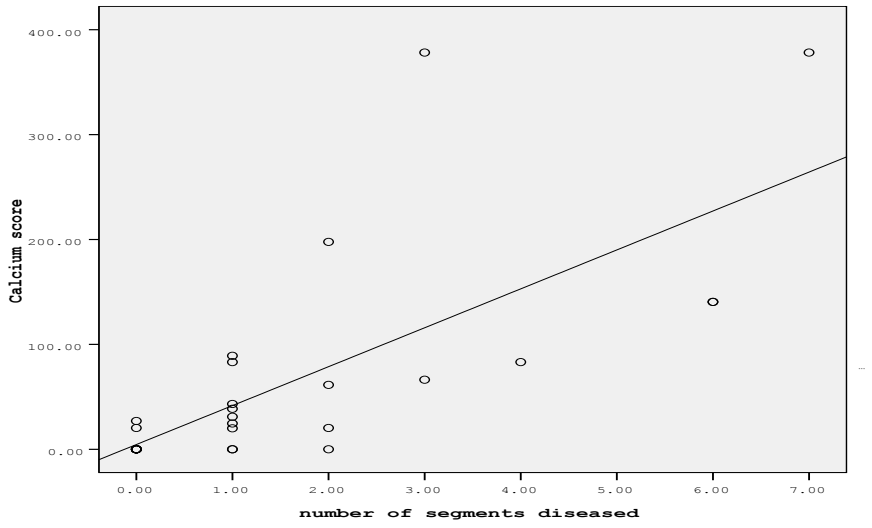

Figure 5: Simple line presents Calcium score (HU) in relation to the number of segments diseased

There was a significant relation between metabolic syndrome (diabetes, triglycerides, and HDL) components with the calcium score, the number of vessel disease and number of segments diseased respectively (Table 4), (Figures 6, 7, 8 and 9).

Table 4: Individual components in relation to calcium score, number of vessel disease, and number of segment affected.

Metabolic syndrome	Calcium score		Number of vessel disease		Number of segment affected	
	r value	p value	r value	p value	r value	p value
Waist circumference	0.08	0.1	0.006	0.7	0.006	0.7
Diabetes	0.625	<0.0001**	324	0.001*	324	0.001*
Hypertension	0.08	0.1	330	0.6	028	0.4
Triglycerides mg/dl	0.422	0.0001*	548	0.005*	508	0.0001*
HDL mg/dl	0.625	<0.0001**	379	0.16	324	0.001*

Moreover, various combinations of metabolic syndrome components was significantly related to the calcium score, number of vessel disease as well as number of segment disease respectively (Table 5). All the combinations were highly significantly related to calcium score (<0.0001), except the combination of hypertension + central obesity + triglycerides was significantly related to calcium score ($p<0.05$) (Table 5). All the combinations were significantly related to both the number of vessel and segments diseased (Table 5).

Table 5: Various combinations related to MSCT parameters.

Metabolic syndrome combinations	Calcium score		Number of vessel disease		Number of segment disease	
	r value	p value	r value	p value	r value	p value
Diabetes, hypertension and HDL	0.6	<0.0001**	0.328	0.01*	0.328	0.01*
Diabetes, hypertension and triglyceride	0.539	<0.0001**	0.427	<0.001*	0.427	0.001*
Diabetes, hypertension and central obesity	.536	<0.0001**	295	0.018*	295	0.018*
Diabetes, central obesity and triglyceride	530	<0.0001**	425	0.001*	425	0.001*
Diabetes, central obesity and HDL	591	<0.0001**	346	0.008*	346	0.008*
Diabetes, triglyceride and HDL	600	<0.0001**	455	0.001*	455	0.001*
Hypertension, central obesity and triglyceride	445	0.002*	420	0.002*	420	0.002*
Hypertension, central obesity and HDL	506	<0.0001**	294	0.018*	294	0.018*
Hypertension, triglyceride and HDL	560	<0.0001**	454	0.001*	454	0.001*
central obesity, triglyceride and HDL	577	<0.0001**	459	0.01*	459	0.01*

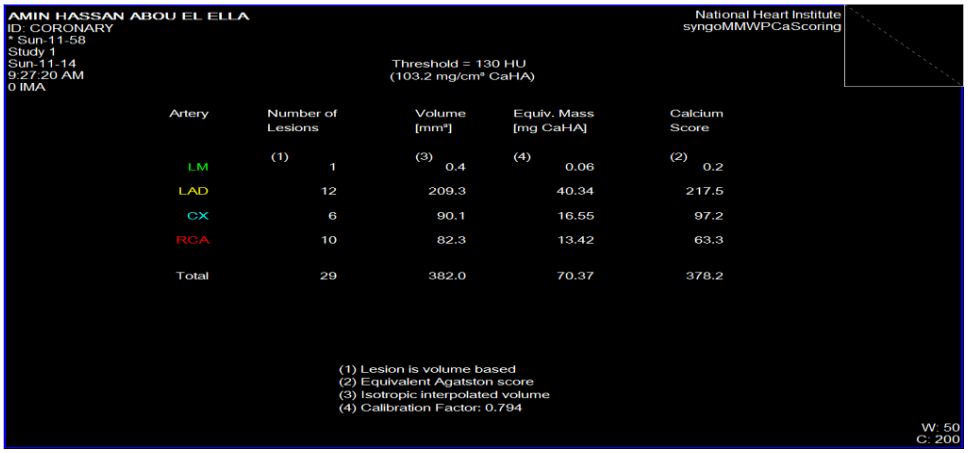

Figure 6: 56 year's old diabetic and hypertensive patient who has 3 vessel disease and 7 segments affected

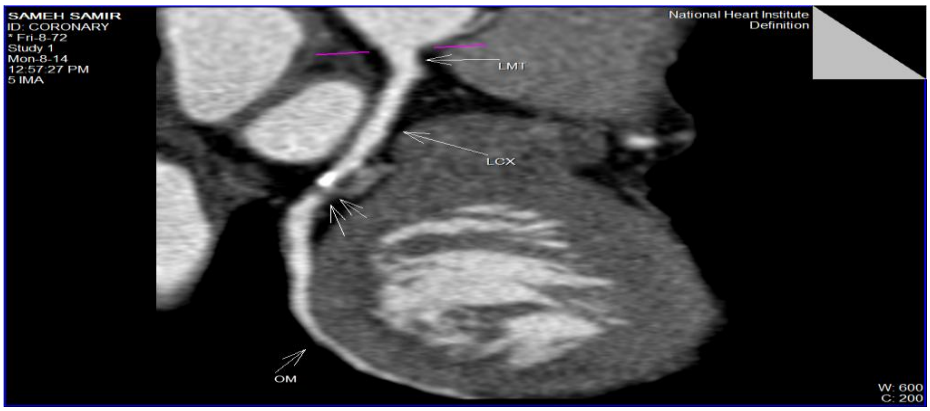

Figure 7: Male patient 55 years diabetic and hypertensive with CCS 89.1 with one segment affected and one vessel affected. The figure shows LCX.

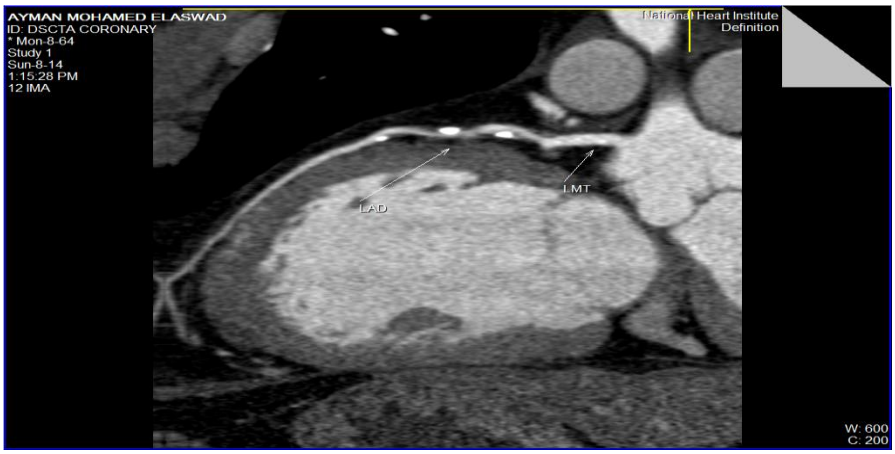

Figure 8: Shows 3 calcific lesions in LAD. The patient is 50 years hypertensive, with 1vessel disease

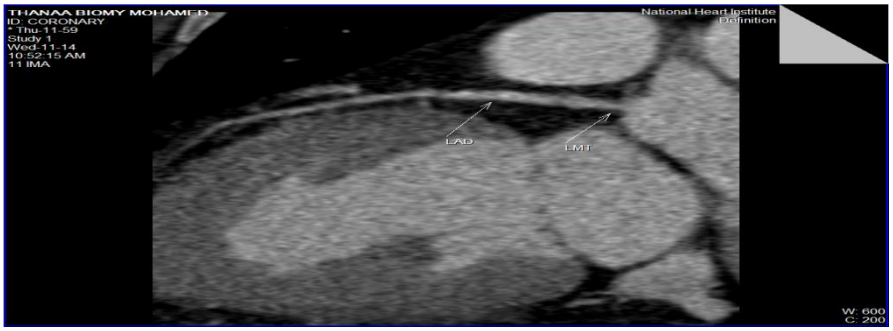

Figure 9: Shows non-calcific osteal LM. The patient is female55 years, diabetic and hypertensive.

Discussion

This prospective cohort study evaluated metabolic syndrome components in relation to the calcium score, number of vessels and segments diseased. There was a significant relation between the calcium score and the number of vessels and segments diseased.

In the present study mean age of the study group was 52±8, Male predominance 53%, with mean BMI 29±3, and mean waist circumference 101±12 cm. 63% were diabetic patients, 77% were hypertensive, 37% were smokers, and 37% had a family history of CVD. Triglycerides were elevated in 67% and HDL was low in 63%. No patient in the study group was alcoholic.

Considering metabolic syndrome and cardiovascular risk, only few available studies being based on small samples showing contradictory results are present [9]. Some authors have assessed the association between metabolic syndrome, diabetes and severity of angiographic CAD in cross-sectional and longitudinal studies, but they either considered one gender or studied ethnicities other than Caucasian, or they did not compare diabetic and non-diabetic individuals [10].

Several studies demonstrated relations between the coronary calcification and the severity of coronary artery disease and clinical events. Ho et al. [11] reported that as CACS increased, there was a corresponding increase in frequency of MDCT coronary disease and a CACS > 400 was associated with increased risk of significantly coronary stenosis. Also, Church et al. [12] reported that CACS can identify individuals at increased risk for coronary heart disease events who otherwise would be considered low-risk based on clinical assessment and CACS of zero is associated with very low risk for coronary heart disease in the short to intermediate term regardless of the number of risk factors present [13]. Also Fallavollita et al. [14] compared the detection of calcium with coronary angiography and found that calcium scanning had 85% sensitivity and 45% specificity in patients with significant stenosis, defined as greater than 50% diameter narrowing on angiography [14].

The first Rumberger guideline based on Agatston score (AS) using Electron Beam Computed Tomography (EBCT) [8] related calcium score to the plaque burden with a clinical interpretation, where a zero calcium score was associated with no plaque burden and either very low risk of cardiovascular disease, or likelihood of coronary artery disease presence <5% or even a negative examination. In the present study the mean calcium score was 61±100. Calcium score was zero in 40%, whereas 43.3% had above zero till 100, and 16.7% had a calcium score above 100. We used 100 as the calcium score cut off point in dividing the study group based on the results of a previous study by Cheng et al. [15]. We found a significant relation between metabolic syndrome components (diabetes, triglycerides, and HDL) with the calcium score, the number of vessel and segments diseased respectively.

The best available evidence consistently showed that individuals with metabolic syndrome are at increased risk of cardiovascular events (two-fold increase in cardiovascular outcomes – cardiovascular mortality, myocardial infarction and stroke – and a 1.5-fold increase in all-cause mortality) [16]. They also demonstrated that cardiovascular risk was still high in patients with the metabolic syndrome but without diabetes in accordance with the present study [10]. Timoteo et al. [10] found diabetes was highly correlated with CAD and the most important components of metabolic syndrome to predict CAD were increased glucose and triglycerides, with abdominal obesity being protective simulating our results.

Whereas in the MESYAS study [17] metabolic syndrome components conferred very different intensities of independent risk, from the high independent risk of hypertriglyceridemia to the almost complete absence of an independent effect of overweight. On the contrary the Framingham Study [18], revealed that three MetS components (waist circumference above normal, hypertriglyceridemia, and hypertension) significantly predict the cardiovascular events in that study population. Hypertriglyceridemia in their study was also significantly related to the severity of angiographic finds. But other parameters of MetS were not related to the severity of different angiogram findings (single vessel/double vessel/ triple vessel). In contradiction to our study as well as that by Timoteo et al. 2012 and MESYAS study [10, 17].

In the present study the mean number of vessel disease was 1±1, there was a significant relation between calcium score and number of vessels diseased. The mean number of segments disease was 2±2.There was also a significant relation between calcium score and number of segments diseased. Moreover, various combinations of metabolic syndrome components was significantly related to the calcium score, number of vessel disease as well as number of segment disease respectively. All the combinations were highly significantly related to calcium score (<0.0001), except the combination of hypertension + central obesity + triglycerides was significantly related to calcium score ($p<0.05$). All the combinations were significantly related to both the number of vessel and segments diseased.

The prognostic importance of the metabolic syndrome compared to that of the sum of its individual components has repeatedly been challenged [19]. In a larger study of stable CAD patients, the presence of metabolic syndrome identified increased risk of death or myocardial infarction but did not have independent prognostic significance after adjustment for its constituent components. Hypertension, low HDL cholesterol and elevated glucose most strongly predicted events [20]. In our study though HDL, glucose and triglycerides were significantly related to atherosclerosis defined by calcium score, number of segment and vessel diseased, yet we could not find a relation between hypertension as an individual component of metabolic syndrome and atherosclerosis. This may be due to acute cardiovascular events having different pathophysiological mechanisms from those in stable coronary atherosclerotic plaque. Vulnerable plaques are generally characterized as having a thin inflamed fibrous cap over a large lipid core with activated macrophages near the cap [21]. Among the components of metabolic syndrome, abdominal obesity and low serum HDL cholesterol were significant independent predictors for culprit coronary plaque rupture [21].

This study though a prospective cohort was a single center of small number and lacked the measurement of sensitivity and specificity of individual metabolic syndrome components in relation to calcium score, number of diseased vessels and segments, we recommend a larger multicenter study to be conducted measuring both the sensitivity and specificity of various components of metabolic syndrome in defining the risk of atherosclerosis. We conclude that metabolic syndrome with variable combinations of individual metabolic syndrome components increase the risk coronary atherosclerosis assessed MDCT, as calcium score and coronary plaques detected in the vessels and segments affected.

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