

Aortic Valve Sclerosis Severity Index is a Predictor of Coronary Artery Disease Severity in Diabetic Patients with Ischemic Heart Disease

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ABSTRACT

Background: The degree of aortic valve sclerosis can play a major role as an independent risk factor for coronary artery disease as in conditions like diabetes mellitus, hypertension and hyperlipidemia. Therefore, it can be directly linked to coronary artery diseases (CAD) severity making its assessment and measurement an important step before the costly or invasive investigations to diagnose CAD. The link between diabetes mellitus and CAD is firmly confirmed. DM in general confers a two-fold excess risk of vascular outcomes (coronary heart disease, ischaemic stroke, and vascular deaths) independent of other risk factors.

Objective: To assess the association between aortic valve sclerosis severity index and severity of coronary artery disease and hence if it could be also used as a bedside predictor of severity of CAD.

Patients and Methods: The study enrolled 100 diabetic patients with ischemic heart disease who were indicated for coronary angiography. Echocardiography was done for all patients to assess the aortic sclerosis severity index. Assessment of severity of CAD was done for all patients using SYNTAX score, number of affected vessels and degree of stenosis were also assessed.

Results: There was statistically significant positive strong correlation between average aortic valve sclerosis score index with both SYNTAX score and number of affected vessels ($r = 0.944$, P value < 0.001 and $r = 0.611$, P value < 0.001 respectively).

Conclusion: Aortic valve sclerosis severity index can be used as a predictor of severity of coronary artery disease in diabetic ischemic patients.

Keywords: CAD, AVSSI, SNTAX score.

INTRODUCTION

Atherosclerosis is a major health problem affecting cardiovascular system, which makes coronary artery diseases (CAD) the leading cause of death in developed countries and one of major health problems in developing countries. It is a degenerative disease affecting blood vessels and leads to catastrophic cardiovascular events. It is characterized by basement membrane disruption, inflammation, cell infiltration, lipid deposition and calcification⁽¹⁾.

The Emerging risk factor collaboration, a meta-analysis of 102 prospective studies, showed that diabetes mellitus (DM) involves a two-fold excess risk of vascular outcomes (coronary heart disease, ischaemic stroke, and vascular deaths) independent of other risk factors⁽²⁾. Both relative and absolute risk levels are higher in long-standing DM and microvascular complications, including renal disease or proteinuria⁽³⁾.

In the 2016, European Guidelines on cardiovascular disease prevention in clinical practice reported that individuals with DM and cardiovascular disease (CVD), or DM with target organ damage, such as proteinuria or kidney failure, are at very high risk (10-year risk of CVD death $> 10\%$). Patients with DM with three or more major risk factors or with a DM duration > 20 years are also at very high risk⁽⁴⁾.

Moreover, coronary artery disease is mostly silent in people with diabetes⁽⁵⁾. Because of that, screening

asymptomatic people with diabetes for silent myocardial ischaemia is an appealing concept. However, many factors argue against implementing a broad-based screening program. In addition, aortic valve diseases became a major health problem with increasing prevalence of aging and senility rate and advancement of medical facilities⁽⁶⁻⁸⁾.

Aortic valve sclerosis (AVS) is defined as increased thickness and progressive calcification of aortic valves that causes no obstruction to ventricular output (antegrade velocity across the valve of less than 2.5 m/s)⁽⁹⁾.

The initial lesions in both AVS and CAD involve lipid deposition and focal sclerosis, so atherosclerosis affection of coronary artery is akin to its effect on aortic valve endothelium⁽¹⁰⁾. Being the site of frequent turbulence and mechanical stress from blood flow, the aortic valve serves as a focus for the deposition of lipids involved in the process of atherosclerosis. Recently many studies focused on aortic valve sclerosis as a degenerative disease sharing common histopathological mechanisms with coronary artery atherosclerosis⁽¹¹⁾. It has the advantage of being proceeding in its nature so it can be a mirror of what is happening inside coronary arteries. Moreover, it has a predictive value of coronary angiography in patients with ischemic heart disease. Therefore, it can be directly linked to CAD severity making its assessment and measurement an important



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step before more costly or invasive investigations to diagnose CAD ⁽¹²⁾.

However, the relationship between aortic valve sclerosis and presence of coronary artery disease in diabetic patients is yet under-investigated. Therefore, in our study we aimed at assessment of the association between aortic valve sclerosis severity index and severity of coronary artery disease and to be used as a predictor of severity of CAD in diabetic patients.

PATIENTS AND METHODS

The study was a descriptive observational study. It included 100 diabetic patients with ischemic heart disease who presented with an indication for coronary angiography. The study was carried out in the Cardiology Department of Aswan University Hospital during the period between May 2019 and January 2020.

Ethical approval and written informed consent:

An approval of the study was obtained from Aswan University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Exclusion criteria: Patients with congenital aortic valve disease, aortic stenosis, more than mild aortic regurgitation, rheumatic heart disease, chronic kidney disease, cardiac valve replacement or systemic illnesses were excluded. Besides, patients with hyperparathyroidism, malignancy, vitamin D disorders, diseases associated with high bone turnover rate e.g. multiple myeloma, Paget's disease, tuberculosis or sarcoidosis were also excluded.

All patients were subjected to the following:

- (1) Careful history taking and clinical examination focusing on age, sex, special habits especially smoking and history of hypertension. History of diabetes mellitus is verified based on the guidelines of the American Diabetes Association ⁽¹³⁾. Family history of premature CAD and dyslipidaemia was also inquired. Patients' body weight and height were measured and body mass index (BMI) was calculated.
- (2) Electrocardiographic (ECG) evaluation: to document ischaemic changes.
- (3) Laboratory assessment including serum creatinine to verify the visibility of coronary angiography.
- (4) Transthoracic Echocardiography was carried out using a Philips IE33 machine using (X5-1) transducer. All the patients were examined in the left lateral decubitus position. Echocardiographic images were acquired from the standard views (parasternal long-axis, parasternal short axis at level of the great vessels, apical four-chambers, apical five-chambers and apical two-chambers). Images were stored on a hard disc for better offline analysis and reported by an echocardiographer who was blinded to the patients' data.

A zoom view of the parasternal short-axis window of the aortic valve, which was fully closed at end-diastole, was used to determine the aortic valve sclerosis

score. Gain settings were adjusted in modes to optimize image quality and avoid effect of tissue harmonic imaging which can give a false impression of increased valve cusps thickness and sclerosis ⁽¹⁴⁾.

The score was classified as:

- Grade 0: Normal and non-thickened valve (thickness < 2mm).
- Grade 1: Thickened non-calcified valve (thickness >2mm).
- Grade 2: Mildly calcified valve (<1/3 of valve area was highly echogenic).
- Grade 3: Moderately calcified valve (1/3–2/3 of valve area).
- Grade 4: Severely calcified valve (>2/3 of valve area).

The grading of the sclerosis score was individually determined for the non-coronary, right coronary and left coronary cusps. Their average was defined as the average aortic valve sclerosis score index (AAVSSI) of each patient ⁽¹⁵⁾.

Left ventricular ejection fraction (LVEF) was calculated by Simpson modified method from apical imaging planes. Peak early diastolic velocity (E wave) was determined by pulsed Doppler echocardiography in the apical 4-chamber view; the cursor was placed across the mitral valve at the tips of leaflets. Early mitral annular diastolic velocity (e) was obtained by tissue Doppler echocardiography in apical 4-chamber view; the cursor was placed at the septal mitral annulus and the E/e ratio was calculated. Grading of diastolic dysfunction was based on the guidelines of the European Association of Cardiovascular Imaging ⁽¹⁶⁾.

- (5) Coronary angiography for all patients to assess the severity and the extent of CAD. Coronary angiography was performed through femoral artery access. Evaluation of all coronary angiograms was made by two observers. Significant CAD was considered as > 50% stenosis in the left main or > 70% stenosis in other coronary arteries ⁽¹⁷⁾ and online SYNTAX score was calculated to assess the severity and complexity of CAD ⁽¹⁸⁾.

Statistical analysis

An independent t test was conducted to compare continuous variables and the chi-square and Fisher's exact tests were performed to compare categorical variables. Continuous variables were expressed as mean \pm standard deviation, and categorical variables as frequency and percentage. A multivariate linear regression analysis was conducted to determine the independent correlation between average aortic valve sclerosis score index and other study variables. P values ≤ 0.05 were considered significant. We performed all statistical analyses using the Statistical Package for the Social Sciences version 18 (SPSS, Inc., Chicago, IL, USA).

RESULTS

The patients were recruited from Cath lab Unit of Cardiology Department, Aswan University Hospital.

Table (1): The demographic, clinical, echocardiographic and angiographic characteristics of the study population

Parameter	
Age (mean \pm SD) in years	57.9 \pm 9.1
Sex; male (%)	52 (52)
Smoking (%)	37 (37)
Type II DM (%)	90 (90)
Hypertension (%)	48 (48)
Dyslipidemia (%)	72 (72)
Family history of premature CAD (%)	36 (36)
Body mass index (mean \pm SD)	26.7 \pm 3.2
Clinical diagnosis	
• Chronic coronary syndrome	32 (32)
• Post ACS	68 (68)
Ejection fraction (mean \pm SD)	48.3 \pm 7.4
Diastolic function	
• Normal (%)	0 (0)
• Diastolic dysfunction grade I (%)	32 (32)
• Diastolic dysfunction grade II (%)	56 (56)
• Diastolic dysfunction grade III (%)	12 (12)
E/e ratio (mean \pm SD)	9.97 \pm 2.69
Aortic valve sclerosis score index (mean \pm SD)	1.59 \pm 1.04
SYNTAX score (mean \pm SD)	11.8 \pm 6.8
Number of affected major vessels (mean \pm SD)	1.5 \pm 0.7

The study sample was divided into 3 tertiles according to the result of echocardiographic assessment of average aortic valve sclerosis score index (AAVSSI):

- (1) **Group I:** It included 34 patients with the lowest AAVSSI, the mean AAVSSI was 0.37 ± 0.25 (range 0.0-0.66).
- (2) **Group II:** It included 32 patients with mean AAVSSI of 1.69 ± 0.35 (range 1.0-2.0).
- (3) **Group III:** It included 34 patients with the highest AAVSSI, their mean was 2.72 ± 0.42 (range 2.33-3.66).

Table (2): The demographic, clinical, echocardiographic and angiographic differences between the three groups

Parameter	Group I n = 34	Group II n = 32	Group III n = 34	P value
Age (mean \pm SD) in years	51.6 \pm 5.9	56.2 \pm 5.5	65.7 \pm 8.9	0.0001
Sex; male (%)	12 (35.3)	18 (56.2)	22 (64.7)	0.04
Smoking (%)	31 (91.2)	18 (56.2)	14 (41.2)	0.0001
Type 2 DM (%)	34 (100)	25 (78.1)	31 (91.2)	0.012
Hypertension (%)	12 (35.3)	20 (62.5)	16 (47.1)	0.08
Dyslipidemia (%)	20 (58.8)	22 (68.8)	30 (88.2)	0.02
Family history of premature CAD (%)	10 (29.4)	14 (43.8)	12 (35.3)	0.47
Body mass index (mean \pm SD)	26.1 \pm 2.7	26.8 \pm 2.7	27.2 \pm 3.9	0.33
Clinical diagnosis				0.006
Chronic coronary syndrome	16 (47.1)	12 (37.5)	4 (11.8)	
Post-ACS	18 (52.9)	20 (62.5)	30 (88.2)	
Ejection fraction (mean \pm SD)	51.9 \pm 7.3	48.4 \pm 5.8	44.5 \pm 7.1	0.0001
Diastolic function				0.0001
Normal (%)	0 (0)	0 (0)	0 (0)	
Diastolic dysfunction grade I (%)	18 (52.9)	10 (31.2)	4 (11.8)	
Diastolic dysfunction grade II (%)	16 (47.1)	20 (62.5)	20 (58.8)	
Diastolic dysfunction grade III (%)	0 (0)	2 (6.2)	10 (29.4)	
E/e ratio (mean \pm SD)	8.6 \pm 1.8	9.3 \pm 2.2	11.9 \pm 2.8	0.0001
Aortic valve sclerosis score index (mean \pm SD)	0.37 \pm 0.25	1.69 \pm 0.35	2.72 \pm 0.42	0.0001
SYNTAX score (mean \pm SD)	4.7 \pm 1.2	11.3 \pm 2.8	19.4 \pm 4.3	0.0001
Number of affected major vessels (mean \pm SD)	1.1 \pm 0.3	1.4 \pm 0.5	2.1 \pm 0.7	0.0001

Determinants of average aortic valve sclerosis score index (AAVSSI):

Demographic and clinical characteristics: The AAVSSI was found to have relationship with the patients' age. Males, smokers, those with type II DM and Dyslipidemia were found to be more affected by higher AAVSSI. Moreover, those patients who had history of acute coronary syndrome had higher AAVSSI than those with chronic coronary syndrome (table 2 and figure 1).

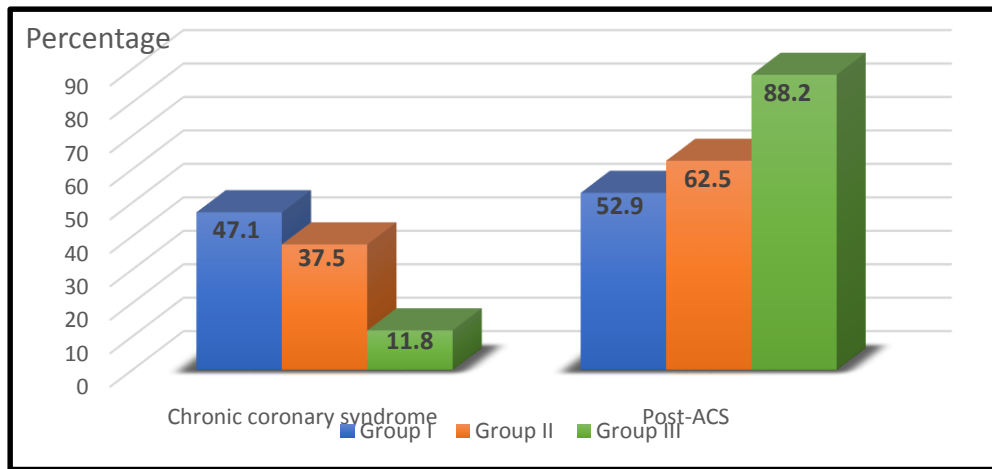


Figure (1): Relationship between patients' presentation and AAVSSI

Echocardiographic characteristics: Left ventricular systolic function was inversely related to AAVSSI (Table 2). There was moderate negative correlation between left ventricular ejection fraction and AAVSSI ($r = -0.42$, p value 0.0001) (Figure 2). In addition, there was markedly impaired diastolic function and high E/e ratio were associated with higher AAVSSI (Table 2). High E/e ratio had moderate positive correlation with AAVSSI ($r = 0.54$, p value 0.0001) (Figure 2).

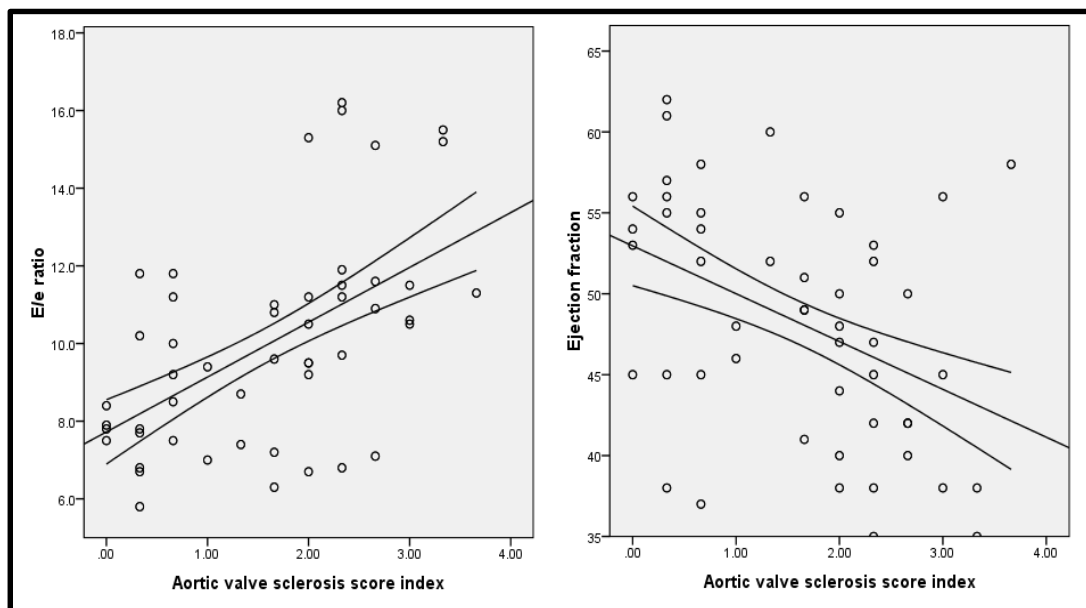


Figure (2): Correlation between AAVSSI, E/e ratio and left ventricular ejection fraction

Angiographic characteristics: The extent of coronary artery disease was found to be related to AAVSSI. High SYNTAX score and increased number of affected epicardial coronary arteries were associated with high AAVSSI (Table 2) and Figure 3). Moreover, there was a strong positive correlation between AAVSSI and SYNTAX score and number of affected epicardial coronary vessels ($r = 0.94$, p value 0.0001, $r = 0.62$, p value 0.0001, respectively).

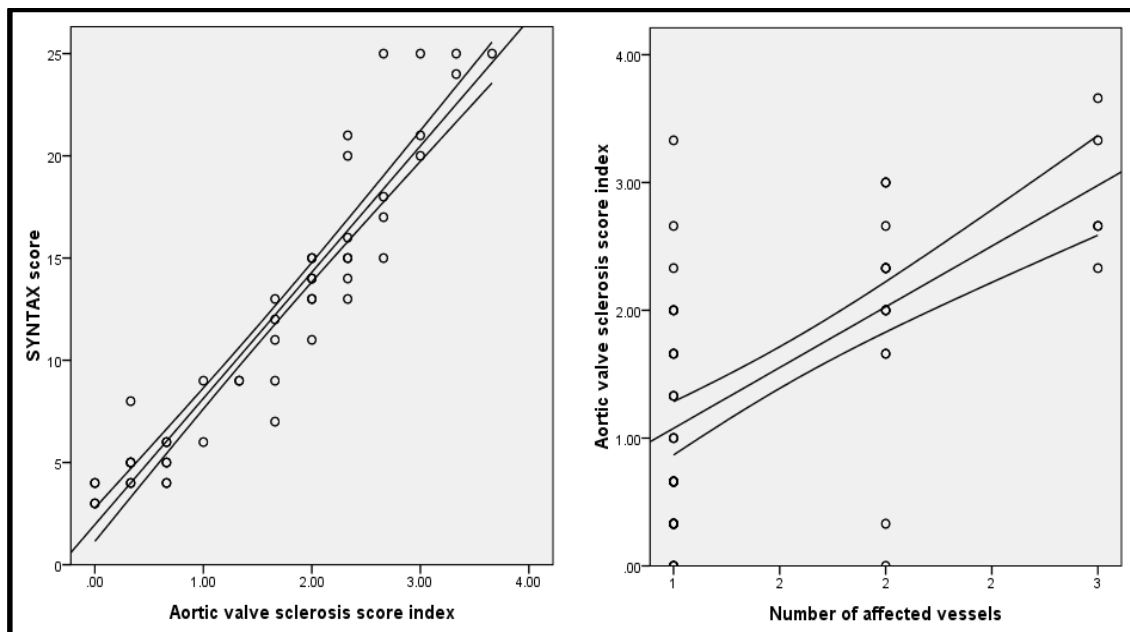


Figure (3): Correlation between AAVSSI, SYNTAX score and number of affected vessels.

Predictors of severe coronary artery disease: We assigned high SYNTAX score (≥ 20) to be the outcome. All the study variables were used to build up a logistic regression model in order to detect the actual predictors for high SYNTAX score among the study population. Being hypertensive and high AAVSSI were found to be good predictors for severe coronary artery lesions in our study model (Table 3).

Table (3): Logistic regression model of the predictors for high SYNTAX score among the study population

Parameter	Exp (B)	Confidence Interval		P value
Old age	1.01	0.85	1.21	0.8
Male gender	0.09	0.01	2.80	0.9
Smoker	0.33	0.03	3.43	0.4
Hypertension	26.41	1.22	572.32	0.04
Ejection fraction	0.79	0.59	1.06	0.1
AAVSSI	760.21	8.08	916.23	0.004

DISCUSSION

The current epidemic of type 2 diabetes and its complications are on a dramatic rise in both the developed and the developing world. CAD is often asymptomatic in these patients until the onset of myocardial infarction (MI) or sudden cardiac death⁽¹⁹⁾. Although coronary arteriography is considered the gold standard for identifying obstructive lesions, it is never used as an initial screening test. It is indicated in patients who show evidence of ischemia on a stress test or for those who continue to be symptomatic despite a negative stress test (suspected false negative result). Therefore, many efforts should be exerted to identify and accurately assess risk in those patients and implement maximum medical treatment plus considering invasive methods for confirming the diagnosis⁽²⁰⁾. Searching for an inexpensive, easily performed method, which offers real time results in addition to traditional risk factors assessment, could confer effective risk stratification and further risk reduction.

Aortic valve sclerosis (AVS) is defined by

echocardiography as thickening and calcification of the normal trileaflet aortic valve without obstruction to the left ventricular outflow and considered as a marker of systemic atherosclerosis. Atherosclerotic burden may be related to the coronary artery lesion complexity⁽²¹⁾. AVS may reflect the atherosclerotic process, and the relationship between AVS and coronary atherosclerosis could be demonstrated⁽²²⁻²⁴⁾.

Histopathologically, the early lesion of AVS resembles arterial atherosclerotic plaques characterized by focal accumulation of extracellular matrix proteins, plasma lipoproteins and a scanty chronic inflammatory infiltrate of macrophages and lymphocytes⁽²⁵⁾.

Over the last few years, many studies were conducted in a trial to evaluate the relation between AVS and CAD and if AVS, using echocardiography, could be used as risk factor or predictor for presence of CAD. Yet such trials has not been able to provide causality despite many positive results. We have intentionally selected wide scope of patients either presented with acute or chronic coronary syndromes and we tried to find a firm correlation between AVS and

extent, complexity and severity of CAD using SYNTAX score.

In agreement with our results, early observational studies have proved the association of hypercholesterolemia, smoking, diabetes mellitus, hypertension, age with calcified aortic valvular disease (26-28). However, the prospective Helsinki aging study of 550 adults over age 55 found that only age, hypertension and BMI were independent predictors of AVS (29). Comparable to our results **Nabati and Favaedi** (30) found that patients with an average AVSSI >1 were older and more hypertensive. **Kim et al.** (31) showed that symptomatic patients with stable angina (without prior cardiac history) who had AVS on a transthoracic echocardiogram had a higher rate of significant CAD compared to those without AVS. Similarly, in patients without known cardiac disease presenting to hospital with chest pain, AVS was found to be an independent predictor of obstructive CAD (odds ratio 3.73) (32). Surprisingly, when considering the age, the association only was statistically significant for those < 60 years old. In the younger group, 71% with AVS had significant CAD versus 24% without AVS (P=0.041). This raised the suspicion that the presence of AVS in younger patients (< 60 years) may be indicative for early systemic atherosclerotic process, not a degenerative condition (32). In consistence with our results, **Soydinc et al.** (22) in a study of 160 patients showed that AVS was associated with the presence of triple vessel CAD and was independently associated with high Gensini score. In a trial conducted by **Korkmaz et al.** (33) aiming to investigate the relation between AVS and coronary artery lesion complexity in acute coronary syndrome patients using SYNTAX score, it was found that AVS was significantly and independently associated with a high SYNTAX score in acute coronary syndrome patients. **Nabati and Favaedi** (30) studied 225 patients admitted with non- ST-elevation myocardial infarction or unstable angina. The prevalence of significant CAD and three-vessel CAD was higher among patients with an average AVSSI >1. Also, in concordance with our findings among the echocardiographic variables; LVEF and e' velocity were significantly lower and E/e' was significantly higher in patients with an AVSSI >1.

On the contrary to our results, a retrospective study by **Bhatt et al.** (11) found that AVS was not independently associated with number of obstructed vessels or lesions with different degrees of obstruction in both major and minor epicardial arteries and mean SYNTAX score. One of the major limitations of their study was being retrospective study with variant interpretations of both echocardiographic and angiographic reports, which were not limited to specific persons and hence this carried the possibility of inter-observer variability.

In a recent Egyptian study conducted in 2018 on 200 patients with chronic coronary syndrome and an indication for coronary angiography. They concluded

that AVS is strongly correlated with the extent of coronary artery disease (34). However, unlike our study that recruited patients with both acute and chronic coronary syndromes, their patients were only those with chronic coronary syndromes. Our study population were diabetic patients who were at highest risk. Moreover, for the assessment of extent of coronary atherosclerosis, they also depended on a rather old score, Gensini score; unlike ours, which used SYNTAX, score (34). Another study carried out by El Moneum in 2019 stated that there was a strong relationship between average AVSSI and severity of coronary artery disease, which is consistent with other high-risk echocardiographic findings (35). However, his study population consisted of 100 patients with acute coronary syndrome. Again, unlike our population which consisted of both acute and chronic coronary syndrome and only diabetics (35).

In view of our results, we highly recommend using aortic valve sclerosis index using echocardiography for screening of CAD in DM patients as they have greater risk of silent ischemia. Sensitivity and specificity of diagnosis of CAD could be increased if we combine echocardiography assessment with other non-invasive tests like stress ECG testing before proceeding into invasive coronary angiography.

CONCLUSIONS

Coronary heart disease is an emerging pandemic. Every effort should be done to combat its deleterious effects. One of these strategies is the early detection and assessment of its severity. This is better carried out through non-invasive tools such as echocardiography. AVS is a good predictor for the presence of underlying coronary artery disease especially in a high-risk population such as diabetics.

List of abbreviations:

CAD: Coronary artery disease.
DM: Diabetes mellitus
CVD: Cardiovascular disease
AVS: Aortic valve sclerosis
BMI: Body mass index
ECG: Electrocardiography
AAVSSI: Average aortic valve sclerosis score index
LVEF: Left ventricular ejection fraction
Post-ACS: Post-acute coronary syndrome
MI: Myocardial infarction
AVS: Aortic valve sclerosis

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