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Research Article

CAC: An Under-Utilized Tool for Screening of ASCVD in Diabetes

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ABSTRACT

Diabetes Mellitus is the silent killer of the 21st century affecting 425 million people all over the world. The situation is worse in south east Asia particularly India where the prevalence is increasing at a rapid pace. The overall prevalence of diabetes in all 15 states of India was 7.3%. Coronary artery disease (CAD) contributes the highest in morbidity, mortality and financial burden of diabetes. Observational studies and RCTs report the prevalence of silent myocardial ischaemia in asymptomatic DM as 22%. There are many ways to estimate cardiovascular risk in asymptomatic diabetes people like clinical risk score, various biomarkers and other modalities like exercise stress test, echocardiography, Ankle Brachial Index (ABI), Carotid Intima Media Thickness (CIMT), Coronary Artery Calcium Score (CAC), CT angiography, Cardiac MRI, Nuclear Imaging etc. In this article we tried to review various modalities and their usefulness in screening asymptomatic ASCVD. Out of all available modalities CAC score is found to be very cost effectiveness and sensitive way to predict ASCVD. Still CAC is an underutilized modality to screen asymptomatic ASCVD in diabetes people.

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Introduction

Diabetes Mellitus is like a silent killer and is becoming more and more grievous with time [1]. According to the IDF there are 425 million of people suffering from diabetes mellitus in 2017 across the world and 72.9 million in India [2]. As per ICMR INDIAB, 62 million individuals also have diabetes mellitus and 77 million have prediabetes [3]. The overall prevalence of diabetes in 15 states of India is 7.3%. Patients with clinical CAD are generally classified into three categories: low risk, with a cardiac mortality risk 1% per year; high risk, with a cardiac mortality risk 3% per year; or intermediate risk, with a cardiac mortality risk between 1 and 3% per year. The overall population of asymptomatic patients with type 2 diabetes falls into the intermediate cardiac risk category. Overall yearly CVD event rate in middle-aged people with diabetes in middle and high-income countries is 14 to 47 per 1,000 people, among these, 2-26 per 1,000 are coronary artery disease events, and 2-18 per 1,000 are strokes [2]. There is not much population-based data available in India comparing the prevalence of CAD in people with and without T2DM. In the Chennai Urban Population Study CAD had a

prevalence of 21.4% among individuals with T2DM as compared to 14.9% among those with impaired glucose tolerance and 9.1% among those with normal glucose tolerance [4]. More than 65% of patients with T2DM die of cardiovascular disease; of these, nearly 80% are attributable to coronary artery disease (CAD).

The categorization of people with diabetes into different cardiovascular risk groups may allow recognition of those who might benefit more from aggressive preventive intervention. Several investigations modalities have been tested to stratify ASCVD risk in asymptomatic diabetic patients but only few were able to yield clinically significant prognostic information. These are various clinical Risk scores, cardiac biomarkers and modalities like ankle brachial index (ABI), electrocardiogram (ECG), echocardiography, carotid intima media thickness (CIMT), exercise stress test, coronary calcium score, CT angiography, MRI heart, radionucleotide imaging etc. There is still a lack of consensus as far as screening for ASCVD in asymptomatic people with diabetes is concerned. In this article we tried to look at the usefulness of various

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modalities to predict risk of ASCVD in asymptomatic type 2 diabetes people.

Methods

A targeted literature review was done using keywords cardiovascular disease, cardiovascular risk stratification, Atherosclerotic cardiovascular disease, Type 2 diabetes, coronary calcium score. Literature was examined to evaluate recommendation for screening in asymptomatic diabetes people for ASCVD which includes recommendation by authorities, clinical studies and meta-analysis.

Discussion

ASCVDs are a group of disorders of the heart and blood vessels and they include:

- i. Coronary heart disease: disease of the blood vessels supplying the heart muscle;
- ii. Cerebrovascular disease: disease of the blood vessels supplying the brain;
- iii. Peripheral arterial disease: disease of blood vessels supplying the arms and legs [2].

I ASCVD Risk in Patients with Diabetes

Diabetes has been considered as a “cardiovascular risk equivalent”. but recent evidences indicate that ASCVD risk in T2DM is not universally similar to the risk of patients with prior cardiovascular disease but is highly heterogeneous. A meta-analysis of 13 epidemiological studies, including 45,108 patients with and without diabetes observed that the CHD risk was 43% lower in T2DM without CHD than in individuals with a prior myocardial infarction without diabetes. In another meta-analysis of observational studies among patients with T2DM found a 28.5% of patients were having CAC score of zero, indicating a similar 5-year survival rate as in patients without diabetes. Currently, the 2013 ACC/AHA guidelines, the 2016 ADA standards of diabetes care and the 2016 European Society of Cardiology (ESC) no longer consider diabetes as a coronary risk equivalent. The recent ESC guideline considers that diabetes risk approaches the CHD risk when patients have more than 10 years of disease or when in the presence of renal dysfunction or microalbuminuria. Patients younger than 40 years with a shorter duration of diabetes are currently defined as being part of a lower risk category.

II ASCVD Risk Stratification in Diabetes [5-8]

- i. Assessment of individual risk factors and comorbidities.
- ii. Assessment by various biomarkers.
- iii. Assessment by different risk score calculators.
- iv. Assessment through diagnostic modalities.

III Assessment of Individual Risk Factors

Advance age, male sex, family history of premature coronary heart disease, smoking and other co-morbidities are individual known risk factors for the development of CV risk. Advancing age is the strongest non-modifiable risk factor for CVD. The incidence of a new myocardial infarction is higher in men than in women in patients with diabetes as well as without diabetes, but when considering the mortality rate from

coronary causes, women with diabetes are at a higher risk than men. Family history of premature coronary heart disease, defined as in male < 55 years and in female < 65 years in any first degree relative is also one of the major risk factors. Active smoking is associated with the highest risk of total mortality and cardiovascular events among patients with diabetes.

Smoking cessation is associated with a reduced risk in total mortality and cardiovascular events in patients with diabetes. There are many co-morbidities which if present in people with diabetes increases the risk of ASCVD [9]. Hypertension is often the result of underlying diabetic kidney disease in type 1 diabetes while in type 2 diabetes, it usually coexists with other cardio-metabolic risk factors. Dyslipidemia is the most common population attributable risk factor for myocardial infarction. The risk of CAD is reduced by 2-3% for every 1% drop in total cholesterol. Other co-morbidities are duration of diabetes, presence of chronic hyperglycemia, severe hypoglycemia, low eGFR and microalbuminuria, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea (OSA), erectile dysfunction (ED) etc.

Table 1: Various Variables of CV Risk Assessment Model.

VARIABLE	FRS	JBS	ACC/AHA	WHO
Age	30-74	30-84	20-79	35-75
Gender	+	+	+	+
Ethnicity	-	+	+	-
Diabetes	+	+	+	+
Smoking	+	+	+	+
F/H/O Premature CVD	-	+	-	-
H/O AF	-	+	-	-
H/O CKD	-	+	-	-
H/O RA	-	+	-	-
Hypertension	+	+	+	-
SBP	+	+	+	+
BMI/ Weight	+	+	-	-
TC	+	+	+	+
HDL	+	+	+	-

IV Assessment by Risk Score Calculators

There are many ASCVD risk assessment models available like Framingham Risk score (FRS), World Health Organization risk prediction charts (WHO), ACC/AHA Atherosclerotic Cardiovascular Disease (ASCVD) risk score), SCORE (Systematic Coronary Risk Evaluation) high and low cardiovascular risk regions, QRISK2 (QRESEARCH cardiovascular risk algorithm), the 3rd Joint British Societies' risk calculator (JBS) [10-13]. Salam *et al.*, in his study found that FRS was the most useful CVD risk assessment model in young Indian patients [14]. FRS was likely to identify the number of patients at ‘high-risk’ as compared to JBS and ACC/AHA. While another study by Manish Bansal *et al.*, shows that in Indian patients presenting with acute MI, JBS was likely to identify the largest proportion of the patients as at ‘high-risk’ compared to WHO, FRS and ACC/AHA risk scores [12]. Sharmini *et al.* found in their study that FRS and SCORE high model more useful in prediction cardiovascular risk as compared to WHO/ISH model [15]. Large-scale prospective studies are needed to confirm these findings. Thus though there is an abundance of risk equations developed for primary and secondary prevention, there remains a need for

additional research to provide sufficient clinical guidance for risk estimation, particularly in high-risk or secondary prevention settings.

V Cardiac Biomarkers

Many cardiac biomarkers are associated with increased CV risk but the addition of circulating biomarkers for CV risk assessment has limited clinical value. These are High Sensitivity C-reactive protein (hs-CRP), fibrinogen (inflammatory markers), high-sensitivity cardiac troponin T (hs-TnT), N-terminal pro-B-type natriuretic peptide (NT-pro BNP), microalbuminuria etc.

VI CV Risk Assessment Through Diagnostic Modalities

i Resting ECG

A resting ECG may detect silent MI in 4% of individuals with DM. Additionally, prolonged corrected QT interval is associated with increased CV mortality in T1DM, whereas increasing resting heart rate is associated with risk of CVD in T1DM and T2DM. Low heart rate variability (a marker of diabetic CV autonomic neuropathy) has been associated with an increased risk of fatal and non-fatal CAD.

ii Exercise ECG

Exercise stress test is low cost, simple and widely available test but the goals of the stress test in diabetic population are more diverse than the nondiabetic population [16]. The stress test looks up on exercise-induced abnormalities like ST-segment depression, ventricular arrhythmia, angina pectoris, poor post-exercise heart rate recovery or maximal exercise capacity. Overall sensitivity of exercise stress test varies 45-50% in various studies with specificity of around 80% and negative predictive value around 40-45%. Thus, normal stress tests do not rule out CAD as well there may be many other reasons for false positive stress tests. There are also many people with diabetes with impaired exercise tolerance who are not able to do the target exercise during stress tests due to impaired exercise tolerance or other physical limitations. Moreover, as silent ischaemia and autonomic neuropathy is one of specific features of diabetes CVD there is always a risk of sudden cardiac death during or post exercise test in diabetes population particularly with high CV risk such as old age, long duration of disease, smokers, associated comorbidities etc.

iii Echocardiography

Prognostic data for using 2D-ECHO in asymptomatic patients is not available. Several studies have demonstrated the prognostic value of stress echocardiogram in the DM population.

Table 2: Various CV risk assessment modalities.

	Sensitivity %	Specificity %	PPV %	NPV %
Exercise Stress Test	47	81	85	41
Stress Echo	82	54	84	50
Nuclear Imaging	86	56		

iv Cardiac MRI and Nuclear Imaging

The value of these advanced imaging techniques in routine practice has not yet been demonstrated [17]. Asymptomatic subjects with significant atherosclerosis burden (i.e. CAC score >400) may be referred for functional imaging like Nuclear perfusion scan and cardiac MRI.

v CIMT: Carotid Wall Intima-Media Thickness

Carotid wall intima-media thickness (CIMT) is the distance from the lumen intima interface to the media adventitia interface of the artery wall, determined by a carotid artery ultrasound. In patients with T2DM, CIMT above 1.9 mm is predictive of coronary artery stenosis. In patients with DM, carotid intima media thickness has not shown incremental value over the CAC score to predict CAD or CV events. CIMT had been deemed reasonable for cardiovascular risk assessment in asymptomatic adults who are at intermediate risk per the 2010 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and 2012 European Society of Cardiology guidelines, but this recommendation was dropped in the 2013 ACC/AHA guidelines due to results from several studies showing lack of a significant relationship with CHD events.

vi ABI: Ankle Brachial Index [18, 19]

The ABI is a simple, noninvasive clinical test. Most studies have used a cut-off point of <0.90 [18]. A low ABI score is associated with elevated cardiovascular risk. In a systematic review including 9 studies, the sensitivity and specificity of a low ABI as a predictor of future CVD events were respectively 16.5% and 92.7% for coronary heart diseases, 16.0% and 92.2%, for incident stroke and 41.0% and 87.9% for cardiovascular mortality. Thus, ABI has a high specificity but a very low sensitivity, limiting its utility as a screening test for CAD. There is also a lack of standardization regarding both the method of measuring ABI and the cutoff point for abnormal ABI. There is a need for a uniform method of ABI to be used in studies to screen for obstructive coronary artery disease.

vii CAC Score: Coronary Artery Calcium Score

Coronary artery calcium score (CAC) is determined by electron-beam (EBCT) and multi-detector (MDCT) computed tomography. The determination of the CAC score by computed tomography is based on axial slices, with a thickness of 3 mm, without overlapping or gaps, limited to the cardiac region, acquired prospectively in synchrony with the electrocardiogram at a predetermined moment in the R-R interval, usually in the mid/late diastole, without the use of intravenous contrast medium [20, 21]. The effective dose of radiation is usually low, typically less than 1.5 mSv, which is the highest effective dose recommended for use in image acquisition, according to the Society of Cardiovascular Computed Tomography.

Calcification is identified as areas of hypoattenuation of at least 1 mm² with > 130 Hounsfield units (HU) or ≥ 3 adjacent pixels. The main systems for the quantification of the CAC score are the Agatston method, determination of the volume of calcium, and determination of the calcium mass score. The Agatston method uses the weighted sum of lesions with a density above 130 HU, multiplying the area of calcium by

a factor related to maximum plaque attenuation: 130-199 HU, factor 1; 200-299 HU, factor 2; 300-399 HU, factor 3; and ≥ 400 HU, factor 4. When assessed by CAC score prevalence of CAD risk was 35.7% in a study in asymptomatic diabetes patients. CAC has a strong correlation with the total coronary atherosclerotic burden and is able to define CHD risk, being an independent predictor of cardiovascular disease [22].

Table 3: Clinical interpretation of the degree of coronary calcification.

Degree of calcification	Clinical interpretation
Zero calcium score	Very low risk of future coronary events
CAC <100 and <75th percentile for sex, age and race	Low risk of future coronary events. Low probability of myocardial ischemia
CAC > 100 or > 75th percentile for sex, age and race	Higher risk of future coronary events (aggravating factor) Consider reclassifying the individual to high risk
CAC > 400	Higher probability of myocardial ischemia

Coronary artery calcium score is an accurate method to determine presence and extent of coronary atherosclerosis, especially in patients with diabetes [23]. American College of Cardiology Foundation /American Heart Association (ACCF/AHA) consensus, data from six large studies that collectively included 27,622 asymptomatic patients were aggregated and the relative risk of major cardiovascular events was calculated for patients with a positive CAC score and for those with a CAC score of zero. The following results were obtained: CAC score of 100–400—relative risk of 4.3; CAC score of 401–999—relative risk of 7.2; CAC score = 1000—relative risk of 10.8. In MESA Study comparing the improvement in prediction of incident CHD and CVD between six risk markers in 6814 patients revealed that CAC has highest increment of sensitivity and specificity to the FRS as compared to all other markers [24]. In the PREDICT study involving 589 type 2 diabetes patients with no history of cardiovascular disease shows CAC was a highly significant independent predictor of events on follow up of 4

years. ($p < 0.001$). A doubling in CAC was associated with a 32% increase in risk of events and there was a progressive increase in hazard ratio according to the CAC score level, compared to CAC <10.

In asymptomatic T2DM patients CAC is also predictive for mortality [25, 26]. In a study including 10,377 asymptomatic individuals with 903 T2DM found that the increase in mortality was proportional to increases in CAC on median follow up of 5.18 years. In addition, CAC score 0 offered a similar survival rate for both groups with or without diabetes. CAC score also offers long-term predictive value for all-cause mortality in asymptomatic patients with diabetes [27, 28]. In a 15-year cohort study with 9715 nondiabetic individuals and 810 T2DM patients, 34% of T2DM patients were having baseline CAC score zero (CAC = 0). The adjusted HR (95% CI) for mortality at 15 years was respectively: CAC [0]: 2.53 (1.74–3.69); CAC [1–399]: 2.07 (1.64–2.62); CAC [>400]: 1.88 (1.41–2.51). Interestingly, a CAC zero conferred a similar mortality rate between T2DM and non-DM patients for the first 5 years. After 5 years, however, the risk of mortality increased significantly for diabetic patients even in the presence of a baseline CAC = 0.

The absence of coronary artery calcium does not rule out noncalcified plaque, and clinical judgement about risk should prevail [3]. Coronary artery calcium measurement is not intended as a ‘screening’ test for all but rather may be used as a decision aid in selecting adults to facilitate the clinician patient risk discussion [29, 30]. MESA and Astro-CHARM (Astronaut Cardiovascular Health and Risk Modification) are risk estimation tools that incorporate both risk factors and coronary artery calcium for estimating 10-year CHD and ASCVD risk, respectively. The overall evidences support the use of CAC screening for CV risk stratification and to guide management in the asymptomatic DM patient, as recommended with a Class IIa indication in the 2010 AHA/ACC guidelines. ADA still does not recommend CAC score for routine use in risk stratification of patients with diabetes.

Table 4: Recommendation for the use of the CAC score in asymptomatic patients [31].

Guideline	Low risk	Low risk + DM	Low risk + F/H/O premature CAD	INTERMEDIATE RISK	HIGH RISK
ADA	NO	NO	NO	NO	NO
ESC / EASD				IIb	
ACC/AHA*	IIb	IIb	IIb	IIb	IIb
Dirtriz da SBC/CBR	II	IIa	IIa	I	III
AACE		IIb	IIb	IIb	
ACR	Typically inappropriate		Can be appropriate	Appropriate	Typically inappropriate

*IIb: If, after risk assessment, the treatment based on the decision is uncertain, evaluation with the CAC score can be considered in order to define the most appropriate therapeutic strategy.

VII What Various Guidelines Says

i ADA

ADA recommends to assess cardiovascular risk factors systematically at least annually in all patients with Diabetes for prevention and management of both ASCVD and heart failure [31]. These risk factors include obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease, and the presence of albuminuria. The 10-year risk of a first ASCVD event should be assessed by ASCVD risk calculator (Risk Estimator Plus) to

better stratify ASCVD risk. In asymptomatic patients, routine screening for coronary artery disease is not recommended except baseline ECG. Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥ 40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

ADA supports that the screening of asymptomatic patients with high ASCVD risk is not recommended. Coronary artery screening methods, such as calcium scoring, may improve cardiovascular risk assessment in people with type 2 diabetes but their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

ii ESC/EASD

ESC advocates use of SCORE risk chart for cardiovascular risk assessment along with other risk factors. ESC/EASD 2019 guideline recommends a resting ECG for CV risk assessment in patients with diabetes and hypertension or if CVD is suspected [32]. Routine assessment of microalbuminuria should be carried out to identify patients at risk of developing renal dysfunction and CVD. Other tests, such as transthoracic echocardiography, coronary artery calcium (CAC) score, and ankle brachial index (ABI), may be considered to test for structural heart disease or as risk modifiers in those at moderate or high risk of CVD. Routine assessment of novel biomarkers is not recommended for CV risk stratification.

iii The American Heart Association and American College of Cardiology

As per 2019 AHA/ACC guideline, adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardio-vascular disease (ASCVD) risk estimation [33]. For adults 20-39 years of age, it is reasonable to assess traditional ASCVD risk factors at least every 4 to 6 years.

In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk ($\geq 7.5\%$ to <20% 10-year ASCVD risk), it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions. These factors may include having a family history of premature ASCVD, chronic inflammatory disease (rheumatoid arthritis, lupus or HIV infection), South Asian ancestry, a history of preeclampsia or preterm delivery, early menopause, erectile dysfunction, chronic kidney disease (CKD), metabolic syndrome, persistently elevated inflammatory markers or elevated lipid biomarkers. After these clinically available risk-enhancing factors have been considered, if there is still uncertainty about the reliability of the risk estimate for individuals in the borderline or intermediate risk categories, further testing to document subclinical coronary atherosclerosis is reasonable to more accurately reclassify the risk estimate upward or downward.

In adults at intermediate risk ($\geq 7.5\%$ to <20% 10-year ASCVD risk) or selected adults at borderline risk (5% to <7.5% 10-year ASCVD risk), if risk-based decisions for preventive interventions remain uncertain, it is reasonable to measure a coronary artery calcium score to guide clinician-patient risk discussion. In these groups, coronary artery calcium measurement can reclassify risk upward (particularly if coronary artery calcium score is ≥ 100 Agatston units (AU) or ≥ 75 th age/sex/race percentile) or downward (if coronary artery calcium is zero) in a significant proportion of individuals. For adults 20-39 years of age and

for those 40-59 years of age who have <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk with the ACC/AHA 30-year/lifetime risk estimator may be considered.

iv American Association of Clinical Endocrinologists/American College of Endocrinology

In February 2017, the American Association of Clinical Endocrinologists and the American College of Endocrinology published updated “Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease” which states that the 10-year risk of a coronary event should be determined by assessment using one or more of the following tools: 1) the Framingham Risk Assessment Tool, 2) the Reynolds Risk Score, 3) the Multi Ethnic Study of Atherosclerosis (MESA) 10-year ASCVD (atherosclerotic cardiovascular disease) Risk with Coronary Artery Calcification (CAC) Calculator and 4) the UK Prospective Diabetes Study (UKPDS) Risk Engine for patients with type 2 diabetes. Although each of these tools can be used to predict 10-year risk, the MESA risk score is emerging as the preferred tool using traditional risk factors and CAC to predict 10-year coronary heart disease (CHD) risk.

Conclusion

The CAC score is an independent marker of risk for cardiac events, cardiac mortality, and all-cause mortality. In addition, it provides additional prognostic information to other cardiovascular risk markers. The well-established indications for the use of the CAC score include stratification of global cardiovascular risk for asymptomatic patients: intermediate risk based on the Framingham risk score (class I); low risk based on a family history of early CAD (class IIa); and low-risk patients with diabetes (class IIa).

In symptomatic patients, the pre-test probability should always be given weight in the interpretation of the CAC score as a filter or tool to indicate the best method to facilitate the diagnosis. Therefore, the use of the CAC score alone is limited in symptomatic patients. In patients with diabetes, the CAC score helps identify the individuals most at risk, who could benefit from screening for silent ischaemia and from more aggressive clinical treatment.

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