Coronary Artery Calcium Screening in Persons with Metabolic Syndrome and Diabetes: Implications for Prevention

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Abstract

Diabetes and metabolic syndrome are major risk factors for coronary heart disease (CHD). Many patients suffering CHD events are not adequately identified by traditional risk assessment, suggesting the need for early detection of subclinical CHD to identify those at highest risk. Coronary artery calcium (CAC) screening has added utility in categorizing patients with intermediate and high risk of CHD events, and a growing body of evidence suggests its use for CHD risk assessment in persons with metabolic syndrome and diabetes mellitus. These studies demonstrate the presence and extent of CAC to be greater in those with these conditions, compared to those without, and that CHD risk varies greatly according to the extent of CAC both in persons with and without metabolic syndrome and diabetes mellitus. More recently, guidelines regarding the use of CAC screening have been extended to those with diabetes mellitus, helping to further stratify those patients that may benefit from more intensive therapy. This review evaluates the role and possible benefits of CAC screening, with a focus on those with metabolic syndrome and diabetes mellitus for evaluating the risk for CHD.

Introduction

BECAUSE THE INCIDENCE OF diabetes mellitus is occurring at an increasingly earlier age,¹ primary prevention and early screening have become essential for altering negative outcomes. A broader focus has also led to examination of a quarter of American adults with a precursor of diabetes called metabolic syndrome, a cluster of cardiovascular risk factors that includes central obesity, hypertension, dyslipidemia, and glucose intolerance.² Over the past decade there has been conflicting evidence to whether diabetes mellitus itself is a risk equivalent for coronary heart disease (CHD)^{3,4}; investigators have demonstrated that those with diabetes and no prior myocardial infarction (MI) history have similar risks for MI as those without diabetes and a prior MI history.⁵ Importantly, the prevalence of silent MI and ischemia among asymptomatic persons with diabetes has been shown to range from 22% to 58% based on different patient populations.^{6–8} These studies come at a time when evidence is accumulating regarding newer coronary artery disease (CAD) diagnostic modalities such as computed tomography (CT) angiography, cardiac magnetic resonance imaging, and coronary artery calcium (CAC) scoring. The sensitivity and

the outcomes based on these tests may further complicate the strategies for diagnosing and staging CHD in asymptomatic patients with metabolic syndrome and diabetes.

Some have suggested that due to lack of evidence of the benefit in routine CAD screening for all asymptomatic patients with diabetes, the focus should be for those who have a high risk of having a cardiovascular event in the short term.⁹ Despite earlier guidelines, recently the 2010 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults stated that CAC screening was reasonable for cardiovascular risk assessment in asymptomatic adults at least 40 years old and with diabetes.¹⁰ Here we evaluate recent literature that describes the potential benefits for screening patients with subclinical metabolic syndrome and diabetes mellitus with CAC for presence and severity of subclinical CHD.

CAC as a Screening Tool

Screening tools have been in place for many years for detecting conditions such as occult cancers to prevent morbidity and mortality. This has not been the case for

atherosclerotic disease and its complications. The traditional use of the office-based Framingham risk score (FRS), although widely recommended, has the significant limitation that some who suffer a CHD event do not necessarily exhibit multiple risk factors required to place one at significant risk on the basis of the FRS.¹¹

Beginning in 1996, the AHA issued statements for the potential use of CAC in high-risk asymptomatic patients. Currently, CAC has become an established rapid noninvasive tool that quantifies the severity of CAC in atherosclerosis.¹² Cardiac CT, using either multidetector row CT or electron beam tomography, detects and quantifies coronary calcium, an established marker of atherosclerosis.¹³ Cross-sectional analyses of baseline relationships have shown that coronary artery calcium score (CACS) is significantly associated with other risk factors for CHD, such as age, male gender, and duration of diabetes.¹⁴ Furthermore, CAC is an established independent indicator of subclinical atherosclerosis in those with metabolic syndrome and diabetes.^{15–18}

CAC Recommendations and Utility in Asymptomatic Individuals

In 2006, the AHA Writing Group suggested the use of CAC for those with high and intermediate risk for CAD to better stratify individuals who would benefit from aggressive lipid-lowering therapies.¹⁹ This recommendation was based largely on data from a large prospective study that found that while both the FRS and CAC were able to predict CHD event risks independently from one another, a CAC score >300 added to CHD risk stratification based on the FRS.²⁰ CACS was shown to provide further risk stratification in those with a 10-year FRS of at least 10%.

Recommendations have continued with a 2010 AHA/ACC statement providing a class IIa recommendation for the use of CAC in all asymptomatic adults at intermediate cardiovascular risk (10%–20% 10-year risk using FRS) and IIb recommendation for those at low intermediate risk (6%–10% 10-year risk).¹⁰ Studies in the past have shown the prominence of CAC in those symptomatic patients with documented CAD.²¹ More recently, the Multi-Ethnic Study of Atherosclerosis (MESA) study showed the benefit of CAC in a wide range of ethnically diverse individuals despite differences in prevalence and extent of coronary calcification.²² Higher calcium scores conferred an increased risk for major events, even after adjustment for standard risk factors, with the most significant increase in risk being among participants with CACS greater than 100. Doubling of CACS was associated with a 20% increase in risk for a major CHD event and 26% for any CHD event in the ethnically diverse population of 6722 persons.

CAC has also been seen to be an effective predictor for cardiovascular risk for those who could be classified as low risk. Among low-risk women from the MESA, without diabetes and younger than 79 years, there was a six-fold greater risk for CHD and five-fold risk for cardiovascular disease (CVD) events in women with prevalent CAC as compared with nondetectable CAC.²³ For those women defined as being at low risk, which includes the vast majority of US women younger than 70, 5% were seen to have CAC scores of 300 or higher, which correlated to a high relative risk and absolute risk for CHD and CVD events. A separate study of asymptomatic men and women between the ages of 40 and

50 from the Prospective Army Coronary Calcium project showed that the presence of any CAC was associated with an 11.8-fold increase risk for acute CHD after controlling for the FRS.²⁴ This showed the presence of an independent relationship between CAC and incident CHD in asymptomatic low-risk men. Taylor et al. note that screening individuals between the ages of 40 and 50 will still ensure limited over identification due to the low prevalence of CAC in this age group. Nonetheless, their analysis shows that CAC screening would be only cost effective if an optimal criterion for selection was established in this age group.

The true benefit of CACS for CHD risk assessment is likely to be dependent on specific cut points for different groups of patients. Past data have supported 75th percentile age-specific cutoffs for intermediate risk individuals as an indicator for aggressive treatment.²⁵ Other studies have shown the benefit of increasing absolute scores in this same population.²⁶ Data from MESA have shown that the use of absolute CAC cut points was more beneficial in predicting incident CHD than age, sex, race, or ethnicity-based percentiles.²⁷ Through estimations with use of area under the receiver-operator characteristics curve (AUC), a model using absolute CAC cut points was best fitting. AUC values for women were 0.73 for age- and sex-specified percentiles versus 0.76 for absolute CAC scores. Males had similar results with AUC values of 0.73 for age- and sex-specified models versus 0.77 for absolute CAC scores. When hazard ratios (HRs) were calculated for risk of CHD events associated with an absolute CACS across constant age, sex, race, and ethnicity CAC percentiles, an increasing trend for both unadjusted and adjusted FRS was seen in the CAC 101–400 and >400 groups. In contrast, when risk of CHD events associated with age, sex, race, and ethnicity CAC percentiles were calculated across constant absolute CACS, there was no trend in either unadjusted or FRS-adjusted analyses. This study showed that the strongest correlation to CHD events was found when using CAC based on cut points, in this case, CACS of 1–100, 101–400, and >400.

CAC in Metabolic Syndrome

CAC has been independently associated with many metabolic syndrome components, such as intra-abdominal fat obesity, insulin resistance, hypertension, and fasting serum glucose in addition to being inversely related to high-density lipoprotein (HDL).²⁸ With further multivariate analysis, CAC continued to be associated with intra-abdominal adiposity. Our previous work has highlighted the use of CAC as a measure of atherosclerosis in patients with metabolic syndrome (in the absence of diabetes).¹⁵ CAC prevalence ranged from 34% in those without any metabolic risk factors to 50%, 56%, 54%, 63%, and 58% incrementally increasing for each additional metabolic risk factor (up to 5) (trend $P < 0.001$). The prevalence of CAC above the 75th percentile showed a similar significant trend. These results showed that there was a graded association with CAC prevalence and number of metabolic risk factors. Importantly, CAC was found to provide complementary, almost mutually exclusive, information to FRS for identifying those at high risk; while 24.7% of subjects were at $\geq 20\%$ FRS and 21.2% of subjects had a CAC value $\geq 75^{\text{th}}$ percentile, 40.9% of subjects fit either or both criterion, suggesting many such persons with significant CAC (and presumably at increased CHD risk) would not

FIG. 1. Prevalence of coronary artery calcium (CAC) by disease and gender. MS, metabolic syndrome; DM, diabetes mellitus. (Adapted from Wong et al., *J Am Coll Cardiol* 2003;41:1547–1553.)

have been identified on the basis of FRS alone. Figure 1 shows the respective values of CAC prevalence for males and females based on disease categorization. Prevalence for males and females in any calcium value category were significant across disease categories ($P < 0.001$ and $P < 0.05$, respectively). Interestingly, women with metabolic syndrome were found to have similar prevalence of any CAC as women with diabetes despite age similarities between the two groups.

The utility of CAC has also been established as an indicator for the likelihood of exhibiting inducible ischemia on the basis of stress myocardial perfusion single-photon emission computer tomography (MPS) in those with metabolic syndrome and diabetes mellitus.²⁹ Figure 2 shows that for those with CACS > 100 , regardless of metabolic abnormality (metabolic syndrome or diabetes mellitus), ischemic MPS was low ($< 3\%$).³⁰ In contrast, individuals with a metabolic abnormality who also had a CACS between 100 to 399, had a four-fold significant increase in ischemia ($\geq 5\%$) as compared to those without metabolic syndrome. Furthermore, multivariate analysis revealed the presence of metabolic abnormalities (metabolic syndrome and/or diabetes) provided additional independent information to CAC for the prediction of inducible myocardial ischemia. These observations indicated that those with metabolic syndrome or diabetes mellitus have a lower threshold of subclinical atherosclerosis indicated by CAC that may be associated with an increased likelihood of myocardial ischemia.

CAC may also provide useful diagnostic information for those with multiple metabolic syndrome factors. Previously, we showed that those with four or five cardiometabolic risk factors and without diabetes had almost as high of a prevalence of CAC (53%) as those with both diabetes mellitus and metabolic syndrome (58%).³¹ Multivariate analysis adjusted for cardiovascular risk factors shows that those with four or five cardiometabolic risk factors (without diabetes) had a significantly higher likelihood of any CAC [odds ratio (OR)=1.46, $P < 0.01$], as well as CAC $\geq 75^{\text{th}}$ percentile (OR=1.46, $P < 0.01$). These were similar odds to those with diabetes mellitus and without metabolic syndrome (1.59 for

FIG. 2. Frequency of myocardial ischemia during myocardial perfusion single-photon emission computer tomography (MPS) across four coronary calcium score categories. CACS, coronary artery calcium score. (Adapted from Wong et al., *Diabetes Care* 2005;28:1445–1450.)

any CAC and 1.58 for CAC $\geq 75^{\text{th}}$ percentile). These results showed that the odds of CAC among those with four or five cardiometabolic risk factors were similar to those with diabetes and without metabolic syndrome.

Although there are no guidelines specifically recommending CAC screening in those with metabolic syndrome, many (but not necessarily all) of those with metabolic syndrome would fall under the 2010 AHA/ACC guidelines indicating CAC screening for those at low intermediate to intermediate 10-year risk of CHD. However, given that such risk assessment is based on the FRS, which does not contain key metabolic syndrome risk factors such as abdominal obesity or hyperglycemia, some might consider metabolic syndrome to be associated with higher long-term risk than what their “traditional” risk factors might predict, therefore warranting most (if not all) could be indicated for CAC screening for more accurate risk assessment.

CAC in Asymptomatic Individuals with Diabetes

A disproportionate percentage of CHD events occur in those with diabetes. More accurate CHD risk assessment in those with diabetes may help to identify where we can best intensify therapy to hopefully reduce the burden associated with cardiovascular events in this population. Because CAC has been shown to be more prevalent in individuals with diabetes as compared to those without diabetes in almost all age groups,¹⁸ research has continued to address the predictive values of CAC progression in patients with diabetes. Anand et al. showed that in asymptomatic persons with type 2 diabetes, many established cardiovascular risk factors are able to predict CAC,³² but are not predictive of myocardial ischemia.^{6,32} CAC, on the other hand, is capable of predicting myocardial ischemia and can be considered as a more reliable marker than most cardiovascular risk factors such as age, systolic blood pressure, and duration of diabetes. The study showed the added benefit of CAC with use of myocardial perfusion scintigraphy through a first-order

FIG. 3. (A) Annual cardiovascular disease (CVD) event rates by calcium score categories in subjects with diabetes, metabolic syndrome, or neither disease. (Adapted from Malik et al., *Diabetes Care* 2011;34:2285–2290.) (B) Annual coronary heart disease (CHD) event rates by calcium score categories in subjects with diabetes, metabolic syndrome, or neither disease. DM, diabetes mellitus; MetS, metabolic syndrome. (Adapted from Malik et al., *Diabetes Care* 2011; 34:2285–2290.)

interaction between CAC scores and the extent of myocardial perfusion abnormality when predicting event-free survival ($P=0.003$). Anand et al. concluded that CAC is the most reliable indicator of CAD risk of established cardiovascular risk factors because it was the strongest predictor of short-term cardiovascular events.

Raggi et al. showed similar results in their observational study of 10,377 asymptomatic patients with diabetes (903) and without diabetes. They showed CACS of 281 ± 567 and 119 ± 341 in those with diabetes and those without diabetes respectively ($P<0.0001$).³³ The presence of any degree of CAC deposits in diabetic mellitus patients led to a higher risk for all-cause mortality than for nondiabetic patients. Additionally, the study found no difference in survival between those with and without diabetes that had no baseline CAC. The prospective cohort Patients with Renal Impairment and Diabetes Undergoing Computed Tomography (PREDICT) study showed the benefits for CACS in 589 patients. CACS added to the predictive power of the Framingham and the United Kingdom Prospective Diabetes Study (UKPDS) risk scores for predicting CHD risk, and in the case of UKPDS, CVD risk.³⁴ With the addition of CACS to the FRS, Framingham CHD risk was markedly reduced but still significant ($P=0.05$), whereas the CACS remained significant ($P<0.001$). Similarly with the addition of CACS to the UKPDS model, the significance of UKPDS CHD risk was reduced ($P=0.02$) and CACS remained significant ($P<0.001$), despite PREDICT participants already being diagnosed and many treated for diabetes for a mean of 7 years. The study identified a group of individuals with low CACS for whom statin therapy may not be necessary and a high-risk group for whom intensive preemptive care would be ideal.

Within a larger cohort of asymptomatic subjects with diabetes than that of the PREDICT study, Becker et al. also showed the predictive value of CAC in asymptomatic patients with diabetes mellitus. The prospective study of 716 patients over 8 years showed an initial Agatston score of 475 ± 208 for those who suffered a MI or cardiac death as compared to 236 ± 199 ($P<0.01$) for those without any cardiac event.³⁵ Receiver-operating characteristics were used for prediction of MI using Agatston CACS, UKPDS score, and Framingham score. The area under the curve using the

Agatston score (0.76, 0.73–0.82) was significantly higher as compared to the UKPDS (0.63, 0.59–0.66) and the FRS (0.66, 0.62–0.68). Although the PREDICT study showed added benefit with use of CACS, this study showed better accuracy in predicting MI using the Agatston CAC as compared to the UKPDS and FRS.

Most recently, our findings from MESA demonstrated the incremental value of CAC for CVD prediction in those with diabetes and metabolic syndrome. In Figure 3, we show that the unadjusted rates for CHD and CVD increased with increasing levels of CAC within each disease group. We further report adjusted HRs for CHD events in the range of CAC levels of 1–99 to ≥ 400 as compared to a reference group of 0 CAC showed ranges of 2.9–6.2 in those with diabetes, 3.9–11.9 in those with metabolic syndrome, and 2.6–9.5 in those with neither metabolic syndrome nor diabetes mellitus.³⁶ HRs for similar groups for CVD events showed ranges of 2.0–4.0 in those with DM, 2.5–6.7 in those with metabolic syndrome, and 2.3–5.3 in those with neither metabolic syndrome nor diabetes mellitus. The study shows that CAC screening may improve CVD and CHD risk stratification for metabolic syndrome and diabetes mellitus patients because those with high levels of CAC are at significantly higher risk than those without or with low CAC levels. As CAC is increased in both those with diabetes mellitus and metabolic syndrome,^{15,22,37} the relative progression of CAC becomes clinically important as it may correlate with both future myocardial infarctions,³⁸ as well as all-cause mortality.³⁹

Using MESA, we have additionally shown increased relative risks for incident CAC in those with metabolic syndrome (without diabetes mellitus), diabetes mellitus (without metabolic syndrome), and with both by 1.7, 1.9, and 1.8, respectively, compared to nondiseased individuals.⁴⁰ Figure 4 shows the median annualized percent change in CAC among those with baseline CAC increases with diabetes mellitus or metabolic syndrome status among gender. Adjusted absolute CAC progression predicted CHD in those with metabolic syndrome ($HR=4.1$, $P<0.01$) and diabetes mellitus ($HR=4.9$, $P<0.05$) among those in the highest tertile of CAC increase versus those without increase. Such results provide the stimulus to provide individualized treatment for CHD in those with diabetes, who would benefit most from aggressive treatment.⁴

FIG. 4. Mean absolute progression of coronary artery calcium (CAC) stratified by gender and metabolic syndrome/diabetes mellitus status. MetS, metabolic syndrome; DM, diabetes mellitus. (Wong et al., *JACC Cardiovasc Imaging* 2012;5:358–366.)

Conclusion

Recommendations for use of CAC screening in asymptomatic individuals with diabetes have developed over time. Studies have shown that asymptomatic persons with diabetes have increased prevalence of CAC, increased progression of CAC, and increased incidence of CVD with higher absolute values and greater progression of CAC. Currently there is no definitive study that has shown whether CAC screening (and the resulting changes in medical management that may occur from it) can ultimately improve clinical outcomes, either in an asymptomatic intermediate risk population or in those with diabetes mellitus or metabolic syndrome. Such a trial has also not been done with other imaging modalities, and it remains to be seen whether the health care society will require such trials to be done to continue screening those that physicians already feel may benefit in terms of enhanced risk assessment and/or treatment individualization. Furthermore, additional studies in the future will be needed to address if the CAC screening technique is a cost-efficient mechanism for altering the course of future cardiovascular risk. Nonetheless, diabetic patients are established to be at greater cardiovascular risk than their nondiabetic counterpart, justifying the need to initiate indicated preventive techniques as early as possible. While the cost of CAC screening has decreased and availability increased, with the accumulating data suggesting its clinical utility in those with metabolic syndrome and diabetes mellitus, the utility of other screening modalities such as coronary CT angiography should also be investigated in these populations. However, the expense and availability of coronary CT angiography may make it more difficult to justify except in those with symptoms and with equivocal biomarkers or stress test. CAC screening is accurate and invaluable as a completely noninvasive and relatively time-efficient screening modality without high radiation burden when stratifying patients who may benefit from additional testing or aggressive therapy. Thus, screening of coronary calcium in asymptomatic persons with metabolic syndrome or diabetes mellitus may

more promptly and reliably identify those at highest risk who could benefit from intensified therapeutic options.

Author Disclosure Statement

No competing financial interests exist.

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