Atherosclerosis In The Person With Diabetes

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BACKGROUND

It is well established that persons with diabetes mellitus (DM) have a higher cardiovascular risk than non-diabetics. In diabetic persons, cardiovascular disease (CVD) is a significant cause of morbidity and mortality. This is evident as they tend to have a larger atherosclerotic plaque burden. The National Cholesterol Educational Program’s most recent guidelines recommends that DM be considered a coronary artery disease (CAD) equivalent, owing to the high incidence of atherosclerotic related events, and that anti-atherosclerotic medications be instated routinely at age 40, regardless of symptoms. This is because many diabetics with CAD (or underlying atherosclerosis) may present with atypical symptoms or remain asymptomatic.

The prevalence of significant coronary atherosclerosis in a truly representative population of patients with Type II diabetes has not been identified and it is estimated that 20% of people with diabetes have established CAD. In an asymptomatic and uncomplicated cohort of patients with Type II diabetes, 46.3% had evidence of coronary artery calcification (CAC) reflective of coronary atherosclerosis. The prevalence of CAD (mostly non-obstructive), by multislice CT angiography, was 80% in a group of 70 asymptomatic Type II patients with diabetes. The majority of these patients had diffuse involvement of all three coronary arteries. Even when other variables have been controlled, asymptomatic diabetics have significantly more atherosclerosis than patients without diabetes, and as the calcium score on cardiac CT increases, mortality increases for diabetic patients and remains higher than in patients without diabetes. In asymptomatic patients the prevalence of atherosclerosis and silent ischaemia are high suggesting the need for screening in this population.

Methods to detect atherosclerosis non-invasively:

Atherosclerosis is a systemic disease with a predilection for the aorta and its large branches, coronary arteries, cerebral arteries and arteries in the lower extremities. Persons with atherosclerosis in one arterial site are more likely to have it in other arteries as well. Measurement of subclinical atherosclerosis is currently used as a marker and a predictor of increased risk of clinical CAD.

Computed Tomography Measures of Coronary Artery Calcium (CAC): CAC is a highly sensitive tool to detect and quantify atherosclerosis in asymptomatic patients with both type I and type II diabetes. Monitoring CAC may enable the assessment of the progression and regression of coronary atherosclerosis, risk factors and medical intervention.

CAC and abdominal aortic calcification (AAC) have been shown to be associated with CVD in persons with type II diabetes. CAC is a more reliable indicator of CAD risk than established cardiovascular risk factors, perhaps because measuring atherosclerotic plaque takes into account both known and unknown risk factors and their probable interactions.

Traditional risk factors are of little value in identifying diabetic patients with advanced but asymptomatic CAD. Anand et al. showed that subclinical atherosclerosis measured by CAC is superior to the established cardiovascular risk factors for predicting silent myocardial ischaemia and short term CV outcomes. They also demonstrated that CAC was a better predictor of events than myocardial perfusion scintigraphy (MPS). Asymptomatic diabetics with high calcium scores have a high prevalence of inducible ischaemia on stress imaging. A prospective study revealed 48% of diabetic patients with CAC scores more than 400 had silent ischaemia on single photon emission tomography imaging, and in those with a score more than 1000, 71.4% had inducible ischaemia. Rozanski et al. showed that with a CAC score of <100, myocardial ischaemia was unlikely, but was common in diabetics with CAC >400.

Several outcome studies have been reported. Becker et al. demonstrated that increasing CAC scores were associated with increasing risk of CV events. The study involved 716 asymptomatic diabetic patients observed over 8 years. The hazard ratio (H.R) for diabetic men with a CAC of 0-10 was 1, increasing to 9.5 with a CAC >400 (p<0.0001).
With coronary calcium excluded (score of zero), no cardiac events were seen. Raggi et al. evaluated the prognostic value of CAC screening in 903 asymptomatic diabetic and 9474 non diabetic subjects and concluded that the all-cause mortality is increased in degree to the CAC. Diabetic subjects without CAC have a low short-term risk of death.

The PREdictive value of DiMinutive Colonic adenoma Trial (PREDICT) evaluated CAC score in asymptomatic type II diabetes, concluding that the CAC score is a strong predictor of events, and can further enhance prediction provided by established risk models. A recent Multiethnic Study of Atherosclerosis (MESA) study examining 6635 people aged 45-84 years with and without metabolic syndrome (MetS) and DM revealed that compared to carotid intima-media thickness (CIMT), which did not add more to risk prediction over Framingham risk score (FRS), CAC was a significant predictor of coronary heart disease (CHD) and (CVD). They showed that compared to a CAC score of 0, increasing CAC scores (1-99, 100-399, and >400) were associated with increase in CHD risk of 3.9 to 7.7-fold among those with DM. CIMT was not a significant predictor for CHD events in the same population (HR 2.2, P>0.05). It was consistent with Folsom et al. reports from the overall MESA cohort, where CAC was a stronger predictor of CVD events than was CIMT.

![Figure 1. Patient with diabetes showing extensive coronary calcification](image)

B-Mode Ultrasound Measurement of Carotid Intima - Media Thickness (IMT). Non-invasively visualises the lumen and walls of carotid arteries, aorta and femoral arteries. Studies demonstrated that in patients with diabetes, CIMT is much greater than in non-diabetic subjects of the same age. In type II diabetes the main determinants of IMT were related to both post-glucose insulin levels and abnormal lipoprotein profiles. Treatment of these factors is thought likely to reduce the atherosclerotic burden in diabetics.

Ankle –Brachial Blood pressure Index (ABI): detects subclinical peripheral artery disease (PAD). Population-based studies have demonstrated the relationship of a low ABI with prevalent clinically manifest CVD arising from other arterial territories. However, diabetics are prone to having stiff vessels and the ABI may be falsely elevated in this population.

A study done looking at ABI and CIMT as atherosclerosis markers in Japanese diabetics showed persons with abnormal ABI or CIMT demonstrated higher prevalence of both CHD and CVD than compared to those with normal values, suggesting that measuring an abnormal value for both may indicate significant atherosclerosis.

C reactive protein (CRP) - A recent study by Bowden et al. analysed CRP and subclinical cardiovascular disease in the diabetes heart study. A comparison was done assessing levels of CRP against measurement of CAC and CIMT. Both CAC and CIMT showed positive association but the lack of association of CRP with subclinical CVD measurement was consistent with other reports of studies on relatively healthy subjects evaluating CAC and CIMT, confirming that CRP is not a strong independent predictor of subclinical atherosclerosis. In MESA, CRP was not an independent predictor of future events among the general population (6814 persons) or persons with diabetes.

Preventive management of younger diabetic patients

Life-long therapy with the use of cholesterol reducing medication and aspirin is not universally recommended for diabetic persons < 40 years of age. The National Cholesterol Education Program recommendation specifically states: "For persons with type 2 diabetes, who otherwise are at lower risk, clinical judgment is required as to the intensity of LDL-lowering therapy." Therefore the potential importance of CAC screening in younger patients is that it may lead to appropriate earlier use of aggressive medical therapy with the intent of decreasing morbidity and mortality rates. The La Monte et al. study showed that the presence of CAC was associated with increased (CHD) event rates among study participants who were less than 40 years of age and older than 65 years, and in participants with no baseline CHD risk factors.

Tracking atherosclerosis in persons with diabetes

Serial evaluation of CAC scores may be useful in tracking the progress of coronary atherosclerotic plaque and evaluating the effectiveness of medical treatment for reducing cardiovascular risk. Costacou et al. showed that consistent baseline predictors of CAC progression in persons with long duration type I diabetes were body mass index (BMI), non-high density lipoprotein cholesterol, diabetes duration, and albumin excretion rate, all recognised CAD risk factors. Anand et al. found that CAC progression was frequent, especially in diabetic persons with a pre-existing CAC. Those that showed no baseline CAC, progression was less frequent. They concluded looking at the 398 type II asymptomatic diabetic subjects without prior CAD, baseline CAC severity and suboptimal glyemic control are strong risk factors for CAC progression.

Budoff et al. showed that use of statins in diabetics can slow atherosclerosis (CAC progression), and further evidence from IMT shows that anti-hypertensives and cholesterol-lowering medications can slow atherosclerosis. Another study showed that comprehension about the results of increased CAC was strongly associated with the induction of risk reducing behaviors. Those with an increased CAC were more likely to start medical therapy, adhere to a healthy diet and participate in regular exercise. Those with a CAC of 0 did not exhibit behaviour associated with a greater projected risk, concluding that a score of 0 does not carry false reassurance resulting in negative behavioural outcomes.
**CONCLUSION**

Persons with diabetes, whether symptomatic or asymptomatic, are predisposed to developing atherosclerosis. Atherosclerosis occurs earlier and progresses more rapidly in diabetics than in non-diabetic people. Those at high risk for future MI and CAD can be identified by the determination of CAC independent of accompanying cardiovascular risk factors. Available studies demonstrate that CAC predicts CV events better than either IMT or CRP. In the presence of calcification, aggressive medical therapy should be given and potentially intensified depending on the degree of calcification. Diabetics with a CAC 0 are at a very low risk of developing cardiovascular events (0% in most studies to date) but long term data and prospective evaluation is lacking.

**REFERENCES**


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