



The role of non-invasive imaging in the risk stratification of asymptomatic diabetic subjects

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Received 11 May 2005; revised 30 June 2005; accepted 13 July 2005

KEYWORDS

Diabetes;
Coronary artery disease;
Atherosclerosis;
Non-invasive imaging;
Myocardial ischaemia;
Coronary calcium

Aims Coronary artery disease (CAD) is the leading cause of death in patients with diabetes. Patients often present with advanced and asymptomatic disease. Proposed strategies that may favourably affect CAD risk and outcomes in this patient population include identifying diabetic patients with subclinical disease at high risk of future cardiac events. The purpose of this article was to review the role of both atherosclerosis imaging tests (coronary calcium imaging and high-resolution ultrasound assessment of carotid intima-media thickness) and functional imaging techniques [stress echocardiography and radionuclide myocardial perfusion imaging (MPI)] in the diagnostic and prognostic evaluation of asymptomatic diabetic subjects.

Methods and results We identified studies using MEDLINE searches (1966 to April 2005) and by reviewing reference lists. A comprehensive list of search terms was applied. All stress echocardiography and MPI studies evaluating the prevalence and/or prognostic value of myocardial ischaemia ($n = 19$) and coronary calcium imaging studies ($n = 2$) evaluating the prognostic value of subclinical atherosclerosis in diabetic patients were included.

Conclusion Asymptomatic myocardial ischaemia can be detected in a significant proportion of diabetic subjects by non-invasive imaging tests such as MPI and stress echocardiography. The results of ongoing and future studies may be helpful in guiding the selection of asymptomatic diabetic subjects to undergo non-invasive imaging, establishing the cost-effectiveness of various testing strategies and their impact on prognosis.

Introduction

Diabetes mellitus is a major source of cardiovascular morbidity and mortality in developed and developing countries. Currently, the worldwide prevalence of diabetes is estimated to be around 194 million. This figure is expected to rise to almost 333 million by the year 2025.¹ Type 2 diabetes constitutes 85–95% of all patients with diabetes. Cardiovascular disease is the cause of death in 65–70% of persons with diabetes.² In general, diabetic patients have more extensive atherosclerosis with a higher prevalence of multi-vessel coronary artery disease (CAD), frequent silent myocardial ischaemia, and infarction with a higher cardiac event rate when compared with non-diabetic patients.^{3–5} Some studies have even suggested that diabetic patients without CAD have the same risk for future cardiac death as non-diabetic patients with established CAD.⁶ Even once CAD becomes manifest

clinically, diabetic patients continue to have a worse prognosis compared with non-diabetic patients both acutely after the event and during long-term follow-up.^{5,7}

Although there has been a marked decline in mortality because of CAD in the overall population in the past three decades, reducing CAD mortality in patients with diabetes has proved exceptionally difficult. Non-diabetic men have experienced a 36% decline in cardiovascular mortality when compared with a 13% decline for diabetic men. Similarly, cardiovascular mortality has decreased 27% in non-diabetic women but increased 23% in diabetic women.⁸ Proposed strategies that may favourably affect CAD risk and outcomes in this patient population include identifying diabetic patients with subclinical disease at high risk of future cardiac events. Such subjects are likely to be good candidates for aggressive risk factor management. Accordingly, the purpose of this review is to outline the evidence supporting how modern imaging methods can be used to identify asymptomatic type 2 diabetic subjects with subclinical CAD.

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The necessity for accurate cardiovascular risk stratification in diabetics: symptom/risk factor based approach vs. detection of subclinical disease

Evidence from autopsy studies suggest that almost 75% of diabetic decedents without clinical CAD have high-grade coronary atherosclerosis.³ At the same time, diabetic patients are less likely to experience symptomatic disease. The Framingham study reported that the incidence of painless myocardial infarction was higher in diabetic patients when compared with non-diabetics.⁹ Angina is three-fold less common in diabetics when compared with non-diabetics with the same degree of ST-segment changes on exercise electrocardiography.⁴ The prevalence of myocardial perfusion abnormalities is the same in diabetic patients without known CAD and non-diabetic patients with known CAD.¹⁰ Cardiac autonomic neuropathy altered neural processing in the peripheral and central nervous systems, and increased levels of endogenous endorphins have been proposed as possible mechanisms contributing to silent myocardial ischaemia in diabetic patients.¹¹ Taken together, these observations imply that symptoms are not a reliable means of identifying diabetic patients with CAD.

Although established CAD risk factors remain important causative factors for atherosclerosis in patients with diabetes, data from longitudinal studies suggest that once subclinical atherosclerosis has developed, it becomes the primary determinant of the risk of clinical CAD.¹² Furthermore, given that atherosclerosis is the pathologic lesion underlying most clinical manifestations of cardiovascular disease, its direct quantification by imaging tests could provide an integrated measure of the pathological effects of cardiovascular risk factors, both known and unknown. Conceptually, imaging tests can be divided into those which define the anatomic extent of atherosclerotic disease and those which define its physiological consequences. The former category ('atherosclerosis imaging tests') includes coronary calcium imaging and high-resolution ultrasound assessment of carotid intima-media thickness (c-IMT). The latter ('functional imaging tests') includes stress echocardiography and myocardial perfusion imaging (MPI), which form the cornerstone of non-invasive evaluation of obstructive CAD.

Atherosclerosis imaging

Rupture or erosion of vulnerable but haemodynamically insignificant plaque underlies 70% of acute coronary syndromes.¹³ Consequently, there is a strong argument for using atherosclerosis imaging (either directly in the coronary arteries or in the carotid arteries as a surrogate) to evaluate the risk of incident CAD.

Carotid intima-media imaging by ultrasound

There is considerable evidence that c-IMT is a surrogate marker of subclinical CAD in the general population. The same appears to be true in diabetic patients. Several cross-sectional studies have shown that c-IMT is increased in diabetic subjects when compared with non-diabetic subjects.¹⁴ The Insulin Resistance and Atherosclerosis Study (IRAS) showed that diabetic subjects without known CAD

have similar common and internal c-IMT when compared with non-diabetic subjects with CAD. This study also showed that the progression of c-IMT was 25% greater in diabetic subjects when compared with non-diabetic subjects, even after adjusting for established cardiovascular risk factors. Furthermore, this study noted that progression was most rapid in individuals with undiagnosed diabetes, implying that poor glycaemic control may accelerate subclinical atherosclerosis.¹⁵ Similarly, the Epidemiology of Diabetes Interventions and Complications study shows that intensive insulin therapy in type 1 diabetes slows progression of c-IMT when compared with conventional therapy, implying that improved glycaemic control is responsible.¹⁶

However, there are several important issues that must be addressed before measurements of c-IMT can be recommended for general clinical use. First, there are no standardized protocols for assessing c-IMT. Different laboratories employ different scanning protocols, methods of measuring carotid arterial thickness, ways of summarizing the measurements gathered, and instrumentation. Consequently, there are no widely accepted age- and gender-adjusted reference ranges. Secondly, although in expert hands the inter- and intra-observer variabilities of c-IMT measurements may be low, it is an operator-dependent technique. As small variations in c-IMT can transform the interpretation of clinical risk, these considerations are extremely pertinent.

Coronary calcium imaging by computed tomography

Histological, sonographic, and fluoroscopic studies show that the extent of coronary calcification is closely associated with total coronary artery atherosclerotic plaque burden.^{17,18} Coronary calcification is also closely associated with coronary artery plaque on a site-by-site basis.¹⁸ Many studies have shown that coronary artery calcium (CAC) scores predict incident CAD in the general population.^{19,20} The radiation dose for coronary calcium scoring ranges from 1 to 1.3 mSv for electron beam computed tomography (EBCT) and 1.5–6.2 mSv for multi-slice computed tomography (MSCT).²¹ No prior patient preparation or interruption of medication is generally required for coronary calcium imaging.

In a prospective study of 269 diabetic (mean age 66 ± 7 ; 81% male) and 1043 non-diabetic patients, Qu *et al.*²² showed that CAC was more prevalent in diabetic patients. Although diabetic patients with CAC were four times as likely to suffer a cardiovascular event when compared with non-diabetic patients, the prognostic value of CAC was weaker in diabetic patients when compared with non-diabetics. However, a recent, large observational study by Raggi *et al.*,²³ comprising 903 diabetic subjects (mean age 57 ± 10 years; 57% male) and 9474 non-diabetic low-to-intermediate risk subjects, demonstrates that diabetic subjects with no detectable CAC had an excellent 5-year survival, which was not significantly different to non-diabetics (98.8 and 99.4%, respectively, corresponding to an annual mortality rate of 0.36 and 0.12%; $P = 0.05$), implying that coronary calcium continues to be a robust prognostic marker even in the presence of type 2 diabetes. The study also showed that all-cause mortality in asymptomatic patients with diabetes increased in proportion to

their baseline CAC scores. Consequently, a risk stratification approach using the combination of CAC scores and clinical variables was superior to each individually. The differing results observed in the aforementioned trials may be partly attributed to patient selection criteria and the scanning protocols utilized. Qu *et al.*²² studied a smaller cohort of mostly high-risk male diabetic subjects who were on average 10 years older and used a scanning protocol with a lower sensitivity for detection of CAC. However, it is possible that other factors specific to patients with diabetes, such as rapid progression of atherosclerosis, autonomic dysfunction, increased tendency for plaque rupture, and pro-thrombotic tendency, may also influence the likelihood of cardiovascular events, and thereby attenuate the relationship between calcified plaque burden and cardiovascular risk. Furthermore, although atherosclerotic plaque is an intimal lesion, patients with diabetes are more likely to have vascular calcification of the arterial media (Mönckeberg's sclerosis), which is less clearly related to cardiovascular risk.²⁴ However, Mönckeberg's sclerosis has not been reported to occur in the coronary arteries, allowing one to conclude that when calcification is seen in the coronary arteries, it is almost certainly associated with intimal plaque.²⁴

Functional imaging

Stress echocardiography and MPI are well-established functional imaging techniques for assessing patients with suspected CAD and for evaluating prognosis in patients with known CAD.^{25,26}

Stress echocardiography

Although the prognostic value of stress echocardiography is well established in the general population,²⁷ its role in

diabetic patients is much less defined. Six studies^{28–33} have used stress echocardiography to assess prognosis in patients with diabetes (*Table 1*) and have included both symptomatic and asymptomatic subjects and subjects with known CAD. Stress protocols have included physical exercise and pharmacological stress (with dobutamine or dipyridamole). Approximately 5–20% of patients will have a suboptimal test because of either a poor acoustic window or inability to reach an adequate exercise load or poor chronotropic response to dobutamine. All of these studies report that stress echocardiography has incremental prognostic power when compared with the established cardiovascular risk factors.

However, several important features can be abstracted from the aforementioned studies. First, a normal stress echocardiogram is not as reassuring in patients with diabetes as in non-diabetics.²⁸ For example, the annual hard event rate associated with a normal study ranges from 1.5 to 6% in diabetics, whereas the corresponding rate in non-diabetic patients ranges from 0.6 to 2.7%.^{27–29} Secondly, event rates rise sharply after the second year. Elhendy *et al.*²⁹ reported that event rates were 0% in diabetic patients with a normal stress echocardiogram for the first 2 years, but rose to 1.8, 2.6, and 3.2% for the third through fifth years, respectively. Thus, the 'warranty period' of a normal study is less in diabetic subjects. These findings have significant implications because they indicate that stress echocardiography cannot be used to identify a very low-risk cohort of diabetic patients.

However, stress echocardiography can accurately identify a very high-risk cohort. Elhendy *et al.*²⁹ showed that the event rate in diabetic patients with inducible ischaemia in a single vascular territory was similar to that of patients with a normal stress echocardiogram (7.6 and 8.7% at 5 years, respectively). In contrast, those with ischaemia in two or three vascular territories had a substantially higher mortality (32.8% at 5 years).

Table 1 Stress echocardiography studies

References	Number of patients	Patient characteristics and age (years)	Mean follow-up (months)	Type of stress	Abnormal stress echo cardiography (%)	Annual event rate (death + MI) (%)
Kamalesh <i>et al.</i> ²⁸	89 DM 144 non DM	Known or suspected CAD, 64 ± 11	25	Exercise/ dobutamine	0	DM: 6 Non-DM: 2.7
Elhendy <i>et al.</i> ²⁹	563	Known or suspected CAD, 64 ± 11	36 ^a	Exercise	60	Normal SE: 1.5 Abnormal SE: 4.7
Bigi <i>et al.</i> ³⁰	259	Known or suspected CAD, 64 ± 8	24 ± 22	Dobutamine/ dipyridamole	Positive SE: 42 ^b	Negative SE: 3 Positive SE: 7.9 ^b
Marwick <i>et al.</i> ³¹	937	Known or suspected CAD, 59 ± 13	3.9 ± 2.3 years	Exercise/dobutamine	40	Normal SE: 4 Abnormal SE: ~10
D'Andrea <i>et al.</i> ³²	325	Known or suspected CAD, 59 ± 9	34	Dobutamine/ dipyridamole	Positive SE ^b : 46	Negative SE: 6.4 Positive SE: 13.8 ^b
Sozzi <i>et al.</i> ³³	396	Suspected CAD, unable to exercise, 61 ± 11	36 ^a	Dobutamine	82	Normal SE: 4.8 Abnormal SE: 6.2

DM, diabetes mellitus, SE, stress echocardiogram.

^aMedian follow-up.

^bPositive SE signifies the presence of reversible ischaemia on stress echocardiography.

Myocardial perfusion imaging

It is recognized that perfusion abnormalities precede abnormalities in systolic function in the ischaemic cascade.³⁴ Accordingly, head-to-head comparisons between MPI and stress echocardiography have shown a higher sensitivity for MPI for the detection of multi-vessel and single-vessel CAD.³⁵ In pooled studies including both diabetic and non-diabetic patients and symptomatic as well as asymptomatic patients, an unequivocally normal stress MPI has been associated with a cardiac event rate of <1% per year.³⁶ With abnormal stress MPI studies, the extent and severity of myocardial ischaemia strongly predicts short- and long-term risks of coronary events.²⁶ Felsher *et al.*³⁷ were the first to confirm that this same pattern is found in diabetics and that an abnormal stress MPI predicts a poor cardiac prognosis. At least eight subsequent studies have confirmed that event rates vary with the size of perfusion defect^{38–45} and that dipyridamole and dobutamine-atropine stress protocols can substitute exercise (Table 2). Vanzetto *et al.*³⁸ showed that in diabetics evaluated with thallium-201 MPI, the annual hard event rate was 5.2% in patients with two or less than two perfusion defects but 23.26% in patients with two or more than two defects. Similarly, in a single-centre retrospective study using dual-isotope MPI (rest thallium-201/stress technetium-99 m sestamibi), with exercise or adenosine pharmacological testing, Kang *et al.*³⁹ showed that hard cardiac event rates in diabetics with mild, moderate, and severe perfusion defects were 1–2, 3–4, and >7% per year, respectively. In general, diabetic patients had an approximately two-fold higher hard event rate when compared with non-diabetic patients (4.3 vs. 2.3%; $P < 0.001$). Giri *et al.*⁴⁰ also showed that despite the higher rates of revascularization, diabetic patients had an almost two-fold increase in the hard cardiac event rate (8.6%) when compared with non-diabetics (4.5%). However, similar to the stress echocardiography trials, the earlier-mentioned studies also demonstrate that a normal MPI is less reassuring in diabetics than in non-diabetics, providing a limited 'warranty period' of 2 years at most.⁴⁶

Three studies have examined the relationship between myocardial perfusion abnormalities and prognosis in asymptomatic diabetic patients. De Lorenzo *et al.*⁴² showed that an abnormal MPI significantly increased the annual incidence of hard cardiovascular events (9%) when compared with a normal MPI (2%). Furthermore, in this study, established risk factors were related neither to the extent of abnormalities on MPI nor to the cardiovascular events. In a subsequent larger study comprising 1737 patients, Zellweger *et al.*⁴³ showed that frequency of abnormal MPI (39%) and annual critical event rate in asymptomatic diabetics was comparable to that of diabetic patients with angina (44%). Similarly, Miller *et al.*¹⁰ studied 27 165 patients, of whom 4736 were diabetic, and found that the prevalence of an abnormal MPS was the same in asymptomatic and symptomatic diabetic patients (58.6 vs. 59.5%); this was significantly higher than in asymptomatic non-diabetic (46.2%) and symptomatic non-diabetic (44.4%) patients. A subsequent follow-up study confirmed the increased prevalence of severe angiographic CAD and mortality in those diabetic patients with severe asymptomatic ischaemia.⁴⁴

The only large prospectively designed study of asymptomatic ischaemia in unselected type 2 diabetics is the

ongoing Detection of Ischaemia in Asymptomatic Diabetics (DIAD) study by Wackers *et al.*⁴⁷ This multi-centre study included 522 patients (aged 50–75; mean HbA_{1c} = 7.1 ± 1.5) with no prior CAD. Even in this comparatively low-risk population, there was a 22% prevalence of an abnormal MPI study, with marked perfusion abnormalities occurring in 6% of patients. This study also demonstrated that traditional cardiovascular risk factors and novel biomarkers (hs-C-reactive protein, homocysteine, lipid subfractions, and plasminogen activator inhibitor-1) were not predictive of abnormal myocardial perfusion. In comparison, male gender, duration of diabetes, and the presence of cardiac autonomic dysfunction were strong predictors of ischaemia. This cohort of diabetic patients is being followed-up, but results of follow-up are not expected before 2006.

The safety of MPI is well established. Although transient minor side effects are frequent with pharmacological stress MPI, the incidence of serious adverse events is rare.⁴⁸ Beta-blockers, calcium channel blockers, and nitrates should be stopped 24 h prior to a diagnostic MPI, because these drugs may diminish the sensitivity for detection of myocardial ischaemia. The radiation exposure to the patient varies between 10 mSv for a 1000 MBq 99 mTc tetrofosmin study and 18 mSv for an 80 MBq thallium study.⁴⁸

Although MPI is more expensive than exercise ECG, it has been demonstrated that its higher accuracy and lower non-diagnostic rate combined with the ability to provide additional prognostic information results make it a more cost-effective initial test in patients with suspected CAD or stable angina.^{49,50} Very few studies have directly compared the cost-effectiveness of MPI and stress echocardiography. Lee *et al.*⁵¹ showed that in view of the lower event rate with a negative MPI, the more expensive MPI strategy was more cost-effective than the less expensive stress echocardiography strategy.

Comparison with non-imaging tests

Other techniques that have been used to detect asymptomatic myocardial ischaemia in diabetic patients include exercise electrocardiography and continuous ambulatory ST-segment Holter monitoring.

Exercise electrocardiography

A negative exercise electrocardiogram portends a good prognosis in patients able to achieve adequate levels of exercise stress.⁵² However, the high prevalence of obesity, degenerative joint disease, poor physical fitness, and peripheral vascular disease, together with left ventricular hypertrophy, electrocardiographic conduction abnormalities, and chronotropic incompetence associated with diabetic cardiac autonomic neuropathy, render it difficult to achieve an adequate workload and also markedly diminish the specificity for detecting a significant coronary artery stenosis as well as increasing the false-positive rate.

Ambulatory ST-segment monitoring

Ambulatory ST-segment monitoring was historically the earliest method by which asymptomatic myocardial ischaemia was recognized, and several studies have shown that in patients with known CAD, the test provides prognostic information.⁵³ However, its prognostic value has not been studied

Table 2 Myocardial perfusion imaging studies

References	Number of patients	Patient characteristics and age (years)	Mean follow-up (months)	Abnormal MPI (%)	Stress type and tracer	Annual event rates (death + myocardial infarction) (%)
<i>Retrospective studies</i>						
Felsher <i>et al.</i> ³⁷	123	Suspected CAD, 56 ± 8	36	56	Exercise, thallium	Normal MPI: 1.25 Abnormal MPI: 4.8
Vanzetto <i>et al.</i> ³⁸	158	High-risk patients with known or suspected CAD, 63 ± 9	23 ± 17	Abn MPI: 56 moderate/ severe Abn MPI: 11	Exercise or dipyridamole, thallium	Normal/mild Abn MPI: 5.2 Moderate/severe Abn MPI: 23.3
Kang <i>et al.</i> ³⁹	1271 DM 5862 non-DM	Known or suspected CAD, 67 ± 11	24 ± 8	Multi-vessel disease: DM—25; non-DM—16	Exercise or adenosine, ²⁰¹ Tl + ^{99m} Tc-MIBI	DM: 4.3 (Normal MPI: 1–2; moderate/severe Abn MPI > 7); Non-DM: 2.3
Schinkel <i>et al.</i> ⁴¹	207	Known or suspected CAD, 61 ± 10	4.1 ± 2.4 years	Abn MPI: 64	Dobutamine, ^{99m} Tc-MIBI	Normal MPI: 0.7 ^a Abn MPI: 6.6 ^a
Giri <i>et al.</i> ⁴⁰	929 DM 3826 non-DM	Known or suspected CAD, 65 ± 11	2.5 ± 1.5 years	Abn MPI: DM—48; Non-DM—42	Exercise/adenosine, ²⁰¹ Tl + ^{99m} Tc-MIBI	DM: 3.4 (Normal MPI: 3; multi-vessel ischaemia: 8.9) Non-DM: 1.8
DeLorenzo <i>et al.</i> ⁴²	180	Asymptomatic with no previous CAD, 61 ± 10	36 ± 18	Abn MPI: 26	Exercise/dipyridamole, ^{99m} Tc-MIBI	Normal MPI: 2 Abn MPI: 9
Cosson <i>et al.</i> ⁴⁵	362	Asymptomatic, no previous CAD, 58 ± 9	41 ± 24	Abn MPI: 33.4	Exercise/dipyridamole/ ²⁰¹ Tl	Normal MPI: 1.2 Abn MPI: 9.4
Zellweger <i>et al.</i> ⁴³	1737	No previous CAD; 47% asymptomatic; 44% angina; 9% SOB; 60 ± 13	24	Abn MPI: asymptomatic—39, angina—44, SOB—51	Exercise/adenosine, ²⁰¹ Tl + ^{99m} Tc-MIBI	Asymptomatic: normal MPI—2.2; Abn MPI—3.4 Angina: normal MPI—3.2; Abn MPI—5.6 SOB: normal—7.7; Abn—13.2
Miller <i>et al.</i> ¹⁰	4736 DM 22 429 non-DM	No previous CAD DM (Symptomatic: 63%)	70 ± 42	DM Asymptomatic: 58.6; Symptomatic: 59.5	Exercise or pharmacologic stress	Low risk MPI: 3.6 Intermediate risk MPI: 5 High-risk MPI: 5.9
Rajagopalan <i>et al.</i> ⁴⁴		Non-DM (Symptomatic: 72%) 60 ± 14		Non-DM Asymptomatic: 46.2; Symptomatic: 44.4.	²⁰¹ Tl or ^{99m} Tc-MIBI	
<i>Completed/ongoing prospective studies</i>						
MiSAD 2004 ⁵⁹	925	Asymptomatic low-risk, 54 ± 6	60	Abn MPI: 6.4	Exercise	Abn MPI: 0.2
DIAD 2004 ⁴⁷	522	Asymptomatic low-risk, 61 ± 7	Ongoing	Abn MPI: 22 Moderate/ severe Abn: 6	Exercise + adenosine ^{99m} Tc-MIBI	NA
Anand <i>et al.</i> 2004 ⁶⁰	400	Asymptomatic low-risk, 53 ± 8	Ongoing	EBCT data (%) CAC ≤ 10: 55 CAC 11–100: 20 CAC > 100: 25 MPI data (%) (CAC > 100) Abn MPI: 48 Markedly Abn MPI: 20	Exercise + dipyridamole ^{99m} Tc-MIBI	NA

MPI, myocardial perfusion imaging; Abn, abnormality; DM, diabetes mellitus; MIBI, sestamibi; SOB, shortness of breath on exertion; EBCT, electron beam computed tomography; MiSAD, Milan study of atherosclerosis in diabetes.

^aMortality rate only.

specifically in diabetic patients. The Asymptomatic Cardiac Ischaemia Pilot (ACIP) study, which evaluated silent ST-segment changes in patients with angiographically documented CAD, showed that diabetic patients had less ambulatory ST-segment changes despite the more severe CAD.⁵⁴ In general, this technique has never gained widespread popularity, and there are currently no guidelines advocating its use for screening asymptomatic diabetic patients.

Combination testing: synergisms between functional testing and atherosclerosis imaging tests

Previous studies in patients with low-risk treadmill scores have shown that incorporating a clinical score into a testing strategy can enhance the yield of MPI and improve cost-effectiveness, but specific data on the use of clinical risk models to improve the yield of detection of CAD in asymptomatic diabetic subjects is lacking.⁵⁵ The ADA consensus guidelines recommend screening for CAD in those diabetic patients with an abnormal resting electrocardiogram indicative of myocardial infarction, carotid or peripheral arterial disease, symptoms suspicious of CAD, or presence of two or more than two cardiovascular risk factors.⁵⁶ The emerging evidence supports the appropriateness of functional testing in patients with a greater likelihood of CAD (abnormal resting electrocardiogram, carotid or peripheral vascular disease, and symptoms of dyspnoea)^{43,44} and also suggests that the yield of functional tests such as MPI in lower risk asymptomatic diabetic patients is likely to be low.⁴⁷ The DIAD trial also showed that the rate of high-risk scans was similar in patients with two or more than two risk factors vs. those with less than two risk factors.

Other criteria that have been proposed to identify asymptomatic diabetic patients who may benefit from MPI include presence of microvascular disease,⁵⁷ age ≥ 65 , duration of diabetes >10 years,⁵⁸ and abnormal exercise ECG.⁵⁹ An alternative and more recently evolving strategy for enhancing the clinical- and cost-effectiveness of MPI in asymptomatic diabetics is to perform CAC imaging to identify those patients with subclinical CAD. Using this approach, Anand *et al.*⁶⁰ have prospectively evaluated 400 asymptomatic diabetics (age 30–65) without known CAD or macrovascular disease. MPI was performed in all patients with moderate/severe subclinical atherosclerosis (CAC score >100 Agatston units) and a random sample ($n = 50$) of those without (CAC score ≤ 100) moderate/severe subclinical atherosclerosis. Coronary calcification was absent/insignificant (CAC score ≤ 10) in 55% of patients, whereas mild (11–100), moderate (101–400), and severe CAC scores (>400) were observed in 20, 13, and 12% of patients, respectively. MPI was normal in those patients with CAC score ≤ 10 . In contrast, 48% of those with CAC score >100 had abnormal MPI (12% of the overall study population), with 20% having high-risk MPI scans (5% of the overall study population). In a multi-variate logistic regression model, the CAC score was the strongest predictor of myocardial ischaemia, followed by male gender and the duration of diabetes. This strategy allowed the authors to identify proportionately as many asymptomatic diabetic patients with high-risk scans as the DIAD study (5 vs. 6%) while performing only a quarter as many MPI studies as DIAD.

Conclusion

In conclusion, asymptomatic CAD is common in patients with type 2 diabetes. Its prevalence ranges from $\sim 20\%$ in uncomplicated diabetic patients to $>50\%$ in those with complications (abnormal resting electrocardiogram, carotid or peripheral vascular disease, and symptoms of dyspnoea). Conventional risk factors are of limited value in identifying type 2 diabetic patients with advanced but asymptomatic CAD. Stress echocardiography is a useful non-invasive method of risk stratification; however, there is limited experience with this technology in the diabetic population. Recently, accumulated data support both the diagnostic and prognostic values of MPI in diabetic patients. Although the yield of MPI in asymptomatic diabetic patients with complications is excellent, it is unlikely to be cost-effective if used indiscriminately to screen all asymptomatic diabetic patients. Consequently, there is growing interest in the sequential use of atherosclerosis imaging tests (EBCT/MSCT) to assess CAC and MPI in asymptomatic diabetics. This strategy could provide excellent discrimination of a low-risk population (no CAC), a moderate-risk population with evidence of non-obstructive CAD (with CAC and normal MPI), which warrants aggressive risk factor management, and a high-risk population with obstructive CAD (with moderate-severe CAC and abnormal MPI), which may benefit from invasive angiography and revascularization. Initial studies utilizing this strategy have revealed promising results, but the clinical and cost-effectiveness of such approaches need to be evaluated in future prospective trials.

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