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Subclinical cardiovascular disease in type 2 diabetes mellitus: To screen or not to screen

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Abstract

The prevalence of type 2 diabetes mellitus (T2DM) has risen in recent decades, and cardiovascular disease remains the leading cause of death in this population. Several clinical trials have demonstrated the benefit of tight control of risk factors on the incidence and mortality of cardiovascular disease. However, in clinical practice, few patients achieve the therapeutic goals. The current diagnostic procedures for subclinical cardiovascular disease in T2DM patients have not been shown to improve prognosis or mortality, probably because they do not categorize cardiovascular risk. Thus, clinical practice guidelines do not systematically recommend screening for subclinical atherosclerosis in these patients, although it is known that patients with extracoronary atherosclerosis, microangiopathy and poorly-controlled cardiovascular risk factors are at high risk for cardiovascular disease. Improvements in the reliability of diagnostic tests, with fewer side effects and better cost efficiency, may better help to stratify cardiovascular risk in this group of patients, and further evaluation on this topic should be considered.

Key words: Cardiovascular disease; Type 2 diabetes mellitus; Cardiovascular risk

Core tip: The prevalence of type 2 diabetes mellitus (T2DM) has risen in recent decades, and cardiovascular disease remains the leading cause of death in this population. Several clinical trials have demonstrated the benefit of tight control of risk factors on the incidence and mortality of cardiovascular disease. The current diagnostic procedures for subclinical cardiovascular disease in T2DM patients have not been shown to improve prognosis or mortality, probably because they do not categorize cardiovascular risk. Improvements in the reliability of diagnostic tests, with fewer side effects and better cost efficiency, may better help to stratify cardiovascular risk in this group of patients, and further evaluation on this topic should be considered.

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INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is rising dramatically in industrialized countries[1]. According to the National Health and Nutritional Examination Survey, 19.7 million Americans had diagnosed diabetes, representing 8.3% of the adult population, and an additional 8.2 million were undiagnosed[2]. In Europe, population studies report a T2DM prevalence of 13.8%, although many cases are undiagnosed[3]. Cardiovascular

disease is the leading cause of mortality and morbidity in this specific population and is responsible for most of the increased health care costs[4]. Traditionally, T2DM has been considered a coronary risk equivalent[5]. Although this topic is the subject of debate[6-10], there is unanimous agreement that strict control of cardiovascular risk factors in T2DM patients reduces the incidence of cardiovascular disease[11].

T2DM is often associated with several other cardiovascular risk factors. Therefore, cardiovascular prevention in these patients should be multifactorial. Studies assessing the impact of multifactorial risk factor intervention obtained substantial improvements compared with those evaluating single risk factor interventions[12,13].

The effectiveness of a multifactorial intervention was demonstrated in the Steno-2 study, where patients with T2DM and microalbuminuria were randomized to intensive or conventional multifactorial intervention over 7.8 years. A target-driven, long-term, intensified intervention aimed at multiple risk factors, particularly through low-density lipoprotein (LDL) cholesterol lowering and blood pressure control, achieved a 50% reduction in vascular events in this specific population[11].

In addition, many of the benefits of controlling risk factors in patients with T2DM disappear when control ceases, at a similar rate as the benefits are obtained[13-15]. For example, in the UKPDS study, patients with newly-diagnosed T2DM who presented an increase in blood pressure levels during follow-up almost immediately had an increase in the risk of cardiovascular episodes[14]. Furthermore, intravascular ultrasound studies have shown that coronary atherosclerosis regression is more difficult to attain in patients with diabetes than in those without[16], and therefore prevention and early treatment of the disease are essential.

The proportion of patients achieving therapeutic goals in cardiovascular risk factors in clinical practice[17] is very low, mainly in those at high cardiovascular risk, as is the case of patients with T2DM. In this respect, only 28% of T2DM patients reach a blood pressure level < 140/90 mmHg, and 22% less than 130/90 mmHg. Of greater concern is the fact that among known hypertensive patients, 40% did not follow a specific therapeutic strategy. Regarding lipid goals, only 35% of T2DM patients reached on LDL cholesterol concentration below 100 mg/dL. Another alarming fact is that 62% of patients requiring lipid-lowering therapy do not receive pharmacologic treatment[18].

Given the poor risk factor control in clinical practice, it is essential to evaluate strategies for early diagnosis of cardiovascular disease in T2DM patients, especially since the disease is often asymptomatic and has worse prognosis in these subjects than in non-diabetics[19]. A substantial percentage of patients with T2DM have silent myocardial ischemia, and these patients are at greater risk for cardiovascular events[20]. Therefore, the diagnosis of silent coronary disease may help to identify subjects at very high risk and consequently aid the implementation of more aggressive risk reduction strategies in this subgroup of patients.

Recent American Diabetes Association (ADA) guidelines[17] recommend only advanced or invasive cardiac tests in the presence of typical or atypical symptoms or abnormal baseline electrocardiogram (ECG). The rationale for not indicating screening tests in asymptomatic patients at high cardiovascular risk is simply because these patients are already supposed to be being treated to attain strict metabolic goals, although as previously stated, this is not so in the majority of cases[18]. Moreover, we must take into account that technologic progress renders diagnostic techniques increasingly sensitive and less invasive and thus their applicability may vary in the short-mid term. Therefore, we considered it of interest to carry out a review of factors that may predispose to silent cardiovascular disease in T2DM and of diagnostic tests that can be considered in selected cases.

RISK FACTORS FOR CARDIOVASCULAR DISEASE IN T2DM PATIENTS

The expert consensus published by the ADA in 2007[21] defines asymptomatic T2DM patients as being at high risk for myocardial ischemia if they display any of the characteristics shown in Tables 1 and 2.

Evidence of other atherosclerotic vascular disease

Atherosclerosis is a systemic process, and patients with T2DM have a greater atherosclerotic burden at any level of the arterial tree[22,23]; therefore, involvement of only one vascular territory is highly unlikely.

Screening for peripheral arterial disease (PAD) is widely accepted and has been extensively implemented in clinical practice. Thus, patients diagnosed with T2DM require an annual evaluation of their feet, including inspection, examination of sensitivity and palpation of pedal pulses and a questionnaire addressed to identify intermittent claudication. Periodic determination of the ankle-brachial index is also recommended[17]. Ninety per cent of patients with established PAD have coronary atherosclerosis on angiography[24]. In accordance with this observation, the presence of PAD is a predictor of symptomatic coronary artery disease, with a relative risk of 6.6 (95%CI: 2.9-15)[25]. Studies in patients who have suffered a stroke showed an 18%-38% prevalence of asymptomatic heart disease[26-28]. Thus, patients with extra-coronary atherosclerosis are at high risk of coronary involvement, and therefore screening strategies should be considered along with aggressive treatment of cardiovascular risk factors.

Microalbuminuria

Microalbuminuria and chronic kidney disease are clearly associated with cardiovascular disease. The incidence of coronary heart disease or cardiac death 5 years after kidney failure diagnosis is 40%[29], and the age-adjusted hazard ratio for the development of coronary heart dis-

Table 1 Clinical characteristics of diabetic patients with increased risk of coronary heart disease

Evidence of other atherosclerotic vascular disease
Renal disease
Abnormal resting electrocardiogram
Diabetes complications including autonomic neuropathy
Age > 45 yr
Male sex
Traditional risk factors
Blood pressure
Dyslipidemia
Smoking
Inactivity
Abdominal obesity
Novel cardiac risk factors
C-reactive protein
Homocysteine
Lipoprotein(a)

ease is 1.66 (95%CI: 1.24-1.92) when microalbuminuria is present, and may rise to 2.84 (95%CI: 1.80-4.46) in the case of macroalbuminuria[30]. Although the pathophysiologic explanation for this association is not fully understood, factors associated with the development of microalbuminuria or renal failure, such as a nocturnal rise in blood pressure, increased lipoprotein(a) and homocysteine levels or elevation of inflammatory markers and insulin resistance could play a role.

In any event, multiple observational studies confirmed this association, and thus patients with T2DM and any renal impairment stage should be considered at high risk for asymptomatic coronary artery disease.

ECG

Baseline ECG is a rapid, cheap, simple and accessible method of screening for coronary heart disease. The finding of pathologic Q waves, ST-segment changes or left bundle branch block requires further testing to evaluate coronary artery disease in these patients, who should no longer be classified as "asymptomatic". Unfortunately, the number of cases detected with a baseline ECG alone is very low.

The exercise stress test is widely available in most hospitals and provides useful information regarding the ST-segment abnormalities suggestive of ischemia, although it does not constitute a very powerful marker of prevalent or incident coronary heart disease[28,31]. In patients with T2DM, sensitivity for detecting coronary artery disease is 47% and specificity 81%[32]. In addition to low sensitivity, the exercise stress test may have a limited role in diabetic patients who are typically deconditioned, overweight and possibly ataxic from peripheral neuropathy. In some studies, over 50% of subjects are not able to complete the exercise stress test[33].

Exercise capacity is probably a more relevant factor, since decreased exercise capacity has been linked to increased mortality and cardiovascular events in healthy people[34] and in patients with T2DM, with an odds ratio for coronary heart disease of 2.21 (95%CI: 1.41-3.46)[35].

Table 2 Key messages

Cardiovascular disease is the leading cause of mortality in patients with T2DM
Control of cardiovascular risk factors has been shown to significantly reduce the incidence of cardiovascular disease in T2DM patients
Control level of cardiovascular risk factors in patients with T2DM in clinical practice is poor
Systematic screening of cardiovascular disease has not been shown to improve the prognosis of patients with T2DM
In patients with atypical symptoms or ECG abnormalities, cardiovascular disease screening is warranted

T2DM: Type 2 diabetes mellitus; ECG: Electrocardiogram.

Autonomic neuropathy

Systematic screening for autonomic neuropathy at the time of T2DM diagnosis[17] is recommended; however, it is probably the most underdiagnosed chronic complication of diabetes. It is usually associated with other microvascular complications such as retinopathy or nephropathy, and its major clinical manifestations include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudoriparous dysfunction and hypoglycemia unawareness. In patients with at least one microvascular complication it may be indicated to perform a Valsalva or deep breathing test to assess the presence of cardiac autonomic neuropathy.

Since 1962, it has been assumed that patients with T2DM may have coronary episodes with few or no symptoms, and this has been attributed, at least in part, to possible cardiac denervation due to neuropathy[36]. As previously mentioned, the presence of diabetic autonomic neuropathy is a significant predictor of coronary ischemia[37]; conversely, between 65% and 92% of diabetic patients with myocardial ischemia have autonomic neuropathy[38,39]. Thus, in all T2DM patients, but especially those with other cardiovascular risk factors, it is important to perform routine screening for autonomic neuropathy. Patients with diabetic autonomic neuropathy should undergo cardiac evaluation before initiating more intense physical activity than their usual.

Retinopathy

As in other microangiopathic complications, the presence of retinopathy is also related to the incidence of coronary artery disease in these patients[40,41]. In this regard, after adjusting for age, body mass index, waist circumference, smoking status, lipids, glycosylated hemoglobin, T2DM duration and treatment, the odds ratio for the development of heart disease was 3.75 (95%CI: 2.0-7.4) in men and 3.81 (95%CI: 2.2-7.3) in women with proliferative retinopathy or who had received laser therapy[41]. Statistical significance was also maintained after adjustment for the presence of hypertension and nephropathy. In accordance with these results, the relative risk for the prevalence of symptomatic coronary artery disease in patients with established retinopathy was 1.98 (95%CI: 1.44-2.74)[42].

Traditional risk factors

Typically, patients with T2DM have other classic associated cardiovascular risk factors such as hypertension or dyslipidemia which increase their cardiovascular risk. Therapeutic intervention for these factors contributes to a reduction in vascular risk[11]; however, previous studies demonstrated that in clinical practice it is very difficult to achieve the therapeutic goals for these risk factors recommended by clinical guidelines[18].

On the other hand, previous studies suggested that traditional cardiac risk factors are not associated with abnormal stress tests in asymptomatic diabetic patients[37]. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study concluded that markedly abnormal myocardial perfusion results occurred with equal frequency among patients with two or more and less than two risk factors.Thus, the presence or absence of major cardiovascular risk factors is not a suitable parameter to determine which T2DM patients require screening for asymptomatic coronary artery disease.

SCREENING TESTS

No validated algorithm for the screening of asymptomatic coronary artery disease in T2DM patients has been established. In this respect, choice of the diagnostic procedure will depend on the available scientific evidence, experience in each center and degree of coronary heart disease suspicion, based on the variables mentioned previously. The scientific evidence on the available diagnostic procedures for coronary heart disease: echocardiography, myocardial perfusion imaging and computed tomography for coronary calcium, will be reviewed.

Echocardiography

Resting echocardiogram is not routinely recommended in normotensive patients since its sensitivity and specificity for coronary heart disease detection are low[43]. Severe changes in contractility are more typical of the acute phase of myocardial infarction; moreover, segmental wall abnormalities do not exclusively constitute an ischemic etiology, since they may also be present in patients with non-ischemic heart diseases.

Therefore, resting or stress echocardiography after exercise or dobutamine is not routinely recommended in asymptomatic T2DM patients since no studies have provided data on its benefits. The usefulness of this test is limited to patients with known coronary heart disease to assess reversible ischemia, myocardial viability and risk stratification.

Myocardial perfusion imaging

Single-photon emission computed tomography after exercise or pharmacologic administration is one of the most widely performed screening tests in asymptomatic T2DM patients. The presence of a fixed or reversible perfusion defect is associated with a three-fold increased risk for cardiovascular episodes in patients over 60 years of age[44]. In the DIAD study, participants with type 2 diabetes and no symptoms of CAD were randomly assigned to be screened with adenosine-stress radionuclide myocardial perfusion imaging (MPI) or not to be screened and be prospectively followed for a mean period of 5 years. Patients with a normal/low-risk scan showed an annual cardiovascular event incidence of 0.4% compared with 2.4% in those with a moderate to large perfusion defect[45]. Therefore, if the benefits of this test, which is minimally invasive and of acceptable cost are considered, it should probably be recommended as a first-line diagnostic procedure for silent myocardial ischemia in T2DM patients.

Computed tomography

The use of Multi-detector computed tomography (CT) as a noninvasive assessment of the coronary artery tree is becoming more frequent in addition to angiographic methods in patients with or without T2DM diabetes who have had an acute myocardial infarction.

In asymptomatic patients or in those with mild symptoms the assessment of coronary artery calcium (CAC) is most commonly used, which is a specific marker of atherosclerosis. It can be visualized and measured noninvasively by computed tomography. The quantity of calcium within coronary arteries is typically scored as the area affected on the scan, multiplied by a weighting factor depending on the Hounsfield unit density of the calcium deposits[46]. Given the radiation exposure, careful patient selection for this test is mandatory. Coronary calcification in men < 40 years of age and in women < 50 years of age is infrequent; therefore, CT scanning is generally not recommended in these age groups. Several studies have shown the coronary artery calcium score to be valuable in identifying patients at high risk of inducible myocardial ischemia[47,48]. These studies consistently observed that the likelihood of ischemia in patients with a calcium score $\leqslant 100$ is negligible, whereas the probability of inducible ischemia in those with a score of $\geqslant 400$ is relatively high, even in oligoasymptomatic patients[49].

The presence of CAC is predictive for future cardiovascular events in both asymptomatic diabetic individuals and in nondiabetic subjects. However, for every increase in CAC, there is a greater increase in the mortality rate for diabetic than for nondiabetic subjects[50]. Moreover, diabetic patients with low CAC scores (Agatston Score $\leqslant$ 10) had a low prevalence of inducible myocardial ischemia and a low cardiovascular event rate[49,50]. Therefore, assessment of CAC might be useful in identifying diabetic individuals with a low risk of silent myocardial ischemia. Nevertheless, the use of CAC scoring for risk stratification in asymptomatic diabetic patients is not currently endorsed by the ADA recommendations[17] since there is insufficient evidence of the long-term benefits of early diagnosis.

CAN EARLY DIAGNOSIS OF CARDIOVASCULAR DISEASE IMPROVE CARDIOVASCULAR OUTCOMES?

Despite all this evidence, the possible benefits of early

detection of cardiovascular disease in asymptomatic T2DM patients have not been confirmed in randomized trials. In the DIAD study, the cardiac event rates were not significantly reduced by MPI screening for myocardial ischemia[45]. Additionally, observational studies have shown that, on occasions, alterations in the coronary arteries of these patients can become spontaneously reversible[51]. Finally, studies comparing intensive medical treatment with revascularization procedures showed similar results[52,53]. Therefore, from a clinical and cost-benefit point-of-view, there is not enough evidence at present to recommend screening in these patients.

However, it should be taken into account that these studies were conducted in asymptomatic patients diagnosed early with cardiovascular disease. Therefore, both patient compliance and the intensity of monitoring by the physician were higher than those observed in real life, and this fact may have influenced the results. On the other hand, the DIAD study found a six-fold increased incidence of cardiac events in patients with moderate to large perfusion defects compared to those with a normal/low-risk scan[45], which supports the hypothesis that screening for asymptomatic coronary disease can be useful even though the low prevalence could have influenced the statistical power to demonstrate the possible benefits, including cost-benefit.

DIAGNOSTIC STRATEGY

In the absence of categorical scientific evidence to date, the sequence of tests to be performed in high-risk patients is not established. In this sense, after performing a baseline ECG, the availability of technical and financial resources, and experience in each center can play a role in choosing the most appropriate diagnostic management. Overall, the most common recommendation is to start with a resting ECG and then a myocardial perfusion imaging by SPECT, although the increasingly widespread and cheap use of multi-detector CT can change this trend in the coming years.

CONCLUSION

Systematic screening for cardiovascular disease in asymptomatic patients with T2DM is not recommended since there is insufficient evidence at present that the benefits of early detection outweigh the costs and side effects of the different diagnostic tests. However, as mentioned previously, this situation may change in the near future given the advances in reliability and efficiency of the different diagnostic tests.

Professionals responsible for the medical care of patients with T2DM should focus on optimizing the control of cardiovascular risk factors and evaluate, only in selected cases, the need to further investigate the presence of cardiovascular disease.

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