Silent coronary artery disease in patients with diabetes mellitus

Michael J. Zellweger, Matthias E. Pfisterer

Department of Cardiology, University Hospital Basel, Switzerland

Summary

Coronary artery disease (CAD) represents the leading cause of death in diabetic patients. Silent myocardial ischaemia more often occurs in diabetics than in non-diabetics. It has been well recognised that silent myocardial ischaemia is not different from symptomatic ischaemia with respect to prognosis and adverse events. Asymptomatic high-risk diabetic patients therefore might benefit from routine screening for silent ischaemia and risk stratification; furthermore, silent ischaemia has to be treated accordingly.

Key words: coronary artery disease; diabetes; silent ischaemia; testing strategies

Introduction

The overall prevalence of CAD among patients with diabetes is higher than in non-diabetic patients and may be as high as 55% among patients with diabetes [1]. Furthermore, CAD represents the leading cause of death in patients with diabetes [2, 3]. Most of the published studies present data on type 2 diabetes (more than 90% of all diabetic patients). Less data is available for type 1 diabetes. Therefore, most of our statements also focus on type 2 diabetes.

Since diabetics often present with silent myocardial ischaemia, they lack an important clinical “warning symptom” of their CAD. Data from the Framingham Study suggest that asymptomatic patients with multiple risk factors have an annual cardiac death rate of approximately 3% [2, 4]. These findings from the literature put forward several questions regarding diabetes mellitus and CAD: why is myocardial ischaemia often silent in these patients? How can it be detected? What is its relevance? And how should it be managed? The present review will address these issues and tries to provide guidelines on how to risk stratify and treat these patients.

Silent myocardial ischaemia

Silent myocardial ischaemia is a term usually used to describe myocardial ischaemia in the absence of pain but in the presence of other evidence of ischaemia. Chest pain represents the “tip of the iceberg” in the ischaemic cascade (Figure 1).

In general the prevalence of silent myocardial ischaemia varies depending on the test used for patient screening and on the patient population screened. In a general patient population approximately 10 to 15% of acute myocardial infarctions are silent [5]. After myocardial infarction 20–30% of patients present with silent ischaemia [6]. During balloon inflation (PTCA), up to 38% of patients do not experience chest pain [7, 8]. Furthermore, up to 70% of ischaemic episodes occur silently in patients with known angina [9, 10].

When diabetics and non-diabetics without evidence of CAD are screened for ischaemia, there is a higher incidence of silent ischaemia in the former, 6.4–22% and 2.5–11%, respectively [11–15].
Why silent ischaemia?

The perception of pain during ischaemia may be reduced by several factors in a general population (table 1).

Pain response to ischaemia is often blunted in diabetics. Janand-Delenne et al [16] designed a study to estimate the prevalence of silent myocardial ischaemia and define a high-risk diabetic population by systematically testing diabetic patients without evidence or symptoms of CAD. Silent ischaemia occurred in 21% of them. Patients who presented with silent ischaemia and had CAD at coronary angiography for verification of CAD more often had peripheral macroangiopathy and a higher prevalence of retinopathy. No correlation was found between silent ischaemia and duration of diabetes, HbA1c level, renal status, or cardiovascular risk factors except for family history of CAD.

Nesto et al [17] studied 50 patients with diabetes and 50 patients without diabetes, all with evidence of ischaemia on exercise thallium scintigraphy (= patients who suffer from CAD). The two groups had similar clinical and treadmill characteristics and did not present significant differences in the extent of infarction or ischaemia, but 36 (72%) of patients with diabetes compared with 16 (32%), p =0.01, patients without diabetes had no angina (silent ischaemia). In this study, there was no statistically significant difference when the extent of retinopathy, nephropathy, or peripheral neuropathy of diabetic patients was compared with non-diabetic patients. Weiner et al. [18] evaluated the prevalence of silent ischaemia in a patient population with documented CAD (>70% diameter narrowing of the coronary artery on coronary angiography). The prevalence of silent ischaemia during exercise treadmill tended to be higher in diabetic (n = 113) as compared to non-diabetic (n = 1321) patients, 40 vs 33%, respectively, (p = not significant). Diabetic patients, however, were older, had a higher prevalence of moderate or severe congestive heart failure, more severe CAD, and a shorter exercise capacity.

Langer et al. evaluated the sympathetic innervation in diabetic patients using metaiodobenzylguanidine (MIBG) imaging [19] after having concluded in another study that silent myocardial ischaemia in asymptomatic diabetic men occurred frequently and in association with autonomic dysfunction, suggesting that diabetic neuropathy might be implicated in the mechanism of silent ischaemia [11]. Based on MIBG findings they concluded that in contrast to normal subjects, diabetics had evidence of a significant reduction in MIBG uptake, most likely on the basis of autonomic dysfunction. Furthermore, diabetics with silent myocardial ischaemia had evidence of a diffuse abnormality in MIBG uptake, suggesting that abnormalities in pain perception might be linked to sympathetic denervation. Ambeptiya et al. [20] measured the anginal perceptual threshold in 32 diabetic and 36 non-diabetic control patients, of whom all had typical exertional angina. Anginal perceptual threshold was defined as the time interval from onset of 1mm ST depression to the onset of angina during the exercise test. The anginal perceptual threshold was prolonged in patients with diabetes in association with autonomic and sensory neuropathy (measured as maximal heart rate variability in the Valsalva maneuver during deep breathing and standing; furthermore conduction velocity, and median nerve sensory function was measured in amplitude, conduction velocity, and latency). The authors concluded that the altered perception of myocardial ischaemia might result from damage to the sensory innervation of the heart.

Rosen et al. [21] postulated that silent ischaemia was linked to a central pain perception disorder. They performed PET scanning of the brain to assess regional cerebral blood flow during induction of myocardial ischaemia by dobutamine infusion. They described that, while blood flow augmentation (indicative of enhanced metabolic activity) to the thalamus occurred in patients with silent and symptomatic ischaemia, only those with symptoms had frontal cortical activation. Therefore, abnormal central processing of afferent pain messages might play an important role in silent myocardial ischaemia, too.

Hikita et al.[22] measured β-endorphin levels during exercise and compared diabetics with non-diabetics. The β-endorphin level and pain threshold were significantly higher in non-diabetic patients with silent ischaemia than in diabetics.

In summary there could be several explanations for the different patterns of symptoms in patients with diabetes mellitus, including central

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<th>Factors favouring the development of silent myocardial ischaemia in a general population.</th>
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<td>Lesser severity and duration of ischaemia</td>
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<td>Prior Q-wave myocardial infarction</td>
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<td>Diabetes mellitus</td>
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<td>Coronary collateral flow*</td>
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<td>Autonomic nerve dysfunction</td>
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<td>Psychological characteristics, such as decreased awareness of somatic pain and other body sensations</td>
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<td>Lower depression scores</td>
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<td>Enhanced secretion of endogenous opiates may minimise perception of pain</td>
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* collateral flow may be so marked, that myocardial perfusion becomes normal.
mechanisms such as different thresholds of pain sensitivity, β-endorphin levels, and peripheral mechanisms such as the presence of autonomic neuropathy leading to sensory denervation. The American Diabetes Association (ADA) states in its consensus paper that patients with symptomatic autonomic neuropathy are at increased risk for sudden death; however, they question whether there is enough scientific data to conclude that cardiac autonomic neuropathy contributes to silent ischaemia [23].

Prognostic considerations of silent ischaemia in diabetics

There is limited data about prognosis of diabetic patients with silent myocardial ischaemia. In general, it has been shown that cardiovascular mortality rate is more than doubled in diabetic men and raised more than four-fold in diabetic women, when compared with their non-diabetic counterparts [1, 2]. Weiner et al. demonstrated that when myocardial ischaemia (whether silent or symptomatic) was present during exercise testing, the long term survival among diabetics was worse than that of non-diabetics. In contrast, when ischaemia was absent, there was no higher mortality risk for diabetic patients (figure 2). Importantly, survival rates among patients with silent ischaemia were similar to those of symptomatic patients regardless of diabetic status. These findings are consistent with another survival analysis by Pancholy et al. [26] which demonstrated no significant difference in the event-free survival in 521 patients with symptomatic or silent ischaemia over the time period of 2 years. The extent of perfusion abnormality and history of diabetes were the most important predictors of events. Thus, the limited prognostic data in the literature points to a worse outcome among patients with diabetes mellitus and silent ischaemia compared to patients without ischaemia.

Management of diabetic patients with silent ischaemia

For clinicians, whether and when to examine patients with diabetes who have no clear evidence of CAD poses a difficult question. In type 1 diabetics, who often present without the traditional risk factors, duration of diabetes is the most important predictor of premature CAD. Because type 1 diabetes often starts early in life, CAD can occur as early as in the 3rd and 4th decade of life [23]. In contrast, type 2 patients frequently have many other risk factors and usually present in the 5th or 6th decade of life or later. Often, diabetes is first identified when the patient presents with angina, MI, or heart failure. Furthermore, diabetics with silent ischaemia may present in an atypical manner e.g. with symptoms of easy fatigability, exertional dyspnoea, or indigestion.

The American Diabetes Association (ADA) and the American College of Cardiology (ACC) convened a conference in 1998 to provide guidance to physicians faced with these issues [23]: Indications for testing patients with diabetes are listed in table 2. The most important are resting ECG abnormalities suggestive of CAD, peripheral or carotid occlusive disease and multiple risk factors. The association of peripheral atherosclerosis with CAD justifies cardiac testing since it has been reported that most diabetic patients with lower-extremity occlusive arterial disease die from
cardiovascular disease [23]. A diminished or absent posterior tibial pulse found by palpation, or a femoral bruit on auscultation, have a relatively high sensitivity for identifying lower extremity occlusive arterial disease [27].

In addition, multiple risk factors in the same patient substantially increase the possibility of identifying significant CAD that requires intervention. Regarding autonomic neuropathy, however, there is insufficient data according to the American Diabetes Association to consider this as an independent risk factor for CAD in diabetic patients. As a result, it is not included among the risk factors that warrant cardiac testing. Only if there is definite evidence of cardiac autonomic neuropathy in a patient over age 35 with a history of diabetes for >25 years, cardiac testing should be considered.

In addition, a recent meta-analysis suggested that in patients with type 2 diabetes, an increase in microalbuminuria predicts a high mortality rate from cardiovascular disease [28] and should be included as a reason for further testing. Figure 3 describes the suggested testing algorithm for the asymptomatic diabetic patient. Although a resting ECG with abnormalities suggestive of CAD warrants further testing, the utility of ambulatory monitoring of ECG ST-segment changes to detect CAD in general asymptomatic populations has been disappointing and not cost-effective [23]. Paillole et al have reported sensitivity and specificity of 25% and 88%, respectively for ambulatory ECG monitoring [29]. In addition, in the Asymptomatic Cardiac Ischaemia Pilot (ACIP) study, ambulatory monitoring showed less measurable ischaemia in diabetic patients despite more extensive CAD. The use of such testing is therefore not recommended in asymptomatic diabetic patients [30].

In patients who are able to perform an adequate exercise test (>85% of the age adapted heart rate) and have a normal resting ECG allowing the interpretation of ST-changes during stress, an exercise stress test is the first step in the evaluation of the diabetic patient. However, it has been reported by several authors that patients with diabetes often are not able to exercise sufficiently. Sensitivity and specificity of 75% and 77%, respectively, have been reported for the detection of ischaemia in diabetic patients [29]. Only myocardial perfusion SPECT seems to have a comparable accuracy for the diagnosis of CAD in diabetic and non-diabetic patients [31]. For myocardial perfusion scintigraphy, sensitivities and specificities of 80–90% and 50–86%, respectively, have been described for the detection of ischaemia in diabetic patients [29, 31]. For stress echocardiography similar sensitivities and specificities may be expected as for myocardial perfusion SPECT, if there is a good acoustic window; however “diabetic cardiomyopathy” may limit this test to identify CAD in diabetics. Currently, outcome data in diabetic patients following stress echocardiography is still too limited to define its role as prognostic tool.

Electron beam-computed tomography (EBCT) is a non-invasive technology for evalu-
ing the extent of coronary artery atherosclerosis that relies on the detection of coronary artery calcium. Schurgin et al. used EBCT to evaluate calcium in the coronary arteries of 139 consecutive diabetic patients [32]. Patients with diabetes had a significantly higher calcium score (≥400) compared with the randomly assigned control group. Scores in the range ≥400 have been reported to be highly predictive for abnormal stress myocardial perfusion SPECT and subsequent coronary events [32]. EBCT might be of interest in screening asymptomatic diabetic patients in the future. Whenever a positive test result is obtained, stress imaging techniques should be considered for further testing [23].

Non-invasive testing for asymptomatic coronary disease may be helpful for the identification of diabetic patients with severe coronary obstruction in whom coronary angiography and revascularisation should be considered, although the benefit of percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) in patients with silent ischaemia and diabetes has not yet been proven in large trials. In large studies, few data include diabetic patients free of clinical symptoms of CAD. Further studies are warranted to demonstrate if treatment of asymptomatic diabetic patients will improve survival and quality of life in these patients.

Furthermore, CAD generally is a progressing disease. If the decision is taken to manage a patient medically (optimised therapy of additional risk factors), re-evaluation of myocardial perfusion and left ventricular function should be considered regularly. A repeat exercise stress test should be considered in 3–5 years if clinical status is unchanged. Close follow-up means shorter intervals between evaluation and follow-up stress test, i.e. 1–2 years. Pretest risk is assigned based on the presence of other vascular disease and risk factors.

### Table 3

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<tr>
<th>Pre-test risk</th>
<th>Exercise test results</th>
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<td>high 4–5 risk factors</td>
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<td>moderate 2–3 risk factors</td>
<td>+</td>
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<tr>
<td>low 0–1 risk factors</td>
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* Routine follow-up
++ Close follow-up
+++ Imaging (myocardial perfusion SPECT or stress echo)
++++ Cardiology referral/possible coronary angiography

When initial exercise stress testing is done in asymptomatic diabetic patients, the type of follow-up depends on the pretest risk and degree of abnormality on the stress test. Normal follow-up indicates annual re-evaluation of symptoms and signs of CAD and ECG. A repeat stress test should be considered in 3–5 years if clinical status is unchanged. Close follow-up means shorter intervals between evaluation and follow-up stress test, i.e. 1–2 years. Pretest risk is assigned based on the presence of other vascular disease and risk factors.

### Implications and recommendations

In summary, CAD plays an important role in diabetic patients and determines largely the morbidity and mortality of these patients. Close follow-up therefore is essential. As outlined in figure 3, patients with an abnormal resting ECG or signs of myocardial infarction need stress-imaging (myocardial perfusion SPECT or stress echo). Patients with cerebral or peripheral vascular disease or with more than 2 risk factors in addition to their diabetes should undergo exercise stress testing, if their resting ECG allows interpretation of ischaemic changes during stress testing. Otherwise they also should undergo an imaging stress test. Of note, whenever a patient does not reach >85% of his age adapted heart rate during treadmill/ergometry testing, pharmacological stress testing has to be considered. However, asymptomatic patients with not more than 1 risk factor in addition to diabetes and a normal resting ECG do not need routine stress testing but routine follow-up and risk factor modification. Recommendations for coronary angiography and revascularisation should be individualised and determined by the severity and extent of perfusion defects on myocardial perfusion SPECT and the configuration of the stenoses, the size and distribution of the affected vessels. However, little is known in the literature about improvement in prognosis and quality of life in diabetic patients with silent ischaemia who undergo revascularisation. Optimised medical therapy and risk factor modification are the cornerstones of CAD-therapy and are indispensable also when a patient has undergone revascularisation!

In general, patients who are able to reach more than 10 METs or >200–250 Watts during stress testing have a good prognosis irrespective of ECG changes [33]. A normal perfusion study in diabetic
patients during an adequate treadmill/ergometry test provides a high degree of reassurance that there is minimal chance of advanced coronary disease, ie, these patients have a very good prognosis [4].

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References


Correspondence:
Michael J. Zellweger, MD
Department of Cardiology
University Hospital Petersgraben 4
CH-4031 Basel
e-mail: mzellweger@ubbs.ch
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