Cardiac imaging for risk stratification in asymptomatic diabetes

Scholte, A.J.H.A.

Chapter 5

Prevalence and predictors of an abnormal stress myocardial perfusion study in asymptomatic patients with type 2 diabetes mellitus

AJHA Scholte, JD Schuijf, AV Kharagjitsingh, P Dibbets-Schneider, MPM Stokkel, EE van der Wall, JJ Bax

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Abstract

Purpose

The purpose of this study was to evaluate the prevalence of an abnormal stress myocardial perfusion study in a cohort of truly asymptomatic patients with type 2 diabetes mellitus using myocardial perfusion imaging by means of single photon emission computed tomography (SPECT). Secondly, we determined which clinical characteristics may predict an abnormal stress myocardial perfusion study in this population.

Methods

A total of 120 asymptomatic patients (mean age 53 ± 10 years) with type 2 diabetes mellitus and one or more risk factors for coronary artery disease were prospectively recruited from an outpatient diabetes clinic. All patients underwent myocardial perfusion imaging by means of adenosine ^{99m}Tc sestamibi SPECT. Images were evaluated for the presence of perfusion abnormalities as well as other nonperfusion abnormalities that may indicate extensive ischemia, including left ventricular dysfunction (defined as a left ventricular ejection fraction <45%), transient ischemic dilatation and adenosine-induced ST-segment depression. Multivariable analysis was performed using a backward selection strategy to identify potential predictors for an abnormal stress myocardial perfusion study. Finally, all patients were followed up for 12 months to determine the occurrence of cardiovascular events: (1) cardiac death, (2) nonfatal myocardial infarction, (3) unstable angina requiring hospitalization, (4) revascularization, or (5) stroke.

Results

Of the 120 patients, 40 (33%) had an abnormal stress study, including myocardial perfusion abnormalities in 30 patients (25%). In 10 (8%) patients, indicators of extensive (possibly balanced ischemia) were observed in the absence of abnormal perfusion. The multivariable analysis identified current smoking, duration of diabetes and cholesterol/high-density lipoprotein (HDL) ratio as independent predictors of an abnormal stress study. During a follow-up period of 12 months six (5%) patients had a cardiovascular event.

Conclusion

The current study revealed a high prevalence of abnormal stress myocardial perfusion studies in patients with type 2 diabetes mellitus despite the absence of symptoms. In contrast to earlier studies current smoking, duration of diabetes and cholesterol/HDL ratio were identified as independent predictors of an abnormal study.

Introduction

Diabetes mellitus is a devastating disease affecting millions of individuals. Prevalence of the disease is expected to grow exponentially due to aging of the population, increased prevalence of obesity, and unhealthy life-styles. In patients with type 2 diabetes mellitus, cardiovascular diseases are a major cause of mortality and morbidity, with coronary artery disease (CAD) being the leading cause of death.[6] Moreover, atherosclerosis and CAD appear to develop differently in patients with diabetes as compared to nondiabetic individuals. Frequently, CAD develops at a younger age and shows faster progression without the development of symptoms.[8, 9] Consequently, subclinical or silent myocardial ischemia is frequently present in patients with diabetes, yet difficult to detect as a results of the absence of symptoms.

To improve identification of diabetic patients at high risk for cardiovascular events, assessment of myocardial perfusion by means of single photon emission computed tomography (SPECT) imaging has been proposed.[20, 22] Although several studies have described the prevalence of myocardial ischemia in type 2 diabetes mellitus patients, only a limited number of studies have prospectively included truly asymptomatic patients with diabetes. These prospective studies have shown a prevalence of silent myocardial ischemia ranging from 15% to 22%.[36, 43] In order for screening to be cost-effective, one should find strategies to "enrich" the target population of asymptomatic patients with diabetes. Accordingly, it has been proposed that noninvasive evaluation should be performed only in a subset of diabetic patients with certain clinical characteristics suggesting higher risk of CAD and a cardiovascular event, thereby increasing the yield of abnormal studies. Accordingly, clinical predictors are needed to identify those patients with a higher likelihood of silent myocardial ischemia.

The purpose of this study was to evaluate the prevalence of an abnormal stress myocardial perfusion study in a cohort of truly asymptomatic patients with type 2 diabetes mellitus using myocardial perfusion imaging by means of SPECT. Secondly, we determined which clinical characteristics may predict an abnormal stress myocardial perfusion study in this population indicative of cardiovascular disease.

Materials and methods

Patients

A total of 120 asymptomatic patients with type 2 diabetes mellitus were included in this study, of whom 100 (83%) had also participated in a previous study.[84] All patients were referred from a diabetic outpatient clinic to our hospital for cardiovascular risk stratification. The diagnosis of diabetes was established by the referring physician and confirmed by patient history and/or the use of insulin or oral hypoglycaemic agents.[1]

Inclusion criteria consisted of confirmed type 2 diabetes mellitus in combination with complete absence of angina or angina-equivalent symptoms. Exclusion criteria were: known or suspected CAD, stress test or coronary angiography before referral, history of coronary revascularization, treatment with antianginal medication, electrocardiographic evidence of Q-wave myocardial infarction, ischemic ST segment or T-wave changes or complete left bundle branch block and active bronchospasm, excluding the use of adenosine. Asymptomatic status was confirmed using the Rose questionnaire for angina.[15]

ECG-gated SPECT

Data acquisition

ECG-gated SPECT imaging was performed using a 2-day protocol (stress and rest) with ^{99m}Tc sestamibi (^{99m}TcMIBI). All patients were instructed not to consume caffeine-containing products for 24 hour before testing. Adenosine was infused at a rate of 140 µg/kg body weight per minute for 6 minutes with a simultaneous handgrip exercise. Blood pressure was measured and recorded at rest and every minute during adenosine infusion and the recovery phase. Twelve-lead electrocardiography (ECG) was recorded each minute and continuously monitored (leads aVF, V1 and V5) for the development of arrhythmia or ST-segment deviation. At the end of the third minute of infusion, ^{99m}TcMIBI (500 MBq) was injected intravenously. Imaging was performed 120 minutes after radiopharmaceutical injection using a triple-head SPECT gamma camera (GCA 9300/HG; Toshiba Corporation, Tokyo, Japan), using low-energy, high resolution collimators. Image were acquired using a circular 360° orbit, 60 projections and 40 seconds per projection.[61, 62] No attenuation correction was applied. The cardiac images were processed in the usual manner and short-axis, horizontal-long axis and vertical-long axis views were reconstructed. Patient motion was evaluated by examining the raw cine images.

Data analysis

Reconstructed short- and long-axis views as well as polar map formats (normalized to the maximum tracer activity) were used for semi-quantitative visual interpretation. The myocardium was divided into 17 segments and each segment was evaluated in consensus by two expert observers using a four-point scoring system (0 >75% tracer uptake, 1 50-75% tracer uptake, 2 25-50% tracer uptake, 3 <25% tracer uptake).[66, 85]

The summed stress score (SSS) and summed rest score (SRS) were obtained by summation of the individual segmental scores in stress and rest, respectively. The summed difference score (SDS) was calculated by subtracting the SRS from the SSS, which represents both the extent and severity of perfusion abnormalities.[86]

Perfusion defects were identified on the stress images (tracer activity less than 75% of maximum) and divided into ischemia (reversible defects), scar tissue (fixed defects) or mixed (scar and ischemia). Reversible perfusion defects, as defined by SDS ≥2, were graded as mild, (SDS 2-4) or moderate to severe (SDS ≥4). Fixed defects were considered present if SRS ≥2 and SDS <2. Perfusion defects were allocated to the coronary artery territories (left descending, left circumflex and right coronary arteries).[87] Using the gated images, regional wall motion was analyzed to improve differentiation between true perfusion abnormalities and attenuation artefacts. In addition, SPECT data were evaluated for other abnormalities indicative for (possibly extensive) CAD, or balanced ischemia. Left ventricular ejection fraction (LVEF), at rest and during stress, was derived from the end-diastolic volume (EDV) and end-systolic volume (ESV). Patients with resting LV dysfunction (LVEF <45%) were classified as having an abnormal study.[36, 88] Also, SPECT images revealing increased radiotracer lung uptake and transient ischemic dilation (TID) (reflected by a ratio of stress and rest short-axis volumes of the LV larger than 1.21) of the LV were categorized as abnormal.[36, 89, 90] Finally, flat or down-sloping ST-segment depression ≥1 mm at 80 ms after the J-point in two or more leads on the ECG during adenosine infusion was also interpreted as an abnormal test result.[63] Thus, an abnormal vasodilator stress SPECT myocardial perfusion imaging study was defined as; 1 abnormal myocardial perfusion, 2 LVEF < 45 %, 3 TID, 4 increased lung uptake and 5 ischemic ST depression during adenosine infusion.

Follow-up

Information during 12 months of follow-up was obtained by clinical visits or telephone interviews. A cardiovascular event was defined as the occurrence of: (1) car-

diac death, (2) nonfatal myocardial infarction, (3) unstable angina requiring hospitalization, (4) revascularization, or (5) stroke. Cardiac death was defined as death caused by acute myocardial infarction, ventricular arrhythmias, or refractory heart failure. Nonfatal myocardial infarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram.[91] Finally, also the number of diagnostic conventional coronary angiograms was recorded.

Statistical analysis

Categorical baseline characteristics are expressed as numbers and percentages, and compared between two groups with the chi-square test. Continuous variables are expressed as mean (standard deviation) and compared with the two-tailed *t* test for independent samples.

Uni- and multivariable analysis of baseline characteristics was performed to identify potential predictors for an abnormal stress myocardial perfusion study. Odds ratios were calculated with 95% confidence intervals as estimates of the risk associated with a particular variable. A backward selection strategy was used and included all variables identified in the univariable analysis with $p \leq 0.2$. Statistical analyses were performed using SPSS software, version 12.0 (SPSS, Chicago, Illinois) and *p*-values <0.05 were considered statistically significant.

Results

Patient characteristics

In total 122 patients were referred prospectively from the outpatient diabetic clinic and enrolled in the present study. Two patients were excluded from the analysis due to poor image quality. Thus, the final study population included 120 consecutive asymptomatic patients with type 2 diabetes.

Baseline characteristics of the 120 patients analyzed are presented in Table 1. Briefly, the mean age was 53 ± 10 years and 75 patients (62%) were male. The mean duration of diabetes was 9.5 ± 7.3 years. Oral anti-diabetic medication was used by 59% of patients, whereas 24% used insulin. Overall, only 23% of the patients received aspirin and 57% statin therapy.

Table 1. Patient characteristics; comparison between patients with normal and abnormal stress myocardial perfusion studies.

Variables	All patients n=120	Abnormal study n=40	Normal study n=80	*P* value
Male	75 (62)	23 (58)	52 (65)	0.42
Female	45 (38)	17 (42)	28 (35)	0.42
Age (years)	53±10	53±10	53±10	1.00
Diabetes-related risk factors				
Duration (years)	9.5±7.3	11.8±8.4	8.3±6.4	0.03
Age at time of diagnosis of diabetes (years)	43±12	41±13	45±10	0.05
HbA_1C	7.3±1.6	7.5±1.6	7.3±1.6	0.39
Treatment				
Oral	70 (59)	20 (50)	50 (63)	0.19
Insulin and oral	18 (15)	66 (15)	12 (15)	0.98
Insulin	29 (24)	13 (33)	16 (20)	0.14
Peripheral vascular disease (PVD)	12 (10)	5 (13)	7 (9)	0.52
Peripheral neuropathy (PNP)	25 (21)	7 (18)	18 (23)	0.53
Peripheral vascular and neuropathy	17 (14)	9 (23)	8 (10)	0.06
Body mass index (kg/m^2)	29.1±5.4	29.0±4.5	29.1±5.7	0.92
Waist circumference (cm)	103±14	104±14	102±14	0.66
Hypertension	65 (54)	23 (58)	42 (53)	0.60
Hypercholesterolemia	68 (57)	27 (68)	41 (51)	0.90
Family history of CAD	65 (54)	18 (45)	47 (59)	0.15
Smoking				
Past	25 (21)	5 (13)	20 (25)	0.11
Current	27 (23)	16 (40)	11 (14)	0.001
Medication				
Aspirin	27 (23)	9 (30)	16 (20)	0.35
ACE inhibitors	42 (35)	14 (35)	28 (35)	1.0
ARB	27 (23)	14 (25)	17 (21)	0.64
Statins	68 (57)	27 (68)	41 (51)	0.09
Serum markers				
Total cholesterol (mmol/l)	4.8±1.2	4.5±1.3	4.9±1.1	0.09
LDL (mmol/l)	3.1±1.1	3.0±1.3	3.1±1.0	0.45
HDL (mmol/l)	1.4±0.6	1.5±0.5	1.4±0.6	0.48
Triglycerides (mmol/l)	2.0±1.2	1.8±0.9	2.1±1.4	0.24
Cholesterol/HDL ratio	3.7±1.3	3.4±1.0	3.9±1.4	0.03
Creatinine (mmol/l)	77.6±20.1	75.2±20.0	78.8±20.2	0.36
Urine albumin-creatinine ratio	11.6±30.2	10.3±26.0	12.4±32.5	0.75
CRP	9.3±9.1	11.1±12.7	8.2±6.1	0.26
ApoA1	1.4±0.2	1.5±0.2	1.1±0.3	0.51
ApoB	0.9±0.3	0.8±0.3	0.9±0.3	0.16
Fibrinogen	3.9±0.9	4.1±1.2	3.8±0.8	0.26

ACE, angiotensin converting enzyme; Apo, apolipoprotein; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CRP, chain reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Prevalence of an abnormal stress myocardial perfusion study

Perfusion abnormalities

Regional perfusion abnormalities were present in 30 patients (25%). Of these patients 22 (73%) patients showed reversible defects, 4 (13%) patients had fixed defects and 4 (13%) patients had partially reversible defects. Ten patients (33%) showed mild ischemia (SDS<4), 17 (57%) showed moderate ischemia (SDS 4-8) and 3 (10%) showed severe ischemia (SDS >8).

The anatomic location of the perfusion defects was as follows: the left anterior descending territory in 19 patients (63%), left circumflex territory in 3 (10%), and right coronary artery territory in 7 (23%). In 2 (7%) patients, more than two vascular territories were involved.

LVEF and volumes

Data on rest LVEF and end-diastolic volumes (EDV) and end-systolic volumes (ESV) were available in 117 (98%) patients. The mean LVEF was 61.4 ± 11.4% with a mean EDV of 82.2 ± 27.7 ml and a mean ESV of 33.1 ± 19.4 ml. Stress data regarding LVEF, EDV and ESV were available in 92 patients (77%) with a mean LVEF of 59.5 ± 11.4% and a mean EDV and ESV of 83.6 ± 30.2 ml and 35.6 ± 21.7 ml, respectively, during stress.

In patients with perfusion abnormalities, mean LVEF, EDV and ESV were respectively 58.0 ± 12.6%, 85.0 ± 29.0 ml and 37.9 ± 22.6 ml at rest and 57.5% ± 12.8%, 90.0 ± 37.0 ml and 41.8 ± 28.2 ml during stress. Eight patients had LV dysfunction at rest (LVEF <45%), of which 4 patients also showed abnormal perfusion.

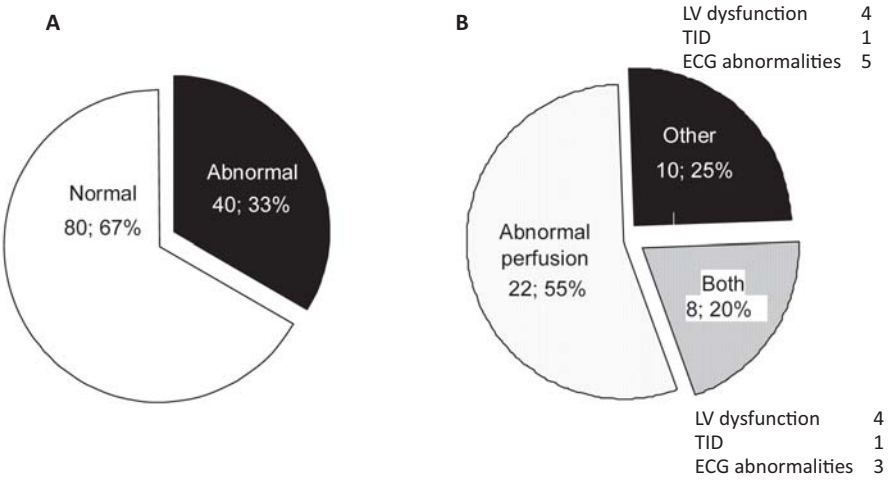
Transient ischemic dilatation, increased lung uptake and ST segment ECG changes

Transient ischemic dilatation (TID) was noted in two patients, one of which showed normal perfusion. In none of the patients was increased radiotracer lung uptake was observed, but adenosine-induced ST segment depression was detected in eight patients (7%). Three of these patients also showed perfusion abnormalities. Accordingly, an abnormal stress myocardial perfusion study was observed in 40 (33%) patients. The results are summarized in Figure 1.

Predictors of an abnormal stress myocardial perfusion study

Baseline and clinical characteristics of patients with normal and abnormal stress myocardial perfusion studies are summarized in Table 1. Patients with an abnormal stress study had a significantly longer duration of diabetes and were significantly younger at

Figure 1. Distribution of stress myocardial perfusion results.



A. Of 120 patients, 40 had an abnormal stress myocardial perfusion study. B. Observations in patients with abnormal studies. *Other,* nonperfusion abnormalities that may indicate extensive, possibly balanced ischemia; *TID,* transient ischemic dilatation.

the time of diagnosis (p=0.03 and p=0.05 respectively) as compared to patients with normal stress tests. Also, patients with an abnormal study were significant more often current smokers and had a lower cholesterol/ high-density lipoprotein (HDL) ratio (p=0.001 and p=0.03, respectively).

In Table 2, the univariable analysis of the clinical baseline characteristics to predict an abnormal stress myocardial perfusion study is shown. Subsequently, multivariable analysis was performed using a backward selection strategy and included all variables identified in the univariable analysis with $p \leq 0.2$. As indicated in Table 3, multivariable analysis demonstrated current smoking, duration of diabetes and cholesterol/HDL ratio to be significant independent predictors of an abnormal stress myocardial perfusion study.

Follow-up

During a follow-up period of 12 months six patients (5%) had a cardiovascular event. Five patients underwent revascularization, percutaneous coronary intervention in two and coronary artery bypass grafting in three. Finally, one patient had a stroke. In addition, five patients underwent diagnostic conventional coronary angiography not followed by intervention.

All patients undergoing revascularization presented with abnormal SPECT findings. In two patients with severe ischemia on SPECT, coronary angiography revealed significant

Table 2. Univariable predictors of an abnormal stress myocardial perfusion study.

	Odds ratio	95% confidence interval	*P* value
Gender (M/F)	0.73	1.59-0.34	0.42
Age (years)	1.00	0.96-1.04	1.00
Diabetes-related risk factors			
Duration (years)	1.07	1.01-1.13	0.02
Age at time of diagnosis of diabetes (years)	0.97	0.93-1.00	0.05
HbA_1C	1.11	0.87-1.42	0.39
Treatment			
Oral	1.67	0.77-3.59	0.19
Insulin and oral	1.02	0.35-2.94	0.98
Insulin	0.53	0.22-1.25	0.15
Peripheral vascular disease (PVD)	0.67	0.20-2.27	0.52
Peripheral neuropathy (PNP)	0.73	0.28-1.93	0.57
Peripheral vascular and neuropathy	2.61	0.92-7.40	0.07
Body mass index (kg/m^2)	1.00	0.93-1.07	0.92
Waist circumference (cm)	1.01	0.98-1.04	0.65
Hypertension	1.22	0.57-2.63	0.61
Hypercholesterolemia	0.09	0.89-4.37	0.09
Family history of CAD	0.57	0.27-1.24	0.16
Smoking			
Past	0.43	0.15-1.24	0.12
Current	4.18	1.71-10.26	0.02
Medication			
Aspirin	1.52	0.63-3.67	0.36
ACE inhibitors	1.00	0.45-2.22	1.00
ARB	1.24	0.51-3.02	0.64
Statins	1.98	0.89-4.37	0.09
Serum markers			
Total cholesterol (mmol/l)	0.75	0.53-1.06	0.10
LDL (mmol/l)	0.87	0.61-1.24	0.45
HDL (mmol/l)	1.27	0.66-2.48	0.48
Triglycerides (mmol/l)	0.81	0.56-1.16	0.25
Cholesterol/HDL ratio	0.69	0.49-0.97	0.03
Creatinine (mmol/l)	0.95	0.87-1.02	0.15
Urine albumin-creatinine ratio	1.00	0.98-1.01	0.75
CRP	1.04	0.97-1.11	0.29
ApoA1	1.72	0.34-8.53	0.51
ApoB	0.33	0.07-1.55	0.16
Fibrinogen	1.34	0.86-2.06	0.19

ACE, angiotensin converting enzyme; Apo, apolipoprotein; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CRP, chain reactive protein; F, female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, male.

Table 3. Multivariable logistic regression analysis

	Odds ratio	95% confidence interval	*P* value
Current smoker	7.12	2.51-20.23	<0.001
Cholesterol/HDL ratio	0.60	0.41-0.89	0.01
Duration diabetes	1.07	1.01-1.13	0.02

two-vessel disease and was followed by percutaneous coronary intervention. In addition, three patients underwent coronary artery bypass grafting following the observation of significant three-vessel disease on conventional coronary angiography. In these patients, severe balanced ischemia had been suspected based on SPECT. Balanced ischemia had also been suspected in the additional five patients who underwent conventional coronary angiography without revascularization. In these patients, no significant stenoses were observed. Of note, the SPECT study was normal in the patient who developed a stroke.

Discussion

In the present study 33% of patients with type 2 diabetes mellitus had an abnormal stress myocardial perfusion study indicative for cardiovascular disease, including perfusion abnormalities (25%) as well as other relevant abnormalities (8%). In addition, the variables current smoking, duration of diabetes and cholesterol/HDL ratio were identified as independent predictors of an abnormal stress myocardial perfusion study.

Prevalence of abnormal stress myocardial perfusion study indicative for cardiovascular disease

Various studies have evaluated the prevalence of silent myocardial ischemia in both retrospective and prospective settings. Studies using nuclear imaging to assess the prevalence of ischemia in asymptomatic diabetic patients have shown perfusion abnormalities in 6% to 59% of patients.[19, 25-38] Most likely, these widely differing estimates of CAD in asymptomatic patients reflect differences in study design and inclusion criteria. In the investigation by Miller et al a high prevalence of abnormal stress SPECT studies (59% of patients) was reported. However, in this retrospective study also patients with anti-anginal medication and Q waves and ST-T abnormalities on the

ECG were included, indicating a higher risk population.[25] In the Milan Study on Atherosclerosis and Diabetes (MiSAD) exercise electrocardiography was used in asymptomatic patients with diabetes as an initial test to select candidates for stress myocardial perfusion imaging. Possibly because of the low accuracy of exercise ECG for detection CAD, the overall prevalence of observed silent CAD was low: 97 (13%) of 735 enrolled patients had an abnormal exercise test that was confirmed in only 52 (53% by myocardial perfusion imaging), yielding an overall prevalence of silent ischemia of only 6%.[30] The patients enrolled in our study were truly asymptomatic patients with type 2 diabetes without any clinical evidence of CAD and prospectively recruited from a single diabetes care center. The stress myocardial perfusion study was abnormal in 40 patients (33%), including 20 patients (17%) with moderate to severe ischemia. Slightly lower values were reported in the DIAD trial by Wackers et al. The DIAD trial evaluated prospectively silent myocardial ischemia in 522 asymptomatic patients with at least two risk factors, by using gated ^{99m}Tc MIBI SPECT.[36] This study showed a prevalence of 22% abnormal SPECT studies, including markedly abnormal perfusion images with moderate or large stress defects in 33 patients (6%).

The discrepancy of the prevalence of silent myocardial ischemia between our study and the DIAD trial can be explained by differences in baseline characteristics of the included patients. In our study more subjects were male, the age at diagnosis of diabetes was lower and consequently the duration of diabetes was longer. In addition, more patients were insulin dependent and a higher percentage of patients were current smokers, factors which are in general associated with more advanced CAD.

Predictors of an abnormal stress myocardial perfusion study indicative for cardiovascular disease

In the present study current smoking, duration of diabetes and cholesterol/HDL ratio were identified as independent predictors for an abnormal stress myocardial perfusion study. In contrast, none of the established risk factors could predict abnormal myocardial perfusion in the DIAD trial, except for cardiac neuropathy. Also in another prospective investigation, established cardiovascular risk factors failed to predict myocardial ischemia.[43] Accordingly, a large variation in results exists among investigations. Large prospective trials therefore are needed to confirm whether variables such as duration of diabetes may potentially be helpful to improve identification of asymptomatic diabetic patients at higher risk for perfusion abnormalities and possibly cardiovascular events.

Clinical implications

At present, screening for CAD in asymptomatic patients with diabetes type 2 is still a heavily debated topic.[82, 83] Nevertheless, this population may benefit from identification of silent myocardial ischemia since clinical outcome may be considerably improved by initiation of aggressive therapy at an early stage as recently shown by Wackers et al.[92]

However, as the overall percentage of asymptomatic diabetic patients with ischemia appears to be low, selection criteria are needed to identify patients at higher risk for ischemia and who may benefit from myocardial perfusion imaging. Since in several previous studies established risk factors for CAD and clinical patient characteristics failed to identify high risk patients, alternative markers, such as coronary calcium, have been proposed. The presence of coronary calcium is a direct marker for coronary atherosclerosis, and can be relatively easily assessed. In the general population, several investigations have demonstrated a strong relation between increasing coronary calcium scores and a higher prevalence of ischemia as well as coronary events.[55, 93] Accordingly, coronary calcium may be useful to select patients requiring further evaluation by means of myocardial perfusion imaging. This concept was recently evaluated in 510 asymptomatic diabetic patients by Anand et al.[43] In this study only patients with considerable calcium (reflected by a calcium score >100) were referred to stress myocardial perfusion imaging. A random sample of 53 patients without considerable calcium (calcium score ≤100) were also referred to serve as a control group. The extent of coronary calcifications correlated well with the prevalence and severity of myocardial perfusion abnormalities. Moreover, patients with extensive calcium (calcium score >400) were shown to have a high likelihood (48%) of myocardial ischemia while patients without considerable calcium (calcium score ≤100) the likelihood of ischemia was low (18%). Finally, the calcium score was demonstrated to be superior to the established risk factors in predicting silent ischemia and cardiac events.

Importantly however, severe calcifications have also been observed in patients with normal myocardial perfusion studies[55, 68], and abnormal perfusion studies may occur in the absence of (extensive) calcifications. To some extent, the presence of extensive noncalcified atherosclerosis may account for this discrepancy. Indeed, Scholte et al recently compared multislice computed tomography (MSCT) angiography to coronary calcium scores in 70 asymptomatic patients with type 2 diabetes. Atherosclerosis was present on MSCT in 55% of patients with no or minimal calcium, suggesting the presence of substantial noncalcified rather than calcified plaque burden.[69] Moreover, a subsequent investigation that correlated coronary calcium scores, MSCT and myocardial perfusion imaging

in a small cohort of asymptomatic patients with type 2 diabetes failed to demonstrate a consistent interrelationship between these three modalities.[84] In this study, all three tests were abnormal in only 5% of patients. In contrast, in almost half of patients with abnormal SPECT no significant abnormalities were observed during both coronary calcium scoring and MSCT. Accordingly, it is conceivable that the various imaging modalities that are available reflect distinctly different aspects of CAD. Possibly, incorporation of both predictive baseline characteristics and atherosclerotic markers such as coronary calcium score may yield the most optimal algorithm for the identification of silent myocardial ischemia in asymptomatic patients with type 2 diabetes.

In such an algorithm, assessment of coronary calcium could be the initial test. In patients with extensive coronary calcium, the likelihood of ischemia is high, regardless of the presence of additional risk factors.[43] Consequently, patients with calcium scores >400 should be referred for evaluation of ischemia. In contrast, the likelihood of ischemia is low in patients with minor calcifications (calcium scores <100), and most patients will not require further testing. Indeed, as the expected prevalence of patients with ischemia is low, referral to ischemia testing will therefore probably not be cost-effective.

However, patients with moderate calcium (calcium scores between 100 and 400) represent an uncertain category and possibly, referral to ischemia testing should be based on the presence of additional risk factors such as the duration of diabetes. Unfortunately, no data are currently available to support this stepwise approach. Large prospective studies should address the safety, cost-effectiveness and outcome of such proposed algorithms.

Limitations

Only a limited number of patients were included in the present study. In addition, no comparison to other imaging modalities, such as coronary calcium scoring, was systematically available. With regard to data acquisition, no attenuation correction was performed. This may partially explain the higher prevalence of perfusion abnormalities in comparison with other studies. However, only a small proportion of the perfusion abnormalities were located in the inferior region. Moreover, the use of gated image acquisition allowed systematic analysis of regional wall motion, thereby improving differentiation between true perfusion abnormalities and attenuation artefacts. Although duration of diabetes and cholesterol/HDL ratio value was demonstrated to be independent predictors for silent myocardial ischemia, exact cut-off values could not be determined.

Finally, while myocardial ischemia due to CAD is the main cause of LV dysfunction in

patients with diabetes mellitus type 2, diabetic myocardial disease (without CAD) is undoubtedly multifactorial and this may explain the number of patients with LV dysfunction at rest.[94]

Conclusion

A high prevalence of abnormal stress myocardial perfusion studies indicative for cardiovascular disease in asymptomatic patients with type 2 diabetes mellitus was observed. In discrepancy to earlier studies current smoking, duration of diabetes and cholesterol/HDL ratio could be identified as independent predictors of an abnormal stress myocardial perfusion study.