CARDIAC IMAGING FOR RISK STRATIFICATION IN ASYMPTOMATIC DIABETES

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Voor mijn ouders

Aan Cacha, Julie, Beer en Faye

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Chapter 1

General introduction

Background

Diabetes mellitus (DM) is the most common endocrine disease worldwide, and is primarily defined by the level of hyperglycemia. Current diagnostic criteria for the presence of DM as recommended by the American Diabetes Association are:

1: fasting (no caloric intake for at least 8 hours) venous plasma glucose concentration ≥ 7.0 mmol/l, or

2: symptoms of hyperglycemia and a casual plasma glucose ≥ 11.1 mmol/l, or

3: two hour plasma glucose ≥ 11.1 mmol/l after an oral glucose tolerance test.[1]

Recent estimates indicate that there were 171 million people in the world with diabetes in the year 2000, and this was projected to increase to 366 million by 2030.[2] In 2005, an estimated 1.1 million people died from the complications of DM of which almost half of the deaths occurred in people under the age of 70 years. 55% of DM related deaths were in women.[3] The estimated prevalence of diabetes in the Netherlands in 2030 is 5.1%, based on an estimated population of 12.5 million people aged between 20-79 years.[4] The total amount of healthcare costs for patients with DM in 2005 in the Netherlands was 814 million euro, 1.2% of the total healthcare costs.[5]

DM can be classified into DM type 1 and DM type 2. DM type 1 (also called type 1 diabetes, T1D, T1DM, insulin-dependent DM, juvenile diabetes) is an autoimmune disease, which results in the destruction of insulin-producing ß cells of the pancreas. Lack of insulin causes an increase in fasting blood glucose, which begins to appear in the urine once above the renal threshold. Glycosuria or glucose in the urine causes the patient to urinate more frequently, and drink more than normal (polydipsia). Classically, these were the characteristic symptoms which prompted the discovery of the disease. DM type 2 (formerly called non-insulin-dependent or adult-onset DM) results from the body's ineffective use of insulin, and is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. DM type 2 comprises 90% of all diabetic people worldwide, and is largely the result of excess body weight and physical inactivity. While it is initially often managed by increasing exercise and dietary modification, medications are usually needed as the disease progresses. Furthermore, DM type 2 is often associated with obesity, hypertension and elevated cholesterol (combined hyperlipidemia), often termed as the metabolic syndrome. Symptoms may be similar to those of DM type 1, but are often less marked. Long term complications of DM include microvascular damage (the eyes, kidneys and peripheral nerves) and macrovascular injuries (ischemic

heart disease, stroke and peripheral vascular disease). These complications reduce life expectancy and quality, and significantly increase morbidity. Due to the often masked symptoms of DM type 2, the disease may only be diagnosed several years after onset when complications have already occurred. Often, the prognosis of patients with DM depends on the presence of cardiovascular disease. Coronary artery disease (CAD) is the leading cause of morbidity and mortality in individuals with DM type 2.[6] The 10-year mortality rate in patients with known CAD and diabetes exceeds 70%.[7] Some studies suggested that the risk for future cardiac death in patients with DM without known CAD is similar to that in nondiabetic patients with overt clinical CAD.[7] In addition, early and late outcomes of diabetic patients with acute coronary syndromes are worse than those of their nondiabetic counterparts. To compound the problem, CAD is frequently in an advanced state in diabetic patients when it manifests clinically, and myocardial ischemia is often asymptomatic in these patients.[8, 9] The aforementioned adverse clinical outcomes in patients with DM underscore the need to develop practical approaches to detect CAD in an earlier stage before clinical symptoms occur. Early detection of CAD and myocardial ischemia may be important to reduce the burden of cardiovascular disease, morbidity and mortality in asymptomatic patients with DM type 2. Identification of these asymptomatic diabetic patients is important as early intervention may improve long term survival. From a clinical perspective, patients with high risk characteristics on testing for myocardial ischemia may benefit from coronary revascularization. With regard to pharmacological therapy, the knowledge that a patient with diabetes has CAD may indicate the need to initiate or intensify pharmacological treatment with aspirin, statins and ACE inhibitors. A number of noninvasive tests are now available to detect myocardial ischemia, coronary atherosclerotic disease, cardiac nervous innervation and left ventricular dysfunction. In this thesis, several cardiac imaging techniques were used for risk stratification of asymptomatic patients with DM type 2.

Myocardial perfusion imaging by single photon emission computed tomography

Myocardial perfusion imaging (MPI) is a functional cardiac imaging method used to diagnose ischemic heart disease. The underlying principle is that under conditions of stress, diseased myocardium receives less blood flow than normal myocardium. A cardiac specific radiopharmaceutical (Technetium-99m, ^{99m}Tc) is administered. Thereafter, the heart rate is increased either by exercise or pharmacologically with adenosine, dobutamine or dipyridamole to induce myocardial stress. Pharmacological stress can be used for diabet-

ic patients, who cannot achieve maximal cardiovascular stress because of polyneuropathy or peripheral artery disease. Single photon emission computed tomography (SPECT) is a nuclear medicine tomographic imaging technique that uses gamma rays emitted by the injected radiopharmaceutical. SPECT imaging is performed by using a gamma camera to acquire multiple 2-dimensional images from multiple angles. A computer is used to apply a tomographic reconstruction algorithm to the multiple projections, yielding a 3-dimensional dataset. This dataset may then be manipulated to show thin slices along any chosen axis of the body. To acquire SPECT images, the gamma camera is rotated around the patient. Projections are acquired at defined points during the rotation, typically every 3 to 6 degrees. In most cases, a full 360 degree rotation is used to obtain an optimal reconstruction. The time taken to obtain each projection is also variable, but 15 till 20 seconds are typical. This gives a total scan time of 15 until 20 minutes. SPECT imaging performed after stress reveals the distribution of the radiopharmaceutical, and therefore the relative blood flow to the different regions of the myocardium. Diagnosis is made by comparing stress images to a set of images obtained at rest. Homogeneous myocardial uptake of the tracer indicates normal myocardium and perfusion. Absence of the tracer means clinically significant infarction or coronary stenosis. A defect at stress images that normalizes at the rest images indicates an inducible perfusion abnormality, and it corresponds to a significant coronary stenosis. A defect both at stress and rest images (a fixed defect) indicates an area with loss of viable myocardium, such as secondary to myocardial infarction. Cardiac-gated acquisitions are possible with SPECT. Triggered by the electrocardiogram to obtain differential information about the heart in various parts of its cycle, gated myocardial SPECT can be used to obtain quantitative information about myocardial perfusion, thickness, and contractility of the myocardium during various parts of the cardiac cycle. It also allows calculation of left ventricular ejection fraction, stroke volume, and cardiac output.[10]

Multislice computed tomography coronary angiography and calcium scoring

Multislice computed tomography (MSCT) coronary angiography is a noninvasive imaging technique which can visualize the coronary arteries and detect significant stenoses. The latest generation 64-slice computed tomography scanner allows high resolution and nearly motion-free coronary imaging. Coronary stenoses are detected with high sensitivity and a normal scan accurately rules out the presence of significant coronary stenoses.[11] To achieve images of good quality, patients need to be prepared with an in-

travenous cannula for contrast injection. Also one hour before the scan, beta-blockers may be needed to slow the heart rate and improve image quality. An optimal scan protocol has to be performed to result in a high spatial resolution and a high temporal resolution scan with low radiation exposure to the patient.[12] First, a calcium score without contrast can be obtained, using prospective electrocardiographic triggering. The presence of calcium serves as a marker for the presence, location and extent of calcified plaque in the coronary arteries. Because calcium is a marker for CAD, the amount of calcium detected on a cardiac CT scan is a helpful prognostic tool. Coronary artery calcium (CAC) can be identified as a dense area at the location of a coronary artery exceeding the threshold of 130 Hounsfield units. The amount of calcification, expressed as the calcium score, may help to predict the likelihood of a myocardial infarction. An overall (Agatston) score for each coronary artery and each patient can be recorded, grading the extent of CAD. The CAC score scan can be followed by 64-slice MSCT coronary angiography performed during electrocardiographic gating and the administration of non-ionic contrast (50-100 ml). The whole scanning process is completed after 10-15 minutes. Large amounts of data are obtained and transferred to a remote workstation for post processing and subsequent evaluation. The MSCT coronary angiography images can be evaluated visually for the presence of luminal stenoses and plaque characterization.[13]

^{123}I-metaiodobenzylguanidine myocardial scintigraphy

^{123}I-metaiodobenzylguanidine (^{123}I-*m*IBG) is a neurotransmitter and analogue of norepinephrine. ^{123}I-*m*IBG myocardial scintigraphy is an imaging modality that allows evaluation of cardiac sympathetic innervation in vivo. It enables both the assessment of global as well as regional cardiac sympathetic innervation by visualization of the uptake and storage of radiolabeled neurotransmitters to presynaptic nerve terminals. After blocking thyroid uptake, ^{123}I-*m*IBG is intravenously injected at rest. Fifteen minutes post injection; anterior planar images of the chest are acquired and stored in a 256 x 256 matrix. Thereafter, a 360 ° SPECT study is acquired using a gamma camera (4˚/step, 35 seconds/projection, 128 x 128 matrix). Repeated planar and SPECT studies are acquired at approximately 4 hours post-injection. Early (15 minutes post-injection) and late (4-hour delayed) planar images are processed to determine the heart-to-mediastinum ratio (HMR). The planar *m*IBG images are analyzed using regions of interest (ROI) to calculate the uptake ratios and washout percentages. Therefore, a ROI is drawn manually over the left ven-

tricle. A second rectangular ROI is drawn over the upper mediastinum and the opposite arm and used as a reference background region. The HMR of average counts per pixel is calculated for the early and delayed images. After correcting for the physical decay of ^{123}I, early and delayed HMR values are then used to compute the myocardial washout ratio (WR) of *m*IBG as follows: WR= [early heart counts-early mediastinum counts] – [delayed heart counts-delayed mediastinum counts] / [early heart counts-early mediastinum counts] x 100%. Polar map formats (normalized to 100%) are used for visual interpretation and semi-quantitative analysis.

Global left ventricular strain

Global left ventricular longitudinal strain using automated functional imaging (AFI), provides a new imaging technique based on two-dimensional strain imaging.[14] The software analyzes motion by tracking speckles (natural acoustic markers) in the ultrasonic image in two dimensions. The frame-to-frame changes of the speckles are used to derive motion and velocity. For this purpose, one single cardiac cycle is needed from each apical view (apical long axis, four- and two-chamber views). First, the end-systolic frame is defined in the apical long-axis view. The closure of the aortic valve is marked, and the software measures the time interval between R-wave and aortic valve closure. This interval is used as a reference for the four- and two-chamber view loops. After defining the mitral annulus and the left ventricular apex with three index points at the end-systolic frame in each apical view, the automated algorithm traces three concentric lines on the endocardial border, the mid-myocardial layer and epicardial border, including the entire myocardial wall. The tracking algorithm follows the endocardium from this single frame throughout the cardiac cycle, and allows for a further manual adjustment of the region of interest to ensure that all myocardial regions are included throughout the cardiac cycle. The left ventricle is divided in 6 segments in each apical view and the tracking quality is validated for each segment. Then, the myocardial motion is analyzed by speckle-tracking within the ROI. Finally, the automated algorithm, using a 17-segment model, provides the peak systolic longitudinal strain for each left ventricular segment in a “bull‘s eye” plot, with the average value of peak systolic longitudinal strain for each view and the averaged global longitudinal peak systolic strain for the complete left ventricle. In general, longitudinal strain values are presented as negative values; a larger negative value indicates more longitudinal shortening. For strain analysis, digital cine-loops are processed off-line using commercially available software.

Study population

From May 2005, DM type 2 patients who were asymptomatic for CAD and had ≥1 risk factor for CAD were referred from an outpatient diabetic clinic in The Hague (Diabetes Zorg Haaglanden) to the Leiden University Medical Center for cardiac risk stratification. First, the patients were seen at the outpatient cardiology clinic and were confirmed as being asymptomatic using the Rose questionnaire.[15] Furthermore, a physical examination, blood analysis and standardized 2-dimensional transthoracic echocardiography were performed. Every eligible patient underwent MPI by SPECT, MSCT coronary angiography and CAC scoring. In patients with normal MPI, ^{123}I-*m*IBG myocardial scintigraphy was performed. Depending on the results of these investigations, pharmacological therapy was started. If necessary, the patients were referred for invasive coronary angiography, possibly followed by percutaneous coronary intervention or coronary artery bypass grafting. After the initial investigations, all patients were seen at the outpatient cardiology clinic every year. These visits included an ECG and physical examination. Two years after the initial visit, a second MPI by SPECT, transthoracic echocardiography and blood analysis were performed. All data were systematically and prospectively entered in a database. The extensive database formed the basis for the studies presented in this thesis. At the time of writing this thesis, patients are still followed-up.

Aim and outline of this thesis

The aim of this thesis was to investigate the role of noninvasive cardiac imaging modalities to identify asymptomatic DM type 2 patients with increased cardiovascular risk. For this purpose we used the data obtained from the earlier mentioned database.

In **chapter 2**, we focused on the potential roles of stress MPI and computed tomography CAC scoring as two complementary approaches for screening asymptomatic patients with diabetes. In addition, on the basis of the available evidence in the literature, we proposed a potential algorithm for this purpose.

Chapter 3 describes an observational study that prospectively evaluated the comparative prevalence of the presence of coronary atherosclerosis by stress SPECT, CAC scoring and MSCT coronary angiography, and their diagnostic interrelationships in asymptomatic patients with DM type 2.

The prevalence of CAD in a large cohort of asymptomatic patients with DM type 2 using MSCT coronary angiography was evaluated in **chapter 4**. Furthermore, the plaque

composition of the coronary lesions was also evaluated, and the relationship between calcium scoring and noninvasive angiography was explored.

The purpose of the study in **chapter 5** was to evaluate the prevalence of an abnormal stress MPI study in a cohort of truly asymptomatic patients with DM type 2 using MPI by SPECT. Secondly, we determined which clinical characteristics may predict an abnormal stress MPI study in this population, indicating the presence of cardiovascular disease.

In **chapter 6**, the difficulty of adequate risk stratification for patients with asymptomatic diabetes was illustrated in a case report of an asymptomatic DM type 2 patient, who suffered a silent myocardial infarction after the initial screening.

The aim of the study described in **chapter 7** was to evaluate whether subclinical left ventricular systolic dysfunction was independently related to coronary atherosclerosis. Furthermore, it was investigated whether it could provide incremental information over baseline characteristics to identify patients with coronary atherosclerosis.

In **chapter 8** we describe the prevalence of cardiac autonomic neuropathy in a cohort of truly asymptomatic patients with DM type 2 using heart rate variability and ^{123}I-metaiodobenzylguanidine myocardial scintigraphy.

Chapter 9 contains the summary and conclusions of the results of this thesis.

Chapter 2

Screening of asymptomatic patients with type 2 diabetes mellitus for silent coronary artery disease. Combined use of stress myocardial perfusion imaging and coronary calcium scoring

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Abstract

Diabetes mellitus and coronary artery disease constitute an ominous clinical combination. Rates of morbidity and mortality as a result of cardiovascular complications are high in patients with type 2 diabetes mellitus. Screening for silent coronary artery disease, to detect the disease in an early stage and to be able to initiate early appropriate treatment, has recently become an important focus of clinical investigation. Recent prospective studies have shown that the overall prevalence of silent coronary artery disease in truly asymptomatic individuals with diabetes is about 20% to 25%. It is of practical and clinical importance to explore ways to "enrich" the target screening population. In this editorial point of view the relative roles of stress radionuclide myocardial perfusion imaging and coronary calcium scoring are examined. The two methodologies appear to have complementary values for the screening of asymptomatic individuals with diabetes mellitus. A screening algorithm involving sequential use of coronary calcium scoring and subsequent stress radionuclide myocardial perfusion imaging is proposed.

Introduction

The prevalence of diabetes mellitus has reached epidemic proportions and constitutes a major public health problem. Worldwide, it affects almost 200 million individuals, and this number is expected to increase exponentionally as the population ages and obesity and sedentary life style become increasingly ubiquitous. In the United States almost 1.3 million individuals are diagnosed with diabetes each year.[16]

Cardiovascular complications, including coronary artery disease (CAD), are the leading causes of morbidity and mortality in individuals with type 2 diabetes mellitus.[6] The overall prevalence of CAD has been reported to be as high as 60% in patients with diabetes referred for stress testing.[17] The 10-year mortality rate in patients with known CAD and diabetes exceeds 70%.[7] Some studies suggest that the risk for future cardiac deaths in patients with diabetes without known CAD is similar to that in non-diabetic patients with overt clinical CAD.[7] In addition, early and late outcomes of diabetic patients with acute coronary syndrome are worse than those of their nondiabetic patient counterparts.

To compound the problem, myocardial ischemia is often asymptomatic in patients with diabetes mellitus, and CAD is frequently in an advanced state when it becomes clinically manifest.[8, 9] Coronary artery bypass grafting in patients with diabetes has been shown to improve the survival rate and may be superior to percutaneous coronary intervention, possibly due to the presence of more diffuse atherosclerosis.[9] Moreover, the need for repeated percutaneous coronary intervention or coronary artery bypass grafting is significantly greater in patients with diabetes as compared to nondiabetic patients.[18]

The previously described adverse clinical outcomes in patients with diabetes underscore the need to develop practical approaches for detecting CAD in an early stage before clinical complications have occurred. A number of noninvasive tests are available to detect myocardial ischemia: exercise electrocardiography, stress myocardial perfusion imaging (MPI), and stress echocardiography. Other noninvasive techniques may be able to detect the generalized process of atherosclerotic disease, such as imaging of the vessel wall of carotid arteries via high-resolution ultrasound or coronary artery calcium (CAC) scoring via computed tomography (CT). It is currently unclear whether, for the purpose of screening, detection of these early markers of CAD is preferred over the actual visualization of myocardial ischemia. In this editorial point of view we will focus on the potential roles of stress MPI and CT CAC scoring as two complementary approaches for screening asymptomatic patients with diabetes. In addition, on the basis of the available evidence in the literature, we propose a potential algorithm for this purpose.

MPI in symptomatic patients with diabetes mellitus

Although the role of stress MPI for risk stratification is well established in the general population, similar data are relatively scarce in patients with diabetes mellitus. Several studies in the literature suggest a high prevalence of abnormal MPI studies in diabetic patients (Table 1). Zellweger et al noted that this high prevalence was dependent of the clinical presentation: i.e. angina or shortness of breath. Patients with diabetes who presented with shortness of breath had a significantly higher incidence (51%) of abnormal MPI than patients who complained of angina (44%).[19] Symptomatic patients with diabetes in addition had a significantly higher hard and total cardiac event rate than patients without diabetes. Giri et al observed that the cardiac events rate in diabetic patients was 8.6%, as compared to 4.5% in non-diabetic patients.[20] As in the general population, stress MPI is able to stratify patients with diabetes in high- and low-risk prognostic groups (Table 1). The cardiac event rate for any given MPI abnormality was higher in diabetic patients than in nondiabetic patients, ranging from 3.6 % to 13.2, and diabetic women had the worst outcome. Moreover, patients with diabetes and normal MPI had a higher cardiac event rate than non diabetic patients, ranging from 0.7 % to 3.6 %. Not only is the outcome of patients with diabetes and normal MPI not as favourable as in patients without diabetes (< 1%), the "warrantee" period of normal MPI appears also to be shorter than 2 years.[20] It is conceivable that his may be attributed to accelerated progression of atherosclerosis in the diabetic state.

MPI in asymptomatic patients with diabetes mellitus

Nesto et al reported in 1990 that 57% of asymptomatic patients with diabetes mellitus and peripheral vascular disease had evidence of silent CAD on stress MPI.[26] A number of subsequent studies have confirmed the presence of silent ischemia in asymptomatic patients with diabetes. [19, 25-38] The reported prevalence of silent ischemia, however, varied markedly between studies, from 6% to 59%.[19, 30, 34, 36, 38-40] This wide range in the prevalence of silent ischemia is most likely related to differences in patient selection, stress methodology, imaging techniques and interpretive definitions.

Reviewing the available literature on stress testing in asymptomatic patients with diabetes, one can distinguish 3 types of studies (Table 2): (A) retrospective database analyses of patients referred for stress testing who had diabetes, (B) retrospective database analyses of known asymptomatic patients with diabetes referred for stress testing, and (C) prospective studies in truly asymptomatic patients with diabetes. Because of selection

Table 1. MPI in symptomatic patients with diabetes

Year	Author (ref)	Nr Pts	Tracer	Stressor	Abnormal MPI (%)	Mean F/U (m)	HE in abnormal MPI (%/yr)	HE in normal MPI (%/yr)
1987	Felsher[21]	123	^{201}TL	Exercise	56	36	4.8	1.3
1999	Kang[22]	1271	^{201}TL,MIBI	Exercise, Adenosine	41	24±8	3.9-7.9	1.2
2002	Schinkel[23]	207	MIBI	Dobutamine	64	49±29	6.6*	0.7*
2002	Giri[20]	929	^{201}TL,MIBI	Exercise, Adenosine	48	36±18	5.0-6.4	3.6-3.9
2003	Berman[24]	5333	^{201}TL,MIBI	Adenosine	37-62	27±9	4.7-9.0*	1.8-2.5
2004	Zellweger[19]	911	^{201}TL,MIBI	Exercise, Adenosine	44-51	24	5.6-13.2	2.0-3.3
2004	Miller[25]	2998	^{201}TL,MIBI	Exercise, Adenosine, Dipyridamole, Dobutamine	60	70±42	3.6-5.9	NA

F/U, follow-up; HE, hard events (cardiac death or non-fatal myocardial infarction); MIBI, technetium-99m sestamibi; MPI, myocardial perfusion imaging; NA, not available; ^{201}TL, thallium-201 chloride. *= only cardiac death.

bias, the first type of study in the literature (section A, Table 2) typically showed a high prevalence (41%-58%) of abnormal stress MPI results and a high cardiac event rate.[20, 22, 38] It is likely these patients were referred for stress testing because of typical or atypical symptoms and/or perceived clinical high risk. No details with regards to the type of diabetes mellitus or its treatment, duration, or comorbidity were generally available. The second type of studies in the literature (section B, Table 2) showed a lower prevalence of abnormal stress MPI and cardiac event rate.[19, 25, 34, 37] Nevertheless, these patients may not be representative of asymptomatic patients with diabetes in the larger population, because they were referred for stress MPI, for example, before noncardiac surgery. The mean prevalence of silent ischemia ranged from 26%-39%, although Miller et al reported abnormal MPI in 59% of presumably asymptomatic patients.[25] Because of the retrospective nature of these two types of studies, there remains uncertainty about the true prevalence of silent ischemia in asymptomatic patients with diabetes.

Prospective studies in asymptomatic patients with diabetes mellitus

Several prospective studies have been performed in truly asymptomatic patients with diabetes mellitus (section C, Table 2).[30, 31, 36, 40-42] In general, these studies showed a lower prevalence of silent CAD, ranging from 6% to 22%. However, there were important differences in design and stress testing methodology. These methodological differences

Table 2. Prevalence of abnormal MPI and cardiac events in retrospective data base analyses and prospective studies in patients with type 2 diabetes mellitus.

Year	Author (ref)	Nr Pts	Mean F/U (m)	Tracer	Stressor	Abnormal MPI (%)	HE with abnormal MPI (%/yr)	HE with normal MPI (%/yr)
A: Retrospective database analysis in patients with diabetes								
1999	Kang[22]	1271	24±8	^{201}TL,MIBI	Exercise, Adenosine	41	3.9-7.9	1.2
2002	Giri[20]	929	36±18	^{201}TL,MIBI	Exercise, Adenosine	48	5.0-6.4	3.6-3.9
2005	Rajagopalan[38]	1427	70±42	^{201}TL,MIBI	Exercise, Adenosine, Dipyridamole, Dobutamine	58	5.9-3.6	1.6
B: Retrospective database analysis in asymptomatic patients with diabetes								
2002	De Lorenzo[34]	180	36±18	MIBI	Exercise, Dipyridamole	26	9	2
2004	Zellweger[19]	826	12-102	^{201}TL,MIBI	Exercise, Adenosine	39	3.4	1.6
2004	Miller[25]	1738	70±42	^{201}TL,MIBI	Exercise, Adenosine, Dipyridamole, Dobutamine,	59	NA	NA
2005	Prior[37]	133		^{201}TL,MIBI	Exercise, Dipyridamole	37	NA	NA
C: Prospective studies in asymptomatic patients with diabetes								
1999	Janand[31]	203	-	^{201}TL	Exercise, Dipyridamole	19	NA	NA
2001	Penfornis[41]	56	-	^{201}TL	Exercise, Dipyridamole	21	NA	NA
2002	Faglia[30]	925	60	^{201}TL	Exercise	6	3.9#	0.44#
2004	Cossson[40]	262	42±24	^{201}TL	Exercise, Dipyridamole	16	0.75	3.4
2004	Wackers[36]	1123	60	MIBI	Adenosine	22	Results expected in 2007	
2005	Anand[42]	510	18±5	MIBI	Exercise, Dipyridamole	13	NA	NA

F/U, follow-up; HE, hard events: cardiac death, nonfatal myocardial infarction, #= HE included resting and effort angina; MIBI, technetium-99m sestamibi; MPI, myocardial perfusion imaging; ^{201}TL, thallium-201 chloride.

may explain the variation in observed prevalence of silent CAD. For example, in the Milan Study on Atherosclerosis and Diabetes (MiSAD) asymptomatic patients with diabetes had exercise electrocardiography as the first diagnostic test.[30] Only if this test was abnormal, stress MPI was performed. It is possible that, because of the insensitivity of exercise electrocardiography, the overall observed prevalence of observed silent CAD was low (6%). Moreover, fatal cardiac event rate was low as well. Janand-Delenne et al and Cosson et al performed either exercise electrocardiography or thallium-201 imaging, whereas Penfornis et al used exercise electrocardiography, stress MPI or stress echocardiography.[31, 40, 41] Currently, 2 prospective studies in asymptomatic patients with diabetes are still ongoing. Only in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study was the same stress test (adenosine Tc-99m Sestamibi MPI) consistently performed in all 522 randomized patients.[36] In the DIAD study 22% of patients had abnormal MPI results. In the study by Anand et al, 510 asymptomatic patients with diabetes had pre-screening performed using electron-beam CT (EBCT). If the EBCT CAC score was 100 Agatston units or greater, stress MPI was performed.[43] The imputed prevalence of silent CAD in their study was 13%. These 2 recent prospective studies indicated that the prevalence of silent CAD in truly asymptomatic patients is considerably lower than was suggested by retrospective database analyses. Thus, in order for screening to be cost-effective, one should find ways to "enrich" the target population of asymptomatic patients with diabetes.

Value of CAC scoring in patients with diabetes mellitus

CT techniques (EBCT, multislice CT) allow for noninvasive detection and quantification of CAC, an early marker of CAD.[44] Various studies have recently demonstrated the prognostic significance of CAC scores in the general population.[45-48] Because of the previously mentioned ominous association between CAD and diabetes mellitus, the prevalence of CAC has been explored in patients with diabetes without known CAD.[49] In a cohort study of 30,904 asymptomatic individuals, including 1,075 diabetics, the median CAC score was in general higher in patients with diabetes than in patients without diabetes. In addition, the likelihood of having a CAC score in the highest age/gender quartile was 70% greater for patients with diabetes. Raggi et al investigated the prognostic value of CAC in subjects with and without diabetes mellitus.[50] In a cohort of 10,377 asymptomatic individuals, which included 903 diabetics, the mean CAC score and death rate were significantly higher in subjects with diabetes than in those without diabetes. Moreover, for every increase in CAC score, there was a greater increase in mortality for diabetic

patients than for patients without diabetes. In contrast, patients with diabetes and no evidence of CAC had a similar survival compared to that of individuals without diabetes and no detectable CAC. Qu et al noted that subjects with diabetes and low CAC score had a four-fold increase in hard cardiac event rate compared with nondiabetic subjects with a low CAC score.[51] On the other hand, the prognostic value of CAC as a continuum was weaker in patients with diabetes than in patients without diabetes.

Elkeles et al found a close relationship between waist-hip ratios, systolic blood pressure and CAC score.[52] Thus, CAC scoring may be linked to the metabolic syndrome in type 2 diabetics. In asymptomatic individuals, Moser et al noted that the prevalence of CAC was significantly increased when more than 3 cardiac risk factors were present.[53] Thus, the presence of multiple cardiac risk factors could be used as a justification for CAC screening. Furthermore, an Agatston score of 400 or greater appeared to be a logical threshold for initiating further testing with stress MPI.[53] These data suggest that CAC scoring may have value as an approach to enrich target population of asymptomatic patients with diabetes for screening.

Relative values of CAC score and ischemia on MPI for detecting CAD

Currently, only limited data are available on the relative values of CAC and MPI for detection silent CAD and prognostication. He et al prospectively examined 3,895 asymptomatic subjects with EBCT; 411 of these underwent stress MPI.[54] Only 6.8% of these subjects had known diabetes mellitus. The likelihood of stress-induced myocardial ischemia on MPI increased in parallel to the CAC score, in particular at CAC scores of 400 or greater. Of patients with CAC score 400 or greater, 46% had demonstrable stress-induced myocardial ischemia on MPI.

Berman et al evaluated 1,195 patients without known CAD, including 51% asymptomatic individuals and 11.6 % patients with diabetes.[55] The authors noted that the likelihood of stress-induced myocardial ischemia on MPI was very low (<2%) if the CAC score was lower than 100 Agatston units. However, when the CAC score exceeded 400 Agatston units, a relatively high percentage of patients had abnormal MPI studies. These data suggested a role for CAC scoring as a gatekeeper for patients who may benefit from further risk stratification with stress MPI. Alternatively, 56% of patients with normal MPI had CAC scores of 100 and greater, indicating that absence of stress-induced myocardial ischemia does not exclude preclinical presence of atherosclerosis.

Wong et al similarly explored the interaction between CAC scoring and stress MPI in

1,043 patients without known CAD.[56] Of the patients, 313 had metabolic abnormalities, including 140 patients with diabetes mellitus and 173 patients with metabolic syndrome. Again, a CAC score lower than 100, which occurred in approximately 2 % of patients, was associated with absence of stress-induced ischemia on MPI. The likelihood of stress-inducible ischemia increased in parallel with increasing CAC score. It was noted that the presence of diabetes mellitus or metabolic syndrome significantly increased the likelihood of abnormal MPI. For instance, of patients with CAC score of 400 and greater, 13.6% of patients without metabolic abnormalities had stress induced ischemia, whereas this occurred in 23.4% of those with metabolic abnormalities.

As mentioned previously, one recent study explored the combined use of CAC assessment with EBCT and MPI in patients with asymptomatic diabetes.[43] Anand et al evaluated 510 asymptomatic patients with type 2 diabetes using EBCT to assess CAC. Stress MPI was performed in 127 (25%) patients with a CAC score greater than 100 Agatston units. For comparison, 53 randomly selected patients with a CAC score of 100 or less also underwent stress MPI. None of the patients with CAC score of 10 or less had abnormalities on MPI. An increasing prevalence of abnormal MPI studies was noted in patients with higher CAC score. Specifically, 18.4% of patients with a CAC score between 11 and 100 had ischemia, whereas 71.4% of patients with a CAC score greater than 1000 had ischemia. It should be noted that the incidences of abnormal MPI again are higher than those observed in the nondiabetic cohorts.[55] These observations suggest that sequential use of EBCT and MPI may optimize screening of asymptomatic diabetic patients and that EBCT may be used as gatekeeper for stress MPI. The clinical relevance of these findings is further underlined by the prognostic data in the study by Anand et al. During a mean follow-up of 18±5 months, no events occurred in patients with a CAC score of 10 or less; as compared with 82% of events occurring in patients with a CAC score greater than 400. Of note, the CAC score and the extent of abnormalities on MPI were the only predictors of future cardiac events.

Conclusion

Stress-induced abnormalities on MPI and positive CAC scores represent two different aspects of CAD. The first one reflects the pathophysiologic consequences of luminal obstructive CAD, whereas the second one indicates the presence of the atherosclerotic process with calcium deposition in the vessel wall.

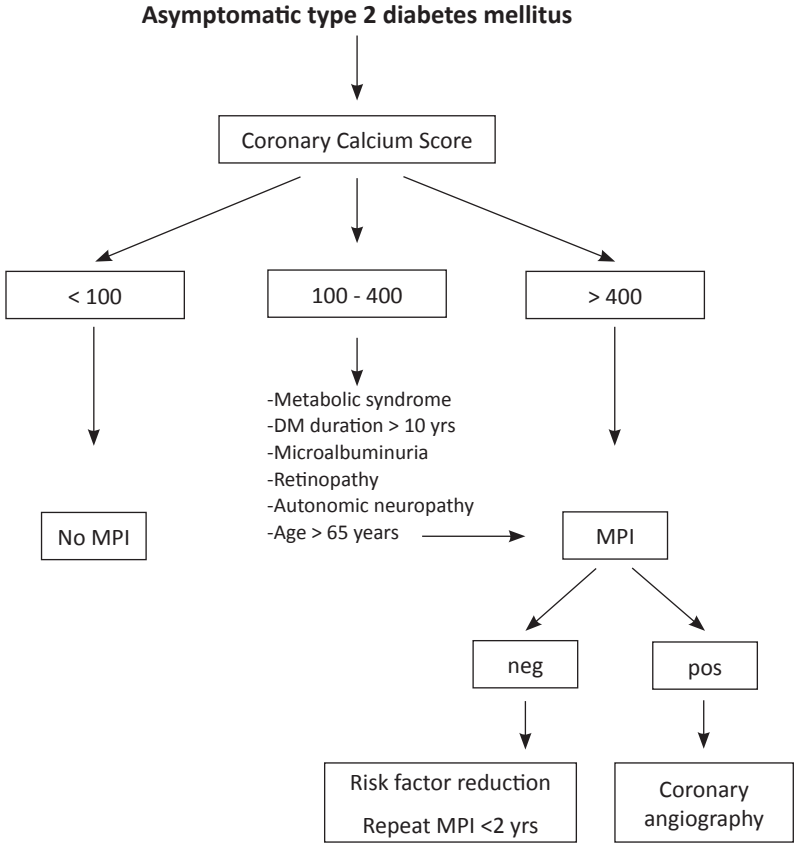
The recent findings of truly prospective studies in asymptomatic patients with diabetes mellitus, suggest a relatively low prevalence of silent CAD as evidenced by abnormal MPI. Although in most patients the MPI abnormalities were relatively modest, a significant number of patients had markedly abnormal test results.

CAC may occur in patients with and without abnormal MPI, but with increasing severity of CAC scores, the prevalence and severity of stress-induced MPI abnormalities increase. The screening of populations predisposed to CAD is performed to rule out (presumably indicating good prognosis) as well as to rule in (and treat) disease. At this time, it is not entirely clear, although presumed, that early detection of silent CAD and its treatment improves long-term outcome of asymptomatic individuals. Because of the relatively low overall prevalence of silent CAD (approximately 22%) it appears that screening all asymptomatic patients with diabetes mellitus by stress MPI may not be cost effective. Moreover, only a small number of patients may have severe MPI abnormalities. Thus it is important to device ways to enrich the target population. It has been suggested that conventional cardiac risk factors, duration of diabetes, macro and microvasculopathy, circulating markers such as C-reactive protein or plasminogen activator inhibitor-1 might be helpful to construct a “high-risk profile” for asymptomatic patients with diabetes mellitus. In the DIAD study none of these variables was associated with MPI abnormalities. Only male gender, body-mass-index and marked cardiac autonomic dysfunction were statistically associated with markedly abnormal MPI. The study by Anand et al suggests that CAC scoring might be an approach to identify an “enriched” asymptomatic patient population.

We propose an algorithm for the screening of asymptomatic diabetics (Figure 1). The first step of screening consists assessment of the CAC score by CT scanning. If the Agatston score is lower than 100, the yield of stress MPI is likely to be low and may not be indicated. If the Agatston score is between 100 and 400 and any of the following is present: metabolic syndrome, age greater than 65 years, duration of diabetes greater than 10 years, microalbuminuria, retinopathy, autonomic cardiac neuropathy, stress MPI appears justified. If the Agatston score is greater than 400, stress MPI is definitely indicated. If stress MPI shows evidence of myocardial ischemia, coronary angiography is indicated. If stress MPI is normal, aggressive medical treatment should be instituted and stress MPI has to be repeated within two years.

Prospective studies may be conducted to evaluate the effectiveness of such a screening approach and answer the following questions: Does the stepwise approach outlined in the algorithm yield higher prevalence of silent CAD? Is the outcome in patients with

Figure 1. Algorithm for screening of asymptomatic patients with diabetes mellitus.



MPI, myocardial perfusion imaging; DM, diabetes mellitus

low CAC score indeed favourable? Whether screening and early detection of disease ultimately result in improve outcome can only be evaluated in a large randomized treatment trial. It is conceivable that the BARI-2 trial will provide a partial answer to this pertinent question.

Chapter 3

Different manifestations of coronary artery disease by stress SPECT myocardial perfusion imaging, coronary calcium scoring and multislice CT coronary angiography in asymptomatic patients with type 2 diabetes mellitus

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Abstract

Background

We sought to assess prospectively evidence for silent coronary artery disease (CAD) in asymptomatic patients with type 2 diabetes mellitus by stress single-photon emission-computed tomography (SPECT) myocardial perfusion imaging, coronary artery calcium (CAC) scoring and multislice computed tomographic (MSCT) coronary angiography.

Methods

One hundred asymptomatic patients (aged 30 to 72 years) with type 2 diabetes mellitus and one or more risk factors for CAD were prospectively recruited from an outpatient diabetes clinic. All patients underwent adenosine technetium-99m sestamibi SPECT imaging, CAC scoring and 64-slice MSCT coronary angiography.

Results

Twenty-three patients (23%) had abnormal stress SPECT imaging consistent with inducible myocardial ischemia, whereas 60 patients (60%) had positive CAC scoring (18 patients [18%] with significant CAC >401), and 70 patients (70%) had abnormal MSCT coronary angiography (24 patients [24%] with significant ≥50% stenosis).

Of 77 patients with normal SPECT, 44 had a positive CAC score (10 patients [13%] >401) and 54 showed CAD on MSCT angiography (16 patients [21%] ≥50% stenosis). Of 23 patients with an abnormal SPECT, 16 patients had a positive CAC score (8 patients [35%] >401) and 16 patients had CAD on MSCT angiography (8 patients [35%] ≥50% stenosis). Overall, 17 patients (17%) had >2 significantly abnormal diagnostic test results, and 5 patients having three tests significantly abnormal.

Conclusion

In this cohort of asymptomatic patients with type 2 diabetes mellitus, different modalities visualized different aspects of silent coronary atherosclerosis. Anatomical evidence of coronary atherosclerosis (CAC and MSCT) occurred more frequently than functional evidence (stress SPECT). However, clinically significant manifestations of CAD were observed in about one-quarter to one-fifth by each modality, either separately or combined. The relative prognostic value of each modality needs to be determined by a follow-up of this cohort.

Introduction

Diabetes mellitus has become a worldwide healthcare problem and its prevalence continues to increase.[2, 16] Cardiovascular complications are the most common causes of mortality and morbidity in patients with type 2 diabetes mellitus.[7] Moreover, life expectancy is significantly affected by the presence or absence of cardiovascular disease in patients with diabetes mellitus.[57] Early identification of patients with diabetes and coronary artery disease (CAD) is essential for early initiation of appropriate treatment, which may affect favourably an otherwise poor outcome. However, the detection of CAD in patients with diabetes remains a challenge, because CAD is often without symptoms.

In the DIAD study the overall prevalence of silent myocardial ischemia by single-photon emission computed tomography (SPECT) was 22%. This included stress-induced regional myocardial perfusion abnormalities (16%) as well as ischemic electrocardiogram (ECG) changes during adenosine infusion or abnormal left ventricular function (6%).[36] Anand et al suggested that the diagnostic yield of screening by stress SPECT imaging could be enhanced by coronary artery calcium (CAC) scoring as first test.[43] In recent years, direct noninvasive visualization of CAD has become feasible with multislice computed tomographic (MSCT) coronary angiography. This technique allows for evaluation of the degree of luminal stenosis and noncalcified plaque in addition to calcifications.[58, 59] At the present time, it is unclear which of these three noninvasive diagnostic techniques is most effective for the detection of clinically important silent CAD in asymptomatic patients with type 2 diabetes mellitus.

The current observational study was designed to evaluate prospectively, in asymptomatic patients with type 2 diabetes, the comparative prevalence of evidence for coronary atherosclerosis by stress SPECT, CAC scoring and MSCT coronary angiography and their diagnostic interrelationship.

Methods

Patients and study protocol

Consecutive asymptomatic patients with type 2 diabetes mellitus were recruited in one outpatient diabetes clinic from May 2005 until January 2006. Inclusion criteria consisted of: (1) type 2 diabetes mellitus; (2) no angina or angina-equivalent symptoms; (3) a normal resting ECG. Exclusion criteria were: (1) known or suspected CAD; (2) history of coronary revascularization; (3) treatment with anti-anginal medication; (4) ventricular

and supraventricular arrhythmias; (5) contraindications for the use of iodinated contrast media (allergy and/or glomerulal filtration rate < 60 ml/min/1.73m^2). Asymptomatic status was determined using the questionnaire of Rose et al for angina.[15] The Framingham risk score of Wilson et al was used to calculate low, intermediate and high 10-year risk for coronary heart disease.[60]

Vasodilator stress SPECT myocardial perfusion imaging

Electrocardiogram-gated technetium-99m sestamibi (^{99m}Tc-sestamibi; 30 mCi) SPECT myocardial perfusion imaging was performed using a 2-day stress and rest protocol. All patients were instructed to abstain from caffeine-containing products from 24 hour before testing. Vasodilator stress was performed by intravenous infusion of adenosine (140 µg/kg/minute for 6 minutes) with simultaneously handgrip exercise. During adenosine infusion, blood pressure and 12-lead ECG were recorded every minute and during recovery. Ischemic ECG changes were defined as greater than 1-mm flat or downsloping ST-segment depression in two or more leads during adenosine infusion. SPECT imaging commenced 120 minutes after radiopharmaceutical injection using a triple-head SPECT gamma camera (GCA 9300/HG, Toshiba Corporation, Tokyo, Japan). Image acquisition was performed in concordance with the American Society of Nuclear Cardiology (ASNC) guidelines using a circular 180° orbit, 64 projections and 20 seconds/projection.[61, 62] No attenuation correction was applied. One experienced observer (FJTW), blinded to clinical data and results of CAC scoring and MSCT angiography, interpreted reconstructed stress-rest short- and long-axis slices by visual analysis. Images were categorized as either normal or abnormal. When abnormal, defect reversibility and stress defect severity were assessed using 17-segment colour-coded polar maps with normal reference files. Left-ventricular perfusion abnormalities were categorized on the basis of quantification as small (0 to 5% of the left ventricle), moderate (≥5 and <10%), or large (≥10%), as previously described.[36] Ischemic ECG changes during adenosine infusion are highly specific for CAD and were interpreted as abnormal stress SPECT result.[63]

Multislice computed tomography

MSCT was performed using a 64-slice Toshiba multislice Aquilion system (Toshiba Medical Systems, Tokyo, Japan). First, a coronary calcium scan without contrast was obtained using prospective triggering, followed by 64-slice MSCT angiography performed during electrocardiographic gating and the administration of non-ionic contrast at 5 mL/s ac-

cording to the protocols as described previously.[64, 65] If the heart rate was greater than or equal to 65 beats/minute additional oral β-blockers (metoprolol, 50 or 100 mg, single dose, 1 hour before examination) were provided as tolerated. Axial data sets were transferred to a remote workstation (Vitrea 2, Vital Images, Plymouth, Minnesota, USA) for post processing and subsequent evaluation.

Coronary artery calcium score

The CAC was assessed by two experienced observers (JWJ, JDS) using dedicated software (Vitrea 2, Vital Images). The CAC was identified as a dense area at the location of a coronary artery exceeding the threshold of 130 Hounsfield units (HU). An overall Agatston score was recorded for each coronary artery and per patient. Standard categorization of Agatston scoring was applied: less than 10, minimal; 11 to 100, mild; 101 to 400, moderate; 401 to 1000, severe; and greater than 1,000, extensive.

Coronary angiography

The MSCT coronary angiograms were evaluated by the same two experienced observers (JWJ, JDS), who were unaware of the results of SPECT imaging. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification and determined to be evaluable or not by visual inspection.[66] Subsequently, interpretable segments were evaluated for the presence of luminal stenoses, both by scrolling through the axial images and by inspecting curved multiplanar reconstructions. Significant coronary obstruction was defined as the presence of at least 1 stenosis of greater than 50% luminal narrowing, as assessed visually. Nonobstructive CAD was defined by the presence of atherosclerosis but not exceeding 50% luminal narrowing. Normal arteries were defined as the absence of any evidence of coronary atherosclerosis.

Statistical analysis

Categorical baseline characteristics are expressed as numbers and percentages. Continuous variables are expressed as mean (± standard deviation). Statistical analyses were performed using SPSS software (version 12.0, SPSS, Inc., Chicago, Illinois, USA) and SAS software (SAS system, release 6.12, SAS Institute, Inc., Cary, North Carolina). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

In total, 176 consecutive patients were screened. Sixty-nine (39%) patients were ineligible for the study. Twenty-five (14%) patients had an abnormal resting ECG, including 4 patients with atrial fibrillation. Nineteen (11%) patients were on anti-anginal medication for chest-pain symptoms. Seven (4%) patients had contraindications for the use of iodinated contrast media. Eighteen (10%) patients had a questionnaire of Rose et al that was positive for angina.

Consequently, 107 (61%) patients were eligible for the study. Four patients refused to participate; one patient was later excluded because of uninterpretable SPECT images, and 2 patients because of an uninterpretable MSCT. Thus, the final study population consisted of 100 patients (65 men; age, 53 ± 10 years). The patient characteristics are shown in Table 1.

The mean duration of diabetes mellitus was 9.4 ± 7.0 years. Most of the patients were on oral anti-diabetic therapy (61%). Statins were used by 54% of the patients. Thirty-seven patients had complications of diabetes mellitus, such as peripheral vascular disease (n=14), peripheral neuropathy and retinopathy.

SPECT myocardial perfusion imaging

Twenty patients (20%) had regional perfusion abnormalities (Figure 1). Eighteen of these perfusion abnormalities were reversible defects. Most regional perfusion abnormalities were relatively small; only 3 patients had moderate-sized perfusion defects. Ischemic ECG changes during adenosine infusion occurred in 6 patients. Three of these patients had also regional perfusion abnormalities: two were small and one was moderate in size. The other three patients had normal perfusion. In total, 23 patients (23%) had abnormal stress perfusion studies (Figure 1).

CAC scoring

No CAC was present in 40 patients (40%). Sixty patients (60%) had evidence of CAC. By Agatston scoring the amount of calcium was minimal in 5 (5%) patients, mild in 21 (21%) patients, moderate in 16 (16%) patients and severe in 18 patients (18%). Of 18 patients with Agatston score greater than 401, 7 patients had a score greater than 1,000 (Figure 1).

Table 1. Clinical characteristics of 100 asymptomatic patients with type 2 diabetes.

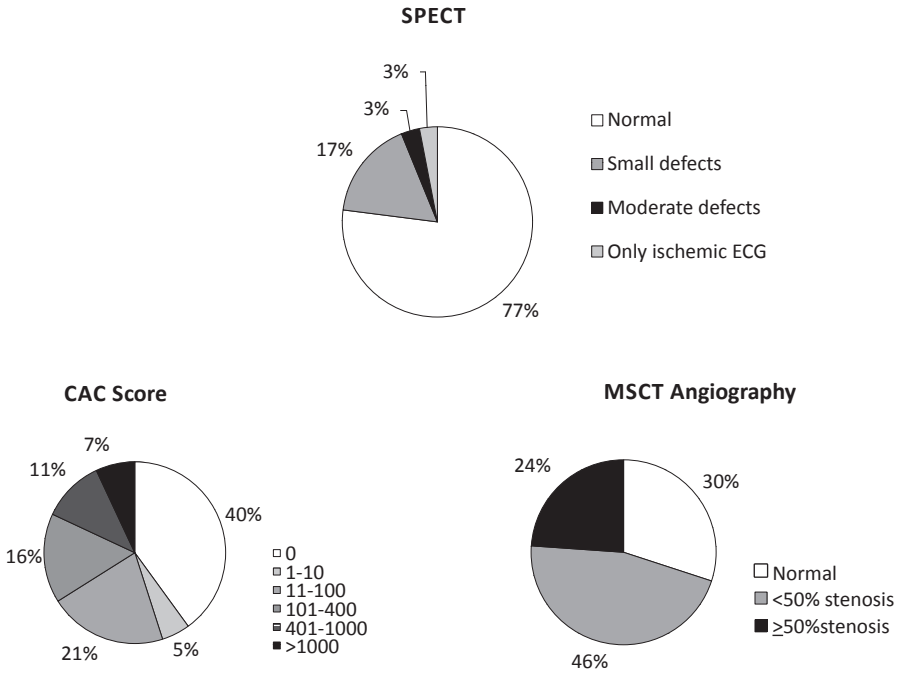
Gender (M/F)	65/35
Age (yrs)	53 ± 10
Diabetes-related risk factors	
Diabetes duration (yrs)	9.4 ± 7.0
Age at time of diagnosis of diabetes (yrs)	44 ± 12.0
HbA_{1C} (%)	7.3 ± 1.6
Treatment	
Diet only	0 (0%)
Oral	61 (61%)
Insulin and oral agent	16 (16%)
Insulin	23 (23%)
Retinopathy	12 (12%)
Peripheral vascular disease*	14 (14%)
Body mass index (kg/m^2)	29 ± 5.0
Waist circumference (cm)	102 ± 13.0
Microalbuminuria	45 (45%)
Hypertension	51 (51%)
Hypercholesterolemia	53 (53%)
Family history of CAD^	51 (51%)
Smoking	
Past	24 (24%)
Current	12 (12%)
Medication	
Aspirin	21 (21%)
ACE-inhibitors/ARB	35 (35%)/20 (20%)
Statins	54 (54%)

Values are presented as number (ratio in %) or mean ± standard deviation.
ACE, angiotension converting enzyme; ARB, angiotensin receptor blockers; HbA_{1c}, haemoglobin A_{1c}; CAD, coronary artery disease; yrs, years; kg, kilogram; m^2, square meter.
* Peripheral vascular disease was determined based on clinical history
^ A positive family history was defined by the diagnosis of CAD in parents or siblings before the age of 50 years

MSCT coronary angiography

MSCT coronary angiography was normal in 30 patients (30%). The remaining 70 patients (70%) showed luminal narrowing of one or more coronary arteries (Figure 1). Forty-six had nonobstructive atherosclerosis, 11 had single-vessel involvement (24%), 16 had two-vessel involvement (35%) and 19 had three-vessel involvement (41%). Twenty-four patients (24%) had significant luminal narrowing greater than 50%, and none had single-vessel involvement, 8 (33%) had two-vessel involvement and 16 (67%) with three-vessel involvement. One patient had greater than 50% left main coronary artery stenosis.

Figure 1. Distribution (%) of diagnostic findings on stress single-photon emission computed tomography (SPECT), coronary artery calcium (CAC) scoring and multislice computed tomography (MSCT) angiography in 100 asymptomatic patients with type 2 diabetes.



Framingham risk score and abnormal test results

The relationship between Framingham risk score and abnormal findings on stress SPECT, CAC and MSCT coronary angiography is shown in Table 2. No relation between risk score and abnormal imaging findings was observed.

SPECT imaging and CAC

The relationship between CAC scoring and stress SPECT imaging is shown in Figure 2. Of 77 patients with normal SPECT imaging, 33 (43%) had no CAC, but CAC was present in 44 (57%). The mean CAC score in these 44 patients was 278 ± 394. The CAC score was minimal in 4 patients (9%), mild in 15 patients (33%) and moderate in 15 patients (33%). Ten patients (13%) with normal SPECT had a CAC score greater than 401, which was severe in 8 patients, and extensive (greater than 1,000) in 2 patients.

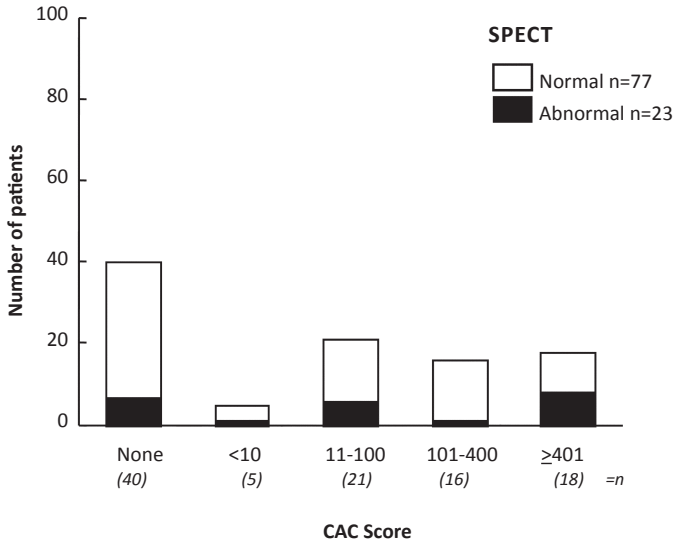
Of 23 patients with abnormal SPECT imaging, 7 patients (30%) had no evidence of CAC.

Table 2. Relation between abnormal SPECT, CAC score greater than or equal to 401 AU, MSCT coronary angiography indicating stenosis greater than or equal to 50% and Framingham risk score in 100 asymptomatic patients with type 2 diabetes.

	Low risk n=39	Intermediate risk n=42	High risk n=19
Abnormal SPECT	12 (31%)	6 (14%)	5 (26%)
CAC score ≥ 401 AU	5 (13%)	8 (19%)	5 (26%)
MSCT coronary angiography ≥ 50% stenosis	4 (10%)	14 (33%)	6 (32%)

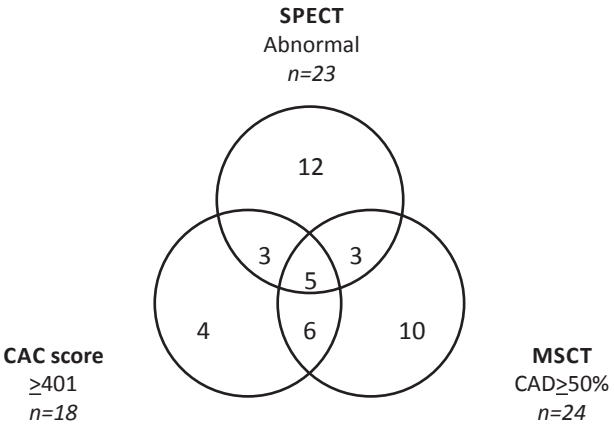
AU, Agatston units; CAC score, coronary artery calcium score; MSCT, multislice computed tomography; SPECT, single-photon emission computed tomography.

Figure 2. Coronary Artery Calcium (CAC) score and number of patients with normal and abnormal single-photon emission computed tomography (SPECT) imaging.



In the 16 remaining patients (70%) with abnormal SPECT images, the mean CAC score was 1,581 ± 2,469 (*P* = NS compared to patients with normal SPECT). The CAC score was minimal in 1 patient, mild in 6 patients and moderate in 1 patient. Eight patients (35%) had a CAC score greater than or equal to 401. Fourteen of 66 patients (21%) with CAC less than or equal to 100 had abnormal stress SPECT, compared to 9 of 34 patients (26%) with CAC greater than 100 (*P* = 0.7). Of note, two of three patients with ischemic ECG changes without perfusion abnormalities had CAC score greater than or equal to 401 (954 and 8,730, respectively).

Figure 3. Ven diagram showing the interrelationship between abnormal stress SPECT, CAC score greater than or equal to 401 and obstructive (≥50%) CAD on MSCT. In 17 patients (17%) more than 2 diagnostic tests were abnormal; 5 patients had three abnormal test results.



CAC score, coronary artery calcium score; CAD, coronary artery disease, MSCT, multislice computed tomography; SPECT, single-photon emission computed tomography.

SPECT imaging and MSCT coronary angiography

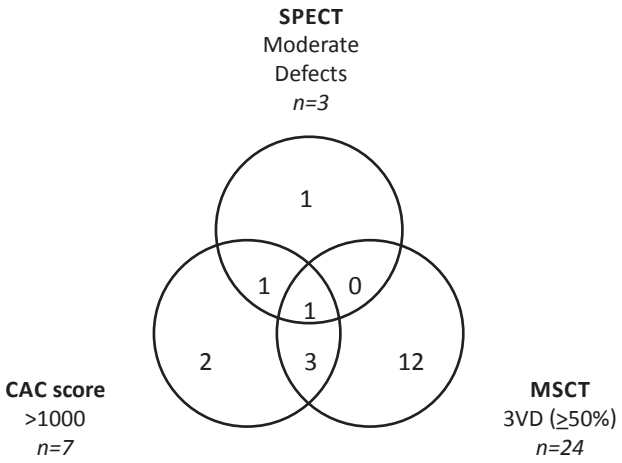
Of the 77 patients with a normal SPECT, 23 (30%) had a normal MSCT coronary angiogram. However, in the remaining 54 patients (70%) with normal SPECT, MSCT angiography was abnormal, 38 had nonobstructive (less than 50%) luminal narrowing and 16 patients had stenoses greater than or equal to 50% stenoses.

Of 23 patients with abnormal SPECT imaging, 7 patients (30%) had a normal MSCT coronary angiogram. Of the remaining 16 patients (70%) with abnormal SPECT, 8 patients had nonobstructive luminal narrowing and 8 patients had stenosis greater than or equal to 50%. Of note, all 3 patients with ischemic ECG changes during adenosine infusion, without perfusion abnormalities on SPECT, had nonobstructive CAD on MSCT.

SPECT imaging, CAC and MSCT coronary angiography

Figure 3 shows the interrelationship of clinically significant, abnormal diagnostic test results. Seventeen patients (17%) had more than 2 abnormal diagnostic tests, whereas in 5 patients all 3 tests were abnormal. Figure 4 shows the interrelationship for 3 patients with moderate myocardial perfusion defects. Two of 3 patients had also other abnormal test results.

Figure 4. Ven diagram showing the interrelationship between moderate-sized myocardial perfusion defects on SPECT, extensive (>1,000) CAC score, and three-vessel CAD (stenosis ≥50%) on MSCT.



CAC score, coronary artery calcium score; CAD, coronary artery disease; MSCT, multislice computed tomography; 3VD, three-vessel disease.

Referral for invasive angiography

In total, 7 patients were referred for invasive angiography. Three of 7 patients had both abnormal MSCT and SPECT. Invasive angiography demonstrated in all 3 patients significant multivessel CAD, requiring percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Three other patients underwent invasive angiography because of abnormal MSCT (but normal SPECT). Invasive coronary angiography showed nonobstructive CAD in 2 patients, whereas 1 patient had significant CAD for which he underwent CABG. Finally, 1 patient was referred because of abnormal SPECT in combination with nonobstructive CAD according to MSCT. Invasive angiography showed significant single-vessel disease, which was subsequently treated with PCI.

Discussion

To the best of our knowledge, this is the first study to evaluate the prevalence of manifestations of coronary atherosclerosis in asymptomatic patients with type 2 diabetes by three distinctly different noninvasive diagnostic imaging variables. Anatomical evidence of coronary atherosclerosis by CAC and MSCT coronary angiography occurred more fre-

quently than functional evidence of CAD by abnormal stress SPECT imaging. However, when only clinically significant abnormalities were considered, i.e., stress myocardial perfusion defects (including ischemic ECG changes), a CAC score greater than 401 and coronary artery stenosis greater than or equal to 50%, the observed prevalences were rather similar: 23%, 18%, and 24%, respectively. Although only 5% of patients had all three tests abnormal, more than 2 abnormal tests occurred in 17% of patients. These prevalences are in the range of 22% prevalence of silent ischemia recently reported in a similar patient population in the DIAD study.[36]

Several recent studies evaluated the interrelationship between abnormal SPECT imaging, CAC scoring and MSCT coronary angiography, either separately or in combination.[55, 67, 68] These investigations suggested that abnormal findings on each of these modalities must be viewed as complementary. In a study from our own institution, comparing SPECT with MSCT coronary angiography, anatomic evidence of atherosclerosis was frequently not associated with inducible ischemia. Conversely, normal stress myocardial perfusion images did not exclude atherosclerosis.[67] With regards to CAC, patients with abnormal SPECT images have higher likelihood of significant CAC; the prevalence of an abnormal SPECT study parallels the increasing severity of CAC score.[55] However CAC (even severe) occurred also in patients with normal SPECT images.[55, 68] These observations are in agreement with a long-established notion that no tight correlation exists between apparently anatomically significant CAD and stress-inducible ischemia. The present study illustrates similar inconsistent interrelationships in Figure 3 and 4. Possibly, plaque extent, location and composition, are also important predictors of ischemia in addition to the degree of stenosis or extent of coronary artery calcifications.

The studies cited above were performed in general symptomatic and asymptomatic patient cohorts with known or suspected CAD. How these data apply to asymptomatic patients with diabetes is unclear. Wong et al showed that CAC scores greater than 400 in patients with metabolic syndrome and diabetes indicated markedly increased risk for inducible myocardial ischemia.[56] Anand et al suggested CAC scoring as a methodology for pre-screening asymptomatic patients with diabetes to enhance the yield of stress SPECT myocardial perfusion imaging.[43] The authors observed that few patients with CAC less than 100 had stress SPECT myocardial perfusion abnormalities. In our study however patients with CAC less than 100 had similar prevalence of abnormal SPECT images as patients with CAC greater than 100. In addition to the presence of microvascular disease, a possible explanation for this finding could be a relatively high proportion of patients with noncalcified atherosclerosis. A recent study comparing computed tomography an-

giography to CAC observations in asymptomatic patients with type 2 diabetes showed that CAD was present in 55% of patients with CAC <10, indicating the presence of noncalcified rather than calcified plaque burden.[69] Accordingly, it is conceivable that in our study, the presence of noncalcified atherosclerosis could have attributed to myocardial ischemia in patients with a CAC score less than 100.

Thus, the three diagnostic imaging variables reflect different aspects of the atherosclerotic process. Myocardial perfusion defects may be caused by flow-limiting epicardial coronary artery stenoses, but also by microvascular disease and endothelial dysfunction, and remains at present the only technique established for clinical decision making with regard to medical or interventional treatment. CAC indicates calcium accumulation in the vessel walls and consequently atherosclerosis with or without vascular remodelling. Coronary artery stenoses on MSCT coronary angiography indicate luminal narrowing, but the technique cannot distinguish between lesions that are physiologically relevant and not.

Limitations

An important limitation of our study is that the study population was relatively small. Our observations need to be confirmed in a larger patient cohort of asymptomatic patients with diabetes mellitus. Having demonstrated important discrepancies in manifestations of atherosclerosis between the three noninvasive diagnostic imaging modalities, the significance of this observation is not clear. Is one modality more valuable than the other? Only follow-up of this patient cohort and outcome data on future hard cardiac events will provide insight in this conundrum. Indeed, follow-up data of these patients are currently being acquired.

Conclusion

In this cohort of asymptomatic patients with type 2 diabetes mellitus, different noninvasive diagnostic modalities visualized different aspects of silent coronary atherosclerosis. Anatomical evidence of coronary atherosclerosis (CAC and MSCT) occurred more frequently than functional evidence (stress SPECT). However, presumably clinically significant manifestations of CAD were observed in about one-quarter to one-fifth of the cohort by each modality, either separately or combined. The relative prognostic value of each modality will be determined by follow-up in this cohort.

Chapter 4

Prevalence of coronary artery disease and plaque morphology assessed by multislice computed tomography coronary angiography and calcium scoring in asymptomatic patients with type 2 diabetes

AJHA Scholte, JD Schuijf, AV Kharagjitsingh, JW Jukema, G Pundziute, EE van der Wall, JJ Bax

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Abstract

Objective

The purpose of the study was to evaluate the prevalence of CAD as well as plaque morphology in asymptomatic patients with type 2 diabetes using multislice computed tomography (MSCT). In addition, the relation between calcium score and MSCT findings was explored.

Design

In 70 patients, coronary calcium scoring and noninvasive coronary angiography were performed. Angiograms showing atherosclerosis were further classified as obstructive (≥50% luminal narrowing) CAD or not. Plaque type (noncalcified, mixed and calcified) was determined. Finally, the relation between calcium score and MSCT findings was explored.

Results

A calcium score <10 was observed in 31 (44%) patients. A calcium score of 10-100 was observed in 14 (20%) patients while a score of 101-400 or >400 was identified in respectively 12 (17%) and 13 (19%) patients. Noninvasive coronary angiography showed CAD in 56 (80%) patients.

322 coronary segments with plaque were identified, of which 132 (41%) contained noncalcified plaques, 65 (20%) mixed plaques and 125 (39%) calcified plaques. The percentage of patients with obstructive CAD paralleled increasing calcium score. The presence of CAD was noted in 17 (55%) patients with no or minimal calcium (score <10).

Conclusion

MSCT angiography detected a high prevalence of CAD in asymptomatic patients with type 2 diabetes. A relatively high proportion of plaques were noncalcified (41%). Importantly, a calcium score < 10 did not exclude CAD in these patients. MSCT might be a useful technique to identify CAD in asymptomatic patients with type 2 diabetes with incremental value over calcium scoring.

Introduction

Diabetes mellitus has reached epidemic proportions and has become a major public health problem. Almost 200 million individuals are known to have diabetes and this number is expected to increase exponentionally. In the USA almost 1.3 million new subjects are diagnosed with diabetes each year.[16]

Cardiovascular complications, including coronary artery disease (CAD), are the leading causes of morbidity and mortality in individuals with type 2 diabetes mellitus.[6] The overall prevalence of CAD has been reported to be as high as 60% in patients with diabetes referred for stress testing.[17] The 10-year mortality in patients with known CAD and diabetes exceeds 70%.[7] The poor clinical outcome in patients with diabetes underscores the need to develop practical approaches for detecting CAD at an early stage. Moreover, in patients with diabetes mellitus, CAD has frequently progressed to an advanced state before it becomes clinically manifest.[8, 9]

The role of single photon emission computed tomography (SPECT) in asymptomatic diabetics has recently been evaluated. The Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics (DIAD) study is an ongoing randomized study using gated SPECT for risk stratification in asymptomatic patients with diabetes type 2. In 22% of patients (silent) myocardial ischemia was noted, with 16% showing abnormal perfusion on SPECT.[36]

Recently, multislice computed tomography (MSCT) has been proposed as an alternative imaging modality for the evaluation of patients with known or suspected CAD.[59] MSCT allows anatomic, noninvasive imaging of the coronary arteries, including detection of coronary atherosclerosis by assessing the coronary artery calcium burden (calcium scoring) and by performing noninvasive angiography. This technique has the potential to detect CAD at an early stage. With the recently introduced 64-slice MSCT, high sensitivity and specificity for the detection of significant (≥50% luminal narrowing) stenoses have been reported and this technique has been validated against conventional coronary angiography and intravascular ultrasound.[65, 70-77] The purpose of this study was to evaluate the prevalence of CAD in a large cohort of asymptomatic type 2 diabetic patients using MSCT angiography. The plaque constitution of the coronary artery lesions was also evaluated, and the relation between calcium scoring and noninvasive angiography was explored.

Design

Patients

Seventy-three asymptomatic patients with type 2 diabetes mellitus were included. All patients were referred from an outpatient diabetic clinic to our institution for assessment of cardiovascular risk. Inclusion criteria consisted of type 2 diabetes mellitus, no angina or angina-equivalent symptoms. Exclusion criteria were: known or suspected CAD; history of coronary revascularization; treatment with anti-anginal medication; ventricular and supraventricular arrhythmias; contraindications for the use of iodinated contrast media. Patients were excluded from analysis when an irregular heart rate during MSCT data acquisition rendered the MSCT data set uninterpretable. Asymptomatic status was confirmed using the Rose questionnaire for angina.[15] The study was part of a clinical study for patients referred to the MSCT for which clinical approval was obtained.

MSCT, data acquisition

Imaging was performed using a 64-slice MSCT scanner (Aquilion 64, Toshiba Medical Systems, Japan). If the heart rate was ≥ 65 beats/min, additional oral beta-blockers (metoprolol 50 mg, single dose, 1 hour before scan) were provided when tolerated.

First, a prospectively triggered coronary calcium scan was performed before MSCT angiography. Accordingly, data were acquired with a collimation of 64 x 0.5 mm and a tube rotation time of 400 milliseconds, and tube current of 300 mA at 120 kV for patients with normal posture (BMI< 30 kg/m^2). In case of patients with higher body mass indexes (>30), tube current was increased to 350 or 400 mA at 135 kV. The temporal window was set at 75% after the R-wave for electrocardiographically triggered prospective reconstruction. 80 to 110 ml non-ionic contrast material, depending on the total scan time, was administered with a flow rate of 5 ml/sec (Iomeron 400®, Bracco Atlanta Pharma, Konstanz, Germany). Automated detection of peak enhancement in the aortic root was used for timing of the scan. All images were acquired during an inspiratory breath hold of approximately 10 seconds, with simultaneously registration of the patient's electrocardiogram. Subsequently, data sets were reconstructed and transferred to a remote workstation as previously described.[75] Briefly, images were initially reconstructed at 75% of the cardiac cycle. In case of motion artefacts, a representative single slice was reconstructed throughout the cardiac cycle in steps of 20 milliseconds to determine the most optimal additional reconstruction phases.

MSCT, data analysis

Coronary artery calcium score

The coronary artery calcium score was assessed with the application of dedicated software (Vitrea 2, Vital Images, USA). Coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 Hounsfield units. An overall Agatston score was recorded for each patient.

Coronary plaque assessment

All angiograms were evaluated by two experienced observers (JWJ, JDS) unaware of the clinical history of the patients. In case of disagreement, a joint reading was performed and a consensus decision was reached. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification.[66] Only segments with a diameter > 1.5 mm (as measured on the MSCT coronary angiogram) were included. First, each segment was classified as interpretable or not. Then, the interpretable segments were evaluated for the presence of any atherosclerotic plaque using axial images and curved multiplanar reconstructions. Coronary plaques were defined as structures > 1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue, as described previously.[58]
As adequate distinction between a single lesion and the presence of diffuse atherosclerosis extending over several segments may be difficult in some cases, it was chosen to perform the analysis on a segmental basis, also in order to improve reproducibility of the results. One coronary plaque was assigned per segment. Subsequently, the type of plaque was determined using the following classification: 1) noncalcified plaques, plaques having lower density compared with the contrast-enhanced vessel lumen; 2) calcified plaques, plaques with high density; and 3) mixed plaques, plaques with noncalcified and calcified elements within a single plaque. Finally, it was determined whether the lesion was obstructive or not, using a threshold of 50% luminal narrowing. For each patient the number of diseased vessels and number of each type of plaque was determined. Patients without plaques were considered normal; an abnormal MSCT was defined in the presence of ≥ 1 coronary plaque.

Statistical analysis

Continuous variables were expressed as mean and standard deviation. Proportions were expressed in percentages. Statistical analysis was performed using SPSS 12.0 software.

Results

Patient Characteristics

In total 73 patients were referred from the outpatient diabetic clinic and enrolled in the present study. Three patients (4%) were excluded from the analysis because of an irregular heart rate during MSCT data acquisition, which rendered the MSCT data set uninterpretable. Baseline characteristics of the 70 analyzed patients are provided in Table 1. The majority of the patients were male (74%). The mean duration of diabetes was 110 ± 88 months.

MSCT

Coronary artery calcium score

As shown in Figure 1, coronary calcium was absent or the calcium score was less than 10 in 31 (44%) patients. A calcium score of 10-100 was observed in 14 (20%) patients, a score of 101-400 in 12 (17%) patients, and 13 (19%) patients had a calcium score >400.

Coronary angiography

MSCT identified 14 (20%) patients without CAD and 56 (80%) patients with CAD.

A total of 38 (54%) patients had nonobstructive CAD, and 18 (26%) patients had obstructive CAD (at least 1 significant (≥50%) stenosis) (see Figure 2).

In the 38 patients with nonobstructive CAD, 10 (26%), 8 (21%), and 20 (53%) had 1-, 2-,

Figure 1. Bar graph showing the coronary calcium score categories in the study population.

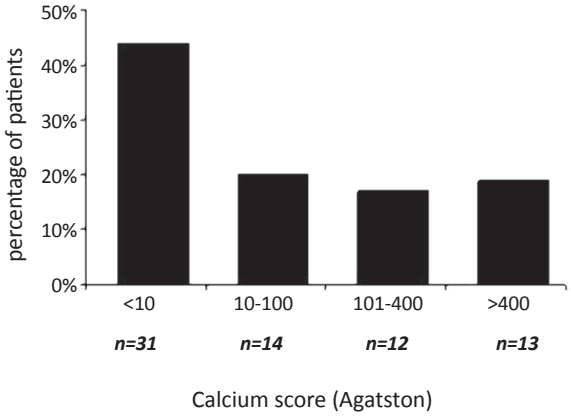


Table 1. Characteristics of the study population (n=70)

Clinical characteristics	
Age (yrs)	54 ± 11
Gender (male)	52 (74%)
BMI(kg/m^2)	29 ± 5
Circumferential length (cm)	101 ± 13
Age at diabetes diagnosis (yrs)	45 ± 12
DM duration (months)	110 ± 88
Hypercholesterolemia	36 (51%)
Hypertension	36 (51%)
Smoking	15 (21%)
Family history of CAD	37 (53%)
Laboratory findings	
Creatinine (µmol/L)	84 ± 20
HbA1C (%)	7.2 ± 1.6
Cholesterol (mmol/l)	4.8 ± 1.1
Microalbuminuria/Creatinine ratio (> 3.5µg/µmol)	26 (37 %)
Medical therapy	
Insulin	13 (19%)
Oral agent	44 (63%)
Insulin plus oral agent	11 (16%)
ACE inhibitors	24 (34%)
AT-2 blockers	15 (21%)
Statins	33 (47%)
Aspirin	16 (23%)
DM related complications	37 (53%)
(Peripheral vascular disease, polyneuropathy, retinopathy)	

Data are means ± SD or n (%) ACE, angiotensin converting enzyme; AT-2, Angiotensin 2; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus.

and 3-vessel disease, respectively. Regarding the 18 patients with obstructive CAD, 1, 2, and 3 vessels were significantly diseased in 0 (0%), 4 (22%), and 14 (78%) patients.

Plaque morphology

A total of 15 (1.3%) of 1190 coronary segments were not interpretable due to motion artefacts. In the 56 patients with CAD, 322 coronary segments with plaques were observed.

Fifty-nine (18%) plaques were obstructive and 263 (82%) plaques were nonobstructive. 132 (41%) contained noncalcified plaques, 65 (20%) mixed plaques and 125 (39%) calcified plaques, as illustrated in Figure 2B.

Figure 2. Prevalence of CAD in 70 patients with asymptomatic type 2 diabetes mellitus. (A) Only 20% of patients showed normal coronary arteries. Plaque morphology in 322 diseased coronary segments showing a relative high proportion of non-calcified plaques.(B)

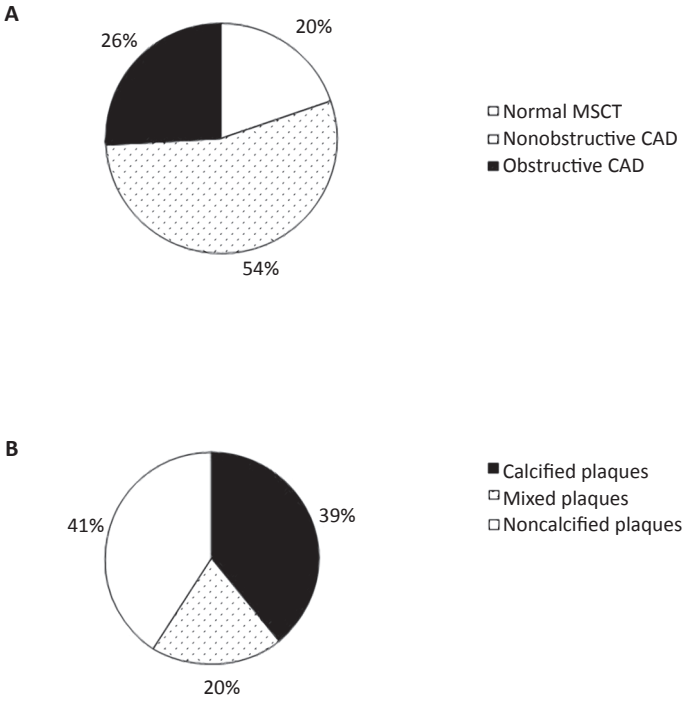
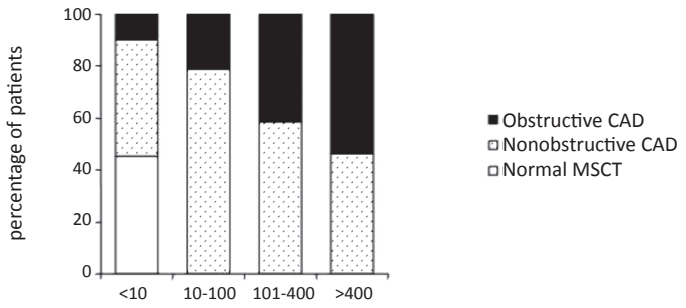


Figure 3. Bar graph demonstrating the distribution of both obstructive and nonobstructive coronary artery disease (CAD) per coronary artery calcium (CAC) score category.



Coronary calcium score versus coronary angiography

Comparison of the coronary artery calcium score and MSCT angiography showed that the percentage of patients with obstructive CAD paralleled the increasing calcium score; increasing from 10% in patients with minimal calcium (score <10) to 54% in patients with calcium score >400 (Figure 3). Still, in patients with minimal calcium (score <10), the presence of CAD was detected on noninvasive coronary angiography in 55% (n=17) of the patients. In these patients, CAD was nonobstructive in 82% (n=14) and obstructive in 18% (n=3) patients.

Discussion

The main findings of this study can be summarized as follows. First, MSCT could detect CAD in 80% of asymptomatic patients with type 2 diabetes. In addition, in 56% of patients an elevated calcium score (>10) was observed. Although most patients presented with nonobstructive CAD, in 26% of the patients at least 1 significant coronary artery stenosis was detected. Furthermore, in the majority of patients with nonobstructive CAD, diffuse disease was noted involving the entire coronary tree.

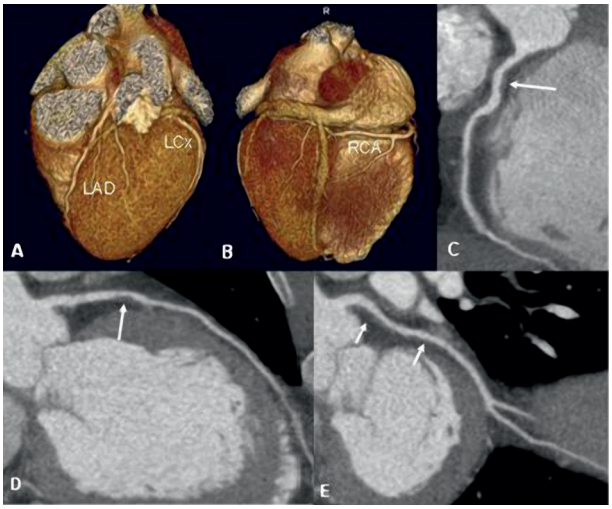
Second, coronary plaque composition was explored and revealed a relatively high proportion of noncalcified (41%) plaques.

Finally, the relation between the coronary calcium score and CAD on noninvasive angiography was evaluated. In line with the high prevalence of noncalcified plaques, considerable atherosclerosis was noted in patients without (or minimal) coronary artery calcium. These findings suggest that noninvasive angiography with MSCT may provide additional information to calcium scoring for detection of CAD.

Prevalence of CAD

In diabetic patients, the diagnosis of CAD is frequently missed or delayed since the typical symptoms of myocardial ischemia are often masked. Before symptoms of ischemia occur, diffuse multi-vessel atherosclerosis is often present. It has been shown that risk and mortality from CAD in patients with type 2 diabetes are similar to patients without diabetes and previous myocardial infarction.[7] Moreover, the combination of CAD and diabetes strongly increases adverse outcome and underscores the need to develop practical approaches for detecting CAD at an early stage before clini-

Figure 4. Example of a patient with noncalcified atherosclerosis on MSCT.



In (A) and (B) 3D volume rendered reconstructions are provided, showing the left anterior descending (LAD) and left circumflex (LCx) coronary artery in (A), whereas the right coronary artery (RCA) can be observed in (B). C- E) curved multiplanar reconstructions of respectively the RCA, LAD and LCx. In all three coronary arteries, atherosclerosis in the absence of calcifications can be observed (white arrows).

cal complications have occurred. This approach may permit prevention of complications and reduce morbidity and mortality in these patients.

Two recent studies used nuclear imaging with SPECT and showed a prevalence of (silent) myocardial ischemia ranging from 18% to 22% in truly asymptomatic patients with type 2 diabetes.[36, 43] However, SPECT reflects only indirectly the presence of CAD, since it is based on the detection of coronary lesions that result in compromised blood flow during stress, whereas the actual prevalence of any atherosclerosis in asymptomatic patients with diabetes mellitus may be higher. Indeed, in the current study with MSCT, CAD was observed in 80% of asymptomatic patients with type 2 diabetes mellitus. Furthermore, the majority of patients showed diffuse involvement of all three coronary arteries. The high prevalence of coronary atherosclerosis among diabetic patients without clinical CAD has been defined previously in a large autopsy cohort of 293 decedents.[76] In line with the current observations, coronary atherosclerosis was observed in almost 75% of individuals with 50% having diffuse multi-vessel CAD.

Noninvasively, calcium scoring has been proposed to determine the prevalence of atherosclerosis. Previous studies in the general population have demonstrated that the extent of coronary artery calcium strongly correlates with the overall magnitude of atherosclerotic plaque burden and subsequent risk of coronary events.[77-79]

In the current study, coronary calcifications (calcium score >10) were observed in 56% of patients. Moreover, extensive calcifications were observed in 19% of patients. These observations are in line with previous investigations.[49, 80]

Plaque morphology

In addition to the presence of (significant) CAD, plaque characteristics were also assessed in the current study. Analysis of the relative proportion of nonobstructive and obstructive plaques revealed that plaques were mainly nonobstructive (82%). A similar relation between diabetes and nonobstructive plaques has been shown in studies using invasive coronary angiography.[81] It is important to realize that many of these nonobstructive lesions will not be associated with stress-inducible ischemia, thus showing normal perfusion during stress nuclear imaging. Nonetheless, plaque rupture has been suggested to occur frequently in nonobstructive plaques[49, 80-82] and detection of an increased nonobstructive plaque burden using atherosclerosis imaging may therefore be of clinical importance in asymptomatic patients with diabetes.

With regard to plaque constitution, 41% of the plaques were classified as noncalcified plaques, 20% as mixed and 39% as calcified plaques. Recently, Mollet et al reported on plaque constitution in patients with stable CAD using MSCT. In this population, plaques were noncalcified in 24%, while the vast majority of lesions (65%) were calcified.[79] Accordingly asymptomatic diabetic patients appear to have a higher prevalence of noncalcified plaques which are mainly nonobstructive. These findings are of clinical importance, since these plaques may be vulnerable to rupture and may be related to the high cardiovascular mortality and morbidity in diabetic patients. Indeed, in a large study by Raggi et al involving 903 asymptomatic diabetic patients, similar event rates were observed at a lower calcium score as compared to non-diabetic patients, suggesting that noncalcified plaques may (to some extent) determine the event rate in diabetic patients.[78]

Value of calcium scoring versus noninvasive angiography to detect CAD

In a next step, the relationship between calcium score and the extent of CAD on MSCT was investigated. The prevalence of obstructive CAD paralleled the increasing calcium score, with 54% of patients with a calcium score >400 having at least 1 significant stenosis. Nevertheless, a calcium score <10 was associated with normal coronary arteries on MSCT in only 45% of patients, whereas 55% of patients still had (noncalcified) athero-

sclerosis. These findings underscore the additional value of noninvasive angiography to calcium scoring for assessment of CAD using MSCT.

Clinical Implications

Identification of CAD in asymptomatic patients with type 2 diabetes can be of clinical relevance since clinical outcome may considerably improve if aggressive medical therapy is initiated at an early stage. Screening of asymptomatic diabetic patients however, is a heavily debated topic.[82, 83] Recently, calcium scoring has been suggested as a first screening tool for CAD in asymptomatic diabetic patients.[43] However, the recent findings indicate that noncalcified atherosclerotic plaques are frequently present, in the absence of coronary artery calcium. Whether screening of asymptomatic patients is useful, and whether calcium scoring with or without MSCT angiography has a role in this process, needs to be addressed in large future studies.

Limitations

Several limitations should be mentioned. First, only a limited number of patients were studied and data concerning the prevalence of atherosclerosis as determined by MSCT in larger populations are needed. Also, despite the excellent diagnostic accuracy of MSCT, uninterpretable segments due to motion artefacts remain problematic. In the current study, 3 (4%) patients were excluded from analysis for this reason. Finally, the radiation burden (10-15 mSv) of MSCT remains a drawback of this imaging modality. However, a reduction in radiation burden is anticipated with the new generation of 256-slice MSCT scanners and dose-modulation strategies that are currently being developed.

Conclusion

MSCT angiography detected a high prevalence of CAD in asymptomatic patients with type 2 diabetes. A relatively high proportion of plaques was noncalcified (41%) and calcified (39%). Accordingly, a calcium score < 10 did not exclude CAD in this particular cohort of patients and appeared of limited value. MSCT angiography may provide additional information over calcium scoring in asymptomatic patients with diabetes type 2.

Chapter 5

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

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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.

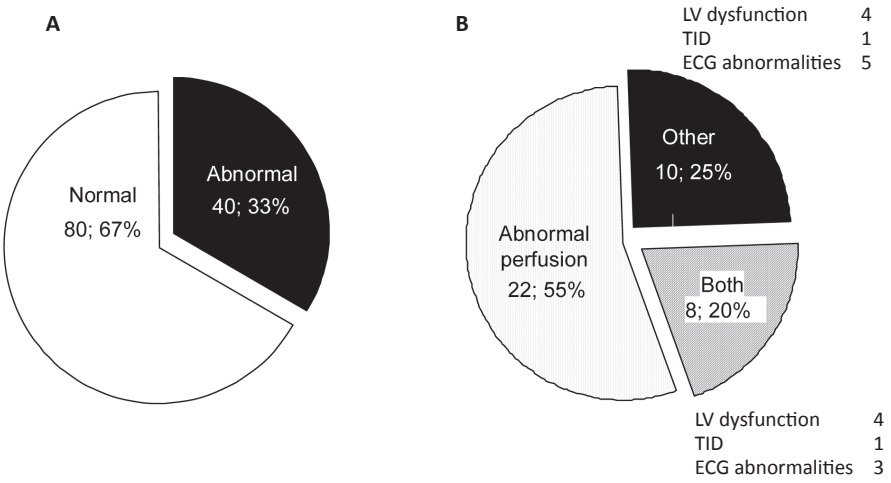
Transient ischemic dilatation, increased lung uptake and ST segment ECG changes

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.

Chapter 6

The difficulty of adequate risk stratification for patients with asymptomatic diabetes

AJHA Scholte, JD Schuijf, MPM Stokkel, A de Roos, JJ Bax

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Case report

A 43–year old man with diabetes type 2 was referred for cardiovascular risk assessment two years ago. Other risk factors for coronary artery disease included hypercholesterolemia, smoking and a family history of coronary artery disease.

The patient was asymptomatic. Physical examination was unremarkable; his body mass index was 22 kg/m^2 and his blood pressure of 125/80 mmHg. Hypercholesterolemia was well regulated with statin administration (total cholesterol 3.52 mmol/L, low-density lipoprotein cholesterol 2.23 mmol/L, high-density cholesterol 0.94 mmol/L). ECG showed normal sinus rhythm and no additional abnormalities (Figure 1).

Myocardial perfusion imaging (MPI) was performed with gated single photon emission computed tomography (SPECT) using technetium-99m sestamibi (500 MBq). Pharmacological stress was performed using adenosine; the stress ECG showed no abnormalities. On gated SPECT, left ventricular ejection fraction was 68% during stress as well at rest; MPI showed no perfusion abnormalities during stress or at rest (Figure 2).

In addition, no coronary calcium was observed during calcium scoring (total coronary calcium score 0). However, contrast-enhanced multislice computed tomography coro-

Figure 1. ECG showing sinus rhythm and no abnormalities.

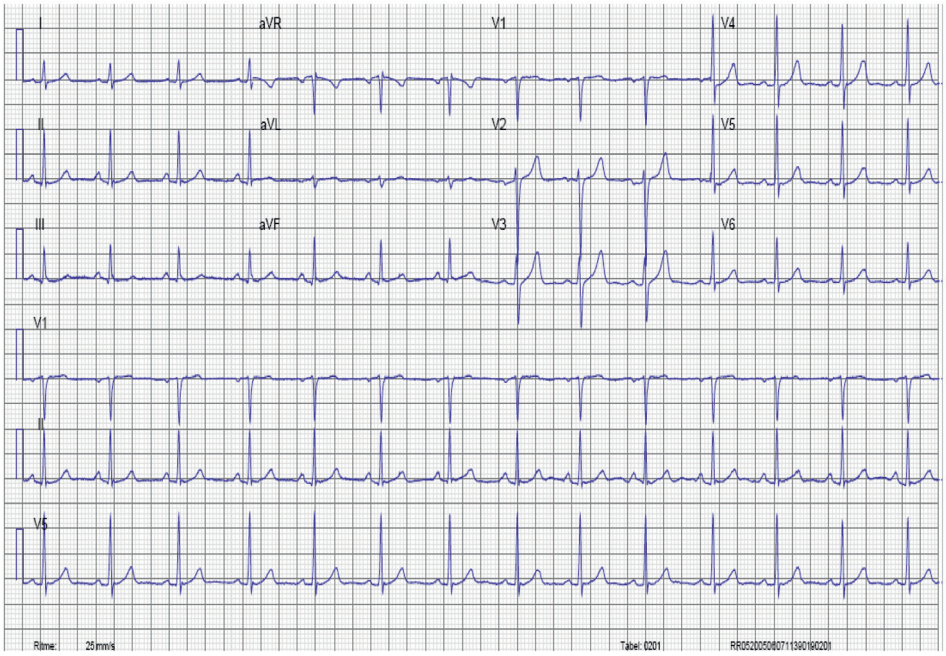
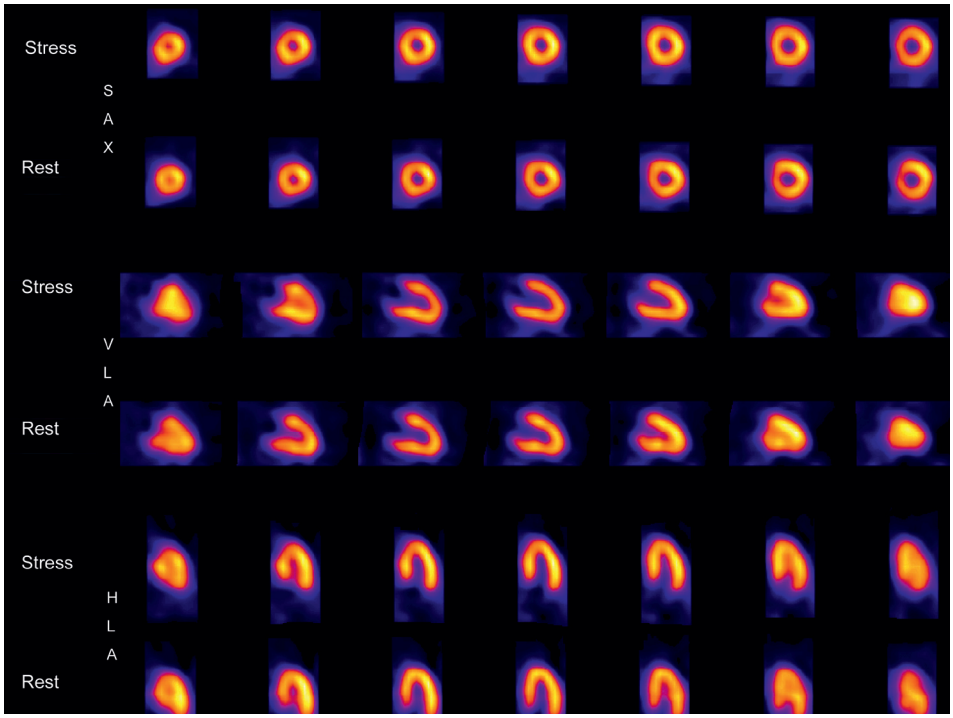


Figure 2. SPECT myocardial perfusion imaging showing normal perfusion at stress and rest. Short-axis (SAX), vertical long-axis (VLA) and horizontal long-axis (HLA) slices are shown. The top rows are the stress images, and the bottom rows are the rest images.

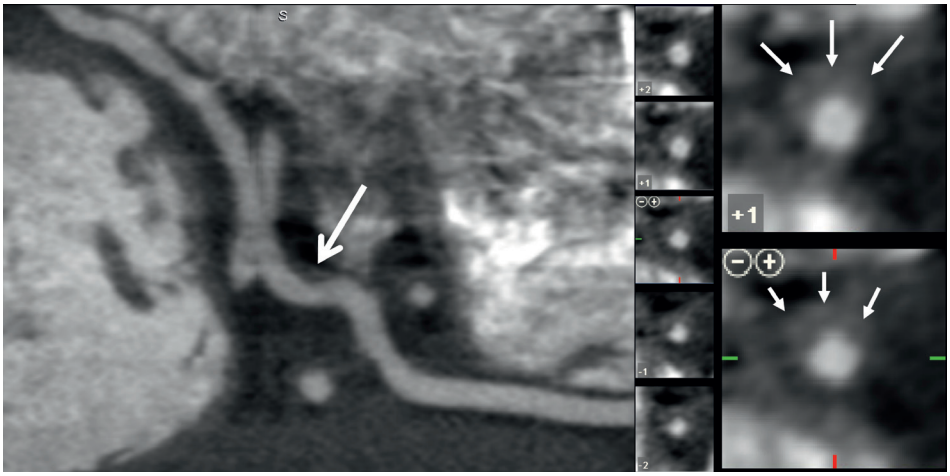


nary angiography revealed the presence of diffuse nonobstructive (<50% luminal narrowing), noncalcified plaques as illustrated in Figure 3. Risk factor modification was advised (exercise, stop smoking) and aggressive medical therapy was initiated (aspirin, statins, ACE inhibitor).

Two years after the index evaluation, the patient was evaluated at the outpatient clinic. He was asymptomatic, but the ECG revealed new development of negative T-waves in leads II, III, aVF, V5 and V6 (Figure 4). Accordingly, myocardial perfusion imaging SPECT was repeated and showed a large irreversible defect in the inferolateral wall, with partial reversibility in the inferior wall (Figure 5). Resting echocardiography showed hypokinesia in the inferolateral regions with moderate (grade 2+) mitral regurgitation.

To evaluate the extent of infarcted myocardium, contrast-enhanced (gadolinium) magnetic resonance imaging was performed (Figure 6) and revealed subendocardial infarc-

Figure 3. Noninvasive coronary angiography with 64-slice computed tomography revealed the presence of noncalcified atherosclerosis with predominantly outward remodelling. In the mid-segment of the right coronary artery a large noncalcified lesion without significant stenosis (arrow) was detected (A). Cross-sectional images (B, enlargement C) confirmed the presence of substantial noncalcified plaque (arrows) which showed predominantly outward remodelling without compromising the vessel lumen.



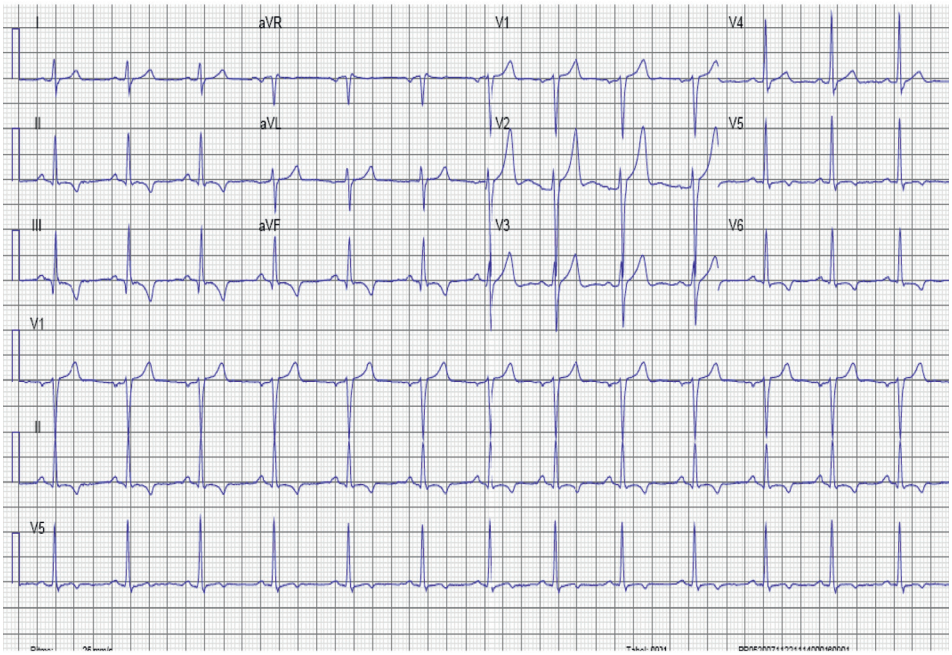
tion in the inferolateral wall. The resting cine MRI short-axis slices confirmed hypokinesia in the inferolateral regions (online Movie 1).

On the basis of these imaging results, the patient was referred for invasive coronary angiography, which revealed a proximal occlusion of the right coronary artery with retrograde filling from the left anterior descending coronary artery (online Movies 2 and 3). Accordingly, the patient was scheduled for percutaneous coronary intervention.

Screening of asymptomatic patients with diabetes type 2 for silent CAD is a heavily debated topic.[95] Despite early identification of atherosclerosis, followed by risk factor modification and aggressive medical therapy, infarction occurred 2 years later.

These findings emphasize, on the one hand the need for risk stratification (preferably with noninvasive imaging) in asymptomatic diabetic patients, but on the other hand that the current imaging techniques are not perfect for prediction of events. We have imaging techniques that provide highly accurate information on stress-inducible ischemia. It is clear that patients with ischemia have an increased risk for future cardiovascular events, and invasive evaluation (with possible intervention) is needed.

Figure 4. An ECG obtained after 2 years reveals new negative T waves in leads II, III, aVF, V5 and V6.



This patient however had normal myocardial perfusion imaging results while at stress and rest.

More recently, techniques have become available that permit early identification of atherosclerosis (calcium scoring), and also provide preliminary information on plaque composition (multislice computed tomography angiography). In this patient, calcified plaques were not present, but noncalcified lesions were observed. Recent preliminary data indicate that noncalcified plaques are associated with acute coronary syndromes and suggest a relatively high vulnerability of these plaques.[96, 97] These noncalcified plaques were the only substrate underlying the recent myocardial infarction. This highlights the potential value of modern imaging technology, but at the same time, illustrates that better understanding of plaque vulnerability is needed to further develop imaging for optimal risk stratification in asymptomatic diabetic patients.

Figure 5. Repeat SPECT myocardial perfusion imaging was performed two years after the index SPECT (Figure 2) was obtained. An irreversible defect is shown in the inferolateral region (thick arrows), whereas reversibility is demonstrated in the inferior wall (thin arrows).

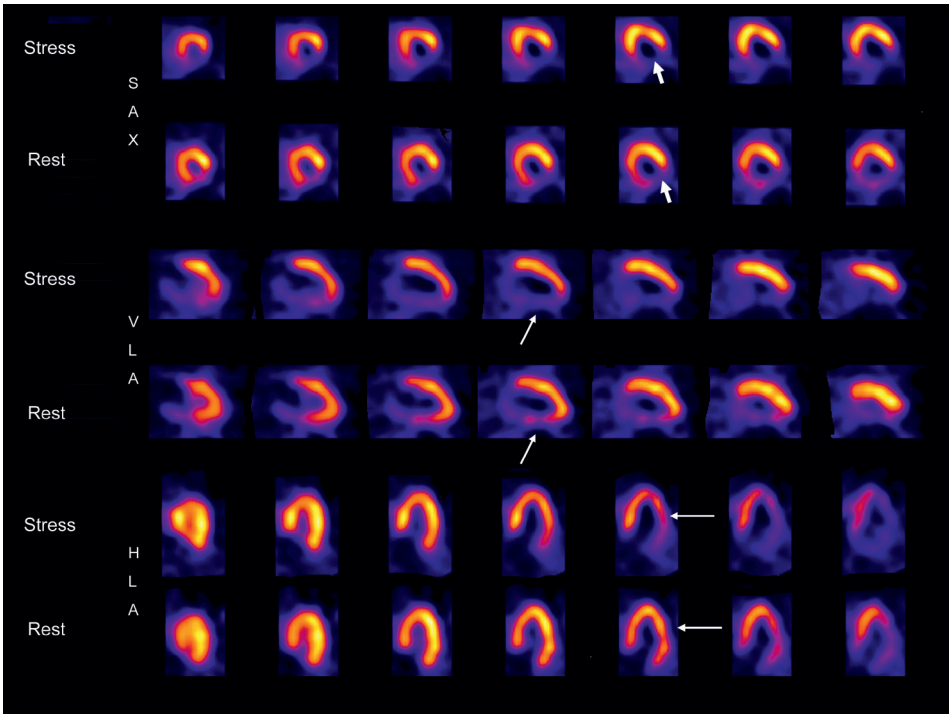
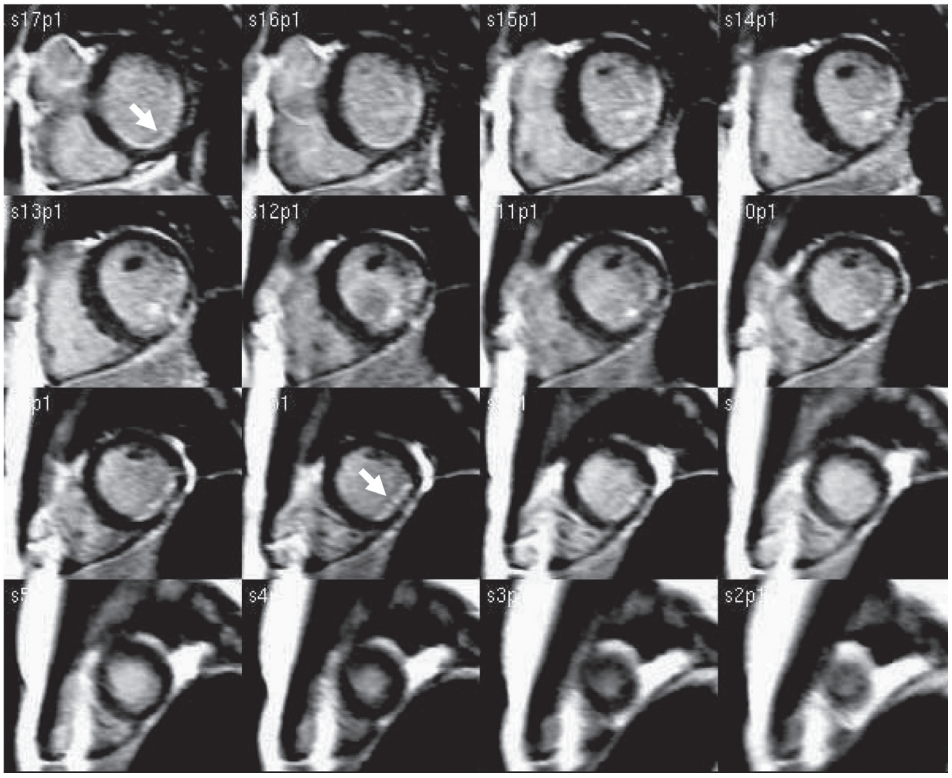


Figure 6. Contrast-enhanced magnetic resonance imaging; short-axis slices are shown. Evidence of subendocardial scar tissue is observed (arrows).



Chapter 7

Subclinical left ventricular dysfunction and coronary atherosclerosis in asymptomatic patients with type 2 diabetes

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Submitted

Abstract

Background

The presence of subclinical left ventricular (LV) dysfunction in asymptomatic patients with type 2 diabetes has been previously described. However, whether there is a link between subclinical LV dysfunction and subclinical coronary atherosclerosis is unknown. Accordingly, the aim of the present study was to evaluate whether subclinical LV systolic dysfunction is independently related to subclinical coronary atherosclerosis in type 2 diabetic patients and if it could provide incremental information over baseline characteristics to identify high risk patients.

Methods

A total of 234 asymptomatic, type 2 diabetes mellitus patients without overt LV systolic dysfunction and 80 controls matched by age, gender, LV ejection fraction and cardiovascular risk factors underwent coronary artery calcium (CAC) scoring and 2-dimensional (2D) echocardiography. LV global longitudinal strain (GLS) was assessed using automated function imaging (AFI).

Results

Patients with coronary atherosclerosis (CAC>0) (n=139), had more impaired GLS as compared to patients without coronary atherosclerosis (CAC=0) (n=95) (-18.0 ± 2.8 % vs. -16.3 ± 3.0 %, p <0.001). At multivariate analysis, male gender, hypertension, hypercholesterolemia and GLS were independently associated with coronary atherosclerosis. The addition of GLS to other selected independent clinical variables significantly improved the ability to predict coronary atherosclerosis in these patients (χ^2 = 58.92; p = 0.001).

Conclusion

As compared to patients without coronary atherosclerosis, diabetic patients with coronary atherosclerosis showed a more impaired GLS. The presence of subclinical LV systolic dysfunction provides significant incremental value for the identification of patients having coronary atherosclerosis.

Introduction

Cardiovascular complications, including coronary artery disease (CAD), are the leading causes of morbidity and mortality in individuals with type 2 diabetes.[6] The poor clinical outcome of patients with diabetes underscores the need to develop practical approaches for detecting CAD at an early stage for early initiation of appropriate treatment, which potentially may affect favourably an otherwise poor outcome.[57] However, the detection of CAD in patients with diabetes remains challenging because CAD is often asymptomatic. Noninvasive assessment of the coronary artery calcium (CAC) score, by means of electron-beam computed tomography or multislice computed tomography (MSCT), noninvasive imaging of the coronary arteries, by means of MSCT coronary angiography, and myocardial perfusion imaging, by means of single photon emission computed tomography (SPECT), have been recently proposed to improve identification of asymptomatic diabetic patients at high-risk for cardiovascular events.[36, 43, 84]

Recently, subtle abnormalities of left ventricular (LV) systolic function have been reported in patients with type 2 diabetes using automated function imaging (AFI), a novel method based on 2-dimensional speckle-tracking echocardiography.[98] However, in asymptomatic diabetic patients the relation between subclinical LV systolic dysfunction and the presence of coronary atherosclerosis is still unclear. Accordingly, the purpose of the present study was to evaluate whether subclinical LV systolic dysfunction is independently related to coronary atherosclerosis and if it could provide incremental information over baseline characteristics for the identification of asymptomatic diabetic patients having CAD. AFI was used to identify the presence of subclinical LV systolic dysfunction, while the presence of coronary atherosclerosis was assessed by means of CAC scoring.

Methods

Patient population

A total of 289 consecutive asymptomatic outpatients with type 2 diabetes underwent CAC scoring for screening of CAD. Two-dimensional echocardiography was performed in all patients on the same day. Patients with angina or angina-equivalent symptoms, history of CAD, cardiomyopathy, significant (moderate or severe) valvular heart disease, congenital heart disease, rhythm other than sinus and conduction abnormalities

were excluded. In addition, patients were excluded in case of suboptimal echocardiographic window. Asymptomatic status was confirmed using the Rose questionnaire for angina.[15] History of CAD was defined as the presence of previous acute coronary syndromes, percutaneous or surgical coronary revascularization or angiographically documented coronary stenosis ≥50% luminal diameter.[67] Hypertension was considered if systolic blood pressure was ≥140 mmHg or diastolic blood pressure was ≥90 mmHg, and if patients were on antihypertensive treatment, regardless of their blood pressure values. Hypercholesterolemia was defined by a total cholesterol level >5.0 mmol/L or use of cholesterol lowering medication. In addition, 80 subjects without diabetes were included in the present study as control group. The subjects of the control group were matched by age, gender, LV ejection fraction (LVEF) and Framingham risk score according to Wilson et al.[60] The aforementioned exclusion criteria were also applied for the control group. Control individuals underwent CAC scoring and 2D echocardiography on the same day.

Coronary artery calcium score, data acquisition and analysis

CAC scoring was performed using a 64-slice MSCT scanner (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan). For this purpose, a nonenhanced low dose ECG-gated scan was performed with prospective triggering at 75% of the R-R interval. Scan parameters were as follows: collimation 4 x 3.0 mm, gantry rotation time 0.5 second, tube current 200-250 mA and tube voltage 120 kV. CAC score was determined by an experienced observer using dedicated software (Vitrea 2, Vital Images, Minnetonka, Minnesota, USA). Total CAC score was calculated for each patient using the Agatston method.[99] The presence of coronary atherosclerosis was defined as a CAC score >0.

Two-dimensional echocardiography, data acquisition and analysis

Two-dimensional echocardiography was performed with the patient in the left lateral decubitus position using a commercially available system (Vivid 7, General Electric Vingmed, Milwaukee, Wisconsin, USA) equipped with a 3.5-MHz transducer. Standard M-mode, 2-dimensional images and Doppler and colour-Doppler data were acquired from the parasternal and apical views (4-, 2- and 3-chamber) and digitally stored in cine-loop format. Analyses were performed offline using Echo PAC version 7.0.0 (GE Healthcare, Horten, Norway). LV diameters, end-diastolic thickness of the interventricular septum

and the posterior wall were measured on the parasternal long-axis M-mode recordings. LV end-systolic and end-diastolic volumes were assessed and LVEF was calculated from the apical 4- and 2-chamber views using the Simpson's rule.[100] Subsequently, LV mass was determined using the formula by Devereux et al and normalized for body surface area (LV mass index, g/m^2).[101] Based on the recommendations of the American Society of Echocardiography, transmitral and pulmonary vein flows were derived with pulsed-wave Doppler tracings.[102] In addition, early (E) and late (A) diastolic waves, deceleration time (DT) of E wave and pulmonary vein systolic (PVs) and diastolic (PVd) velocities were obtained. Diastolic function was then classified as normal, when the E/A ratio = 0.9-1.5, DT = 160-240 ms and PVs ≥ PVd.[103] The LV global left ventricular strain (GLS) was assessed offline (Echo PAC version 7.0.0) using AFI as previously described.[14, 104] The software analyzes motion by tracking speckles (natural acoustic markers) in the 2D ultrasonic image. The frame-to-frame changes of the speckles are used to derive motion and velocity. For this purpose, one single cardiac cycle is needed from each LV apical view (apical long-axis, 4- and 2-chamber views). Mean frame rate of the obtained images was 70 fps (range 40-100 fps).

First, the end-systolic frame is defined in the apical long-axis view. The closure of the aortic valve is marked and the software measures the time interval between R wave and aortic valve closure. This interval is used as a reference for the 4- and 2-chamber view loops. After defining the mitral annulus and the LV apex with 3 index points at the end-systolic frame in each apical view, the automated algorithm traces 3 concentric lines on the endocardial border, the mid-myocardial layer and epicardial border, including the entire myocardial wall. The tracking algorithm follows the endocardium from this single frame throughout the cardiac cycle, and allows for a further manual adjustment of the region of interest to ensure that all myocardial regions are included throughout the cardiac cycle. The LV is divided in 6 segments in each apical view and the tracking quality is validated for each segment.

Finally, the automated algorithm, using a 17-segment model, provides the peak systolic longitudinal strain for each LV segment in a "bull's eye" plot, with the average value of peak systolic longitudinal strain for each view and the averaged GLS for the entire left ventricle. In general, LV GLS values are presented as negative values; a more negative value indicates a larger extent of longitudinal strain. The intra- and interobserver agreement for GLS measurements has been reported previously, with an intraclass correlation coefficient of 0.95 for intra-observer comparisons and 0.92 for inter-observer comparisons.

Statistical analysis

The study population was divided according to the absence or presence of coronary atherosclerosis. Continuous variables are expressed as mean and standard deviation (SD) and categorical variables are expressed as numbers and percentages. Differences in continuous and categorical variables between patients with and without coronary atherosclerosis were assessed using the Student t-test and the chi-square test, respectively. Comparisons among groups were performed using the one-way analysis of variance test with Bonferroni post-hoc analysis. Univariable and multivariable logistic regression analysis (enter model) were performed to evaluate the association between the presence of coronary atherosclerosis and baseline clinical (age, gender, coronary risk factors, diabetes-related risk factors and complications) and echocardiographic (LV mass index, LVEF, presence of diastolic dysfunction and GLS) characteristics. Only significant (p <0.05) univariable predictors were entered as covariates in the multivariate model. Odds ratios and 95% confidence intervals were calculated. In order to determine the potential incremental value of LV GLS over the other selected independent predictors of coronary atherosclerosis, the chi-square distribution of the multivariable model was compared with chi-square distribution of the same model without LV GLS, applying the model chi-square step.

In addition, the optimal cut-off value for LV GLS to predict coronary atherosclerosis in asymptomatic, type 2 diabetes patients was determined by receiver operating characteristic (ROC) curve analysis. The optimal cut-off value was defined as the value that provided the maximal sensitivity and specificity to distinguish between asymptomatic, type 2 diabetic patients with and without coronary atherosclerosis.

All statistical tests were 2-sided and a p value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software package (SPSS 15.0, Chicago, Illinois, USA).

Results

Patient characteristics

From the initial cohort of 289 patients, 35 (12%) had suboptimal echocardiographic window, precluding reliable AFI analysis, and were not eligible for the study. Consequently, 234 patients were included in the final analysis. Baseline and echocardiographic characteristics of the overall study population and of patients with and without coronary atherosclerosis are summarized in Table 1. The mean age was 52 ± 11 years and 134 (57%) patients

were male. Almost half of the patients were on insulin therapy. In the total population, average CAC score was 319 ± 901 (range 0-8730). CAC was absent in 95 (41%) patients. In the remaining 139 (59%) patients, an average CAC score of 537 ± 1120 was observed with 41 (29%) and 19 (14%) patients having a CAC score >400 or >1000, respectively.

Table 1. Clinical and echocardiographic characteristics of the study population in relation to coronary atherosclerosis

	Overall	**Coronary atherosclerosis**		***p* value**
	n=234	**CAC score = 0 (n=95)**	**CAC score > 0 (n=139)**	
Age (years)	52 ± 11	46 ± 11	56 ± 10	<0.001
Male gender, n (%)	134 (57)	42 (44)	92 (66)	0.01
Hypertension, n (%)*	133 (57)	34 (36)	37 (58)	<0.001
Smoking, n (%)	54 (23)	18 (19)	36 (26)	0.22
Hypercholesterolemia, n (%) #	143 (61)	44 (46)	99 (71)	<0.001
Positive family history, n (%)	113 (48)	43 (45)	70 (50)	0.44
Diabetes-related risk factors				
Diabetes duration (years)	13 ± 11	10 ± 8	14 ± 12	<0.001
Age at time of diagnosis DM (years)	40 ±15	36 ± 13	42 ± 15	0.08
HbA_{1C} (%)	7.8 ± 1.7	7.7 ± 1.6	7.9 ± 1.7	0.57
Treatment, n (%)				
Oral	89 (38)	35 (37)	54 (39)	0.76
Insulin	97 (42)	35 (37)	54 (39)	0.66
Insulin and oral agent	42 (18)	15 (16)	27 (19)	0.48
Retinopathy, n (%)	48 (21)	11 (12)	37 (27)	0.005
Nephropathy	32 (14)	9 (9)	23 (17)	0.12
PVD, n (%)	33 (14)	11 (12)	22 (16)	0.36
PNP, n (%)	89 (38)	23 (24)	66 (48)	<0.001
Body mass index (kg/m^2)	28 ± 6	28 ± 6	28 ± 5	0.73
Waist circumference (cm)	100 ± 14	98 ± 14	101 ±14	0.14
Medication, n (%)				
Aspirin	53 (23)	11 (12)	42 (30)	0.001
ACE-inhibitors	70 (30)	12 (13)	58 (42)	<0.001
Statins	118 (50)	31 (33)	87 (63)	<0.001
Serum markers				
Total cholesterol (mmol/l)	4.7 ± 1.1	4.6 ± 1.0	4.8 ± 1.2	0.12
LDL (mmol/l)	3.0 ± 1.0	2.9 ± 1.0	3.0 ± 1.0	0.39
HDL (mmol/l)	1.4 ± 0.6	1.4 ± 0.5	1.4 ± 0.6	0.55
Cholesterol/HDL ratio	3.6 ± 1.3	3.5 ± 1.2	3.8 ± 1.3	0.07
Triglycerides (mmol/l)	1.7 ± 1.1	1.6 ± 1.1	1.8 ± 1.2	0.13

Table1. continued

	Overall n=234	Coronary atherosclerosis		*p* value
		CAC score = 0 (n=95)	CAC score > 0 (n=139)	
Two-dimensional echocardiography				
LV ejection fraction (%)	68 ± 10	68 ± 9	68 ± 11	0.90
LV enddiastolic volume (ml)	118 ± 29	117 ± 25	119 ± 32	0.72
LV endsystolic volume (ml)	39 ± 17	38 ± 14	39 ± 19	0.69
E wave (m/sec)	0.71 ± 0.18	0.75 ± 0.21	0.69 ± 0.16	0.06
A wave (m/sec)	0.69 ± 0.19	0.66 ± 0.18	0.72 ± 0.19	0.04
E/A	1.08 ± 0.35	1.20 ± 0.41	1.00 ± 0.29	<0.001
DT E Wave (msec)	179 ± 55	175 ± 46	181 ± 61	0.38
PVs (m/sec)	0.52 ± 0.11	0.52 ± 0.11	0.52 ±0.12	0.87
PVd (m/sec)	0.41 ± 0.10	0.43 ± 10	0.40 ± 0.10	0.05
PV s/d	1.30 ± 0.35	1.26 ± 0.32	1.34 ± 0.36	0.08
E' (cm/sec)	6.37 ± 2.13	7.05 ± 2.34	5.89 ± 1.83	<0.001
E/E'	12.56 ± 6.73	12.16 ± 6.67	12.84 ± 6.78	0.45
LV diastolic dysfunction, n (%)	158 (68)	53 (23)	105 (45)	0.002
LV mass index (g/m^2)	83 ± 22	80 ± 19	85 ± 24	0.07
LV GLS (%)	-17.0 ± 3.0	-18.0 ± 2.8	-16.3 ± 3.0	<0.001

A, atrial; ACE, angiotensin converting enzyme; DM, diabetes mellitus; DT, deceleration time; E, early; E', early prime; GLS, global longitudinal strain; HDL, high density lipoprotein; LDL, low density lipoprotein; LV, left ventricular; PNP, polyneuropathy; Pv, pulmonary vene; PVD, peripheral vessel disease.
* Blood pressure ≥140/90 mm Hg or treatment with antihypertensive medication, #total cholesterol level >5.0 mmol/L or use of cholesterol lowering medication

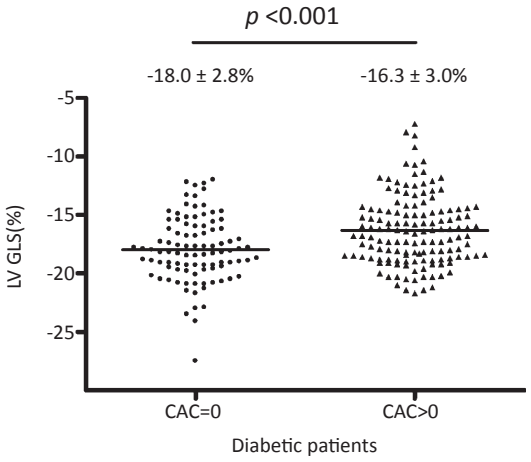
Regarding the echocardiographic characteristics, the LVEF was within normal limits (68 ± 10%) and the LV mass index was 83 ± 22 g/m^2. The mean GLS was -17.0 ± 3.0%. Diastolic dysfunction was observed in 158 (68%) patients.

Comparison between patients with and without coronary atherosclerosis

Clinical data

Clinical and echocardiographic characteristics of the study population are presented in Table 1. As compared to patients without coronary atherosclerosis (n=95), patients with coronary atherosclerosis (n=139) were significantly older and had a longer duration of diabetes (p <0.001 for both comparisons); in addition, patients with coronary atherosclerosis had more frequently hypertension, hypercholesterolemia, retinopathy and polyneuropathy (p <0.01 for all comparisons).

Figure 1. Scatter-plot illustrating the individual values of LV GLS in asymptomatic, type 2 diabetic patients with and without coronary atherosclerosis (defined by CAC score). Diabetic patients with CAC>0 had significantly more impaired LV GLS as compared to diabetic patients with CAC=0.



CAC, coronary artery calcium; GLS, global longitudinal strain; LV, left ventricular

Two-dimensional echocardiography

No difference in LVEF was observed between patients with and without coronary atherosclerosis. However, in patients with coronary atherosclerosis, impaired GLS was observed as compared to patients without coronary atherosclerosis (-16.3±3.0% vs. -18.0±2.8%; p <0.001) (Figure 1). In addition, the prevalence of diastolic dysfunction was significantly higher among patients with coronary atherosclerosis (45% vs. 23%; p=0.002).

Comparison between patients with diabetes mellitus and control patients

The patients with type 2 diabetes were compared with a control group (n=80) matched by age, gender, LVEF and Framingham risk score according to Wilson et al (Table 3).[105] The controls were divided into two groups according to the CAC score: 41 patients had CAC =0, 39 patients had CAC > 0. The controls with CAC = 0 showed the most preserved values of LV GLS (-19.4 ± 1.8 %) whereas the patients with diabetes and CAC score > 0 had the most impaired LV GLS values (-16.3 ± 3.0 %; ANOVA p < 0.001) (Table 4).

Predictors of coronary atherosclerosis

The results of the univariate and multivariate logistic regression analysis performed to identify potential predictors of coronary atherosclerosis are provided in Table 2. At univar-

Table 2. Univariable and multivariable logistic regression analysis to determine independent predictors for coronary atherosclerosis

	Univariable		Multivariatble	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
Age (years)	1.10 (1.06-1.13)	<0.001	1.04 (0.91-1.18)	0.61
Male	2.47 (1.45-4.22)	0.001	2.70 (1.36-5.36)	0.005
Hypertension	4.44 (2.54-7.75)	<0.001	2.58 (1.30-5.13)	0.007
Smoking	1.51 (0.73-2.86)	0.21	-	-
Family history of CAD	1.23 (0.73-2.07)	0.44	-	-
Hypercholesterolemia	2.94 (1.70-5.09)	<0.001	2.41 (1.26-4.63)	0.016
Diabetes duration (years)	1.04 (1.01-1.08)	0.003	1.10 (0.96-1.25)	0.17
Age at time of diagnosis DM (years)	1.03 (1.01-1.04)	0.006	1.10 (0.92-1.20)	0.45
HbA_{1C} (%)	1.088 (0.93-1.28)	0.31	-	-
Retinopathy	2.77 (1.33-5.76)	0.006	1.80 (0.67-4.90)	0.24
Nephropathy	1.90 (0.84-4.30)	0.13	-	-
PVD	1.44 (0.66-3.12)	0.36	-	-
PNP	2.83(1.59-5.03)	<0.001	1.69 (0.82-3.50)	0.16
LV mass index (g/m^2)	1.01 (1.00-1.02)	0.07	-	-
LV ejection fraction (%)	1.00 (0.97-1.03)	0.91	-	-
Diastolic dysfunction	2.45 (1.40-4.28)	0.002	0.71 (0.33-1.51)	0.37
LV GLS (%)	1.23 (1.11-1.30)	<0.001	1.20 (1.07-1.36)	0.003

CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; GLS, global longitudinal strain; LV, left ventricular; OR, odds ratio; PNP, peripheral neuropathy; PVD, peripheral vessel disease.

Table 3. Comparison of age, gender, LV ejection fraction and Framingham risk score between the control group and the study population.

	Control group (n=80)	**Diabetes study population (n=234)**	***p* value**
Age (years)	54 ± 8	52 ± 11	0.15
Male (%)	37 (46%)	134 (57)	0.09
LV ejection fraction (%)	66 ± 5	68 ± 10	0.21
Framingham risk score	11 ± 6	12 ± 9	0.12

LV, left ventricular

Table 4. Comparison of LV GLS, between age, sex and Framingham risk score matched controls and the diabetic study population.

	Control group (n=80)		**Diabetes study population (n=234)**		***p* value**
	CAC score = 0 (n=41)	CAC score > 0 (n=39)	CAC score = 0 (n=95)	CAC score > 0 (n=139)	
LV GLS (%)	-19.4 ± 1.8#	-17.8 ± 1.6	-18.0 ± 2.8	-16.3 ± 3.0*	0.001

# $p < 0.02$ versus the other groups, * $p = 0.032$ versus diabetes and CAC score = 0
CAC, coronary artery calcium; GLS, global longitudinal strain; LV, left ventricular

iate analysis age, male gender, hypertension, hypercholesterolemia, duration of diabetes, age at time of diagnosis, retinopathy, peripheral vascular disease, peripheral neuropathy, diastolic dysfunction and GLS were significantly related to coronary atherosclerosis. At multivariate analysis, male gender (OR = 2.70; 95% CI 1.36-5.36; p=0.005), hypertension (OR = 2.58; 95% CI 1.30-5.13; p=0.007, hypercholesterolemia (OR = 2.30; 95% CI 1.17-4.54; p=0.016) and GLS (OR = 1.20; 95% CI 1.07-1.36; p=0.003) were independent factors associated with coronary atherosclerosis. As shown in Figure 2, adding GLS to the other selected independent variables significantly improved the ability to predict coronary atherosclerosis. Finally, ROC curve analysis was performed to obtain a cut-off value of LV GLS to identify asymptomatic type 2 diabetic patients at a high risk of having coronary atherosclerosis. A cut-off value of -17.5% predicted the presence of coronary atherosclerosis with a sensitivity and specificity of 62% for both (area under the curve: 0.65) (Figure 3).

Discussion

The results of the present study can be summarized as follow: 1) as compared to diabetic patients without atherosclerosis, diabetic patients with coronary atherosclerosis showed an impaired GLS, even though LVEF was still preserved (reflecting the presence of subclinical LV systolic dysfunction) 2) the presence of subclinical LV systolic dysfunction provides significant incremental value for the identification of patients having coronary atherosclerosis.

Coronary atherosclerosis and subclinical LV systolic dysfunction in diabetes mellitus

In diabetic patients, the diagnosis of CAD is frequently missed or delayed since the typical symptoms of myocardial ischemia are often masked. Before symptoms of ischemia

Figure 2. Bar graph illustrating the incremental value of LV global longitudinal strain (GLS) by automated function imaging to predict coronary atherosclerosis. The addition of GLS to a model including baseline clinical characteristics (male gender, hypertension and hypercholesterolemia) results in incremental risk stratification of type 2 diabetic patients for having coronary atherosclerosis.

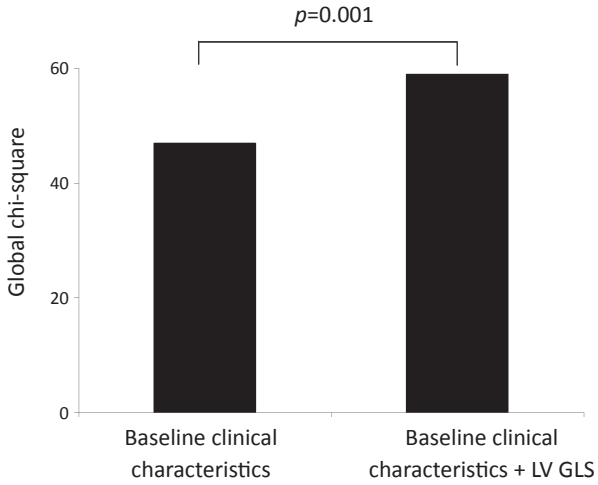
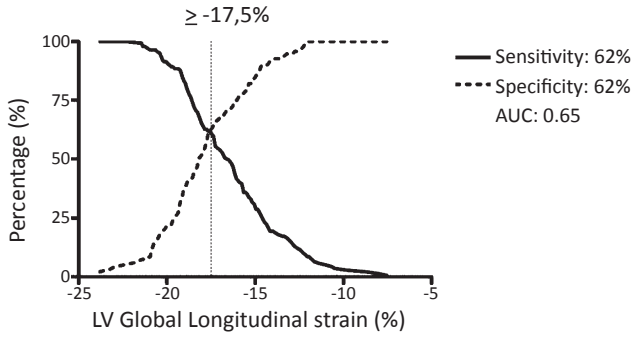


Figure 3. ROC curve analysis, showing the optimal cut-off value for LV GLS to predict coronary atherosclerosis.



AUC = area under the curve

occur, diffuse multi-vessel atherosclerosis is frequently present. It has been shown that risk and mortality from CAD in patients with type 2 diabetes are similar to patients without diabetes and previous myocardial infarction, indicating increased event risk in diabetic patients.[7] In addition, CAD is one of the main causes of overt LV dysfunction and heart failure in this group of patients.[106] Accordingly, early identification of coronary atherosclerosis in asymptomatic diabetics may be beneficial, allowing timely detection of patients at increased risk, and appropriate selection of further diagnostic and therapeutic procedures. In the present study, noninvasive assessment of CAC score was performed in a large cohort of asymptomatic patients with type 2 diabetes for CAD screening purpose; moreover, conventional transthoracic echocardiography and speckle-tracking echocardiography were performed to evaluate the presence of diastolic and subclinical systolic dysfunction, respectively. The relationship between LV dysfunction and subclinical coronary atherosclerosis was then evaluated. Previous studies in the general population have demonstrated that the extent of CAC strongly correlates with the overall magnitude of atherosclerotic plaque burden.[107, 108] The extent of CAC is affected by age, gender, and traditional cardiovascular risk factors. A threshold value of 400 as the cut-point for high risk for obstructive CAD has been found in previous studies.[109] However, such scores are very rare in men <60 years old and almost nonexistent in women <65 years old. In screening for a disease as prevalent as CAD, such stringent criteria for a positive scan may not be appropriate when screening asymptomatic individuals.In line with previously published studies, diastolic dysfunction was frequently observed in diabetic patients (68%)[110-116]; of note, the prevalence of diastolic dysfunction was higher in diabetics with as compared to those without coronary atherosclerosis (45% versus 23%). More interestingly, GLS (i.e. active myocardial deformation), assessed by speckle-tracking echocardiography, was impaired in diabetic patients with as compared to those without coronary atherosclerosis (-16.3 ± 3.0% vs. -18.0 ± 2.8%), reflecting the presence of subclinical LV systolic dysfunction. GLS, indeed, was found to be independently related to the presence of coronary atherosclerosis, and provided significant incremental value over other baseline patient characteristics for the identification of patients having CAD.

Previous studies have underscored the presence of subclinical LV dysfunction in asymptomatic patients with type 2 diabetes.[117-119] The underlying pathophysiology of diabetic cardiomyopathy includes several processes that act synergistically and hyperglycemia is considered as the central factor that triggers several adaptive and maladaptive responses.[120] These responses lead to accelerated apoptosis of the myo-

cardial fibers, myocardial fibrosis and increased content of collagen. Particularly, the deposits of collagen are thought to contribute to arterial and myocardial stiffness and endothelial dysfunction. The subendocardial fibers, oriented longitudinally, are the first to be involved in these processes and, therefore, subclinical LV systolic dysfunction can be identified with the assessment of LV GLS. A reduced GLS indicates, at these early stages, an impairment of the subendocardial shortening. In addition to these mechanisms, atherosclerotic plaques formation may further negatively impact on LV longitudinal function. However, the relation between subclinical LV dysfunction and asymptomatic coronary atherosclerosis was not yet investigated in this group of patients. The findings of the present study extend the available knowledge, suggesting a link between subclinical LV systolic dysfunction and asymptomatic coronary atherosclerosis. Small vessel micro-embolization, endothelial dysfunction or chronic ischemia may indeed induce subclinical myocardial damage. This may lead to decreased GLS of the longitudinal fibers, which are more susceptible to ischemia and explain the observations by the current study.[121] Interestingly, similar data have been previously reported by other authors in different study populations, partially supporting the present findings. Stein and co-workers, for instance, observed a relation between subclinical LV impairment (evaluated by tissue-Doppler imaging) and coronary atherosclerosis (evaluated by coronary angiography and/or intravascular ultrasound) in 26 asymptomatic patients with type 1 diabetes.[122] Edvarsen et al investigated the relation between regional coronary calcium score and regional left ventricular systolic strain (assessed by tagged magnetic resonance imaging) in 509 asymptomatic patients without history of CAD and with normal LVEF.[123] Although the patients were older and had lower CAC scores as compared to our population, an independent relation between impairment of regional LV systolic function and coronary atherosclerosis was observed.

Clinical implications

The results of the present study indicate that LV GLS may allow the identification of subclinical systolic dysfunction in diabetic patients, possibly related to the presence of subclinical coronary atherosclerosis. As mentioned before, the poor clinical outcome in patients with type 2 diabetes underscores the need to develop practical approaches for detecting coronary atherosclerosis at an early stage for early initiation of appropriate treatment.

To improve the identification of diabetic patients at high risk of cardiovascular events, SPECT myocardial perfusion, CAC score and MSCT coronary angiography has been proposed.[36, 43, 84, 124] However, these techniques may be limited available and associated with non-negligible radiation exposure, especially taking into account that periodical screening exams are often performed in the diabetic population. Possibly, routine screening for subclinical LV dysfunction with 2D speckle-tracking echocardiography can be the first line approach to identify those patients with higher likelihood of coronary atherosclerosis who need further clinical explorations.

Conclusion

Subclinical LV systolic dysfunction is independently related to the presence of subclinical coronary atherosclerosis in patients with type 2 diabetes. In addition, subclinical LV systolic dysfunction has significant incremental value over other baseline patient characteristics to predict coronary atherosclerosis.

Chapter 8

Diabetic cardiovascular autonomic neuropathy by ^{123}I metaiodobenzylguanidine myocardial scintigraphy and heart rate variability in asymptomatic patients with type 2 diabetes mellitus

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Submitted

Abstract

Purpose

The purpose of this study was to evaluate the prevalence of cardiac autonomic neuropathy (CAN) in a cohort of truly asymptomatic patients with type 2 diabetes mellitus using heart rate variability (HRV) and ^{123}I-metaiodobenzylguanidine (^{123}I-*m*IBG) myocardial scintigraphy.

Methods

88 asymptomatic patients with type 2 diabetes mellitus were prospectively recruited from an outpatient diabetes clinic. In patients with normal myocardial perfusion CAN was assessed by HRV and ^{123}I-*m*IBG myocardial scintigraphy. Two or more abnormal tests were defined as CAN positive (ECG-based cardiac autonomic neuropathy) and one or less as CAN negative. CAN assessed by ^{123}I-*m*IBG scintigraphy was defined as abnormal if: heart/mediastinum ratio<1.8, washout>25%, or total defect score>13.

Results

The prevalence of CAN in asymptomatic patients with type 2 diabetes and normal myocardial perfusion assessed by HRV and ^{123}I-*m*IBG scintigraphy was respectively, 27% and 58%. Furthermore, in almost half of patients with normal HRV, ^{123}I-*m*IBG scintigraphy showed CAN.

Conclusion

The current study revealed a high prevalence of CAN in patients with type 2 diabetes mellitus. Secondly, disagreement between HRV and ^{123}I-*m*IBG scintigraphy for the assessment of CAN was observed.

Introduction

Diabetes mellitus is an increasing health care problem.[2, 16] Cardiovascular complications including coronary artery disease (CAD), are the most common causes of mortality and morbidity in patients with type 2 diabetes mellitus.[7] Because patients with diabetes mellitus type 2 often suffer from CAD without symptoms, risk stratification is needed to identify patients at high risk for CAD. In the DIAD (Detection of silent myocardial Ischemia in Asymptomatic Diabetic subjects) study the overall prevalence by single photon emission computed tomography (SPECT) of silent myocardial ischemia was 22%.[36] Although traditional risk factors failed to predict silent myocardial ischemia, cardiac autonomic neuropathy (CAN) assessed by heart rate variability (HRV), was a strong predictor for silent myocardial ischemia in this study. Furthermore, it is known that CAN is one of the most common diabetes-associated complications and has been associated with increased risk of mortality and major cardiovascular events.[125-129] However, although CAN assessed by HRV is a sensitive method to detect neuropathy, it is less accurate in detecting sympathetic dysfunction.[130] The sympathetic cardiac innervation can nowadays be assessed directly and noninvasively with ^{123}I-*m*IBG myocardial scintigraphy in many clinical disorders, including diabetes.[131-135]

How HRV and ^{123}I-*m*IBG myocardial scintigraphy compare in asymptomatic patients with diabetes is unknown. The current observational study evaluated the prevalence of CAN according to HRV versus ^{123}I-*m*IBG myocardial scintigraphy.

Methods

Patient population

All patients were referred from an outpatient diabetic clinic to our institution for risk stratification. This included adenosine stress SPECT myocardial perfusion imaging to assess myocardial ischemia and HRV to assess CAN. The diagnosis of diabetes was established by the referring physician and confirmed by patient history or the use of medication such as 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. Asymptomatic status was confirmed using the Rose questionnaire for angina.[15] Exclusion criteria were: known CAD; stress test or coronary angiography before referral, history of coronary revascularization, treatment with anti-anginal 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 as stressor for SPECT myocardial perfusion imaging. In patients with normal myocardial perfusion (stress and rest) ^{123}I-*m*IBG myocardial scintigraphy was performed to evaluate the prevalence of sympathetic CAN compared to the prevalence of CAN assessed by HRV.

Adenosine stress SPECT myocardial perfusion imaging

Data acquisition and analysis were performed as described before.[84] Briefly, ECG-gated SPECT imaging was performed using a 2-day protocol (adenosine and rest) with technetium-99m sestamibi (99mTcMIBI). 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. Imaging was performed 120 minutes after tracer injection using a triple-head SPECT camera (GCA 9300/HG, Toshiba Corporation, Tokyo, Japan) using low-energy, high resolution collimators. Image acquisition was performed using a circular 360° orbit, 60 projections and 40 second/projection[61, 62] No attenuation correction was applied. The cardiac images were processed in the usual manner and short-axis, horizontal and vertical long-axis views were reconstructed. The adenosine stress SPECT myocardial perfusion imaging study was considered normal in case of 1) both SRS and SDS <2, 2) resting LVEF ≥45%, and 3) absence of increased lung uptake, TID or flat or down sloping ST-segment depression ≥ 1mm at 80 ms after the J-point in two or more leads on the ECG during adenosine infusion.

Cardiovascular autonomic reflex tests

Data acquisition

To assess cardiovascular autonomic neuropathy (CAN), heart rate variability (HRV) was measured during the following 4 cardiovascular reflex tests and recorded with the aid of a Holter ECG .[136, 137]

1. HRV at rest over 150 consecutive beats,
2. HRV during deep breathing at 6 cycles per minute over 120 consecutive beats,
3. HRV during Valsalva manoeuvre,
4. Immediate heart rate response to standing from the recumbent position.

A final test measured the difference in systolic blood pressure between supine and upright position. No patients were receiving drugs influencing HRV, such as neuroleptic drugs or clozapine. Antihypertensive medications such as angiotensin converting enzyme (ACE)- inhibitors and angiotensin receptor blockers (ARB) were stopped one week before HRV measurements.[138, 139]

Data analysis

All Holter ECG recordings were analyzed by two experienced observers unaware of the clinical history of the patients. In case of disagreement, a joint reading was performed and a consensus decision was reached. For the evaluation of HRV at rest, coefficient of variation (CV) was used.[140] HRV during deep breathing was evaluated by calculating the E-I ratio (ratio of the mean longest to shortest R-R interval during respectively inspiration and expiration).[141] The 'Valsalva ratio' was calculated as the ratio of the longest R-R interval following release to the shortest R-R interval during the maneuver.[142] Immediate heart rate response to standing up was calculated as the '30-15 ratio', defined as the longest R-R interval of beats 20-40 divided by the shortest R-R interval of beats 5-25 with beat one being the first one during the process of getting up. The shortest R-R interval came always prior to the longest R-R interval within the calculation of the '30-15 ratio'. Age related normal ranges were used for evaluation of these 4 cardiovascular reflex tests.[143] Patients were excluded from analysis when either one or more recordings of HRV during Holter monitoring consisted of too few consecutive beats for interpretation or in case of extra systoles impairing interpretation. A decrease of systolic blood pressure equal to or greater than 30 mmHg within 2 minutes after standing was defined as an abnormal heart rate response.[144]

Thus, CAN assesses by HRV was classified according to the number of abnormal cardiovascular reflex tests. Two or more abnormal tests were defined as CAN positive (ECG-based cardiac autonomic neuropathy) and 1 or less as CAN negative.[145, 146]

^{123}I-*m*IBG myocardial scintigraphy imaging protocol

Data acquisition

Patients were instructed not to take tricyclic antidepressants drugs, sympathetic agents, or other drugs known to interfere with *m*IBG uptake. Thyroid uptake of unbound ^{123}I was blocked with sodium iodine solution given orally 60 minutes before ^{123}I-*m*IBG injection. 185 MBq of ^{123}I-*m*IBG (GE Healthcare, USA) was injected in 60 seconds intravenously at

rest. Fifteen minutes post injection anterior planar images of the chest were acquired and stored in a 256 x 256 matrix. Thereafter, a 360° SPECT study was acquired using a double-head gamma camera (GCA 9300/HG, Toshiba Corporation, Tokyo, Japan) (4˚/ step, 35 sec/projection, 128 x 128 matrix). Repeat planar and SPECT studies were acquired at approximately 4 hours post-injection. All camera heads were equipped with low-energy high-resolution collimators and all acquisitions were performed with a 15% energy window centered at the 159 keV photopeak of ^{123}I.

Data analysis and image interpretation

Planar images

Early (15 min post-injection) and late (4-hour delayed) planar images were processed to determine the heart-to-mediastinum ratio (HMR). The planar *m*IBG images were analyzed using regions of interest (ROI) to calculate the uptake ratios and washout percentages. Therefore, a ROI was drawn manually over the left ventricle. A second rectangular ROI over the upper mediastinum and opposite arm were used as a reference background region. The HMR of average counts per pixel was calculated for the early and delayed images. After correcting for the physical decay of ^{123}I, early and delayed HMR values were then used to compute the myocardial washout ratio (WR) of *m*IBG as follows:

WR= [early heart counts-early mediastinum counts] – [delayed heart counts-delayed mediastinum counts] / [early heart counts-early mediastinum counts] x 100%.

Since most available evidence supports the use of the delayed MIBG images (and the derived HMR and WR) for risk stratification, abnormal delayed HMR and WR were defined as lower than 1.8 and higher than 25%, respectively.[147, 148]

SPECT images

Polar map formats (normalized to 100%) were used for semi-quantitative and visual interpretation. The delayed myocardial SPECT images were divided into 17 segments and each segment was evaluated in consensus by two expert observers, using a 4-point scoring system (0: >70% tracer uptake, 1: 50-70% tracer uptake, 2: 30-50% tracer uptake, 3: <30% tracer uptake).[66, 85] As a result, the summed score for each study could theoretically range from 0 to 51 (17 x 3). The total defect score (TDS) was calculated as the sum of all defect scores. The TDS was converted to percentage of the total denervated myocardium. The percentage denervation in the LV was calculated as follows: (TDS/ 51 [maximum score =17x3] x 100. Based on the study by Kasama et

al, a TDS >18 was considered abnormal; when corrected for a 4-point scoring system (as used in the current study), a TDS >13 would be considered abnormal.[149] Next, the location of defects was evaluated, and categorized as inferior, apical, lateral, anterior or septal. In addition, patients were categorized as having 1 defect allocated to 1 region (see above), having ≥2 defects, or diffusely reduced MIBG uptake. Thus, CAN assessed by ^{123}I-*m*IBG scintigraphy was defined as abnormal if: HMR<1.8, WO>25%, or TDS>13.

Statistical analysis

Categorical baseline characteristics were expressed as numbers and percentages. Continuous variables were expressed as mean (± standard deviation). Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA) and SAS software (The SAS system, release 6.12, Cary, NC, USA: SAS Institute Inc.). A P-value <0.05 was considered as statistically significant.

Results

Patient characteristics

From the clinical registry, 110 consecutive patients with normal SPECT perfusion studies were identified and available for ^{123}I-*m*IBG scintigraphy. Of these, 22 (20%) patients were excluded due to incomplete datasets (n=13) or poor MIBG image quality (n=9).

Thus, the final patient population consisted of 88 patients (56 men, age 53 ± 10 years). The patient characteristics are shown in Table 1. The mean duration of diabetes was 9.8 ± 8.2 years. Most of the patients were on oral anti-diabetic therapy (61%). ACE inhibitors/ARB was used in 35% and 21% of patients. Twenty-eight patients had complications of diabetes, such as peripheral neuropathy and/or peripheral vascular disease.

Cardiac autonomic neuropathy assessed by HRV

Of the 88 patients, CAN was classified according to the number of abnormal cardiovascular reflex tests. Thirty (34%) of these patients had ≥1 abnormal cardiovascular reflex test. Twenty-four (27%) patients were considered to have ≥2 abnormal tests and were categorized as CAN positive.

Table 1. Patient characteristics of 88 asymptomatic patients with diabetes type 2. Data between parentheses indicate percentages.

Variables	Patients n=88
Male	56(64)
Age (years)	53±10
Diabetes-related risk factors	
Duration (years)	9.8±8.2
Age at time of diagnosis of diabetes (years)	44±12
HbA_1C	7.4±1.6
Treatment	
Oral/Insulin	54(61)/21(24)
Oral and Insulin	11(13)
Peripheral vascular disease/peripheral neuropathy	9(10)/19(22)
Peripheral vascular and neuropathy	11(13)
Body mass index (kg/m^2)	29.2±5.7
Waist circumference (cm)	103±15.0
Hypertension	47(53)
Hypercholesterolemia	46(52)
Family history of CAD	52(59)
Current Smoking	12(14)
Medication	
Aspirin	18(21)
ACE inhibitors/ARB	31(35)/18(21)
Statins	45(51)
Total cholesterol (mmol/l)	4.9±1.1
LDL (mmol/l)	3.2±.1.1
HDL (mmol/l)	1.4±0.6
Cholesterol/HDL ratio	3.8±1.3
Triglycerides (mmol/l)	2.0±1.2
Creatinine (mmol/l)	78.5±20.0
Urine albumin-creatinine ratio	12.4±32.8
CRP (mg/l)	8.3±5.8
Apolipoprotein A1 (g/l)	1.4±0.30
Apolipoprotein B (g/l)	0.9±0.30
Fibrinogen (g/l)	3.9±0.90

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

Cardiac autonomic neuropathy assessed by ^{123}I-*m*IBG

Of the 88 patients, 37 patients (42%) had a normal ^{123}I-*m*IBG study. In the remaining 51 patients (58%), the ^{123}I-*m*IBG study was abnormal. Of these 51 patients, 22 patients (43%) had 1 criterium for an abnormal ^{123}I-*m*IBG study; the remaining 30 patients (57%) had ≥2 criteria. In the total 88 patients, 36 (41%) patients had a HMR<1.8 (mean 1.62±0.13) and 32 (36%) patients had a WO>25% (mean 34± 8). A TDS>13 (mean 43±18) was observed in 25 (28%) patients.

Location of ^{123}I-mIBG defects on SPECT

Thirty-nine patients (44%) had no defects on the delayed ^{123}I-*m*IBG images. The majority (n=22, 25%) of the innervation defects were located in the inferior wall. Seven patients showed defects in the apex, whereas 3 patients had defects in the anterior wall. Eight patients had diffuse diminished tracer uptake over the entire LV and 9 patients had defects in more than 2 regions. In the 25 patients with a TDS>13 the location of the defects were as follows: inferior wall n=7, apex n=4, diffuse diminished n=7 and ≥ 2 regions n=6.

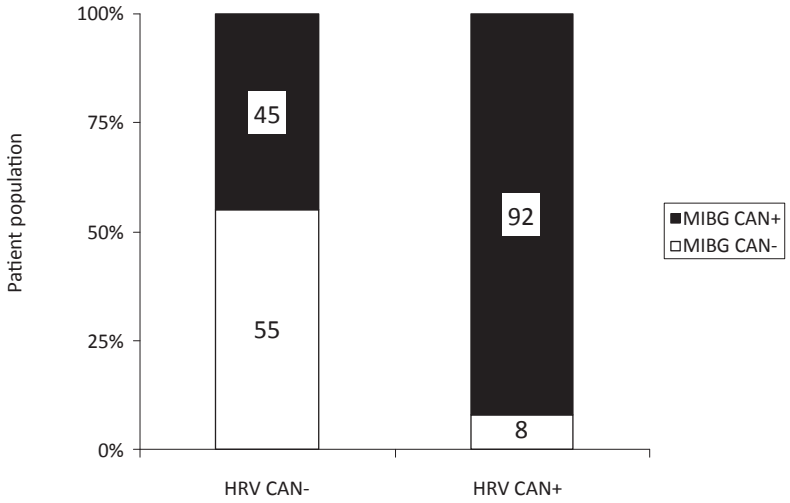
Cardiac autonomic neuropathy assessed by ^{123}I-*m*IBG versus HRV

The agreement and disagreement between HRV and ^{123}I-*m*IBG for the assessment of CAN is shown in Figure 1. Of the 64 patients without CAN according to HRV, 35 patients (55%) had a normal ^{123}I-*m*IBG study. Of the 24 patients with CAN according to HRV, 22 (92%) had an abnormal ^{123}I-*m*IBG study. In particular, 15 (63%) patients had HMR<1.8 (mean 1.57±0.16), 13 (54%) patients had a WO>25% (mean 35±10) and 12 (50%) patients had a TDS>13 (mean 51±24). 12 patients (50%) had ≥2 criteria for an abnormal ^{123}I-*m*IBG study. However, in the remaining 29 patients (45%) with normal HRV, ^{123}I-*m*IBG scintigraphy was abnormal. In particular, twenty-one patients (72%) had a HMR<1.8 (mean 1.66±0.10), 18 patients (62%) had a WO>25% (mean 34±7) and 13 patients (45%) had a TDS>13 (mean 26±11). 15 patients (52%) had ≥2 criteria for an abnormal ^{123}I-*m*IBG study.

Discussion

In the present study, the prevalence of CAN in asymptomatic patients with type 2 diabetes and normal myocardial perfusion was assessed by HRV and ^{123}I-*m*IBG scintigraphy;

Figure 1. Agreement and disagreement between HRV and ^{123}I-*m*IBG scintigraphy for the assessment of cardiovascular autonomic neuropathy



CAN, cardiac autonomic neuropathy; HRV, heart rate variability.

the prevalence of CAN was 27% according to HRV and 58% on ^{123}I-*m*IBG scintigraphy. Importantly, in almost 50% of the patients with normal HRV, ^{123}I-*m*IBG scintigraphy showed CAN, suggesting that ^{123}I-*m*IBG imaging may be more sensitive for the assessment of CAN than HRV.

CAN is one of the most important complications of diabetes mellitus. It results from damage to the autonomic nerve fibers innervating the heart and blood vessels, which causes abnormalities in heart rate control and impairs vascular dynamics. Clinical manifestations of CAN include exercise intolerance, intra-operative cardiovascular instability, orthostatic hypotension, asymptomatic ischemia and painless myocardial infarction.[150] Furthermore, CAN is associated with poor outcome related to ventricular arrhythmias and sudden cardiac death.[125-129] [151] In clinical practice, CAN is generally assessed using HRV. When CAN has progressed significantly, it may result in a reduction of HRV.[152] Measuring the HRV has shown to be a simple, noninvasive method to evaluate the sympatheticovagal balance at the sinoatrial level and can identify patients at elevated risk for cardiac arrhythmias and sudden death.[153, 154]

Therefore, assessing HRV is potentially important in the management of patients with diabetes. In the current study, a series of simple bedside tests that are fairly sensitive in detecting CAN were used.[126] In 1976 already, Ewing et al published the results of 37 diabetic patients with symptoms and clinical features suggestive of autonomic neuropa-

thy who were followed for 33 months.[125] The authors concluded that simple autonomic function tests provided significant prognostic information, with abnormal tests being associated with a high mortality. These results were confirmed in a larger population (n=605) of the Hoorn study with a follow-up period of 9 years.[127] Mortality during the follow-up was 17% (n=101 patients); patients with diabetes and impaired autonomic function had a twofold mortality risk.

^{123}I-*m*IBG is an analog of the false neurotransmitter guanethidine. It is taken up by adrenergic neurons in a similar fashion to norepinephrine and does not undergo intracellular metabolism. When labelled with ^{123}I, it can be used to visualize adrenergic receptors in the myocardium using scintigraphic imaging.[155] At present, cardiac ^{123}I-*m*IBG imaging has mainly been used for prognostification of patients with heart failure. In a pooled analysis, including almost 1800 patients derived from 8 studies, a decreased late H/M ratio or increased myocardial ^{123}I-*m*IBG washout was associated with a worse outcome compared to patients with normal ^{123}I-*m*IBG scintigraphy parameters.[156] In patients with diabetic neuropathy and/or CAN, Ziegler et al investigated prospectively the effect of glycemic control on myocardial sympathetic innervation using ^{123}I-*m*IBG scintigraphy, at baseline and at 4 year follow-up.[157] Among the patients with a poorly controlled HbA1c, (mean ≥7.6%) ^{123}I-*m*IBG uptake deteriorated after 4 years.

Conversely, Schnell and co-workers reported that global and regional ^{123}I-*m*IBG uptake in 22 asymptomatic patients with type 1 insulin-dependent diabetes did neither significantly regress nor progress on average ^{123}I-*m*IBG uptake over 3 year follow-up. These results suggested hat CAN seemed to be a persistent phenomenon in intensive treated diabetic patients.[158] Recently, Nagamachi et al investigated retrospectively the long-term (mean 7.2 ± 3.2 years) prognostic value of ^{123}I-*m*IBG scintigraphy for both cardiac events and mortality in 144 patients with type 2 diabetes and normal myocardial perfusion.[131] A decreased delayed H/M ratio (<1.7) was an independent predictor of long-term mortality. A combination of ^{123}I-*m*IBG scintigraphy parameters (delayed H/M ratio <1.7, WR >25%) and HRV was independently predictive of cardiac events.

Previous data have suggested that ^{123}I-*m*IBG scintigraphy may be more sensitive than HRV for detection of CAN in diabetic subjects.[137, 157] Schnell and colleagues demonstrated that 14 (93%) of 15 diabetic patients without CAN according to HRV had an abnormal ^{123}I-*m*IBG study.[137]

The role of CAN in asymptomatic diabetic patients has been described by Valensi et al.[159] In this study, 75 patients with at least two cardiovascular risk factors, were evaluated for silent myocardial ischemia and CAN with a 3-7 years follow-up period. Eleven (15%)

patients had a major cardiovascular event and multivariate analysis demonstrated that CAN was a better predictor of major cardiac events than silent myocardial ischemia. Furthermore, Langer et al investigated CAN according to HRV and ^{123}I-*m*IBG scintigraphy in 23 normal subjects and 65 asymptomatic patients with diabetes type 2 and silent myocardial ischemia.[160] The authors showed that ^{123}I-*m*IBG uptake was largely diminished in diabetic patients, especially in those with clinically detectable CAN; moreover diffuse abnormalities in ^{123}I-*m*IBG uptake were observed in patients with silent myocardial ischemia.

In the present study, we performed a systematic, head-to-head comparison between HRV and ^{123}I-*m*IBG scintigraphy in 88 asymptomatic patients with type 2 diabetes to evaluate the presence of CAN. The current study has included much more patients than the previous studies, but although the inclusion criteria were different, our results are in line with previous reports observing a significantly higher proportion of CAN with ^{123}I-*m*IBG scintigraphy compared to HRV.[137, 161, 162] The fact that more patients exhibit abnormalities in ^{123}I-*m*IBG imaging as compared to HRV, underscores the suggestion that abnormalities in cardiac sympathetic innervation occur prior to ECG-based (HRV) cardiac autonomic dysfunction.[137] An alternative explanation is that ^{123}I-*m*IBG scintigraphy mainly reflects sympathetic innervation, whereas HRV may be more related to parasympathetic function.[163] It remains to be determined which of these two parameters may be more useful to predict long-term outcome.

While HRV and other traditional parameters provide an impression of global innervation abnormalities, ^{123}I-*m*IBG scintigraphy with SPECT provides information on regional innervation. The findings in the current study indicated that regional abnormalities occur often in patients with asymptomatic diabetes. Other studies using ^{123}I-*m*IBG scintigraphy, in populations with varying cardiovascular diseases, have also shown regional innervation abnormalities.[137, 161, 162, 164] For example, Langer et al evaluated 65 diabetic patients and noted significantly impaired ^{123}I-*m*IBG uptake in the inferior wall and apex.[160] Additional studies have shown that abnormalities in CAN tend to occur first in the inferior regions of the myocardium and then progressively spread to adjacent segments.[165, 166] It may well are that these regions of reduced innervation may be more prone to cardiac arrhythmias, but this remains to be determined.

It is noteworthy that reduced ^{123}I-*m*IBG uptake has also been reported (to a lesser extent) in normal subjects and was related to attenuation artefacts; although we did not correct for attenuation in the current study, only individuals with normal SPECT perfusion studies were included, which reduces the likelihood of attenuation artefacts.[167]

Clinical implications

Diabetic CAN is a serious and common complication of diabetes. It is related to an increased risk of cardiovascular mortality and morbidity. Therefore, early detection of CAN in diabetic patients is of importance for appropriate risk stratification. Of all established diabetes-related and cardiac risk factors in patients with asymptomatic diabetes, poor glycemic control is of great importance in the development and progression of CAN.[157, 165] At the same time, poor glycemic control is associated with poor outcome.[168] Accordingly, early detection of CAN is of utmost importance. As observed in the current study, ^{123}I-*m*IBG scintigraphy appears more sensitive than HRV to detect CAN in asymptomatic diabetic patients, without myocardial perfusion abnormalities; identification of these patients may permit risk factor modification, and intensive medical treatment, aiming at better glycemic control, which in turn may favourably affect outcome.[169-172] Indeed, several studies have shown that improvement of CAN (as evidenced by HRV) can be achieved by weight loss with regular exercise.[173, 174] Furthermore, progression of CAN can also be delayed by intensive medical therapy, thereby reducing the risk of premature mortality.[175]

Conclusion

The poor long-term prognosis of asymptomatic diabetic patients and CAN justifies early risk stratification. In the current head-to-head comparison between ^{123}I-*m*IBG scintigraphy and HRV, ^{123}I-*m*IBG scintigraphy identified significantly more patients with CAN as compared to HRV. These findings suggest that ^{123}I-*m*IBG myocardial scintigraphy may be suited for early detection of CAN. Prospective studies are needed to evaluate the prognostic value of ^{123}I-*m*IBG myocardial scintigraphy in asymptomatic diabetic patients.

Chapter 9

Summary, conclusions and future perspectives

Summary

Diabetes mellitus (DM) is an endocrine disease and primarily defined by the level of hyperglycaemia. The prevalence of this disease is high and is still increasing. Ninety percent of all diabetic patients have DM type 2. Cardiovascular disease is one of the most important complications of DM, and the prognosis of patients with DM is mainly dependent on the presence of coronary artery disease (CAD). In patients with DM type 2, CAD is often in an advanced state but asymptomatic. These asymptomatic patients with DM type 2 have an increased risk for cardiovascular morbidity and mortality, and early identification of these patients is important. In this thesis, we evaluated the value of different cardiac imaging techniques for risk stratifying in asymptomatic patients with DM type 2. The general introduction of this thesis (**chapter 1**) provides an overview of the prevalence of DM, its complications and the background of different noninvasive imaging modalities that are used for risk stratifying these patients. Moreover, the outline and the aims of this thesis are described. In **chapter 2,** we focused on the potential role of stress myocardial perfusion imaging (MPI) and computed tomography coronary artery calcium (CAC) scoring as two complementary approaches for screening asymptomatic patients with DM type 2. Recent studies suggested a relatively low prevalence of silent CAD as evidenced by abnormal MPI. However, with increasing severity of CAC scores, the prevalence and severity of stress-induced MPI abnormalities increased. We proposed an algorithm for the screening of asymptomatic diabetic patients, in which depending on the CAC score and specific patient characteristics, stress MPI may be justified. In **chapter 3,** we prospectively assessed for the presence of silent CAD in asymptomatic patients with DM type 2 by single photon emission computed tomography (SPECT) MPI, CAC scoring, and multislice computed tomography (MSCT) coronary angiography. We concluded that different imaging modalities visualized different aspects of silent coronary atherosclerosis. Anatomical evidence of coronary atherosclerosis (as determined by CAC and MSCT) occurred more frequently than functional evidence of ischemia (stress SPECT). However, clinically significant manifestations of CAD were observed in about one-quarter to one-fifth of patients by each imaging modality, either separately or in combination. The purpose of the study in **chapter 4** was to evaluate the prevalence of CAD as well as plaque morphology in asymptomatic patients with DM type 2 using MSCT. In addition, the relation between CAC score and MSCT findings was explored. MSCT coronary angiography detected a high prevalence of CAD (80%), of which a relatively high proportion of plaques were noncalcified (41%). Importantly, a CAC score <10

AU did not exclude the presence of CAD in these patients. In **chapter 5**, the prevalence of an abnormal stress MPI by means of SPECT in a cohort of truly asymptomatic patients DM type 2 was evaluated. We also determined which clinical characteristics may predict an abnormal stress myocardial perfusion study in this population. The study revealed a high prevalence (33%) of abnormal stress MPI studies. In contrast to previous studies, current smoking status, duration of DM type 2 and cholesterol/HDL ratio were identified as independent predictors of an abnormal stress MPI study. In **chapter 6**, we described a case report of a patient, who suffered a silent myocardial infarction, despite early identification of coronary atherosclerosis, followed by risk factor modification and aggressive medical therapy. The aim of the study described in **chapter 7** was to evaluate whether subclinical left ventricular systolic dysfunction was independently related to coronary atherosclerosis and if it provided incremental information over baseline characteristics to identify patients with coronary atherosclerosis. Compared to patients without atherosclerosis, diabetic patients with coronary atherosclerosis showed an impaired global left ventricular strain. The presence of subclinical left ventricular systolic dysfunction provided significant incremental value for the identification of patients with coronary atherosclerosis. The purpose of the study in **chapter 8** was to evaluate the prevalence of cardiac autonomic neuropathy (CAN) in patients with DM type 2, using heart rate variability (HRV) and ^{123}I-metaiodobenzylguanidine (^{123}I-*m*IBG) myocardial scintigraphy. The study revealed a high prevalence of CAN in patients DM type 2. In addition, ^{123}I-*m*IBG scintigraphy was more sensitive than HRV for the assessment of CAN.

Conclusions and future perspectives

In this thesis, we evaluated several different cardiac imaging techniques for risk stratifying asymptomatic patients with DM type 2. We concluded that different imaging modalities visualized different aspects of silent coronary atherosclerosis, and anatomic presence of coronary atherosclerosis by CAC and MSCT occurred more frequently than functional evidence of ischemia by stress MPI SPECT.

Secondly, a relatively high proportion (40%) of the plaques identified was noncalcified calcified, and a CAC score <10 AU did not exclude atherosclerosis.

Moreover, several independent predictors for an abnormal stress MPI were identified. Furthermore, in asymptomatic patients with DM type 2 and coronary atherosclerosis, subclinical left ventricular dysfunction reflected by an impaired global left ventricular

strain proved to be of incremental value for identifying coronary atherosclerosis. Finally, ^{123}I-*m*IBG myocardial scintigraphy seemed to be a more sensitive method to detect diabetic cardiovascular autonomic neuropathy compared to heart rate variability.

The prognostic value of all these cardiac imaging techniques for risk stratification of asymptomatic patients with DM type 2 will be determined in future follow-up studies. However, one has to realize that all these different cardiac imaging techniques, visualize different aspect of cardiac disease. Of course, also the costs of all these techniques must be taken into account. The challenge is to risk stratify diabetic patients to identify those at increased risk for cardiovascular morbidity and mortality. For this purpose, integration of the different imaging modalities may be most beneficial. If eventually, adequate treatment of that patient will indeed lead to an improved outcome, must be clarified in future studies.

Samenvatting in het Nederlands

Samenvatting

Diabetes mellitus (suikerziekte) is een stofwisselingsziekte, die gekenmerkt wordt door te hoge waardes van het suikergehalte in het bloed. Het is een veel voorkomend ziektebeeld en de prevalentie neemt nog steeds toe. Het merendeel (90%) van de patiënten met diabetes mellitus heeft diabetes mellitus type 2, ook wel ouderdomssuiker genoemd. Hart- en vaatziekten zijn de belangrijkste gevolgen van dit ziektebeeld. De levensverwachting van patiënten met diabetes mellitus wordt vooral bepaald door aderverkalking van de kransslagaders (coronairlijden). Coronairlijden bij patiënten met diabetes mellitus verloopt vaak zonder symptomen (asymptomatisch). Het identificeren van deze asymptomatische patiënten met diabetes mellitus is belangrijk, omdat er voor hen een verhoogd risico bestaat op het krijgen van hart- en vaatziekten. Diverse beeldvormingstechnieken van het hart, kunnen gebruikt worden voor deze risicostratificatie. In dit proefschrift wordt de rol bestudeerd van diverse beeldvormingstechnieken, die gebruikt kunnen worden voor risicostratificatie in een groep van asymptomatische patiënten met diabetes mellitus type 2. In **hoofdstuk 1** van dit proefschrift wordt een overzicht gegeven van de prevalentie van diabetes mellitus type 2, de gevolgen hiervan en achtergrondinformatie over de verschillende beeldvormingstechnieken die gebruikt worden voor risicostratificatie in deze patiëntengroep. **Hoofdstuk 2** beschrijft de, in de literatuur gevonden, prevalentie van zuurstoftekort (ischemie) van de hartspier (myocard) tijdens inspanning, gemeten met behulp van myocardperfusie scintigrafie. Met deze techniek wordt met behulp van radioactief materiaal, de zuurstofopname van de hartspier tijdens rust en inspanning in beeld gebracht. Dit is een *indirecte* maat voor de ernst van het coronairlijden. Coronairlijden kan *direct* in beeld gebracht worden met de multislice computer tomografie (MSCT) scan. Hierbij wordt o.a. gebruik gemaakt van de calciumscore. De calciumscore is een maat is voor verkalking van de kransslagaders. Uit bestudering van de literatuur, blijkt dat myocardischemie, gemeten met perfusiescintigrafie, relatief weinig voorkomt. Echter, de prevalentie van myocardischemie blijkt toe te nemen, indien de patiënt een hogere calciumscore heeft. Naar aanleiding van deze bevindingen wordt een algoritme voor het screenen van asymptomatische patiënten met diabetes mellitus type 2 voorgesteld. **Hoofdstuk 3** beschrijft een groep patiënten, waarin met behulp van myocardperfusie scintigrafie, de calciumscore en niet-invasieve coronair angiografie verschillende aspecten van coronairlijden in kaart werden gebracht. Anatomisch bewijs voor coronairlijden met de calciumscore en niet-invasieve coronair

angiografie, bleek vaker voor te komen dan myocardischemie tijdens inspanning. Klinisch relevant coronairlijden werd met de 3 verschillende technieken apart of gecombineerd in 20 tot 25% gezien. Het doel van het onderzoek beschreven in **hoofdstuk 4** was om met behulp van de MSCT scan allereerst de prevalentie van coronairlijden te onderzoeken in asymptomatische patiënten met diabetes mellitus type 2. Vervolgens is de samenstelling van de atherosclerotische plaques die tot een vernauwing leiden in de kransslagaders bestudeerd. Daarnaast, is de relatie tussen de calciumscore en de samenstelling van de vernauwing geëvalueerd. Er bleek sprake te zijn van een hoge prevalentie (80%) van coronairlijden in deze specifieke groep van patiënten. Een relatief hoog percentage (41%) van de vernauwingen bleek geen kalk te bevatten. Belangrijk om te noemen is, dat een lage calciumscore, een vernauwing van de kransslagader niet altijd uitsloot.

Hoofdstuk 5 beschrijft een studie, waarbij de prevalentie van een afwijkende myocardperfusie scintigrafie werd onderzocht. Vervolgens is er ook gekeken of er bepaalde patiënten kenmerken konden worden vastgesteld, die voorspellend waren voor een afwijkende myocardperfusie scintigrafie. In deze patiëntengroep, bleek er een hoge prevalentie te zijn van afwijkende perfusie scans. In tegenstelling tot eerdere studies bleek roken, de duur van diabetes mellitus en de verhouding cholesterol/HDL onafhankelijke voorspellers te zijn voor een afwijkend onderzoek. **Hoofdstuk 6** beschrijft een casus, waarbij ondanks het vroegtijdig vaststellen van coronairlijden, adequate aanpak van de risicofactoren en het instellen van medicatie, een hartinfarct wordt doorgemaakt zonder klachten. In **hoofdstuk 7** worden de resultaten gepresenteerd van metingen van de linker kamerfunctie van het hart met ultrageluid (echo). In de patiënten werd met behulp van echocardiografie, vervorming (strain) van de linker kamer hartspier gemeten. Het bleek dat in patiëntengroep met diabetes mellitus type 2 en coronairlijden, de strain verlaagd is ten opzichte van de groep patiënten zonder coronairlijden. In **hoofdstuk 8** werd geïnventariseerd, wat de prevalentie van autonome dysfunctie van het hart in de patiëntengroep is. Autonome dysfunctie betekent dat de zenuwen, die het hart aansturen, niet goed functioneren. Dit kan worden vastgesteld door het meten van de variatie in hartritme en in beeld worden gebracht met behulp van ^{123}I- gelabeld *m*IBG. Ondanks het feit dat autonome dysfunctie van het hart vaak wordt gemeten, leek ^{123}I-*m*IBG scintigrafie een gevoeligere methode te zijn, voor het vastleggen van autonome dysfunctie van het hart bij asymptomatische patiënten met diabetes mellitus type 2.

Conclusies en toekomstperspectief

In dit proefschrift werd, met behulp van verschillende beeldvormingstechnieken van het hart, getracht om tot een inschatting van het risico van asymptomatische patiënten met diabetes mellitus type 2 te komen. Uit het onderzoek bleek onder meer, dat in deze patiëntengroep met de verschillende beeldvormingstechnieken, verschillende aspecten van asymptomatisch coronairlijden in kaart konden worden gebracht. Anatomisch bewijs voor coronairlijden (calciumscore en niet-invasieve angiografie) bleek vaker voor te komen dan functioneel bewijs van coronairlijden (myocardperfusie scintigrafie). Er kon worden geconstateerd, dat in 80% van deze patiëntenpopulatie, met de MSCT scan anatomisch bewijs voor coronairlijden werd gezien. In 40% van de kransslagaders met atherosclerose, werden niet-verkalkte vernauwingen gezien. Belangrijk om te vermelden hierbij is, dat een lage calciumscore, coronairlijden niet altijd uitsloot.

Daarnaast is het mogelijk geweest om onafhankelijke factoren te identificeren voor een afwijkend myocard perfusiescintigrafie onderzoek. Met behulp van het meten van de strain van de linker kamerfunctie, konden binnen deze patiëntengroep, de patiënten met coronairlijden worden geïdentificeerd. Tenslotte, bleek dat ^{123}I-*m*IBG scintigrafie een gevoeligere methode was voor het opsporen van autonome dysfunctie van het hart, dan het meten van de variabiliteit in het hartritme. De voorspellende waarde van bovengenoemde beeldvormingstechnieken voor het inschatten op een cardiaal risico van asymptomatische patiënten met diabetes mellitus type 2, zal moeten worden bepaald in follow-up studies. Men dient zich echter wel realiseren, dat elke beeldvormingstechniek een specifiek aspect van het hart in kaart brengt. Hierbij moet uiteraard ook rekening worden gehouden met de kosten die elk onderzoek met zich meebrengt. Mogelijk is integratie van de diverse beeldvormingstechnieken de beste strategie. Uiteindelijk zal met een *combinatie* van de bovengenoemde beeldvormingstechnieken *die* patiënt moeten worden geïdentificeerd, die een aanzienlijk hoger risico op een toekomstig myocardinfarct heeft.

Of uiteindelijk adequate behandeling van *die* patiënt tot een verbeterde uitkomst zal leiden, moet worden verhelderd in toekomstige studies.

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 11 december 1968 te Mook en Middelaar. Na het behalen van het VWO examen in 1987 aan het Bonhoeffer College te Castricum startte hij met de studie Tandheelkunde. Een jaar later begon hij met de studie Geneeskunde aan de Vrije Universiteit te Amsterdam, waar hij in 1995 het artsexamen behaalde. Tijdens de opleiding geneeskunde verrichtte hij wetenschappelijk onderzoek op het gebied van de cardiologie in Mainz, Duitsland, bij Prof.dr. R. Erbel en in New York, Verenigde Staten, bij Dr. J. Machac. De vooropleiding interne geneeskunde werd verricht in het Gooi-Noord ziekenhuis te Blaricum (1998-2000, opleider Dr. P. Niermeyer) en de opleiding tot cardioloog in het Onze Lieve Vrouwe Gasthuis te Amsterdam (2001-2003, opleider Dr. G.J. Laarman) en het Leids Universitair Medisch Centrum (2004-2005, opleider Prof.dr. E.E. van der Wall). Sinds 2005 is hij staflid van de afdeling Hartziekten van het Leids Universitair Medisch Centrum met als aandachtsgebied niet-invasieve cardiale beeldvorming (echocardiografie en nucleaire cardiologie). Het promotieonderzoek werd verricht in de periode 2005-2009 op de afdeling Hartziekten van het LUMC.