Computed tomography coronary angiography : from quantification of coronary atherosclerosis to risk stratification of patients

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Chapter 10

Changes in ischaemia as assessed with single-photon emission computed tomography myocardial perfusion imaging in high-risk patients with diabetes without cardiac symptoms: relation with coronary atherosclerosis on computed tomography coronary angiography

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Abstract

Purpose: The study aims 1) to evaluate changes in myocardial ischemia on single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) after 2 years in a cohort of high risk patients with diabetes without cardiac symptoms or known coronary artery disease (CAD) and 2) to assess the value of baseline computed tomography coronary angiography (CTA) derived coronary atherosclerosis parameters to predict changes in myocardial ischemia.

Methods: The population consisted of 100 high risk patients with diabetes without cardiac symptoms referred for cardiovascular risk stratification. All patients underwent coronary artery calcium (CAC) scoring, CTA and SPECT MPI. After 2 years follow-up, SPECT MPI was repeated to evaluate potential progression of ischemia.

Results: In total, 20% of patients presented with ischemia at baseline. Of these 20 patients, 7 (35%) still had ischemia at follow-up, whereas 13 (65%) showed resolution and 4(20%) showed progression of ischemia at follow-up. Of the 80 patients without ischemia at baseline, 65 (81%) had a normal MPI at follow-up and 15 patients (19%) presented with new ischemia. There were no significant differences in the CAC score or the extent, severity and composition of CAD on CTA between patients with and without ischemia at baseline. Similarly, no differences could be demonstrated between patients with and without ischemia at follow-up or between patients with and without progression of ischemia.

Conclusion: The rate of progression of ischemia in high risk patients with diabetes without cardiac symptoms is limited. Few patients presented with new ischemia, whereas some patients show resolution of ischemia. Atherosclerosis parameters on CTA were not predictive of new onset ischemia or progression of ischemia.

Introduction

Cardiovascular death is the main cause of death in patients with diabetes mellitus (DM).[1] Moreover, patients with DM often have silent myocardial ischemia on single photon emission tomography (SPECT) myocardial perfusion imaging (MPI) and coronary artery disease (CAD) in an advanced stage on coronary computed tomography angiography (CTA).[2-8] After 2-3 years of follow-up, a limited number of patients present with new ischemia.[9] However, no clinical variables predictive of new ischemia have yet been established. Potentially, atherosclerotic plaque characteristics on CTA could be associated with the onset of new ischemia. Therefore, the aim of this study was to: 1) evaluate changes in myocardial ischemia after 2 years in a cohort of high risk patients with diabetes without cardiac symptoms and 2) to assess the value of baseline CTA derived coronary atherosclerosis parameters to predict changes in myocardial ischemia on SPECT MPI in these patients.

Methods

Patients

The patient population consisted of 159 high risk patients with diabetes without cardiac symptoms referred from a diabetic out-patient clinic for cardiovascular risk stratification as previously described.[10, 11] Inclusion criteria for the study were: confirmed diagnosis of type 2 DM, normal resting electrocardiogram (ECG), absence of cardiac symptoms. Patients with known CAD or treated with anti-anginal medication were excluded, as well as patients with a previous stress test or coronary angiography. All patients underwent clinical evaluation, including laboratory testing, coronary artery calcium (CAC) scoring, coronary CTA and SPECT MPI between May 2005 and January 2006. After 2 years follow-up, SPECT MPI was repeated as prospectively scheduled to evaluate myocardial ischemia as indicated in the guidelines that were applicable at that time.[12] Patients were treated according standard clinical care and based on test results.

The patient's medical records were evaluated to assess if the patient underwent coronary revascularization between the 2 SPECT MPI studies. Clinical data were prospectively entered into the departmental Cardiology Information System (EPD-Vision©, Leiden University Medical Center, the Netherlands) and retrospectively analysed. The Institutional Review Board of the Leiden University Medical Center approved this retrospective evaluation of clinically collected data, and waived the need for written informed consent.

SPECT myocardial perfusion imaging

Image acquisition.

ECG-gated technetium-99m sestamibi (^{99m}Tc-sestamibi;1000MBq) SPECT MPI was performed using a 2-day stress and rest protocol. Patients had to refrain from caffeine-containing products 24-hours before testing. Vasodilator stress was performed using adenosine (140µg/kg/minute, intravenous for 6 minutes) with simultaneous handgrip exercise. Blood pressure and 12-lead ECG were recorded during adenosine stress. SPECT imaging was performed, 120 minutes after injection of the radiopharmaceutical, using a triple-head SPECT gamma camera (GCA 9300/HG, Toshiba Corporation, Tokyo, Japan). Images were acquired using a circular 360 degrees orbit in 64 projections and 20 second per projection.[13] Attenuation correction was not performed.

Quantification of myocardial ischemia.

The SPECT MPI datasets were sent to an independent, dedicated core-lab (INVIA, Ann Arbor, Michigan, USA), blinded of patients' history or scan order. By using Corridor4DM (INVIA, Ann Arbor, Michigan, USA), myocardial perfusion and reversibility (ischemia) was quantified as follows. [14, 15] First, the stress dataset was normalized to the maximum pixel intensity within the myocardium; all values were multiplied by 100/value of the maximum pixel. Second, the rest dataset was normalized in the same manner using the peak in the location of the peak intensity in the stress map. The extent of hypoperfusion in the stress study was expressed as a percentage of the entire left ventricle. Comparing the rest and the stress study, allowed for assessment of reversibility by comparing the areas of hypoperfusion on the stress study to the same areas in the rest study; a ≥10% increase in tracer uptake was used to define reversibility. Reversibility was expressed as percentage of the entire left ventricle. Change in ischemia was calculated as the differences in reversibility between the baseline and follow-up study. To facilitate the analysis, patients were stratified into two groups based on differences in reversibility between the baseline and follow-up study. Any increase in ischemia was defined as progression, whereas a decrease in ischemia was defined as regression.

Coronary computed tomography angiography

Image acquisition.

Patients were scanned with either a 64-slice CT scanner (Aquilion 64, Toshiba Medical System, Otowara, Japan) or a 320-row volumetric scanner (Aquilion ONE, Toshiba Medical System, Otowara, Japan). Contra-indications for CTA were, 1) impaired renal function (glomerular filtration rate <60 ml/min/1.73m^2), 2) pregnancy, 3) (supra-)

ventricular arrhythmias, 4) known allergy to contrast agent, 5) severe claustrophobia. Non-contrast CT and contrast CTA were performed according to standard clinical practice. Prior to CT examination, beta-blocking medication was administered if the heart rate was ≥65 beats per minutes, unless contra-indicated. Datasets were sent to a remote workstation for analysis.

Image analysis.

Evaluation of the CTA was performed on a dedicated workstation (Vitrea FX, Vital Images, Minnetonka, MN, USA). For each patient the Agatston CAC score was measured. Thereafter, the CTA datasets were evaluated for the presence, severity and composition of coronary atherosclerosis as previously described.[16] In brief, each segment of the coronary tree was scored as normal (<30%), non-obstructive (30-50%) or obstructive (≥50%) CAD. Coronary plaque composition was assessed as non-calcified, calcified or mixed-plaque. Per patient, the number of segments with atherosclerosis and the number of each type of plaque were assessed. Significant coronary artery disease was defined by the presence of a coronary lesion with ≥50% stenosis.

Statistical analysis

For reasons of uniformity summary statistics for all continuous data are presented as mean ± SD. Normality of the data was confirmed by comparing the histogram with a normal probability curve. Categorical data are presented as absolute numbers and percentages. First, clinical patient characteristics were compared between patients with and without ischemia at baseline. Second, in a similar fashion, patients with and without ischemia at follow-up were compared. Third, patients with and without progression of ischemia were compared likewise. Thereafter, the CTA parameters of the extent, severity and composition of coronary atherosclerosis were compared between all patient groups. Statistical significance was assessed using non-parametric tests for continuous data with a non-normal distribution and t-test for data with a normal distribution. Chi-square tests were applied to categorical data. All statistical tests were two-sided and a P-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (Version 20.0, SPSS Inc., Chicago, Illinois).

Results

Patient characteristics

The population consisted of 159 patients. In 36 patients, one of the two SPECT MPI studies was not performed (for logistical reasons). The datasets of the remaining

123 patients were sent to an independent core-lab for quantification of myocardial ischemia. In 16 patients quantitative analysis could not be performed due to protocol violations or insufficient image quality. The results of 107 patients were available for analysis, 7 patients underwent planned revascularization between the two studies and were therefore excluded. The final patient cohort consisted of 100 patients. Table 1 demonstrates the baseline characteristics of the population. In total, 62 patients were male, half of the patients presented with hypertension or hypercholesterolemia. Mean diabetes duration was 113 ± 87 months. In Table 1, the medical therapy at baseline is described. In total, 52 patients received statin therapy, 17 aspirin and 31 ACE-inhibitors. At follow-up, in 23 patients statin therapy was added and 8 patients received additional ACE-inhibitors. Aspirin was added in 22 patients. At follow-up, 19 patients received anti-angina medication (i.e. beta-blockers, calcium-antagonists or nitrates).

SPECT MPI results

Median time between the 2 SPECT MPI studies was 30 (IQR 27-33) months. As shown in Figure 1, 20% of patients presented with ischemia at baseline, without need of revascularization. Of these 20 patients, 7 (35%) patients still had ischemia at follow-up, whereas 13 (65%) patients showed resolution of ischemia and 4 showed progression of ischemia at follow-up. Of the 80 of patients without ischemia at baseline, 65 (81%) had a normal study at follow-up and 15 patients (19%) presented with new ischemia. Figure 2 demonstrates the rate of progression of ischemia. In patients with a normal baseline SPECT MPI, 19% of the patients presented with progression of ischemia. In Table 1, the baseline results stratified according to the presence of baseline ischemia are demonstrated. Except for family history and low-density lipoprotein (LDL)-cholesterol, there were no significant differences between patients with or without myocardial ischemia at baseline. In Table 2, the difference in characteristics between patients with and without ischemia at follow-up is shown. Remarkably, there were no significant differences between both patients groups. Table 3 summarizes the differences between baseline characteristics between patients with and without progression of ischemia. DM duration was significantly longer among patients who showed progression of ischemia (180 ± 97 vs. 135 ± 83 months, P=0.049). The remaining baseline characteristics were comparable between patients with and without progression of ischemia. At follow-up, 5 patients presented with onset of chest-pain, of which 1 had progression of ischemia and 4 presented without new ischemia. Of the 19 patients in whom anti-anginal medication was added, 2 presented with progression of ischemia (P=0.295). There was no relation between the onset of symptoms and new ischemia or progression of ischemia.

Table 1. Clinical characteristics of the population in relation to baseline ischemia.

	Total (N=100)	Ischemia (n=20)	No ischemia (n=80)	P- value
Age(years)	53 ± 10	54 ± 11	53 ± 10	0.791
Gender(% male)	62 (62%)	15 (75%)	47 (59%)	0.181
Hypertension† n(%)	52 (52%)	7 (35%)	45 (56%)	0.089
Hypercholesterolemia‡ n(%)	51 (51%)	11 (55%)	40 (50%)	0.689
Family history of CAD* n(%)	56 (65%)	5 (25%)	51 (64%)	**0.002**
Smoking n(%)	19 (19%)	6 (30%)	13 (13%)	0.161
Diabetes-related factors				
Age at time of diagnosis(years)	43 ± 12	45 ± 15	43 ± 11	0.443
Diabetes duration(months)	113 ± 87	99 ± 95	117 ± 85	0.409
HbA_1C(%)	7.5 ± 1.6	7.7 ± 1.5	7.5 ± 1.7	0.633
Diabetes-related complications				0.857
PVD n(%)	9 (9%)	2 (10%)	7 (9%)	
PNP n(%)	23 (23%)	6 (30%)	17 (21%)	
PVD and PNP n(%)	10 (10%)	2 (10%)	8 (10%)	
Diabetes-related treatment				0.617
Oral	61 (61%)	14 (70%)	47 (59%)	
Insulin	19 (19%)	2 (10%)	17 (21%)	
Oral and insulin	17 (17%)	3 (15%)	14 (17%)	
Medication at baseline				
Aspirin n(%)	17 (17%)	6 (30%)	11 (14%)	0.084
ACE-inhibitors n(%)	31 (31%)	7 (35%)	24 (30%)	0.665
ARB	26 (26%)	5 (25%)	21 (26%)	0.909
Statins n(%)	52 (52%)	14 (70%)	38 (48%)	0.072
Serum markers at baseline				
Total cholesterol(mmol/l)	4.8 ± 1.1	4.4 ± 1.0	3.9 ± 1.3	0.074
LDL(mmol/l)	3.1 ± 1.1	2.7 ± 0.9	3.3 ± 1.1	**0.049**
HDL(mmol/l)	1.4 ± 0.6	1.3 ± 0.4	1.4 ± 0.6	0.401
Cholesterol/HDL ratio	3.9 ± 1.4	3.9 ± 1.5	3.9 ± 1.3	0.971
Triglycerides(mmol/l)	2.0 ± 1.3	1.9 ± 0.8	2.1 ± 1.3	0.602

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; DM, diabetes mellitus; HDL, high density lipoprotein; LDL, low density lipoprotein; PNP, polyneuropathy; PVP, peripheral vessel disease

†Blood pressure ≥140/90 mmHg or treatment with antihypertensive medication; ‡ total cholesterol level >5.0mmol/L or use of cholesterol lowering medication; *defined as the presence of coronary artery disease in first-degree family members at age <55 years in men and <65 years in women; #body mass index ≥30

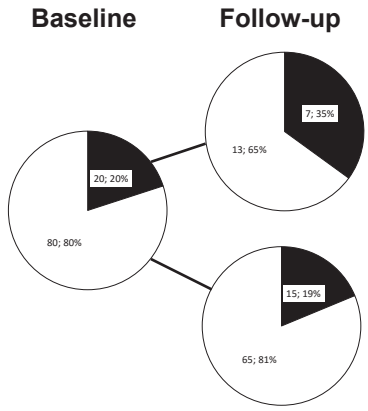

Figure 1. Distribution of myocardial ischemia on SPECT MPI at baseline and after 2 years follow-up.
Pie charts of the distribution of myocardial ischemia on SPECT MPI stratified according to baseline ischemia. Black represents ischemia, white represents a normal SPECT MPI.

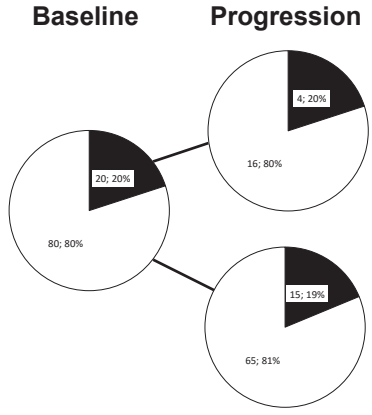

Figure 2. Distribution of progression of myocardial ischemia on SPECT MPI at baseline and after 2 years follow-up.
Pie charts of the distribution of progression myocardial ischemia on SPECT MPI stratified according to baseline ischemia. At baseline black marks ischemia, white represents a normal SPECT MPI. For follow-up, black marks progression of ischemia.

CTA results

93 of the 100 patients underwent coronary CTA and 98 patients CAC scoring. The median time between the first SPECT MPI and CTA was 22 (IQR 4 - 46) days. In Table 4 the CTA results are demonstrated, stratified according to the presence of baseline and follow-up ischemia. A comparison was made for the presence, extent and composition of coronary atherosclerosis on CTA. For all parameters, there were no significant differences between patients with and without ischemia at baseline.

Table 2. Clinical characteristics of the population in relation to follow-up ischemia.

	FU ischemia (n=22)	FU no ischemia (n=78)	P- value
Age(years)	54 ± 12	53 ± 9	0.641
Gender(% male)	13 (59%)	49 (62%)	0.750
Hypertension† n(%)	11 (50%)	41 (53%)	0.832
Hypercholesterolemia‡ n(%)	11 (50%)	40 (51%)	0.915
Family history of CAD* n(%)	10 (46%)	46 (59%)	0.259
Smoking n(%)	4 (18%)	15 (19%)	0.912
Diabetes-related factors at FU			
Age at time of diagnosis(years)	43 ± 15	43 ± 10	0.912
Diabetes duration(months)	136 ± 99	113 ± 85	0.300
HbA_1C(%)	7.7 ± 1.8	7.7 ± 1.5	0.876
Diabetes-related complications at FU			0.571
PVD n(%)	2 (9%)	7 (9%)	
PNP n(%)	6 (27%)	18 (23%)	
PVD and PNP n(%)	7(32%)	4 (5%)	
Diabetes-related treatment at FU			0.224
Oral	9 (41%)	42 (54%)	
Insulin	3 (14%)	18 (23%)	
Oral and insulin	9 (41%)	16 (21%)	
Medication at FU			
Aspirin n(%)	12 (55%)	25 (32%)	0.054
ACE-inhibitors n(%)	10 (45%)	28 (36%)	0.415
ARB n(%)	6 (27%)	22 (28%)	0.931
Statins n(%)	17 (77%)	57 (73%)	0.692
Beta-blockers n(%)	2 (9%)	6 (8%)	0.831
Calcium-antagonists n(%)	1 (5%)	12 (15%)	0.182
Nitrates n(%)	0 (0%)	1 (1%)	0.594
Serum markers at FU			
Total cholesterol(mmol/l)	4.2 ± 1.1	4.5 ± 1.0	0.382
LDL(mmol/l)	2.6 ± 0.9	2.7 ± 0.9	0.548
HDL(mmol/l)	1.2 ± 0.3	1.3 ± 0.4	0.432
Cholesterol/HDL ratio	3.6 ± 1.0	3.7 ± 1.2	0.645
Triglycerides(mmol/l)	2.0 ± 1.7	1.9 ± 1.0	0.751

Abbreviations and definitions as in Table 1.

Similarly, no differences could be demonstrated between patients with and without ischemia at follow-up or between patients with and without progression of ischemia. Overall, 24 (26%) patients presented with obstructive CAD on CTA (of note: patients who underwent revascularization between the two SPECT MPI studies were

Table 3. Clinical characteristics of the population in relation to progression of ischemia.

	Progression (n=19)	No progression /regression (n=81)	P- value
Age(years)	53 ± 12	53 ± 10	0.794
Gender(% male)	10 (53%)	52 (64%)	0.350
Hypertension† n(%)	9 (47%)	43 (53%)	0.653
Hypercholesterolemia‡ n(%)	9 (47%)	42 (52%)	0.725
Family history of CAD* n(%)	10 (53%)	46 (57%)	0.742
Smoking n(%)	4 (21%)	15 (19%)	0.800
Diabetes-related risk factors at FU			
Age at time of diagnosis(years)	41 ± 13	44 ± 11	0.320
Diabetes duration(months)	180 ± 97	135 ± 83	**0.049**
HbA_1C(%)	8.1 ± 1.5	7.7 ± 1.6	
Diabetes-related complications at FU			0.455
PVD n(%)	2 (11%)	7 (9%)	
PNP n(%)	4 (21%)	20 (25%)	
PVD and PNP n(%)	4 (21%)	7 (9%)	
Diabetes-related treatment at FU			0.249
Oral	8 (42%)	43 (53%)	
Insulin	3 (16%)	18 (22%)	
Oral and insulin	8 (42%)	17 (21%)	
Medication at FU			
Aspirin n(%)	10 (53%(	27 (33%)	0.117
ACE-inhibitors n(%)	9 (47%)	29 (36%)	0.350
ARB n(%)	5 (26%)	23 (29%)	0.856
Statins n(%)	16 (84%)	58 (73%)	0.260
Beta-blockers n(%)	2 (11%)	6 (32%)	0.652
Calcium-antagonists n(%)	0 (0%)	13 (16%)	0.061
Nitrates n(%)	0 (0%)	1 (1%)	0.626
Serum markers at FU			
Total cholesterol(mmol/l)	4.3 ± 1.0	4.5 ± 1.0	0.469
LDL(mmol/l)	2.6 ± 0.9	2.7 ± 0.9	0.653
HDL(mmol/l)	1.2 ± 0.25	1.3 ± 1.2	0.435
Cholesterol/HDL ratio	3.7 ± 1.2	3.7 ± 1.2	0.154
Triglycerides(mmol/l)	1.9 ± 1.7	1.9 ± 1.0	0.435

Abbreviations and definitions as in Table 1.

excluded). In patients with ischemia at baseline, more had obstructive CAD (33% vs. 24%, P=0.476) but these differences were not significant. These patients also had a higher mean CAC score (19 (IQR 0-115) vs. 4 (IQR 0-101), P=0.390), but the

Table 4. Coronary atherosclerosis on CTA in relation to the SPECT MPI results.
Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease

	All patients (n=93)	BL ischemia (N=18)	BL no ischemia (N=75)	P-value	FU ischemia (N=19)	FU no ischemia (N=74)	P-value	Progression (N = 17)	No progression /regression (N=76)	P-value
Coronary stenosis										
No. of plaques ≥30%	3.6 ± 3.8	4.1 ± 3.7	3.5 ± 3.9	0.542	4.2 ± 3.4	3.4 ± 4.0	0.196	3.8 ± 3.3	3.5 ± 4.0	0.452
No. of non-obstructive lesions <50%	3.0 ± 3.2	3.1 ± 2.9	3.0 ± 3.3	0.762	3.1 ± 2.4	3.0 ± 3.4	0.441	2.8 ± 2.5	3.0 ± 3.4	0.714
No. of obstructive lesions ≥50%	0.6 ± 1.3	0.9 ± 1.8	0.5 ± 1.1	0.361	1.16 ± 1.9	0.42 ± 1.0	0.131	1.0 ± 1.7	0.5 ± 1.1	0.250
No. of patients with obstructive CAD	24 (26%)	6 (33%)	18 (24%)	0.476	7 (37%)	17(23%)	0.434	6 (35%)	18 (24%)	0.546
Coronary plaque type										
No. of calcified lesions	0.9 ± 2.0	0.7 ± 1.8	1.0 ± 2.0	0.330	1.0 ± 1.6	1.4 ± 2.2	0.424	0.7 ± 1.0	1.0 ± 2.1	0.614
No. of mixed lesions	1.1 ± 1.9	1.7 ± 2.4	0.9 ±1.7	0.144	1.8 ± 2.5	0.9 ± 1.6	0.159	1.6 ± 2.3	1.0 ± 1.8	0.249
No. of non-calcified lesions	1.3 ± 2.1	1.4 ± 1.9	1.3 ±2.2	0.445	1.2 ± 1.7	1.4 ± 2.2	0.842	1.2 ± 1.8	1.3 ± 2.2	0.760
Coronary artery calcium (CAC)										
CAC score	170 ± 451 10 (0-104)	211 ± 378 19 (0-115)	160 ± 468 4 (0-101)	0.390	295 ± 792 47 (0-164)	136 ± 299 0 (0-100)	0.118	236 ±812 16 (0-81)	154 ± 316 4 (0-112)	0.408
No. patients with CAC score = 0	45 (46%)	7 (37%)	38 (48%)	0.377	6 (28%)	39 (51%)	0.072	6 (32%)	39 (49%)	0.162

difference was not statistically different. In patients presenting with progression of ischemia, obstructive CAD occurred more often (35% vs. 24%, P=0.546) and CAC scores were slightly higher (16 (IQR 0-81) vs. 4 (IQR 0-112), P=0.408), but these differences were also not significant.

Discussion

The present study demonstrated a low rate of progression of ischemia after 2 years in high risk patients with diabetes without cardiac symptoms. Moreover, no relation between atherosclerosis parameters on CTA and changes of ischemia was observed.

Previous studies have investigated the role of screening with SPECT MPI for silent ischemia in asymptomatic diabetic patients.[17] Most importantly, in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, 1123 diabetic patients without any suspicion of CAD were randomized between screening with SPECT MPI and no screening.[18] Of the 522 patients who underwent SPECT MPI, 133 (22%) presented with an abnormal study, the majority (73%) of which were regional perfusion abnormalities.[9] Except for gender, diabetes duration and heart rate response to Valsalva (performed as part of cardiac autonomic function testing), no clinical characteristics or laboratory markers could accurately predict the presence of silent ischemia in these patients. Second, Lorenzo *et al*. included 180 asymptomatic diabetic patients who underwent SPECT MPI and were followed for a mean period of 36 months.[19] In total, 46 patients (26%) of the patients presented with an abnormal MPI. No differences in characteristics were observed between patients with and without myocardial ischemia. However, at present only one study has focused on progression of ischemia in these patients. In DIAD-2, 358 of the initial 522 patients underwent a second SPECT MPI study to evaluate the change in myocardial perfusion after a 3 year interval.[9] Similar to the present study, of the 71 (20%) patients who presented with an abnormal SPECT MPI study at baseline, 56 (79%) showed resolution of ischemia after 3 years, whereas only a limited number of patients (10%) with a normal baseline examination presented with new ischemia. Likely this resolution of ischemia was caused by intensified medical therapy after recommendations in the American Diabetes Association (ADA) guidelines.[20] Similarly, in the present report medical therapy was intensified at follow-up. However, no relation between added anti-anginal medication and ischemia progression could be established. Comparable to the present report, in DIAD-2 the value of clinical characteristics to predict the risk of new ischemia was limited. Only peripheral vessel disease (PVD) and elevated LDL-cholesterol levels where associated with new onset of ischemia.

Presumably, the relative low rate of progression of ischemia is caused by accurate medical therapy. If these diabetic patients are treated according guidelines based on the outcomes of testing, the clinical follow-up is prosperous. It seems that medical treatment outweighs the potential negative effect of other clinical characteristics. It would however have been unethical to refrain patients from appropriate medical therapy.

In the present report, there was no significant difference between the median CAC score in patients with and without baseline ischemia. In contrast, Anand *et al.* showed a significant association between the CAC score and myocardial ischemia in 510 asymptomatic diabetic patients.[21] MPI was performed in all patients with a CAC score >100 and in a random sample of patients with a CAC score ≤100. The CAC score was significantly associated with the presence of myocardial ischemia. Of particular interest, all patients with a CAC score ≤10 presented with a normal SPECT MPI. Furthermore, in the current report, no correlation was demonstrated between coronary atherosclerosis parameters of the extent, severity or composition of coronary atherosclerosis on CTA and baseline ischemia on SPECT MPI. Indeed, several studies have previously demonstrated the limited correlation between the coronary stenosis severity on CTA and ischemia on SPECT MPI, both in patients with stable angina and asymptomatic diabetic patients.[11, 22] However, for the present study, it was hypothesized that CTA could be able to identify different coronary atherosclerotic plaque characteristics which could predict changes in myocardial ischemia on SPECT MPI. The relation between coronary plaque type and the presence of myocardial ischemia has previously been studied.[23-25] Lin *et al.* included 163 low-to-intermediate risk symptomatic patients who underwent both CTA and SPECT MPI.[25] Besides stenosis severity, mixed plaque was significantly associated with the presence of myocardial ischemia. Moreover, van Velzen *et al.* evaluated 514 patients with SPECT MPI and coronary CTA.[23] The presence of mixed or calcified plaque independently predicted myocardial ischemia. In contrast, Bauer *et al.* focused on the relation between non-calcified CAD on CTA and myocardial ischemia in 72 patients.[24] It was demonstrated that coronary arteries with a perfusion defect in the corresponding vascular territory had significantly larger non-calcified plaque volumes, but there was no difference in calcified plaque volume. The underlying pathophysiological relation between coronary plaque composition and myocardial ischemia is unknown. Possible, mixed plaques with a relatively large plaque burden are prone to rupture, causing myocardial ischemia, whereas the more advanced stage of calcified plaque is relatively stable. Especially in a patient without baseline ischemia, rupture of a hemodynamically non-significant plaque could cause onset of ischemia. However, the relation between CTA atherosclerosis parameters and progression of atherosclerosis has not been described earlier. Moreover, in the present study, no association could be established between

CTA coronary atherosclerosis and changes in myocardial ischemia. There was no significant difference in the different plaque types between patients with and without onset of new ischemia or progression of ischemia. Nor could a difference in the presence of non-obstructive CAD between both patient groups be established. Moreover, the CAC score was similar in both groups. The relative disagreement between atherosclerosis on CTA and ischemia on SPECT MPI could be caused by the fact that the two different modalities evaluate different manifestations of CAD. CTA only allows assessment of coronary artery stenosis in the major epicardial coronary arteries. On the other hand, SPECT MPI visualizes perfusion defects which could be caused by either stenosis in a major epicardial coronary artery and/or by microvascular disease and endothelial dysfunction. However, it is well known that especially in diabetic patients, microvascular disease plays an important role in the onset of myocardial ischemia.[6]

Limitations

Some limitations need to be considered. First, a limited number of patients is included. Second, patients who underwent revascularization were excluded, which may have affected results. And furthermore, additional SPECT parameters such as left ventricular ejection fraction, transient ischemic dilatation or ECG abnormalities were not incorporated in the current analysis.

Conclusions

The rate of progression of ischemia in high risk patients with diabetes without cardiac symptoms is limited. Few patients presented with new ischemia, whereas some patients show resolution of ischemia. Atherosclerosis parameters on CTA were not predictive of new onset ischemia or progression of ischemia. Neither baseline characteristics, CAC score nor atherosclerosis parameters on CTA were predictive of the onset of new ischemia or were correlated with progression of ischemia.

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