Myocardial perfusion abnormalities in asymptomatic type 2 diabetic patients

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Objective: **The prevalence of coronary artery disease (CAD) is high in patients with diabetes. Because ischemia and infarction are often silent in diabetic patients, diagnosis of CAD occurs inevitably late. It is essential to identify the presence of CAD in diabetic patients to start early treatment. Therefore, the aim of this study was to determine the prevalence of abnormal myocardial perfusion in asymptomatic type 2 diabetic patients using myocardial perfusion imaging.**

Methods: **Fifty-nine patients with type 2 diabetes, who did not have any history of CAD, but did have risk factors underwent myocardial perfusion single-photon emission computed tomography (SPECT) imaging using ^{99m}Tc-tetrofosmin and a 2-day stress–rest protocol. Two nuclear medicine specialists independently interpreted the images. Statistical analysis was performed to determine if there is a correlation between the presence of perfusion abnormalities and the history of diabetes (duration of disease, type of treatment, level of control, and presence and type of complications). The influence of other factors such as age, sex, smoking history, and family history of CAD, with abnormal scans were also studied.**

Results: **Of the 59 patients, abnormal scans were detected in 22 (37%) including 16 with reversible defects due to stress-induced ischemia. Hence the prevalence was 37%. Duration of diabetes, use of insulin, nephropathy, and neuropathy were significantly associated with abnormal scans ($p = 0.048$, $p = 0.045$, $p = 0.006$, and $p = 0.03$, respectively). Additionally, positive family history of CAD was highly associated with perfusion abnormalities ($p < 0.001$). No significant association was found between other risk factors, such as hyperlipidemia and the presence of perfusion defects.**

Conclusions: **We found a high prevalence of myocardial perfusion abnormalities in asymptomatic type 2 diabetic patients. Perfusion abnormalities on myocardial perfusion SPECT images were associated with disease duration, insulin use, nephropathy, and neuropathy. Asymptomatic diabetic patients might be candidates with CAD abnormalities that can be studied using myocardial perfusion SPECT.**

Keywords: Diabetes, Silent myocardial ischemia, Single photon emission computed tomography, ^{99m}Tc-tetrofosmin

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Introduction

Coronary artery disease (CAD) is the leading cause of death in patients with diabetes. Silent myocardial ischemia and unrecognized myocardial infarction is higher in diabetic population than in nondiabetics [1–4]. Silent ischemia is defined as objective documentation of myocardial ischemia in the absence of angina or anginal equivalents. Early diagnosis of CAD is important to start effective treatment and reduce cardiovascular complications and mortality.

A variety of techniques is available in the management of patients with CAD, such as rest and stress electrocardiography (ECG), rest and stress echocardiography, rest and stress myocardial perfusion single photon emission computed tomography (SPECT), multislice spiral computed tomography, electron beam computed tomography, magnetic resonance imaging (MRI), and coronary angiography.

Myocardial perfusion SPECT imaging is a well-established, noninvasive, and safe imaging procedure.

Type 2 diabetes is a prevalent disease in the Kuwaiti population. Unfortunately, type 2 diabetes is also spreading to adolescents and even children in Kuwait. There is a high prevalence of risk factors for cardiovascular disease and consequently elevated risk for morbidity and mortality from CAD in Kuwaitis with type 2 diabetes [5]. The aim of this study was to determine the prevalence of abnormal myocardial perfusion in asymptomatic type 2 diabetic patients using rest and stress myocardial perfusion SPECT imaging and to study the impact of variables such as age, sex, duration of diabetes, treatment type, complications, and level of control.

Abbreviations

CAD	Coronary artery disease
SPECT	Single photon emission computed tomography
ECG	Electrocardiogram
ECHO	Echocardiography
MSCT	Multi-slice spiral computed tomography
EBCT	Electron beam computed tomography
MRI	Magnetic resonance imaging
CA	Coronary angiography
QGS	Quantitative gated SPECT
SD	Standard deviation
MSCT-CA	Multi-slice computed tomography-coronary angiography
DIAD	Detecting ischemia in asymptomatic diabetics

Materials and methods

This was a cross-sectional, observational, descriptive, and analytical study that included 59 consecutive type 2 diabetic patients with no symptoms and no prior diagnosis of CAD but presence of any risk factor including hypertension, smoking, family history, and/or hyperlipidemia, who were referred for myocardial perfusion SPECT imaging from primary care polyclinics to Mubarak Al-Kabeer Hospital over a 1-year period. All study participants were informed of the methods and objectives and a written informed consent was obtained from each patient. The Institutional Ethics Committee of the Faculty of Medicine, Kuwait University and the Ministry of Health approved the study.

A conventional 2-day stress–rest protocol was performed on all the patients. Treadmill exercise with modified Bruce protocol and if there was a contraindication to physical exercise, pharmacological stress using dipyridamole or dobutamine was performed. A 740–925 MBq (20–25 mCi) dose of ^{99m}Tc-tetrofosmin was injected at peak stress and images were obtained 60 minutes after the injection. The rest studies were done on a separate day. An activity of 740–925 MBq (20–25 mCi) of ^{99m}Tc-tetrofosmin was injected at rest and imaging was started 60 minutes after radiopharmaceutical injection. The images were obtained using GE Millennium MG dual head γ cameras (General Electric Company, Fairfield, CT, USA) equipped with low energy general purpose and low energy high resolution collimators. The patients were in a supine position with a three-lead ECG attached for gating purposes. Imaging was acquired using an elliptical orbit with 72 projection data sets. The matrix size was 64×64 pixels, with a zoom of 1.33 and a 20% symmetrical energy window centered over the 140 keV photopeak. Processing of the images was done using filtered back projection techniques. A Butterworth filter with a cut-off frequency of 0.43 cycles/pixel and power of 7 were used. The quantitative gated SPECT program of Cedars Sinai was used to generate three-dimensional and tomographic images of the heart that were displayed in vertical long axis, horizontal long axis, and short axis. Visual analysis was performed by two expert readers who were blinded to the patients' clinical status at the time of evaluation. Any disagreement was resolved by consensus. Perfusion defects were categorized as mild, moderate, and severe perfusion defects and absent perfusion. Additionally, the

perfusion defects were also classified according to size (small, medium, and large area). The number of walls affected and reversibility status on rest images were noted. Perfusion defects with partial reversibility, and complete reversibility, and fixed perfusion defects were considered abnormal. Furthermore, regional wall motion was analyzed and the findings were grouped into normokinesia, hypokinesia, akinesia, and dyskinesia.

Statistical analysis

The variables studied were either quantitative or qualitative. Quantitative variables included patient's age, duration of diabetes, HgbA1c levels, and number of risk factors. For qualitative variables such as: sex; insulin or oral hypoglycemic use; family history of CAD; corisk factors such as hypertension, hyperlipidemia, obesity, and smoking; and complications of diabetes such as nephropathy, neuropathy, retinopathy, and peripheral vascular disease. SPSS software, version 17.0 (IBM, Chicago, IL, USA) was used for statistical analysis. Qualitative variables were represented by absolute (n) and relative frequency (%), and quantitative variables were represented by mean ± standard deviation (SD). Comparison of qualitative variables was done using Chi-square or Fisher exact test, and comparison of quantitative variables was done using Student t test. Statistical significance was achieved when $p < 0.05$.

Table 1. General patient characteristics.

Variable	Mean ± SD or n (%)
Age (y)	50 ± 11
Weight (kg)	85 ± 18
Females	20 (34%)
Males	39 (66%)
Pharmacological stress	32 (54%)
Physiological stress	27 (46%)
Diabetes	
Duration (y)	8 ± 6
Treatment	
Oral hypoglycemic agents only	48 (81%)
Insulin only	5 (9%)
Insulin + oral medications	6 (10%)
Glycosylated hemoglobin HbA1c (%)	8.5 ± 1.6
Diabetic complications	
Retinopathy	1 (2%)
Nephropathy	15 (25%)
Neuropathy	17 (29%)
Peripheral vascular disease	0 (0%)
Cardiovascular risk factors	
Hypertension	24 (54%)
Dyslipidemia	34 (58%)
Smoking	17 (29%)

SD = standard deviation.

Table 2. Characteristics of perfusion defects.

Characteristics of abnormal myocardial perfusion single-photon emission computed tomography		
Feature	n	%
Abnormal	22	37
Severity of defects		
Mild	10	45
Moderate	6	27
Severe	5	23
Absent perfusion	1	5
Number of walls affected		
Single	14	64
2 walls	5	23
3 or more walls	3	13

Results

The patient characteristics, including duration of diabetes, treatment complications and cardiovascular risk factors are described in Table 1. The mean age of the patients was 50 ± 11 years (range: 26–78 years). Regarding the prevalence of CAD risk factors, 15 patients had a family history of CAD (25%), 17 were past or current smokers (29%), 24 were hypertensive (41%), 34 were hyperlipidemic (58%), and 32 were obese (54%). Thirty-three patients (56%) had two or more CAD risk factors in addition to diabetes.

Diabetes duration ranged from 1 year to 30 years, with a mean duration of 8 ± 6 years. Forty-eight patients were treated with oral antidiabetic medications alone, six with a combination of insulin and oral medications, and five with insulin only. The level of diabetic control among the population varied, and was represented by HgbA1c levels. The HgbA1c levels ranged from 5.5% to 12.9%, with a mean value of 8.5 ± 1.6%. More than half of the patients were free from complications of diabetes (58%). Nephropathy was a complication in 15 patients, neuropathy in 17 patients, and retinopathy in one patient only. None of the patients examined had peripheral vascular disease or foot ulcers.

Of the 59 patients, 22 (37%) had abnormal myocardial perfusion SPECT images (Table 2). In these abnormal scans, reversible perfusion defects were observed in 16 (73%) patients and fixed perfusion defects in six (27%) patients. Of the 22, perfusion defects were mild in 10 (45%), moderate in six (27%), severe in five (23%) patients, and absent perfusion in one (5%) patient. There was involvement of a single wall in 14 (64%) patients, two

walls in five (23%), and three or more walls in three (13%) patients.

Among the 59 patients, 49 (83%) had normokinesia, nine (15%) hypokinesia, and one (2%) akinesia (2%). All patients showing wall motion abnormalities had fixed or severe perfusion defects. Wall motion abnormalities were related to two entities: duration of the diabetes and hypertension. Normal wall motion was significantly related to shorter duration of disease ($p = 0.045$). Furthermore, hypertension and wall motion abnormalities were significantly correlated ($p = 0.038$).

In this study, more men had abnormal scans than women (41% of men vs. 30% of women), but the difference was not significant. Additionally, there was no relationship between age and abnormal scans. Abnormal scans were found to be significantly related to longer duration of disease, treatment with insulin, and presence of complications in general ($p = 0.048$, $p = 0.045$, $p = 0.022$, respectively). More specifically, abnormal scans were highly associated with presence of nephropathy ($p = 0.006$) and presence of neuropathy ($p = 0.030$). Although suffering from retinopathy was not statistically correlated to abnormal scans, the only patient with retinopathy had an abnormal scan reading. Neither continuous glycated hemoglobin levels, nor grouped levels ($\leq$7% and >7%) were significantly related to abnormal scans.

The presence of abnormal scans was highly associated with family history of CAD ($p < 0.001$). Other risk factors such as hypertension, hyperlipidemia, smoking history, and obesity were not significantly correlated to abnormal scans (Table 3). Furthermore, the number of risk factors in each individual was not related to abnormalities either.

Discussion

The reported prevalence of silent CAD is 2.5–11% in nondiabetic patients, whereas it is 12–57% in diabetic patients [1–4]. Silent ischemia is defined as objective documentation of myocardial ischemia in the absence of angina or anginal equivalents.

There are various diagnostic tests in the management of CAD but they all have their own limitations. Rest ECG is normal in more than half of the patients with chronic stable angina [6].

Multislice computed tomography–coronary angiography is a minimally invasive procedure with a negative predictive value ranging from 95% to 97%, sensitivity from 82% to 100%, and specificity from 78% to 98% [6], but substantial radiation exposure and the use of potentially nephrotoxic contrast agents are the limitations. Coronary angiography is an invasive procedure with a risk of major complications. The complication rates using dynamic exercise with myocardial perfusion SPECT are low. The radiation dose to

Table 3. Correlation of myocardial perfusion scan results with patients and disease characteristics.

	Myocardial perfusion SPECT		
	Normal	Abnormal	
Factor (*n*)	*n* (%)	*n* (%)	*p*
General characteristics			
Male (39)	23 (59)	16 (41)	NS
Age ≥55 y (16)	10 (63)	6 (16)	NS
Risk factors			
Obesity (32)	20 (63)	12 (37)	NS
Hyperlipidemia (34)	22 (65)	12 (35)	NS
Hypertension (24)	14 (58)	10 (42)	NS
Smoking (17)	12 (71)	5 (29)	NS
Family h/o CAD (15)	2 (13)	13 (87)	<0.001
2 or more risk factors (33)	21 (64)	12 (36)	NS
Diabetes History			
Duration >10 y (11)	5 (39)	6 (61)	0.048
Treatment with insulin (11)	4 (36)	7 (64)	0.045
HgbA1c >7% (48)	31 (65)	17 (35)	NS
Complications			
Nephropathy (15)	5 (33)	10 (67)	0.006
Neuropathy (17)	7 (41)	10 (59)	0.03
Retinopathy (1)	0 (0)	1 (100)	NS

NS = not significant; SPECT = single-photon emission computed tomography.

the patients from myocardial perfusion SPECT imaging is within acceptable limits. The diagnostic accuracy of exercise, dipyridamole, adenosine, and dobutamine myocardial perfusion imaging in detecting ≥50% coronary stenosis defined angiographically ranges from 69% to 96%, 77% to 97%, 80% to 95%, and 66% to 94%, respectively [7].

In this study, asymptomatic type 2 diabetic patients had a high prevalence (37%) of abnormal myocardial perfusion. Most of the perfusion abnormalities were reversible defects that could pose an increased risk in future adverse cardiovascular events. The 37% prevalence of abnormal myocardial perfusion of this study is within the range of 17% to 59%, reported previously [2,8–12]. Detecting ischemia in asymptomatic diabetics (DIAD) study reported abnormal perfusion in 22% of the patients [8]. The higher prevalence ischemia in this study than in the DIAD study could be secondary to differences in population characteristics because we did not exclude patients with abnormal resting ECG as was done in the DIAD study Equally importantly, the patients in our study had higher rates of positive family history of CAD and mean HgbA1C readings. The presence of a family history of CAD is an established risk factor for developing CAD [11]. The higher level of HgbA1C in our study (8.5%) than that of DIAD study (7.1%) could account for the poorer control of diabetes that inevitably led to more abnormal scans. In another study, high-risk scans were present in 43% of patients with Q waves, and in 26% patients with Q waves and/or ST-T wave abnormalities [11].

Although, we did not find a significant relationship between glycated hemoglobin levels and abnormal scans, Araz et al. [13] demonstrated a significant correlation between high HbA1c levels and silent ischemia. Poulsen et al. [14] reported that the arbitrary cut off level of HbA1c >8.5% was a strong predictor of myocardial ischemia. Nevertheless, having a group of patients with poorer glycemic control, as indicated by higher glycated hemoglobin levels in our population, clearly meant that more abnormal scans were expected.

Another established risk factor for the development of CAD is male sex. Although a larger percentage of men in our population had silent ischemia compared to women (41% men vs. 30% women), the difference was not significant. However, studies with larger number of patients did show that male sex was a significant predictor of abnormal scans [8,11,13,15].

In this study, the finding that age was not correlated with prevalence of silent ischemia confirmed those of previous studies [8,13]. However, in two other separate studies, the patients with silent ischemia were significantly older [11,16].

In our study, the finding that other classic risk factors such as smoking, hypertension, hyperlipidemia, and obesity were not predictors of silent ischemia also confirmed those of previous studies [8,11]. Our study did not reveal any relationship between the cumulative number of risk factors and the presence of silent ischemia. In the DIAD study, the number of abnormal myocardial scans was equally distributed between patients with two or more and less than two risk factors [8].

The finding that diabetes of >10 years in duration was associated with more abnormal scans was similar to the findings of previous studies [8,17] in which it was reported that increasing duration of diabetes was correlated with abnormal scans. The finding that the use of insulin was significantly related to abnormal scans was not reported in the other studies [8,11,13]. The use of insulin is a last resort in treatment of type 2 diabetes when it is advanced or uncontrolled. Therefore, it was logical to find that insulin use was associated with abnormal cardiac scans. Presence of complications of diabetes such as nephropathy, neuropathy, retinopathy, and peripheral artery disease also indicates that diabetes is at an advanced stage. Our study established a relationship between nephropathy and neuropathy and silent ischemia. Moderate or large perfusion abnormalities were strongly associated with symptoms of autonomic neuropathy in the DIAD study [8]. Although retinopathy was not significantly associated with abnormal scans, the only patient suffering from retinopathy in our study had an abnormal scan.

A major limitation of this study was the small number of patients, but SPECT cardiac imaging can be useful for detecting CAD in asymptomatic diabetes type 2 patients.

Conclusion

In this study, using myocardial perfusion SPECT imaging perfusion, abnormalities were detected in significant proportion in the asymptomatic diabetics. Most of the perfusion abnormalities were inducible ischemia. Inducible ischemia was significantly related to the presence of family history of CAD, long duration of diabetes, treatment with insulin, and the presence of nephropathy and neuropathy.

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