

The myocardial perfusion scintigraphy in asymptomatic diabetic patients

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ABSTRACT

Introduction: Asymptomatic diabetic patients are at increased risk of cardiovascular complications. Myocardial perfusion scan may be effective in risk evaluation in this population.

Methods: 106 asymptomatic diabetic patients (age: min: 37, max: 82, mean: 57.73±8.88), including 56 females (52.8%) and 50 males (47.2%) were enrolled in the study. Myocardial perfusion scintigraphy was performed by Gated Single Photon Emission Computed Tomography (Gated-SPECT) method. Perfusion and function status was evaluated by qualitative and semi-quantitative parameters.

Results: By visual analysis totally 40 out of 106 patients (37.7%) showed abnormal scan. From which, 26(24.5%) showed involvement in one, 13(12.3%) in two, and 1(0.9%) in all three vessel territories. By semi-quantitative method, from 103 patients, 28 (27.2%) were abnormal and 75 (72.8%) were normal. From all the asymptomatic diabetic patients, 11 patients (10.4%) had dilated left ventricles. Transient Ischemic Dilation (TID) was noted in 10 patients (9.4%), and Transient Right ventricle visualization in 7 patients (6.6%). Heart failure (EF<45%) was observed in 14% of asymptomatic diabetic patients. From underlying factors, long duration of diabetes disease correlated to abnormal myocardial perfusion imaging (MPI) findings (Odds Ratio: 2.77; CI: 1.07-7.12). Severe coronary artery disease leading to the pattern of severe ischemia or infarction in MPI, was significantly higher in men than women (P=0.05). Also smoking correlated with higher involvement of LAD coronary artery (P=0.011) and as compared with RCA territory (P=0.079).

Conclusion: In asymptomatic diabetic patients myocardial perfusion scintigraphy can be used in early diagnosis of coronary artery disease (CAD) and can be suggested as screening study in these patients.

Key words: Asymptomatic ischemia; Diabetes mellitus; Myocardial perfusion scintigraphy; Gated SPECT

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INTRODUCTION

The number of patients with diabetes mellitus increases every year by 5%, adding approximately 1.5 million new cases annually. There has been a rising prevalence of individuals with diabetes (type I and type II) over the last three decades, with an estimated 170 million patients affected worldwide in 2000, which is expected to reach over 360 million by 2030 [1]. Importantly, 80% of the mortality among diabetics can be attributed to cardiovascular causes [2]. In Iran, the prevalence of DM adjusted for the world population was predicted to reach 8% in 2010. Most of this population has type 2 diabetes [2, 3]. Compared to the nondiabetic population, patients with diabetes mellitus have an increased risk of developing cardiovascular disease and an increased risk for death from myocardial infarction or congestive heart failure [4-6].

To maximize the effect of appropriate treatment of cardiovascular disease, it is important that diabetic patients at risk of developing or have already developed coronary artery disease (CAD) are identified as early as possible. A major hurdle toward this goal is that CAD in patients with diabetes is frequently silent; when clinically manifest, it is often in an advanced stage. Twenty-five percent of patients with diabetes mellitus in the Framingham Study had electrocardiographic evidence of prior unrecognized infarction, and half of these individuals were asymptomatic [7, 8]. Less than a third of diabetic patients with exercise-induced ischemia on myocardial perfusion imaging (MPI) had angina during exertion, compared to more than two-thirds of nondiabetic patients. A number of studies have demonstrated unequivocally that the presence or absence of traditional risk factors for CAD in patients with diabetes is not helpful for predicting silent myocardial ischemia. Therefore, other clinical and diagnostic algorithms need to be explored for identifying diabetic patients at increased cardiovascular risk [4]. Given the poorer prognosis of CAD in the diabetic population than in the nondiabetics, an earlier diagnosis has potential benefits in reducing mortality and morbidity such as earlier interventional therapy, heightened patient awareness of atypical signs of myocardial infarct and better compliance with risk-factor modification regimens. It is also expected that early therapeutic intervention may slow disease progression and decrease risk while CAD may be more likely to be modifiable [5].

Since the beginning of clinical nuclear cardiology, myocardial perfusion scintigraphy has become a mature technique for evaluating CAD and several studies have specifically shown its prognostic power in patients with diabetes [9]. ECG-gated SPECT acquisition is currently the state-of-the-art method of

performing MPI that attempts to discern attenuation artifacts from true perfusion defects by evaluating the presence or absence of concordant wall motion. Furthermore, it allows left ventricular systolic and diastolic volumes, as well as ejection fraction (EF) to be determined with excellent correlation with other methods [10, 11]. Silent ischemia is frequent and associated with similar or poorer prognosis as non-silent disease. Current opinion is to recommend stress myocardial perfusion scintigraphy in symptomatic or high-risk asymptomatic patients. The effectiveness of this approach is still under study, but the preliminary results are encouraging. Myocardial perfusion imaging can play an important role in improving clinical management of CAD in patients with diabetes [9, 10, 11]. Important questions remain to be debated regarding who to screen, when to screen, and how to do this in a cost-effective manner.

METHODS

Study population

In an outpatient setting, 106 patients who were referred to our nuclear medicine department for myocardial perfusion imaging were retrospectively studied. All patients had asymptomatic diabetic disease who had no history of cardiac symptoms, CHF, previous MI, CABG, PCI, valvular heart disease, cardiomyopathy and LBBB.

Patient preparation

For myocardial perfusion imaging the patients were instructed to fast at least 4 hours before the study. Possible interfering medications with dipyridamole study mainly xanthine containing drugs were stopped 48 hrs before the stress phase. Also caffeine containing foods and beverages were avoided for at least 24 hrs.

Image acquisition sequence

A commercial sestamibi kit (AEOI, Tehran, Iran) was used and the labeling and quality control procedures were performed according to the manufacturer's instructions. A dose of 666-814 MBq of Tc-99m sestamibi was given 4 min following the standard pharmacological stress with intravenous injection of 0.56 mg/kg dipyridamole over 4 min period. In the presence of dipyridamole side effects such as vertigo, chest pain, headache and electrocardiographic changes, 250 mg aminophylline was slowly injected intravenously 5 min after radiotracer injection. Single photon emission tomography (SPECT) with standard acquisition protocol was performed about 60 min after radiotracer injection, using a rotating, dual head gamma camera (Solus, ADAC, Milpitas, CA)

equipped with a low-energy high resolution parallel hole collimator.

Patients were in a supine position during the image acquisition. Thirty-two azimuth images, with 30 s/projections, were obtained in a 180-degree circular orbit, beginning from 45 degrees right anterior oblique to 135 degrees left posterior oblique with step and shoot acquisition on a 64×64 matrix and 38.5 cm detector mask (1.22 zoom). Rest images were obtained on the following day using the same imaging protocol. No attenuation correction was used in the imaging process.

Image analyses and interpretation reconstruction of the images was carried out by Pegasys software (ADAC system). An expert nuclear physician used the cine-display of the rotating planar projections to assess sub-diaphragmatic activities, attenuations and patient motion to optimize the technical quality of the images.

The raw data were prefiltered by ramp and subsequently by butterworth filters with frequency cut-off of 0.45 and order of 9.0. Also the data were quantitatively processed using Auto-QUANT software package (Cedars-Sinai Medical Center, Los Angeles, CA, USA) based on 20 segment analysis.

Quantitative values, including ejection fraction (EF), transient ischemic dilatation (TID), summed stress score (SSS), summed rest score (SRS), summed difference score (SDS), summed motion score (SMS), summed thickness score (STS), end diastolic volume (EDV), end systolic volume (ESV) and stroke volume (SV) were obtained.

The patients were stratified in two groups by semi-quantitative assessment of myocardial perfusion status indicated by SSS, normal ($SSS \leq 3$), and abnormal ($SSS > 3$).

Qualitative interpretation of scans, including homogeneity of uptake, visual perfusion status of myocardial walls and visual TID evaluation was assessed by two nuclear medicine physicians; in cases of disagreement a third opinion was also obtained. By this visual analysis the patients were classified in four groups: Normal perfusion, mild ischemia, moderate to severe ischemia and infarction (with or without viable tissue).

Statistical analysis

We used SPSS statistical software (SPSS version 17.0) for statistical analysis. To compare quantitative values including EF, TID, SSS, SRS, SDS, EDV, ESV and SV, wilcoxon signed rank test was used. To evaluate the qualitative data Chi-Square test was used. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A hundred and six asymptomatic diabetic patients (age: min: 37, max: 82, mean: 57.73 ± 8.88), including 56 females (52.8%) and 50 males (47.2%) were enrolled to our study. The majority of the patients (97.2%) had type II diabetes mellitus. The duration of the known disease in 75.2% of patients was < 10 years, and in 24.8% was ≥ 10 years. 50 patients out of 106 patients were hypertensive (47.2%), and 66 patients (62.3%) were hyperlipidemic. 18 patients (17%) were smokers and 88 patients (83%) were non-smokers. The frequency of positive family history for CAD in these asymptomatic diabetic patients was 25 out of 106 (23.6%), and 81 (76.4%) had no family history indicative of CAD.

The frequency for peripheral artery disease (PAD) was 17.1%, and 82.9% had no history of such disease. 34.3% of these patients had history of diabetic neuropathy.

In evaluating the frequency of coronary artery disease by visual analysis, totally 40 out of 106 patients (37.7%) showed abnormal scan indicative of coronary artery disease. From which, 26 (24.5%) showed involvement in one, 13 (12.3%) in two, and 1 (0.9%) in all three vessel territories. By semi-quantitative method and regarding $SSS > 3$ as abnormal perfusion, from 103 patients who underwent gated method, 28 (27.2%) were abnormal and 75 (72.8%) were normal.

Abnormal perfusion of the myocardial walls within LAD territory (anterior and anteroseptal walls), by visual analysis was totally 33%, from which 19.8% demonstrated mild ischemia, 4.7% moderate ischemia, 2.8% severe ischemia, 3.8% severe ischemia with infarct component and finally 1.9% were categorized as infarction.

The frequency for LCX territory (inferolateral and anterolateral walls) was totally 20.7%; from which 14.2% were mild ischemia, 2.8% moderate ischemia, 2.8% severe ischemia and 0.9% were infarction.

For RCA territory (inferior and inferoseptal walls) the total frequency of abnormality was 24.5%, including 12.3% mild ischemia, 4.7% moderate ischemia, 1.9% severe ischemia, 4.7% severe ischemia with infarction and 0.9% infarction.

From all the asymptomatic diabetic patients, 11 patients (10.4%) had dilated left ventricles. Transient Ischemic Dilatation (TID) was noted in 10 patients (9.4%), and Transient Right ventricle visualization in 7 patients (6.6%). Heart failure ($EF < 45\%$) was observed in 14% of asymptomatic diabetic patients.

Evaluation of the relation between underlying risk factors with the scan results by semi-quantitative method is shown in Table 1.

Table 1: Relation between underlying risk factors with the scan results by semi-quantitative method.

		Normal Scan (75 patients)	Abnormal Scan (28 patients)	Difference between two groups P value
Sex	Female	43(78.2%)	12 (21.8%)	0.190
	Male	32(66.7%)	16 (33.3%)	
Hypertension		34 (45.3%)	15 (53.6%)	0.456
Diabetes Type	Type I	3 (100%)	0 (0.0%)	0.561
	Type II	72 (72.0%)	28 (28.0%)	
Hyperlipidemia		46 (61.3%)	19 (67.9%)	0.542
Smoking		11 (14.7%)	7 (25.0%)	0.219
Family History of CAD		19 (25.3%)	6 (21.4%)	0.681
Peripheral Artery Disease		7 (14.6%)	5 (25.0%)	0.305
Neuropathy		17 (35.4%)	7 (35.0%)	0.974
Duration of Diabetes>10 years		15 (20.0%)	11 (39.3%)	0.033

Among all the underlying factors, long duration of diabetes disease is statistically higher in patients with abnormal MPI (Odds Ratio: 2.77; CI: 1.07-7.12).

Evaluation of the relation of underlying risk factors with myocardial perfusion pattern in different territories of coronary arteries reveals that severe coronary artery disease leading to the pattern of severe ischemia or infarction in MPI, is significantly more in men than women (in LAD territory: P=0.015 and in RCA territory: P=0.05). Also it is shown that smoking has significant direct relationship with increased involvement of LAD coronary artery (P=0.011) and to lesser degree in RCA territory (P=0.079). Quantitative assessment by gated method was performed in 103 patients out of 106 ones.

Evaluation of quantitative left ventricular (LV) function parameters measured by gated myocardial

perfusion SPECT (GSPECT) in two groups of patients with normal and abnormal semi-quantitatively determined myocardial perfusion scan (SSS≤3 and SSS>3, respectively) is shown in Table 2.

Comparison of quantitative parameters of LV function including EF, EDV, ESV and TID in two groups of patients with normal and abnormal perfusion determined by semi-quantitative method (SSS≤3 and SSS>3, respectively), reveals that EF, EDV and ESV are significantly related to myocardial perfusion abnormality (P=0.001) (i.e.; higher values of EDV and ESV and lower values of EF are in close proximity of coronary arteries abnormality as indicated by SSS>3).

Table 2: Comparison of quantitative LV function parameters in patients with normal perfusion (SSS≤3) and abnormal perfusion (SSS>3).

	SSS≤3	SSS>3	P value
TID	0.14±0.97	0.14±0.10	0.314
EDV	18.83±58.76	44.52±91.74	0.001
ESV	12.69±21.7	40.33±50.41	0.001
EF	10.70±64.5	15.47±52.12	0.001

DISCUSSION

Diabetes is associated with a two- to four-fold increase in the risk of developing coronary artery disease (CAD) [5, 6]. Moreover, CAD is the leading cause of death among diabetic patients. The risk of major coronary events (myocardial infarct or cardiac death) in patients with diabetes without previous myocardial infarction is comparable with that of non-diabetic patients with previous infarct [12]. Frequently, CAD will be occult in diabetic patients and the first sign may be a myocardial infarct or death. With established CAD, prognosis is worse in diabetic patients than nondiabetic patients; diabetic patients have an increased risk of death at first myocardial infarction with two-fold and three-fold higher short-term mortality in men and women, respectively [13].

Patients with diabetes are often affected by occult CAD and have an increased prevalence of silent myocardial infarct and ischemia. The lack of warning symptoms in relation to diabetes is thought to be due to autonomic neuropathy affecting cardiac chest pain perception. Silent myocardial ischemia has been found in about 22–42% of asymptomatic patients, depending on the study population and definition criteria [14-17].

Taken together, other studies show that coronary artery disease is frequently occult in the diabetic population, varying from about 20% of truly asymptomatic diabetic patients [17] to >50% in patients with indirect signs of CAD [18-25]. This frequency in our study was 27.2% by semi-quantitative method, and 37.7% by visual analysis which are consistent with previous studies. The involvement was mostly in one coronary territory (24.5%), and abnormality in two or three vessels territory was seen in 12.3% and 0.9% of the patients, respectively.

Considering the severity of ischemia, Wackers et al. results reveal a total 22% prevalence of silent myocardial ischemia, including 5% with severe perfusion abnormalities [17]. Mohagheghie et al. reported that occult CAD was present on perfusion scan in 1/3 of patients with diabetes without abnormal electrocardiographic findings or evidence of peripheral arterial disease [26]. In a prospective study on a large group of asymptomatic DM patients, more ischemia was present by exercise MPI than ECG. In this study DM was independently associated with abnormal MPI [27].

In our study, severe CAD in asymptomatic diabetic patients was from 1.9% in RCA to 3.8% in LAD territory. Moderate ischemia was seen in 2.8% in LCX to 4.7% in LAD and RCA territories. Frequency

of mild ischemia was from 12.3% in RCA to 19.8% in LAD region. Infarction was noted from 0.9% in LCX and RCA territories to 1.9% in LAD. In a study by Harshad et al. abnormal perfusion SPECT was detected in 43% of diabetics and 11% of controls, while coronary angiography showed significant coronary stenosis in 68.4%, insignificant in 21% and no stenosis in 10.6% patients. Further analysis by MPI showed that sensitivity of 86.6% and specificity of 51% [20]. In diabetic patients with a normal perfusion scan, the yearly cardiac event rate is 1.2% to 2%, compared with 1% in the nondiabetic population. In patients with an abnormal myocardial perfusion scan, the cardiac event risk is increased three to eight fold compared with patients with a normal scan. The severity of the perfusion abnormality is related to outcome [28]. Prognosis of silent ischemia was examined in the Coronary Artery Surgery Study (CASS), which showed similar risk in those with symptomatic ischemia and worse risk in those with three-vessel disease. In the subgroup of diabetic patients, Weiner et al. found that silent ischemia had a worse prognosis in diabetic than in nondiabetic patients [29].

There is currently a debate centered on which strategy to adopt to screen asymptomatic diabetes for silent CAD, as reflected by the many reviews, viewpoints and editorials in the recent literature [30-34].

Coronary angiography does not allow the direct visualization of coronary microcirculation in humans *in vivo*. However, its indirect assessment using the coronary flow reserve is possible with quantitative PET [35]. The fact that stress MPI has been shown to present incremental prognostic value over coronary angiography [36] may be due to its ability to indirectly assess microcirculatory abnormalities. Coronary angiography cannot be used for screening as it bears an unacceptable risk in asymptomatic patients.

Utility of stress MPI in this population for prognosis and risk stratification have been reviewed [30, 37-40]. MPI also keeps its ability to provide added prognostic value for risk stratification of CAD in diabetic patients [41-46]. When comparing the results of stress MPI with coronary angiography, we and others have found that between 40%- 70% of diabetic patients with abnormal stress MPI had no significant epicardial disease [16, 21, 22, 41, 47, 48]. Rather than being all false-positive, these abnormal stress MPI studies are more likely to reflect true myocardial perfusion abnormalities due to a reduced capacity to increase blood flow in relation to diffuse atherosclerosis and/or abnormalities of the microcirculation that is underestimated by coronary angiography [5]. Indeed, dysfunction of the coronary

vasodilatory capacity, both in epicardial vessels and resistance coronary vessels have been present in relation to diabetes and before obstructive CAD are present in the epicardial coronary arteries [49, 50]. Furthermore, myocardial blood flow is also influenced by autonomic neuropathy a well-known complication of diabetes that can produce perfusion abnormalities [51]. Also, it is shown that in patients with diabetes mellitus, myocardial perfusion abnormalities in the absence of obstructive epicardial CAD are associated with endothelial dysfunction [52], and that subclinical atherosclerosis is common in patients with diabetes which may result in silent ischemia [19].

Giri et al. have shown that abnormal stress MPI was an independent predictor for myocardial infarct and cardiac death and that patients with diabetes had higher event rates than patients without diabetes, the highest being for diabetic patients with ischemia (17.1% infarction rate) and for multivessel fixed defect (13.6% cardiac death rate). This study also demonstrated the added value of stress MPI over the clinical parameters [43].

No clear agreement exists about who in asymptomatic diabetic patients to be screened [5]. Neither the treadmill tolerance test nor the American Diabetes Association Guidelines are sufficiently adequate screening methods to detect asymptomatic CHD [53]. No traditional cardiovascular risk factor has been demonstrated to have sufficient sensitivity and specificity to predict silent myocardial ischemia in diabetes [54].

Considering the results of our paper in Iranian population in addition to other worldwide studies, we suggest to perform stress myocardial perfusion scan as a screening test on asymptomatic diabetic patients. It should be considered even if the study is normal, as CAD progression is thought to be accelerated in the presence of diabetes with increased rate of conversion from normal-to-abnormal MPI as compared to nondiabetic population [32.1% vs. 21.2%] [5, 55], it is suggested that the study should be repeated every 3-5 years in diabetic patients without new cardiovascular risk factors; and a shorter 1-2 year interval in the case of multiple or new cardiovascular risk factors [43, 56]. This strategy could specially be used in higher risk asymptomatic patients in whom coronary revascularization may improve the outcome beyond that achieved by currently recommended medical management [57].

Regarding the relation of gender with abnormalities of the MPI, there are controversial. In some the abnormal scans were more frequent in diabetic women than men. Wu et al. study suggest that asymptomatic postmenopausal women had more abnormalities in MPI and those with DM had a higher SSS and SDS than age-matched men, [58],

while in some others, ischemia by MPI was less in women than men [27]. Our study shows no significant difference between males and females in regard abnormal MPI findings (0.19).

Our study shows that among underlying risk factors for coronary artery diseases, long duration of diabetes mellitus and smoking are strong predictors of myocardial perfusion abnormalities.

The severity of coronary artery disease in a way resulting in infarction or severe ischemia is significantly more in men than women (in LAD territory: $P=0.015$; In RCA territory: $P=0.05$, and in LCX territory: $P=0.015$). Smoking is another important risk factor which significantly increases abnormal myocardial perfusion in LAD and to lesser degree in RCA territory.

We also demonstrated that the myocardial functional values including EF, EDV and ESV are more impaired in those diabetic patients with ischemic pattern. In other study it is shown that TID in diabetic patients without regional myocardial perfusion abnormality is an important sign of CAD especially when TID ratio exceeds 1.16 [59]. It means that asymptomatic diabetic patients not only have more abnormal perfusion, but also accompanied with ventricular functional compromise.

CONCLUSION

Diabetic patients, even without symptoms of cardiovascular disease, are quite likely to have impaired myocardial perfusion and function. Gated MPI can be helpful in early diagnosis of these complications, providing non-invasive information regarding myocardial perfusion and function. This method might be suggested as a screening tool for early diagnosis of cardiovascular disease in diabetic patients.

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