Prevalence of silent myocardial ischemia in working-age patients with type 2 diabetes mellitus

Alexander Kiško¹, Marika Vereb², Radoslav Dobránsky³, Marian Babčák¹,
Lubica Derňarová¹, Jan Kmec¹, Jozef Leško⁴, František Neméth¹,
Maria Marcinková⁵, Zuzana Farkašová¹

¹ University in Prešov, Faculty of Health Care; Cardiology Clinic, ProCare Prešov, Prešov, Jurkovičova 19. 08001 Prešov, Slovak Republic.

² Institute of Nuclear Medicine, Klinikum Kassel, Klinikum Kassel. D-34125 Kassel, Germany.

³ Diabetic & Metabolic Disorders Clinic, ProCare Prešov, Jurkovičova 19. 08001 Prešov, Slovak Republic.

⁴ VIVAMED Ltd, Nuclear Medicine, Hollého 14. 08181 Prešov, Slovak Republic.

⁵ Cardiology Clinic, ProCare Prešov, Jurkovičova 19. 08001 Prešov, Slovak Republic.
alexander.kisko@unipo.sk; mudr.marika.vereb.@gmail.com; dobranskyrado@gmail.com;
babcak@fnspresov.sk; lubica.dernarova@unipo.sk; kmecj@fnspresov.sk; lesko@vivamed.sk;
frantisek.nemeth@unipo.sk; marcinkova8@gmail.com; zuzana.farkasova@unipo.sk

Abstract

Introduction: Data confirm a relatively high prevalence of silent myocardial ischemia (SMI) in elderly patients with type 2 diabetes mellitus (T2DM), while no data are available regarding working-age subjects (≤ 60 years). **Methods:** Medical records of 192 patients with T2DM aged ≤ 60 years (110 male patients; 57.3%), who had undergone myocardial perfusion imaging (MPI) between 2010 and 2014 followed by coronary angiography in case of abnormal result, were retrospectively analysed. **Results:** MPI was positive in 35 patients (18.2%); of those 31 (88.6%) had angiographically confirmed coronary stenosis. The positive predictive value of the MPI for predicting angiographic coronary stenosis in this age subgroup was 88.9%. Univariate analysis revealed post-stress LVEF drop $\geq 5\%$ ($p < 0.03$) and NT-proBNP levels detected in stress ($p < 0.05$) to be associated with greater risk of ischemia in working-age T2DM patients. In multivariate analysis, LVEF drop $\geq 5\%$ ($p < 0.03$) remained an independent predictor of SMI.

Conclusion: Prevalence of SMI in diabetic working-age patients was similar to that observed in studies of subjects over 65 years-old. Post-stress LVEF drop $\geq 5\%$ and NT-proBNP levels can contribute to more precise identification of SMI. Our data suggest that “aggressive” management strategy should be implemented to reduce the risk of cardiac events in T2DM patients of working-age.

Keywords: scintigraphy, silent myocardial ischemia, diabetes mellitus

Myocardial ischemia is often asymptomatic in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) is frequently in an advanced stage when it becomes clinically manifested. Silent myocardial ischemia (SMI) is defined as objective evidence of myocardial ischemia in the absence of typical chest discomfort or other anginal equivalents. It is a common, under-recognized marker of a significant underlying CAD associated with future cardiovascular events and poor prognosis. SMI is an important public health issue, and its early detection may prevent many episodes of sudden cardiac death annually (Cosson et al., 2005; Le Feuvre et al., 2011; Vasiliadis et al., 2014). Diabetic patients have a higher prevalence of SMI and recognised myocardial infarction than patients without diabetes (MacDonald et al., 2014). There are some data about the prevalence of SMI in T2DM patients in elderly at high risk for cardiovascular disease (Inoguchi et al., 2000; Faglia et al., 2002; Lima et al., 2004; Mohagheghie et al., 2011; Rawshani et al., 2017). However, data about the prevalence of SMI in working-age subgroup of the diabetic population remain limited.

Stress single-photon emission computed tomography (SPECT) is a validated imaging tool providing information on the physiological significance of flow-limitation and is also a cost-effective for risk assessment of the major adverse cardiac events in the general and diabetic populations. SPECT could accurately assess both myocardial perfusion and ventricular function in diabetic patients, providing important information for their management and is helpful in these situations (De Keyzer et al., 2011). Moreover, left ventricular (LV) function analysis in SPECT can enhance its prognostic and diagnostic ability, particularly in the prediction of SMI (Sharir et al., 1999). We sought to evaluate the prevalence of SMI detected by SPECT myocardial perfusion imaging (MPI) in association with some less recognised diagnostic predictors of it in T2DM asymptomatic patients of working-age.

Methods

We retrospectively analysed medical records of 192 (110 male pts; 57.3%) chronologically consecutive asymptomatic working-age (≤ 60 years) patients with T2DM, who had undergone MPI subsequently followed by coronary angiography in case perfusion abnormalities were found. MPI was performed from 2010 to 2014 at a single outpatient care centre with nuclear medicine unit, according to the EANM procedural guidelines for stress-rest ECG gated SPECT one-day protocol using ^{99m}Tc -tetrofosmin (Verberne et al., 2015). Perfusion images were judged blindly by two specialists independently using the 17-segment ASNC model, and SMI was diagnosed consensually as myocardial perfusion abnormalities without associated symptoms. Stress (cycle ergometry) and rest myocardial perfusion abnormalities were described as reversible (ischemia), fixed (scar), or mixed (scar and ischemia). The summed stress score (SSS) and summed rest score (SRS) were obtained, with the summed difference score (SDS) being the difference between the two. A mild ischemic defect was

defined as showing the presence of a SDS ≥ 2 . A moderate perfusion defect was defined as a SDS ≥ 2 in > 1 segment, and severe perfusion defect was defined as a SDS ≥ 3 in > 1 segment in stress images. Calculation of left ventricular ejection fraction (LVEF) and ventricular volumes was performed by using quantitative software for endocardial and epicardial boundaries automatically tracing. Patients with abnormal MPI were referred for coronary angiography. Angiographic images were assessed blindly to the MPI data and significant stenosis was defined as $\geq 50\%$ for LAD, and $\geq 75\%$ for other coronary arteries.

LV dysfunction was defined as post-stress LVEF drop $\geq 5\%$ and/or transient ischemic dilatation of LV in stress against rest. The levels of NT-proBNP were measured at rest and within 3 minutes in the early recovery stage of exercise testing.

All participants gave written informed consent before enrolment in the study, which was conducted in accord with the principles of the Declaration of Helsinki. All patients were carefully assessed for classic coronary risk factors: age, sex, obesity, smoking, essential hypertension, dyslipidaemia, a family history of CAD, duration of diabetes, diabetic complications (Table 1).

Table 1: Clinical and laboratory characteristics of the subjects included in the study.

<i>Clinical and laboratory characteristics</i>	<i>Diabetic patients (n=192)</i>
Age (years)	52.3 $\pm$ 6.7
Male (n/%)	110/57.3
Obesity (n/%)	151/78.6
Smoking (n/%)	3/1.56
Hypertension (n/%)	107/55.7
Dyslipidaemia (n/%)	140/72.9
Family history of CAD (n/%)	28/14.6
Duration of diabetes (years)	5.0 $\pm$ 3.2
Retinopathy (n/%)	20/10.4
Nephropathy (n/%)	13/6.8
Neuropathy (n/%)	7/3.6
Glucose (mmol/l)	7.8 $\pm$ 2.6
HbA1c (%)	7.2 $\pm$ 1.3
High-sensitivity CRP (mg/l)	2.2 $\pm$ 2.3
Total-C (mmol/l)	6.2 $\pm$ 3.5
HDL-C (mmol/l)	0.96 $\pm$ 0.4
LDL-C (mmol/l)	4.2 $\pm$ 1.8
Triglycerides (mmol/l)	3.9 $\pm$ 2.4

Note: Data are expressed as the mean $\pm$ SD, number and percentage.

Continuous variables were expressed as mean values $\pm$ standard deviation, and frequencies as the number and percentage of patients. Between-group comparisons were made by means of non-parametric Mann–Whitney *U* test.

Bivariate associations were tested using t test and Fisher's exact test. To identify the factors independently related with SMI univariate and multivariate analysis was performed. *P* values of <0.05 were considered statistically significant. Statistical analyses were carried out using IBM SPSS Statistics V.19 software.

Results

MPI results showed that 157 (81,8%) patients had normal myocardial perfusion, while 35 (18.2%) patients showed perfusion defects on MPI (Table 2). In 33(17.2%) cases it was defined as reversible and in 2(1.0%) as mixed.

Table 2: MPI results.

Result	MPI (n=192)
Negative (n%)	157/81.8
Positive (n%)	35/18.2

Note: Data are expressed as number and percentage.

12 (33.4%) out of the 33 reversible perfusion defects were described as mild, 14 (42.4%) – moderate, and 7 (22.2%) – severe.

31 (88.6%) patients out of the 35 with abnormal MPI findings represented an abnormal coronary angiography. In 15(48.4%) out of the 31 patients it was defined as 1 vessel disease, in 10 (32.3%) – 2 vessels disease and in 6 (19.3%) – 3 vessels disease. 9 (29.0%) patients with positive angiographic results represented diffuse disease and vessel occlusion was detected in 2 (6.5%). Coronary anatomy did not allow any revascularisation procedure in 13 (41.9%) of the patients with abnormal coronary angiography.

These results emphasize the incremental diagnostic value of MPI for evaluation of SMI in this specific subgroup of the diabetic population. MPI have showed a very good degree of specificity of the test (97.6%) with a positive predictive value of 88.9% for predicting angiographic coronary stenosis (Table3).

Table 3: Evaluation of MPI in predicting angiographic coronary stenosis.

Statistic	Value	95% CI
Sensitivity (%)	69.5	61.5–82.6
Specificity (%)	97.6	79.9–99.3
PPV (%)	88.9	73.6–95.6
NPV (%)	50.6	48.9–52.3

Note: PPV: positive predictive value; NPV: negative predictive value; CI: confidence intervals

We observed that retinopathy (OR 2.32; 95%-CI: 1.05–5.13; $p>0.05$), nephropathy (OR 2.12; 95%-CI: 1.0–6.13; $p>0.05$), and neuropathy (OR 1.70; 95%-CI, 1.07–2.71; $p>0.05$) were not associated with abnormal MPI.

Post-stress LVEF drop $\geq 5\%$ was observed in 32 (91.4%) patients out of the 35 with abnormal MPI findings. In 29 (82.9%) cases it was associated with post-stress transient ischemic dilatation of LV. Patients with LVEF drop $\geq 5\%$ had higher SDS ($p<0.01$), but no significant difference in rest LV values ($p>0.05$) compared to patients without perfusion defects.

There was no significant difference between mean rest NT-proBNP level in MPI-negative against MPI-positive subgroups (182 ± 8 ng/l vs. 198 ± 6 ng/l, $p>0.05$), but patients with SMI had a significantly higher mean post-stress NT-proBNP level (889 ± 92 ng/l vs. 226 ± 8 ng/l; $p<0.05$).

Univariate analysis revealed post-stress LVEF drop $\geq 5\%$ ($p<0.03$) and NT-proBNP level detected in early recovery stage of stress testing ($p<0.05$) to be associated with greater risk of ischemia in working-age T2DM pts. In multivariate analysis, LVEF drop $\geq 5\%$ ($p<0.03$) remained to be an independent predictor of SMI.

Discussion

T2DM is a chronic metabolic disease, which results not only in significant direct medical costs but also in indirect productivity losses due to disability and early mortality in working age population. Almost 75% of diabetic decedents without clinical CAD have high-grade coronary atherosclerosis. Autopsy studies have identified a high prevalence of coronary atherosclerosis in patients with diabetes, even among those without clinical CAD (Goraya et al., 2002). The prevalence of SMI in the diabetic population is very variable in the different studies, ranging from 12% to almost 57%, and it is 3 to 6 fold higher than in asymptomatic non-diabetic population (Inoguchi et al., 2000; Wackers et al., 2004; Freeman, 2006; Le Feuvre et al., 2011). Several mechanisms are integrated in the SMI genesis. Endothelial dysfunction secondary to T2DM may play a role, leading to an inappropriate coronary flow response to increasing myocardial metabolic needs (coronary vascular tone abnormality). It is also due to an increased pain feeling threshold in diabetic patients, probably secondary to an elevated beta-endorphins rate. These two abnormalities are associated with an impaired autonomic nervous system.

The patients enrolled in the study were truly asymptomatic, working-age subjects with T2DM, free from known CAD. There were not typical clinical signs of angina at the time of referring patients for MPI. The patients were referred mostly from the clinics for diabetes and metabolic disorders or internal diseases. They were on contemporary medical treatment and were under reasonable metabolic control. Yet, 35 patients (18.2%) had evidence of SMI, including 21 with moderate-to-severe reversible perfusion abnormalities and 30 with stress-induced ST-segment changes. The prevalence of perfusion abnormalities

in our study was somewhat lower than the 22% observed in the DIAD study (Wackers et al., 2004) but a bit greater than 15,7% obtained in an earlier study from France (Janand-Delenne et al., 1999). However, the lower prevalence reported in this earlier study likely reflects differences in patients selection. Subjects were of younger age, with T1DM and T2DM and perfusion abnormalities were assessed visually with somewhat less sensitive technique. Moreover, imagings were performed only if the initial exercise ECG stress test was abnormal or equivocal. Thus, patients who would have had perfusion abnormalities were likely missed. On the other hand, it should be noted that the prevalence of perfusion abnormalities in DIAD study is considerably higher than that reported in our study, reflecting the results of adenosine perfusion imaging in a slightly older sample of patients (50-75years).

In a recent study of silent CAD detection in a cohort of 102 asymptomatic T2DM subjects (57±7years), attending 5 Italian outpatient clinics, a significant higher prevalence of silent CAD was observed in subjects with abnormal vs. normal ECG (23 vs. 4%; $P=0.004$), but not in subjects with high vs. low pre-test silent CAD risk (14 vs. 9%; $p=0.472$). An abnormal ECG was defined to be a strong, independent predictor of silent CAD (OR 8.9; CI 1.27-62.5; $p=0.028$) in T2DM (Vigili de Kreutzenberg et al., 2017).

Our second goal was to identify predictors of MPI abnormalities. Demographics, traditional cardiac risk factors, diabetes complications, and biomarkers were analysed. Overall predictors of SMI in working-age cohort of T2DM patients were post-stress LVEF drop $\geq 5\%$ and NT-proBNP levels detected in stress. In univariate analysis, only post-stress LVEF drop $\geq 5\%$ was the factor associated with moderate-to-large perfusion defects abnormalities that raise substantial clinical concern. In working-age patients with diabetes, post-stress LVEF drop showed to be an independent predictor of stress-induced ischemia and increases the risk of subsequent cardiac events in T2DM patients. However, a fall in LVEF is detectable also in patients with normal myocardial perfusion. These findings suggest that a post-stress LVEF drop may be related to a specific diabetic cardiomyopathy in the absence of myocardial perfusion abnormalities. Diabetic complications such as retinopathy, nephropathy and neuropathy showed not to be significantly associated with either test abnormality or marked perfusion defects. In addition, traditional cardiac risk factors (male gender, hypertension, smoking and family history, or dyslipidaemia), previously reported as risk factors for CAD and poor outcome (De Keyzer et al., 2011) were not associated with SMI in working-age T2DM patients.

Conclusions

Prevalence of T2DM in working-age population is high and still rising in Europe. Both diabetes and pre-diabetic states are risk factors for CAD. Their emergence starts many years before clinical events appear, developing silently, in parallel with the progression from pre-diabetic status to T2DM (Alegria-Barbero, 2014). Our study suggests that 18.2% of asymptomatic working-age pa-

tients with T2DM have SMI. More importantly, 13.7% of them have markedly abnormal (moderate-to-severe) myocardial perfusion abnormalities. This justifies screening for SMI by non-invasive and cost-effective technique such as SPECT MPI in subpopulation of T2DM patients of the working-age. LV function testing may have an important role in the SMI risk assessment because of the association shown in the present study between LVEF drop $\geq 5\%$, NT-proBNP levels detected in stress and perfusion defects occurring. The presented data address only the prevalence, severity, and possible predictors of SMI at the time of enrolment into the study and suggest that advanced intervention procedures including “aggressive” drug management should be implemented to reduce the risk of cardiac events in forthcoming future. Follow-up evaluation should allow to define the relationship between abnormal perfusion imaging and the prevalence of cardiac events in asymptomatic T2DM patients of working-age and to evaluate the effectiveness of “aggressive” preventive strategies.

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