Correlation between myocardial perfusion imaging findings and future cardiac events in patients with type 2 diabetes mellitus

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SUMMARY

Introduction/Objective Myocardial perfusion imaging (MPI) is clinically useful for the evaluation of coronary artery disease (CAD) in patients with diabetes mellitus (DM). However, the prevalence of ischemia and its ability to predict future cardiac events is less clear. The aim was to determine the incidence of cardiac events in diabetic patients and relationship between them and MPI findings.

Methods Two cohorts of patients, 98 diabetics and 100 non-diabetics, with medium- to high-risk of CAD without previous coronary revascularization were studied prospectively. All of them were outpatients underwent 99mTc-sestamibi MPI with dipyridamole. The data about cardiac events were collected during follow-up period of two years.

Results Cardiac events occurred in 17.3% diabetics and in 8% non-diabetics (p = 0.048). Diabetics had shorter estimated event-free time 24.7 months (95% CI 23.2–26.2) versus non-diabetics 28.5 months (95% CI 27.4–29.5) (p = 0.046). The independent predictors of cardiac events were male sex (p = 0.010), previous myocardial infarction (p < 0.001), presence of the symptoms of angina (p = 0.014) and all variables derived from MPI findings. After adjustment for variables derived from MPI findings, the significant predictors in diabetics were size of stress perfusion defect (p = 0.022), summed stress score (p = 0.011) and summed difference score (p = 0.044).

Conclusion In diabetic patients, the cumulative rate of cardiac events was higher and the event-free survival was worse. MPI could help in prediction of cardiac events in diabetics and the most important predictors were size of stress perfusion defect, summed stress score and summed difference score.

Keywords: myocardial perfusion imaging, diabetes mellitus, coronary artery disease, cardiac events

САЖЕТАК

Увод/Циљ. Перфузиона сцинтиграфија миокарда (ПСМ) је корисна у евалуацији коронарне артеријске болести (КАБ) код оболелих од тип 2 дијабетеса (Т2Д). Ипак, преваленци исхемије код њих и могућност предвиђања будућих срчаних догађаја су нејасни. Циљ је био одредити инциденцу срчаних догађаја код оболелих од Т2Д и везу између њих и налаза ПСМ.

Методе Проспективно су испитиване две групе болесника са средњим до високим ризиком за КАБ, 98 са Т2Д и 100 без, који нису имали ранију коронарну реваскуларизацију. Свима је урађена 99mTc-sestamibi ПСМ са дипиримадолом. Подаци о срчаним догађајима су сачувани током двогодишњег праћења.

Резултати Срчани догађаји су настали код 17,3% испитаника са Т2Д и 8,0% испитаника без Т2Д (p = 0.048). Испитаници са Т2Д су имали краће време преживљавања без срчаног догађаја 24,7 месеци (95% CI 23,2–26,2) према 28,5 месеци (95% CI 27,4–29,5) код оних без Т2Д (p = 0,046). Независни предиктори настанка срчаних догађаја су били мушки пол (p = 0,010), присуство ангинозних тегоба (p = 0,014) и све варијабле добијене из налаза ПСМ. Код испитаника са Т2Д, након корекције и прилагођавања са варијаблама добијеним из налаза ПСМ, значајнији предиктори су били величина испада перфузии у отпредењу (p = 0,022), 33м суммирани индекс напрега (SSS) (p = 0,011) и суммирани разлика индекс (SDS) (p = 0,044).

Закључак Код оболелих од Т2Д, кумулативна стопа срчаних догађаја је била виша, а време преживљавања до настанка срчаног догађаја краће. ПСМ може помоћи у предвиђању будућих срчаних догађаја код оболелих од Т2Д, а најважнији предиктори су били величина испада перфузии у отпредењу, SSS и SDS.

Кључне речи: перфузиона сцинтиграфија миокарда; дијабетес; коронарна артеријска болест; срчани догађаји
INTRODUCTION

Coronary artery disease (CAD) has now become a common cause of mortality and morbidity worldwide [1]. Furthermore, caring for patients with known or suspected CAD poses tremendous economic pressure on healthcare resources, not only due to costs related to testing and treatment, but also those associated with loss of productivity in afflicted individuals [1]. The worldwide prevalence of diabetes mellitus (DM) is increasing, concurrently with obesity and other comorbid conditions [2]. Despite significant advances in medical and invasive therapy, CAD is the leading cause of morbidity and mortality in patients with DM [3]. The diagnosis of CAD is complicated by the often atypical presentation of patients with DM attributable to concomitant autonomic neuropathy and other disorders. It is important to identify CAD early in these patients to optimize medical therapy and lifestyle modifications, and especially important to identify and aggressively treat those at the highest risk of events. The value of single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in the evaluation of diabetic patients has been widely investigated [4, 5]. MPI is clinically useful for the evaluation of CAD in patients with DM. In diabetic patients with suspected or known CAD, a strong evidence base has been accumulated that MPI provides diagnostic and incremental prognostic information [4, 6, 7, 8]. The prognostic impact of ischemia together with other clinical and stress variables has previously been reported [4]. However, the prevalence of ischemia and its ability to predict those who experience future cardiac events is less clear in patients with DM with or without symptoms referred for MPI.

The aim of the study was to determine the incidence of cardiac events in diabetic patients and relationship between them and MPI findings.

METHODS

Patient selection

The study population consisted of two cohorts of patients with medium- to high-risk of CAD without previous coronary revascularization. In study group, there were 98 patients
with diabetes mellitus type 2 and 100 patients without diabetes in control group. All of them were outpatients underwent $^{99m}$Tc-sestamibi SPECT MPI with pharmacologic stress using dipyridamole. The test was requested for assessment of myocardial ischemia in all patients. The patients in study group had previously diagnosed DM and were treated with insulin or oral hypoglycemic agents. Selection of patients was performed so that the groups were matched with no significant differences between them regarding classical risk factors of CAD (age, sex, body mass index, smoking, arterial hypertension, previous myocardial infarction and symptoms of angina). The study was conducted prospectively under the rules of the Declaration of Helsinki. The informed consent was obtained from all subjects before testing. The local medical ethics committee approved the study protocol. Before the test, a structured interview was performed and a clinical history was obtained, including assessment of cardiac risk factors. Furthermore, the measurements of patient height and weight were performed. Hypertension was defined as blood pressure above 140/90 mmHg or need for antihypertensive medication. Dyslipidemia was defined as need for lipid-lowering medication. Subjects were considered symptomatic if they were experiencing chest pain or shortness of breath thought to be of possible cardiac origin.

**Stress protocol and SPECT MPI**

Stress testing and stress/rest gated SPECT MPI was performed as per guidelines of the EANM (European Association of Nuclear Medicine) [9]. Patients underwent intravenous vasodilator stress using dipyridamole (0.56 mg/kg over 4 minutes). At 4 minutes after completion of the dipyridamole infusion, a bolus of 550 MBq $^{99m}$Tc-sestamibi (technetium-99m methoxy-isobutyl-isonitrile) was intravenously injected. In the event of chest pain, significant ST depression or other symptoms, a dose of 125 mg of aminophylline was administered intravenously 2 minutes after injection of the radiotracer. SPECT MPI was performed using 2-day protocol. Each participant had gated stress using 8 frames per R-R cycle and non-gated rest SPECT MPI. For resting studies, 550 MBq of the same tracer was injected at least 24 hours after the stress test. Image acquisition was performed with a commercially available SPECT camera system (Optima™ NM/CT 640, GE Healthcare). Radiopharmaceutical dosing, SPECT acquisition, and image processing were performed within previously mentioned guidelines established by EANM [9]. All images were obtained
60 minutes after radiotracer injection using rotating dual-head gamma camera equipped with low-energy, high-resolution, parallel hole collimator with 30% (± 15%) symmetric energy window centered at 140 keV. Sixty-four projections (40 seconds per projection), with a 64x64 matrix were obtained over a 180º orbit. No attenuation or scatter correction was used.

**Image interpretation**

Relative perfusion distribution was analyzed semiquantitatively using standardized segmentation of 17 myocardial segments. Each segment was scored by the consensus of two experienced observers using a 5-point scoring system (0 = normal; 1 = equivocal; 2 = moderate; 3 = severe reduction; and 4 = absence of tracer uptake in a segment). The summed stress score (SSS) was obtained by adding the scores of the 17 segments of the stress images. The summed rest score (SRS) was obtained by similarly adding the scores of the 17 segments of the rest images. The sum of the differences between each of the 17 segments on the stress and rest images was defined as the summed difference score (SDS), a variable representing the amount of ischemia present. A scan was considered normal if the SSS was 3 or lower, mildly abnormal if the SSS was between 4 and 8, moderately abnormal if the SSS was between 9 and 13 and severely abnormal if the SSS was more than 13, as previously reported [10, 11]. The SDS < 2 were considered as no ischemia; 2 to 4 mild ischemia; 5 to 8 moderate ischemia; and > 8 severe ischemia [10, 11]. An automated software program the Emory Cardiac Toolbox™ (ECTb™, Emory University School of Medicine, Atlanta, Georgia, USA) was used to calculate left ventricular ejection fraction (LVEF) and the variables incorporating both the extent and severity of perfusion defects.

**Patient follow-up**

Collection of follow-up data was obtained by reviewing hospital records, by contacting the patient’s general practitioner and/or by contacting the patient by phone during the period of approximately two years. The date of the last review or consultation was used to determine follow-up time. End points were developments of cardiac events: cardiac mortality, nonfatal
myocardial infarction (MI) or coronary revascularization by percutaneous coronary intervention or coronary artery bypass grafting. Cardiac mortality was defined as a death caused by acute MI, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac mortality. Nonfatal MI and coronary revascularization were confirmed by reviewing hospital records. Patients with other-cause mortality were excluded from the study.

**Statistical analysis**

Baseline characteristics of patients were compared by Student t or Mann-Whitney U tests for continuous variables and chi-square or Fisher exact tests for categorical variables where appropriate. Univariate Cox proportional hazard regression model was used to identify independent predictors of cardiac events. The risk of a variable was expressed as a hazard ratio with corresponding 95% confidence interval (CI). Univariate Cox regression model was used to investigate association between cardiac events and DM, after adjustment for variables derived from MPI findings LVEF, end diastolic volume (EDV), end systolic volume (ESV), systolic volume (SV), presence of stress defect, presence of ischemia, SSS, SRS, and SDS. Survival curves as a function of time (months) were generated with the Kaplan-Meier method. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using the statistical software platform IBM® SPSS® Statistics (Version 22).

**RESULTS**

**Study population and MPI findings**

The demographics, clinical characteristics and MPI results among diabetics and non-diabetics are shown in Table 1 and Table 2 respectively. There were no significant differences of the prevalence of classical risk factors between the groups except of dyslipidemia and family history of diabetes, which were higher among diabetics (p = 0.004 and p < 0.001). Perfusion and non-perfusion variables were obtained from MPI for all
patients. Diabetics had lower LVEF ($p = 0.018$), higher ESV ($p = 0.039$) and higher proportion of them were with abnormal ESV ($p = 0.049$). There were no significant differences of perfusion variables between the groups.

**Follow-up, outcomes, and survival analysis**

Median of follow-up period did not differ significantly between the 2 groups (26 vs. 24 months; $p = 0.184$). During this period of time, cardiac events occurred in 17.3% diabetics and in 8% nondiabetics ($p = 0.048$) (Table 3).

Event-free survival curves were constructed using the Kaplan-Meier method to account for censored survival times (Figure 1). Diabetics had shorter estimated event-free time 24.7 months (95% CI 23.2–26.2) versus non-diabetics 28.5 months (95% CI 27.4–29.5) ($p = 0.046$).

**Predictors of cardiac events**

The results of the univariate Cox proportional hazards analysis predicting cardiac events are given in Table 4. The independent predictors were male sex ($p = 0.010$), previous myocardial infarction ($p < 0.001$), presence of the symptoms of angina ($p = 0.014$) and all variables derived from MPI findings. DM was not significant, but borderline predictor of cardiac events in univariate Cox proportional hazards analysis. The association between cardiac events and DM was determined using univariate Cox regression model after adjustment for variables derived from MPI findings (Table 5). The significant predictors were size of stress perfusion defect ($p = 0.022$), SSS ($p = 0.011$) and SDS ($p = 0.044$).
DISCUSSION

In our study the groups were matched and there were no significant differences between them regarding classical risk factors of CAD (age, sex, body mass index, smoking, arterial hypertension, previous MI and symptoms of angina) except of prevalence of dyslipidemia and family history of diabetes, which were higher among diabetics \((p = 0.004 \text{ and } p < 0.001)\). These were expected since diabetics have higher prevalence of dyslipidemia and 2 to 4 times higher prevalence of family history of diabetes than non-diabetics [12, 13].

We found that diabetics had lower LVEF \((p = 0.018)\), in accordance with some other studies. Ehl et al. showed that diabetics had a lower LVEF determined by MPI than non-diabetics \((p = 0.001)\) and this difference could be demonstrated regardless of CAD extent (no significant differences of SSS, SRS and SDS) and might in part explain their generally worse cardiac survival compared with non-diabetics [14]. Chareonthaitawee et al. found that 1 of 6 asymptomatic diabetic patients without known CAD referred for MPI had reduced LVEF. The annual mortality rates of the groups with and without reduced LVEF were 7% and 4%, respectively [15].

In recent years, a large body of literature has established the prognostic significance of MPI in general population [7, 16, 17]. It was shown that patients with normal stress MPI studies had remarkably low cardiac event rates \((<1\% \text{ per year})\) and the event rate was proportional to the extent of stress-induced hypoperfusion. In patients with a normal MPI SPECT, there was an annual death rate of 0.3% compared with 2.9% in patients with severely abnormal scans [10]. The nonfatal MI rate in another study also increased in relation to the SSS [3].

Diabetic patients have multitude of characteristic features including higher prevalence of multi-vessel and small vessel CAD, frequent silent myocardial ischemia and infarction with higher cardiac event rates, and the presence of autonomic dysfunction. This together with the prevalence of diabetic cardiomyopathy contributes to a higher cardiovascular mortality [18, 19]. Furthermore, diabetic patients have higher prevalence of cardiovascular co-morbidities as compared to patients without diabetes [20, 21]. Two-thirds of diabetic patients will die of heart or vascular disease, and patients with CAD and diabetes mellitus
have worse outcomes and a much higher cardiac event rate than their nondiabetic counterparts [22, 23].

Our study demonstrates that the two-year cumulative rate of cardiac events was higher (17.3% vs 8%) and the event-free survival was worse in diabetics (24.7 vs 28.5 months) than that seen in patients without DM. We found that the independent predictors of cardiac events were male sex, previous myocardial infarction, presence of the symptoms of angina and all variables derived from MPI findings, but in diabetics the most important predictors were size of stress perfusion defect, SSS and SDS. There are a lot of similar evidences in previous work of many authors. Kang et al. showed that diabetics had a higher event rate than nondiabetics with the same SSS [24]. Giri et al. showed in a multicenter trial that diabetics with ischemic defects had increased cardiac events than nondiabetics with the same level of ischemia. Despite this, an abnormal scan was an independent predictor of cardiac death and MI in both diabetic and nondiabetic groups [4].

In the previous analyses of perfusion imaging, the cardiac event rates in diabetic patients were significantly higher compared with nondiabetic patients, and the event rates in diabetic patients were related to the presence or absence of perfusion abnormalities. Kang et al. showed a higher cardiac event rate in diabetic patients than in nondiabetic patients, and the severity and size of the perfusion abnormalities as evaluated by the SSS, were significantly related to the probability of a cardiac event [24]. Giri et al. demonstrated the incremental value of perfusion imaging in predicting cardiac events [4], and De Lorenzo et al. showed that risk is related to the number of territories involved, and the extent and severity of the stress defects in both men and women [6]. Similarly, Berman et al. further demonstrated that the SSS predicted outcome in both diabetic men and women. Outcome was significantly higher in diabetic patients than in nondiabetics, and the severity of the defect predicted the event rates [25]. Cardiac events are, however, significantly higher in diabetic patients with an abnormal scan, resulting in a three- to eightfold increased risk compared with diabetic patients with a normal scan, and the severity of the perfusion abnormality in the diabetic population is proportionately related to outcome [26]. These findings are consistent with the assumption that diabetes contributes to an accelerated path of CAD complications. Diabetic patients are predisposed to a more aggressive form of vascular disease with diffuse coronary atherosclerosis and significantly higher incidence of cardiac events [4].
CONCLUSION

Our study adds to the body of evidence that the MPI continues to have an important diagnostic and prognostic value in evaluation of CAD, particularly in diabetics. In diabetic patients, the cumulative rate of cardiac events was higher and the event-free survival was worse than in patients without DM. We found that MPI could help in prediction of cardiac events in diabetics and the most important predictors were size of stress perfusion defect, summed stress score and summed difference score.

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REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018;137(12):e67–e492. DOI: 10.1161/CIR.0000000000005558. PMID: 29386200.

2. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:e271–281. DOI: 10.1016/j.diabres.2018.02.023. PMID: 29496507.

3. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation. 2003;107(23):2900–2907. DOI: 10.1161/01.CIR.0000072790.23090.41. PMID: 12771008.

4. Giri S, Shaw LJ, Murthy DR, Travin MI, Miller DD, Hachamovitch R et al. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation. 2002;105(1):32–40. DOI: 10.1161/01.hco.100.10528. PMID: 11772873.

5. Kumar D, Sethi RS, Bansal S, Namgyal PA, Sehgal AK, Malik TS. Diagnostic Accuracy of Stress Myocardial Perfusion Imaging in Indian Diabetic Patients: A Single Centre Experience. Indian J Nucl Med. 2017;32(3):177–183. DOI: 10.4103/0972-3919.207873. PMID: 28680199.

6. De Lorenzo A, Lima RS, Siqueira-Filho AG, Pantoja MR. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. Am J Cardiol. 2002;90(8):827–832. DOI: 10.1016/s0002-9149(02)02702-9. PMID: 12372568.

7. De Lorenzo A, Souza VF, Glerian L, Lima RS. Prognostic Assessment of Diabetes Using Myocardial Perfusion Imaging: Diabetes Mellitus is Still a Coronary Artery Disease Equivalent. Open Cardiovasc Med J. 2017;11:76–83. DOI: 10.2174/1874192401711010076. PMID: 29290832.

8. Mitjevska IP, Baneva N, Srbinovska E, Stojanovska L, Apostolopoulos V, Boseski M. Prognostic implications of myocardial perfusion imaging and coronary calcium score in a Macedonian cohort of asymptomatic patients with type 2 diabetes. Diab Vasc Dis Res. 2017;14(4):285–294. DOI: 10.1177/1479164116680776. PMID: 28393566.

9. Verberne HJ, Acampa W, Anagnostopoulos C, Ballinger J, Bengel F, De Bondt P et al. EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. Eur J Nucl Med Mol Imaging. 2015;42(12):1929–1940. DOI: 10.1007/s00259-015-3139-x. PMID: 26290421.

10. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation. 1998;97(6):535–543. DOI: 10.1161/01.cir.97.6.535. PMID: 9494023.

11. King SH, Choi HI, Kim YH, Lee EY, Ahn JM, Han S et al. Impact of Follow-Up Ischemia on Myocardial Perfusion Single-Photon Emission Imaging in Patients with Coronary Artery Disease. Yonsei Med J. 2017;58(5):934–943. DOI: 10.3349/ymj.2017.58.5.934. PMID: 28792136.

12. García-Ulloa AC, Lecucha-Fonseca C, Del Razo-Olvera FM, Aguilar-Salinas CA, Galaviz Ki, Narayan K MV, et al. Clinician prescription of lipid-lowering drugs and achievement of treatment goals in patients with newly diagnosed type 2 diabetes mellitus. BMJ Open Diabetes Res Care. 2021;9(1):e001891. DOI: 10.1136/bmjdr-2020-001891. PMID: 33568360.

13. Moonesinghe R, Beckles GLA, Liu T, Khoury MJ. The contribution of family history to the burden of diagnosed diabetes, undiagnosed diabetes, and prediabetes in the United States: analysis of the National Health and Nutrition Examination Survey, 2009–2014. Genet Med. 2018;20(10):1159–1166. DOI: 10.1038/gim.2017.8. PMID: 29369292.

14. Ehl NF, Kühne M, Brinkert M, Müller-Brand J, Zellweger MJ. Diabetes reduces left ventricular ejection fraction irrespective of presence and extent of coronary artery disease. Eur J Endocrinol. 2011;165(6):945–951. DOI: 10.1530/EJE-11-0687. PMID: 21903896.

15. Chareonthaitawee P, Sorapij P, Rajagopalan N, Miller TD, Hodge DO, Frye RL et al. Prevalence and prognosis of left ventricular systolic dysfunction in asymptomatic diabetic patients without known coronary artery disease referred for stress single-photon emission computed tomography and assessment of left ventricular function. Am Heart J. 2007;154(3):567–574. DOI: 10.1016/j.ahj.2007.04.042. PMID: 17719308.

16. Nakajima K, Nakamura S, Hase H, Takeishi Y, Nishimura S, Kawano Y et al. Risk stratification based on J-ACCESS risk models with myocardial perfusion imaging: Risk versus outcomes of patients with chronic kidney disease. J Nucl Cardiol. 2020;27(1):41–50. DOI: 10.1007/s12350-018-1330-8. PMID: 29948890.

DOI: https://doi.org/10.2298/SARH210329062S Copyright © Serbian Medical Society
17. Koh AS, Lye WK, Chia SY, Salunat-Flores J, Sim LL, Keng FYJ et al. Long-Term Prognostic Value of Appropriate Myocardial Perfusion Imaging. Am J Cardiol. 2017;119(12):1957–1962. DOI: 10.1016/j.amjcard.2017.03.026. PMID: 28456317.

18. Lu CH, Pei D, Wu CZ, Kua HC, Liang YJ, Chen YL, et al. Predictors of abnormality in thallium myocardial perfusion scans for type 2 diabetes. Heart Vessels. 2021;36(2):180–188. DOI: 10.1007/s00380-020-01681-2. PMID: 32816060.

19. Morales DCV, Bhavnani SP, Ahlberg AW, Pullatt RC, Katten DM, Polk DM et al. Coronary risk equivalence of diabetes assessed by SPECT-MPI. J Nucl Cardiol. 2019;26(4):1093–1102. DOI: 10.1007/s12350-017-1114-6. PMID: 29214611.

20. Pintaudi B, Scatena A, Piscitelli G, Frison V, Corrao S, Manicardi V et al. Clinical profiles and quality of care of subjects with type 2 diabetes according to their cardiovascular risk: an observational, retrospective study. Cardiovasc Diabetol. 2021;20(1):59. DOI: 10.1186/s12933-021-01251-4. PMID: 33676499.

21. Leutner M, Haug N, Bellach L, Dervic E, Kautzky A, Klimek P, et al. Risk of Typical Diabetes-Associated Complications in Different Clusters of Diabetic Patients: Analysis of Nine Risk Factors. J Pers Med. 2021;11(5):328. DOI: 10.3390/jpm11050328. PMID: 33922088.

22. Hage FG, AlJaroudi WA. Review of cardiovascular imaging in the Journal of Nuclear Cardiology 2019: Single-photon emission computed tomography. J Nucl Cardiol. 2020;27(4):1171–1179. DOI: 10.1007/s12350-020-02167-4. PMID: 32410057.

23. Branch M, German C, Bertoni A, Yeboah J. Incremental risk of cardiovascular disease and/or chronic kidney disease for future ASCVD and mortality in patients with type 2 diabetes mellitus: ACCORD trial. J Diabetes Complications. 2019;33(7):468–472. DOI: 10.1016/j.jdiacomp.2019.04.004. PMID: 31088728.

24. Kang X, Berman DS, Lewin HC, Cohen I, Friedman JD, Germano G et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. Am Heart J. 1999;138(6 Pt 1):1025–1032. DOI: 10.1016/s0002-8703(99)70066-9. PMID: 10577431.

25. Berman DS, Kang X, Hayes SW, Friedman JD, Cohen I, Abidov A et al. Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol. 2003;41(7):1125–1133. DOI: 10.1016/s0735-1097(03)00085-8. PMID: 12679212.

26. Freeman M. Myocardial perfusion imaging in diabetes mellitus. Can J Cardiol. 2006;22 Suppl A:22A–25A. DOI: 10.1016/s0828-282x(06)70975-8. PMID: 16485056.
Table 1. Baseline characteristics of the cohorts

| Baseline characteristics       | DM (n = 98) | non-DM (n = 100) | p     |
|--------------------------------|------------|------------------|-------|
| Male, n (%)                   | 55 (56.1)  | 45 (45)          | 0.118 |
| Age, years                    | 66.8 ± 7.2 | 66.9 ± 7.7       | 0.952 |
| Body mass index, kg/m²        | 30.2 ± 4.8 | 29.2 ± 5         | 0.137 |
| Hypertension, n               | 96         | 97               | NS    |
| Previous MI, n (%)            | 18 (18.4)  | 18 (18)          | 0.947 |
| Smokers (anytime), n (%)      | 50 (51)    | 51 (51)          | 0.998 |
| Smokers (current), n (%)      | 11 (11.2)  | 15 (15)          | 0.432 |
| Dyslipidemia, n (%)           | 72 (73.5)  | 54 (54)          | 0.004 |
| Family history of DM, n (%)   | 61 (62.2)  | 28 (28)          | < 0.001|
| Family history of CAD, n (%)  | 73 (74.5)  | 76 (76)          | 0.806 |
| Symptoms of angina, n (%)     | 61 (62.2)  | 64 (64)          | 0.798 |

DM – diabetes mellitus; MI – myocardial infarction; CAD – coronary artery disease
Table 2. Myocardial perfusion imaging findings

| Characteristics                        | DM (n = 98) | non-DM (n = 100) | p          |
|----------------------------------------|-------------|------------------|------------|
| LVEF US, %                             | 54.7 ± 9.9  | 57.8 ± 6.9       | 0.013      |
| LVEF SPECT, %                          | 64 ± 14.3   | 68.6 ± 12.3      | 0.018      |
| LVEF SPECT ≥ 50%, n (%)                | 84 (85.7)   | 92 (92)          | 0.159      |
| EDV, ml                                | 104 (43–318)| 97 (41–214)      | 0.133      |
| ESV, ml                                | 34 (4–245)  | 29.5 (6–140)     | 0.039      |
| SV, ml                                 | 67.5 ± 16.4 | 67.5 ± 16.8      | 0.983      |
| Abnormal ESV, n (%)                    | 27 (27.6)   | 16 (16)          | 0.049      |
| SSS                                     | 0 (0–19)    | 0 (0–23)         | 0.093      |
| SRS                                     | 0 (0–18)    | 0 (0–20)         | 0.606      |
| SDS                                     | 0 (0–15)    | 0 (0–18)         | 0.094      |
| Abnormal stress MPI (SSS ≥ 4), n (%)   | 33 (33.7)   | 24 (24)          | 0.133      |
| Severity of stress defect, n (%)       |             |                  | 0.095      |
| SSS < 4 – no defect                    | 65 (66.3)   | 76 (76)          |            |
| SSS 4–8 – mild                         | 13 (13.3)   | 13 (13)          |            |
| SSS 9–13 – moderate                    | 12 (12.2)   | 7 (7)            |            |
| SSS >13 – severe                       | 8 (8.2)     | 4 (4)            |            |
| Ischemia (SDS≥2), n (%)                | 18 (18.4)   | 12 (12)          | 0.212      |
| Severity of ischemia, n (%)            |             |                  | 0.145      |
| SSS < 2 – no ischemia                  | 80 (81.6)   | 88 (88)          |            |
| SSS 2–4 – mild                         | 0 (0)       | 6 (6)            |            |
| SSS 5–8 – moderate                     | 6 (6.1)     | 2 (2)            |            |
| SSS >8 – severe                        | 12 (12.2)   | 4 (4)            |            |

DM – diabetes mellitus; LVEF – left ventricular ejection fraction; US – ultrasound; SPECT – single photon emission computed tomography; EDV – end diastolic volume; ESV – end systolic volume; SV – systolic volume; SSS – summed stress score; SRS – summed rest score; SDS – summed difference score; MPI – myocardial perfusion imaging
Table 3. Follow-up period and outcomes

| Characteristics | DM (n = 98) | non-DM (n = 100) | p    |
|-----------------|------------|-----------------|------|
| Follow-up, months | 26 (2–28)  | 24 (3–30)       | 0.184|
| Cardiac event n (%) |            |                 |      |
| Cardiac death   | 2 (2)      | 1 (1)           |      |
| Non-fatal MI    | 2 (2)      | 2 (2)           |      |
| Revascularization | 13 (13.3) | 8 (8)           | 0.048|

DM – diabetes mellitus; MI – myocardial infarction
### Table 4. Predictors of cardiac events in the univariate Cox analysis

| Variable                                      | HR (95% CI)       | p     |
|-----------------------------------------------|-------------------|-------|
| DM                                            | 2.3 (0.99–5.3)    | 0.053 |
| Sex (f/m)                                      | 0.3 (0.1–0.8)     | **0.010** |
| Body mass index                                | 1 (0.9–1.1)       | 0.867 |
| Hypertension                                   | 0.6 (0.1–4.2)     | 0.574 |
| Previous myocardial infarction                 | 5.9 (2.7–12.9)    | **< 0.001** |
| Smokers (anytime)                              | 2.7 (1.1–6.4)     | **0.027** |
| Smokers (current), n (%)                       | 0.9 (0.3–3)       | 0.877 |
| Dyslipidemia                                   | 1.3 (0.5–2.9)     | 0.596 |
| Family history of DM                           | 1.7 (0.7–3.6)     | 0.213 |
| Family history of CAD                          | 1 (0.4–2.6)       | 0.938 |
| Symptoms of angina                             | 4.5 (1.4–15.1)    | **0.014** |
| LVEF SPECT, %                                  | 0.9 (0.9–1)       | **< 0.001** |
| Presence of normal LVEF SPECT                  | 0.2 (0.1–0.4)     | **< 0.001** |
| EDV, mL                                        | 1.01 (1.01–1.02)  | **< 0.001** |
| ESV, mL                                        | 1.01 (1.01–1.02)  | **< 0.001** |
| Presence of normal ESV                         | 0.2 (0.1–0.4)     | **< 0.001** |
| SV, mL                                         | 1.02 (1.00–1.05)  | **0.025** |
| Presence of stress perfusion defect            | 119.1 (4–3574.9)  | **0.006** |
| Size of stress perfusion defect, %             | 1.1 (1.1–1.2)     | **< 0.001** |
| Presence of ischemia                           | 82.4 (19.3–351.1) | **< 0.001** |
| Size of ischemia, %                            | 1.2 (1.1–1.2)     | **< 0.001** |
| SSS                                           | 1.2 (1.2–1.3)     | **< 0.001** |
| SRS                                           | 1.1 (1.1–1.2)     | **< 0.001** |
| SDS                                           | 1.3 (1.2–1.4)     | **< 0.001** |
| Abnormal stress MPI (SSS≥4)                    | 498.2 (3.6–69325.6) | **0.014** |
| Severity of stress defect                      | 5.2 (3.5–7.8)     | **< 0.001** |
| Ischemia (SDS≥2)                               | 112.5 (26.3–481)  | **< 0.001** |
| Severity of ischemia                           | 4.6 (3.2–6.6)     | **< 0.001** |

HR – hazard ratio; CI – confidence interval; DM – diabetes mellitus; CAD – coronary artery disease; LVEF – left ventricular ejection fraction; SPECT – single photon emission computed tomography; EDV – end diastolic volume; ESV – end systolic volume; SV – systolic volume; SSS – summed stress score; SRS – summed rest score; SDS – summed difference score; MPI – myocardial perfusion imaging
**Table 5.** Association between cardiac events and diabetes mellitus using univariate Cox regression model after adjustment for variables derived from myocardial perfusion imaging findings

| Adjusting variable                              | HR (95% CI)       | p  |
|-------------------------------------------------|-------------------|----|
| LVEF SPECT, %                                   | 1.8 (0.8–4.2)     | 0.180 |
| Presence of normal LVEF SPECT                   | 2.1 (0.9–4.8)     | 0.094 |
| EDV, mL                                         | 1.9 (0.8–4.5)     | 0.148 |
| ESV, mL                                         | 1.9 (0.8–4.4)     | 0.153 |
| Presence of normal ESV                          | 1.8 (0.8–4.3)     | 0.167 |
| SV, mL                                          | 2.3 (1–5.3)       | 0.054 |
| Presence of stress perfusion defect             | 1.9 (0.8–4.5)     | 0.129 |
| Size of stress perfusion defect, %              | 2.8 (1.2–6.6)     | **0.022** |
| Presence of ischemia                            | 1.6 (0.7–3.8)     | 0.263 |
| Size of ischemia, %                             | 2.2 (0.9–5.3)     | 0.069 |
| SSS                                             | 3.2 (1.3–7.9)     | **0.011** |
| SRS                                             | 2.3 (1–5.3)       | **0.052** |
| SDS                                             | 2.4 (1–5.8)       | **0.044** |
| Abnormal stress MPI (SSS ≥ 4)                   | 1.8 (0.8–4.2)     | 0.161 |
| Severity of stress defect                       | 1.7 (0.7–4)       | 0.223 |
| Ischemia (SDS ≥ 2)                              | 2.2 (0.9–5.1)     | 0.079 |
| Severity of ischemia                            | 0.9 (0.4–2.2)     | 0.802 |

HR – hazard ratio; CI – confidence interval; LVEF – left ventricular ejection fraction; SPECT – single photon emission computed tomography; EDV – end diastolic volume; ESV – end systolic volume; SV – systolic volume; SSS – summed stress score; SRS – summed rest score; SDS – summed difference score; MPI – myocardial perfusion imaging
Figure 1. Kaplan–Meier event-free survival curves