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Diabetes and vasclar disease research

Prognostic implications of myocardial perfusion imaging and coronary calcium score in a Macedonian cohort of asymptomatic patients with type 2 diabetes

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Running Title: Prognostic implications in type 2 diabetic patients

Abstract

Aim: Type-2 diabetes is a risk factor for coronary artery disease (CAD), however, a number of studies have shown that patients are asymptomatic for CAD. The presence of CAD in asymptomatic patients with type-2 diabetes were evaluated to determine its impact on management decision and prognosis.

Methods: Seventy five patients underwent SPECT myocardial perfusion imaging for detection of suspected CAD. We used 17 segment model for perfusion and function analysis. Multislice computed tomography was performed in 45 patients to assess coronary calcium score (CAC). Complete laboratory analyses with lipid values and standard risk factors were analyzed. Forward logistic regression analysis was used to assess predictive parameters for myocardial ischemia during the follow up period of 20±4 months.

Results and Conclusion: Silent myocardial ischemia and subclinical CAD can be detected in a significant proportion of asymptomatic patients with type-2 diabetes. Diabetic patients with normal myocardial perfusion imaging had an excellent 2 year prognosis with optimal medical therapy and intensive risk factor control. In comparison, an abnormal myocardial perfusion imaging led to an increased risk of cardiovascular events. Myocardial perfusion imaging and CAC are valuable tools for risk-stratification and optimal treatment decision in this asymptomatic diabetic cohort of Macedonian patients. .

Key words

Type 2 diabetes - Coronary artery disease - Myocardial ischemia - Myocardial perfusion imaging - Coronary calcium score

List of abbreviations

AICS, acute ischemic coronary syndrome; BMI, body mass index; CABG, coronary artery bypass surgery; CAC, coronary artery calcium; CAD, Coronary artery disease; ECG, electrocardiograph; ESC, European society of cardiology; HDL, high density lipoprotein; LDL, low density lipoprotein; LV, left ventricle; LVEF, left ventricular ejection fraction; MPI, myocardial perfusion imaging; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; SDS, summed differential score; SPECT, single photon emission computed tomography; SRS, summed rest score; SSS, summed stress score; TID, transient ischemic dilation; WMI, wall motion index.

Introduction

The risk of type-2 diabetes increases with age, especially over the age of 50. Coronary artery disease (CAD) is the leading cause in morbidity, mortality and cost of management of patients with type-2 diabetes. Acute myocardial infarction or sudden cardiac deaths are often the first clinical presentations in asymptomatic diabetic patients due to the insufficient screening for CAD [1]. These events are linked to increased morbidity, mortality and socioeconomic burden. The dilemma on the cost effectiveness of screening for myocardial ischemia in asymptomatic diabetic patients in relation to the optimal therapeutic approach is still ongoing. There is controversy whether noninvasive imaging such as, myocardial perfusion imaging (MPI) improves type-2 diabetic patient management and prognosis. Proposed strategies that may favourably affect CAD risk and outcomes in high risk asymptomatic population include identifying patients with subclinical disease at high risk of future cardiac events. Current risk score models (SCORE, FRAMINGHAM, PROCAM) show inferiority for individual risk stratification and ability to predict the presence of ischemia [2-4]. MPI with gated single photon emission computed tomography (SPECT) is a non-invasive imaging scan of the heart commonly used to diagnose and evaluate prognosis of patients with known or suspected CAD [1,2]. There is increased interest in the use of coronary artery calcium (CAC) imaging to assess early subclinical atherosclerosis and total atherosclerosis burden, in patients with intermediate cardiovascular risk [3-5]. CAC is also a proven prognostic parameter in diabetic patients [6, 7]. Whilst simple categorical risk factors, such as, hypertension, hyperlipidemia, obesity, smoking, age etc, cannot effectively discriminate which asymptomatic high risk type-2 diabetic patients will or will not have ischemia on stress testing [5]. it is still possible however, that risk factor burden may predict risk of cardiovascular events in individual patients. Herein, we assessed the prognostic value of coronary atherosclerosis and myocardial ischemia in asymptomatic diabetic patients of a Macedonian cohort. We also determined how noninvasive imaging could influence treatment strategies in these patients.

Methods

Study design and data source

A prospective cohort study was designed and 75 consecutive asymptomatic patients with type-2 diabetes (41 male, 34 female; age range 63 ± 9 years), without previously known or established CAD were included in the study. All patients completed the World Health Organization Rose Angina Questionnaire for confirmation of the asymptomatic status. Screening for myocardial ischemia was performed using MPI SPECT imaging in the nuclear cardiology laboratory at our clinic in the period of October 2012 - November 2013. Prospective follow-up was complete in all 75 patients (100 %) with a median period of 20 months (16 - 24months). CAC scores were performed and data evaluated using Agatston units. 2D transthoracic echocardiography was used for assessment of systolic and diastolic left ventricular function with GE VIVID7 echo machine. We have screened 93 diabetic patients, from which 75 with preserved left ventricular systolic function and left ventricular ejection fraction (LVEF>50%), assessed by echocardiography Simpson's rule enrolled the study and were included in the final patient cohort. Distribution of study subjects are presented in Flow Chart 1.

All patients underwent a physical examination and included blood pressure measurements, weight, height, waist circumference, body mass index (BMI) and risk factors analysis. Full blood examination with high density lipoprotein (HDL), low density lipoprotein (LDL), non-HDL and triglyceride levels, fasting glucose levels, % glycated hemoglobin (HbA1c), and blood creatinine levels were performed within a maximum of 2 weeks prior to MPI. Medical history was evaluated and corrected according to target risk factor goals based on latest European society of cardiology (ESC) recommendations for cardiovascular prevention and hypertension treatment for all patients. Clinical and laboratory characteristics are shown in (Table 1). The following *inclusion criteria* were used: asymptomatic patients with type-2 diabetes, normal rest left ventricular function with EF > 50 %. *Exclusion criteria were*: typical stable angina pectoris, previously known or established CAD (history of myocardial infarction, acute coronary syndromes, previous percutaneous intervention or coronary artery bypass surgery), LVEF < 50 % at rest, severe valvular disease, atrial fibrillation, left bundle branch block, presence of pace maker, severe chronic pulmonary disease. The study was approved by the Human Ethics Committee of the Medical Faculty, University St. Ciril and Methodius in Skopje, Macedonia. All patients signed an informed consent.

Definition of study variables

Risk factor definitions were made according to the most recent ESC guidelines on hypertension, hyperlipidemias and cardiovascular prevention: arterial hypertension (systolic blood pressure (SBP) > 140 bpm or diastolic BP > 90 bpm), dyslipidaemia (LDL > 1.8 mmol/l; high-density lipoprotein < 1.1 and 1.0 mmol/l for females and males respectively and triglycerides > 1.7 mmol/l), family history of myorcardial infarction or sudden cardiac death in an immediate male relative < 55 years or female < 65 years, smoker (current smoker or those who quit in the past 6 months). BMI ≥ 30 kg/m² was used to define to define obese patients. Type-2 diabetes mellitus was defined as established disease in patients treated with oral anti-diabetic medication or insulin following initial treatment with oral anti-diabetic therapy. Newly diagnosed diabetes was defined as having either one of the following criteria, base on the ESC guidelines on pre-diabetes and diabetes: fasting glucose of 7.0 mmol/L or non-fasting glucose 11.0 mmol/L in 2 separate samples, HbA1c > 6.5 % or pathologic oral glucose tolerance test in patients with fasting glucose over 6.5 without previously known or treated diabetes. Electrocardiography (ECG) abnormalities at rest were defined as the presence of ST-T abnormalities, Q-waves, T-wave inversion.

Myocardial perfusion SPECT imaging (MPI)

MPI SPECT imaging was performed using one day rest stress protocol with radiotracer technetium (Tc-99m) sestamibi, using 15 mCi for the rest and 25 mCi for the stress study. We used single head gamma camera Siemens e-cam, with commercially available quantitative gated and perfusion SPECT software package (4DM-SPECT). Patients were instructed to refrain from caffeine-containing beverages for at least 12 hours (h), nitrates for 24 h, and beta-blockers for 48 h before the study. All patients underwent pharmacological stressing with dipyridamole. We used the 17-segment model for quantitative Bull's eye analysis of regional

myocardial perfusion and function. Myocardial perfusion was assessed by 5 point score system (0-normal radiotracer uptake; 1- mild, 2-moderate; 3- severe hypo perfusion; 4- absent uptake). Semi quantitative analysis of regional perfusion at rest and stress was performed using summed stress score (SSS), summed rest score (SRS) and summed differential score (SDS), aimed to assess the presence and extend of myocardial ischemia. Scan abnormalities were defined as follow: SSS < 4 normal perfusion; 4-8 mild; 9-13 moderate; > 13 severely abnormal scan. SDS < 6 mild (< 10 % of left ventricle (LV)); SDS 7-10 moderate (10-15 % of LV); SDS > 10 severe ischemia (> 15 % of LV). Fixed defects were defined as SRS > 4. Any perfusion abnormality was defined as SDS > 4 and/or SRS > 4. LV volumes, left ventricular ejection fraction (LVEF) at rest and stress, presence of transit ischemic LV dilation (TID), visualisation of right ventricle and lung uptake were also analyzed. Regional wall motion analysis was assessed by a 6 point scoring system at rest and stress (0 - normal wall motion, 1 - mild, 2 - moderate; 3 - sereve hypokinesia, 4 - akinesia, 5 - dyskinesia) using wall motion score index.

Results considered normal were those that showed a homogenous distribution of the radiotracer throughout the LV myocardium at the stress and resting images and with normal systolic movement and thickening. The fixed perfusion defects, present in both images and with a segmental contractile deficit and systolic thickening were interpreted as fibrosis. Transient perfusion defects, present at the stress phase and absent at the resting phase, with normal range of movement and thickening, were considered to be ischemia. When the recovery of these defects was only partial, with a contractile deficit, it configured the simultaneous existence of fibrosis and ischemia.

Coronary Calcium Score (CAC) Imaging

For CAC imaging, a non-enhanced, prospectively ECG-gated scan was obtained by use of a 128-slice CT scanner (Siemens Somatom Definition 128 AC+, single source). The estimated effective radiation dose for this protocol was bellow 1 mSv. Image reconstruction was performed at 55 % of the R-R interval with prospective gating usage. The total calcium burden in the coronary arteries was measured according to the scoring algorithm of Agatston. On the basis of the total Calcium score expressed in Agatston Units (AU), patients were placed into 5 categories, as previously reported [8]: CAC 0- no evidence of atherosclerosis; CA 1-10AU (minimal or insignificant CAC), 11–100 (mild CAC), 101–400 (moderate CAC), 401–1.000 (severe CAC). Total CAC score and CAC score in each coronary artery was evaluated.

Coronary angiography

All patients with at least moderate myocardial ischemia (SDS >7) underwent coronary angiography. Invasive coronary angiograms were evaluated by consensus of 2 interventional cardiologists who were unaware of the SPECT and CAC imaging results. Segments were classified as normal, as having nonobstructive disease or as having significant stenosis (50 % stenosis). Presence, localization, severity of coronary stenosis and number of vessels involved were analyzed using Syntax score. Percutaneous coronary intervention with stenting or coronary artery bypass surgery was performed according to the latest myocardial ESC revascularization guidelines, based on invasive cardiologist's team decision.

Medical therapy and life style advice

Medical therapy was reviewed in detail and all patients underwent an optimal medical treatment with life style and risk factor control advice and targets based on the latest ESC guidelines for cardiovascular prevention and management of stable CAD.

Follow up

Patients were prospectively followed for a median of 20 ± 4 months. The following were considered as cardiovascular events: sudden cardiac death; acute coronary syndrome (ACS) with or without ST-segment elevation; myocardial revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) and cerebrovascular events (cerebrovascular insult-CVI). The follow-up of the sample was carried out by six months clinical visits until the end of the follow up period, or in earlier periods in case of change in clinical symptoms or clinical event.

Statistical analysis

Statistical analysis was performed with the use of the SPSS statistical package (version 18.0). Categorical variables were compared using chi-square test and continuous variables using unpaired Student t test. Normality of variables distribution was performed. Categorical values were expressed in percentages, continued as mean value ± SD. Linear regression analysis was used to determine whether there was a correlation between the CAC score and perfusion abnormalities on SPECT. Multivariate forward stepwise logistic regression analysis was built in order to identify factors associated independently with the presence of silent myocardial ischemia and prognosis. The analysis includes age, gender, hypertension, hyperlipidemia, smoking, obesity, diabetes duration, MPS perfusion scores, ECG ST segment depression during pharmacological stress and CAC. The criterion for entrance into the model was a univariate probability value of $p<0.05$ and $p>0.10$ for removal from the model. $P<0.05$ was considered to be statistically significant for all statistical tests. Cumulative event-free survival rates as a function over time were obtained using the Kaplan-Meier method. Cardiac event-free survival curves were compared using the log-rank test. To identify the association between clinical and imaging variables and outcomes, Cox regression analysis was used.

Results

Follow-up was attained in all 75 patients. Study demographics consisted of 41 male (55 %) and 34 female patients (45 %), with mean age of 65 and 69 years respectively, as shown in (Table 1). The prevalence of metabolic risk factors, blood examination and medical therapy are presented in Table 1. All patients had on average 2 risk factors. The risk factors for the cardiovascular disease were distributed as follows: 76 % of systemic arterial hypertension; 51.4 % of dyslipidemia; 14 % of cigarette-smoking, 12 % with obesity and 44 % of family history for coronary history. Average duration of diabetes was 8 ± 3 years. 11 patients (15 %) used insulin therapy.

Myocardial SPECT findings

The stress phase was carried out through pharmacological stress with dipyridamole in all patients. Total of 1275 segments were analyzed. All patients showed normal rest left ventricular function with EF > 55.0 % assessed by Gated SPECT. Fifty six patients (74.6 %) had normal MPI results. The scintigraphy results were abnormal in 19 patients (25.3 %). Stress inducible ischemia was found in 18 patients (24.0 %). Ischemia plus fibrosis with fixed perfusion defects were found in 3 patients and fixed defects only in 1 patient, which could indicate the presence of previous silent myocardial infarction. Mild ischemia was found in 6 patients - summed difference score (SDS) < 4, moderate ischemia (SDS 7-10) in 7 and severe ischemia (SDS > 10) in 5 patients (Figures 1 and 2). Average wall motion index (WMI) in patients with ischemia was 1.25. Patients with severe ischemia had a drop of LVEF during stress study by > 5.0 % and transit ischemic dilation (TID). There was a correlation with diabetes and stress ECG changes with the presence of myocardial ischemia (r=0.54 and r=0.58 respectively). When the scintigraphy results were analyzed we noted that the patients with abnormal perfusion were significantly older male population (p=0.01), when compared to the group with normal perfusion.

Coronary calcium Score findings

CAC score was assessed in total 135 coronary arteries. Subclinical atherosclerosis was present in 35 patients from 45 (77.7%) who had CAC score evaluated. Ten patients had CAC score 0 AU; 4 patients had CAC score 1-10 AU; 15 patients had mild CAC score (11-99 AU); 7 patients had moderate CAC (100-399 AU) and 9 patients had severe CAC (401-1000 AU). No patients had extensive CAC > 1000 AU. Calcium was present in the in the left anterior descending coronary artery (LAD) in 17 patients, in the left circumflex artery (LCX) in 6 patients, and right coronary artery (RCA) in 12 patients, respectively. The average calcium score in the LAD (289 ± 72) was significantly higher than those in the LCX (115 ± 56) and in the RCA (192 ± 68). Patients with moderate and severe ischemia had CAC score 667 ± 112AU. Patients with normal MPI scan had an average CAC score of 25 ± 18AU.

The subclinical atherosclerosis group were older, predominantly males and 15 were smokers. Independent predictors of subclinical atherosclerosis were age (≥ 65 years) [odds ratio (OR): 1.068, 95.0 % confidence interval (CI): 1.05-1.92, p=0.026], diabetes (OR: 1.89, 95 % CI: 1.1-2.76, p=0.052) and smoking (OR: 1.73, 95 % CI: 1.2-2.21, p=0.041) in multivariate forward logistic regression analysis.

Relationship Between CAC Imaging and Gated SPECT

The relationship between the prevalence and severity of myocardial perfusion abnormalities and the extent of CAC is shown in Figure 3. Nine patients with normal SPECT results showed atherosclerosis with mild CAC score (11-99 AU). Contrary, 8 patients with moderate CAC and 6 patients with severe CAC had abnormal perfusion. The mean CAC score was significantly higher in subjects with at least moderate ischemia than in those who had normal SPECT results (667 ± 112 vs. 149 ± 45; p<0.001).

Predictors of Myocardial ischemia

Stepwise forward logistic regression analysis for prediction of stress-induced ischemia in the model that included CAC, showed OR 2.4 (95.0 % CI 1.7−3.6) for stress-induced ECG changes, OR 2.8 for CAC > 400 (95.0 % CI 1.9-3.2) and OR 3.9 for presence of type-2 diabetes over 10 years (95.0 % CI 2.3−6.6) is shown in Table 2. The second stepwise forward logistic regression model which did not include CAC, showed OR 2.1 (95 % CI 1.3−3.4) for male gender, OR 2.4 for hyperlipidemia (95.0 % CI 1.7-3.8) and OR 3.7 for presence of type-2 diabetes over 10 years (95.0 % CI 2.2−5.7) is shown in Table 3 and 4. Relationship between percentage and severity of myocardial perfusion abnormalities and extent of CAC is presented in Figure 2 .

Cardiovascular events and frequency of revascularization procedures during follow-up

There were no cardiac deaths, myocardial infarctions or heart failure during the follow up period. All patients with moderate severe ischemia were referred for coronary angiography (n=12). From 12 patients with at least moderate ischemia, 8 patients had significant CAD and underwent PCI revascularization (66.6 %) (Table 4, 5). Two patients had PCI to RCA, 3 patients had PCI to LAD and 1 patient had PCI to LAD and LCx. Other 4 patients had angiographycally non significant CAD and received an advice for intensive medical treatment. Patients with mild ischemia (SDS <7) and normal MPI findings were put on intensive medical therapy and life style modification. The average CAC score in these patients was 590 ± 145. Three patients were hospitalized due to non-stable angina, two with previous severe ischemia and one with normal MPI study. Patients with normal MPI had a low revascularization rate of 1.3 % during the follow up period, and no other cardiovascular events in the follow up period. Revascularization rate in the studied cohort was 2.1 % during the follow up period of 20 ± 4 months. Univariate analysis of variables that influence future events,presented with following predictive values: Hyperlipidemia (score 2.275, p=0.031), DMT2 duration over 10 years (score = 3.125, p=0.021), CAC>400 (score = 2.117, p=0.018) and SDS>7 (score = 4.173, p=0.0012). Results of univariate analysis are summarized in Table 6. SDS>7 (OR: 2.0371, p=0.001) and diabetes duration over 10 years (OR: 1.9136, p=0.002), stepped into the multivariate model, showed independent predictive values (Table 7). Kaplan Maier curves (Figure 3) showed significant difference between event free survival and degree of myocardial ischemia (Long rank p=0.000, Chi-square 62.319).

Discussion

This study showed diabetes duration, stress ECG ST segment depression and coronary calcium score >400AU as predictors of at least moderate myocardial ischemia in high risk asymptomatic patients in logistic regression model which includes CAC. Male gender, hyperlipidemia and diabetes duration over 10 years were predictors of silent ischemia in the second model which excluded CAC. The aim of screening for silent CAD in high risk patients is to detect disease in the early stage, taking into consideration that up to 60.0 % of male and 42.0 % of female patients, the first initial presentation of CAD is acute myocardial infarction and 40.0 % with sudden cardiac death [1,2]. There has been a long debate and conflicting opinions concerning the optimal screening approach in asymptomatic patients with high cardiovascular risk. The

scientific data gives arguments that, atherosclerosis and myocardial ischemia imaging in selected asymptomatic moderate and high risk adults to be used, although prognostic implications of this approach are not clear [3]. The prevalence of silent ischemia ranges between 22-63.0 % in diabetic patients. We noted that 18 patients (24.0 %) had stress inducible ischemia and 12 of them had at least moderate ischemia. Our results showed high negative predictive value of the normal myocardial scintigraphy scan and good intermediate prognosis in diabetic patients. Four patients in our study (5.3 %) had fixed perfusion defects alone and in combination with ischemia, which indicate 5.3% had previous silent myocardial infarctions. This finding is correlation with the previous studies data, which reports the incidence of silent IM of 5% (18.20). The study reports the revascularization rate of 2.1 % for 20 ± 4 months. Eight patients with at least moderate ischemia (66.6 %) underwent PCI revascularization. Three patients from our study were hospitalized for ACS (4.0 %), two with previous incomplete revascularization and severe ischemia and one patient with normal study. All patients with normal MPI study (74.6 %) had good prognosis with no hard events, and revascularization rate of 1.3 % during the follow up period of 20 ± 4 months. Multivariate Cox regression analysis showed SDS > 7 and diabetes duration over 10 years as independent predictor of CV events (OR 2.0371, $p<0.001$ and OR 1.9136, $p<0.002$), after adjustment for hyperlipidemia and CAC > 400.

The concept of diabetes as CAD equivalent was introduced following the Finnish population-based study [3]. Based on several epidemiological studies, diabetic patients are considered as high risk population [5]. However, it has been argued that CAD risk equivalence in diabetes is also influenced by additional risk factors, target organ damage and the presence of vascular disease. The use of vascular imaging may improve the individual risk assessment in diabetic patients. Acampa and co-workers found significant risk reclassification after MPS use in diabetic patients with suspected or known CAD [6]. The value of noninvasive imaging of diabetic vascular disease has been confirmed in several studies and also in our previous study [7,9].

From a management and prognostic perspective, the important question is whether we are able to improve the overall state for diabetic patients? Will vascular damage and ischemia assessment improve long term prognosis? Recommended risk stratification models have evident inferiorities, which do not include many additional risk factors such as, diabetes, family history and obesity. These models do not predict the presence of myocardial ischemia or atherosclerosis which has prognostic information. From the data we have thus far, patients with at least moderate myocardial ischemia with 10 % or more of the left ventricle involved, are suitable candidates for invasive treatment, although the long term benefits of this approach are still not confirmed in prospectively randomized ischemia based treatment studies. In fact, there was no significance in the BARI 2D trial in relation to survival [10]. Furthermore, there was no significance between major cardiovascular events in patients treated with medical therapy or revascularization [10].

The occurrence of ischemia as detected by SPECT myocardial scintigraphy in asymptomatic type-2 diabetic patients, demonstrated, that myocardial ischemia was highly prevalent in type-2 diabetic patients (34.0 %) vs 17.0 % in control subjects [11]. The findings of reversible perfusion defects were only significantly associated with the presence of type-2 diabetes. The proof of CAD presence suggests the necessity to increase pharmacological therapy and risk factor

control. In addition, the presence of atherosclerosis may also improve patient compliance and acceptance of life-style changes.

A number of studies involving CAD screening in type-2 diabetic patients did not show any correlation amongst the number of associated risk factors to inducible ischemia as assessed SPECT imaging [12-13]. However, these studies did not evaluate, severity, duration, and, treatment modalities of risk factors, in patients with long term type-2 diabetes. Furthermore, differences between the studies may also be a reflection of the differences between diabetes management, glucose and risk factor control and diabetes complications in different countries. European guidelines on cardiovascular prevention and treatment of stable CAD as well as American guidelines on screening for CAD in asymptomatic adults indicates that imaging of atherosclerosis and functional imaging of CAD have a place and can be used in this population [4,14]. An important clinical question however, is whether ischemia should be screened in order to make a treatment decision. From a clinical point of view, the management dilemma should not be between medical versus invasive treatment, but rather which patient and when should invasive treatment be offered. In fact, the large ongoing ISCHEMIA Trial may answer many of these dilemma's and may provide the best initial treatment strategies for patients with stable CAD who have at least moderate ischemia on non-invasive imaging tests.

In a meta-analysis study which evaluated type-2 diabetic patients who had normal MPI SPECT readings, it was noted that the rate of cardiac death or non fatal myocardial infarction per annum was significantly lower (0.6%) in non type-2 diabetic patients compared to type-2 diabetic patients [16]. The extent and severity of myocardial ischemia is a strong risk predictor of coronary events [16-19]. In fact, the annual rates for cardiac events in type-2 diabetic patients varied, with mild (1-2 %), moderate (3-4 %) and severe (7.0 %) perfusion defects [18]. The only large prospective study for detection of asymptomatic ischemia in non-selected type-2 diabetic patients with no prior CAD noted that 22% of patients presented with an abnormal MPI SPECT, and severe perfusion abnormalities were noted in 6.0 % of the patients [13]. Of interest, males, duration of diabetes and the presence of cardiac autonomic dysfunction strongly correlated to ischemia [13]. Herein, we noted abnormal MPS results in 25.3 % of the patients. Stress inducible ischemia was found in 18 patients (24.0 %), from which 12 patients had moderate and severe ischemia. We had confirmed the impact of myocardial ischemia detected by MPI on management decision in high risk asymptomatic patient in our previous study [15]. The study showed that type-2 diabetic patients without a history of CAD and normal MPI have a relatively good 2 year prognosis. We found 4 false positive results of myocardial perfusion imaging (4 of 12 had myocardial perfusion abnormalities with normal coronary angiography). These findings could be explained that microvascular dysfunction is often present in diabetic patients with multiple risk factors. This process could lead to heterogeneous myocardial perfusion and myocardial ischemia, without the presence of significant CAD. The repetitive episodes of myocardial ischemia due to microvascular dysfunction in larger myocardial regions, could result in fibrosis, myocardial remodeling and development of diabetic cardiomyopathy.

A large observational study demonstrates that coronary calcium can be used as a prognostic marker even in patients with type-2 diabetes. Type-2 diabetic patients with zero CAC demonstrated an excellent 5-year survival rate but was not significantly different to control subjects (98.8 % and 99.4 % respectively, $p<0.05$) [8]. However several studies evaluating CAC in diabetic patients opponent the established opinion that DM type 2 is per se CAD equivalent. CV risk in diabetic

patients actually is quite heterogenic and not all diabetic patients had the same risk. CAC 0 put the patient in lower risk group with expected good intermediate prognosis. The determinant factors to use coronary artery calcium as a screening method of atherosclerosis should be based on individual clinical approach and patient risk assessment. This test might be performed if the results are expected to influence the management decision. In fact, high risk patients can be re-stratified into a lower risk category by presence of zero calcium score, which also selects patients with good long term prognosis [20, 21, 22]. In our study patients with moderate and severe ischemia had Agatston CAC score 667 ± 112. The presence of atherosclerosis is not necessarily the entity that leads to perfusion abnormalities. However, scintigraphic findings do not exclude the presence of obstructive CAD, but only indicates the absence of hemodinamicaly significant CAD. In a study using MPI, the prevalence of silent ischemia was 18% in individuals with a CAC score of 100–400, with abnormal MPI findings in 45 % of patients with a CAC score over 400 [23]. Our results are in correlation with other studies underlying no absolute linearity of increasing CAC values and myocardial ischemia findings, since these methods assess different aspects of CAD. We found that diabetic patients with normal myocardial perfusion imaging had good 2 year prognosis with optimal medical therapy. The risk for cardiovascular events increased as a function of perfusion scan abnormality. Larger prospective clinical trials with longer follow up period are necessary to demonstrate the prognostic influence and ability of risk reclassification with SPECT imaging in asymptomatic diabetic patients.

Study limitations

The small sample we have evaluated could represent a limitation of our study. Nevertheless, our results could aid in improving our understanding of the relationship between functional and anatomic aspects of CAD in asymptomatic type-2 diabetic patients and their prognostic implications. CAC was performed in only 45 patients due to technical reasons.

Conclusion

Presence of silent myocardial ischemia in asymptomatic type-2 diabetic patients is high, and increases with diabetes duration. CAC imaging may be useful in identifying patients with extensive atherosclerosis without stress-induced ischemia, who may be referred for risk factor modification and aggressive medical treatment. CAC over 400 Agatston units, male gender and diabetes duration over 10 years predicted the risk of silent ischemia in our study. Multivariate regression analysis showed SDS > 7 as MPI variable and diabetes duration over 10 years as predictors of CV events. These results indicate that myocardial perfusion imaging and CAC are valuable tools for risk-stratification and optimal treatment decision in this asymptomatic diabetic cohort of Macedonian patients.

Declaration of conflicting interests

The authors declare that there is no conflict of interest

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Figure Legends

Flow chart 1. Distribution of study subjects

Figure 1. Severity of ischemia in the studied population (n=18)

Figure 2. Relationship between percentage and severity of myocardial perfusion abnormalities and extent of coronary artery calcification

Figure 3. Kaplan-Meier survival curves as a function of myocardial perfusion scintigraphy results and severity of myocardial ischemia

Table 1
Clinical characteristics of the study population

Variables	Patients n = 75
Age	65 ± 9 years
Gender	41 males, 34 females
Hypertension	57.0 (76 %)
Hyperlipidemia	39.0 (52 %)
Obesity	12.0 (16 %)
Peripheral artery disease	7.0 (9.3 %)
HbA1c	7.4 ± 1.2 %
Ejection fraction	61.0 ± 6.0 %
Family history of CAD	33.0 (44.0 %)
Active smoker	10.0 (13.3 %)
HDL	0.9 ± 0.4 mmol/l
LDL	3.2 ± 0.4 mmol/l
Triglycerides	2.3 ± 0.6 mmol/l
Mean risk factors per patient	2.0 ± 1.0
ACE/ARBs	75.0 (100 %)
C-ant	54.0 (72.0 %)
Diuretic	48.0 (64.0 %)
Beta-blocker	21.0 (28.0 %)
Statins	75.0 (100 %)
Aspirin	75.0 (100 %)
Insulin	11.0 (15.0 %)
Oral hypoglycemic agent	56.0 (75.0 %)

Abbreviations: HDL-high density cholesterol; LDL-low density cholesterol; CAD-coronary artery disease; hs-CRP- high sensitivity CRP

Table 2
Model 1. Multivariate Stepwise logistic regression analysis for predictors of stress induced ischemia (model includes CAC)

	B	S.E.	Wald	df	Sign	OR	95%	
DM >10 year	1.855	0.221	5.110	1	0.000	3.352	2.748	6.287
ECG SSTD	1.061	0.568	6.989	1	0.000	2.176	1.984	3.277
CAC	1.487	1.578	7.413	1	0.003	2.367	1.916	3.198

Abbreviations: DM, type-2 diabetes mellitus; CAC, coronary calcium score; ECG SSTD, electrocardiogram stress ST depression; OD, odds ratio; CI, confidence interval; S.E, standard error

Table 3
Model 2. Multivariate Stepwise logistic regression analysis for predictors of stress induced ischemia (model excludes CAC)

	B	S.E.	Wald	df	Sign	OR	95% CI	
Male gender	1.942	0.931	5.259	1	0.000	2.145	1.398	3.471
HLP	**1.048**	**0.429**	**5.841**	**1**	**0.000**	**2.476**	**1.781**	**4.163**
DM >10y	1.637	1.579	7.415	1	0.003	3.732	2.296	5.731

Abbreviations: HLP- hyperlipidemia; DM, type-2 diabetes mellitus; CAC, coronary calcium score; OD, odds ratio; CI, confidence interval; S.E, standard error

Table 4
Frequency of revascularization procedures and acute coronary syndromes during follow-up period

Patients (n=75)			
	Revascularized < 30 days	**Revascularized > 30 days**	**ACS rate/2 years**
Myocardial ischemia n=18	7	1	3 (4.0%)
Normal MPS study n=57	0	1	0
CAC 1-10	0	0	0
CAC 11-99	1	0	0
CAC 100-399	6	1	0
CAC 400-999	1	0	2

Abbreviations: ACS, acute coronary syndrome; CAC, coronary calcium score; MPS, myocardial perfusion imaging

Table 5
Cox regression analysis of predictors of cardiac events

	Score	df	Significance
Age	0.149	1	0.789
HTA	0.047	1	0.816
HLP	**2.275**	**1**	0.**031**
Obesity	0.172	1	0.599
Smoking	0.001	1	0.861
DM>10	**3.125**	**1**	0.**021**
DM5-10	1.892	1	0.176
CAC>400	**1117**	**1**	0.**018**
CAC100-399	1.925	1	0.151
SDS>7	**4.173**	**1**	0.**012**
SDS<7	0.168	1	0.733

Method: Forward Stepwise (Conditional LR).
Abbreviations: HTA, Hypertension; HLP, hiper-lipidemia; DM, diabetes mellitus; CAC, calcium score; SDS, summed differential score

Table 6.
Multivariate analysis for predictors of cardiac events

	B	**S.E.**	**Wald**	**df**	**Sign**	**R**	**Exp (B)**
SDS>7	5.6271	3.924	5.2693	1	0.001	2.0371	24189.3681
DM >10y	-5.5982	2.151	4.2539	1	0.002	1,9136	0.0163

Abbreviations: DM, type, 2 diabetes mellitus; SDS, summed stress score;

Flow chart 1.

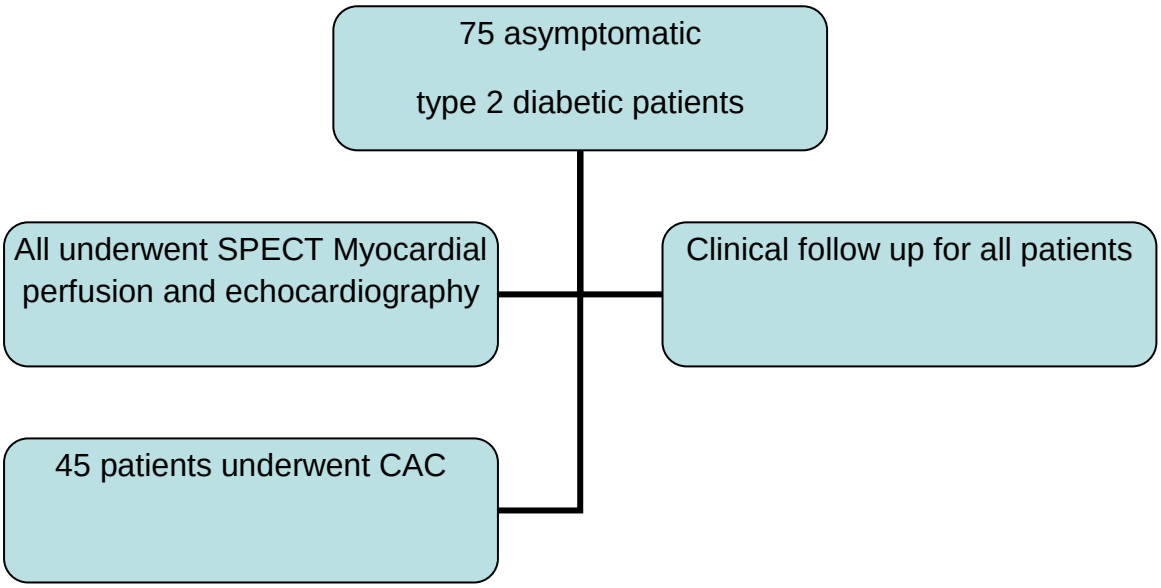


Figure 1.

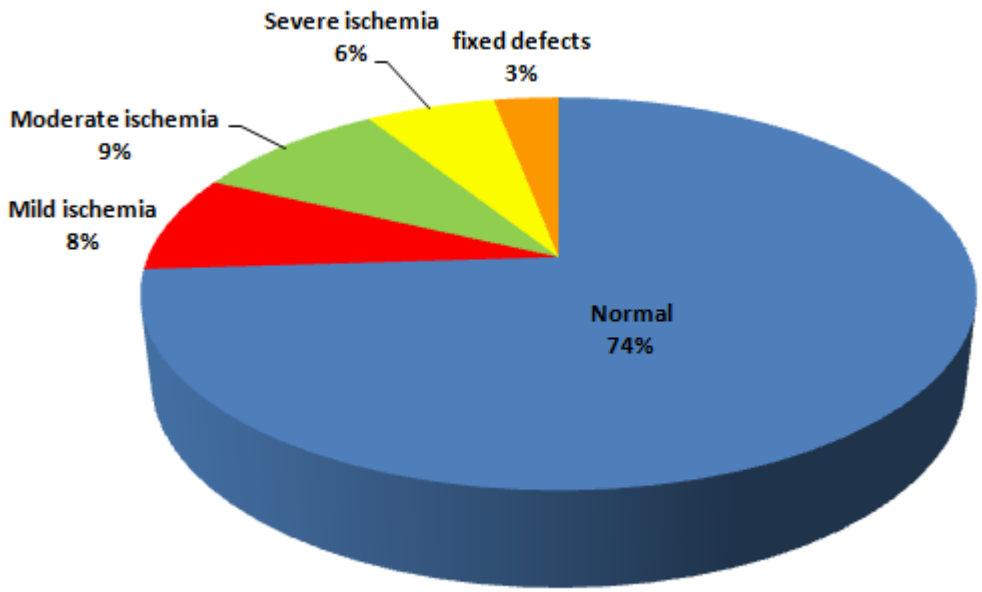


Figure 2.

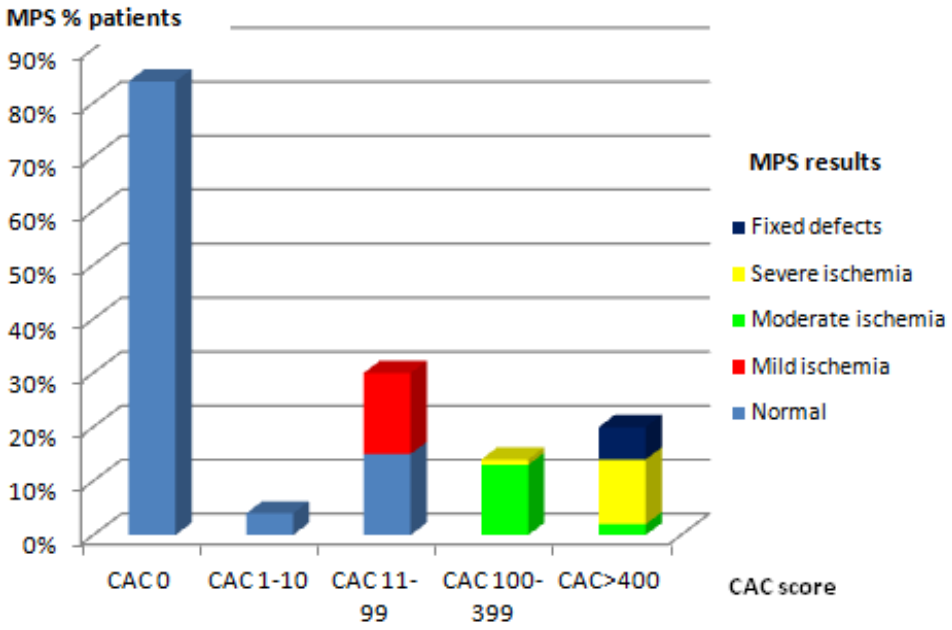
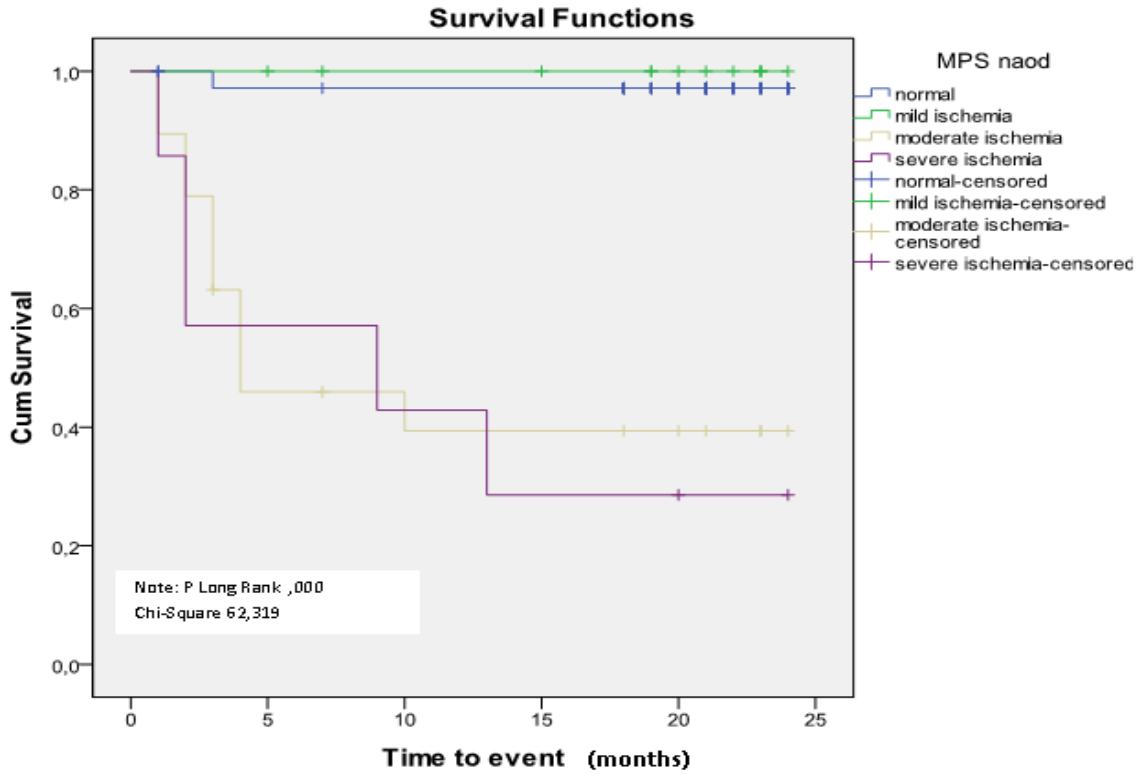


Figure 3.


Survival Functions
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
5
10
15
20
25
Time to event (months)
Note: P Long Rank ,000
Chi-Square 62,319
MPS naod
normal
mild ischemia
moderate ischemia
severe ischemia
normal-censored
mild ischemia-censored
moderate ischemia-censored
severe ischemia-censored