Original article

Factors Associated With Abnormalities On Myocardial Perfusion Scintigraphy In Diabetic Patients

Fatores Associados a Anormalidades na Cintilografia de Perfusão Miocárdica de Pacientes Diabéticos

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Abstract

Diabetes mellitus (DM) is the greatest risk factor for coronary artery disease. In addition to a long duration of diabetes, the presence of peripheral arterial disease and smoking are strong predictors of abnormalities on myocardial perfusion scintigraphy (MPS). This study aimed to assess the impact of risk factors in diabetic patients on MPS results and compare them with those of non-diabetic patients in a nuclear medicine clinic. A retrospective cross-sectional study was performed through the analysis of the medical records of patients who underwent MPS in 2010–2019. A total of 34,736 medical records were evaluated. Analyzing the stress phase of MPS, DM patients required two-fold more pharmacological stimulation than non-diabetic patients for MPS. Factors that negatively impact the MPS results were also evaluated, and DM (33.6%), insulin therapy (18.1%), systemic arterial hypertension (69.9%), dyslipidemia (53%), sedentary lifestyle (83.1%), use of pharmacological stress (50.6%), typical chest pain (8.5%), and limiting angina during the test (1.7%) were significantly associated ($p < 0.001$) with test abnormalities.

Keywords: Diabetes Mellitus; Ventilation-Perfusion Scan; Pharmacological Stress.

Resumo

O diabetes melito é o maior fator de risco para doença arterial coronariana. Além da longa duração de diabetes, outros fatores, como presença de doença arterial periférica e tabagismo são fortes preditores para anormalidades na cintilografia de perfusão do miocárdio. O objetivo deste estudo foi avaliar o impacto dos fatores de risco de pacientes diabéticos nos resultados da cintilografia de perfusão do miocárdio e comparar com os resultados de pacientes não diabéticos em uma clínica de medicina nuclear. Foi realizado um estudo transversal retrospectivo por meio da análise de prontuários de pacientes que realizaram cintilografia miocárdica no período de 2010 a 2019. Foram avaliados 34.736 prontuários. Analisando a fase de estresse da cintilografia de perfusão do miocárdio, os portadores de diabetes melito precisaram receber estímulo farmacológico duas vezes mais que os não diabéticos para sua realização. Também foram avaliados fatores que tivessem impacto negativo no resultado da cintilografia de perfusão do miocárdio, e foi visto que o diabetes melito (33,6%), a insulinoterapia (18,1%), a hipertensão arterial sistêmica (69,9%), a dislipidemia (53%), o sedentarismo (83,1%), o uso de estresse farmacológico (50,6%), a dor torácica típica (8,5%) e a angina limitante durante o teste (1,7%) estiveram associados significativamente (p<0,001) a anormalidades neste exame.

Palavras-chave: *Diabetes mellitus; Cintilografia de ventilação/perfusão; Fatores de risco.*

Introduction

Diabetes mellitus (DM) has become a disease of high prevalence, morbidity, and mortality worldwide, causing serious public health problems, especially in underdeveloped or developing countries.[1] An estimated 382 million people currently live with DM, a figure that is projected to grow to 592 million people by 2035, with around 11 million cases in Brazil.[2] About 5.1 million people died from DM complications in 2013.[3,4] This increased incidence is mainly due to population aging and new eating habits, obesity, and sedentary lifestyles, which have become common in today's society.[1,3]

DM is a major disease that has both early and late complications, all of which have poor prognosis if left untreated.[5,6]

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Manuscript received 11/23/2021; revised 2/26/2022; accepted 3/2/2022

DOI: 10.47593/2675-312X/20223501eabc274

The Framingham study pointed out that DM patients have a two- to four-fold greater risk of developing coronary heart disease than individuals without DM.[7] This happens because the atherosclerotic process progresses earlier and more rapidly in DM patients than in the general population.[2,8]

The main causes of death in patients with DM are acute myocardial infarction (AMI) and stroke, but they do not always show clinical signs and symptoms compatible with these acute arterial events, which greatly delays the start of cardiovascular treatment.[3,5] Haffner et al. estimated that patients with coronary artery disease (CAD) and DM have a greater than 70% higher risk of death within 10 years and reported that the mortality rate from cardiovascular diseases in DM patients without a history of AMI was similar to that of patients without type 2 DM and a history of AMI. In addition, the association of DM and CAD is already seen in the early stages of glucose intolerance and abnormal fasting glucose levels.[6,9]

Thus, the early diagnosis of these patients is relevant to avoiding negative outcomes. In addition to investigating traditional risk factors, cardiovascular disease screening in DM patients should also be complemented by other tests, such as electrocardiography (ECG), echocardiography, exercise stress testing, myocardial perfusion scintigraphy (MPS), and magnetic resonance imaging.[10]

The American Diabetes Association recommends that DM patients with typical or atypical symptoms of CAD or a resting ECG showing changes suggestive of AMI should undergo echocardiography or MPS under physical or pharmacological stress. The exercise test is the most indicated for asymptomatic patients aged over 35 years who are sedentary and planning to start physical activity or patients with arteriopathy (peripheral, carotid) or at least two risk factors (systemic arterial hypertension [SAH], dyslipidemia, smoking, family history of AMI, and albuminuria).[11]

MPS presents a specificity of 74% and sensitivity of 88% in CAD assessments . Nevertheless, the 2020 Brazilian Nuclear Cardiology Guideline highlights that patients at intermediate risk of ischemic heart disease benefit more from MPS than patients at low risk.[12,13]

The Basel Asymptomatic High-Risk Diabetics' Outcome Trial multicenter study of 400 DM patients without CAD history or symptoms revealed that male sex, long-term DM, peripheral arterial disease, smoking, and high systolic blood pressure were strong predictors of MPS abnormalities. When more than three factors were present, 47% of patients had abnormal scan findings. The study also showed that 22% of evaluated patients had silent CAD.[6]

In contrast, the Detection of Ischemia in Asymptomatic Diabetics clinical trial questioned the usefulness of MPS as a screening test. The study assessed 1,123 patients with type 2 DM without symptoms of coronary heart disease and previously recognized coronary disease, reporting a small rate of cardiac events not significantly reduced by myocardial ischemia screening with adenosine perfusion scintigraphy during a follow-up of 4.8 years.[7]

Thus, this study aimed to compare the impact of cardiovascular risk factors on MPS results between diabetic and non-diabetic patients.

Methods

This clinical, retrospective, cross-sectional, and observational study analyzed the medical records of patients undergoing MPS between February 2010 and May 2019 in a private nuclear medicine service in the city of Curitiba, Paraná, Brazil.

In this interval, 44,584 patients underwent MPS. Of them, 9,848 were removed for meeting the exclusion criteria (history of previous CAD, congenital heart disease, being younger than 18 years, and unknown DM status). The final sample consisted of 34,736 patients, who were divided into two groups: 7,968 (22.9%) were diabetic and 26,768 (77.1%) were non-diabetic.

The collected and analyzed variables included imaging test results (fibrosis and ischemia), age, body mass index (BMI), presence of SAH (previous documentation of blood pressure > 140/90 mmHg in two or more occasions and/or history of antihypertensive drug use), DM (previous documentation of fasting blood glucose > 126 mg/dL, blood glucose > 200 mg/dL after oral glucose tolerance test, glycated hemoglobin higher than 6.5%, and/or history of hypoglycemic drug use), dyslipidemia (low-density lipoprotein cholesterol > 100 mg/dL, triglycerides > 150 mg/dL, and/or high-density lipoprotein cholesterol < 45 mg/dL), smoking, sedentary lifestyle (aerobic physical activity for less than 30 min three times a week), chest pain (typical or atypical), positive family history of CAD, use of insulin, need for pharmacological stimulation in the stress phase of the test, and presence of angina (according to the angina index, which assesses the presence of angina during exercise testing and its test limitations).

MPS was performed by single photon emission computed tomography, in which three-dimensional and tomographic images of the heart were obtained (in the long horizontal, long vertical, and short axis views) after isotonic exercise on a treadmill or pharmacological stress in cases of patients who were unable to perform exercise; and at rest, 60 min after intravenous administration of the 99mTc-SESTAMIBI radiotracer. Transient or persistent perfusion defects were considered criteria for the diagnosis of myocardial ischemic disease, and the presence of these defects categorized the MPS findings as positive.

The data were stored in a database and subsequently analyzed using Stata software. The qualitative variables are expressed as absolute (n) and relative (%) frequencies, while quantitative variables are expressed as mean and standard deviation. Differences between quantitative variables were calculated using Student's t-test. Differences between qualitative variables were calculated using the chi-square or Fisher's exact test when indicated. The significance level was set at $p < 0.05$ (5%).

This study was authorized by the Research Ethics Committee of Positivo University (Plataforma Brasil: 4316693), which waived the need for informed consent because of its retrospective nature of data collection from medical records, lack of patient risk, and lack of directly or indirectly interfering with treatment.

Results

Of the 34,736 evaluated patients, 7,968 (22.9%) had DM; of those, 2,602 (32.6%) showed MPS changes (fibrosis and/or ischemia). As for the 26,768 (77.1%) non-diabetic evaluated patients, 19.2% underwent MPS (Table 1).

Mean age and BMI were significantly higher in patients with DM ($p < 0.001$). DM patients had a higher prevalence of SAH, dyslipidemia, and sedentary lifestyle ($p < 0.001$) and needed pharmacologically induced stress during the test. In addition, smokers ($p < 0.001$) and male subjects ($p = 0.047$) showed a higher prevalence of non-DM (Table 2).

Most participants were asymptomatic, and atypical chest pain was more prevalent than typical chest pain in both groups (Table 3). Among our population, 33,328 (95.9%) patients experienced no pain during cardiovascular stress testing (95.8% of non-diabetic versus 96% of diabetic participants). In both groups, 0.5% of the patients had angina with test limitations and just over 3% had angina without test limitations ($p = 0.88$).

The group of patients with changes on MPS had a higher rate of DM and insulin dependency, older age, higher BMI, SAH, dyslipidemia, sedentary lifestyle, use of pharmacological stress testing, chest pain, and angina during exercise testing (Table 4; $p < 0.001$). Male patients were more prevalent in the group without changes on MPS ($p < 0.001$), while smoking and a family history of CAD showed no statistically significant intergroup differences.

Table 1 – Myocardial perfusion scintigraphy results by study group.

Results	Changed		Unchanged		p value
	Diabetic	Non-diabetic	Diabetic	Non-diabetic	
	2,602 (32.7%)	5,144 (19.2%)	3,089 (67.3%)	21,624 (80.8%)	
Changes					**p<0.001**
Fibrosis + ischemia	97 (1.2%)	203 (0.8%)	---	---	
Fibrosis	129 (1.6%)	331 (1.2%)	---	---	
Ischemia	2,376 (29.8%)	4,610 (17.2%)	---	---	

Table 2 – Profiles of diabetic versus non-diabetic patients undergoing myocardial perfusion scintigraphy.

Variable	Non-diabetic (n = 26,798 [77.1%])	Diabetic (n = 7,968 [22.9%])	Valor p
Age (years)	60.03±12.91	64.92±10.58	<0.001
Men (Overall: 16,564 [47.68%])	12,842 (48.0%)	3,722 (46.7%)	0.047
Body mass index	27.62 ± 4.82	29.60 ± 5.28	<0.001
Systemic arterial hypertension	14,368 (53.7%)	6,296 (79.0%)	<0.001
Dyslipidemia	12,277 (45.9%)	5,000 (62.8%)	<0.001
Family history of CAD	4,769 (17.8%)	1,370 (17.2%)	0.2
Sedentary lifestyle	20,315 (75.9%)	6,385 (80.1%)	<0.001
Current smoking	2,663 (9.9%)	681 (8.5%)	<0.001
Pharmacological stress	7,202 (26.9%)	3,089 (38.8%)	<0.001
Insulin therapy	---	1,125 (14,1%)	---

CAD, coronary artery disease.

Discussion

DM and its effect on the cardiovascular system are associated with risk factors, with atherosclerosis being ascribed a central role in the etiology of cardiac ischemic events. The hypothesis for the initial atherosclerotic lesion is based on endothelial dysfunction, which presents as an early marker of cardiovascular disease.[14]

Traditional cardiovascular risk factors include those disrupting or attacking the oxidative metabolism of this tissue, which

Table 3 – Symptoms of diabetic versus non-diabetic patients undergoing myocardial perfusion scintigraphy.

Variable	Non-diabetic (n = 26,798 [77.1%])	Diabetic (n = 7,968 [22.9%])	P value
Chest pain			**0.002**
Absent	18.221 (68.3%)	5.511 (69.5%)	
Atypical	7.011 (26.3%)	1.947 (24.5%)	
Typical	1.439 (5.4%)	474 (6.0%)	
Angina index			**0.88**
Absence of pain	25.654 (95.8%)	7.647 (96.0%)	
Non-limiting angina	969 (3.6%)	280 (3.5%)	
Limiting angina	144 (0.5%)	41 (0.5%)	

Table 4 – Myocardial perfusion scintigraphy results by risk factors.

Variables (n; %)	Myocardial perfusion scintigraphy result		P value
	Changed (N = 7,746 [22.2%])	Unchanged (N = 26,990 [77.7%])	
Diabetes	2.602 (33.6%)	5.366 (19.9%)	<0.001
Insulin therapy	471 (18.1%)	654 (12.2%)	<0.001
Age	66.21 ± 11.92	59.70 ± 12.39	<0.001
Men	3.251 (42.0%)	13.313 (49.3%)	<0.001
Body mass index	28.50 ± 5.17	27.95 ± 4.94	<0.001
Systemic arterial hypertension	5.414 (69.9%)	15.250 (56.5%)	<0.001
Dyslipidemia	4.109 (53.0%)	13.168 (48.8%)	<0.001
Family history of coronary artery disease	1.354 (17.5%)	4.785 (17.7%)	0.61
Sedentary lifestyle	6.438 (83.1%)	20.262 (75.1%)	<0.001
Smoking	776 (10.0%)	2.568 (9.5%)	0.19
Pharmacological stress	3.907 (50.6%)	6.384 (23.7%)	<0.001
Chest pain			**<0.001**
Absent	4.960 (64.5%)	18.772 (69.8%)	
Atypical	2.080 (27.0%)	6.878 (25.6%)	
Typical	654 (8.5%)	1.259 (4.7%)	
Angina index			**<0.001**
Absence of pain	7.077 (91.4%)	26.224 (97.2%)	
Non-limiting angina	536 (6.9%)	713 (2.6%)	
Limiting angina	133 (1.7%)	52 (0.2%)	

were also seen in this study: age, male sex, SAH, dyslipidemia, hyperglycemia, sedentary lifestyle, and overweight.[14,15]

Although smoking and a family history of CAD are established risk factors in the literature, they were not statistically significant in this study. The lack of information on smoking history and on diseases affecting family members interfered with the research results.

Endothelial dysfunction has been documented in patients with DM, insulin resistance, or a high risk for the development of type 2 DM. Such patients require multidisciplinary follow-up to stop the progression of DM complications and assess the prognosis.[14]

Our sample demonstrated that DM is such an important risk factor that it stands out compared to others. Of all variables analyzed, DM is an alarming risk factor, alone or in combination.

During examination, patients are subjected to exercise stress testing or pharmacological stress testing to assess the cardiac response to exertion. DM patients may be unable to complete a symptom-limited exercise test due to obesity, peripheral vascular disease, or peripheral neuropathy, thus requiring pharmacological stress testing. In this study, the use of pharmacological stress and the presence of chest pain were higher in DM patients, being linked to more MPS changes than in non-diabetic patients.[7]

Studies by Caobelli F et al and Bourque JM et al also discussed the relationship between these factors. Both stated that a greater need for pharmacological stress is related to the presence of more comorbidities and physical limitations, consequently leading to a worse prognosis. Caobelli reinforced that diabetic patients tend to have worse health conditions (presence of peripheral arterial disease, lower aerobic capacity, reduced strength compared to healthy patients, and others). The author also emphasized that the longer the DM duration, the greater the limitations and risk of complications.[16,17]

The present study has some biases that limit its objectivity. The first is its sample, since the participants undergoing MPS had clinical indications and were not randomly selected from the general population. Another challenge was the scarcity of data on continuous-use medications, time of DM progression, smoking history, complete lipid profile, and adequate comorbidity and symptom control related to the MPS results. We emphasize that the patient profiles involved healthcare bias due to the presence of multiple comorbidities and the need for increased health care. DM patients more commonly require frequent medical appointments and greater attention to their health, which could have caused statistically significant changes.

Conclusion

Diabetic patients had a higher prevalence of risk factors and abnormal MPS results than non-diabetic patients. Thus, DM, physical inactivity, arterial hypertension, dyslipidemia, typical chest pain, limiting angina during pharmacological stress, need for pharmacological stress testing, and insulin therapy significantly influenced the test results. In addition, DM patients have a greater need for pharmacological stimulation to undergo MPS testing than non-diabetic patients.

Authors' contributions

Research conception and design: LAF Bettini, MG Dopheide; Data collection: AC Freitas, LAF Bettini; Data analysis and interpretation: MG Dopheide, H Porath; Statistical analysis: AL Cruz, BS Watanabe; Manuscript writing: BS Jaya, AC Freitas; Critical review of the manuscript for important intellectual content: H Bigarella, H Porath, L Moreira.

Conflict of interest

The authors have declared that they have no conflict of interest.

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