

Application of Anatomical and Functional Modalities in Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Patients- A Review Article

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Abstract

Cardiovascular disease (CAD) screening in asymptomatic patients with diabetes mellitus is controversial. An exercise stress test is a safe and effective initial testing for Ischemic Heart Disease (IHD) screening. Treadmill stress test is not the best screening method for a particular patient who is not able to exercise, abnormal electrocardiogram (ECG) or positive exercise treadmill test (ETT) and other anatomical or functional studies are recommended to evaluate for the myocardial ischemia. This concept is supported by the high rate prevalence of silent myocardial ischemia, CAD and cardiovascular events rate. Coronary angiography is an expensive and invasive test which is considered as gold standard for diagnosis obstructive CAD and not be used for screening. In this review article we discussed about anatomical modalities (Coronary Artery Calcium Score (CACs)) and nuclear imaging (SPECT) for evaluation of silent ischemia.

Keywords: Cardiovascular disease, Ischemic heart disease, Treadmill test.

Introduction

American Centers for Disease Control and Prevention (CDC) reported approximately 21 million people have diabetes mellitus (DM) in the United States which 15million with and 6 million without diagnosis of diabetes (1). More than 95% of this patients have type 2 diabetes.(1)

Diabetic patients have an increased risk of developing coronary artery disease (CAD) and hard cardiovascular event compared to the non-diabetic people. Prevalence of CAD in diabetic patients was reported about 43% to 53% without considering age and gender.(2,3) Diabetic patients have progressive disease

with decreased survival compared to general population. (4-8)

Mechanism of silent ischemia in diabetes mellitus:

CAD is a main reason of mortality in diabetic patients. (9) It is essential that diabetic patients at risk of cardiovascular disease (CVD) which should be detected as early as possible. Most burden of DM is related to CVD. (8) Atypical angina and silent ischemia are frequently seen in diabetic patients and these manifestations are a major challenge in detection of CAD in patients with DM (10).

About 25% of diabetic patients have evinced of Myocardial infarction in ECG; however 50% of them were asymptomatic. (11) Cardiac autonomic neuropathy is likely related to increased risks of silent myocardial ischemia but predictive value was low. (12)

Increased in vitro platelet activation is coincidence with cardiac autonomic dysfunction which may be associated with myocardial perfusion abnormality and coronary vasculopathy. Suggested that cardiac autonomic dysfunction was most strong predictor for silent ischemia (13). Also male gender, diabetes duration were strong predictors of reversible ischemia. (13)

A smaller amount of diabetic patients with positive myocardial perfusion scan revealed angina during exercise compared to general population (14-15). The prevalence of silent ischemia in patients with diabetes was unclear and studies reported a difference range 21% to 59%. (14-16)

Endothelial dysfunction:

Endothelial dysfunction could contribute the pathogenesis of vascular disease in patients with diabetes mellitus. Additionally myocardial perfusion abnormalities in patients

without obstructive epicardial CAD are associated with endothelial dysfunction. (17) Trial evidences revealed diabetes mellitus and insulin resistance are associated with endothelial dysfunctions, which could accentuate atherosclerosis process. (18) Also vasodilator response nitric oxide (NO)-mediated vasodilation is impaired in diabetic patients. (19,20)

In Asymptomatic diabetic patients without obstructive epicardial CAD abnormal myocardial perfusion is a common finding which is associated with endothelial dysfunction. (20)

Clinical factors and silent myocardial ischemia:

Numerous studies suggest several clinical factors to predict silent ischemia including:

Traditional risk factors for CAD, micro/macro albuminuria, retinalvasculopathy, HbA1c, BMI, period of diabetes, C-reactive protein, peripheral neuropathy disease, lipoprotein (a), peripheral arterial disease, and cardiac autonomic dysfunction. (21-25)

The above mentioned predictors can be useful for selection CAD screening tests.

Screening modalities:

When the high-risk diabetic patients were selected, it is important to choose the optimal test to discover Silent myocardial ischemia (SMI) and CAD.

Although resting ECG is suggested annually, due to its low negative predictive value in patients with normal ECG that including major diabetic population, ECG is not recommended to screening silent myocardial ischemia alone. (26)

Stress test with physical exercise is first choice method for detection of CAD; however it is related to the ability to reach an adequate 85%

of the target heart rate. But in diabetic population exercise capacity was reduced and achieve to maximal heart rate is not ever possible in these patients because of obesity, peripheral vessel disease, peripheral neuropathy and other co-morbidities. (25-26) Third to half of this population were not able to reach optimal exercise stress test level. (26) Therefore unable patients were appropriate candida for pharmacologic stress test.

Single Photon Emission Computed Tomography:

Clinical role of Single Photon Emission Computed Tomography (SPECT), as a non-invasive method to evaluation myocardial perfusion is increasing universal, mainly in the screening. Medical stress test with SPECT imaging assesses myocardial ischemia with sensitivity of 91-96% and specificity of 75-82%.

SPECT myocardial perfusion scan is a confirmed nuclear medicine method for detection of myocardial ischemia. gated SPECT is perfusion images which synchronized with ECG and provide information about cardiac function including left ventricular ejection fraction (LVEF), end diastolic and end systolic volumes, regional LV function (wall motion and wall thickening) and diastolic parameter. The data of gated SPECT has incremental prognostic value more than coronary angiography in patients with known or suspected CAD. (27)

The nuclear cardiology advantages are more than clinical findings, Stress and resting ECG, as it defines the severity and extent of ischemic myocardium. Reversible perfusion abnormality in SPECT can describe a silent ischemia in diabetics. (27)

Stress test can be performed with exercise stress test and pharmacologic stress test

(dipyridamole, adenosine). The incremental prognostic value of pharmacologic myocardial perfusion imaging (MPI) is comparable with exercise stress test. (28)

SPECT has higher sensitivity and specificity than ECG stress test for detection if myocardial ischemia. Also Sensitivity and specificity of Stress MPI is equal in nondiabetics and diabetics population. (29)

Coronary Artery Calcium Score (CACS):

Some studies suggested strong association between the coronary calcium and theatheromatous plaque burden. (30,31) Valuation of subclinical coronary atherosclerosis with CACS (table 1) make an available chance to identify asymptomatic patients who are high risk (32) Moreover, coronary calcium can predict future coronary events (33,34) .In diabetic patients CACS can be an effective test for detection of silent CAD. Presence of DM may be considered as a CACS indication regardless the risk of CAD. In comparison with non-diabetic population diabetic patients have higher CACS (35) and diabetes was the strongest predictor for a higher CAC score. Additionally CACS was an independent predictor of primary cardiovascular endpoint events such as coronary death, nonfatal MI, coronary revascularization, as well as stork. (36,37)

CACS are associated with obstructive CAD in angiography. CACS of 0 nearly ruled out significant angiographic CAD and suggested that diabetic patients with no visible coronary calcium had excellent survival. There was not detected significantly difference in comparison with non-diabetic population.

Computed Tomographic Angiography:

Table 1. Coronary artery calcium score (CACS)

CAC score agatston unit	Coronary calcification category
0	Absent
1-10	Minimal
11-100	Mild
101-400	Moderate
401-1000	Severe
>1000	Extensive

CT Angiography is a noninvasive technique that used intravenous contrast injection to visualize the contrast-filled coronary vessels. coronary computed tomographic angiography (CCTA) is a non-invasive test that reveals information about CAD lesion location, severity, and characteristics of atherosclerotic plaque.(38)

As shown in asymptomatic diabetic patients, frequency of atherosclerosis was 64% to 91.4% and significant CAD were observed in 26% to 33.3%. (39-41) and significant CAD is associated with a poorer prognosis and some lesions were located in the Left Main (LM) or proximal LAD artery. Also prognostic role of CCTA in diabetic patients is documented. (42) About one third of diabetic patient with no symptom had significant CAD on CCTA and who are at high risk for cardiac events. CCTA may have a potential role in identifying patients. Some asymptomatic diabetic patients with zero CACS had significant CAD on CTA (43) which suggest additional value of CCTA more than CACS for the evaluation of CAD in asymptomatic type 2 diabetic population. Also suggested that 10% of diabetic patients with negative CACS had non-calcified plaques on CCTA (44). About 2% of patients with CAC scores < 100 Au revealed evidence of ischemic on MPS. About 20% of patient with CAC scores > 1000 Au showed ischemia on MPS.(45)

All patients with a CAC score between 0 and 10 had normal SPECT and good outcome (figure1). Also 23% positive SPECT was seen in asymptomatic diabetic population that who had a CAC of 101 to 400. Prevalence of silent myocardial ischemia in Patients with CAC more than 400 had a 48% and this number increased in CAC > 1.000. (46) .Although

some studies were reported minimal higher sensitivity for CCTA about 50% of patients with positive CCTA had normal MPI which this findings suggest non-flow limiting coronary lesion in CTA without functionally significance. (47)

To use of MPI or CTA for detection of CAD two major questions is considered: first, degree of correlation between CTA and MPI and second, supplementary role of these modalities.

There is frequently a considerable discrepancy between severity of coronary lesion evaluated by CTA and MPI results. MPI and CTA make available complementary anatomical and functional data, which stenotic lesion on anatomical imaging (CCTA or invasive angiography) is not necessarily associated with a hemodynamically significance necessarily.

Also a positive MPI is not necessarily associated with a significant luminal stenosis on anatomical imaging (48-50). An abnormal CTA in the presence of a good coronary flow reserve on MPI is suggestive of subclinical atherosclerosis and aggressive medical therapy should be considered for this cases. (50)

If CTA was used as first non-invasive method to detection of CAD, regarding the CTA findings what type results should be referred to MPI?

Lesions equal or more than 70% in CCTA had hemodynamically significant and abnormal MPI and coronary angiography may be considered as further test regarding the clinical data. CTA lesions less than 50% are associated with normal MPI totally therefore no other testing is suggested. Myocardial perfusion scintigraphy is considered as further testing for lesion 50% to 69% delineated on CCTA (51)

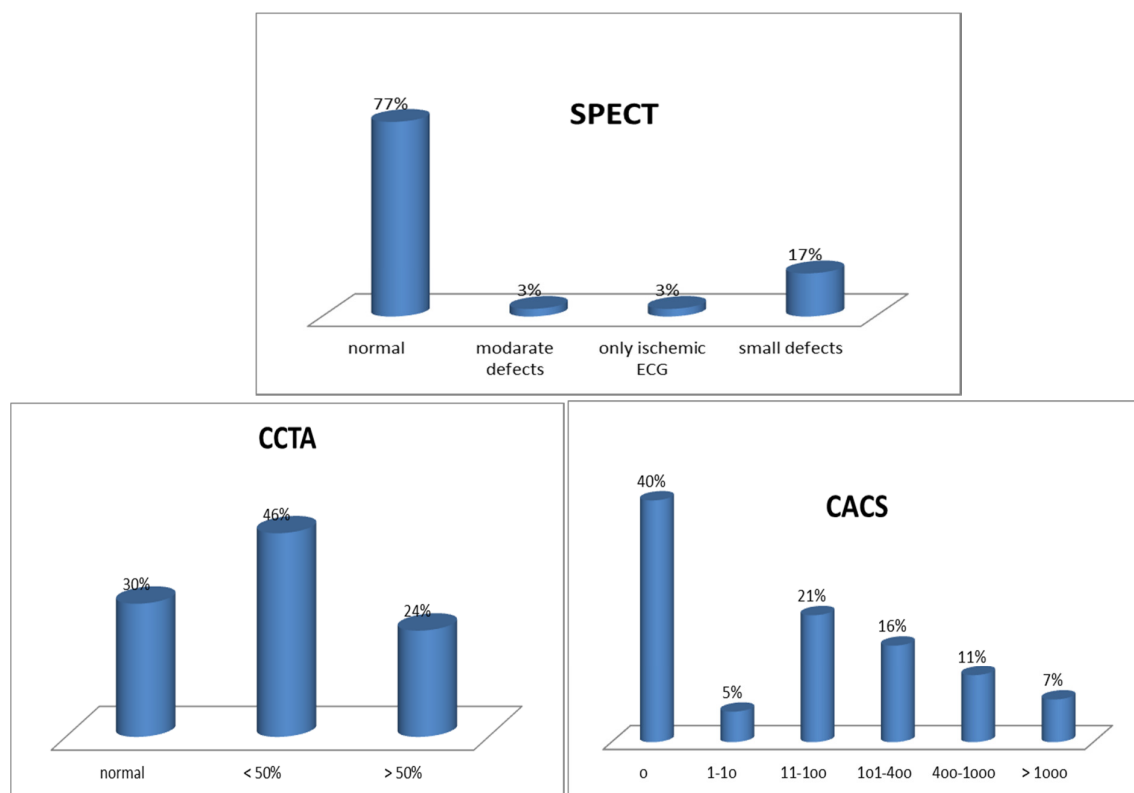


Figure 1. Distribution of findings on SPECT, CAC score and CCTA 2 in asymptomatic diabetic patients. (Source: Scholte AJHA, et al: Different manifestations of coronary artery disease by stress myocardial perfusion imaging, coronary calcium scoring, and multislice CT coronary angiography in asymptomatic patients with type 2 diabetes mellitus, J NuclCardiol 15:503-9, 2008.) 54

Difference algorithms suggested for screening of myocardial ischemia in diabetic patients which two algorithms are noticed in this review article. (52,53)

Implication:

Screening in asymptomatic patients with diabetes is controversial. An exercise stress test is a safe and effective initial testing for IHD screening. Treadmill stress test is not the best screen tests for a particular patient who not able to exercise, abnormal ECG or positive ETT and other anatomical or functional studies are recommended to evaluate for the myocardial ischemia. This concept is supported by the high rate prevalence of CAD and cardiovascular events rate.

Coronary angiography is an expensive and invasive test which is considered as gold

standard for diagnosis obstructive CAD (figure 2).

Conclusion

Noninvasive imaging modalities are useful in diagnostic and prognostic evaluation of coronary artery disease in diabetic. Although there is not enough evidence that confirmed screening silent ischemia is necessary, some clinical predictors (such as traditional risk factors for CAD, micro/macro albuminuria, retinal vasculopathy, HbA1c, BMI, period of diabetes, C-reactive protein, peripheral neuropathy disease, lipoprotein (a), peripheral arterial disease, and cardiac autonomic dysfunction) can help us to selection appropriate criteria to choice proper screening tests in asymptomatic diabetic patients.

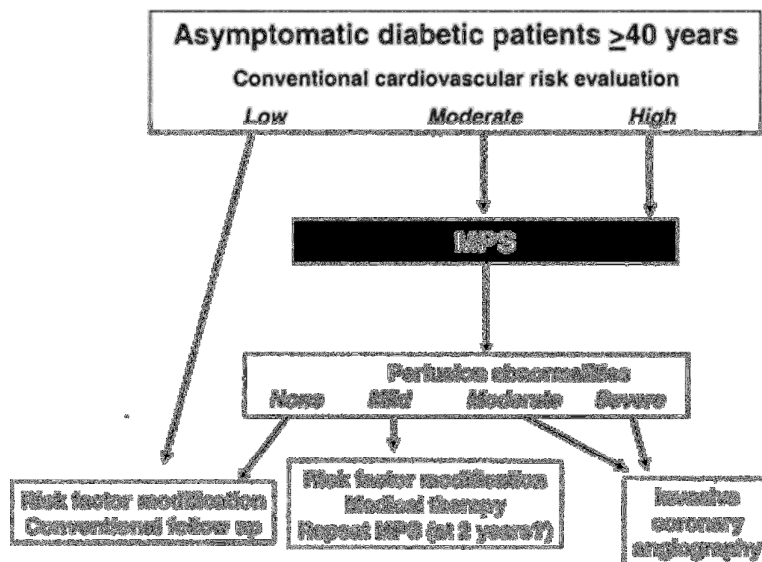


Figure2. Algorithm for Risk Assessment and Management in Asymptomatic Type 2 Diabetic Patients (Adapted with permission from Bax JJ, et al: The potential of myocardial perfusion scintigraphy for risk stratification of asymptomatic patients with type 2 diabetes. Journal of the American College of Cardiology. 2006;48(4):754-60)

Figure2. Algorithm for detection of silent ischemia in Asymptomatic Type 2 Diabetic Patients (source: Peix A. Usefulness of nuclear cardiology techniques for silent ischemia detection in diabetics. MEDICC review. 2013;15(1):33-6.)

References

- Centers for Disease Control and Prevention mortality database: Available at: www.cdc.gov.
- Morrish N, Stevens L, Head J, Fuller J, Jarrett R, Keen H. A prospective study of mortality among middle-aged diabetic patients (the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics) II: associated risk factors. Diabetologia. 1990;33(9):542-8.
- Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia. 1987;30(3):123-31.
- Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. Jama. 1979;241(19):2035-8.
- Granger CB, Califf RM, Young S, Candela R, Samara J, Worley S, et al. Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. Journal of the American College of Cardiology. 1993;21(4):920-5.
- Hammoud T, Tanguay J-F, Bourassa MG. Management of coronary artery disease: therapeutic options in patients with diabetes. Journal of the American College of Cardiology. 2000;36(2):355-65.
- Jacoby RM, Nesto RW. Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course and prognosis. Journal of the American college of cardiology. 1992;20(3):736-44.
- Tabibiazar R, Edelman SV. Silent ischemia in people with diabetes: A condition that must be heard. Clinical Diabetes. 2003;21(1):5-9.
- Farahani VD-A, Razavi-ratki SK, Namiranian N, Emami-Meybodi M, Nough H, Razavi H, et al. Transient Ischemic Dilatation Ratio in Stress Myocardial Perfusion SPECT in Diabetic Patients- A Systematic Review and Meta-Analysis.
- Nesto RW, Phillips RT, Kett KG, Hill T, Perper E, Young E, et al. Angina and exertional myocardial ischemia in diabetic and nondiabetic patients:

- assessment by exercise thallium scintigraphy. *Annals of internal medicine*. 1988;108(2):170-5.
11. Boland LL, Folsom AR, Sorlie PD, Taylor HA, Rosamond WD, Chambless LE, et al. Occurrence of unrecognized myocardial infarction in subjects aged 45 to 65 years (the ARIC study). *The American journal of cardiology*. 2002;90(9):927-31.
 12. Allman KC, Stevens MJ, Wieland DM, Hutchins GD, Wolfe ER, Greene DA, et al. Noninvasive assessment of cardiac diabetic neuropathy by carbon-11 hydroxyephedrine and positron emission tomography. *Journal of the American College of Cardiology*. 1993;22(5):1425-32.
 13. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes care*. 2004;27(8):1954-61.
 14. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *Journal of the American College of Cardiology*. 2006;47(1):65-71.
 15. 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.
 16. Rajagopalan N, Miller TD, Hodge DO, Frye RL, Gibbons RJ. Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *Journal of the American College of Cardiology*. 2005;45(1):43-9.
 17. Djaberri R, op't Roodt J, Schuijff JD, Rabelink TJ, de Koning EJ, Pereira AM, et al. Endothelial dysfunction in diabetic patients with abnormal myocardial perfusion in the absence of epicardial obstructive coronary artery disease. *Journal of nuclear medicine*. 2009;50(12):1980-6.
 18. Boden G, Shulman G. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and β -cell dysfunction. *European journal of clinical investigation*. 2002;32(s3):14-23.
 19. Williams SB, Cusco JA, Roddy M-A, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *Journal of the American College of Cardiology*. 1996;27(3):567-74.
 20. Kaminek M, Myslivecek M, Skvarilova M, Weinbergova O, Metelka R, Husak V, et al. [Prognostic significance of stress tomographic scintigraphy of myocardial perfusion in diabetic patients]. *Vnitřní lékařství*. 2001;47(11):739-43.
 21. Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V. Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes care*. 1999;22(9):1396-400.
 22. Gazzaruso C, Garzaniti A, Giordanetti S, Falcone C, De Amici E, Geroldi D, et al. Assessment of Asymptomatic Coronary Artery Disease in Apparently Uncomplicated Type 2 Diabetic Patients A role for lipoprotein (a) and apolipoprotein (a) polymorphism. *Diabetes care*. 2002;25(8):1418-24.
 23. on Atherosclerosis MS. Prevalence of Unrecognized Silent Myocardial Ischemia and Its Association With Atherosclerotic Risk Factors in Noninsulin-Dependent Diabetes Mellitus. *The American Journal of Cardiology*. 1997;79(2):134-9.
 24. Rutter MK, McComb JM, Brady S, Marshall SM. Silent myocardial ischemia and microalbuminuria in asymptomatic subjects with non-insulin-dependent diabetes mellitus. *The American journal of cardiology*. 1999;83(1):27-31.
 25. Langer A, Freeman MR, Josse RG, Steiner G, Armstrong PW. Detection of silent myocardial ischemia in diabetes mellitus. *The American journal of cardiology*. 1991;67(13):1073-8.
 26. Vanzetto G, Halimi S, Hammoud T, Fagret D, Benhamou PY, Cordonnier D, et al. Prediction of cardiovascular events in clinically selected high-risk NIDDM patients. Prognostic value of exercise stress test and thallium-201 single-photon emission computed tomography. *Diabetes Care*. 1999;22(1):19-26.
 27. Gimelli A, Rossi G, Landi P, Marzullo P, Iervasi G, L'Abbate A, et al. Stress/rest myocardial perfusion abnormalities by gated SPECT: still the best predictor of cardiac events in stable ischemic heart disease. *Journal of Nuclear Medicine*. 2009;50(4):546-53.
 28. 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. *American heart journal*. 1999;138(6):1025-32.
 29. Kang X, Berman DS, Lewin H, Miranda R, Erel J, Friedman JD, et al. Comparative ability of myocardial perfusion single-photon emission computed tomography to detect coronary artery disease in patients with and without diabetes mellitus. *American heart journal*. 1999;137(5):949-57.
 30. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *Journal of the American College of Cardiology*. 2000;36(4):1253-60.
 31. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score

- combined with Framingham score for risk prediction in asymptomatic individuals. *Jama*. 2004;291(2):210-5.
32. Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Journal of the American College of Cardiology*. 2004;44(3):720-32.
 33. O'Malley PG, Taylor AJ, Jackson JL, Doherty TM, Detrano RC. Prognostic value of coronary electron-beam computed tomography for coronary heart disease events in asymptomatic populations. *The American journal of cardiology*. 2000;85(8):945-8.
 34. Raggi P, Callister TQ, Cooil B, He Z-X, Lippolis NJ, Russo DJ, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation*. 2000;101(8):850-5.
 35. Mielke C, Shields J, Broemeling L. Coronary artery calcium, coronary artery disease, and diabetes. *Diabetes research and clinical practice*. 2001;53(1):55-61.
 36. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *Journal of the American College of Cardiology*. 2004;43(9):1663-9.
 37. Qu W, Le TT, Azen SP, Xiang M, Wong ND, Doherty TM, et al. Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects. *Diabetes Care*. 2003;26(3):905-10.
 38. Choi E-K, Choi SI, Rivera JJ, Nasir K, Chang S-A, Chun EJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. *Journal of the American College of Cardiology*. 2008;52(5):357-65.
 39. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Prevalence of subclinical atherosclerosis in asymptomatic diabetic patients by 64-slice computed tomography. *Coronary artery disease*. 2008;19(3):195-201.
 40. Scholte AJ, Schuijf J, Kharagjitsingh AV, Jukema WJ, Pundziute G, Van der Wall EE, et al. Prevalence of coronary artery disease and plaque morphology by multi slice computed tomography in asymptomatic patients with type 2 diabetes. *Circulation*. 2007;116(16):II_837.
 41. Rivera JJ, Nasir K, Choi E-K, Yoon YE, Chun E-J, Choi S-i, et al. Detection of occult coronary artery disease in asymptomatic individuals with diabetes mellitus using non-invasive cardiac angiography. *Atherosclerosis*. 2009;203(2):442-8.
 42. Rana JS, Dunning A, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, et al. Differences in Prevalence, Extent, Severity, and Prognosis of Coronary Artery Disease Among Patients With and Without Diabetes Undergoing Coronary Computed Tomography Angiography Results from 10,110 individuals from the CONFIRM (CORonary CT Angiography Evaluation For Clinical Outcomes): an International Multicenter Registry. *Diabetes care*. 2012;35(8):1787-94.
 43. Park G-M, Lee S-W, Cho Y-R, Kim CJ, Cho JS, Park M-W, et al. Coronary computed tomographic angiographic findings in asymptomatic patients with type 2 diabetes mellitus. *The American journal of cardiology*. 2014;113(5):765-71.
 44. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schömig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *Journal of the American College of Cardiology*. 2006;48(2):312-8.
 45. Berman DS, Wong ND, Gransar H, Miranda-Peats R, Dahlbeck J, Hayes SW, et al. Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *Journal of the American College of Cardiology*. 2004;44(4):923-30.
 46. Anand DV, Lim E, Hopkins D, Corder R, Shaw LJ, Sharp P, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *European heart journal*. 2006;27(6):713-21.
 47. Schuijf JD, Wijns W, Jukema JW, Atsma DE, de Roos A, Lamb HJ, et al. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. *Journal of the American College of Cardiology*. 2006;48(12):2508-14.
 48. Di Carli MF, Dorbala S, Curillova Z, Kwong RJ, Goldhaber SZ, Rybicki FJ, et al. Relationship between CT coronary angiography and stress perfusion imaging in patients with suspected ischemic heart disease assessed by integrated PET-CT imaging. *Journal of Nuclear Cardiology*. 2007;14(6):799-809.
 49. Hacker M, Jakobs T, Hack N, Nikolaou K, Becker C, von Ziegler F, et al. Sixty-four slice spiral CT angiography does not predict the functional relevance of coronary artery stenoses in patients with stable angina. *European journal of nuclear medicine and molecular imaging*. 2007;34(1):4-10.
 50. Gaemperli O, Schepis T, Koepfli P, Valenta I, Soyka J, Leschka S, et al. Accuracy of 64-slice CT angiography for the detection of functionally relevant coronary stenoses as assessed with myocardial perfusion SPECT. *European journal of nuclear medicine and molecular imaging*. 2007;34(8):1162-71.

51. Nicol ED, Stirrup J, Reyes E, Roughton M, Padley SP, Rubens MB, et al. Sixty-four-slice computed tomography coronary angiography compared with myocardial perfusion scintigraphy for the diagnosis of functionally significant coronary stenoses in patients with a low to intermediate likelihood of coronary artery disease. *Journal of Nuclear Cardiology*. 2008;15(3):311-8.
52. Peix A. Usefulness of nuclear cardiology techniques for silent ischemia detection in diabetics. *MEDICC review*. 2013;15(1):33-6.
53. Bax JJ, Bonow RO, Tschöpe D, Inzucchi SE, Barrett E. The potential of myocardial perfusion scintigraphy for risk stratification of asymptomatic patients with type 2 diabetes. *Journal of the American College of Cardiology*. 2006;48(4):754-60.
54. Zaret BL, Beller GA. *Clinical nuclear cardiology: state of the art and future directions*: Elsevier Health Sciences; 2010