The Relationship between Retinopathy in Diabetes Mellitus Type 2 and Severity and Extent of Myocardial Ischemia in Myocardial Perfusion Imaging

Hadi Malek[1] MD, Raheleh Hedayati [2] MD, Nahid Yaghoobi[3*] MD, Mehdi Behnia[4] MD, Fereydoon Rastgou[1] MD, Ahmad Bitarafan Rajabi[1] PhD , Hedieh Amouzadeh[5] MD, Shirin Hosseini[6] Msc, Hassan Firoozabadi[3] MD

Abstract

Objectives: Diabetes mellitus type 2 (DM2) is one of the leading causes of morbidity and mortality owing to its role in the development of cardiovascular disease. This study sought to evaluate the relationship between diabetic retinopathy (DR) and myocardial ischemia using myocardial perfusion imaging (MPI).

Materials and Methods: Thirty-three patients with DM2 (age =59 ± 8 years) were examined for evidence of DR. The subjects were divided into two groups on the basis of the presence [DR(+)] or absence [DR(-)] of diabetic retinopathy. MPI was performed for all the patients as well.

Results: Eighteen and fifteen patients were categorized as DR(+) and DR(-), respectively. Ischemia was significantly more frequent in the DR(+) group than in the DR(-) group (p <0.05). There was also a positive association between the grade of retinopathy and the grade of ischemia (odds ratio (OR)[confidence interval (CI)95%] =7.1 [1.7-29.6], p =0.007). Severe nonproliferative/proliferative DR was independently related to the summed difference and summed stress scores (β=13.2, p =0.024 and β=15.4, p =0.013, respectively).

Conclusion: The results of our study suggest that the presence of DR increases the risk of abnormal perfusion and the degree of retinopathy is correlated with the extent and severity of ischemia in patients with DM2. ***(Iranian Heart Journal 2013; 13(4):6-14).***

Keywords: Diabetes mellitus ■ Diabetic retinopathy ■ Ischemic heart disease ■ Myocardial perfusion imaging

Received January 2013; Accepted for publication January 2013

1- Assistant Professor , Department of Nuclear Medicine and Molecular Imaging, Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran
2- Resident of Nuclear Medicine, Department of Nuclear Medicine and Molecular Imaging, Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran
3- Associate Professor, Department of Nuclear Medicine and Molecular Imaging, Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran
4- Noor Eye Hospital Ophtalmology Research Center, Tehran, Iran
5- Department of Nuclear Medicine and Molecular Imaging , Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran
6- Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran
Corresponding Author:** Nahid Yaghoobi,MD; ***nyaghoobi@yahoo.com, Department of Nuclear Medicine and Molecular Imaging, Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Vali-Asr Ave., Nyayesh Blvd., 19969911151, Tehran, Iran. Tel : +989121031582, Fax: +982122042026
Source of support: The authors hereby declare that they received no support for their work in the any form, including grants and equipments.

Background

Diabets mellitus (DM) is known as the most common metabolic disorder on a global scale. Type 2 diabetes mellitus (DM2) accounts for more than 90% of all cases. Coronary artery disease (CAD) is known as the leading cause of premature morbidity and mortality in DM2 patients insofar as it is responsible for 75% of all cardiovascular-related deaths [1-2]. Moreover, CAD is associated with an unfavorable prognosis in diabetic patients and is usually more advanced at the time of diagnosis, partly as a result of silent myocardial ischemia [3]. The ever-increasing incidence of DM and the higher risk of cardiovascular-related events in its sufferers raise the necessity for screening ischemic heart disease in this population.

For all the debate over the advisability of large-scale screening in asymptomatic individuals with diabetes, positive screening tests and aggressive treatment have significant implications in the clinical management of these patients [4]. Indeed, the American Diabetes Association (ADA), in addressing the significance of the early diagnosis of CAD, recommended specialized screening for diabetic patients deemed high risk [1, 5, 6]. Over the years, multiple simple and inexpensive clinical markers have been proposed in order to identify a subgroup of diabetic patients at higher risk; these markers include retinal vasculopathy [7], micro/macro albuminuria [8], peripheral neuropathy, C-reactive protein, hemoglobin A1c, lipoprotein (a) [9], peripheral arterial disease [10], and cardiac autonomic dysfunction [11].

Many of these variables have a limited practical use in diabetic patients because of either their high prevalence in this population or their suboptimal diagnostic accuracy and inconsistent association with ischemia in various published studies [4, 7]. The presence of diabetic retinopathy as an early and frequent sign of vascular complication has been shown to correlate with the risk for macroangiopathies, which incorporate CAD [11, 12].

Myocardial perfusion imaging (MPI) has greatly improved the diagnosis of CAD amongst clinically suspected patients [13]. Hence, we investigated the association between the presence of diabetic retinopathy along with its severity and myocardial perfusion abnormalities in DM2 patients.

A significant association would allow the usage of diabetic retinopathy as an indicator for the detection of diabetic patients at an increased risk for myocardial perfusion abnormalities and as a marker for the selection of a subgroup of diabetic patients, in whom non-invasive screening with MPI would be warranted.

Material and Methods

This study included 45 DM2 patients, 12 of whom met our exclusion criteria, comprising a history of myocardial infarction or known coronary artery disease, heart failure, uncontrolled hypertension (>180/100 mm Hg), ketoacidosis, acute dysregulation of DM or HbA_1c >9.5%, severe chronic or acute illness, type 1 diabetes mellitus, and known non-diabetic retinal disease. Therefore, following approval by the institutional Ethics Committee, 33 DM2 patients (7 men, 26 women, aged 46-70 years with a duration of 9.1 ± 7.8 years) with no history of prior myocardial infarction or revascularization consented to undergo concurrent fundoscopy in addition to MPI between April and February 2011 in Rajaie Cardiovascular, Medical and Reasearch Center.

All the patients underwent two-day stress-rest protocol, using 99mTc-Sestamibi with an injection dose of 740 MBq in each phase of the study. Post-stress images were obtained either after exercise (16 cases) or after the intravenous administration of

Dipyridamole (17 cases), according to standard protocols [14]. A series of two acquisitions, comprised of post-stress and resting-state acquisitions, was performed for all the patients.

Single-photon emission computed tomographic (SPECT) acquisitions were conducted in the step-and-shoot mode with 32 thirty-second projections, a zoom factor of 1.46, and in a non-circular 180° arc (45° RAO-to-LPO) with a PHILIPS BrightView dual-head gamma camera (USA), equipped with low-energy, high-resolution (LEHR) collimators and an automated body contour detection system. Gated MPI was carried out for all the subjects in the post-stress phase with an acceptance window of 30%. All the data were stored in a 64×64×16 computer matrix and reconstructed with three-dimensional ordered subset expectation maximization (3D-OSEM), using two iterations and eight subsets [15].

The rotating raw images of all the participants were seen visually, and studies with motion artifacts or low-count density were excluded.

The reconstructed and reoriented images were then read independently by two experienced nuclear physicians, blinded to the results of fundoscopy, using the AutoQUANT® 7.0 software for cardiac quantification and functional analysis.

All the images were analyzed both visually and semi-quantitatively on the basis of 17-segment scoring. The summed difference score (SDS) was used for a semi-quantitative evaluation of myocardial ischemia, and ischemia was classified as mild (SDS≤8), moderate (8<SDS≤12), and severe (SDS>13).

Fundoscopic Examination

The presence of diabetic retinopathy was assessed by an experienced ophthalmologist through fundoscopic examination, following mydriasis with Mydrax® 1% in patients with no contraindication. The patients were thereafter divided into two groups of DR(+) and DR(-) on the basis of the presence or absence of diabetic retinopathy, respectively.

Retinopathy was classified as mild nonproliferative, moderate nonproliferative, and severe nonproliferative/proliferative subgroups according to a guideline-based algorithm.

Statistics

The chi-squared test was employed for the categorical and the Student t-test and Mann-Whitney U test for the numerical variables. Multiple linear regression and ordinal logestic regression models were also used to investigate adjusted associations between the variables. The sample population was also calculated by power analysis.

Kappa statistics and Bland-Altman plots were generated in order to determine the level of agreement between the two observers. The data were described as mean ± standard deviation (SD) and as count (%) for the interval and the categorical variables, respectively.

A p value of less than 0.05 was considered statistically significant. The data were managed and analyzed via Statistical Program for Social Sciences (SPSS 15.0 for Windows, SPSS Inc. Chicago, Illinois). Stata 8 SE for Windows (Stata Corporation, Texas, USA) was also utilized for statistical modeling.

Results

Thirty-three patients (26 women and 7 men) at a mean age of 59 ± 8 years were recruited in the study. Of this total, 18 (54.5%) had retinopathy (10 with mild nonproliferative, 3 with moderate nonproliferative, and 5 with severe nonproliferative or proliferative diabetic retinopathy), whereas the remaining 15 (45.5%) patients had no evidence of

retinopathy in fundoscopic examination. The background and demographic descriptive data are listed in Table 1 and the descriptive data are presented in Table 2.

The DR(+) patients had a significantly longer duration of diabetes (p value =0.001), more frequent but shorter duration of hypertension (p value =0.017 and p value =0.040, respectively), and more myocardial ischemia (p value =0.010) than did the DR (-) patients. No significant difference was noted in age, sex, body mass index, symptoms of patients or other risk factors between the two groups.

The comparisons of the clinical characteristics and the risk factors between the DR(+) and DR(-) groups are shown in Table 3. There was a significant difference in the incidence of stress-induced ischemia between the two groups, and the onset of ischemia was greater in the DR(+) population (p value =0.004).

Amongst the patients in the DR(+) group, 10 (55.6%) had mild, 2 (11.1%) moderate, and 3 (16.7%) severe stress-induced myocardial ischemia (Table 4).

The ordinal logistic regression also showed a positive association between the grade of retinopathy and the grade of inducible myocardial ischemia (OR [CI95%]=7.1[1.7-29.6], p value =0.007)(Table5).SDS (β=13.2, p value =0.024) and SSS (β=15.4, p value =0.013) were found to be related to the severity of retinopathy in the linear regression analysis.

According to the kappa statistics and Bland-Altman plots, there was a high interobserver agreement. All the kappa values exceeded 0.8 and both observers were within the acceptable range (mean difference ± 2 SD) in the Blant-Altman plots (figure 1).

Table 1. Background and demographic descriptive data (n = 33)

Age (year)	59 ± 8
Gender (F/M)	26/7(79/21)
Positive for retinopathy	18(54.5)
Negative for retinopathy	15(45.5)
Retinopathy grading *Mild nonproliferative* *Moderate nonproliferative* *Severe nonproliferative/proliferative*	 10(30.3) 3(9.1) 5(15.2)
Positive for ischemia	21(63.6)
Hypertension	14(42.4)
Hypercholesterolemia	15(45.5)
Family history	7(21.2)
Smoking	4(12.1)
Body mass index (kg/m^2)	28.8±4.7
Duration of diabetes (Year)	9.1±7.8
Duration of hypertension (Year)	4.6±2.6

Statistics are numbers (%) or mean ± standard deviation

Table 3. Comparison of clinical characteristics and risk factors between DR(+) and DR(-) Groups

	DR(-) n=15	DR(+) n=18	*P* value
Age (year)	59±4.7	59±10.1	0.818
Gender (F/M)	13/2	13/5	0.312
Body mass index (kg/m^2)	28.8±3.4	28.9±5.5	0.982
Duration of diabetes (Year)	4.4±4.1	12.8±8.1	**0.001**
Hypertension	3(20)	11(61.1)	**0.017**
Duration of hypertension (Year)	6.6±1.9	3.7±2.5	**0.040**
Hypercholesterolemia	9(60)	6(33.3)	0.126
Family history	3(20)	4(22.2)	0.876
Smoking	2(13.3)	2(11.1)	0.846

Statistics are numbers (%) or mean ± standard deviation
Significant *P* values in bold

Table 2. MPI results: Descriptive data (n = 33)

Negative for ischemia	12(36.4)
Mild ischemia	16(48.5)
Moderate ischemia	2(6.1)
Severe ischemia	3(9.1)

Statistics are numbers (%)

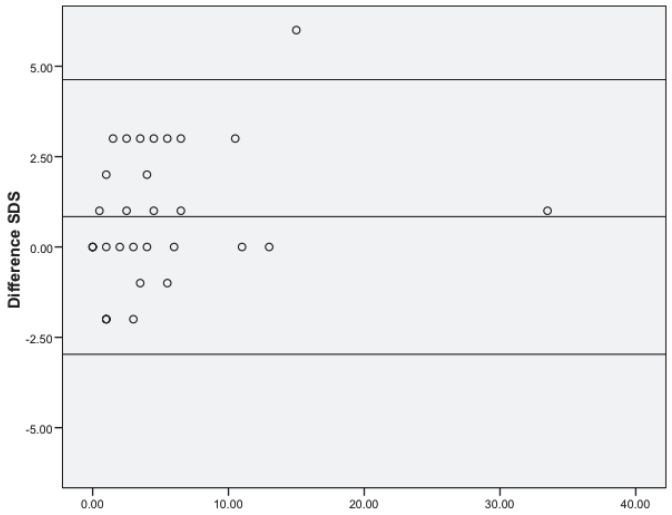

Figure 1- Blant-Altman plot for assessment the agreement between the two readers on summed difference

Table 4. Comparison of MPI findings between DR (+) and DR (-) Groups

	Negative for Retinopathy n = 15	Positive for Retinopathy n = 18	*P* value
Negative for ischemia	9(60)	3(16.7)	**0.004**
Positive for ischemia	6(40)	15(83.3)	
Mild ischemia	*6(40)*	*10(55.6)*	
Moderate ischemia	*0*	*2(11.1)*	
Severe ischemia	*0*	*3(16.7)*	

Statistics are numbers (%) / Significant *P* values in bold

Table 5. Ordinal logistic regression analysis for association between grade of ischemia and grade of retinopathy, adjusted for age, sex and duration of diabetes

	Odds Ratio	Confidence Interval 95%	*P* value
Grade of retinopathy	**7.1**	**1.7-29.6**	**0.007**
Age	0.9	0.9-1	0489
Sex	0.8	0.1-4.8	0.818
Duration of diabetes	0.9	0.8-1.1	0.914

Significant *P* values in bold

Discussion

The results of the present study underscore a relationship between the presence and degree of diabetic retinopathy and the extent and severity of ischemic heart disease detected by gated MPI. Therefore, the presence and severity of diabetic retinopathy are helpful in predicting the occurrence of myocardial perfusion abnormalities in the DM2 patients that are screened for CAD.

The findings of our study are in accordance with those of previous epidemiologic studies, which have demonstrated that patients with diabetic retinopathy have a higher probability of developing cardiovascular disease, including CAD [11, 16]. The five-year follow-up of the Milan Study on Atherosclerosis and Diabetes (MiSAD) showed that diabetic retinopathy was an independent predictor of cardiac events [17]. Cheung et al. demonstrated that in DM2 patients, the presence of retinopathy signs was associated with a higher risk of coronary heart disease events of both fatal and non-fatal types, independent of glycemic levels, cardiovascular risk factors, and large vessel atherosclerosis. This association appears to be graded with retinopathy severity and was significant in both genders, even in non-hypertensive patients [18].

Yoon et al. investigated the relation of diabetic retinopathy with coronary ischemia, using thallium myocardial perfusion scintigraphy, and reported that in symptomatic diabetic patients, the presence of diabetic retinopathy significantly increased the risk of developing myocardial perfusion abnormalities [13]. In a recent

study by Yamada et.al, a significant association was found between the proliferative retinopathy and increased risk of CAD, even after adjustment for classical coronary risk factors [19]. Tryniszewski et al. demonstrated that a comprehensive ophthalmologic assessment of the progression of diabetic retinopathy in DM2 patients might be an indicator of myocardial perfusion abnormalities, detected by MPI [20]. It has also been shown that diabetic retinopathy is an independent risk marker for subclinical atherosclerosis in newly diagnosed DM2 patients; consequently, the presence of diabetic retinopathy may raise the need for a more careful cardiovascular assessment, even in the early stages of the disease [21].

Although the population of our study was composed of both symptomatic and asymptomatic patients, the result of our study can also support the findings of the Cosson et al. study, which showed that the prediction of silent myocardial ischemia could be improved by considering the presence of retinopathy in DM2 patients [22].

CAD can be present in diabetic patients with atypical or even non-related symptoms, increasing the associated morbidity and mortality. Therefore, the early diagnosis of CAD has considerable importance in diabetic patients. Fundoscopic examination is a simple, non-invasive, and routinely employed technique drawn upon in the follow-up of diabetic patients. Our study demonstrated that the risk of abnormal myocardial perfusion was associated with the presence and the degree of diabetic retinopathy in DM2 patients and MPI could be used as a non-invasive method and of widespread use in the detection of myocardial ischemia in this group of patients. To the best of our knowledge, our study is the first investigation of its kind to evaluate the degree of diabetic retinopathy with the extent and severity of myocardial ischemia, using MPI study via the gated SPECT method.

Despite the fact that the patient's age and duration of diabetes can potentially play a role in the prevalence of diabetic retinopathy [23], our multivariate linear regression analysis, encompassing the patients' age, duration of diabetes, and other employed parameters in the model, demonstrated that diabetic retinopathy was a significant independent risk factor allied to ischemic burden, as shown by SSS and SDS.

First and foremost amongst the limitations of the present study, seeking to demonstrate the correlation between diabetic retinopathy and ischemic heart disease, is that the presence or absence of CAD was not confirmed via selective coronary angiography in patients with normal or near normal MPI results. It has been proposed that restricted coronary flow reserve can be present in diabetes patients in the absence of angiographic coronary artery stenosis [24]; be that as it may, multiple studies have reported that the diagnostic accuracy of MPI in CAD detection for diabetics is comparable to that in non-diabetic subjects [25-26].

Despite the fact that the number of patients in the present study seems to be a limiting factor, in view of the results power, it can be concluded that the sample population was sufficient and the results shown here seem to be promising.

Conclusion

It is advisable that MPI be conducted for all DM2 patients who suffer form diabetic retinopathy to investigate the presence of ischemic heart disease and to identify those likely to benefit from further diagnostic or therapeutic procedures for CAD.

Conflicts of interest

The authors hereby declare that they have no financial conflicts of interest.

References

1- Ioannidis G, Peppa M, Rontogianni P, Callifronas M, Papadimitriou C, Chrysanthopoulou G, et al. The concurrence of Microalbuminuria and Retinopathy with Cardiovascular Risk Factors; reliable predictors of Asymptomatic Coronary Artery Disease in Type 2 Diabetes. *Hormones* 2004;3(3):198-203.

2- Elhendy A, Tsutsui JM, O'Leary EL, Xie F, McGrain AC, Porter TR. Noninvasive diagnosis of coronary artery dis ease in patients with diabetes by dobutamine stress real-time myocardial contrast perfusion imaging. *Diabetes Care* 2005;28(7):1662-1667.

3- 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):1396-1400.

4- Fadini GP, de Kreutzenberg SV, Tiengo A, Avogaro A. Why to screen heart disease in diabetes. *Atherosclerosis* 2009;204(1):11-15.

5- Bax, J.J., Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ. Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 2007; 30(10):2729-2736.

6- American Diabetes Association, 1998 Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People With Diabetes. *Diabetes Care* 21: 1551-1559.

7- Wackers FJTH, Bax JJ. Stress Myocardial Perfusion Imaging in Patients with Diabetes Mellitus. In: Zaret BL, Beller JA. *Clinical Nuclear Cardiology: State of the Art and Future Directions*.Philadelphia: Mosbey Elsevier, 2010: 459-467.

8- Rutter MK, McComb JM, Brady S, Marshall SM. Silent myocardial ischemia and microalbuminuria in symptomatic subjects with non-insulin dependent diabetes mellitus. *Am J Cardiol* 1999;83:27–31.

9- 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. *Diabetes Care* 2002; 25:1418–1424.

10- Milan Study on Atherosclerosis and Diabetes Group. Prevalence of unrecognized silent myocardial ischemia and its association with atherosclerotic factors in noninsulin-dependent diabetes mellitus. *Am J Cardiol* 1997;79:134–139.

11- Hiller R, Sperduto RD, Podgor MJ, Ferris FL 3rd, Wilson PW. Diabetic retinopathy and cardiovascular disease in type 2 diabetics. The Framingham Heart Study and the Framingham Eye Study. *Am J Epidemiol* 1988;128:402-409.

12- Norgaz T, Hobikoglu G, Aksu H, Guvel A, Aksoy S, Ozer O. et al. Retinopathy Is Related to the Angiographically Detected Severity and Extent of Coronary Artery Disease in Patients With Type 2 Diabetes Mellitus. *Int Heart J* 2005;46(4):639-646.

13-Yoon JK, Lee KH, Park JM, Lee SH, Lee MK, Lee WR, et al. Usefulness of diabetic retinopathy as a marker of risk for thallium myocardial perfusion defects in non-insulin-

dependent diabetes mellitus. *J Cardiol* 2001;87(4):456-459, A6.

14- Henzlova MJ, Cerqueira MD, Mahmarian JJ, Yao SS; Quality Assurance Committee of the American Society of Nuclear Cardiology. Stress protocols and tracers. *J Nucl Cardiol* 2006.13(6):e80-90.

15- Seret A. The number of subsets required for OSEM reconstruction in nuclear cardiology. *Eur J Nucl Med Mol Imaging* 2006;33(2):231.

16- Rajala U, Pajunpaa H, Koskela P, Keinanen-Kiukaanniemi S. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. *Diabetes Care* 2000;23:957-961.

17 - Faglia E, Favales F, Calia P, Paleari F, Segalini G, Gamba PL, et al. Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study onAtherosclerosis and Diab etes (MiSAD). *Diabetes Care* 2002;25(11):2032-2036.

18 - Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Diabetes Care* 2007;30(7):1742-1746.

19 - Yamada T, Itoi T, Kiuchi Y, Nemoto M, Yamashita S. Proliferative diabetic retinopathy is a predictor of coronary artery disease in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract* 2012;96(1):e4-6.

20 - Tryniszewski W, Kuśmierczyk J, Maziarz Z, Goś R, Mikhailidis DP, Banach M, Rysz J, et al. Correlation of the severity of diabetic retinopathy and the heart muscle perfusion in patients with type 2diabetes.*J Diabetes Complications* 2011;25 (4):253-257.

21 - Son JW, Jang EH, Kim MK, Kim IT, Roh YJ, Baek KH, et al. Diabetic retinopathy is associated with subclinical atherosclerosis in newly diagnosed type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2011;91(2):253-259.

22 - Cosson E, Nguyen MT, Chanu B, Balta S, Takbou K, Valensi P. The report of male gender and retinopathy status improves the current consensus guidelines for the screening of myocardial ischemia in asymptomatic type 2 diabetic patients. *Nutr Metab Cardiovasc Dis* 2012, doi:10.1016/j. numecd.2012.01.009
(1):e4-6.

23 - Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, et al. Diabetic retinopathy. *Diabetes Care* 2003;26(1):226-229.

24 - Akasaka T, Yoshida K, Hozumi T, Takagi T, Kaji S, Kawamoto T. Retinopathy identifies marked restriction of coronary flow reserve in patients with diabetes mellitus. *J Am Coll Cardiol* 1997;30:935–941.

25 - 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. *Am Heart J* 1999;137:949–957.

26 - Wackers FJ. Diabetes and coronary artery disease: The role of stress myocradial perfusion imaging. *Cleve Clin J Med* 2005;72(1):21-5, 29-33.