September 2017

Diabetes and Coronary Artery Disease: Role of Functional Imaging

Maseeh Uz Zaman
Aga Khan University, maseeh.uzzaman@aku.edu

Nosheen Fatima
Aga Khan University, nosheen.fatima@aku.edu

EDITORIAL

Diabetes and Coronary Artery Disease: Role of Functional Imaging

Maseeh uz Zaman and Nosheen Fatima

Diabetes mellitus (DM) is considered a global epidemic, as according to the International Diabetic Federation (IDF), in year 2015, about 415 million people were diabetics with an expected involvement of 642 million people in 2040.[1] Most important concern is that more than 50% of disease burden exists in the Southeast Asia and Western-Pacific regions.[1] More than 90% of these diabetics have type-2 DM, which is non-insulin-dependent. According to the National Cholesterol Education Program (NCEP) guidelines, DM is considered equivalent to coronary artery disease (CAD).[2] CAD is the leading cause of death in diabetics, being responsible for about 80% of the cardiovascular deaths (CVD). The overall prevalence of the CAD in diabetics is about 55%; and out of these, about 20% are asymptomatic.[3] On the contrary, the prevalence of CAD in non-diabetics is 2-4%.[3] CAD in diabetics is more perplexed than non-diabetics because of diffuse disease involving epicardial and small vessels, generalized endothelial dysfunction, and extensive disease at the time of the diagnosis.[4] According to Framingham Study, diabetics have 4- 5-fold increased risk of left ventricular dysfunction and congestive heart failure.[5] It is also a known fact that diabetics tend to have less favorable outcome to revascularization and their overall survival is 10 years shorter than non-diabetics.[5]

Over the last two decades, there has been significant decline in cardiovascular mortality in general population due to the robust development in pharmacotherapy and interventional techniques. Unfortunately, these figures are not impressive in diabetics. According to FINMONICA trial, mortality after the first myocardial infarction is significantly higher in diabetics than non-diabetic population.[6] Furthermore, diabetic women tend to have poor outcome than diabetic male after the hospitalization for acute coronary syndrome (ACS).[7] However, the aggressive medical management, like use of statins, has significantly declined the CV mortality in diabetics as observed in a Scandinavian trial (Scandinavian Simvastatin Survival Study; 4S Trial).[8] Therefore, an early diagnosis of CAD is considered as the key to success in diabetics. According to the American Diabetic Association (ADA) guidelines, published in 2016. Routine screening for CAD in asymptomatic diabetics is not recommended because it does not improve outcomes as long as atherosclerotic CV risk factors are treated.[9] However, it recommends investigation for CAD in diabetics with typical or atypical cardiac symptoms with or without ECG abnormalities. A large number of investigative tools are available for the diagnosis of CAD, ranging from the most commonly used non-invasive exercise tolerance test (ETT) to the invasive coronary angiography as gold standard. Many anatomical imaging modalities like echocardiography, cardiac MR (cMR) and CT angiography (CTA) are available for the diagnosis of CAD. Myocardial perfusion imaging (MPI), being a nuclear cardiology tool, is the most commonly used non-invasive imaging modality around the globe. The reasons for its popularity are non-invasiveness, high sensitivity, and high prognostic value of MPI. In ischemia cascade, perfusion abnormalities appear within few seconds after the vascular insult followed by appearance of systolic wall motion abnormalities within 10 to 20 seconds.[10] Chest pain and ECG abnormalities appear quite late in the ischemia cascade.[10] MPI including single photon emission computerized tomography (SPECT-MPI) and positron emission tomography (PET-MPI) are considered most sensitive modalities for early diagnosis of CAD and precise decision-making in these patients.

Gated SPECT-MPI is the most commonly performed nuclear cardiology procedure since 1970s. Thallium-201 is the traditional radiopharmaceutical; but over the last 2 decades it has essentially been replaced by Technetium-99m labeled Methoxy IsoButyl Isonitrile (Tc-99m MIBI) and Tetrofosmin (Tc-99m Tetrofosmin), due to its high cost and significantly higher radiation exposure. Patients are stressed using dynamic exercise or pharmacological stress (vasodilator or inotrope) in those who are unable to perform physical exercise or having other contraindications. Radiopharmaceutical is administered intravenously at peak stress which is distributed according to regional perfusion, gets fixed into viable myocardium, and gives a snap shot image. In SPECT-MPI, imaging is done after 30-45 minutes after radiotracer administration; and resultant images provide information about perfusion (at peak stress), and wall motion at the time of imaging patient under the gamma camera (scanner). In Pakistan, MPI with SPECT has been in clinical use since late eighties with rapid progress in successive years. Fortunately, the cost of

Department of Radiology, The Aga Khan University Hospital, Karachi, Pakistan.

Correspondence: Dr. Maseeh uz Zaman, Professor & Section Head, NM and PET/CT Imaging, Department of Radiology, The Aga Khan University Hospital, Stadium Road, Karachi. E-mail: maseeh.uzzaman@aku.edu

Received: May 22, 2017; Accepted: June 30, 2017.

MPI in Pakistan is significantly low and affordable for patients. Contribution of good number of publications from Pakistan again proves its popularity in clinical and research domains.[11]

PET-MPI in assessment of CAD is also coming up recently in addition to its major oncological role. However, its current utilization is significantly less as compared to the SPECT-MPI, because of limited number of PET/CT facilities and on-site cyclotrons as well. Major PET isotopes are short lived like Rubidium-82 (half-life 76 seconds), Oxygen-15 water (half-life 20 seconds) and N-13 ammonia (half-life 10 minutes). Recently, Fluorine-18 (half-life 110 minute) labeled Flurpiridaz has been introduced which is under clinical trials. Important benefits of PET radiopharmaceuticals are significantly lower radiation exposure and completion of MPI within 1 hour as compared to 3-4 hours required for SPECT-MPI.[12] Image resolution of PET-MPI is much better than SPECT-MPI and perfusion and wall motion are studied at the time of the injection under the PET camera. In addition, PET-MPI also provides precise quantification of coronary flow reserve (CFR) which is very important tool to diagnose hemodynamically significant large and small vessels CAD.[12] MPI has similar diagnostic accuracy in diabetics and non-diabetic population. Considering invasive coronary angiography as gold standard in diabetic seems not justified because of higher prevalence of small vessel disease in diabetics and significantly lower specificity of MPI. According to a meta-analysis, including more than 8000 patients, there was no significant difference in sensitivity, specificity and normalcy rate for diagnosis of CAD in diabetic and general population.[13] Another study revealed no significant difference in the diagnostic accuracy of diabetic and non-diabetic population having coronary artery stenosis ≥50% and ≥70%.[14] However, MPI has significantly higher prognostic value in diabetic population. Diabetics with abnormal MPIs tend to have higher fatal and non-fatal cardiac events than non-diabetic population. According to a published study including 4,755 patients who had stress MPI and followed for 2.5 years, significantly higher non-fatal MIs and cardiac deaths were seen in diabetic population despite higher incidence of revascularization as well.[15] It is an established fact that negative predictive value of normal MPI is >99%; but according to the large body of data, event rates are significantly higher in diabetic population despite a normal MPI.[15] According to Hakeem *et al*., chronic kidney disease was found to be a confounding factor for cardiac events in diabetics.[16] Based on these clinical facts, it is recommended that warranty period of normal MPI in diabetics should be considered up to two years rather than 2-6 years as assumed for non-diabetic population.[17] According to ACCF/AHA guidelines published in 2010, for low to intermediate risk diabetics, coronary artery calcium (CAC) scoring (Class IIa, B) and for high-risk diabetics, MPI (Class IIb, C) is recommended. A landmark study, Diagnosis of Ischemia in Asymptomatic Diabetes (DIAD) study was conducted on asymptomatic American and Canadian population using adenosine MPI. This study revealed that 22% of asymptomatic diabetics had abnormal MPIs; and on 5 years follow-up, no significant difference in even rates was observed between diabetic and non-diabetics.[18] Another important finding of DIAD study was that majority of the abnormal MPIs got normalized in response to medical management on 3 years follow-up.[18] These findings were in accordance with the previously published COURAGE and BARI-2D trials.

IAEA sponsored a study Ischemia Assessment with Exercise imaging in Asymptomatic Diabetics (IAEA-Diabetes Trial) conducted on Asian, African and Latin American population using exercise MPI.[19] This study revealed higher prevalence of abnormal MPIs in asymptomatic diabetics predominantly in men for unknown reason. This study also concluded that MPI findings were more sensitive than ECG changes in the studied cohorts.[19] Diabetes affects both diastolic and systolic left ventricular functions and it is the diastolic function which appears earlier due to the impaired relaxation of the myocardium. Systolic dysfunction appears later and its severity is correlated with duration and magnitude of hyperglycemia. It is also observed that diabetics with normal perfusion on gated MPI had 4.5-fold increased risk of lower ejection fraction (LVEF <45%) which was more pronounced in men than diabetics women.[20] According to Fadi *et al*., diabetics had 2.7% rise in mortality for 1% decline in LVEF on gated MPI and chronic kidney disease (CKD) was found to be a strong predictor of lower survival in diabetics.[15]

Cardiac autonomic neuropathy (CAN) is common in diabetics and considered as an independent predictor of sudden cardiac death associated with arrhythmias. CAN is imaged by using Iodine-123 Meta Iodo Benzyl Guanethidine (123I-MIBG) SPECT imaging, which shows reduced MIBG uptake and higher washout from myocardium in CAN. In normal individuals, the heart to mediastinum ratio (H/M ratio) of MIBG is around 2.2; but in CAN, it declines progressively depending upon severity of neuropathy. According to ADMIRE-HF trial, patients with H/M ratio ≥1.6 were considered low risk and those with H/M ratio <1.6 had high risk for cardiac failure.[21] Carbon-11 Hydroxy-Ephedrine (11C-HE) PET imaging can also be used for the diagnosis of CAN. Blunted heart rate response during dipyridamole stress or recovery phase of dynamic exercise in stress SPECT-MPI are also considered as predictors of CAN associated higher mortality.[21]

Diabetes is a global epidemic which is considered equivalent to CAD. CAD in diabetics is more advanced, perplexed with poor outcome than non-diabetics.

Screening of asymptomatic diabetics for CAD is not recommended; but for symptomatic diabetics, MPI is a very valid diagnostic tool. Diabetic men tend to have higher prevalence of LV dysfunction despite normal myocardial perfusion, and diabetic women tend to have poorer outcome after hospitalization for ACS. Cardiac autonomic neuropathy in diabetic is common and early diagnosis is important to minimize sudden cardiac death caused by arrhythmia.

REFERENCES

1. Diabetes: facts and figures. http://www.idf.org/about-diabetes/what-is-diabetes. Aaccessed on 01/05/2017.
2. Haffner S. Rationale for New American Diabetes Association Guidelines: Are national cholesterol education program goals adequate for the patient with diabetes mellitus? *Am J Cardiol* 2005; **96**:33-6.
3. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 2015; **6**:1246-58.
4. Karastergiou K, Kaski JC. Medical management of the diabetic patient with coronary artery disease. *Curr Pharm Des* 2008; **14**:2527-36.
5. Mahmood SS, Levy D, RS Vassan, Wang TJ. The framingham heart study and the epidemiology of cardiovascular diseases: a historical perspective. *Lancet* 2014; **383**:999-1008.
6. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, *et al*. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA myocardial infarction register study group. *Diabetes Care* 1998; **21**:69-75.
7. Graham G. Acute coronary syndromes in women: Recent treatment trends and outcomes. *Clin Med Insights Cardiol* 2016; **10**:1-10.
8. Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Færgeman O. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival Study (4S). *Lancet* 1994; **344**:1383-9.
9. American Diabetes Association. Cardiovascular disease and risk management. Sec. 8. In standards of medical care in diabetes-2016. *Diabetes Care* 2016; **39**:S60-S7.
10. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *Am J Cardiol* 1987; **59**: 23C-30C.
11. Fatima N, Zaman M, Ishaq M, Baloch D, Bano M, Bano S. Impact of glycosylated hemoglobin (HBA1C) on the extent of perfusion abnormalities and left ventricular dysfunction using gated myocardial perfusion imaging and clinical outcomes in diabetic patients. *Nucl Med Commun* 2013; **34**:489-94.
12. Nakazato R, Berman DS, Alexanderson E, Slomka P. Myocardial perfusion imaging with PET. *Imaging Med* 2013; **5**: 35-46.
13. 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**:949-57.
14. Kang X, Berman DS, Lewin HC, Cohen I, Friedman JD, Germano G, *et al.* Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. *Am Heart J* 1999; **138**:1025-32.
15. Fadi GH, Iskandrian AE, Cardiovascular imaging in diabetes mellitus. *J Nucl Cardiol* 2011; **18**:959-65.
16. Hakeem A, Bhatti S, Karmali KN, Dillie KS, Cook JR, Xu J, *et al.* Renal function and risk stratification of diabetic and nondiabetic patients undergoing evaluation for coronary artery disease. *JACC Cardiovasc Imaging* 2010; **3**:734-45.
17. Hachamovitch R, Hayes S, Friedman JD, Cohen I, Shaw LJ, Germano G, *et al.* Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? *J Am Coll Cardiol* 2003; **41**:1329-40.
18. 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**:1954-61.
19. Giubbini R, Dondi M, Mutt F, Massardo T, Lusa L, Iskandrian A. Prevalence of ischemic heart disease (IHD) in asymptomatic patients with diabetes mellitus (DM) in developing countries. *J Nucl Med* 2010; **51**:1743-49
20. Htay T, Mehta D, HeoJ, Iskandrian AE. Left ventricular function in patients with type 2 diabetes mellitus. *Am J Cardiol* 2005; **95**:798-801
21. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA. Myocardial Iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. *J Am Coll Cardiol* 2010; **55**:2212-21.