The Cardiology 1 (3-4) : 158-162, 2005

Prevalence of Abnormal Myocardial Perfusion SPECT Imaging and All Cause Mortality, among Asymptomatic Diabetic and Non-diabetic Blacks and Hispanics in an Inner-city Hospital

Narendra C. Bhalodkar, Steve Blum, Bashir Lone, Raman Singh and Ajay Shah,
Albert Einstein College of Medicine Bronx-Lebanon Hospital Center,
Albert Einstein College of Medicine, Bronx, NY, USA

Abstract: Diabetes is a Coronary Artery Disease (CAD) equivalent. Diabetics have extensive CAD, frequent silent ischemia and myocardial infarctions. Mortality in asymtomatic diabetics unergoing SPECT Tc99m-MIBI Myocardial Perfusion Imaging (MPI) is unknown. Performing MPI in asymptomatic diabetics may identify higher proportions of silent CAD. Revirwed 231 MPIs of asymptomatic diabetics (N=75) and non-diabetics (N=156), in Blacks and Hispanics who were referred for evaluation of CAD with no H/O CAD, PAD, MI, angina pectoris, revascularization,cardiomyopathy and valvular heart disease. All-cause mortality from Social Security Death Index was searched, giving at least 36 months of follow up. Diabetics were significantly older, more hypertensives and less likely to be smokers but there were no differences with regards to gender, postmenopausal status, hyperlipedimia, obesity, F/H/O premature CAD, occurrence of chest pain at peak stress and stress EKG abnormalities. Proportion of abnormal MPIs (ischemia only, scar only, ischemia and scar only, separately or all combined together) among both were similar (20%). Gated EF% was significantly lower among diabetics (47.5±18.4 vs. 53.8±14.4, p=0.009). Diabetics had significantaly higher all-cause mortality (25.65 vs. 5.7%, p=0.0002). On multivariate logistic regression analysis only diabetes (OR=7.45) and age (OR=1.05) were significant predictors of mortality. Asymptomatic diabetics compared to non-diabetics had lower EF, similar prevalence of abnormal stress EKG and MPI. However, all-cause mortaliy among diabetics was four fold higher compared to non-diabetics. Our findings suggest that all diabetics still be treated with aggressive risk factor modification, irrespective of their MPI results, to prevent the development and progression of CAD and reduce mortality.

Key words: Asymptomatic diabetics, silent ischemia, myocardial perfusion imaging, mortality

INTRODUCTION

The incidence of diabetes is increasing in epidemic proportions[1,2]. Adult Treatment Panel III guidelines consider diabetes as a CAD equivalent and CAD is the leading cause of death in patients with diabetes[3,4]. Diabetic patients compared with non-diabetics, have more extensive CAD and more frequent silent ischemia and myocardial infarctions[5-9]. The American Diabetes Association (ADA) guidelines recommend stress testing and/or Myocardial Perfusion Imaging (MPI), when two or more additional CAD risk factors are present[10]. The specific value of stress testing with or without MPI in asymptomatic diabetic patients remains unclear and is the subject of ongoing investigations. However, performing MPI in asymptomatic diabetics may identify higher proportions of silent CAD earlier and this may result in prevention of cardiac events, better healthcare and lower healthcare cost.

Reports of the prevalence of abnormal MPI in asymptomatic diabetic patients are varied[11-15]. and it is uncertain whether it is higher compared to non-diabetic patients. Diabetes is an important predictor for myocardial infarction and death in patients with known CAD and even with normal MPI[16]. Blacks and Hispanics have not been adequately included in previous studies; hence there is a paucity of data among these race/ethnicities. This study was undertaken to compare the prevalence of abnormal MPIs and all cause mortality in asymptomatic patients with and without diabetes among Blacks and Hispanics.

MATERIAL AND METHODS

This study was approved by the institutional review board of Bronx Lebanon Hospital Center of Bronx, New york. This was a retrospective study with the population selected from 934 consecutive patients who were referred

Corresponding Author: Narendra C. Bhalodkar, Division of Cardiology, 12th Floor Bronx Lebanon Hospital Center, 1650 Grand Concourse Bronx NY 10457, USA

for evaluation of CAD. Medical history including questionnaire for angina and focused cardiology examination were performed by a cardiologist before performing the stress test. Patients for this study wre selected as follows. First: patients with CAD, peripheral arterial disease, myocardial infarctions, revascularization, cardiomyopathy and valvular heart disease were excluded. Second: Based on the angina questionnaire, chest pain was subdivided in four subgruops: angina pectoris, atypical angina pectoris, atypical chest pain and asymptomatic for chest pain. Third: only those patients (N= 231), determined to be asymptomatic for chest pain, first by their own referring physicians and then by the cardiologist who reinterviewed the patient and confirmed the referring physician's impression, prior to performing a stress test were included in this study. Reasons for referral for stress test in these asymptomatic patients were: to detect CAD, risk stratification and evaluation of ischemia as a pre-operative evaluation and the reasons for referral were similar among diabetics and non-diabetics. In the absence of chest pain, among both diabetics and non-diabetics, patients with other multiple conventional cardiac risk factors, such as age, hypertension, smoking, hyperlipedimia and positive family history of premature CAD, are neverthelesss routinely sent for stress testing at our institution. This practice results from the high prevalence of hyppertension and diabetes among Black and Hispanic patients. Patients on lipid lowering, antihypertension,and antidiabetic treatment at the time of study were defined as having hyperlipedimia, hypertension and diabetes, respectively. Patients who reported smoking $1 cigarettes per day were considered to be smokers. Patients underwent rest and stress Technetium-Tc99m Sestamibi Single-Photon Emission-Computed Tomography (SPECT) MPI with treadmill exercise or pharmacological stress testing (i.e. adenosine, dipyridimole or dobutamine) performed in accordance with standards of the American Society of Nuclear Cardiology[17]. Correction softwares for scatter, attenuation and motion were used in the image reconstruction to reduce artifacts. The left ventricular ejection fraction was derived from ECG-gated images[18]. MPIs were reviewed by one of the two independent cardiologists blinded to patients' histories. The interpretation of the scan was semiquantitatively performed by visual analysis assisted by bullseye (Autoquant, Cedar Sinai, Los Angeles, CA.) analysis. Stress and rest MPI abnormalities were described as revesible (ischemia), fixed (scar only) or mixed (scar with ischemia) and were categorized as small, moderate or large on the basis of quantification. All cause mortality was determined by searching the social security death index database with average follow up of 36 months. Follow up information was available for all the subjects. Patients were divided in two groups, diabetics (N=75) and non-diabetics (N=156) and all comparisons are between them.

Statistical analyses: Data were first analyzed in bivariate mode with either categorical (chi-square or Fisher's exact) tests or analysis of variance for continuous data. At the bivariate level, p#0.05 was considered statistically significant. Multivariate logistic regression analysis was then performed on all variables with a bivariate significant level of # 0.10.

Table 1: Clinical, stress test and MPI variables and all cause mortality among asymptomatic diabetic and non-diabetic patients

	Diabetics (N=75)	Non- Diabetics (N=156)	P value
Clinical variables			
Age (years)	66 ±10.9	62.5 ± 13.0	0.045
Female	46 (61 %)	97 (62 %)	0.91
Postmenopausal	35 (76 %)	59 (61 %)	0.07
Hypertension	69 (92 %)	105 (67 %)	0.00005
Hyperlipedimia	25 (33 %)	38 (24 %)	0.15
Smoking	9 (12 %)	36 (23 %)	0.04
Stress Test Variables			
Treadmill Exercise stress test	16%	42%	0.0001
MPI Variables			
MPI normal	60 (80 %)	125 (80 %)	0.98
MPI ischemia	4 (5.3 %)	15 (9.6 %)	0.14
MPI scar only	5 (6.7 %)	6 (3.9 %)	0.35
MPI scar with ischemia	6 (8.0 %)	10 (6.5 %)	0.52
TID	1.05 ± 0.07	1.04 ± 0.15	0.29
LHR	0.314 ± 0.06	0.312 ± 0.06	0.86
Gated EF%	47.5 ± 18.4	53.8 ± 14.4	0.009
All-Cause mortality over 36 months			
Overall	25.6 %	5.7 %	0.00002
MPI normal	24.0 %	3.1 %	0.0008
MPI abnormal	28.0 %	6.3 %	0.016

Values are mean ± SD or numbers (%) of subjects
MPI = Myocardial Perfusion Imaging
TID = Transient Ischemic Dilation of Left Ventricular Cavity
LHR = Lung Heart Ratio
EF = Ejection Fraction

RESULTS

The clinical characteristics and MPI results of patients with and without diabetes are shown in the (Table 1) The study cohort consisted of 95% Blacks and Hispanics, 62% females, 34% undergoing treadmill exercise. Patients with diabetes were significantly older, more likely to be hypertensive, less likely to be smokers and less likely to undergo exercise treadmill stress test compared to non-diabetics. There were no differences in gender distribution, proportion of postmenopausal females, hyperlipedimia, obesity and family history of premature CAD.

Proportions of abnormal MPIs (20%) were similar among patients with and without diabetes. Proportions of MPIs with ischemia, scar only and scar with ischemia as well as locations, severities and sizes of scan abnormalities were similar in both groups. However, the mean left ventircular ejection fraction (47.5±18.4% vs. 53.8±14.4%, p= 0.009), even though within normal limits, was significantly lower among patients with diabetes. Occurrence of chest pain at peak stress, stress EKG abnormalities, transient ischemic dilatation of the left ventricular cavity and lung heart ratios were similar in both groups.

Over a mean follow up period of 36 months, there were a total of 29 (12.6%) deaths in the whole group. However, diabetics had significantly higher death rate overall (25.6% vs. 5.7%, p=0.00002), in patients with normal MPI (24% vs. 3.1%, p=0.0008) and in patients with abnormal MPI (28% vs. 6.3%, p=0.016). On multivriate logistic regression analyses only diabetes (odds ratio = 7.45, p = # 0.00001) and age (odds ratio = 1.05, p = 0.023) were significantly associated with mortality whereas other variables such as (gender, proportion of postmenopausal females, hyperlipedimia, obesity and family history of premature CAD, occurrence of chest pain at peak stress, stress EKG abnormalities, transient ischemic dilatation of the left ventricular cavity and lung heart ratios, proportions of MPIs with ischemia, scar only and scar with ischemia as well as locations, severities and sizes of scan abnormalities) were not associated with mortality.

DISCUSSION

The prevalence of abnormal MPIs in asymptomatic diabetics in our study is somewhat higher than the 6-9% observed in the two large-scale screening studies performed in Italy and a smaller study in France[11-13]. However, these studies consisted of younger patients,[11-13] relatively healthier patients (retinopathy or nephropathy patients excluded)[11] and used less sensitive imaging technique such as planar rather than SPECT imaging[12,13]. In our study, patients were relatively older (63.8±12.6 vs. 54.2±6, years), patients with diabetic complications were included and we used SPECT imaging with Technetium-Tc99m sestamibi. CAD is considered to be a major problem in postmenausal women and diabetes further reduces the female coronary advantage[19,20]. Additionaly, diabetes has stronger effect on the risk of CAD[21] and cardiovascular deaths[22] in women compared to men. Our study included 63% women (age 65 ± 12.3 years) of whom two-third were post-menaupausal. Our results are consistent with previously reported prevalence of silent ischemia in asymptomatic diabetic patients, 15.7% by Janand DB. *et al*,[12] 26% by De Lorenzo A. *et al*,[14] and recently reported 22% by Wackers FJT *et al*.,[23] However, these three studies did not include a control group of asymptomatic non-diabetic patients. Contrary to our expectations, proportions of abnormal MPIs (20%) were similar among patients with and without diabetes. In agreement with our conclusion, Caracciolo E. *et al*.,[25] found similar prevalence of asymptomatic ischemia in patients with and without diabetes during exercise treadmill testing and ambulatory ischemia monitoring. Nesto RW *et al*,[25] have reported that among patients with positive exercise thallium scintagraphy, during exercise treadmill testing, angina occurred more frequently in diabetic compared to non-diabetic patients. However, the prevalence of angina during stress test in our study was similar among diabetic and non-diabetic patients. In our study, diabetics compared to non-diabetics were older (66 vs. 62.5 years) and this may have contributed to a higher prevalence of hypertension in diabetics. Relatively higher prevalence (75%) of hypertension overall among both groups combined in our study is consistent with previously reported data that Blacks[26] and Hispanics have a higher prevalence of hypertension, especially in diabetics.

Even though, in our study the proportion of abnormal MPIs was similar in asymptomatic patients with and without diabetes, patients with diabetes had significantly higher mortality overall and in subgroups with and without abnormal MPIs. Hachamovitch R. et al, reported that diabetes is a major determinant for events such as myocardial infarction and death even in patients with normal MPI[16]. Our results and those of others,[27-30] suggest that all diabetics should still be treated with aggressive risk factor modification, irrespective of their MPI results, to prevent the development and progression of CAD. Even though, we did not have cause of death, it is highly likely that most of the death were related to cardiovascular diseases as it is the leading cause of death in patients with diabetes[3,4].

In diabetics, myocardial ischemia from small vessel disease[31] may cause left ventricular dysfunction in the absence of the epicardial coronary narrowing or abnormal MPI. This may partly explain significantly reduced gated

left ventricular ejection fractions (even though within normal limits) among patients with diabetes.

Most importantly, to our knowledge, no data exist regarding the prevalence of abnormal MPIs and all cause mortality in asymptomatic Blacks and Hispanics diabetics.

Diabetic patients may be unable to complete symptom-limited treadmill exercise test because of obesity, peripheral vascular disease and peripheral neuropathy. Consistent with these findings , diabetic patients in our study were less likely to undergo treadmill exercise test.

In this study, patients came from a population referred to nuclear laboratory for evaluation of possible CAD; therefore the findings may not be applicable to a broader population. However, patients had no chest pain, myocardial infarction or revascularization, hence represent a population with true diagnostic challange. Due to the retrospective nature of the study we could not assess duration of diabetes.

Major strengths of this study include: first of its kind study to include large numbers of Blacks, Hispanics and females, comparison of asymptomatic diabetics with non-diabetics, inclusion of patients with diabetic complications, use of Technetium-Tc99m Sestamibi radiotracer, SPECT MPI technique, use of correction softwares for scatter, attenuation and motion in the image reconstruction so as to reduce artifacts.

CONCLUSIONS

Asymptomatic diabetic patients compared to asymptomatic non-diabetics, have similar prevalence of abnormal stress EKG and MPIs and have significantly lower ejection fractions. In this study, routine screening for CAD in asymptomatic diabetic patients did not detect more CAD compared to non-diabetic patients. However, diabetics had higher all cause mortality. Therefore, our findings suggest that all diabetics should still be treated with aggressive risk factor modification, irrespective of their MPI results, to prevent the development and progression of CAD and reduce mortality. It remains to be determined whether these findings would be replicated in non-minority populations. Accordingly, a randomized, large scale multicenter, multi-ethnic and racial, prospective study is warranted.

REFERENCES

1. Mokdad, A.H., B.A. Bowman, E.S. Ford, F. Vinicor, J.S. Marks and J.P. Koplan, 2001. The continuing epidemics of obesity and diabetes in the United States. JAMA, 286 :1195-1200.
2. Burke, J.P., K. Williams, S.P. Gaskill, H.P. Hazuda, S.M. Haffner and M.P. Stern, 1999. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: Results From the San Antonio Heart Study. Arch Intern Med,159: 1450-1456.
3. Kannel, W. and D. McGee, 1972. Diabetes and glucose tolerance as risk factors for cardiovascular disease: The Framingham study. Diabetes Care 2:120-126.
4. Investigators, T.B. 1997. Influence of Diabetes on 5-Year Mortality and Morbidity in a Randomized Trial Comparing CABG and PTCA in Patients With Multivessel Disease : The Bypass Angioplasty Revascularization Investigation (BARI). Circulation 96: 1761-1769.
5. Seven-year outcome in the Bypass Angioplasty, 2000. Revascularization Investigation (BARI) by treatment and diabetic status. J. Am. Coll. Cardiol., 35: 1122-1129.
6. Haffner, S.M., S. Lehto, T. Ronnemaa, K. Pyorala and M. Laakso, 1998. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without Prior Myocardial Infarction. N. Engl. J. Med., 339: 229-234.
7. Ruige, J.B., W.J.J. Assendelft, J.M. Dekker, P.J. Kostense, R.J. Heine and L.M. Bouter, 1998. Insulin and risk of cardiovascular disease : A Meta-Analysis. Circulation 97: 996-1001.
8. Pyorala, K., 1979. Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. Diabetes Care, 2: 131-141.
9. Stamler, J., O. Vaccaro, J. Neaton and D. Wentworth, 1996. Diabetes, other risk factors and 12 year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care, 16: 434-444.
10. Consensus development conference on the diagnosis of coronary heart disease, 1998. In people with diabetes: Miami, Florida. American Diabetes Association. Diabetes Care 21:1551-1559.
11. Milan Study on Atherosclerosis and Diabetes, 1997. (MiSAD) G. Prevalence of unrecognized silent myocardial ischemia and its association with atherosclerotic risk factors in noninsulin-dependent diabetes mellitus. The American J. Cardiol., 79: 134-139.
12. Janand-Delenne, B., B. Savin, G. Habib,M. Bory, P. Vague, V. Lassmann-Vague, 1999. Silent myocardial ischemia in patients with diabetes: who to screen. Diabetes Care, 22: 1396-1400.

13. Gazzaruso, C., A. Garzaniti, S. Giordanetti, C. Falcone, E. De Amici and D. Geroldi, *et al*., 2005. Assessment of asymptomatic coronary artery disease in apparently uncomplicated type 2 diabetic patients: A role for lipoprotein(a) and apolipoprotein(a) polymorphism Diabetes Care, 25: 1418-1424.
14. De Lorenzo, A., R.S.L. Lima, A.G. Siqueira-Filho and M.R. Pantoja, 2002. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. The Am. J. Cardiol., 90: 827-832.
15. Nesto, R., 1999. Screening for asymptomatic coronary artery disease in diabetes. Diabetes Care 22: 1393-1395.
16. Hachamovitch, R., S. Hayes, J.D. Friedman, I. Cohen, L.J. Shaw and G. Germano *et al*., 2003. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans1: What is the warranty period of a normal scan? Journal of the American College of Cardiology, 41: 1329-1340.
17. E.G. D and EV G. 2001. Updated imaging guidelines for nuclear cardiology procedures. J. Nuclear. Cardiol., 8:1-58.
18. Lam, P., F. Wackers and Y. Liu, 2001. Validation of new method for quantification of left ventricular function from ECG-gated SPECT. J. Nuclear. Cardiol., pp: 42:93.
19. Howard, B., L. Cowan, O. Go, T. Welty, D. Robbins and E. Lee, 1998. Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. The strong heart study. Diabetes Care, 21: 1258-1265.
20. Kannel, W.B. and P.W. Wilson, 1995. Risk factors that attenuate the female coronary disease advantage. Arch. Intern. Med., 155: 57-61.
21. Juutilainen, A., S. Kortelainen, S. Lehto, T. Ronnemaa, K. Pyorala and M. Laakso, 2004. Gender Difference in the Impact of Type 2 Diabetes on Coronary Heart Disease Risk. Diabetes Care 27: 2898-2904.
22. Tan, H.H., R.R. McAlpine, P. James, P. Thompson, M.E.T. McMurdo and A.D. Morris, *et al*., 2004. Diagnosis of type 2 diabetes at an Older Age: Effect on mortality in men and women Diabetes Care, 27: 2797-2799.
23. Wackers, F.J.T., L.H. Young, S.E. Inzucchi, D.A. Chyun, J.A. Davey and E.J. Barrett, *et al.,* 2004. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: The DIAD study Diabetes Care, 27: 1954-1961.
24. Caracciolo, E.A., B.R. Chaitman, S.A. Forman, P.H. Stone, M.G. Bourassa and G. Sopko, *et al*., 1996. Diabetics with coronary disease have a prevalence of asymptomatic ischemia during exercise treadmill testing and ambulatory ischemia monitoring similar to that of nondiabetic patients : An ACIP Database Study. Circulation, 93: 2097-2105.
25. Nesto, R.W., R.T. Phillips, K.G. Kett, T. Hill, E. Perper, and E. Young *et al*., 1988. Angina and exertional myocardial ischemia in diabetic and nondiabetic patients: assessment by exercise thallium scintigraphy. Ann Intern Med, 108: 170-175.
26. Akinboboye, O.O., O. Idris, A. Onwuanyi, K. Berekashvili and S.R. Bergmann 2001. Incidence of major cardiovascular events in black patients with normal myocardial stress perfusion study results. J Nucl. Cardiol., 8: 541-547.
27. Management of Dyslipidemia in Adults With Diabetes, 2003. Diabetes Care,26: 83S-86.
28. Velmurugan, K., R. Deepa, R. Ravikumar, J.B. Lawrence, H. Anshoo and M. Senthilvelmurugan, *et al.,* 2003. Relationship of lipoprotein(a) with intimal medial thickness of the carotid artery in Type 2 diabetic patients in south India. Diabet. Med., 20: 455-461.
29. Treatment of Hypertension in Adults With Diabetes, 2003. Diabetes Care, 26: 80S-82.
30. Grundy, S.M., A. Garber, R. Goldberg, S. Havas, R. Holman and C. Lamendola, *et al.,* 2002. Prevention conference VI: Diabetes and cardiovascular disease: Writing group IV: Lifestyle and medical management of risk factors. Circulation, 105: 153-158.
31. Zoneraich, S., G. Silverman and O. Zoneraich, 1980. Primary myocardial disease, diabetes mellitus and small vessel disease. Am. Heart. J., 100: 754-755.