ORIGINAL ARTICLE

HIGHER NEGATIVE PREDICTIVE VALUE ON SEVEN YEARS FOLLOW UP OF NORMAL GATED MYOCARDIAL PERFUSION IMAGING IN DIABETIC PATIENTS WITH HBA1C≤7.3% CUTOFF

Nosheen Fatima,[1,2] Sidra Zaman,[3] Areeba Zaman,[3] Anamta Zaman,[5] Unaiza Zaman,[4] Maseeh uz Zaman[1,2]

[1] Karachi Institute of Heart Diseases (KIHD), Karachi, Pakistan.
[2] Department of Radiology, Aga Khan University Hospital (AKUH), Karachi, Pakistan.
[3] Dow Medical College, DUHS, Karachi, Pakistan.
[4] Department of Medicine, Sunny Downstate Hospital, NY, USA
[5] Liaquat College of Medicine and Dentistry, Karachi, Pakistan.

PJR October - December 2021; 31(4): 238-242

ABSTRACT

PURPOSE: This prospective study was carried out to find negative predictive value (NPV) of normal myocardial perfusion imaging (MPI) in diabetic patients with predefined cut-off value of glycosylated hemoglobin A1c (HbA1c) ≤ 7.3%. **METHODOLOGY:** This study was conducted at Karachi Institute of Heart Disease (KIHD) after prior approval from ethical committee. Total 257 diabetic patients who were labeled as normal MPI from June-2011 till March-2012 were included. These patients were followed on telephone for seven years for cardiac events including fatal myocardial infarction (FMI) and nonfatal myocardial infarction (NFMI). Follow up was not available in 33 patients, leaving a cohort of 224 participants. Mean HbA1c was calculated for seven years. Patients were subdivided according to predefined cut-off value of HbA1c 7.3% as determined in previously published study by our group (57 in group A with HbA1c >7.3% and 167 in group B with HbA1c ≤ 7.3%). **RESULTS:** No statistically significant difference was found in age, gender, body mass index, hypertension, dyslipidemia, family history, LV function, Bruce and vasodilator stress protocol in both groups except metabolic equivalent of task (METS) was significantly higher in group B (<0.05). Overall mean survival was significantly higher in group B with HbA1c =7.3 (Mean=80 vs. 71; CI=78-83 vs. 64-78 months in Group B and A respectively; log rank value=5.576; p <0.05). Significantly higher fatal and non-fatal cardiac events on seven years follow up were recorded in group A with HbA1c >7.3% with lower METS <7 (3 vs. 0 FMI and 11 vs. 9 NFMI and annualized event rate 0.75% vs. 0% and 2.8% vs. 0.76% group A and Group B respectively; p<0.05). **CONCLUSION:** We conclude that a negative MPS has a significantly higher NPV and better effort tolerance in diabetics with good glycemic control (mean HbA1c ≤ 7.3%) than diabetics with impaired glycemic control (mean HbA1c >7.3%). Impaired glycemic control is supposed to be associated with impaired endothelial function and demands a correlative study in future.

Keyword: Gated myocardial perfusion imaging; diabetics; HbA1C; METS, fatal MI; non-fatal MI.

Introduction

Diabetes Mellitus (DM) is the leading cause of morbidity and mortality in the developed and developing countries and associated with 2-4 folds higher mortality risk and worse overall prognosis in patients with coro-

Correspondence : Dr. Maseeh uz Zaman
Department of Radiology,
Aga Khan University Hospital (AKUH),
Karachi, Pakistan.
Email: maseeh.uzzaman@aku.edu

Submitted 11 October 2021, Accepted 1 November 2021

nary artery disease (CAD).[1] Glycosylated hemoglobin (HbA1c) is globally accepted as biochemical markers in DM for long term glycemic control than short term glycemic markers like 2 hours postprandial or fasting blood sugar (FBS).[2] Myocardial perfusion imaging (MPI) is an established non-invasive tool used for diagnosis and risk stratification of CAD in diabetic patients. Due to high negative predictive value, MPI is extensively used to exclude clinically significant CAD and high prognostic value for predicting future cardiac events.[3] In previously published study by our group, HbA1c >7.3% was found to have significant predictive value for CAD, left ventricular dysfunction (LVD) and higher incidence of non-fatal myocardial infarctions (NFMI) in diabetic patients.[4] However, the risk of hard event after a normal MPS is a function of the clinical and historical factors of the patients tested. In particular, diabetes is an important clinical variable in determining the risk of events after stress MPI. It has been demonstrated that after a normal stress MPI, diabetic patients are at higher risk (>1%) for cardiac events than non-diabetic subjects (<1%) also after balancing clinical characteristics and stress type by a propensity score analysis.[5] However, the prognostic value of a negative stress MPI in diabetic patients has only been evaluated in single-center studies of relatively limited sample size.[5]

Aim of this study was to find the negative predictive value of normal MPI in diabetic patients with pre-defined cut-off value of HbA1c ≤7.3%.

Material and Methods

Study population:

This prospective study was duly approved by the institutional ethical committee and conducted at Nuclear Cardiology Department of KIHD, Karachi, Pakistan from June 2011 till March 2012 (IEC-KMDC-10029-20y). Total 257 diabetic patients who were labeled as normal GMPI, those referred for diagnosis or risk stratification of CAD were included. These patients were followed-up on telephone for seven years for cardiac events including fatal myocardial infarction (FMI) and nonfatal myocardial infarction (NFMI). Thirty-three patients were lost to follow-up and were excluded from study leaving a cohort of 224 patients. Mean HbA1c was calculated for seven years in each patient. Patients were subdivided according to predefined cut-off value of HbA1c 7.3% as determined in a previously published study4 into Group-A (HbA1c >7.3% - 57 patients) and Group-B (HbA1c ≤ 7.3% -167 patients).

Acquisition Protocol:

All patients underwent same day (stress-rest / rest-stress or stress only if normal) gated SPECT MPI using Tc-99m labeled Methoxy IsoButyl Isonitrile (MIBI). 07-10 mCi of Tc-99m MIBI was administered intravenously for stress and 25-30 mCi for resting study. GMPI acquisitions were performed using dual head (Cardio MD, Philips) dedicated cardiac gamma camera with low energy all purpose (LEAP) collimator, 32 projections around a 180-degree arc and a 64 x 64 matrix. Image reconstruction and left ventricular (LV) functional parameters like LV ejection fraction (LVEF), end diastolic volume (EDV), end systolic volume (ESV), wall motion (WM) and transient ischemic dilatation (TID) were estimated using commercially available Astonish® and Autoquan® software packages respectively.

Stress Protocol:

Dynamic exercise was used in 42% vs. 44% while dipyridamole intervention was performed in 58% vs. 56% in group A and B respectively; p>0.05 (Tab.1). Beta blockers, calcium blocker and long acting nitrate were stopped 24-48 hours prior the test. Tea, coffee and xanthine derivatives were also stopped 12-24 prior in patients scheduled for dipyridamole test. Pharmacological intervention was performed with 0.567 mg/kg of dipyridamole for 4 minute. Tc-99m MIBI was given 1 minute before terminating exercise or 3-4 minute after dipyridamole infusion.

All patients (or a family member in case patient was expired) were interviewed on telephone (12-84 months after MPI) regarding major acute cardiac events like fatal or non-fatal MIs (FMI, NFMI).

Statistical Analysis:

Data was analyzed by using commercially available packages the Medcalc® statistical software version 18.12.1 and statistical package for social sciences (SPSS version 19®). Comparisons between patient groups were performed using Student's t test for continuous variables and the Chi-square (χ^2) test for

categorical variables. Continuous variables were described by mean ± standard deviation (SD). Kaplan Meier survival plots for fatal and non-fatal event were analyzed and log rank test was applied for comparison of survival plots. For all P-values <0.05 were selected as significant.

Variables	Normal GMPI with HbA1c >7.3% n=57	Normal GMPI with HbA1c ≤ 7.3% n=167	X^2 or t-test value	p-values
Age (mean ± SD) yrs	59 ± 10	57 ± 10	-1.304	0.1937
Male	24 (42%)	66 (40%)	0.070	0.7910
Female	33 (61%)	101 (60%)		
Body Mass Index (kg/m^2)	28.318 ± 6.912	27.532 ± 5.997	-0.821	0.4125
HBA1c (mean ± SD)	8.3 ± 1.2	6.4 ± 0.6	-15.575	<0.0001*
Risk Factor				
Hypertension	45 (79%)	140 (88%)	2.798	0.0944
Dyslipidemia	25 (44%)	70 (42%)	0.069	0.7924
Family history CAD	23 (40%)	57 (34%)	0.665	0.4180
Smoker	05 (09%)	21 (13%)	0.642	0.4231
Bruce : Vasodilator group	24: 33	74: 93	0.069	0.7930
METS	7.3 ± 1.8	8.3 ± 1.9	3.476	*0.0006
LV Function (mean ± SD)				
%LV Ejection Fraction	64 ± 9	65 ± 10	0.668	0.5048
End Diastolic Volume (ml)	77 ± 24	78 ± 20	0.309	0.7574
End Systolic Volume (ml)	24 ± 17	27 ± 15	1.259	0.2092
Overall Cardiac events/7 years	14 (25%)	09 (05%)	18.655	<0.0001*
Fatal events /7 years	03 (05%)	00 (00%)	8.420	0.0037*
Non-Fatal events/ 7 years	11 (19%)	09 (05%)	10.591	0.0011*

* p<0.05
GMPI = Gated Myocardial Perfusion Imaging
SD = Standard Deviation
CAD = Coronary Artery Disease
LV = Left Ventricular

Table 1: Demographic comparison of diabetic patients at HbA1c cut off 7.3% with normal myocardial perfusion imaging.

Results

In demographic comparison of both groups, no statistically significant difference was found in mean age, gender, body mass index (BMI), hypertension, dyslipidemia, positive family history of CAD, and smoking (p>0.05). Obesity and female gender was predominant in both groups with statistical similarity (p>0.05). Mean HbA1c was 8.3 ± 1.2% and 6.4 ± 0.6% in Group-A and B respectively (p <0.0001). Exercise effort tolerance was measured by metabolic equivalent tasks (METS) and mean METS was significantly higher in Group-B than Group-A, i.e. 8.3 ± 1.9 vs. 7.3 ± 1.8 respectively (p<0.05). Mean LVEF, EDV and ESV were statistically similar in both groups (Tab.1).

During seven-year follow-up, overall cardiac events (FMI and NFMI) were significantly higher in Group-A than Group-B with a negative predictive value (NPV) of 75% and 95% respectively [p<0.05] (Tab.1 and Fig.1). Mean survival was 71 months vs. 80 months for overall cardiac events (CI=64-78 vs.78-83; log rank=5.756; p<0.05) and 72 months vs. 81 months for NFMI (CI=65-78 vs. 78-83; log rank=4.382; p<0.05) in Group-A and Group-B respectively (Fig.1 and 2). Mean survival was statistically similar for fatal

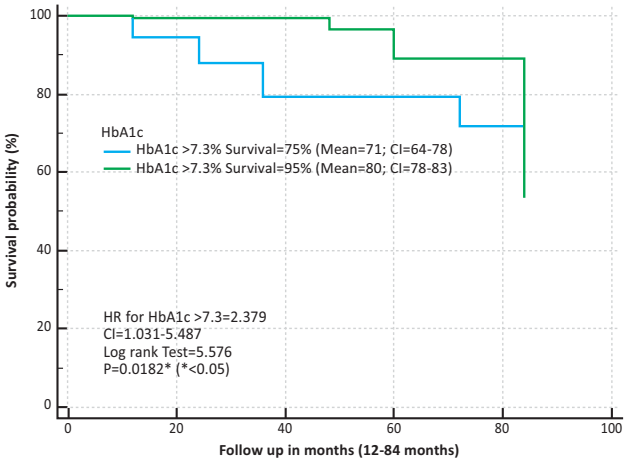

Figure 1: Kaplan Meier survival plot for overall cardiac events in diabetic patients at HbA1c cut off 7.3% who were labeled normal myocardial perfusion imaging.

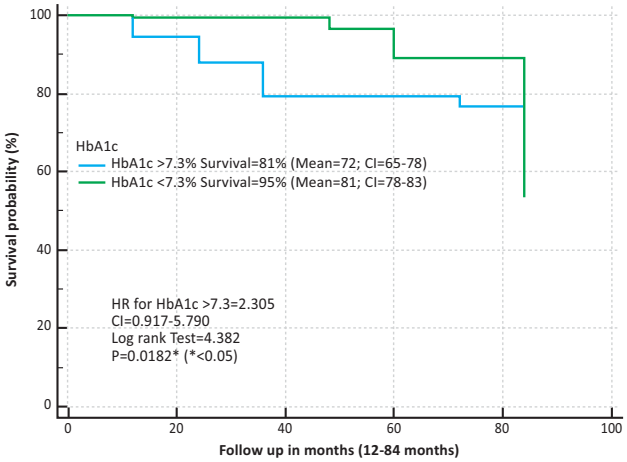

Figure 2: Kaplan Meier survival plot for non-fatal events in diabetic patients at HbA1c cut off 7.3 who were labeled normal myocardial perfusion imaging.

events in both groups (83 months vs. 84 months; CI=82-84 vs. 84; log rank=1.185; p=0.2763; (Fig.3).

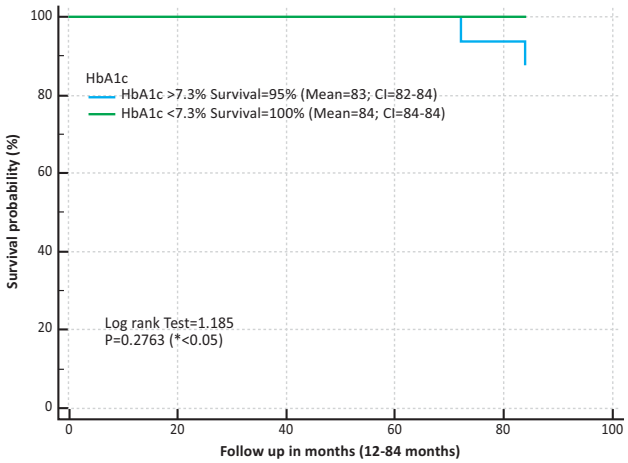

Figure 3: Kaplan Meier survival plot for Fatal events in diabetic patients at HbA1c cut off 7.3 % who were labeled normal myocardial perfusion imaging.

Discussion

Stress myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) has taken a central role in risk stratifying patients with suspected or known coronary artery disease (CAD). Several studies reported that patients with negative stress MPI have an excellent outcome, as less than 1% of patients with a normal study will experience fatal and non-fatal MIs.[6] However, diabetic with normal stress MPS are found to have higher risk (>1%) for cardiac events than non-diabetic subjects (<1%).[5] Worth mentioning, the prognostic value of a negative stress MPS in diabetic patients has only been evaluated in single-center studies of relatively limited sample size.[6]

In this study with 7-year follow-up, diabetics with impaired glycemic control (Group A – HbA1c >7.3%) had significantly higher fatal and non-fatal events than diabetics with better glycemic control (Group B – HbA1c ≤ 7.3%) despite of having normal MPS. Increased risk for major coronary events in Type-2 diabetic has been shown to vary with age, sex and glycemic control.[7] In our study no significant difference was found between two groups for age, gender, risk factors and LVEF estimated by MPS. This certainly enhances the statistical strength of our data. HbA1c reflects glycemia (predominantly post-prandial) over the preceding months and has been found to have strong association with cardiovascular risk. In a meta-analysis by Sarwar and colleagues, a 1% higher HbA1c level was associated with a 20% higher coronary risk, appreciably better than either fasting or postprandial glucose.[8] A recent study revealed that Type-2 diabetic patients with impaired glycemic control (HbA1c ≤7%) had significant endothelial dysfunction (measured by lower flow mediated dilation of brachial artery; FMD) and more severe CAD than those with good glycemic control (HbA1c <7%).[9] In our study effort tolerance (in term of METS) was significantly lower in Group-A which is likely due to lower FMD of coronary and peripheral vessels. In our study significantly higher over-all cardiac, NFMI and FMI events reflects that the glycemic control has a direct impact upon endothelial function during follow-up period in both groups having comparable demographic and risk factors. Impaired glycemic control in Group-A being a temporal phenomenon led to progressive deterioration of endothelial function resulting in higher major events, lower METS (effort tolerance) and NPV than Group-B with better glycemic control.

One of the major limitations of this study is that we did not measure endothelial dysfunction in either group. We also did not have information about treatment of patients to study the impact of drugs on endothelial dysfunction.

We conclude that a negative MPS has a significantly higher NPV and better effort tolerance in diabetics with good glycemic control (mean HbA1c ≤ 7.3%) than diabetics with impaired glycemic control (mean HbA1c >7.3%). Impaired glycemic control is supposed to be associated with impaired endothelial function and warrants a correlative study in future.

Conflict of Interest: None

References

1. Krempf M, Parhofer KG, Steg PG, Bhatt DL, Ohman EM, Röther J, et. Reach Registry Investigators. Cardiovascular event rates in diabetic and nondiabetic individuals with and without established atherothrombosis (from the Education

of Atherothrombosis for Continued Health [REACH] Registry). Am J Cardiol. 2010; **105:** 667-71.

2. Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. Diabetes Care 2011; **34:** S184-90.

3. Kang X, Berman DS, Lewin H. 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.

4. Fatima N, Zaman M, Ishaq M, Baloch DJ, Bano M, Bano S, et. 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. Nuclear Medicine Communications 2013, **34:** 489-94.

5. Acampa Q, Cantoni V, Green G, Maio F, Daniele S, Nappi C, et al. Prognostic value of normal stress myocardial perfusion imaging in diabetic patients: A meta-analysis. J Nucl Cardiol 2014; **21:** 893-902.

6. Acampa W, Petretta M, Cuocolo R, Daniele S, Cantoni V, Cuocolo A. Warranty period of normal stress myocardial perfusion imaging in diabetic patients: A propensity score analysis. J Nucl Cardiol 2014; **21:** 50-6.

7. Eeg-Olofsson K, Zethelius B, Gudbjörnsdottir S, Björn Eliasson, Ann-Marie Svensson, Jan Cederholm. Considerably decreased risk of cardiovascular disease with combined reductions in HbA1c, blood pressure and blood lipids in type 2 diabetes: report from the Swedish national diabetes Register. Diab Vasc Dis Res 2016; **13:** 268-77.

8. Sarwar N, Aspelund T, Eiriksdottir G, Gobin R, Seshasai SR, Forouhi NG, et al. Markers of dysglycaemia and risk of coronary heart disease in people without diabetes: Reykjavik prospective study and systematic review. PLoS Med 2010; **7:** e1000278

9. Chen S, Shen Y, Liu Y, Dai Y, Wu Z, Wang X, et al. Impact of glycemic control on the association of endothelial dysfunction and coronary artery disease in patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2021; **20:** 64.