ORIGINAL ARTICLE

SHORTER WARRANTY PERIOD OF A NORMAL MPS IN DIABETICS WITH IMPAIRED GLYCEMIC CONTROL (HbA1c >7.3)

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ABSTRACT

OBJECTIVE: To find out clinical outcomes in diabetics with normal stress myocardial perfusion scans (MPS) having glycosylated hemoglobin (HbA1c) > or ≤ 7.3. **MATERIAL AND METHOD:** This was a prospective study conducted at nuclear cardiology department of Karachi Institute of Heart Diseases (KIHD), Karachi, Pakistan. Total 251 diabetics who had a normal stress MPS were included. On the basis of their HbA1c these patients were categorized into Group A (HbA1c >7.3) and Group B (HbA1c ≤ 7.3). This cut-off was taken from our previously published study performed upon early cohort.These patients were followed for 05 years for fatal and non-fatal myocardial infarction (FMI and NFMI). Follow-up was not available in 29 patients, who were excluded from the study leaving a cohort of 222. **RESULTS:** Group A included 57 while Group B had 165 diabetics with a mean age of 59 vs. 57 years and male to female ratio of 42:58% vs. 40:60% respectively (non-significant). Mean body mass index (BMI) in Group A and B was 28.318 vs. 27.532 kg/m^2 (non-significant). Mean HbA1c and fasting blood glucose in Group A were significantly higher than Group B (8.363 vs. 6.630 and 135 mg% vs. 120 mg% respectively). No significant difference was seen in prevalence of hypertension, dyslipidemia, family history of coronary artery disease (CAD) and smoking between two cohorts. Dipyridamole stress was used in 58% vs. 56% in Group A and B respectively (non-significant) while no significant difference was seen in effort tolerance (Metabolic Equivalent Task; METS) of participants of both groups. In both groups stress MPS was normal with normal left ventricular function parameters (non-significant). During 05 years follow-up, no significant intergroup difference in FMI incidence was seen (02 vs. 01 FMIs in Group A and B respectively, p-value non-significant). However, significantly high NFMI was seen in Group A as compared to Group B [11 (19.301%) vs. 04 (0.2.420%), significant p value]. Important to note that this difference was significant only in last 03 years of follow-up. **CONCLUSION:** We conclude that diabetics with impaired glycemic control (HbA1c >7.3) had higher non-fatal MIs after 02 years of a normal MPS than diabetics with better control. Warranty period of a normal MPS in poorly controlled diabetics is shorter and frequent retesting in subsequent years is warranted.

Key Words: MPS, Diabetes, Glycosylated Hemoglobin, warranty period, negative predictive value

Introduction

Diabetes Mellitus (DM) is considered as a global epidemic as it is considered to affect 366 million people by year 2030.[1] Coronary artery disease (CAD) is responsible for more than 75% of deaths in diabetics which is considered as arisk equivalent for CAD.[2] For monitoring of diabetes certain biochemical markers like glycosylated hemoglobin (HbA1c; ≥6.5% i.e. diabetes) provides long term glycemic control and

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considered robust indicator of glycemia than short term glycemic markers like 2 hours postprandial or fasting blood sugar (FBS).[3] Indo-Pakistani diabetic population has greater susceptibility to the metabolic syndrome and there is reported higher incidence of CAD associated mortality in diabetic by 2.78 times as compared to 1.46 times in Europeans counterpart.[3] Gated myocardial perfusion study (GMPS) is the most commonly used functional imaging tool for diagnosis and risk stratification of CAD.[4] The negative predictive value (NPV) of a normal GMPS is >99%.[5,6] but relatively higher events have been reported in diabetics with a negative MPS.[7] Impaired glycemic control (HbA1c >7.0) is reported to be associated with higher cardiac event rates.[8,9] The aim of this study was to find out clinical outcomes in diabetics with normal MPS having HbA1c > or ≤ 7.3.

Material and Methods

Study Population: This prospective study was conducted at Nuclear Cardiology Department of Karachi Institute of Heart Diseases (KIHD), Karachi, Pakistan from January 2011 till December 2012. This study was approved by institute ethical review committee. Total 251 diabetics who had a normal stress MPS were included. On the basis of their HbA1c these patients were categorized into Group A (HbA1c >7.3) and Group B (HbA1c ≤ 7.3). This cut-off was taken from our previously published study performed upon early cohort.[10] These patients were followed for 05 years for fatal and non-fatal myocardial infarction (FMI and NFMI respectively). Follow-up was not available in 29 patients, who were excluded from the study leaving a cohort of 222.

Stress Protocol: Patients who were able to perform dynamic exercise were stressed on treadmill according to Bruce or modified Bruce Protocol. 60-90 seconds prior to terminating the exercise, Technetium-99m Methoxy IsoButyl Isonitrile (Tc-99m MIBI) was administered intravenously. After 30-45 minutes gated SPECT images were acquired. Patients with limited effort tolerance were stressed using dipyridamole (0.142 mg/kg/minute for 04 minute) and Tc-99m MIBI was administered 3 minute after vasodilator injection. Beta and calcium blockers and long acting nitrate were stopped 24-48 hours prior the test. Tea, coffee and xanthine derivatives were stopped 24 hours prior in patients scheduled for dipyridamole test. After 30-45 minutes gated SPECT images were acquired

Acquisition Protocol: All patients underwent same day (stress-rest / rest-stress or stress only if normal) gated SPECT MPI using dual head (Cardio-MD, Philips) dedicated cardiac gamma camera fitted with low energy all purpose (LEAP) collimator, 32 projections around an 180 degree arc and a 64 x 64 matrix. Image reconstruction and LV functional parameters like left ventricular ejection fraction (LVEF), end diastolic volume (EDV), end systolic volume (ESV), wall motion (WM) and transient ischemic dilatation (TID) were contemplated by using commercially available Astonish® and Autoquan® software packages respectively. A GMPS with sum stress score (SSS), sum rest score (SRS), sum difference score (SDS) >2 and TID >1.22 was considered abnormal.

Follow Up: All patients (or a family member in case patient has expired) were interviewed on telephone (24-60 months after GMPI) regarding major acute cardiac events (MACE) like fatal or non-fatal MIs. Patients who could not be contacted (29 patients) were excluded from the study population.

Statistical Analysis: Data was analyzed by using commercially available packages the Medcalc® statistical software version 11.3.10 and statistical package for social sciences (SPSS version 17®). 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). Receiver operating characteristics curves (ROC) were plotted for diagnostic strength of HBA1C, fasting blood sugar (FBS) and duration of DM for CAD. Kaplan Meier plot for event free survival and for purpose of comparison of survival curves logrank test was applied. For all P-values <0.05 were selected as significant.

Result

Total 222 diabetics with normal gated MPS were selected and on the basis of HbA1c, these were

categorized in to two groups. Group A (HbA1c >7.3) had 57 patients with a mean age of 59 years, male to female ratio of 42:58% and mean HBA1C 8.363. Group B (HbA1c ≤ 7.3) included 165 diabetics with mean age of 57 years, male to female ratio of 40:60% and mean HbA1c of 6.630. Mean HbA1c, FBS and duration of diabetes were significantly higher in Group A. No significant difference was seen in prevalence of hypertension (77 vs. 85%), dyslipidemia (42 vs. 42%), family history for CAD (39 vs. 35%) and smoking (18 vs. 13%) in Group A and B respectively. In Group A, 42% underwent dynamic stress while 58% had pharmacological stress. In Group B, 44% had dynamic and 56% underwent pharmacological stress (non-significant p-value). Left ventricular functional parameters were normal in both groups (non-significant p-value). During 05 years follow-up, no significant intergroup difference in FMI incidence was seen (02 vs. 01 FMIs in Group A and B respectively, p-value non-significant). However, significantly high NFMIs were seen in Group A as compared to Group B [11 (19.301%) vs. 04 (0.2.420%), significant p value] (Tab. 1). Annualize event rates for overall and NFMIs were significantly higher in Group A (Tab.1). Kaplan Meier survival plot for FMIs revealed no significant difference in survival between 02 groups (Fig. 1 and 2). Kaplan Meier survival plot for NFMIs revealed significant difference in survival between 02 groups only in last 03 years of follow-up (Fig. 3 and 4).

Variables	Group A (HbA1c >7.3) n=57	Group B (HbA1c ≤7.3) n= 165	χ^2/t-test values	p-values
Age (mean ± SD) yrs	59 ± 10	57 ± 10	-1.302	0.194
Male: Female	24:33 (42: 58%)	66:99 (40:60%)	0.0700	0.791
Body Mass Index (kg/m^2)	28.318 ± 6.912	27.532 ± 5.997	-0.820	0.413
HBA1C	8.363 ± 1.183	6.630 ± 0.668	-13.590	*<0.0001
Fating Blood Sugar (mg/dl)	135 ± 18	120 ± 29	-3.666	*0.0003
DM duration (months)	169 ± 94	132 ± 85	-2.756	*0.0063
Risk Factor				
Hypertension	44 (77%)	140 (85%)	1.908	0.167
Dyslipidemia	24 (42%)	70 (42%)	0.000	1.000
Family history CAD	22 (39%)	57 (35%)	0.293	0.588
Smoker	05 (18%)	21 (13%)	0.861	0.353
Stress protocol				
Bruce	24 (42%)	72 (44%)	0.0686	0.793
Persantin	33 (58%)	93 (56%)	0.0686	0.793
%MPHR	89 ± 07	88 ± 09	-0.763	0.446
METs	7.9 ± 2.1	8.0 ± 2.0	0.321	0.748
LV Function				
%LV Ejection Fraction	64 ± 11	65 ± 11	0.592	0.555
End Diastolic Volume (ml)	79 ± 29	80 ± 27	0.236	0.813
End Systolic Volume (ml)	27 ± 21	30 ± 21	0.930	0.354
Cardiac Events (05 years)				
Fatal	02 (3.510%)	01 (0.606%)	0.434	0.510
Non-Fatal	11 (19.301%)	04 (2.420%)	4.915	*0.027
Annualized event rate%				
Overall	4.561%	0.606%	4.136	*0.042
Fatal	0.702%	0.121%	0.528	0.467
Non-Fatal	3.860%	0.484%	3.607	*0.049

*p<0.05
SD= Standard Deviation
DM=Diabetes Mellitus
HbA1c= Glycosylated Hemoglobin
MPHR=Maximum Age Predicted Heart Rate
MET=Metabolic Equivalent Task

Table 1: Patients' demographics of diabetic with normal myocardial perfusion imaging

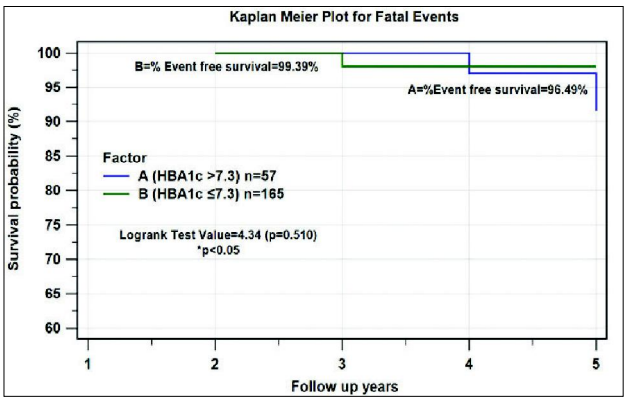

Figure 1: Kaplan Meier Survival plot for fatal cardiac event in both diabetic groups with normal myocardial perfusion imaging results.

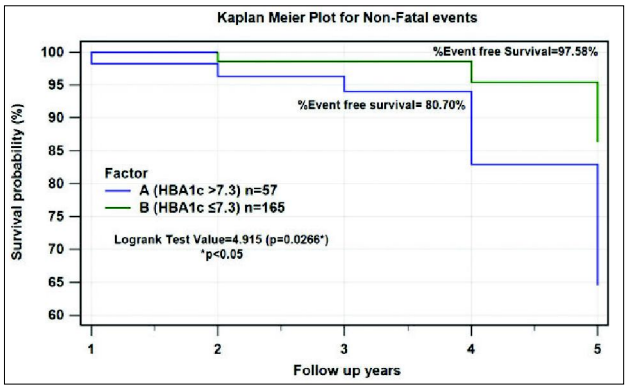

Figure 2: Kaplan Meier Survival plot for non-fatal cardiac event (ischemia or hospitalization) in both diabetic groups with normal myocardial perfusion imaging results.

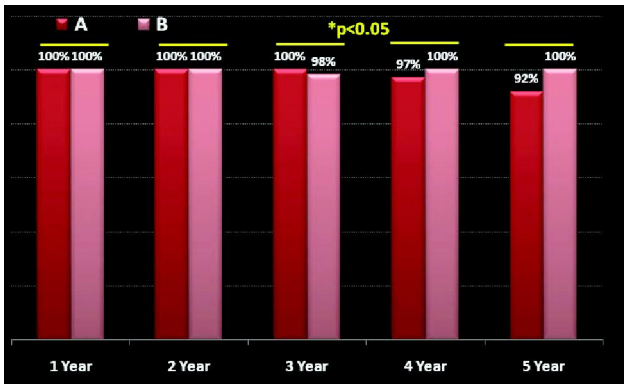

Figure 3: Yearly distribution of % event free survival for fatal cardiac events in both diabetic groups with normal myocardial perfusion imaging results.

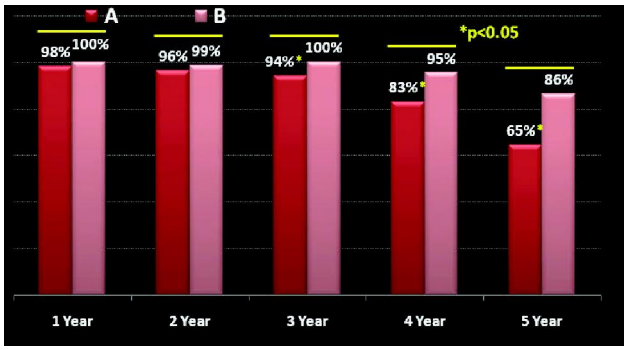

Figure 4: Yearly distribution of % event free survival for non-fatal cardiac events (ischemia or hospitalization) in both diabetic groups with normal myocardial perfusion imaging results.

Variables	Group A with Persantin (n=33)	Group B with Exercise (n=24)	χ^2 values	p-values
Fatal Events	02 (6.06%)	01 (4.166%)	0.0982	0.7540
Non-Fatal Events	05 (15.15%)	04 (16.66%)	0.0234	0.8784
Variables	**Group A with Persantin (n=33)**	**Group B with Exercise (n=93)**	**χ^2 values**	**p-values**
Fatal Events	02 (6.06%)	01 (1.075%)	2.584	0.1080
Non-Fatal Events	05 (15.15%)	03 (3.226%)	5.715	*0.0168
Variables	**Group A with Persantin (n=24)**	**Group B with Exercise (n=72)**	**χ^2 values**	**p-values**
Fatal Events	01 (4.166%)	00 (00%)	3.000	0.08330
Non-Fatal Events	04 (16.66%)	02 (1.212%)	8.825	*0.0030

Table 2: Kaplan Meier Comparative analysis of cardiac events in Persantin and exercise cardiac stress protocol for myocardial perfusion imaging in both groups

Discussion

HBA1C being a good marker of glycated proteins has been used as measure of glycemic control and various studies have found its diagnostic and prognostic significance in diabetics and non-diabetics as well.[10] United Kingdom prospective diabetes study (UKPDS) has shown that adequate glycemic control can reduce the risk of microvascular as well as macrovascular disease in diabetics.[11] A large body of data has shown that significantly low even rate (0.6% for FMI and NFMI) is associated with a normal MPS and 7.4% for abnormal MPS.[12] In this study higher overall event rate despite a normal MPS is in accordance with published data.[7] Higher event rate in Group A (HBA1C > 7.3) is presumably caused by more advanced although subclinical vascular disease in diabetics with impaired glycemic control. This was also seen in a study published by our group revealing HBA1C >7.3 as a reliable predictor of CAD.[10] These facts reveal the importance of counseling by clinicians to their diabetic patients who have normal MPS about the importance of adequate glycemic control in future.

Another important finding of this study is that NPV of normal MPS was low in first 02 years of follow up. But in last 03 years, significantly higher NFMI was observed in Group A (HBA1C >7.3). Similar inference was also observed by Giri et al and a rapid progression of CAD in diabetic was considered as the plausible explanation.[13] These findings show a shorter warranty period of normal MPS in diabetics with impaired glycemic control. Similar facts were observed by Nesto and colleagues who recommended more frequent assessments in diabetics because of associated high cardiac events rates.[14] Our findings are also in concordance with Acampa et al. study concluding a shorter warranty period varying with glycemic control in diabetics with a normal MPS.[15]

We conclude that diabetics with impaired glycemic control (HBA1C >7.3) had higher non-fatal MIs after 02 years of a normal MPS than diabetics with better control. Warranty period of a normal MPS in poorly controlled diabetics is shorter and frequent retesting in subsequent years is warranted.

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