HbA1c and Myocardial Ischemia Detected via Myocardial Perfusion Scintigraphy in Type 2 Diabetes Mellitus

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ABSTRACT

Background/Objective: *Coronary Artery Disease (CAD) is the leading cause of mortality among patients with type 2 diabetes mellitus. Several studies evaluated glycemic control and MPS results with good correlation. In the Philippines, data concerning this matter are few, hence this study.* **Methodology:** *This is a cross-sectional study of selected Filipino patients with type 2 diabetes mellitus without previous cardiac events who underwent stress or pharmacologic stress MPS (Tl-201 or Tc-99m sestamibi) over an 18-month period at the Philippine Heart Center. Electrocardiogram and 2D echocardiogram results were also noted. Patients were grouped into adequate glycemic control (HbA1c < 7.0%) and inadequate glycemic control (HbA1c > 7.0%). Binary logistic regression was computed to determine association of glycemic control to MPS defects.* **Results:** *A total of 206 subjects (114 with HbA1c < 7.0%, 92 with HbA1c > 7.0%), were included in the study, with male predominance. Mean HbA1c values showed direct correlation: the higher the HBA1c values, the more MPS defects. Inadequate glycemic control group had significantly higher subjects with mild and moderate to severe degree of myocardial ischemia ($p < 0.001$). The relative risk of having a significant CAD in the inadequate glycemic control group is 4.30 times more than their counterpart ($p < 0.001$). Factoring the duration of inadequate glycemic control to > 10 years, relative risk increased to 7.63.* **Conclusion:** *The study shows that patients with type 2 diabetes mellitus with inadequate glycemic control have increased MPS defects and higher relative risk for having significant CAD.Diabetic patients with inadequate glycemic control for > 10 years have an even higher risk of having significant CAD.*

Keywords *myocardial perfusion imaging, coronary artery disease, diabetes mellitus type 2, glycated hemoglobin A, diabetes complications*

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INTRODUCTION

Coronary Artery Disease (CAD) is the leading cause of mortality among patients with type 2 diabetes. Patients with this disease usually have myocardial ischemia that are silent and in advanced stage when symptoms manifest (1-2). The risk for myocardial infarction (MI) among diabetics is 2–4 times higher than non-diabetic patients. Patients with diabetes also have a lesser survival rate in an event of an MI attack (3-5). In addition, these subjects have more diffuse, calcified, and extensive CAD (4). Given the poorer prognosis of CAD in the diabetic population, it is important that patients with diabetes are evaluated as early as possible to reduce mortality and morbidity through early interventional therapy and risk-factor modification (6-7).

The best invasive modality for the diagnosis of CAD is coronary angiography (4,8). Despite its advantages over several cardiovascular non-invasive imaging modalities with respect to temporal and spatial

resolution in assessing coronary artery vessel lumen, it also has several disadvantages (4,8). It is very expensive, does not allow direct visualization of coronary microcirculation, has risks for perioperative complications, and is not commonly available (5,8). Moreover, a significant number of patients with diabetes, who present with ischemia through non-invasive testing, do not present with ischemic disease on coronary angiography (8). Thus, coronary angiography cannot be used to screen most asymptomatic diabetic patients for CAD, as risks outweigh the benefits (6). In line with this, Myocardial Perfusion Single-Photon Emission Computed Tomography (MP-SPECT) fills the gap in the evaluation of CAD among patients with diabetes. Myocardial perfusion scintigraphy (MPS) not only provides information about the physiological significance of flow-limiting CAD, but also assesses several independent risk factors for subsequent cardiac events (2,5). It has been suggested that severity of MPS defects among diabetic patients is a predictor of future MI and death (2,8). In the general population, the sensitivity and specificity of MPS-SPECT for detection of CAD are 86% and 74%, respectively, far superior than electrocardiogram (ECG) and exercise tolerance test (ETT) (4,8). The accuracy of MP-SPECT is not significantly different among diabetic and non-diabetic patients (4). Glycosylated hemoglobin (HbA1c), on the other hand, reflects the average blood glucose concentration over the preceding 2 to 3 months (9). Several foreign studies evaluated the correlation of glycemic control and MPS abnormalities among asymptomatic diabetic patients using varying HbA1c values with directly-proportional results: increase in HbA1c correlates with severe MPS abnormalities (8,10–12). In the Philippines, type 2 diabetes is a major problem in terms of economic and disease burden. The prevalence of diabetes as of 2008 was 17.8%, which translates to 1 out of every 5 Filipinos having diabetes (13). Furthermore, current data in the Philippines regarding MPS abnormalities and its relationship to type 2 diabetes are scarce as searched on HERDIN, PubMed and Google Scholar.

In this study, we explore the association of the level of HbA1c to the presence of myocardial ischemia as evaluated by MPS among type 2 diabetes mellitus patients without previous cardiac events. We also want to know the effect of the duration of type 2 diabetes on the MPS defects. The results of this study will contribute valuable information for clinicians in the management of CAD among type 2 diabetics, in terms of relative risk of having significant CAD in a given HbA1c value plus the effect of the duration of inadequate glycemic control.

METHODOLOGY

Study Population and Patient Selection:

This was a cross sectional study of 206 patients with diabetes mellitus, referred for exercise stress or pharmacologic stress (dipyridamole) MPS using thallium-201 chloride (^{201}Tl) or technetium-99m sestamibi (Tc-99m sestamibi) to the Division of Nuclear Medicine of the Philippine Heart Center (PHC) in Quezon City, Philippines for a period of 18 months from January 1, 2016 to June 30, 2017. The subjects included were: 1) adult Filipino patients with diabetes mellitus, 2) adult males, and 3) post-menopausal women. Patients with the following conditions, namely, 1) prior history of MI, 2) previous coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) operations, 3) critically-ill

patients, 4) presence of cardiomyopathy, 5) with valvular heart disease (VHD), and 6) pregnant patients were excluded in the study.

Data Collection Procedure:

A chart review of Filipino type 2 diabetic patients referred for MPS was made. The decisions for stress or pharmacologic stress MPS were made by the referring physicians based on their assessment on the physical and functional status of the patient. Eligible subjects were selected based on the existing electronic medical records (EMR). Demographic data, risk factors, maintenance medications, ECG and 2D echo results, HbA1c values and presence of ischemia based on summed stress score (SSS), were obtained using prepared data collection form. Selection of diabetic patients was based on the history (those who were already diagnosed with type 2 DM). The subjects were grouped into two: 1) with adequate glycemic control (HbA1c < 7.0%), and 2) those with inadequate glycemic control (HbA1c > 7.0%), based on American Diabetes Association (ADA) 2016 recommendation (14). Philippine Heart Center Nuclear Medicine standard protocol for stress and pharmacologic stress MPS was used.

Stress and Acquisition Protocol of MPS:

Stress Protocol

All patients were instructed to discontinue intake of beta blockers and calcium channel blockers 24 hours prior to the procedure. Nitrates were withheld and patients were placed on fasting for 4 hours prior to the study. Oral intake of possible interfering drugs and substances such as xanthine-containing drugs, caffeine-containing foods and beverages was avoided. Treadmill stress test was performed using either NIH or modified Bruce protocol. For stress MPS using ^{201}Tl, an activity of approximately 111 MBq was administered to the patients upon reaching at least 85% of the predicted maximum heart rate. For pharmacologic stress ^{201}Tl, dipyridamole 0.568 mg/kg was infused over 4 minutes and ^{201}Tl with an approximate activity of 111 MBq was given at the 8th minute of the procedure. For stress MPS using Tc-99m sestamibi, an activity of approximately 296 MBq was given during rest and 814 MBq upon reaching 85% of the predicted maximum heart rate. Lastly, for pharmacological stress MPS using Tc-99m sestamibi-dipyridamole, an activity of approximately 296 MBq was given during rest, dipyridamole 0.568 mg/kg was infused over 4 minutes, and Tc-99m sestamibi with an activity of 814 MBq was given upon reaching 85% of the predicted maximum heart rate.

Acquisition Protocol

For ^{201}Tl stress or pharmacological MPS, images were obtained through the Philips Forte dual-head camera using a non-circular 180-degree acquisition for 32 projections at 40 seconds per projection. Two energy windows were used, including 20% window centered at 73 keV peak and a 15% window centered at the 167 keV peak. Images were obtained in supine position. Gated SPECT was performed, obtaining 8 frames per cycle. Images were acquired using a 64 x 64 image matrix with a zoom factor of 1.48. For Tc-99m sestamibi MPS, images were obtained with the same machine, 180-degree acquisition for 64 projections at 40 seconds per projection, at 20% window centered at 140 keV peak. Gated SPECT acquisition was similar to ^{201}Tl. No attenuation or scatter correction was used.

Visual analysis of MPS:

All MPS studies were analyzed by two experienced

observers using a 17-segment scheme. ^{201}Tl or Tc-99m sestamibi uptake was scored using a five-point scale (0 = normal, 1 = mildly decreased, 2 = moderately decreased, 3 = severely decreased, and 4 = absent). The summed stress score (SSS) was used for stratification of ischemia into SSS = 0–3 normal, SSS = 4–8 mildly abnormal, and SSS > 9 moderate to severely abnormal (2,15–16). The summed stress score (SSS) is commonly used as semi-quantitative technique that combines the extent and severity of perfusion abnormalities into a single measure. More extensive perfusion abnormalities are associated with more severe CAD (17). SSS values greater than 3 are equivalent to significant CAD (17).

Identification of Study Variables:

INDEPENDENT VARIABLE: Glycemic control – glucose control for patients with diabetes, for the past 3 months, expressed as HbA1c.

DEPENDENT VARIABLE: Presence of ischemia – perfusion defect seen on stress or pharmacologic stress MPS using ^{201}Tl or Tc-99m sestamibi, expressed as SSS.

CONFOUNDING VARIABLES: age, BMI, duration of diabetes and presence of comorbidities (hypertension, dyslipidemia, and history of smoking).

Statistical Analysis:

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables, median and interquartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables.

One-way analysis of variance was used to compare for variables like age, BMI, and LVEF. Chi-square or Fisher's exact test was used to determine the difference of frequency among categorical variables among three different degrees of myocardial ischemia. Box and whiskers plot was used to show the different distribution of HbA1c value per degree of myocardial ischemia and Kruskal-Wallis test was also used to compare those categories in terms of HbA1c level. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine if inadequate glycemic control will predict ischemia. We also tested the said association adjusted for the defined confounding variables.

Missing variables were neither replaced nor estimated. ull hypothesis was rejected at 0.05 level of significance (α). STATA 13.1 was used for data analysis. Based on previous research (12), we calculated using NCSS-PNSS software that to detect a difference in ischemia among patients with adequate (50%) and inadequate (28%) glycemic control, with power of 80% at a type 1 error rate of 5%, 170 patients were required, 48 for inadequate glycemic control and 122 for adequate glycemic control.

Ethical Considerations:

This study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. The protocol was reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC IERB). The investigators were given a waiver of informed consent as this was a chart review study. The risk to the subject's privacy was minimal and no sensitive information was obtained. The investigator ensured that subject's anonymity was maintained.

RESULTS

A total of 206 subjects who had MPS were confirmed eligible for the study which comprised of 86 ^{201}Tl stress, 65 dipyridamole ^{201}Tl pharmacologic stress, 23 Tc-99m sestamibi stress, and 32 dipyridamole Tc-99m sestamibi pharmacologic stress. Among the diabetic subjects, age was higher in the group with insignificant myocardial ischemia ($p < 0.012$). Inverse pattern was also observed in the insignificant and moderate to severe myocardial ischemia group, with more abnormal ECG findings in the former and elevated number of wall motion abnormality in the latter ($p < 0.005$; $p < 0.001$). The degree of myocardial ischemia distribution based on SSS for inadequate glycemic control group, showed 46.7% (43/92), 16.3% (15/92), and 37% (34/92), for insignificant, mild, and moderate to severe, respectively ($p < 0.001$). Other baseline and clinical characteristics were not different among the groups (Table 1).

Table 1. Distribution of baseline characteristics according to myocardial ischemia

Characteristics	Degree of Myocardial Ischemia				P-value
	Insignificant (n=133)	Mild (n=26)	Moderate to Severe (n=47)	Total (n=206)	
	Frequency (%); Mean ± SD; Median (IQR)				
Age	60.76 ± 9.23	56.5 ± 10.90	56.74 ± 8.89	59.31 ± 9.54	**0.012**
Sex					**0.018**
Male	76 (57.14)	37 (78.72)	19 (73.08)	132 (64.08)	
Female	57 (42.86)	10 (21.28)	7 (26.92)	74 (35.92)	
BMI	27.18 ± 4.98	27.72 ± 4.01	25.53 ± 3.78	26.87 ± 4.66	0.069
Abnormal ECG (−) ischemia	29 (21.80)	5 (19.23)	21 (45.65)	55 (26.83)	**0.005**
Abnormal 2D echo (+) wall motion abnormality	23 (23.23)	8 (38.10)	30 (75)	61 (38.13)	**<0.001**
Comorbidities					
Hypertension	110 (82.71)	23 (88.46)	36 (76.60)	169 (82.04)	0.450
Smoker	30 (22.56)	7 (26.92)	15 (31.91)	52 (25.24)	0.567
Dyslipidemia	45 (33.83)	12 (46.15)	20 (42.55)	77 (37.38)	0.349
Obesity	27 (20.30)	6 (23.08)	4 (8.51)	37 (17.96)	0.129
Treatment					
OHA	105 (78.95)	25 (96.15)	41 (87.23)	171 (83.01)	0.071
Insulin	18 (13.53)	5 (19.23)	12 (25.53)	35 (16.99)	0.171
Statin	99 (74.44)	15 (57.69)	33 (70.21)	147 (71.36)	0.221
ASA Clopidogrel	85 (63.91)	15 (57.69)	36 (76.60)	136 (66.02)	0.182
ARB ACE inhibitors	94 (70.68)	17 (65.38)	30 (63.83)	141 (68.45)	0.643
CCB	61 (45.86)	11 (42.31)	9 (19.15)	81 (39.32)	**0.005**
Beta blockers	46 (34.59)	6 (23.08)	20 (42.55)	72 (34.95)	0.245
Nitrates	19 (14.29)	3 (11.54)	14 (29.79)	36 (17.48)	**0.049**
Chest pain	54 (40.60)	9 (34.62)	12 (25.53)	75 (36.41)	0.178
Heart failure symptoms (−)	48 (36.09)	10 (38.46)	23 (48.94)	81 (39.32)	0.300
Diabetes duration ≥ 10 years	43 (32.33)	7 (26.92)	16 (34.04)	66 (32.04)	0.817
LVEF	64.01 ± 13.39	58.73 ± 15.71	38.74 ± 15.43	57.58 ± 17.53	**<0.001**
Glycemic control					**<0.001**
Adequate (HbA1c <7.0%)	90 (67.67)	11 (42.31)	13 (27.66)	114 (55.34)	
Inadequate (HBA1c ≥ 7.0%)	43 (32.33)	15 (57.69)	34 (72.34)	92 (44.66)	
HbA1c level	6.6 (4.6 to 11.1)	7.15 (6.1 to 9.1)	7.7 (6.1 to 11.8)	6.8 (4.6 to 12.3)	**<0.001**

*Abbreviations: **BMI** – Body Mas Index, **SD** – Standard Deviation; **OHA** – Oral Hypoglycemic Drugs; **ASA** – Aspirin; **ARB** – Angiotensin Receptor Blocker; **ACE** – Angiotensin Converting Enzyme; **CCB** – Calcium Channel Blocker; **LVEF**– Left VentricularEjection Fraction*

The median HbA1c values per degree of myocardial ischemia were 6.6%, 7.15% and 7.7% for the insignificant, mild and moderate to severe, respectively ($p < 0.001$). The insignificant group showed wide variation of HbA1c values above the mean value. Linear trend was noted for the mean HbA1c values in relation to the degree of myocardial ischemia (Figure 1).

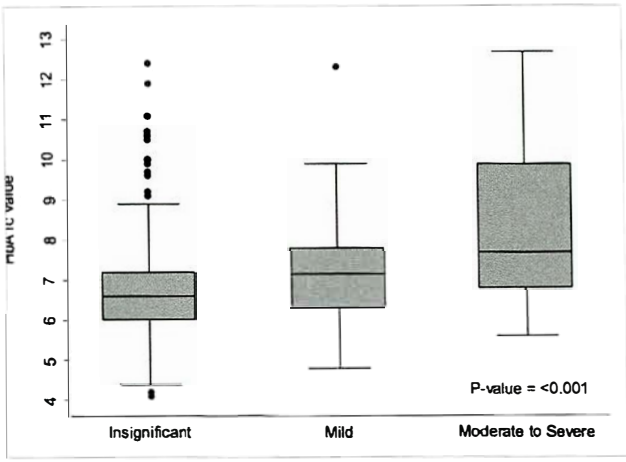

Figure 1. Degree of myocardial ischemia and HbA1c Level

The risk of having significant CAD among type 2 diabetic patients was significantly associated with inadequate glycemic control with an odds ratio of 4.30 (95% CI: 2.26–8.18, $p < 0.001$) (Table 2). Sub-analysis of the data, factoring the duration of diabetes, revealed that type 2 diabetic subjects with inadequate glycemic control for > 10 years have an odds ratio of 7.63 (95% CI: 2.07–28.12) for having significant CAD as compared to their counterpart.

DISCUSSION

This study shows that type 2 diabetic patients with inadequate glycemic control have increased MPS defects and higher relative risk for having significant CAD. The duration of having inadequate glycemic control also contributes significantly to the increase in the risk for CAD.

Among patients with type 2 diabetes, it is well proven that strict glycemic control can reduce vascular complications (18). Equally, increase in relative risk for death from any cause was observed among men (1.24) and women (1.28), for every 1 percentage point increase in HBA1c values (19). In this study, there are more male diabetic subjects. The observed sex difference in diabetes prevalence may be a result of: 1) increased awareness of risk factors in women, who are then more likely to engage in healthy behavior than men; 2) increase in automation due to technology advancement which decreases physical work in men; and 3) diagnosis in men at an early age and at lower BMI than women (20–21).

ECG findings of ischemia did not necessarily translate to abnormal MPS results in this study as compared to the wall motion abnormality in 2D echo.

Table 2. Association of glycemic control and the presence of significant CAD

Glycemic control	With Significant CAD n=73 (35%)	With Insignificant CAD n=133 (65%)	Crude Odds Ratio (95% CI)	Hazard Odds Ratio (95% CI)**
	Frequency (%)			
Inadequate glycemic control HBA1c ≥ 7.0%	49 (67.1)	43 (32.3)	4.27 (2.32 to 7.85)*	4.30 (2.26 to 8.18)*
Adequate glycemic control < 7.0%	24 (32.9)	90 (67.7)		

** p-value < 0.001; ** Adjusted for confounding variables*

which consistently gave a linear pattern. The observed inverse pattern among these two modalities can be attributed to their sensitivity and specificity in detecting CAD (4,8). The findings in ECG results deviate from the study made by Shmendi et al, wherein a direct relationship between ECG findings of ischemia and degree of MPS abnormalities was noted (8). In the UKPDS study, an abnormal ECG is an independent risk factor for all-cause mortality and fatal MI in type 2 diabetic subjects (18). A study by Scheidt-Nave et al. also showed that ECG findings of ischemic heart disease (IHD) are morecommon among asymptomatic non-insulin dependent diabetes mellitus (NIDDM) patients (22). Abnormal ECG findings among this population have been demonstrated to predict inducible myocardial ischemia (23). Among the maintenance medications, the observed higher use of CCB and nitrates in the subjects with insignificant degree of myocardial ischemia can be attributed to the fact that most diabetic patients have hypertension and coronary artery disease as their comorbidities. CCB has shown to slow down progression of diabetic renal disease, atherosclerosis, and to some extent, reverse diabetic cardiomyopathy. Nitrates, on the other hand, are very effective in decreasing angina symptoms of CAD (24–26). Low LVEF values were observed among patients with moderate to severe degree of myocardial ischemia. These observed values are in line with another study where diabetics had a lower LVEF than non-diabetics (27). This phenomenon can be attributed to diabetic cardiomyopathy in terms of loss of normal microvasculature and remodeling of the extracellular matrix, leading to contractile dysfunction of diabetic hearts (28). With respect to the association of type 2 DM and glycemic control towards MPS defects, our results are similar with the findings of Shmendi et al, Lynn Fillipon et al, and DeLuca et al. The study by Shmendi et al. showed that African subjects with HbA1c > 7.0% have a higher risk of abnormal MPS with extensive ischemia as compared to those with HbA1c values < 7.0% (8). Research by Lynn Fillipon et al. revealed that patients with sub-optimal glycemic control (HbA1c > 7.0%) and poor glycemic control (HbA1c > 8.0%) have significantly higher abnormal MPS results compared to their non-diabetic counterpart (11). DeLuca et al. observed that abnormal MPS results are more prominent among diabetic patients with poor glycemic control (HbA1c > 7.6%) compared to patients with optimal glucose control (HbA1c < 7.6%) (12).

The overall information from this present research is crucial in supporting the dictum that early aggressive glucose control and duration of uncontrolled hyperglycemia play an important role in the progression of CAD (29). Our data show that Filipino type 2 diabetic population is no different from the Western, European and even South African type 2 diabetic populations in terms of cardiovascular complications of uncontrolled type 2 diabetes. Inadequate glycemic control and its duration equate to more MPS defects. To the best of our knowledge, there are few current data regarding association of glycemic control and the presence of ischemia based on MPS results among Filipino patients with type 2 DM. The results of this study suggest early aggressive glycemic control and possible incorporation of stress MPS in future clinical practice guidelines in screening for CAD among this population. Stress MPS can be a very helpful, non-invasive method in the early detection and prevention of CAD.

Study Limitations

The retrospective nature of data collection was a limitation of this research, since the accuracy of the data gathered was dependent on the existing medical records. This study cannot predict if a diabetic subject consistently had adequate or inadequate glycemic control during the entire course of the disease, due to the fact that HbA1c values were taken only once. Lastly, this study was also limited by referral bias, as most of the patients referred for MPS at this institution already have multiple CAD risk factors.

CONCLUSION

The study shows that patients with type 2 diabetes mellitus with inadequate glycemic control have increased MPS defects and higher relative risk for having significant CAD. Patients with inadequate glycemic control for > 10 years have an even higher risk of having significant CAD.

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DISCLOSURE OF CONFLICT OF INTEREST

The authors of this paper have no conflict of interest related to the research topic.

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