

Conference Paper

Association Between Type 2 Diabetes Mellitus and the Presence of Myocardial Ischemia among Filipino Patients with Stress Myocardial Perfusion Scintigraphy

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Abstract

Background: Type 2 DM patients usually had poor prognosis for CAD. MPS with SPECT has been extensively used in CAD detection and it's application among type 2 DM population is still under study with promising result. In the Philippines, there are no current available data regarding this matter. Methodology: This was a cross sectional analytical study of randomly selected Filipino patients without previous cardiac events in whom MPS using Thallium-201 were performed over a 24-month period. Association of myocardial ischemia was compared using logistic regression analysis based on total summed stress score (SSS) values. Results: Total of 208 patients (104 type 2 DM and 104 non-type 2 DM) who underwent stress or pharmacologic MPS using Thallium-201 were included in the study. Majority of the subjects were male. Abnormal 2D echo result and lower EF were significantly present among type 2 DM group ($p = 0.044, 0.0005$). Hypertension was more prominent among the list of co-morbidities and has significant relationship with type 2 DM group ($p = 0.025$). The distribution of myocardial ischemia among type 2 DM group with insignificant, mildly abnormal, and moderate to severely abnormal; were 60.6%, 12.5%, and 26.9%, respectively. The presence of having significant CAD ($SSS > 3$) was associated with the type 2 DM group with odds ratio of 2.57 (95% CI: 1.38-4.78, $p = 0.003$) Conclusion: The current study has shown that Filipino type 2 DM patients without previous cardiac events are likely to have significant and more severe scintigraphic evidence of CAD than their non-type 2 DM counterpart.

Keywords: coronary artery disease, Filipino type 2 diabetic patients, myocardial perfusion scintigraphy, myocardial ischemia, summed stress score

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1. Introduction

Diabetes mellitus (DM) is a significant health problem with great importance [1]. It has an estimated worldwide prevalence of 200 million as of 2007 and projected to balloon to 300 million in 2025 [2]. In the Philippines, its prevalence as of 2008 was 17.8%, which translates to 1 out of every 5 Filipinos potentially have type 2 DM [3]. Coronary artery disease (CAD) is the leading cause of death among type 2 DM patients [1], [4]-[7]. Myocardial ischemia in these patients are usually silent and in advanced stage once they clinically manifest [4]-[5], [8]-[9]. The risk for patients with type 2 DM to have myocardial infarction (MI) is 2-4 folds than their non-DM counterparts [5]-[6], [10]. In addition, they generally have a less favorable response to revascularization and have reduced overall long-term survival [4], [9]. However, in the Philippines, early detection of CAD in these population is usually delayed by undergoing screening for CAD thru less sensitive but widely available diagnostic tool in out patient department setting like ECG. Further testing are often done for definitive diagnosis of CAD [6], [11].

The role of single-photon emission computed tomography (SPECT) in evaluation for myocardial ischemia has been extensively studied [1], [4], [6]-[7]. In general, the sensitivity and specificity of SPECT for CAD detection are 86% and 74%, respectively [6, 11]. Its accuracy between patients with and without type 2 DM are also comparable [4], [11]. Although not the "gold" standard for the detection of CAD, nuclear imaging with SPECT offers several advantages over coronary angiography since it is less expensive, has lesser complications due to its non-invasive nature, and provides information about physiologic significance of flow-limiting CAD [6], [11]. Current opinion regarding evaluation of CAD in type 2 DM patients is to recommend stress myocardial perfusion scintigraphy (MPS) [7]. The usefulness of this approach is still under study, however there were promising results [1], [4]-[5], [7], [11]. In the Philippines, there are no current available data regarding this matter.

2. Objectives of the Study

This study aims to determine the association of type 2 DM and the presence of myocardial ischemia among Filipino type 2 DM patients who underwent stress or pharmacologic stress MPS using Thallium-201 so that preventive measures maybe taken in order to reduce morbidity of CAD. This study also determines the distribution of type 2 DM patients with insignificant, mildly abnormal, and moderate to severely abnormal ischemia.

3. Materials and Methods

3.1. Ethical considerations

This study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to the study, the protocol was reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC IERB). The investigator request for the waiver of informed consent due to difficulty of obtaining individual authorization since the last contact with research subjects. The risk to the subject's privacy was minimal and no sensitive information were obtained. The investigator ensured that subject anonymity was maintained.

3.2. Study population and patient selection

This was a cross sectional analytical study of 208 Filipino patients (104 type 2 DM, 104 non-type 2 DM), referred for exercise stress or pharmacologic stress (dipyridamole) MPS using Thallium-201 to the Department of Nuclear Medicine of the Philippine Heart Center (PHC) in Quezon City, Philippines for a period of 24 months, from, June 1, 2014 to May 31, 2016. The subjects included were; 1) type 2 DM and non-DM Filipino patients and 2) adult patients > 19 years old. Patients with these following conditions, namely; 1) prior history of MI, 2) previous history of coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) operations, 3) critically-ill patients, 4) valvular heart disease (VHD), and 6) pregnant patients, were excluded in the study. Sample size calculation for this study was made using STATA SE version 13 software. The minimum sample size computed was > 208, based on % ischemia of diabetic and non-diabetic patients, 44.8% and 25.4% [1] respectively, with alpha = 5% and power of 80%.

3.3. Study maneuver

A chart review of Filipino patients who underwent stress or pharmacologic (dipyridamole) stress MPS using Thallium-201 was made. Eligible subjects were selected based on the existing electronic medical records. A total of 1510 patients undergo MPS for the said inclusive dates, were 638 had MPS using Thallium-201. From 638 eligible patients, they were dichotomized into two groups, type 2 DM and non-type 2 DM groups, then undergo randomization, each having 104 subjects. Demographic data, patients risk factors and presence of ischemia based on summed stress score (SSS),

were obtained using prepared data collection form. For this study, diabetic patients were defined as individuals who had established diabetic history, taking hypoglycemic agent (either oral or insulin). Philippine Heart Center Nuclear Medicine standard protocol for stress and pharmacologic stress MPS using Thallium-201 was used.

3.4. Visual analysis of MPS

All MPS studies were analysed by two experience observers using a 17-segment scheme. Thallium-201 uptake were 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) is commonly used as semiquantitative technique that combines the extent and severity of perfusion abnormalities into a single measure. More extensive perfusion abnormalities are associated with more severe CAD [16]. SSS >3 is synonymous with having significant CAD [12].

3.5. Statistical analysis

Data analysis was done using STATA SE version 13. Quantitative variables were summarized as mean and standard deviation, while qualitative variable was tabulated as frequency and percentage. Association between type 2 DM and presence of myocardial ischemia were estimated and tested using logistic regression analysis with level of significance set at 5%.

4. Results and Discussion

A total of 208 patients (104 type 2 DM, 104 non-type 2 DM) were included in the study. The mean age was 59.1 ± 10.6 years and 57.2 ± years for type 2 DM and non-type 2 DM group, respectively. Male subjects dominate the study subjects (58%). ECG findings of ischemia were comparable among the two groups. Abnormal 2D echo results and lower ejection fraction (EF) values were significantly prominent in the type 2 DM group ($p = 0.044$, 0.0005). Hypertension tops the list among the list of comorbidities and was significantly higher in the type 2 DM group ($p = 0.025$). Angiotensin receptor blocker/inhibitor (ACE/ARB) as BP lowering drug was used more often by type 2 DM group ($p = 0.017$). Other baseline and clinical characteristics had no significant difference among the groups (Table 1).

TABLE 1: Comparison of Baseline Characteristics.

Characteristics	With Type 2 DM (n=104)	Without Type 2 DM (n=104)	P-value
	Frequency (%); Mean \pm SD		
Age	59.1 \pm 10.6	57.2 \pm 10.7	0.197
Sex			1.000
Male	60 (57.7)	60 (57.7)	
Female	44 (42.3)	44 (42.3)	
BMI	27.0 \pm 3.7	26.0 \pm 7.9	0.245
Abnormal ECG (+) ischemia	30 (28.9)	36 (34.6)	0.456
Abnormal echo (+) wall motion abnormality	21 (38.9)	14 (21.2)	0.044
Comorbidities			
Hypertension	85 (81.7)	70 (67.3)	0.025
Smoker	31 (29.8)	21 (20.2)	0.149
Dyslipidemia	47 (45.2)	47 (45.2)	1.000
Obesity	16 (15.4)	10 (9.6)	0.294
Treatment			
Statins	52 (50.0)	55 (52.9)	0.782
ARB/ACE inhibitor	68 (65.4)	50 (48.1)	0.017
ASA/Clopidogrel	57 (54.8)	43 (41.4)	0.071
CCB	34 (32.7)	37 (35.6)	0.770
Beta blockers	35 (33.7)	25 (24.0)	0.168
Nitrates	22 (21.2)	16 (15.4)	0.370
Typical chest pain	16 (15.4)	13 (12.5)	0.689
Atypical chest pain	45 (43.3)	38 (36.5)	0.396
Ejection fraction (%)	59.5 \pm 16.3	66.2 \pm 10.4	0.0005

The distribution of type 2 DM patients with insignificant, mildly abnormal, and moderate to severely abnormal myocardial ischemia based on SSS values were 60.6% (63/104), 12.5% (13/104), and 26.9% (28/104), respectively. Higher moderate to severely abnormal myocardial ischemia was seen in the type 2 DM group (Figure 1).

Presence of scintigraphic evidence of myocardial ischemia or risk of having significant CAD was significantly associated with the type 2 DM group with an odds ratio of 2.57 (95% CI: 1.38-4.78, $p = 0.003$) (Table 2).

TABLE 2: Association between type 2 DM and presence of myocardial ischemia.

	With significant CAD n= 62	Normal n= 146	Odds Ratio (95% CI)	P-value
	Frequency (%)			
Type 2 DM patients	41 (66.1)	63 (43.2)	2.57 (1.38 to 4.78)	0.003
Non Type 2 DM patients	21 (33.9)	83 (56.8)		

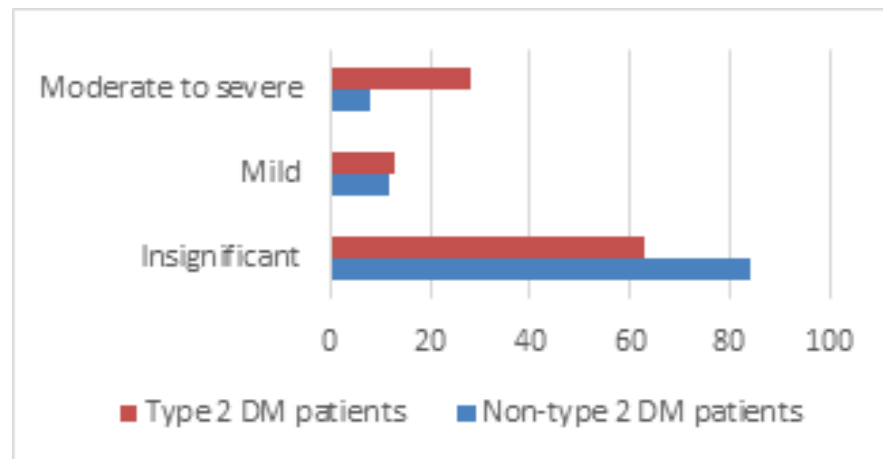


Figure 1: Distribution of myocardial ischemia among the study subjects..

The results of this recent study showed that the risk of having significant CAD expressed in SSS among Filipino patients without previous cardiac events are significantly higher among the type 2 DM group. The frequency and severity of myocardial ischemia, abnormal 2D echo result and low EF values are also more prominent in this group. Among the risk factors examined for CAD, hypertension showed significant relationship with type 2 DM. These findings are in agreement with those reported by Wackers, et al., DeLuca et al., and Shmendi, et al., using Technetium 99m-Sestamibi [4], [8], [11]. In a multi-centered randomized controlled trial study by Wackers, et. al., involving 1123 subjects; silent myocardial ischemia occurred in > 20% asymptomatic type 2 DM patients [4]. DeLuca et. al. study comprising of 836 patients, showed that the prevalence of silent myocardial ischemia detected by MPS among type 2 DM patients without known CAD were significantly higher than their non-type 2 DM counterpart, 34% (67/196) versus 14% (89/640), respectively [8]. In a retrospective chart review of 340 patients, Shmendi et al., demonstrated that the prevalence of more extensive myocardial ischemia using stress or pharmacologic stress MPS was significantly associated with type 2 DM patients than those without the disease (85.6% versus 68%; odds ratio of 2.81, $p = <0.01$) [11].

Screening for CAD in this type 2 DM population are usually hampered by the less sensitive and specific non-invasive diagnostic modalities. ECG is the most widely use technique for risk stratification of patients with suspected CAD [13]. However, studies have showed that resting and exercise ECG were not the most sensitive techniques with low diagnostic accuracy for CAD detection among type 2 DM patients [6], [11]. The appearance of transient ST segment depression, which is the hallmark for myocardial ischemia, is affected by factors other than myocardial ischemia itself. These factors and the fact that ST-T changes occur late in the ischemic cascade, makes exercise ECG

a modest diagnostic accuracy for CAD detection [13]. The sensitivity and specificity of exercise ECG test for CAD detection among type 2 DM patients were 47% and 81% respectively [14]. Another non-invasive diagnostic modality is the stress echocardiography. Exercise and pharmacologic stress ECHO are widely accessible, less expensive and typically well-tolerated. This test is appropriate for symptomatic patients with intermediate pretest probability of CAD and contraindications to regular treadmill stress testing. For CAD detection, exercise stress echo has a sensitivity and specificity of 79-85% and 72%-87%, for general population; 82% and 54%, respectively for type 2 DM population [14]-[15]. There are limited data that specifically address the utility of stress echocardiography in CAD detection among type 2 DM patients [14].

MPS with SPECT is an essential non-invasive diagnostic tool in CAD detection and risk stratification. Although not suggested as a screening tools for CAD detection among type 2 DM Filipino patients, it has significant value in identifying those at risk for CAD and thus in need of more aggressive management [1], [7], [11]. This is important because once CAD in type 2 DM patients becomes symptomatic, these patients will face significant morbidity and mortality. MPS, with the newer detectors, has one of the highest sensitivity and acceptable specificity among the cardiac non-invasive diagnostic tool and has several advantages over the gold standard, coronary angiography in CAD detection in terms of economics and risk of complication [16]. Compared to stress ECG and 2D echo, MPS also has the advantage to plot areas of reversible ischemia with their corresponding affected vascular supply. The result of this study suggested aggressive CAD screening among type 2 DM Filipino patients without previous cardiac events using high sensitivity non-invasive diagnostic tool like MPS for early detection, prevention and treatment of CAD.

4.1. Limitation of the study

The retrospective data collection of this study was a limitation, since the accuracy of the data gathered was dependent on the available medical records. There was also no accurate information about the duration of type 2 DM and degree of glycemic control. Lastly, this study was also limited by referral bias, since majority of the patients referred for MPS in this institution were based on symptoms and majority had multiple CAD risk factors.

5. Conclusion and Recommendation

The current study has shown that Filipino type 2 DM patients without previous cardiac events are likely to have significant and more severe scintigraphic evidence of CAD than their non-type 2 DM counterpart. This study suggest aggressive CAD screening among this population for early detection, prevention and treatment of CAD. Further study are needed with emphasis on glycemic control and duration of type 2 diabetes in relation to MPS defects. Lastly, this present study suggest future incorporation of MPS in clinical practice guidelines for CAD detection among Filipino type 2 DM population.

Author's Note

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References

- [1] Kasim, M., Currie, G. M., Tjahjono, M., Siswanto, B. B., Harimurti, G. M., & Kiat, H. (2013a). Myocardial Perfusion SPECT Utility in Predicting Cardiovascular Events Among Indonesian Diabetic Patients. *The Open Cardiovascular Medicine Journal*, 7, 82-89.
- [2] Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27(5), 1047-1053.
- [3] Jimeno C, Abad L, Andag-Silva A, Cunanan E, Fernando RE, Fojas M, editors (2014). *PPD: compendium of Philippine medicine*. 16th ed. Manila.
- [4] Wackers, F. J. T., Young, L. H., Inzucchi, S. E., Chyun, D. A., Davey, J. A., Barrett, E. J. (2004). Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection

- of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care*, 27(8), 1954-1961.
- [5] Yamasaki, Y., Nakajima, K., Kusuoka, H., Izumi, T., Kashiwagi, A., Kawamori, R., Yamada, N., Nishimura, T. (2010). Prognostic value of gated myocardial perfusion imaging for asymptomatic patients with type 2 diabetes: the J-ACCESS 2 investigation. *Diabetes Care*, 33(11), 2320-2326.
- [6] Bax, J. J., Inzucchi, S. E., Bonow, R. O., Schuiff, J. D., Freeman, M. R., Barrett, E. J., & Global Dialogue Group for the Evaluation of Cardiovascular Risk in Patients with Diabetes. (2007). Cardiac imaging for risk stratification in diabetes. *Diabetes Care*, 30(5), 1295-1304.
- [7] Salehi Y, Fard-Esfahani A, Fallahi B, Aghahosseini F, Beiki D, Emami-Ardekani A, Fard-Esfahani P, Ansari M, Eftekhari M. (2014). The myocardial perfusion scintigraphy in asymptomatic diabetic patients. *Iran J Nucl Med*, 23:27-35.
- [8] DeLuca, A. J., Saulle, L. N., Aronow, W. S., Ravipati, G., & Weiss, M. B. (2005). Prevalence of silent myocardial ischemia in persons with diabetes mellitus or impaired glucose tolerance and association of hemoglobin A1c with prevalence of silent myocardial ischemia. *The American Journal of Cardiology*, 95(12), 1472-1474.
- [9] Bourque JM, Patel CA, Ali MM, Perez M, Watson D, Beller GA. (2013). Prevalence and predictors of ischemia and outcomes in outpatients with diabetes mellitus referred for single-photon emission computed tomography myocardial perfusion imaging. *Circulation Cardiovascular Imaging*, 6(3), 466-77.
- [10] Mariano-Goulart D. (2007). Myocardial perfusion imaging and cardiac events in asymptomatic patients with diabetes. *Heart Metabolism*, 35,1-4.
- [11] Shmendi, A., Pirie, F., Naidoo, D. P., Tlou, B., Pillooy, W., & Motala, A. A. (2014). Myocardial perfusion imaging for evaluation of suspected ischemia and its relationship with glycemic control in South African subjects with diabetes mellitus. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 7, 545-552.
- [12] Leslie, W. D., Tully, S. A., Yogendran, M. S., Ward, L. M., Nour, K. A., & Metge, C. J. (2005). Prognostic value of automated quantification of 99mTc-sestamibi myocardial perfusion imaging. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, 46(2), 204-211.
- [13] Senior, R., Monaghan, M., Becher, H., Mayet, J., Nihoyannopoulos, P., & British Society of Echocardiography. (2005). Stress echocardiography for the diagnosis and risk stratification of patients with suspected or known coronary artery disease: a critical appraisal. Supported by the British Society of Echocardiography. *Heart (British Cardiac Society)*, 91(4), 427-436.

- [14] Albers, A. R., Krichavsky, M. Z., & Balady, G. J. (2006). Stress testing in patients with diabetes mellitus: diagnostic and prognostic value. *Circulation*, *113*(4), 583–592.
- [15] fleischmann, K. E., Hunink, M. G., Kuntz, K. M., & Douglas, P. S. (1998). Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA*, *280*(10), 913–920.
- [16] de Jong, M. C., Genders, T. S. S., van Geuns, R.-J., Moelker, A., & Hunink, M. G. M. (2012). Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis. *European Radiology*, *22*(9), 1881–1895.