Introduction

Transient ischemic dilation (TID) with perfusion defect observed on myocardial perfusion scan (MPS) is a highly sensitive and specific marker for the severity and extent of cardiovascular disease and an independent and powerful predictor for cardiac event. TID could be found due to decrease of blood supply to the subendocardium as a response to cardiac stress and normal at rest. Some studies have shown that there was no difference in left ventricular wall thickness anatomically during the cardiac stress test and during rest in patients with positive TID. TID is often found in type 2 diabetes mellitus (T2DM) patients with asymptomatic cardiovascular complications. Cardiac macro and microvascular involved in long-term complications in a T2DM patient begin with endothelial dysfunction triggered by hyperglycemia.

Keywords: Endothelial dysfunction, endothelin-1, transient ischemic dilation index, type 2 diabetes mellitus
in homeostasis regulation.[12-15] Endothelin-1 (ET-1) plasma level, a potent vasoconstrictor, increases, while nitric oxide (NO), a vasodilator substance, decreases in endothelial dysfunction. The vasoconstrictive effect of ET-1 is more prominent on microvascular including subendocardial compared to macrovascular. Increase in ET-1 represents an endothelial dysfunction.[16]

Ischemic or myocardial infarction complications can develop in T2DM patients, but some of them are without clinical signs or symptoms. The prevalence of myocardial ischemia was found to be hidden in 15-22% of T2DM patients. Diffuse ischemia complications involving subendocardial could be observed in T2DM patients with microvascular disorder.[13,17,11]

The aim of this study was to examine the correlation between TID index and ET-1 plasma levels in T2DM patients without any sign or symptom of cardiovascular complication.

**Materials and Methods**

This study was of a prospective, analytic-correlational, cross-sectional design and was made to examine the correlation between TID index and ET-1 plasma levels in patients with T2DM. The study was conducted at the Department of Nuclear Medicine and Molecular Imaging from August 2013 to June 2014 following approval from the local Research Ethics Committee of Health.

Subjects were uncontrolled T2DM patients [based on glycated hemoglobin (HbA1c) levels] who agree to participate, and informed consent was taken from all. Subjects with a history of coronary heart disease, with stage 1 hypertension or higher based on the Seventh Joint National Committee on Prevention (JNC-7) criteria, having abnormal electrocardiogram (ECG), and having contraindications to adenosine and MPS study were excluded from the study. Subjects who met the inclusion criteria but whose MPS revealed segmental perfusion defect were also excluded.

Adenosine was used as a cardiac pharmacologic stress-test agent with a dose of 140 mcg/kg/min, and monitoring was done using 12-lead ECG. The infusion of adenosine was stopped when it reached the maximum dose, when ECG abnormalities arose, or when side effects of adenosine developed.[19]

MPS was done with the single-photon emission computed tomography (SPECT)-gated technique using a dual-headed gamma camera SPECT/CT (GE Infinia Hawkeye, GE Healthcare, New York, U.S.A) with a low-energy and high-resolution (LEHR) collimator. The imaging protocol including an energy setting at 140 KeV and 15% window width. A total of 30 image projections were collected on a 64 × 64 matrix size for 30 s/frame from the point of view right anterior oblique (RAO) 35° to left posterior oblique (LPO) 215°. Each subject underwent stress/rest gated SPECT MPS using 1-day protocol with 3-4 h interval. Technetium-99m (99mTc)-tetrofosmin was used as a radiopharmaceutical with a dose of 290-370 MBq for stress imaging and 550-740 MBq for rest imaging.

The interpretation of MPS was based on the distribution of 99mTc-tetrofosmin in the myocardium. The uptake of 99mTc-tetrofosmin in the myocardium greater than 70% of the maximum and homogenous distribution in both stress and resting were considered to be normal. Nonhomogenous myocardial tracer uptake and less than 70% maximum uptake were considered to be abnormal (perfusion defects).[19]

The TID index was determined by using standard software available in data processing (Emory Cardiac Toolbox (ECTb™), Emory University, Atlanta, USA). TID index was considered to be abnormal if >1.12.[6,20] ET-1 plasma levels in pg/mL unit were determined by using radioimmunoassay techniques.

Statistical analyses were used to examine the correlation between TID index and ET-1 plasma. The test was considered significant if the P value was less than 0.05.

**Results**

A total of 47 subjects who met the inclusion criteria were included in this study, consisting of 24 (51%) males and 23 (49%) females. The ages ranged 37-74 years (mean: 54.3 ± 8.4 years). There was no significant difference between the proportions of males and females (P = 0.133). Values of HbA1c ranged 6.0-12.8% (mean: 8.1 ± 1.7%). The average and standard deviation (SD) of ET-1 plasma level and TID index were 10.97 (1.74) pg/mL and 1.11 (0.09), respectively. A median of ET-1 plasma level was 10.91 pg/mL and of TID index was 1.12. Abnormal TID index was found in 23/47 (49%) subjects. The Shapiro-Wilk test showed that the data obtained were not normally distributed, with P value for age 0.797, HbA1c 0.003, ET-1 plasma level 0.004, and TID index 0.037 [Table 1].

As the data were not normally distributed, the Mann-Whitney test was applied to compare the differences based on sex. Table 2 showed no significant difference on the TID index based on sex and age groups, with P values of 0.765 and 0.381, respectively. The Spearman rank test showed a significant positive correlation between ET-1 plasma level and TID index in T2DM patients with a correlation coefficient (r) = 0.7 and P < 0.001 [Table 3]. This means that TID index increases with increase of ET-1 plasma level due to endothelial dysfunction [Figure 1].
Discussion

In this study MPS was done using $^{99m}$Tc-tetrofosmin as the preparation of this radiopharmaceutical is simple and the final results were not significantly different compared to thallium-201 ($^{201}$TI). Adenosine was chosen for the pharmaceutical cardiac stress test due to its short duration of action. The side effects of adenosine disappear within 10 s after the discontinuation of adenosine infusion. Adenosine increases myocardial perfusion by 3.5-4 times through the normal coronary artery. Less dilation response to adenosine can be observed in the abnormal compared to the normal coronary artery as well as blood flow to the myocardium. This condition leads to nonhomogenous distribution of $^{99m}$Tc-tetrofosmin in the myocardium. Myocardial perfusion through the abnormal coronary artery that is less than normal is known as “steal phenomenon.” There was no significant side effect of adenosine observed in this study.

TID is used as a term for temporary pseudodilation involving subendocardial during cardiac stress. It was introduced for the first time by Stolzenberg in 1980. Several theories were put forward to explain the mechanism of TID, but many experts believe that TID develops due to subendocardial hypoperfusion during cardiac stress. Perfusion to the subendocardium decreases during cardiac stress, leading to the decrease of tracer uptake in the subendocardium in patients with CAD. Subendocardial hypoperfusion as a basic mechanism of TID is supported by the fact that the end-diastolic volume and left ventricular ejection fraction were not significantly different between stress and rest.

Myocardial perfusion depends on the coronary artery and its branches. The functions of the endothelium are to maintain blood supply and homeostasis in the body through maintaining the balance between vasodilation and vasoconstriction. Increased levels of blood sugar in patients with T2DM can lead to endothelial dysfunction. One of the important markers of endothelial dysfunction is the increase in ET-1 plasma levels, a potent vasoconstrictor. An increased ET-1 plasma level will disturb the balance between vasoconstriction and vasodilation. Increased vasoconstriction will decrease blood supply, including that to the subendocardial.

In this study we found that the range of the TID index was 0.86-1.26. Based on TID index 1.12 as the cut-off value, 23 (49%) out of 47 subjects were found with abnormal

Table 1: Characteristic subject

| Characteristics | n |
|-----------------|---|
| Sex             |   |
| Male            | 24|
| Female          | 23|
| Age (years)     |   |
| <50             | 14|
| 50-59           | 22|
| ≥60             | 11|
| Mean (SD)*      | 5.43 (8.4)|
| Range           | 3-7.4|
| HbA1c (%)       |   |
| Mean (SD)*      | 8.1 (1.7)|
| Median          | 7.7|
| Range           | 6.0-12.8|

*SD: Standard deviation; HbA1c: Glycated hemoglobin

Table 2: TID index based on sex and age

| Variable | TID index | P |
|----------|-----------|---|
| Sex      |           |   |
| Male     | Median: 1.11 | 0.765 |
|          | Range: 0.96-1.26 |   |
| Female   | Median: 1.13 |   |
|          | Range: 0.86-1.25 |   |
| Age      |           |   |
| <50 years| Median: 1.11 | 0.381 |
|          | Range: 0.95-1.22 |   |
| 50-59 years| Median: 1.12 |   |
|          | Range: 0.97-1.25 |   |
| ≥60 years| Median: 1.13 |   |
|          | Range: 0.86-1.26 |   |

*TID: Transient ischemic dilation

Table 3: Correlation between ET-1 level and TID index

| ET-1 (p/mL) | TID index | Correlation coefficient ($r$) | P   |
|-------------|-----------|------------------------------|-----|
| Median      | 11.28     | 1.12                         | 0.7 | <0.001 |
| Range       | 8.02-17.91| 0.86-1.26                   | 0.7 | <0.001 |

*ET-1: Endothelin-1, TID: Transient ischemic dilation
TID index values. Kakhki (2007) found about 8-37% of MPS studies were associated with an abnormal TID index,[3] while Hung et al., found 26% abnormal TID index in a pharmacological stress-redistribution MPS study using ²⁰¹TI-chloride.[23,24,30] These differences in results could be due to the difference in radiopharmaceuticals used.[7] Hung et al. used a single injection of ²⁰¹TI-chloride, and this study used a reinjection of ⁹⁹mTc-tetrofosmin.[28]

Myocardial blood flow depends on the condition of the blood vessels, which is influenced by the ability of blood vessels to maintain the balance between vasodilation and vasoconstriction. The endothelium has an important role in the regulation of blood supply and homeostasis. Endothelial response to any physical stimulus as well as chemical by releasing vasodilator and vasoconstrictor substances in order to maintain homeostasis.[12,31,32] ET-1 plasma levels increase in endothelial dysfunction. ET-1 is a peptide with 21 amino acids acting as autocrine. The role of ET-1 as a potent vasoconstrictor to the vascular smooth muscle was first discussed by Yanagisawa et al. in 1988.[12,32] ET-1 leads to vasconstriction, increases arterial tone, and controls blood pressure.[12,31,33]

In this study the range of ET-1 levels in T2DM patients without cardiovascular complication was 8.02-17.91 pg/mL (mean = 11.48 and SD = 2.19 pg/mL). These results was not much different compared to the results from other studies. Perfetto et al. found that the mean and SD of ET-1 plasma level was 6.8 ± 2.8 pg/mL.[34] Gursel et al. found 10.46 ± 1.24 pmol/L,[13] and Schanze et al. found 11.32 ± 6.76 pg/mL.[35]

In this study, there was no correlation found between ET-1 plasma level and age. This result was similar to that of the study done by Schneider. A different study showed a good correlation between ET-1 and age in type 1 diabetes mellitus (T1DM) patients. This difference may be due to differences in the duration of hyperglycemia. This hypothesis is supported by a study done by Haak et al. He showed that 60% of T1DM patients have ET-1 plasma levels higher than in nondiabetic individuals.[36]

Increase in the TID index is an indicator of subendocardial reversible ischemia due to coronary blood flow disorder as a result of cardiac stress. This ischemia was related to increase of ET-1 plasma levels due to endothelial dysfunction caused by hyperglycemia. This study showed a good positive correlation and statistically significant difference between TID index and ET-1 plasma level with correlation coefficient ($r$) = 0.7 ($P < 0.001$). This means that an increase in the ET-1 plasma level will lead to an increase in the TID index. An other study showed the inability of the coronary endothelium to dilate along with perfusion defects in MPS using ²⁰¹TI as a response to a physical stress test. The other study showed the severity of clinical manifestations of coronary endothelial dysfunction could depend on the involvement of coronary microvascular. A myocardial perfusion defect on MPS as a result of ischemia could be due to a vasodilation disorder of the coronary microvascular.[37]

**Conclusion**

There was a significant positive correlation between TID index and ET-1 plasma level in T2DM patients. The higher the ET-1 plasma level, the higher was the TID index.

**References**

1. Smelley MP, Virnich DE, Williams KA, Ward RP. A hypertensive response to exercise is associated with transient ischemic dilation on myocardial perfusion SPECT imaging. J Nucl Cardiol 2007;14:537-43.
2. Kakhki VR. Different aspects of transient ischemic dilation. Iran J Nucl Med 2007;15:30-3.
3. Russell RR, Zaret BL. Nuclear cardiology: Present and future. Myocardial perfusion imaging in specific groups: Diabetes mellitus. Curr Probl Cardiol 2006;31:557-629.
4. Kakhki VR, Sadeghi R, Zakavi SR. Assessment of transient left ventricular dilation ratio via 2-day dipyridamole Tc-99m sestamibi non-gated myocardial perfusion imaging. J Nucl Cardiol 2007;14:529-36.
5. Scholte AJ, Schuijf JD, Karagiitisingh AV, Dibbets-Schneider P, Stokkel MP, van der Wall EE, et al. Prevalence and predictors of an abnormal stress myocardial perfusion study in asymptomatic patients with type 2 diabetes mellitus. Eur J Nucl Med Mol Imaging 2009;36:567-75.
6. Duarte PS, Smanio PE, Oliveira CA, Martins LR, Mastrococia LE, Pereira JC. Clinical significance of transient left ventricular dilation assessed during myocardial Tc-99m sestamibi scintigraphy. Arq Bras Cardio 2003;81:479-82.
7. Emmett L, Magee M, Freedman SB, Van der Wall H, Bush V, Trieu J, et al. The role of left ventricular hypertrophy and diabetes in the presence of transient ischemic dilation on the left ventricle on myocardial perfusion SPECT images. J Nucl Med 2005;46:1596-601.
8. Emmett L, Van Gaal WJ, Magee M, Bass S, Ali O, Freedman B, et al. Prospective evaluation of the impact of diabetes and left ventricular hypertrophy on the relationship between ischemia and transient ischemic dilation of the left ventricle on single-day adenosine Tc-99m myocardial perfusion imaging. J Nucl Cardiol 2008;15:638-43.
9. Halligan WT, Morris PB, Schoepf UJ, Mischen BT, Spearman JV, Spears JR, et al. Transient ischemic dilation of the left ventricle on SPECT: Correlation with findings at coronary CT angiography. J Nucl Cardiol 2014;55:917-22.
10. Young LH, Wackers FJ, Chyun DA, Davey JA, Barret EJ, Tailfeer R, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: The DIAD Study: A randomized control trial. JAMA 2009;301:1547-55.
11. Scholte AJ, Schuijf JD, Karagiitisingh AV, Dibbets-Schneider P, Stokkel MP, Jukema JW, et al. Different manifestations of coronary artery disease by stress SPECT myocardial perfusion imaging, coronary calcium scoring and multislice CT coronary angiography in asymptomatic patients with type 2 diabetes mellitus. J Nucl Cardiol 2008;15:503-9.
12. Tabit CE, Chung WB, Hamburg NM, Vita JA. Endothelial dysfunction in diabetes mellitus: Molecular mechanisms and clinical implications. Rev Endocr Metab Disord 2010;11:61-74.
13. Michael EW, Noyan G, John FK JR, Joseph AV. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003;42:1149-60.
14. Shahab A. Why does diabetes mellitus increase the risk of cardiovascular disease? Acta Med Indones 2006;38:33-41.
15. Cardillo C, Campia U, Bryant MB, Panza JA. Increased activity of endogenous endothelin in patients with type II diabetes mellitus. Circulation 2002;106:1783-7.
16. Murohara T, Lefer AM. Autocrine effects of endothelin-1 on leukocyte-endothelial interaction: Stimulation of endothelin B receptor subtype reduces endothelial adhesiveness via a nitric oxide-dependent mechanism. Blood 1996;88:3894-900.
17. Scholte JH. Cardiac imaging for risk stratification in asymptomatic diabetes. J Nucl Cardiol 2006;13:11-8.
18. Perfetto F, Tarquini R, Tapparini L, Tarquini B. Influence of non-insulin-dependent diabetes mellitus on plasma endothelin-1 levels in patients with advanced atherosclerosis. J Diabetes Complications 1998;12:187-92.
19. Salerno M, Beller GA. Noninvasive assessment of myocardial perfusion. Circ Cardiovasc Imaging 2009;2:412-24.
20. Wilkes JJ, Hevener A, Olofsky J. Chronic endothelin-1 treatment leads to insulin resistance in vivo. Diabetes 2003;52:1904-9.
21. Hardebeck CJ. Transient ischemic dilation. J Am Coll Cardiol 2004;44:211-3.
22. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57:1103-10.
23. Abidov A, Bax JJ, Hayes SW, Cohen I, Nishina H, Yoda S, et al. Integration of automatically measured transient ischemic dilation ratio into interpretation of adenosine stress myocardial perfusion SPECT for detection of severe and extensive CAD. J Nucl Med 2004;45:1999-2007.
24. Heston TF, Sigg DM. Quantifying transient ischemic dilation using gated SPECT. J Nucl Med 2005;46:1990-6.
25. McLaughlin MG, Danias PG. Transient ischemic dilation: A powerful diagnostic and prognostic finding of stress myocardial perfusion imaging. J Nucl Cardiol 2002;9:663-7.
26. Abidov A, Germino G, Berman DS. Transient ischemic dilation ratio: A universal high-risk diagnostic marker in myocardial perfusion imaging. J Nucl Cardiol 2007;14:497-500.
27. van der Veen BJ, Kuperij N, Stokkel MP. Transient ischemic dilation ratio derived from myocardial perfusion scintigraphy: What are we looking at? J Nucl Cardiol 2010;17:207-15.
28. Hung GU, Lee KW, Chen CP, Lin WY, Yang KT. Relationship of transient ischemic dilation in dipyridamole myocardial perfusion imaging and stress-induced changes of functional parameters evaluated by TI-201 gated SPECT. J Nucl Cardiol 2005;12:268-75.
29. Brodov Y, Guetta V, Di Segni E, Chouraqui P. Clinical predictors of stress-induced transient left ventricular dilation in patients with nonsignificant coronary disease. J Clin Hypertens (Greenwich) 2010;12:693-7.
30. Nacci C, Tarquino M, Montagnani M. Molecular and clinical aspects of endothelial dysfunction in diabetes. Intern Emerg Med 2009;4:107-16.
31. Storey AM, Perry CJ, Petrie JR. Endothelial dysfunction in type 2 diabetes. Br J Diabetes Vasc Dis 2001;1:22-7.
32. Esper RJ, Nordaby RA, Vilariño JO, Paragano A, Cacharrón JL, Machado RA. Endothelial dysfunction: A comprehensive appraisal. Cardiovasc Diabetol 2006;5:4.
33. Lam HC. Role of endothelin in diabetic vascular complication. Endocrine 2001;14:277-84.
34. Kalani M. The importance of endothelin-1 for microvascular dysfunction in diabetes. Vasc Health Risk Manag 2008;4:1061-8.
35. Sánchez SS, Aybar MJ, Velarde MS, Prado MM, Carrizo T. Relationship between plasma endothelin-1 and glycemic control in type 2 diabetes mellitus. Horm Metab Res 2001;33:748-51.
36. Hasdai D, Gibbons RJ, Holmes DR Jr, Higano ST, Lerman A. Coronary endothelial dysfunction in humans is associated with myocardial perfusion defects. Circulation 1997;96:3390-5.

How to cite this article: Kartamihardja AH. Correlation between transient ischemic dilation index and endothelin-1 level in patients with Type 2 diabetes mellitus. World J Nucl Med 2016;15:109-13.

Source of Support: Nil. Conflict of Interest: None declared.