Original article

Correlation between Transient Ischemic Dilation Index and Endothelin-1 Level in Patients with Type 2 Diabetes Mellitus

Achmad Hussein Sundawa Kartamihardja

Department of Nuclear Medicine and Molecular Imaging, Universitas Padjadjaran, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Transient ischemic dilation (TID) is a sensitive and specific marker for detecting the severity and extent of coronary artery disease (CAD), which is closely associated with endothelial dysfunction. TID can be observed on stress-rest myocardial perfusion scan (MPS) due to subendocardial hypoperfusion. Hyperglycemia in type 2 diabetes mellitus (T2DM) could lead to micro- and macrovascular complications and begins with endothelial dysfunction. Endothelin-1 (ET-1), a potent vasocontrictor, increases in endothelial dysfunction. The aim of this study was to examine the correlation between TID index and ET-1 levels in T2DM patients without any sign or symptom of cardiovascular complication. An analytic-correlational cross-sectional study was done on T2DM patients who met the inclusion criteria and agreed to participate by signing an informed consent form. The TID index was calculated automatically using standard software provided by the gamma camera GE-Infinia. Stress-rest MPS was done using technetium-99m (^{99m}Tc)-tetrofosmin and a pharmacological stress test using adenosine. The ET-1 level was determined by radioimmunoassay. Data distribution was analyzed using the Shapiro-Wilk normality test. The Mann-Whitney test was used to compare the average difference of the variables and Spearman's rank for correlation analysis. A total of 47 subjects consisting of 24 (51%) males and 23 (49%) females were included in this study. The age range was 37-74 years (54.3 ± 8.4). The TID index range was 0.86-1.26 (median = 1.12) and abnormal TID index was found in 23/47 (49%) subjects. ET-1 levels range 8.02-17.91 pg/mL (median = 11.08). The results showed no significant differences in age, ET-1 levels, and TID index based on age and sex ($P > 0.05$). There was a significant positive correlation between TID index and ET-1 level with $r = 0.7$ and $P < 0.001$. There was a positive correlation between TID index and ET-1 plasma level in patients with T2DM.

Keywords: Endothelial dysfunction, endothelin-1, transient ischemic dilation index, type 2 diabetes mellitus

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.[1-5] 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.[6-9]

TID is often found in type 2 diabetes mellitus (T2DM) patients with asymptomatic cardiovascular complications.[3,5,10,11]

Cardiac macro and microvascular involved in long-term complications in a T2DM patient begin with endothelial dysfunction triggered by hyperglycemia.

Endothelial dysfunction can be found to be both macro- and microvascular, which leads to an imbalance between vasodilation and vasoconstriction capability

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Address for correspondence:
Dr. Achmad Hussein Sundawa Kartamihardja, Department of Nuclear Medicine and Molecular Imaging, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. E-mail: husseinsundawa@yahoo.com

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.[3,17,11]

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.[18]

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 (^{99m}Tc)-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 ^{99m}Tc-tetrofosmin in the myocardium. The uptake of ^{99m}Tc-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^{tm}), 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 coeficient (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].

Table 1: Characteristic subject

Characteristics	*n*
Sex	
Male	24
Female	23
Age (years)	
<50	14
50-59	22
≥60	11
Mean (SD)*	54.3 (8.4)
Range	37-74
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 cage

Variable	TID index	*P*
Sex		
Male	Median: 1.11	
	Range: 0.96-1.26	
Female	Median: 1.13	0.765
	Range: 0.86-1.25	
Age		
<50 years	Median: 1.11	
	Range: 0.95-1.22	
50-59 years	Median: 1.12	0.381
	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 coeficient (r_s)	*P*
Median	11.28	1.12		
Range	8.02-17.91	0.86-1.26	0.7	<0.001

*ET-1: Endothelin-1, TID: Transient ischemic dilation

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.[18] Adenosine increases myocardial perfusion by 3.5-4 times through the normal coronary artery.[21] Less dilation response to adenosin 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*."[22] There was no significant side effect of adenosine observed in this study.

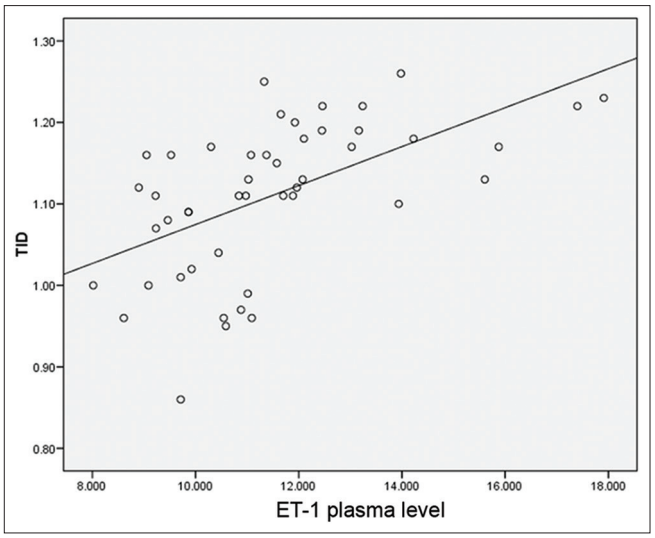

Figure 1: Correlation between ET-1 level and TID index

TID is used as a term for temporary pseudodilation involving subendocardial during cardiac stress.[6,10,16,23] It was introduced for the first time by Stolzenberg in 1980.[7,24-26] 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.[9,24,26,27] 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.[8,24,28,29]

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 vasocontraction. Increased levels of blood sugar in patients with T2DM can lead to endothelial disfunction. 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.[19]

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

TID index values. Kakhki (2007) found about 8-37% of MPS studies were associated with an abnormal TID index,[2] while Hung *et al*., found 26% abnormal TID index in a pharmacological stress-redistribution MPS study using ^{201}TI-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 ^{201}TI-chloride, and this study used a reinjection of ^{99m}Tc-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 vasocontriction. 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.[12,13,31] 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 vasoconstriction, 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 similiar to that of the study done by Schneider. A different study showed a good correlation betwen 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 coeficient (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 ^{201}TI 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.[36]

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.

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