

The Correlation Between Transient Ischemic Dilatation (TID) ratio with HbA_{1c} value in Type 2 Diabetes Mellitus patients who also present with Metabolic Syndrome

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Abstract

Using myocardial perfusion scintigraphy (MPS), perfusion defects are often found in asymptomatic type 2 diabetes mellitus (T2DM) patients. Identification of these patients is very important. T2DM can cause diffuse atherosclerosis and coronary flow reserve abnormalities at the microvascular level, which is a potential cause of false negative results of MPS. One way to solve this problem is by observing the transient ischemic dilatation (TID) ratio. High TID ratio in the presence of normal perfusion is often found and thought to be due to balanced ischemia. T2DM patients who also present with metabolic syndrome (MS) are often said to have worse glucose control, longer duration of disease, the presence of complications, and much higher risk for coronary artery disease (CAD) compared to patients with T2DM only. The increased risks for diabetes seem to be mediated through hemoglobin A_{1c} (HbA_{1c}) concentration. The aim of this study was to find out the relation of TID ratio with HbA_{1c} in T2DM patients with or without MS. From August 2007 to March 2008, 48 T2DM patients with no/mild CAD symptoms underwent one day protocol MPS in our department. The stress tests were done by exercise using ergocycle. TID ratio was automatically measured by using Emory Cardiac Toolbox software (ECToolbox; Syntermed, Inc.). HbA_{1c} concentration, waist circumference, and other factors that would be needed to confirm the diagnosis of MS were also measured. The mean value of TID ratio and HbA_{1c} in T2DM with MS group were 1.12 ± 0.14 and 7.96 ± 2.47 , while in T2DM without MS group were 1.05 ± 0.13 and 8.77 ± 2.83 % respectively. There was no correlation between the value of TID ratio and HbA_{1c} in T2DM patients without considering MS. On the contrary, there was a statistically significant

correlation between them in T2DM patients who also presented MS (T2DM with MS group) at the level of significance $p < 0.05$. One more interesting thing was that the incidence of high TID ratio without perfusion defect was higher in T2DM with MS compared to T2DM alone and all of the patients with this incidence had high HbA_{1c}. The present study has shown that there is a good correlation between TID and HbA_{1c} concentration in T2DM patients who present MS. Poor glucose control and MS are factors that are responsible for TID in T2DM. To increase the sensitivity of MPS in detecting CAD in T2DM patients with MS and poor glucose control, TID ratio measurement is recommended.

Key words : transient ischemic dilatation, hemoglobin A_{1c}, type 2 diabetes mellitus, metabolic syndrome.

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Introduction

Type 2 diabetes mellitus (T2DM) has become one of the major causes of premature illness and death, mainly due to the increased risk of coronary artery disease (CAD) which is responsible for up to 80% of these death (1). Individuals with diabetes have at least a two to four-fold increased risk for having cardiovascular events compared with age-matched individuals without diabetes (2). This risk will be much higher if they have also associated metabolic syndrome (MS) (3).

The term metabolic syndrome was applied to the clustering of risk factors that often accompany obesity and associate with increased risk for both atherosclerotic cardiovascular disease and T2DM. One advantage of identifying this particular cluster of risks is that it should bring together the fields of cardiovascular disease (CVD) and diabetes for a concerted and unified effort to reduce risk for both conditions simultaneously (4).

The MS, irrespective of its definition or of the type of diabetes, was associated with worse glucose control, longer duration of disease, and the presence of complication (5). This relationship may be due to either greater difficulties in achieving glucose control in patients with MS and/or aggravating role of poor glucose control on the variables compounding the MS. MS was an independent risk factor of all complication in T2DM (6). This relationship was expected for cardiovascular complications (7) and also

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Variables	Values	
Age	Mean + SD	57.33+9.68
	Median	57
	Range	38=77
Sex	Male	16 (38.10%)
	Female	26 (61.90%)
CAD	No symptoms	18 (42.86%)
	CCS Class I	42 (57.14%)
MS	MS (-)	20 (47.62%)
	MS (+)	22 (52.38%)
TID	TID > 1.1	18 (42.86%)
	TID ≤	24 (57.14%)
HbA _{1c}	HbA _{1c} > 6.5	31 (73.81%)
	HbA _{1c} ≤6.5	11 (26.19%)

Table 1 Patient characteristics

Variables	T2DM without MS	T2DM With MS	<i>P value</i>
Age			
mean ± SD	59.35 + 10.17	55.50 + 9.04	NS
median	58.5	53	
range	38 -77	41-74	
Sex			
female	10	16	NS
male	10	6	
TID			
mean + SD	1.05 ± 0.13	1.12 ± 0.14	<0.05
median	1.00	1.14	
range	0.92 - 1.40	0.79 - 1.49	
HbA_{1c}			
mean + SD	8.77 ± 2.83	7.96 ± 2.47	NS
median	7.80	7.25	
range	5.2 - 14.9	5.2 - 14.5	
Perfusion			
Normal	11	10	NS
ischemia	9	12	

Table 2 Patient characteristics based on Metabolic Syndrome

microvascular complications (8). T2DM patients who also present the metabolic syndrome carry a much higher risk of CVD than those who have T2DM alone (3).

One way to evaluate the blood glucose control in diabetic patients is by measuring Hemoglobin A_{1c} (HbA_{1c}) concentration, which is an indicator of average blood glucose concentration over the preceding 3 months. HbA_{1c} concentration is related to CAD and all-cause mortality. An increase in HbA_{1c} of 1 percentage point is associated with a 20- 30% increase in mortality and CVS events (9). Reduction in HbA_{1c} is associated with a decrease in risk for microvascular and macrovascular complication (10).

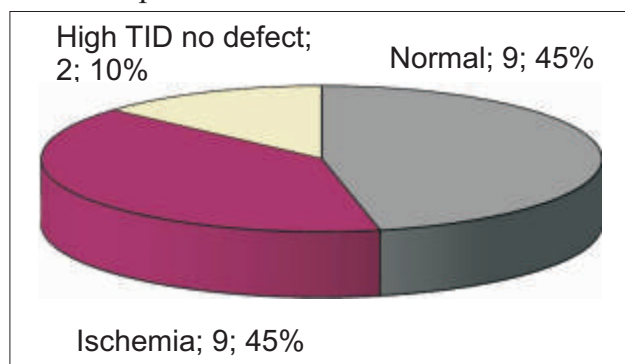
Occult CAD is a common finding among asymptomatic T2DM patients (free of CAD symptom), ranging from 20% in healthier subjects to >50% in more complicated diabetic patients. This poses the challenge of how to efficiently identify these individuals and target them for appropriate therapy. One relatively common finding in diabetic patients is that the extent and severity of perfusion abnormalities on myocardial perfusion scintigraphy (MPS) frequently denotes more extensive and severe ischemia

than predicted by coronary angiography. Although this discrepancy between function and anatomy has been frequently labeled as false-positive finding, it likely reflects severe underlying microvascular dysfunction in the diabetic heart that is underestimated by conventional coronary angiography (11).

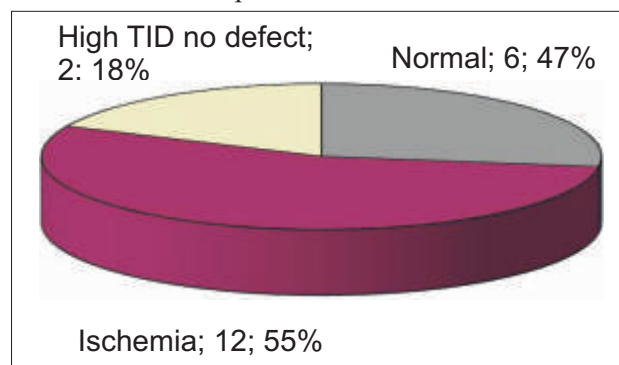
CAD in asymptomatic T2DM patients will be found more often if the false-negative finding of MPS can be avoided. One of the causes of false-negative findings is the homogeneously distributed perfusion defect in the myocardium (appears as normal perfusion), which can be avoided by detecting transient ischemic dilation (TID) (12,13). TID of the left ventricle is a sensitive & highly specific marker for detection of severe & extensive CAD (12). Integration of TID into interpretation of MPS enhances the diagnostic ability of MPS to identify patients with severe and extensive CAD (14).

TID incidence will increase in T2DM patients which is not always related to angiography findings, because TID can be caused by the presence of undetected diffuse atherosclerosis or of coronary flow reserve abnormalities

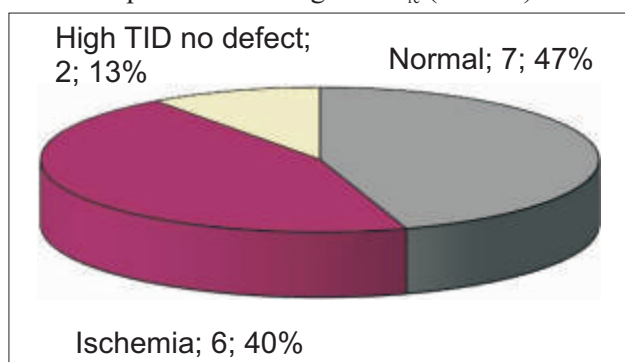
a. T2DM patients



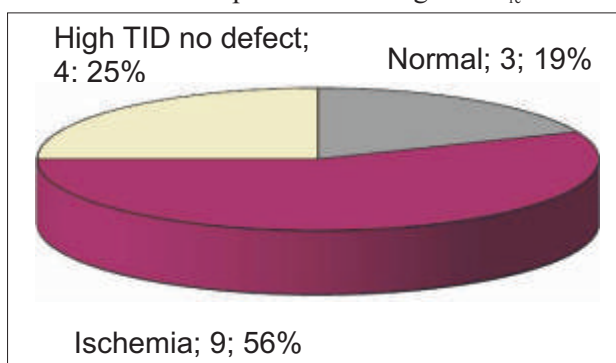
a. T2DM with MS patients



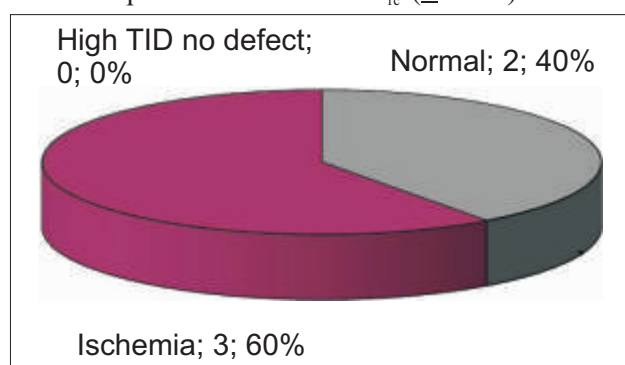
b. T2DM patients with high HbA_{1c} (> 6.5%)



b. T2DM with MS patients with high HbA_{1c}



c. T2DM patient with low HbA_{1c} (≤ 6.5%)



c. T2DM with MS patients with low HbA_{1c}

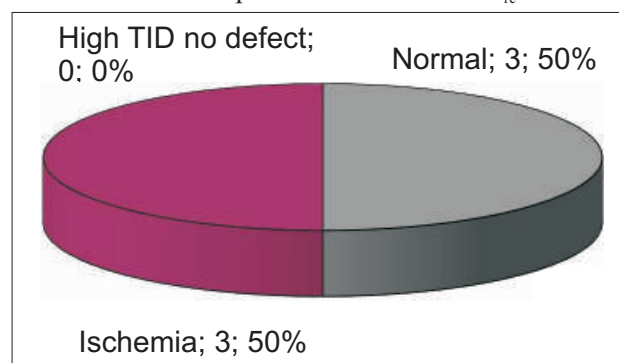


Figure 1. Incidence of perfusion defects and TID in T2DM only patients (a); with high HbA_{1c} (b) and with low HbA_{1c} (c).

Figure 2. Incidence of perfusion defects and TID in T2DM with MS patients (a); with high HbA_{1c} (b); with low HbA_{1c} (c).

(15) related to microvascular disease (16,17). Based on the above assumptions, we hypothesized that there is a correlation between HbA_{1c} and TID in T2DM patients especially who also present with MS.

Materials & Methods

Forty-eight patients were studied. All patients underwent single-day Tc-99m Tetrofosmin MPS between August 2007 and April 2008 in our department. All of them did not have any history of CAD or only had recent mild symptoms (class I) of CAD based on grading of angina pectoris by the Canadian Cardiovascular Society classification system. They also did not have valvular heart disease or non-ischemic cardiomyopathy. Patients with irreversible perfusion defect from MPS were excluded from this study.

A diagnosis of T2DM was based on patient histories and current requirements for diabetic medications. All of them were checked for the possibilities of having MS. According to the new IDF definition, patients were diagnosed as having MS if they had central obesity (by measuring waist circumference) with ethnicity specific values (for South Asians : male ≥ 90 cm and female ≥ 80 cm) and any 2 of the following 4 factors : raised triglycerides ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality, reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) for females or specific treatment for this lipid abnormality, systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension, raised fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed T2DM (3).

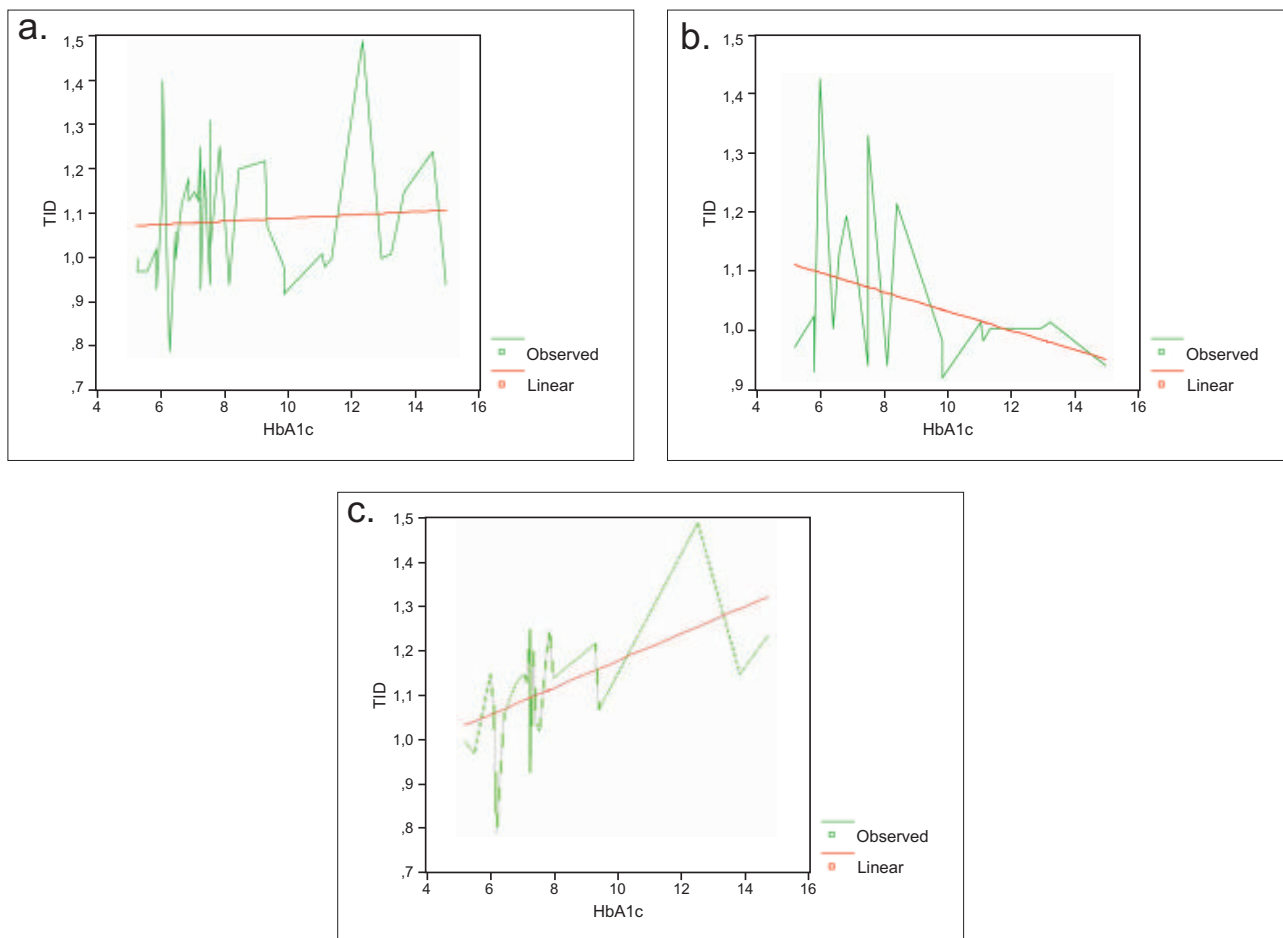


Figure 3. Correlation between TID and HbA_{1c} in entire patient population (a); T2DM without MS patients (b) and T2DM with MS patients (c).

Stress Protocol

Exercise stress was applied using bicycle ergometer in all patients. Exercise peak was determined by the achievement of > 85% of target heart rate, > 2 mm ST segment depression on the exercise electrocardiogram, or significant cardiac symptoms.

All patients underwent a stress-rest MPS protocol. For the stress image, 370 MBq of Tc-99m tetrofosmin (Myoview; GE Healthcare) was injected and 1,110 MBq for the rest image. Rest image was done 3 hours after exercise.

SPECT Protocol

SPECT studies were obtained over a 180° orbit from right anterior oblique to left posterior oblique using Infinia II Hawkeye (GE Medical Systems). A 20% window centered on the 140-keV peak and 64 X 64 matrix was used. Data were processed in the Xeleris Functional Imaging workstation (GE Medical Systems). The reconstruction was performed using Butterworth filter. Transient ischemic dilatation was automatically calculated using Emory Cardiac Toolbox software (ECToolbox; Syntermed, Inc.).

Statistical Analysis

Continuous data are reported as mean \pm standard deviation, median with lower and upper ends. Comparison between groups were performed using χ^2 test or Mann-Whitney test where appropriate. Pearson test was used for correlation analysis. P value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

Characteristics of the patients are described in Table 1. Of 48 patients, 6 were excluded because of irreversible perfusion defects (4), contra-indication to do physical stress test (1), and not being able to do adequate exercise test (1). The waist circumferences of the rest 42 patients were measured. HbA_{1c} and other parameters that were needed to establish the diagnosis of MS were also measured.

There were 18 of 42 (42.86%) patients without having CAD symptoms. In this group, perfusion defects were found in 10 patients (55.55%). Of 8 patients with normal perfusion, 2 patients had TID ratio above 1.1. TID ratio was assumed to be high if more than 1.1 according to Williams for using the same isotope for both stress and rest images (18).

There was significant difference in the TID ratios between the two groups. The mean of TID ratio in T2DM with MS was greater than the one in T2DM without MS. Age, sex, HbA_{1c} value, and perfusion defects were not statistically different between the two groups (Table 2).

There were 2 of 20 (10%) T2DM patients without MS who had no perfusion defect but high TID (Figure 1a). This incidence was higher (13.33%) in patients with high HbA_{1c} (Figure 1b), but not found in patients with low HbA_{1c} (Figure 1c)

In T2DM with MS group, there were more patients having

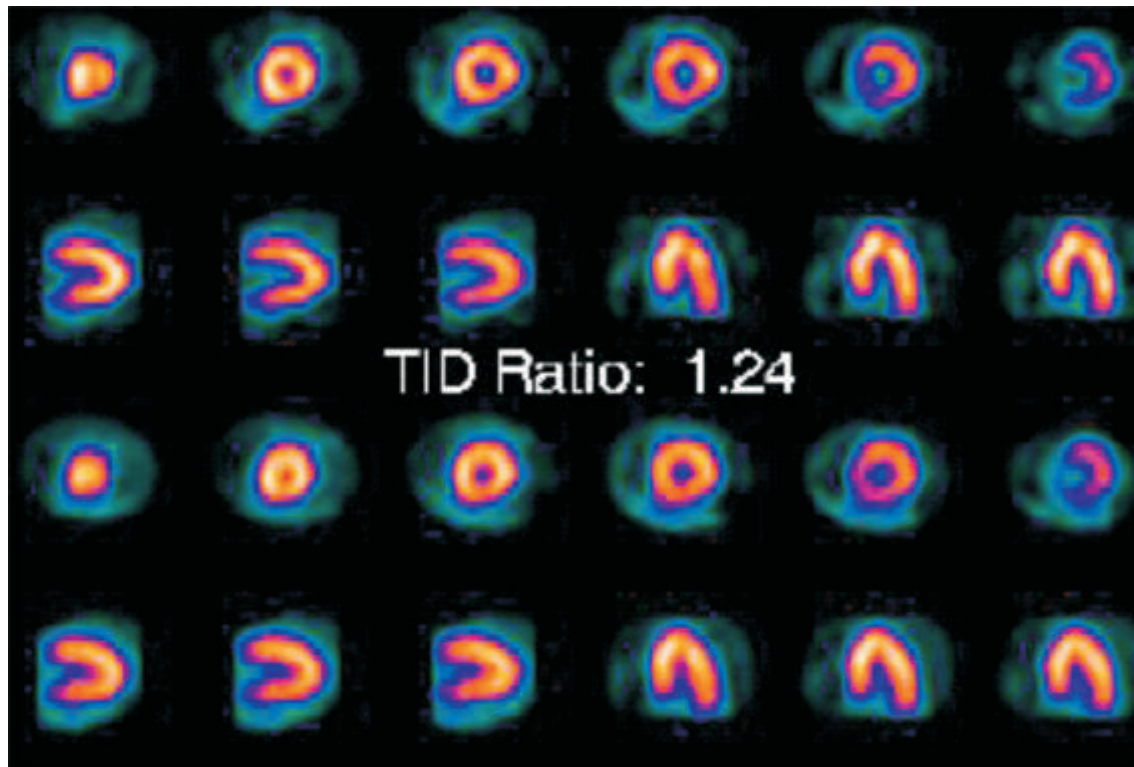


Figure 4. A 65-year-old male, suffering from T2DM with MS (waist circumference 105 cm, trygliceride 190 mg/dL, HDL-C 35 mg/dL, and hypertension) with HbA_{1c} 14.5%, had no perfusion defect in MPS, but high TID ratio (1.24).

no perfusion defect but high TID. This incidence was 18.18 % (4 of 22). This was found to be also higher (25%; 4 of 16) in patients with high HbA_{1c} (Figures 2a, 2b). This incidence was also not found in patients with low HbA_{1c} (Figure 2c). According to Abidov et.al, such patients had intermediate likelihood of developing severe and extensive CAD (14). By determining the TID ratio, it will be possible to identify more such patients of CAD.

The relationship between TID and HbA_{1c} was not observed in the entire sample without considering MS (Figure 3a) and in the T2DM without MS group (Figure 3b). On the contrary, there was a tendency of a positive relationship between TID and HbA_{1c} in the T2DM with MS group (Figure 3c). By using Pearson coefficient of correlation, moderate correlation was observed ($r = 0.549$; $p=0.008$). The value of r^2 was 0.302 meaning that 30.20 % of the changes happened in the TID could be explained by HbA_{1c} through the linier relationship between them, while the rest was explained by other factors.

Discussion

Clinical trials in T2DM have demonstrated that hyperglycemia plays an important role in the pathogenesis of microvascular complication (19). Although diabetic patients with the most severe hyperglycemia have the highest risk of microangiopathy, hyperglycemia is a necessary, but not a sufficient cause of clinically important microangiopathy. Hypertension, dyslipidaemia, obesity (components of MS) and other factors are additional major causes of microangiopathy, creating a state of constant and progressive damage to the vascular wall, manifested by a low-grade inflammatory process and endothelial

dysfunction (20). In diabetes, hyperglycemia and component of MS cause endothelial dysfunction directly or indirectly (21). This endothelial dysfunction is regarded as an important factor in the pathogenesis of micro- and macroangiopathy (22).

The link between myocardial ischemia & obstructive epicardial coronary arteries is well established, but in the past 2 decades a number of studies have reported that abnormalities in the function & structure of the coronary microcirculation also occur in many clinical conditions (23). These abnormalities are related to severe endothelial and smooth muscle cell dysfunction within the coronary microvasculature (11) which can cause coronary flow reserve abnormality (24). Diabetes is a stronger independent predictor of TID than the presence of either severe CAD or ischemia, possibly because of the presence of undetected diffuse atherosclerosis or of coronary flow reserve abnormality related to microvascular disease (15). It seems microvascular-related coronary flow reserve abnormality at least in part explains the phenomenon of high TID without perfusion defect.

The facts above seem to be appropriate with these findings in this study. HbA_{1c} concentration does not have correlation with TID ratio in T2DM without MS patients, but has correlation in T2DM with MS patients. Although hyperglycemia is the driving force of vascular complication in diabetes mellitus, the action of glucose alone seems inadequate and unable to account for the excess of atherosclerosis observed in patients with diabetes. In T2DM, insulin resistance, and MS, the vasculature is exposed to a frontal assault by hypertension, dyslipidemia, inflammation, and impaired fibrinolysis (25). This toxic

metabolic environment increases atherosclerotic risk in T2DM with MS patients (26). Risk factors in MS create a state of constant and progressive damage to the vascular wall, manifested by a low-grade inflammatory process and endothelial dysfunction (20), which is regarded as an important factor in the pathogenesis of micro- and macro-angiopathy (22). In other word, the risk observed in MS inevitably sets the stage for increased vascular disease in T2DM, while hyperglycemia will give additional risk (26). Adamikova et al. found that TID ratio correlated with HbA_{1c} in T2DM patients with proven myocardial ischemia according to exercise MPS (asymptomatic from cardiovascular disease, but had 2/more cardiovascular risk factors) (27). This finding is similar with the one of our T2DM with MS group, but different with the T2DM only group. The difference might be due to the different characteristics of the patients.

Limitations

The population size of this study was relatively small and the duration of the diseases (T2DM and MS) were not assessed, so further studies with larger populations with more detailed criteria are required to determine the effect of the duration of the diseases and which parts of MS are more dominant in resulting TID. The ventricular function could not be assessed since gated SPECT data were not available in all patients.

Further studies are also needed to conduct the studies in 2 different populations separately, population without having any history of CAD and with recent mild symptoms. This study consisted of both population because of the lack of patients and the limitation of time.

Conclusion

TID ratio correlates with HbA_{1c} in T2DM patients who also present with MS. Determination TID ratio is needed to improve the sensitivity of MPS in detecting CAD in T2DM patients who also present with MS with poor glucose control.

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