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Hemoglobin A1C as the Strongest Influencing Factor in relation to Vascular Stiffness in Type 2 Diabetes Mellitus–Metabolic Syndrome Patients

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Keywords: Brachial-Ankle Pulse Wave Velocity (baPWV), HbA1c, Metabolic Syndrome, Type 2 Diabetes Mellitus, Vascular Stiffness.

Abstract: The risk of cardiovascular disease in type 2 diabetes mellitus (T2DM) will be high despite intensive glycemic control. This is because T2DM is often accompanied the condition of metabolic syndrome (MetS). Endothelial dysfunction can be assessed by non-invasive pulse wave velocity (PWV) measurement, which is an arterial stiffness influencing factor. This research aimed to determine the correlation of influencing factors in regard to metabolic syndrome and HbA1c in relation to vascular stiffness as measured by baPWV value in T2DM-Mets. The research was conducted at the Diabetes Outpatient Clinic of Dr. Sutomo General Hospital Surabaya and six Primary Healthcare clinics in Surabaya from December 21, 2010 - March 21, 2012. Subjects fulfilling the inclusion and exclusion criteria were measured with regard to blood pressure, BMI, waist circumference, laboratory examination: Fasting plasma glucose, Post prandial glucose, Hemoglobin A1c and ba-PWV measurements with V Serra-1000 devices. A total of 33 patients with T2DM met the inclusion and exclusion criteria. The result of the statistical analysis shows that there is a significant correlation between the HbA1c value and ba-PWV ($p = 0.036$). Other influencing factors exhibited a non-significant correlation with vascular stiffness ($p > 0.05$). The contribution of metabolic syndrome and HbA1c influencing factors was 4.6% with respect to vascular stiffness (Adjusted $R2 = 0.046$). Together the influencing factors in regard to metabolic syndrome and HbA1c had no significant effect on vascular stiffness ($p = 0.584$). HbA1c is the influencing factor that has the greatest effect on vascular stiffness. There was a significant correlation between HbA1c and vascular stiffness as measured by baPWV compared with other metabolic syndrome components. The contribution of influencing factors in regard to metabolic syndrome and HbA1c was 4.6% against vascular stiffness. Hemoglobin A1c is the influencing factor that has the greatest effect on vascular stiffness.

1 INTRODUCTION

Patients with type 2 diabetes (T2DM) have an increased risk of coronary heart disease than nondiabe. Metabolic changes that occur in diabetes such as hyperglycemia, hyperinsulinemia, insulin resistance and endotheli dysfunction directly affect cardiovascular status. Atherosclerotic cardiovascular disease remains the principal cause of death and isability among patients with diabetes mellitus than in individuals without diabetes mellitus. About two-thirds of deaths in people with diabetes mellitus are attributable to cardiovascular disease: of these, 40% are from ischemic heart disease, 15% from other forms of heart disease, principally congestive heart failure, a 10% from stroke (Barzilay et al., 2015). The risk of complications of type 2 diabetes mellitus (T2DM) is associated with hyperglycaemic conditions. Every 1% reduction in HbA1c may reduce myocardial infarction risk by 14% and 37% for microvascular complications (Stratton et al., 2000).

Hyperglycemia is a major factor in endothelial dysfunction in diabetes mellitus. The risk of cardiovascular disease remains high in people with diabetes mellitus despite intensive glycemic control. This is because T2DM is often accompanied by the condition of metabolic syndrome, among others: abdominal obesity, insulin resistance, hypertension, dyslipidemia, and microalbuminuria. This appears through the prevalence of high coronary heart

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disease in T2DM patients at 19.2% (Alexander et al., 2003; Moreno and Fuster, 2004).

The pathophysiology of cardiovascular complications in patients with T2DM begins with hyperglycemia and hyperinsulinemia (via advanced glycation end product (AGE) accumulation, endothelial dysfunction and altered vasoactive substance activity) leading to stiffness of the arteries. In addition, the presence of hyperglycemia will increase oxidative stress and/or activation of vascular inflammation (Tomiyama et al., 2006).

Endothelial dysfunction can be measured by non-invasive pulse wave velocity (PWV), which is an arterial stiffness influencing factor (Pornratthanong et al., 2006). The measurement of PWV is the most simple, non-invasive, robust, and reproducible method to determine arterial stiffness. Carotid-femoral PWV is considered as the 'gold-standard' measurement of arterial stiffness (Laurent et al., 2006). Brachial-ankle pulse wave velocity (baPWV) is an easy and reproducible measurement of systemic arterial stiffness that is measured by brachial and tibial arterial wave analyses. Carotid-femoral PWV and baPWV are indices of arterial stiffness that exhibit a similar extent of associations with cardiovascular disease risk factors and clinical events (Tanaka et al., 2009). Meta-analysis of cohort studies conducted in the general population with hypertension, diabetes, or end-stage renal disease, and other high-risk individuals have shown that a 1 m/s increase in baPWV is associated with a 12% increase in the risk of cardiovascular events. Thus, the Japanese Circulation Society has proposed that a baPWV of 1800 cm/s is a threshold for the high-risk category (Munakata, 2014; Takashima et al., 2014).

This study aimed to determine the factors that affect the vascular stiffness in patients with T2DM to improve understanding in developing strategies to reduce vascular stiffness.

2 METHODS

This study was a cross-sectional observational study conducted in the Diabetes Outpatient Clinic of Dr. Soetomo General Hospital, Surabaya, and six Primary Healthcare clinics. The research began on December 21, 2010 and ended on March 21, 2012.

The number of samples based on the calculation was 33 subjects. The inclusion criteria were new T2DM or old T2DM patients who were not on OAD therapy for 2 months prior to sampling, aged 40 to less than 60 and willing to participate by signing informed consent. The exclusion criteria were T2DM patients receiving insulin therapy, clinically acute infection, patients receiving statin hypolipidemic therapy in the last two months, receiving antihypertensive therapy class of Angiotensin Receptor Blocker and ACE Inhibitor in the last two months, serum creatinine level ≥ 1.5 mg/dl (male) and ≥ 1.4 mg/dl (women), patients with congestive heart failure, and active smokers or a history of quitting smoking less than 2 months after the study.

Patients who met the inclusion and exclusion criteria were included in the study, followed by basic data taking in the form of anamnesis, physical examination (including blood pressure, height, weight, waist circumference), and laboratory examination of FPG, 2PPG, HbA1c and the measurement of baPWV (Brachial ankle Pulse Wave Velocity). BaPWV is the velocity of the pulse wave, measured using a V-Serra 1000 portable device with a unit of cm/s. The independent variables in this study were HbA1c, FPG, HDL cholesterol, TG cholesterol, waist circumference, HOMA-IR, TNF⟨, and ADMA, while the dependent variable was ba-PWV.

Bivariate statistical tests were performed using Pearson Correlation Test and multivariate analysis using logistic regression. Mean value (α) = 0.05; and power (β) = 90%. The results of the analysis are presented in tabular form. The whole process of analysis used the SPSS program for Windows version 20.0. This research received approval (Ethical clearance) from the Committee on Drugs Abuse Ethics at Dr. Soetomo General Hospital, Surabaya No. 44 / Panke.KKE / VII / 2010. No costs incurred in this study were charged to the subject of research but the researchers, Diabetes Center and Nutrition Surabaya and sponsors of Sanofi-Aventis.

3 RESULTS

Table 1 shows that 57.6% of the subjects were female with the mean age of 51.42 ± 5.1 years and the mean duration of DM suffered by the subjects was 17.45 ± 23.8 months. Based on their nutritional status, the average BMI of the subjects was above the normal value of 26.67 ± 4.7kg/m^2. Serum creatinine values 0.78 ± 0.2 mg/dl and fasting insulin levels were 9.15±5.2 µU/dl.

Table 1: Characteristics of study subjects (n = 33).

Variables	N (%) or Mean ± SB

Female	19 (57.6)
Male	14 (42.4)
Age (year)	51.42 ± 5.1
Body Height (cm)	155.77 ± 7.9
Body Weight(kg)	64.82 ± 12.7
BMI (kg/m^2)	26.67 ± 4.7
DM Duration (Month)	17.45 ± 23.8
Serum creatinine (mg/dl)	0.78 ± 0.2
HOMA-B (%)	50.39 ± 66.0
Fasting insulin (µU/dl)	9.15 ± 5.2

Table 2 below shows the correlation of metabolic syndrome influencing factors and HbA1c to vascular stiffness as measured by baPWV values. The result of statistical analysis shows that there was a significant correlation between HbA1c value and baPWV with medium correlation strength. Other variables showed a non-significant correlation with vascular stiffness ($p > 0.05$).

Table 2: Correlation analysis of Metabolic Syndrome influencing factors with vascular stiffness (n = 33).

Variables	Mean ± SD	p*	r
Waist circumference (cm)	88.94 ± 10.8	0.302	0.185
Triglycerides (mg/dl)	158.79 ± 80.6	0.577	0.101
HDL (mg/dl)	47.6 ± 8.7	0.404	0.150
FPG (mg/dl)	166.06 ± 63.1	0.392	0.154
HbA1c (%)	8.52 ± 0.9	0.036	0.367
Systolic BP (mmHg)	129.7 ± 16.5	0.979	0.005
HOMA-IR	3.69 ± 2.3	0.962	0.009
TNF-α (pg/mL)	8.86 ± 13.4	0.590	0.097
ADMA (mol/L)	0.57 ± 0.1	0.474	0.129
baPWV (cm/s)	1586.82 ± 240.2		

*Analyzed by *Pearson Correlation Test*

Table 3 shows the multivariate analysis of the influencing factors in regard to metabolic syndrome and HbA1c in regard to vascular stiffness as measured by the baPWV values. The contribution of metabolic syndrome and HbA1c influencing factors was 4.6% for vascular stiffness. The rest was caused by other influencing factors (Adjusted R2 = 0.046). Together the influencing factors in regard to metabolic syndrome and HbA1c had no significant effect on vascular stiffness ($p = 0.584$). However, when seen between the influencing factors in regard to the metabolic syndrome and HbA1c influencing factors, it was found that HbA1c is a major influencing factor in regard to vascular stiffness, whereas HOMA-IR is the least influencing factor.

Table 3: Multivariate analysis of Metabolic Syndrome influencing factors in regard to vascular stiffness (n = 33).

Variables	B	p*	*Adjusted R^2*
Waist circumference	4.426	0.433	0,046
Triglycerides			
HDL	0.512	0.434	
FPG	5.147	0.367	
HbA1c	0.991	0.417	
Systolic BP	122.307	0.064	
HOMA-IR	1.597	0.602	
TNF-α	0.146	0.995	
ADMA	3.178	0.456	
	383.684	0.405	

*Analyzed by multiple linear regression (Constant = 1761,187; df = 9; F = 0.845; p = 0.584; method of enter.

4 DISCUSSION

Various epidemiological studies have shown increasing incidence rates and the prevalence of T2DM in different parts of the world. The prevalence of T2DM in Indonesia was higher in women at 6.4% compared to males at 4.9% (Mihardja et al., 2009). In this study, the proportion of patients with T2DM was 21 patients (60%) and 14 patients (40%) who met the inclusion and exclusion criteria. Similar results were also found in the Kholili study in Surabaya with a proportion of 55%female research subjects and 45% men (Kholili, 2008). However, in Japan, the proportion of patients with T2DM is higher in men than women. This was because the prevalence of T2DM in Japan is higher in males than females (Inoue et al., 2012).

Diabetes mellitus prevalence increases gradually in line with increasing BMI. The results of the survey in Indonesia found the prevalence of DM in normal weight subjects was 4.4%, overweight 7.3% and obesity 9.1% (Mihardja et al., 2009). This study found the average value of BMI before the treatment of 26.6 kg/m^2 which corresponds to the overweight category.

Vascular stiffness is due to the complex interaction between structural changes (extracellular matrix and luminal pressure), cellular (endothelial cells and vascular smooth muscle cells) and functional elements of blood vessel walls. These vascular changes are influenced by hemodynamic factors and extrinsic factors such as hormones, salts and glucose regulation. Hypertension, and diabetes and the aging process exacerbate these vascular changes that result in arterial stiffness (Zieman et al., 200 Brillante et al., 2009).

In this study, there was a significant correlation between HbA1c and vascular stiffness as measured

by baPWV compared to other metabolic syndrome components. In Tsubakimoto's study, the results of baPWV correlated strongly with systolic and diastolic blood pressure and moderately correlated with waist circumference, LDL cholesterol, triglycerides, uric acid, FPG, 2hPG, fasting insulin and HbA1c (Tsubakimoto et al., 2006). In Tomiyama's study, plasma glucose and blood pressure elevation at the baseline was a predictor of progression of arterial stiffness. In this study, it was found that blood pressure and fasting plasma glucose levels even below those defining hypertension and diabetes may synergistically lead to the progression of atherosclerotic arterial damage (Tomiyama et al., 2006). In Tsubakimoto's study, baPWV values increased the number of risk factors for metabolic syndrome components (Tsubakimoto et al., 2006).

Hyperglycemia and hyperinsulinemia in several studies present either directly or indirectly (via AGE accumulation, endothelial dysfunction, and changes in vasoactive substance activity) leading to stiffness of the arteries. In addition, elevated plasma glucose results in increased oxidative stress and activation of vascular inflammation that directly leads to arterial stiffness (Tomiyama et al., 2006).

The multivariate analysis of metabolic syndrome influencing factors and HbA1c in regard to vascular stiffness was measured by the baPWV value which showed that the contribution of metabolic syndrome and HbA1c influencing factor in regard to vascular rigidity was 4.6%. The rest was caused by other influencing factors (Adjusted R2 = 0.046). Together the influencing factors in regard to metabolic syndrome and HbA1c had no significant effect on vascular stiffness (p = 0.584). However, between the influencing factors in regard to metabolic syndrome and HbA1c influencing factors, it was found that HbA1c is the strongest influencing factor in regard to vascular stiffness, whereas HOMA-IR is the least influencing factor.

5 CONCLUSION

There was a significant correlation found between HbA1c and vascular stiffness as measured by baPWV compared to the other metabolic syndrome components. The contribution of metabolic syndrome and HbA1c influencing factors was 4.6% in relation to vascular stiffness, the rest being caused by other influencing factors. Hemoglobin A1c was found to be the strongest influencing factor in regard to vascular stiffness, whereas HOMA-IR was the least influencing factor. However, several limitations should be considered in this study. First, control groups are needed as a comparison to assess the relationship between baPWV and MetS. Second, because of the small number of participants, we did not differentiate the proportion by sex, age, and duration of diabetes.

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