

Differences between several atherogenic parameters in patients with Controlled and Uncontrolled Type 2 Diabetes Mellitus

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Abstrak

Tujuan Untuk mengetahui perbedaan nilai antara Index Aterogenik Plasma (AIP), rasio Low Density Lipoprotein teroksidasi (Ox-LDL)/High Density Lipoprotein (HDL) dan rasio Lipoprotein-associated Phospholipase A2 (Lp-PLA2)/HDL yang dapat diperkirakan besarnya risiko penyakit jantung koroner (PJK) pada penderita DM tipe 2 terkontrol dan tidak terkontrol.

Metode Penelitian ini menggunakan disain potong lintang pada 40 penderita DM tipe 2 terkontrol dan 40 penderita DM tipe 2 tidak terkontrol. Metode pengambilan sampel yang digunakan adalah secara consecutive sampling, yaitu setiap penderita yang berkunjung selama kurun waktu penelitian di Laboratorium Klinik Prodia Jakarta yang memenuhi syarat inklusi dan eksklusi. Parameter yang diperiksa adalah trigliserida, HDL, Ox-LDL dan Lp-PLA2. AIP didefinisikan sebagai $\log(TG/HDL-C)$.

Hasil AIP dan rasio (Ox-LDL/HDL) lebih tinggi secara signifikan pada subjek DM tipe 2 tidak terkontrol dibanding DM terkontrol ($0,72 \pm 0,13$ vs $0,47 \pm 0,22$, $p < 0,001$) dan ($1738,8 \pm 625,5$ vs $1418 \pm 535,3$, $p = 0,02$), sedangkan rasio (Lp-PLA2/HDL) tidak berbeda secara bermakna ($5,09 \pm 2,17$ vs $5,95 \pm 3,11$, $p = 0,16$).

Kesimpulan Nilai AIP dan rasio (Ox-LDL/HDL) lebih tinggi secara bermakna pada DM tipe 2 tidak terkontrol dibandingkan dengan DM tipe 2 terkontrol. Parameter ini dapat dimanfaatkan dalam memprediksi risiko aterosklerosis pada penderita diabetes. (*Med J Indones 2010; 19: 103-8*)

Abstract

Aim to assess the differences between Atherogenic Index of Plasma (AIP), ratio of oxidized-Low Density Lipoprotein (Ox-LDL)/High Density Lipoprotein (HDL) and ratio of Lipoprotein-associated Phospholipase A2 (Lp-PLA2)/HDL in predicting the risk of coronary heart disease (CHD) in patients with controlled and uncontrolled type 2 Diabetes Mellitus (T2DM).

Methods The study was done observationally with cross sectional design. A total of 80 patients, consisted of 40 controlled and 40 uncontrolled T2DM. The serum triglyceride (TG), HDL-C, Ox-LDL, Lp-PLA2 were examined in their relationship with T2DM risk. AIP is a ratio calculated as $\log(TG/HDL-C)$.

Results AIP and ratio of Ox-LDL/HDL were significantly higher in uncontrolled than controlled T2DM ($0.72 + 0.13$ vs 0.47 ± 0.22 , $p < 0.001$) and (1738.8 ± 625.5 vs 1418 ± 535.3 , $p = 0.02$), but no significant difference was found in ratio of Lp-PLA2/HDL (5.09 ± 2.17 vs 5.95 ± 3.11 , $p = 0.16$).

Conclusion AIP and ratio of Ox-LDL/HDL value were significantly higher in uncontrolled than in controlled T2DM. These parameters may be beneficial in predicting the risk of atherosclerosis in diabetic patients. (*Med J Indones 2010; 19:103-8*)

Key words: AIP, atherosclerosis, Diabetes mellitus, HDL, Lp-PLA2, Ox-LDL.

Diabetes Mellitus (DM) is continuing to become a health problem since the prevalence of DM has increased dramatically over the past two decades.¹ The patients diagnosed with DM are proven to be prone to atherosclerosis and coronary heart diseases (CHD), especially type 2 Diabetes Mellitus (T2DM). These patients have higher risk of mortality and morbidity for cardiovascular diseases.

The occurrence of Diabetes Mellitus (DM) is due to chronic hyperglycemia and disorder in carbohydrate, fat and protein metabolism, which is related to the

progression of micro- and macro vascular complication such as cardiovascular diseases, retinopathies, neuropathies and nephropathies. This disease is caused by the existence of absolute and relative insulin deficiency. The monitoring of Diabetes Mellitus can be done using the Hemoglobin A1C (A1C). Non-enzymatic glycosidation of n-terminal valine of HbA that resulted in A1C, takes place in erythrocyte and is depending on the level of glucose for 120 day, which corresponds to erythrocyte life-span. Inspection of A1C will reflect the long-range DM controll over a two or three months period.²

Atherogenic index of plasma (AIP) is the new marker of atherogenicity, since the AIP is related directly to the atherosclerosis risk. AIP is the ratio calculated as $\log(TG/HDL-C)$.³ Existence of hypertriglyceridemia will increase the activity of hepatic lipase (HL) which results in the increase of HDL catabolism (degradation of HDL). Each degradation of 1 mg HDL will correlate with 2% increase in the risk coronary heart disease (CHD).⁴⁻⁶

Some researchers have proven that Ox-LDL plays a vital, important role in the progression of atherosclerosis. Moreover, high level of Ox-LDL in circulation is proven to be related to plaque instability of atheroma.⁷

Lipoprotein-associated Phospholipase A2 (Lp-PLA2) is pro-inflammatory, due to the formation of lyso-phosphatidylcholine and oxidized free fatty acid (FFA) which have pro-inflammatory characteristics. Activity of Lp-PLA2 is particularly related to small dense LDL particle, which is atherogenic and is proven to independently predict endothelial dysfunction.⁸

Diabetic dyslipidemia in T2DM, also called atherosclerotic diabetic dyslipidemia, is generally marked by an increase of plasma triglyceride (TG), small dense LDL concentration and apo lipoprotein B, as well as the decrease in HDL cholesterol concentration.⁹ It is reported that AIP has higher predictive value for atherosclerosis.³ Some ratio of pro atherogenic markers when divided by cholesterol HDL, will increase the odds ratio value which means higher predictive value towards atherosclerosis, as compared to pro atherogenic markers alone.¹⁰

Besides, ratio of AIP, Ox-LDL and Lp-PLA2 over HDL can also be calculated. This study will examine the predictive value to atherosclerosis in controlled and uncontrolled T2DM subjects by using the value of AIP, Ox-LDL/HDL ratio and Lp-PLA2/HDL ratio to provide prediction to atherosclerosis development in T2DM, especially uncontrolled T2DM.

METHODS

Study Design

This is a cross-sectional study comparing AIP, ratio of (Ox-LDL/HDL) and ratio of (Lp-PLA2/HDL) and various metabolic profiles between controlled and uncontrolled T2DM. Data collected by interview, medical records, physical examination, and laboratory testing (A1C, fasting plasma glucose, HDL-C, triglyceride, Ox-LDL, Lp-PLA2 level), from May to

September 2009. The study protocol was approved by The Medical Ethics Committee of The Faculty of Medicine University of Hasanuddin Makassar, Indonesia, and all participants have given written informed consent

Subject

Subjects consisted of 80 T2DM patients who were divided into two groups based on A1C value. First group consisted of 40 individuals with A1C < 8 % as controlled T2DM, and the second group consisted of 40 individuals with A1C \geq 8% as uncontrolled T2DM. Subjects were consecutively recruited from Prodia clinical laboratory, Kramat, Jakarta. The inclusion criteria were 35-60 years of age with fasting blood glucose > 126 mg/dl, while the exclusion criteria were chronic kidney disease (serum creatinine > 2.4 mg/dl) and hepatic failure (AST > 66 U/L or ALT > 100 U/L). Subjects taking lipid lowering agents and antioxidant medications are also excluded.

Anthropometric Measurement

Body weight (BW) was measured in kilograms to the nearest 0.1 kg. Height (Ht) was measured in centimeters to the nearest 0.1 cm. Body Mass Index (BMI) was calculated by dividing body weight in kg by height in squared meter.

Waist circumference was measured in centimeters to the nearest 0.1 cm, using a flexible non-elastic tape made by Roche (Roche, Switzerland). Waist circumference was measured at stomach area in the middle of underside arcus costae and Iliacal Crest, in standing position.

Blood Pressure Measurement

Blood pressure was measured using a sphygmomanometer. Subjects were seated for at least 5 minute before the measurement. First and fifth Korotkoff sounds were taken as systolic and diastolic blood pressure, respectively.

Biochemical Assessments

Blood samples were analyzed for glycaemic control (blood glucose and A1C) and classified using local reference by PERKENI, 2006. A1C in blood EDTA samples were measured with High Performance Liquid Chromatography method using reagent manufactured by Biorad (Marnes-la-Coquette, France), serum blood glucose levels were measured by hexokinase method using reagent manufactured by Roche (Mannheim,

Germany). HDL-C in blood serum sample were measured by homogenous method using reagent manufactured by Daiichi (Daiichi pure chemical, Japan), triglyceride (TG) in blood serum sample were measured by GPO-PAP method using reagent manufactured by Roche (Mannheim, Germany). Ox-LDL by ELISA method using reagent manufactured by Mercodia (AB, Uppsala, Sweden), and Lp-PLA2 in blood serum sample were measured by ELISA method using reagent manufactured by diaDexus (Inc., San Francisco, California).

Data Analysis

Statistical analyses were performed by SPSS for windows version 11.5. Univariate analyses were performed to calculate mean, maximum and minimum value and standard deviation (SD). Comparison of AIP, ratio of Ox-LDL/HDL and ratio of Lp-PLA2/HDL levels between controlled and uncontrolled group were analyzed using t test if normally distributed, or with Mann-Whitney non parametric test, if not normally distributed.

RESULTS

The study has recruited 80 subjects consisted of controlled T2DM (A1C < 8%) and 40 individuals with uncontrolled T2DM (A1C > 8 %)

Table 1 shows that both groups are comparable in demographic characteristics.

Table 1. Demographic Characteristics of the Subjects

Parameter	controlled DM	uncontrolled DM
	Mean ± SD	Mean ± SD
Age (year)	54.8 ± 6.1	52.1 ± 5.9
BMI (kg/m ²)	24.6 ± 4.3	25.6 ± 3.6
WC (cm)	90.0 ± 11.5	91.9 ± 7.8
Systole (mm/Hg)	127.3 ± 19.4	133.4 ± 11.5
Diastole (mm/Hg)	82.3 ± 7.5	87.9 ± 13.0

BMI= Body Mass Index; WC = waist circumference

The uncontrolled T2DM subjects had higher, BMI, WC, Systole and Diastole than the controlled T2DM subjects. On the other hand, the uncontrolled T2DM subjects had lower age than their controlled counterparts.

Clinical chemistry data in Table 2 shows that fasting glucose, A1C, total cholesterol, triglyceride and HDL-cholesterol are significantly higher in uncontrolled

T2DM compared to controlled T2DM subjects. Whereas the AST, ALT, Creatinine and LDL-cholesterol was not significantly different.

Table 3 shows the differential analysis between AIP, ratio of Ox-LDL/HDL and ratio of Lp-PLA2/HDL in controlled and uncontrolled T2DM patients. The uncontrolled T2DM subject had higher level of Ox-LDL, AIP and ratio of Ox-LDL/HDL. Whereas the Lp-PLA2 and ratio of Lp-PLA2/HDL were not significantly different in both groups.

Table 2. Biochemical Characteristic of the Subjects

Parameter	controlled DM	uncontrolled DM	P
	Mean ± SD	Mean ± SD	
Fasting glucose (mg/dl)	126.2 ± 34.5	230.1 ± 76.2	0.02
A1C (%)	6.7 ± 0.8	10.8 ± 2.1	<0.001
Total Cholesterol (mg/dl)	192.1 ± 31.5	214.9 ± 50.4	0.019
Triglyceride (mg/dl)	145.2 ± 66.5	216.3 ± 57.8	<0.001
HDL-C (mg/dl)	45.2 ± 8.7	40.7 ± 7.4	0.01
LDL-C (mg/dl)	115.9 ± 26.7	216.3 ± 57.8	0.089
AST (U/L)	25.0 ± 6.3	23.7 ± 7.8	0.06
ALT (U/L)	29.8 ± 17.0	24 ± 12.4	0.08
Creatinin (mg/dl)	1.1 ± 0.3	1.0 ± 4.0	0.47

Table 3. Differential Analysis between AIP, ratio of Ox-LDL/HDL and ratio of Lp-PLA2/HDL in controlled and uncontrolled T2DM patients

Parameter	controlled DM	uncontrolled DM	P
	Mean ± SD	Mean ± SD	
Ox-LDL (mU/L)	60350 ± 18358.5	76008 ± 20074.3	<0.001
Lp-PLA2 (ng/ml)	256 ± 122	224.1 ± 78.9	0.17
AIP	0.47 ± 0.22	0.72 ± 0.13	<0.001
Ratio of Ox-LDL/HDL	1418 ± 535.3	1738.8 ± 625.5	0.02
Ratio of Lp-PLA2/HDL	2.19 ± 0.99	1.84 ± 0.74	0.083

AIP=Atherogenic Index of Plasma; Lp-PLA2 = lipoprotein-associated phospholipase A2

DISCUSSION

Descriptive data showed that there was no significant difference regarding age, BMI, waist circumference, systolic & diastolic blood pressure between controlled and uncontrolled T2DM, indicating that both groups were comparable. Ox-LDL, AIP and ratio of Ox-LDL/HDL showed significant difference, because in uncontrolled T2DM worse diabetic dyslipidemia would occur, whereas Lp-PLA2 and ratio of Lp-PLA2/HDL were not significantly different.

The AIP value from these two groups was significantly different with $p < 0.001^*$. Similar result was obtained by a cohort study in 1433 patients by Dobiasova et al., with various risk of atherosclerosis, including T2DM, hypertension, and dyslipidemia.³ The AIP value increased significantly with increasing atherogenic risk (AIP from 0.24 to 0.51). In patient with T2DM, AIP was among the highest value.

Ratio of Ox-LDL/HDL in uncontrolled T2DM was significantly different from controlled T2DM ($p = 0.02$). This might be related to the worsen condition of diabetic dyslipidemia in uncontrolled T2DM, compared with controlled T2DM, which might be due to degradation of cholesterol HDL and increased small dense LDL. The formation of Ox-LDL will be more likely to occur on small-dense LDL. These findings were supported by a study of small dense LDL by Physicians Health Study by Stampfer et al., on 266 male subjects with fatal and non fatal CHD for 7 years, that indicated significantly different in uncontrolled DM compared to controlled group with relative risk of 1.38.¹¹ Therefore, LDL size was a strong predictor for the formation of Ox-LDL, and thus for CHD risk.²

AIP and ratio of Ox-LDL/HDL were significantly higher in uncontrolled than in controlled T2DM. The explanation is that the occurrence of Diabetes Mellitus is due to chronic hyperglycemia and disorder in carbohydrate, fat and protein metabolism due to the existence of absolute and relative insulin deficiency. The dyslipidemia condition commonly happen to T2DM patient is one of the factors in this risk. Diabetic dyslipidemia is generally accompanied with the increase in triglyceride, small dense LDL and Apo-B, and the decrease in HDL-cholesterol. Diabetic dyslipidemia is associated with insulin resistance, a condition that has emerged as a predilection to type 2 diabetes. When people are insulin resistant, the body does not efficiently use the insulin, which adversely affects levels of blood lipids with increased triglycerides and decreased HDL cholesterol - thus increasing CVD risk.¹²

In uncontrolled T2DM, worse diabetic dyslipidemia would occur with hypertriglyceridemia as the primary dyslipidemia disorder. Other study showed a strong correlation of AIP with lipoprotein particle size which may explain its high predictive value.³ Summarized data of AIP calculated in 8394 subjects from 6 populations and clinical studies demonstrated that AIP values increased with increasing cardiovascular (CV) risk. Thus, blood from umbilical cord, in young

children, and in healthy women have values below 0.1, while in men and subjects with CV risk factors such as hypertension, diabetes, dyslipidemia, this value increased up to 0.4. Based on these data was suggest that AIP values of -0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high CV risk. In that study population men had higher AIP values than women. In a cohort study on patients undergoing coronary angiography, AIP was the best predictor of positive findings in model that included age, BMI, waist circumference, T2DM, blood pressure, smoking, TG, TC, LDL-C, apoB, HDL-C, and TC/HDL-C. AIP was also a highly sensitive marker of differences of lipoprotein profiles in families of patients with premature myocardial infarction and control families. Treatment with ciprofibrate, and combination of statin and niacin dramatically decreased AIP. Combination with hypoglycemic therapy that included pioglitazone decreased AIP in patients with T2DM.¹³

Epidemiology study shows that hypertriglyceridemia is the risk factor of CVD in T2DM. It is well known that triglyceride-rich lipoprotein (VLDL and LDL) is atherogenic, and the occurrence of CHD has been shown to be related with the presence of negative correlation between hypertriglyceridemia and decrease in HDL value and increase in small dense LDL. These conditions are frequently found in T2DM patients and insulin resistance syndrome (central obesity).^{14,15} Similar result was obtained by cohort study of relationship between Ox-LDL, T2DM and obesity-related traits in a bi-racial sample of 2985 subjects at baseline and after 7 years of follow-up. The results showed that Ox-LDL was positively correlated with T2DM fasting glucose, A1C, fasting insulin, and HOMA-IR and negatively correlated with adiponectin.¹⁶

Oxidized LDL (Ox-LDL) has been shown to play an important role in the initiation and development of atherosclerosis.¹⁷ Individuals with T2DM exhibit enhanced LDL oxidizability and accelerated atherosclerosis.^{18,19} Past studies demonstrated the association between LDL oxidation and atherosclerosis by "indirect" methods, such as lag times and propagation rates for LDL oxidation, and antibodies against oxLDL. Recently, some groups have developed "direct" methods for measuring circulating Ox-LDL.²⁰⁻²² Indeed, several lines of evidence have demonstrated that the level of circulating Ox-LDL is significantly higher in patients with T2DM, and becomes a marker and has a positive relationship with coronary artery disease (CAD) and acute coronary syndromes.^{23,24}

However, the predictive value of circulating Ox-LDL for cardiac events in T2DM patients with CAD has not been investigated.

This study firstly, to the best of our knowledge, demonstrated that high levels of circulating Ox-LDL can serve as an independent and significant predictor for future cardiac events in T2DM patients with CAD. Therefore, measurement of circulating Ox-LDL may be helpful for identifying high-risk patients with T2DM and CAD. Level of ratio of Lp-PLA2/HDL in uncontrolled T2DM was lower but not significantly different from controlled T2DM. Similar result was obtained by a cohort study in 889 subjects from the population-based MONICA/KORA Augsburg survey from 1984 until 2002 (with mean follow-up time of 13.5 years). In this large population-based cohort study, elevated concentrations of Lp-PLA2 were not independently associated with incident T2DM in apparently healthy middle-aged men. Since Lp-PLA2 is associated with risk of future CHD but not with incident T2DM, it might represent a more specific marker of vascular inflammation.^{25,26}

From the present study, it is concluded that AIP and ratio of Ox-LDL/HDL value were significantly higher in uncontrolled than in controlled T2DM. These parameters may be useful in predicting the risk of atherosclerosis in diabetic patients

Acknowledgments

We thank Prodia Foundation for Research and Training for their invaluable help in conducting the many procedures of this research.

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