Relationship between AIP with hs-CRP and ADMA on Type 2 Diabetes Mellitus

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Abstract

The aim of this research is to know the correlation between Atherogenic Index of Plasma (AIP) with high sensitive C protein (hs-CRP) and Asimmetric Dimethylarginin (ADMA) in type 2 diabetes mellitus (T2DM). Diabetics proven to be more susceptible to atherosclerosis and coronary heart disease (CDH), especially in patients with T2DM have higher risk and mortality for cardiovascular risk factors. AIP is a strong marker to predict the risk of atherosclerosis and CHD. hs-CRP is an acute phase protein produced in the liver, the part of in the immune system response and in acute inflammatory conditions. ADMA is an inhibitor on Nitric Oxide-forming ensymes, may be used as a marker of endhotelial function. This research methode used cross sectional design. The sample of this research were 80 T2DM patient with inclusion requirement men, age 30-65 years old, fasting glucose ≥ 126 mg/dl, AIC ≥ 6% and willing to sign inform consent. The conclution that AIP and has-CRP increased in patients with T2DM ($p < 0.001$) and there was a significant relationship between AIP and hs-CPR ($r = 0.486$, $p < 0.001$). The AIP score was not correlated with ADMA in T2DM subjects ($r = -0.007$, $p = 0.915$).

Keywords: ADMA, AIP, atherosclerosis, hs-CRP, T2DM.

Introduction

Diabetes Mellitus (DM) patients in the last decade are increasing, especially in developing countries1. WHO predicts that by 2025 if this epidemic is not addressed soon there will be a 150% increase in prevalence. According to the International Diabetes Federation (IDF), the number of DM patients in the world, increased and the cost of its management to 3-fold and 1 in 2 people with DM is still undiagnosed. From various epidemiological studies in Indonesia, the prevalence of DM is 1.5 - 2.3% in the population aged more than 15 years (Williams, 1999).

Type 2 diabetes mellitus (T2DM) is a metabolic disorder and typically results from excess of caloric intake over energy expenditure. It is characterized by a progressive insulin secretory defect due to insulin resistance, which increases the body‘s demand for insulin in order to retain glucose homeostasis.

Diabetics proven to be more susceptible to atherosclerosis and coronary heart disease (CHD), especially in patients with type 2 diabetes have a higher risk and mortality for cardiovascular risk factors associated with insulin resistance contributing to increased risk of CHD. The condition of dyslipidemia that is very common in patients with type 2 DM is one of these risk factors. Diabetic dyslipidemia is generally characterized by elevated plasma triglycerides (TG) and decreased HDL cholesterol concentrations, as well as an increase in small dense LDL concentrations and apolipoprotein B(Dobiasova, 2004) . Aterogenic Index of Plasma (AIP) or Log-defined atherogenic index (TG/HDL-C) is a new marker of atherogenity because AIP is directly related to the risk atherosklerosis (Dobiasova, 2001).

C-reactive protein (CRP) is not only a marker of inflammatory state, but studies have shown that CRP itself is also involved in the pathogenology of atherogenesis, plaque destabilization and aterotrombosis process (Pearson, 2003). Considering the fundamental CRP involvement in the incidence of chronic subtle inflammatory processes and the role of CRP which is not merely a marker (biomarker) but also involved in the pathobiology of vascular disorders, hs-CRP factor selection in the analysis of CHD events The inflammatory phase has an important position (Biasucci , 1999).

Asymmetric dimethylarginine (ADMA) is an inhibitor of the Nitric Oxide (NO) enzyme, currently ADMA is a marker of endothelial function. In addition to being stable, ADMA is easily measured, reflecting NO concentrations and also patobiologically contributing directly to the incidence of endothelial dysfunction (Achan, 2003). The aim of this research is to know the correlation between Aterogenic Index of Plasma (AIP) with high sensitive C Protein (hs-CRP) and Asimmetric Dimethylarginin (ADMA) in T2DM.

Method

The method of research used cross sectional design. The sample of this research are 80 type 2 diabetic patients with inclusion requirement are male, age 30 - 65 years old, fasting glucose examination ≥ 126 mg / dl, A1C ≥ 6% and willing to sign inform consent. Exclusion terms are subjects with impaired renal function, impaired liver enzymes, antioxidants and fat-lowering drugs.

The TG levels in which the sample was taken under fasting conditions were TG levels in blood serum samples measured by the GPO-PAP method, the Modular P 800 (Roche Diagnostic) autoanalyzer tool, the Roche paint reagent no 11730711216 and expressed in mg/dl units. HDL cholesterol levels were HDL cholesterol levels in blood serum samples as measured by homogenous enzymatic method (Daiichi pure chemical), Modular P 800 (Roche Diagnostic) autoanalyzer tools, Daiichi cat no 290268 reagents and expressed in mg/dl units. Hs-CRP levels were hs-CRP levels in blood serum samples as measured by immunochemiluminescence (Siemens) method, Immulite 2000 appliance, Siemens cat reagent no L2CRPA2 and expressed in mg/L units. ADMA levels were ADMA levels in blood serum samples measured by ELISA (DLD Diagnostic, Hamburg, Germany) method, 680 model micro-reader (Roche Diagnostic), DLD Diagnostic paint no EA201/96 and expressed in units of umol/L.

The data obtained is processed through SPSS for Windows program. Analyzes, bivariate and multivariate are performed. The results are narrated and clarified by tables or graphs. For statistical tests, the significance level (significance) used is 5%. The statistical test used to determine the relationship between AIP with hs-CRP and ADMA in patients with T2DM. Pearson correlation test when the data is normally distributed or Spearman test when the data is not normally distributed.

Results

Table 1 shows that there is no significant difference in age, body mass index (BMI), abdominal circumference, systolic and diastolic blood pressure ($p < 0.05$).

Table 1. Formatting rules

Parameter	T2DM	P
	Average ± SD (%)	
Age (years)	53.45 ± 6.1	0.05
BMI (kg/m^2)	25.1 ± 4.3	0.27
WZ (cm)	90 ± 11.5	0.39
SBP (mm/Hg)	127.3 ± 19.4	0.09
DBD	82.3 ± 7.5	0.05

Notes : BMI = body mass index; WZ= waist size; SBP= Systole Blood Pressure; DBP= Diastole blood pressure; SD= *standard deviation*; p=*probability*; *unpaired t test*
*= *significant correlation* (p<0,05)

Table 2 shows that there are significant differences in fasting blood glucose, A1C, AIP and hs-CRP (p <0.05).

Table 2. Demographic Characteristics

Parameter	T2DM Average ± SD (%)	P
	Fasting blood sugar (mg/dl)	177.7± 34.5 0.02*
A1C (%)	6.9 ± 0.8	< 0.001*
AIP (mU/L)	0.47 ± 0.22	< 0.001*
hs-CRP (ng/ml)	2.86 ± 1.22	< 0.001*
ADMA (umol/L)	0.74 ± 0.22	0.337

Notes: AIP=*Atherogenic Index of Plasma*; hs-CRP = high sensitive C reactive protein; ADMA=*Asimmetric Dymetilarginin*; SD= *standard deviation*; p=probability; unpaired t test *= significant correlation (p<0,05)

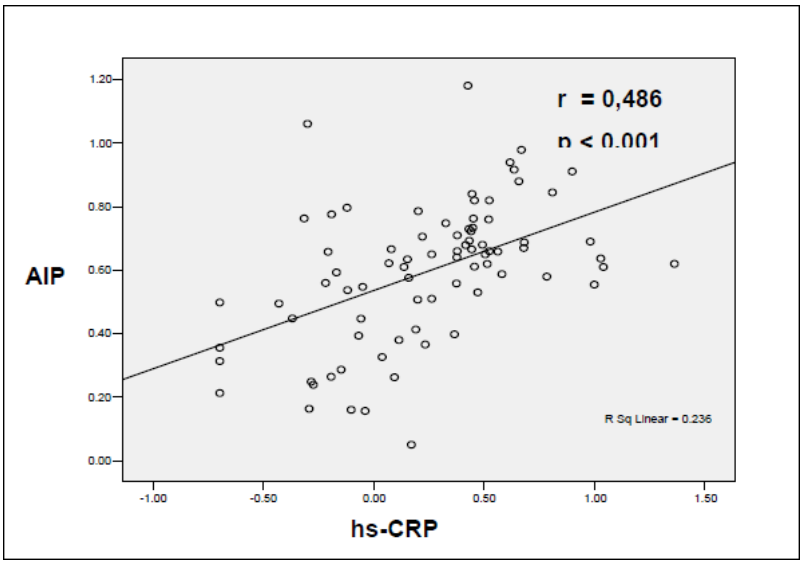

Figure 1. The distribution of AIP values to hs-CRP levels

Figure 1., the distribution of AIP values to hs-CRP levels is shown. From the graph shows that there is a relationship between AIP with hs-CRP (r = 0.486, p <0.001).

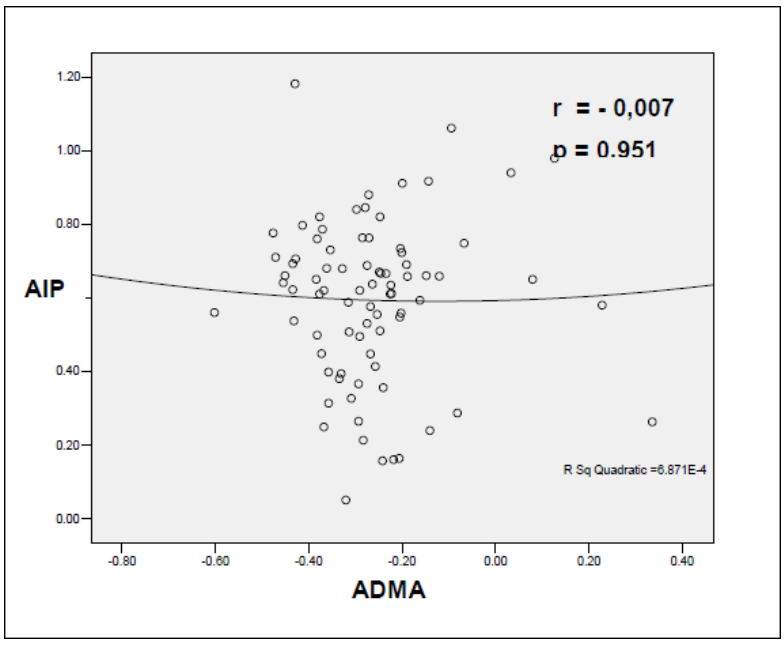

Figure 2. The distribution of AIP values to ADMA levels

Figure 2. AIP values are shown to the ADMA levels. From the graph shows that there is no relationship between AIP with ADMA (r = - 0.007, p = 0.951).

Discussion

Demographic and Biochemical Profile of Research Participants

From the analysis of general descriptive data (Table 1), there were no significant differences in age, body mass index (BMI), abdominal circumference, systolic and diastolic blood pressure (p <0.05). It can be explained that age, body mass index (BMI), abdominal circumference, systolic and diastolic blood pressure were not significantly different due to the collection of samples from the equivalent population.

While the parameters of fasting blood sugar, A1C, AIP and hs-CRP, showed a significant difference (p <0.05) (Table 2), because in patients with T2DM diabetic dyslipidemia worse and characterized by an increase in fasting blood sugar , A1C, triglycerides, and decreased HDL cholesterol. The presence of hypertriglyceridemia will increase hepatic lipase activity (HL) with a result of increased HDL catabolism (decreased HDL levels). Any decrease of 1 mg of HDL will increase the risk of CHD by 2, 8,9,10.

Relationship between AIP with hs-CRP and ADMA

AIP values correlated well with hs-CRP (r = 0.486, p <0.001). This is consistent with a number of epidemiological studies that find an inverse relationship between HDL and CRP concentrations. Some anti-inflammatory properties of HDL may suppress CRP synthesis in the liver11. In T2DM patients will experience diabetic dyslipidemia, generally characterized by elevated plasma triglyceride (TG), decreased HDL cholesterol concentration, increased small dense LDL concentrations, and Apolipoprotein B. (Dobiasova, et al., 2001). This reduced HDL cholesterol condition will increase CRP synthesis. This is supported by the research on Air Force / Texas Coronary Prevention Study (AFCAPS / TexCAPS) which lasted for 5.2 years found the speed of CHD on HDL ≥ 40 mg / dl: 2.1%, HDL 35-39 mg / dl: 2 , 9%, HDL ≤34 mg / dl: 3.4% 12. This shows That in T2DM there will be more severe diabetic dyslipidemia and this condition is directly proportional to the more severe inflammation. In the inflammatory state induced release of cytokines, thus causing changes in metabolism and HDL cholesterol composition (decrease Apo A1, LCAT and PLTP). Changes in the expression of some enzymes are important because they are involved in reverse cholestrol transfers that will cause impaired cholesterol from the cells and uptake cholesterol to the liver. AIP scores do not correlate with ADMA in T2DM subjects (R = - 0.007, p = 0.951). This is consistent with a 2006 cohort study conducted by the American Association for Clinical Chemistry (AACC) in 2006 on a number of individuals with various atherosclerotic risk variations, including type 2 DM, hypertension, and dyslipidemia, with TG levels of 145 to 194 mg / N = 1018, p = 0.872) and HDL cholesterol of 41-49 mg/dl (n = 644, p = 0.2) AIP is the log ratio (TG / HDL-C) directly related to the risk of atherosclerosis. In T2DM subjects will experience diabetic dyslipidemia, generally characterized by elevated plasma triglycerides (TG), decreased HDL cholesterol concentration, increased small dense LDL concentrations, and Apolipoprotein B3. While ADMA is a natural amino acid that circulates in the blood13. ADMA is an endogenous inhibitor of NO synthase (NOS), consequently ADMA inhibits NO formation so that endothelial cell function in regulating blood pressure rhythm is impaired (Vallance, 2004).

Conclusion

It was found that AIP and hs-CRP increased in patients with type 2 DM (p <0.001) and there was a significant relationship between AIP and hs-CRP (r = 0.486, p <0.001). In addition, increased AIP and hs-CRP may increase the risk of atherosclerosis in patients with type 2 diabetes mellitus.

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