The Relationship between ADMA and Anthropometric Indicators, Glucose, Lipid, and Inflammatory Parameters in Obese People

M. Aron Pase[1], Dharma Lindarto[1]*, Brama Ihsan Sazli[1]
[1]*Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik Hospital, Jalan Bunga Lau No 17, Medan 20136, Indonesia*

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Abstract: Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide production and involved in various pathological processes, especially processes involving cardiovascular risk. The purpose of this study was to analyze the correlation between ADMA and anthropometric, glucose, lipid, and inflammatory parameters. The study was a cross-sectional study of 45 obese subjects at H. Adam Malik Hospital. Blood tests were carried out after 8-10 hours of aging against cardiovascular risk parameters: anthropometry (body weight, BMI, and WC), glucose (FPS, PPS, HbA1C, Fasting Insulin, and HOMA-IR), lipid (LDL-C, HDL-C, TG, and sd-LDL), and inflammation (ApoB and hs-CRP) parameters. Results: Of the 45 subjects, the average age was 41.69 ± 5.69 years old, and the average BMI was 33.09 ± 5.05 (Obesity I). ADMA was also found to be correlated significantly with FPG, HBA1c, and TG parameters [r=-0.506, p=0.001; r=-0.334, p=0.013, dan r = -0.315. p=0.017, respectively]. In obesity, ADMA correlated significantly with cardiovascular risk parameters: FPG, HbA1C, and TG.

1 INTRODUCTION

Asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NO) which appears as a risk marker for various disease conditions including end-stage kidney failure (Zoccali *et al.,* 2001), liver failure (Tsikas *et al.*, 2003), heart failure (Kielsten *et al.,* 2003), diabetes (Lin *et al.,* 2002), pre-eclampsia (Sayyidou *et al.,*2003), and atherosclerotic (Boger *et al.,* 1997). It has been observed that ADMA is positively correlated with NO serum concentration and body mass index (BMI) (Borgeraas *et al.,* 2016).

Inflammation measured by C-reactive protein (CRP) is another strong risk marker for predicting cardiovascular death and complications including inflammatory diseases (Goodson *et al.*, 2005), sepsis (Lobo *et al.,* 2005), lung disease (Man *et al.,* 2006), and coronary heart disease (Blake & Ridker, 2002). The interaction between ADMA and CRP is a problem of cardiovascular disease because both ADMA and CRP factors are involved in endothelial dysfunction in humans (Baylis, 2006).

Obesity increases the risk of morbidity due to hypertension, dyslipidemia, T2DM, coronary heart disease (CHD), stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory disorders, and certain types of cancer. Obesity is also associated with an increased risk of all causes of death due to cardiovascular disease (CVD) (National Institute of Health, 1998). Obesity is caused by abnormal or excessive fat accumulation due to metabolic disorders (Colak *et al.,* 2010). According to previous research, the main determinant of obesity is insulin resistance which is associated with endothelial dysfunction (El Assar *et al.,* 2016). Obesity can trigger the activity of tumor necrosis factor in α proinflammatory cytokine, which then inhibits the insulin receptor substrate 1 in the insulin signaling pathway (Peraldi *et al.,* 1996).

Based on several studies, ADMA has a positive correlation with cardiovascular risk factors in prediabetes (Eliana *et al.,* 2011), angina pectoris (Borgeraas *et al.,* 2016), IGT, and obesity (Huang *et al.,* 2018). Therefore, the aim of this study was to investigate the correlation between ADMA and anthropometric, glucose, lipid, and inflammatory parameters in obesity.

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2 MATERIALS AND METHODS

The study design was a cross-sectional study by recruiting 45 nurses (female and male) at H. Adam Malik Hospital aged 30-55 years who met the criteria for obesity (WHO, 2000) and signed an informed consent form. Subjects were excluded from the study if they had secondary illness or obesity that could affect markers of metabolic disorders, lipid profiles, and inflammations such as pregnancy or lactation, acute infection, anemia, menopause, diabetes or hypertension, cardiovascular disease, chronic kidney disease or liver dysfunction, smoking, consuming corticosteroids, estrogen, beta-adrenergic receptor agonists, nitrates, or other vasodilator agents (Kelm *et al.,* 2002). Venous blood samples were collected from the subjects in the morning after 8-10 hours of fasting combined with ethylenediaminetetraacetate (EDTA) containing heparin, then centrifuged.

Prior to the commencement of the study, the study protocol was reviewed and approved by the Institutional Research Ethics Board.

2.1 Biochemical Analysis

Serum glucose levels, HDL cholesterol (HDL-C), and triglycerides (TG) were measured by the enzymatic colorimetric method while Apo-B and hs-CRP levels were measured by the immunoassay method with Hitachi Modular analyzer using the Roche Diagnostic kit. Insulin levels were measured by the chemiluminescence immunoassay method using the DPC Immulite-I analyzer (Diagnostic Products Corp, Los Angeles, CA, USA) kit.

The HbA1c values were measured using the High-Performance Liquid Chromatography (HPLC) method which was in accordance with the American Diabetes Association standard (American Diabetes Association, 2010). ADMA levels were examined using ELISA method with a normal range of 0.4-0.75 µmol/L (80-150 ng/mL) (Miyazaki *et al.,* 1999). The HOMA-IR formula = [(fasting glucose serum (mmol / l) x fasting insulin (µU / ml) / 22,5] was used to determine the index of insulin resistance (Matthews *et al.,* 1985).

2.2 Statistical Analysis

The mean and standard deviation were summarized as descriptive statistics. The Shapiro-Wilk test was used to determine whether a variable was normally distributed. The parametric test was performed on variables with normal distribution, whereas the nonparametric test was performed on variables with the abnormal distribution. Furthermore, the Pearson and Spearman test were used to evaluate the correlation between variables according to the variable distribution. $P < 0.05$ was accepted as an indication of statistical significance. SPSS for Windows 22.0 was used for the statistical analysis.

3 RESULTS

From the 45 obese subjects who met the inclusion criteria, the average age was 41.69 ± 5.69 years, and the average BMI was 33.09 ± 5.05 (Obesity I).

Table 1. shows the characteristics of the research subjects in terms of anthropometric, glucose, lipid, inflammatory parameters in obesity, while Table 2. shows the correlation analysis between ADMA and the subject parameters. There was a significant correlation between the levels of ADMA and fasting blood glucose (FBG), HbA1c, and TG.

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Table 1: Baseline Characteristic of Obese Subjects.

Parameters		Total (mean±SD); n=45
Age	(years)	41.69±5.69
Body weight	(Kg)	78.79±13.26
BMI	(kg/m^2)	33.09±5.05
WC	(cm)	96.34±9.33
ADMA	(umol/l)	0.82±0.13
FPG	(mg/dl)	86.00±10.94
PPG	(mg/dl)	109.84±28.56
HbA1C	(%)	5.56±0.56
Fasting Insulin	(µIU/mL)	9.52±7.32
HOMA-IR		1.24±0.91
LDL-C	(mg/dl)	137.51±33.51
HDL-C	(mg/dl)	47.06±12.84
TG	(mg/dl)	151.22±57.31
sd-LDL	(mg/dl)	1.34±0.26
ApoB	(g/L)	104.31±18.41
hs-CRP	(mg/L)	3.64±2.38

Abbreviations: BMI, body mass index; WC, waist circumference; ADMA, asymmetric dimethylarginine; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance;; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; ApoB: apolipoprotein B; sd-LDL: small dense-LDL; CRP, C-reactive protein;
* $p<0.05$.

Table 2: Relationship Between ADMA and Anthropometry, Glucose, Lipid, and Inflammation Parameters.

Parameters		r	P
Age	(year)	-0.057	0.356
Body weight	(Kg)	-0.056	0.407
BMI	(kg/m^2)	-0.117	0.445
WC	(cm)	-0.100	0.256
FPS	(mg/dl)	-0.506	0.001*
PPS	(mg/dl)	-0.230	0.064
HbA1C	(%)	-0.334	0.013*
Fasting Insulin	(µIU/mL)	-0.102	0.255
HOMA-IR		-0.225	0.069
LDL-C	(mg/dl)	-0.149	0.165
HDL-C	(mg/dl)	0.154	0.157
TG	(mg/dl)	-0.315	0.017*
sd-LDL	(mg/dl)	-0.042	0.392
ApoB	(g/L)	-0.168	0.135
hs-CRP	(mg/L)	-0.059	0.351

Abbreviations: BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; ApoB: apolipoprotein B; sd-LDL: small dense-LDL; CRP, C-reactive protein;
* $p<0.05$.

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4 DISCUSSION

ADMA is believed to be a mediator that affects the risk of atherosclerosis. Several clinical studies have shown that increased ADMA is present in the conditions of chronic kidney insufficiency, dyslipidemia, hypertension, diabetes mellitus, and hyperhomocysteinemia, and other conditions (Landim, Casella & Chagas, 2009). The presence of cardiovascular disease risk factors, especially atherosclerotic disease will induce functional and morphological changes in endothelium, become easily inflamed, thrombosis, and vasoconstriction (Vita & Keaney, 2002). The dysfunctional endothelium can be detected by an imbalance between widening and constricting factors, procoagulant factors, and anticoagulant factors which stimulate and inhibit the development and proliferation of cells (Rubanyi, 1993).

Other clinical evidence also supported that increased plasma ADMA was associated with decreased NO synthesis (Boger *et al.,*1998). Plasma ADMA levels can change rapidly in response to changes in the risk factors. In diabetic patients, a few hours after high-fat eating, plasma ADMA level increases, and vasodilation is reduced (Fard *et al.,* 2000). In low body mass index (BMI) condition, each 0.1 μmol/L increase in the plasma ADMA level was associated with an increased risk of acute myocardial infarct (AMI) with HR (95% CI) 1.21 (1.08-1.35) and cardiovascular death 1.30 (1.13-1.49) (Hoy *et al.,* 2007). ADMA level was 0.40-0.77 μmol/L for the entire population, 0.41-0.79 μmol/L for men, 0.38-0.73 μmol/L for women under 45 years old, and 0.41-0.84 μmol/L for women above 45 years old (Hoy *et al.,* 2007). Past studies showed that plasma ADMA levels were higher in obesity (McLaughlin *et al.,* 2006). In this study, ADMA levels were 0.82 ± 0.13 μmol/L.

Based on several previous studies, plasma ADMA levels were associated with the risk of AMI and cardiovascular death (Borgeraas *et al.,*2016), unchanged with weight loss in obesity (Rudofsky *et al.,*2011), hypertension and insulin resistance (Perticone *et al.,* 2010), resistance insulin at the beginning of diabetes (Nakhjayani *et al.,* 2010), HOMA-IR in prehypertension (Novianti *et al.,* 20013), BMI in overweight (Eid *et al*, 2004), and HOMA-IR in obesity (Hidayat *et al.,* 2011). In this study, ADMA had a significant correlation with FPG, HbA1c, and TG parameters [r = -0.506, p = 0.001; r = -0.334, p = 0.013, and r = -0.315. p = 0.017, respectively] in obesity.

5 CONCLUSION

The association between ADMA and increased cardiovascular risks was related to glucose metabolism, lipid, and insulin resistance with various unknown mechanisms. Thus, further and extensive research should be done to determine the role of ADMA in the risk of cardiovascular disease.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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