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ORIGINAL RESEARCH

# Strong Association of Metabolic Parameters with ADMA and VCAM-1 in Normo-Weight Subjects with Metabolic Syndrome

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**Background:** Metabolic syndrome (MetS) is a risk factor for cardiovascular disease and is linked to obesity. Subjects with MetS who have normo-weight potentially show higher mortality and morbidity.

**Purpose:** This study aims to reveal the critical essential metabolic parameters associated with endothelial dysfunction in MetS subjects with normo-weight compared to obese.

**Patients and Methods:** The study was designed using a case–control approach. Ninety-nine MetS subjects (34 Normo-weight and 65 obese) from the urban population were enrolled in this study. The components of MetS are based on NCEP/ATP III criteria. Asymmetric dimethylarginine (ADMA) and vascular cell adhesion molecule 1 (VCAM-1) as markers for endothelial dysfunction were measured in both groups.

**Results:** Fasting blood glucose (FBG) levels were higher in the normo-weight group (143.38 ± 79.8 mg/dL) compared to the obese group (120.89 ± 46.5 mg/dL). High-density lipoprotein cholesterol (HDL-c) levels in the normo-weight group were lower (42.82 ± 10.1 mg/dL) compared to obesity (45.74 ± 9.3 mg/dL), while triacylglycerol (TAG) levels were higher in the obese (197.25 ± 110.5 mg/dL) compared to the normo-weight group (167.03 ± 98.4 mg/dL), although the differences were statistically not significant (all $p > 0.05$). The difference between ADMA and VCAM-1 levels was statistically not significant in both groups. Correlation between MetS components with endothelial dysfunction parameters shows that metabolic parameters correlate strongly. Interestingly, a stronger correlation between FBG and ADMA was observed in normo-weight ($r = 0.519$) compared to obese groups ($r = 0.445$). In addition, TAG consistently shows a significant correlation with ADMA and VCAM-1 in normo-weight groups.

**Conclusion:** Metabolic parameters, especially FBG and TAG, correlate strongly with endothelial dysfunction parameters in normo-weight subjects with metabolic syndrome.

**Keywords:** ADMA, normal-weight metabolically unhealthy, VCAM-1

## Introduction

Cardiovascular disease remains a significant global threat, with 17.9 million people dying from it in 2016, accounting for 31% of all global deaths.[1] Metabolic syndrome (MetS) is a common condition worldwide linked to an increased risk of cardiovascular events and diabetes mellitus.[2–4] Metabolic syndrome, initially linked to obesity, can also occur in normo-weight adults.[5] Interestingly, recent studies in the US revealed that the mortality rate in normal-weight MetS patients was even higher than in



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obese MetS patients.[6] These findings raise the issue of which MetS criteria influence more to cardiovascular events rather than obesity.[7–10]

Several criteria have been developed to diagnose MetS, including central obesity, elevated TAG, low HDL-c, elevated fasting blood sugar, and hypertension.[2,3] These criteria can also be found in normo-weight subjects.[9,10] Several studies have reported metabolically unhealthy subjects with cardiovascular disease,[5,6,8,10,11] associated with endothelial dysfunction, and alteration in ADMA and VCAM-1 used as surrogate biomarkers.[12–15] This study aims to reveal the metabolic parameters primarily related to endothelial dysfunction, represented by ADMA and VCAM-1 elevation in metabolically unhealthy subjects with normal weight compared to obese.

# Materials and Methods

## Study Design and Subjects

Analytical descriptive design with a case–control approach was conducted in the Cibeber subdistrict, Cimahi, West Java, Indonesia. A total of 256 participated in this study after signing informed consent. Eight subjects were excluded due to having been diagnosed and treated for cardiometabolic diseases. Of 248 subjects examined for MetS based on NCEP/ATP III criteria, 107 subjects were categorized as MetS. Eight people withdrew from the study, enrolling 99 subjects (34 are normal weight). The Research Ethics Committee of Universitas Padjadjaran approved the research protocol No. 1123/UN6.KEP/EC/2022 and confirmed that this study complies with the Declaration of Helsinki.

## Anthropometric and Blood Pressure Measurements

The body mass index (BMI) was determined by the formula weight (kg) divided by squared height ($m^2$) based on the WHO task-forced Asia Pacific criteria.[16] The weight was measured using body weight and body composition OMRON HBF-214 (Singapore), and the height was measured using a portable stadiometer ADE MZ10042 (Hamburg, Germany). The waist circumference (WC) measured at the top of the iliac crests was taken with light clothes using non-stretchable tape. Blood pressure was measured using a digital sphygmomanometer OMRON hem 8712 (Singapore).

## Laboratory Assays

Blood samples were collected after a 12-hour overnight fasting. Fasting blood glucose (FBG) is measured using spectrophotometry using the GOD-PAP method (Proline Glucose GOD FS). HDL cholesterol is measured by the PEG Trinder precipitation method (SEKISUI MEDICAL CO, LTD, Japan). Serum triglycerides were measured using the colorimetric enzymatic test Glycerol Peroxidase Phosphate Acid (GPO-PAP) (Proline triglycerides FS 10'). ADMA was measured using Agilent 6460 Triple Quad with 1290 UPLC with LC/MS-MS method. VCAM-1 was measured using Biorad Microplate Reader 680 with an Enzyme-linked immunosorbent assay (ELISA) method (Human VCAM-1/CD106 Immunoassay). ADMA levels are elevated when ≥100 ug/dl[12,17] while VCAM-1 levels increase when ≥714 ug/dl.[13]

## Statistical Analysis

Data analysis was performed by SPSS v26 (SPSS Inc., Chicago, Illinois, USA). Comparisons were performed by Student's unpaired *t*-test or Mann–Whitney test. The Pearson correlation was used to determine the relationship between metabolic syndrome components with ADMA and VCAM-1 serum. A value of $p<0.05$ was considered statistically significant.

# Results

## The Characteristic of Participants

The characteristics of participants who were metabolic syndrome patients are presented in Table 1. They were divided into normo-weight and obese groups. The mean BMI of the normo-weight group was 23.39 ± 1.3 kg/$m^2$, and the obese group was 30.54 ± 4.7 kg/$m^2$ ($p$=0.000). It was also observed that WC in the obese group was significantly higher than in the normo-weight group (96.99 ± 13.7 cm vs 84.85 ± 6.6 cm, respectively, $p$=0.000). Average fasting blood glucose levels were higher in the normal weight group (143.38 ± 79.8 mg/dL) compared to the obese group (120.89 ± 46.5 mg/dL), although statistically, there was no significant between the two groups ($p$=0.079). Average HDL-c levels in the normal weight group were lower

**Table 1** Study Group Data Based on Body Mass Index (N=99)

| | Metabolic Syndrome Patient | | *p*-value |
|---|---|---|---|
| | Normo-Weight (n=34) | Obese (n=65) | |
| | Mean ± SD | Mean ± SD | |
| Age (years) | 55.32 ± 8.6 | 51.17 ± 10.5 | 0.051 |
| BMI (kg/m$^2$) | 23.39 ± 1.3 | 30.54 ± 4.7 | 0.000* |
| Waist circumference (cm) | 84.85 ± 6.6 | 96.99 ± 13.7 | 0.000* |
| SBP (mmHg) | 147.00 ± 18.6 | 154.91 ± 23.3 | 0.090 |
| DBP (mmHg) | 89.97 ± 10.9 | 97.78 ± 14.8 | 0.098 |
| FBG (mg/dl) | 143.38 ± 79.8 | 120.89 ± 46.5 | 0.079 |
| HDL-c (mg/dl) | 42.82 ± 10.1 | 45.74 ± 9.3 | 0.158 |
| TAG (mg/dl) | 167.03 ± 98.4 | 197.25 ± 110.5 | 0.183 |
| ADMA (ug/dl) | 93.79 ± 17.1 | 92.38 ± 20.8 | 0.735 |
| VCAM-1 (ug/dl) | 771.73 ± 151.53 | 780.44 ± 285.3 | 0.869 |

**Notes**: Data is shown with mean ± SD, *significantly different if p-value <0.05.
**Abbreviations**: BMI, Body Mass Index; WP, Waist Circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FBG, Fasting Blood Glucose; HDL-c, High Density Lipoprotein-cholesterol; TAG, Triglycerides; ADMA, Asymmetric dimethylarginine; VCAM-1, Vascular cells adhesion molecules-1.

(42.82 ± 10.1 mg/dL) compared with obesity (45.74 ± 9.3 mg/dL), although statistically also not significant ($p$ = 0.158). Meanwhile, the average TAG levels were higher in the obese group (197.25 ± 110.5 mg/dL) compared to the normal weight group (167.03 ± 98.4 mg/dL), although statistically, there was also no significant correlation between the two groups ($p$=0.183). The mean serum VCAM-1 level was higher than normal (771.73 ± 151.53 ug/dL and 780.44 ± 285.3 ug/dL), while the average ADMA level is close to the upper limit of normal values in both groups (93.79 ± 17.1 ug/dL and 92.38 ± 20.8 ug/dL), although there was no significant difference.

## The Association Between ADMA and VCAM-1 Level with Age, BMI, and MetS Components

Table 2 shows the association between ADMA and VCAM-1 levels with age, BMI, and MetS components in both groups. ADMA levels positively correlate with age, FBG, and TAG (r range is 0.223–0.652) in both groups. VCAM-1 is positively correlated with FBG and TAG (range of r is 0.329–0.485) in the normo-weight group, while in the obese group, it is positively correlated with age and FBG (range of r is 0.209–0.581) and negatively correlated with HDL-c (r=−0.323). FBG more strongly correlates with ADMA in normo-weight than in obese groups, while FBG correlates with VCAM-1 more strongly in obese than with normo-weight groups. TAG consistently correlates significantly with ADMA and VCAM-1 in normo-weight groups.

# Discussion

Our study aims to elaborate the association between metabolic parameters and endothelial dysfunction in normo-weight and obese subjects with metabolic syndrome and revealed that FBG is strongly associated with ADMA and VCAM-1.

Previous studies have reported that high FBG level is strongly associated with obesity.[18–20] Our study, which is shown in Table 1, uncovered a fascinating outcome where the FBG levels were noticeably greater in the normo-weight group compared to the obese group, despite the difference not being statistically significant. Additionally, our results showed that the concentration of HDL-c was decreased in the normo-weight group when compared to the obese group, although

**Table 2** Association Between Age, BMI, and MetS Components with ADMA and VCAM-1 Level (N=99)

| Variable | ADMA Level (ug/mL) | | | | VCAM-1 Level (ug/mL) | | | |
|---|---|---|---|---|---|---|---|---|
| | Normo-Weight (n=34) | | Obese (n=65) | | Normo-Weight (n=34) | | Obese (n=65) | |
| | *r* | *p*-value | *r* | *p*-value | *r* | *p*-value | *r* | *p*-value |
| Age (years) | 0.346 | 0.002* | 0.223 | 0.020* | 0.148 | 0.086 | 0.209 | 0.027* |
| BMI (kg/m$^2$) | −0.196 | 0.882 | 0.181 | 0.510 | 0.045 | 0.990 | 0.040 | 0.370 |
| WC (cm) | −0.037 | 0.301 | 0.283 | 0.597 | 0.008 | 0.576 | 0.075 | 0.501 |
| SBP (mmHg) | 0.301 | 0.179 | 0.134 | 0.303 | 0.027 | 0.052 | 0.022 | 0.137 |
| DBP (mmHg) | −0.014 | 0.524 | 0.045 | 0.346 | 0.129 | 0.251 | −0.037 | 0.341 |
| FBG (mg/dl) | 0.519 | 0.000* | 0.445 | 0.045* | 0.329 | 0.009* | 0.581 | 0.000* |
| HDL-c (mg/dl) | 0.232 | 0.175 | −0.242 | 0.139 | 0.140 | 0.131 | −0.323 | 0.008* |
| TAG (mg/dl) | 0.652 | 0.000* | 0.522 | 0.006* | 0.485 | 0.001* | 0.399 | 0.270 |

**Notes**: Data is shown with r (coefficient correlation) and p-value (*significantly correlated if *p*-value <0.05).
**Abbreviations**: BMI, Body Mass Index; WP, Waist Circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FBG, Fasting Blood Glucose; HDL-c, High Density Lipoprotein-cholesterol; TAG, Triglycerides; ADMA, Asymmetric dimethylarginine; VCAM-1, Vascular cells adhesion molecules-1.

the difference was not statistically significant. Taken together, these data indicated that the insulin function of normo-weight was worse than those in the obese group.

This study analyzed ADMA and VCAM-1 as they can be used as markers of the early phase of cardiovascular events.[14,21,22] Average ADMA levels were still normal in both groups, while average VCAM-1 levels in both groups had increased. However, no significant difference was observed between normo-weight and obese groups. This phenomenon shows that endothelial injury has occurred in both groups, where the endothelial tone is still good, while the adhesive molecules have already been disrupted.[23]

Endothelial injury in both groups, characterized by elevated VCAM-1 levels, may have been due to high systolic and diastolic levels in both groups. A previous study reported that in subjects with hypertension, VCAM-1 levels increased following high endothelin-1 (ET-1) levels. ET-1 stimulates arterial VCAM-1 expression by producing $O_2^-$ from an ETA receptor/NADPH oxidase pathway in low-renin mineralocorticoid hypertension.[24,25] Previous research has shown that MetS is linked to accelerated aortic stiffening, which is primarily associated with changes in blood pressure. Furthermore, individuals with hypertension have significantly higher levels of aortic stiffness, as measured by pulse wave velocity (PWV), compared to those without hypertension. The arterial structural and functional properties are thought to be related to this increased stiffness.[26,27] In our study, this mechanism might undergo in our subjects, which leads to endothelial dysfunction represented by an increase in VCAM-1 in both groups, as shown in Table 2.

Table 2 shows that the correlation coefficient of endothelial dysfunction in normo-weight is stronger compared to obese, indicated by the r value of FBG and TAG in the ADMA value. This may be related to the "obesity paradox", which explains that the prognosis of obese patients is better than that of normal-weight patients and that metabolic disorders are better indicators than BMI. Obese patients have more metabolic reserves. In addition, the cytokine and neurohormone profiles of obese patients are also cardioprotective. Adipose tissue produces tumor necrosis factor-alpha receptors that can counteract the adverse effects of tumor necrosis factor-alpha. Higher levels of lipoproteins in obese patients can bind to and neutralize lipopolysaccharides that play a role in stimulating the release of inflammatory cytokines. In addition, obese people tend to check themselves early, even in mild pain and get more aggressive treatment because they are considered more risky.[28–30]

Our study reveals that not all MetS components correlate significantly with ADMA and VCAM-1 as markers of endothelial dysfunction. This might be related to the conditions under which this study was conducted in populations

where MetS may still be in its early phase. This is an advantage because this study can detect early the incidence of endothelial dysfunction in people who experience metabolic disorders.

It is known that lipid disorders play a more important role in the incidence of endothelial dysfunction. Still, in this study, it is shown that FBG is consistently associated with VCAM-1. This suggests that carbohydrate metabolic disorders play a more important role than lipids, which may also be related to the paradoxical mechanism of obesity, as a result of a progressive catabolic state and lean mass loss.[30] The results of the study also showed that hyperglycemia triggers an inflammatory response and upregulation of VCAM-1.[31,32]

The MetS components positively correlated with VCAM-1 as markers of endothelial dysfunction were FBG in both groups. Hyperglycemia is the major causal factor in the development of endothelial dysfunction in diabetes mellitus, although the mechanisms underlying this phenomenon are likely to be multifactorial.[33,34] Increasing evidence suggests that the progression of insulin resistance to type 2 diabetes parallels the progression of endothelial dysfunction to atherosclerosis. Insulin resistance is closely linked to visceral adiposity, and early data suggested that free fatty acids were responsible for this association.[33,35,36] This shows that metabolic parameters are more sensitive and play an important role in endothelial dysfunction than the functional disorders represented by SBP and DBP. This means that even if a person is of normal weight, they still have the same risk as an obese person for metabolic syndrome.[37]

Metabolic syndrome or metabolically unhealthy patients were usually diagnosed late and were found in hospitals. In order to gain early awareness in preventing cardiovascular event in the community, this study was done in population setting. Urban areas in Indonesia are known to have high MetS data, including in the Cimahi area, West Java, which is the location of this study.[38–40] The average age of MetS sufferers in this study was more than 40 years, consistent with previous studies.[11,41,42] However, some studies report that MetS can occur at a younger age because the incidence of MetS often parallels the incidence of obesity and type-2 diabetes.[38,43–45] The suggestion for future research is to elaborate molecular mechanisms in vitro regarding how hyperglycemia induced VCAM-1 increase. The results of this study can be used to formulate more precise strategies for early prevention of metabolically unhealthy state.

## Conclusion

Among MetS components, metabolic parameters, especially FBG and TAG, have stronger correlation with endothelial dysfunction parameters (ADMA and VCAM-1) in normo-weight subjects with metabolic syndrome. Moreover, significant correlation between metabolic and endothelial dysfunction parameters was consistently observed in normo-weight metabolically unhealthy subjects.

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## Disclosure

The authors report no conflicts of interest in this work.

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