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Inflammatory and endothelial dysfunction markers in females with metabolic syndrome aged 50–75 years

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ABSTRACT

Introduction: The prevalence of metabolic syndrome (MetS) in Indonesia is 39% and it is higher in females than in males (46% vs. 28%). Features of the syndrome comprise low-grade chronic inflammation and endothelial dysfunction from cardiometabolic abnormalities. High-sensitive C-reactive protein (HsCRP) is a biomarker of cardiovascular disease, whereas ferritin and pentraxin-3 (PTX-3) are markers of chronic inflammation. One of the markers of endothelial dysfunction is an intercellular cell adhesion molecule-1 (ICAM-1). Studies on MetS in women aged 50–70 years and using several markers of inflammation and endothelial dysfunction are rare. The study aimed to determine differences in HsCRP, ferritin, PTX-3, and ICAM-1 level between females with and without MetS aged 50–75 years.

Methods: For this cross-sectional study, 160 females aged 50–75 years from South Jakarta were recruited, divided into MetS and non-MetS (control) groups, 80 participants each. Participants that met the inclusion criteria were assessed for vital signs and metabolic parameters (e.g., lipid profile, fasting blood glucose level, and waist circumference [WC]). The groups were compared using an independent *t*-test for inflammatory (i.e., HsCRP, PTX-3, and ferritin) and endothelial dysfunction (ICAM-1) ($p < 0.05$) biomarkers.

Results: The mean age of the MetS and control groups was 59.6 ± 5.6 and 59.2 ± 5.5 years. MetS criteria included WC of ≥80 cm (95.2%), increased blood pressure level (90.6%); and high-density lipoprotein cholesterol of <50 mg/dL (76.2%). Significant differences were found between the MetS and control groups for ferritin ($p = 0.027$), PTX-3 ($p = 0.045$), and ICAM-1 ($p = 0.004$) but not for HsCRP ($p = 0.136$).

Conclusion: Elevated ferritin, PTX-3 level, and ICAM-1 level are significantly associated with an increased Mets risk in females aged 50–75 years; however, the same is not true for HsCRP.

Keywords: Ferritin; high-sensitive C-reactive protein; intercellular cell adhesion molecule-1; inflammation; metabolic syndrome; pentraxin-3

INTRODUCTION

Currently, metabolic syndrome (MetS) is developing into a global epidemic, with approximately 12–37% of Asians and 12–26% of Europeans suffering from Mets (1). The incidence of MetS in Indonesia is higher in females than in males. The prevalence of MetS in adults aged 45–65 years is 39%, namely 28% in males and 46% in females (2). MetS is a group of symptoms comprising abdominal obesity, hypertension, dyslipidemia, hyperglycemia, and prothrombotic and proinflammatory conditions (3).

The higher prevalence of abdominal obesity in Indonesian females, accounting for 57.5% versus 16.8% in males, explains the higher MetS prevalence in Indonesian females than in males. Individuals with MetS are at an increased risk of morbidity and mortality from cardiovascular disease. MetS is a risk factor for the occurrence of type 2 diabetes mellitus (T2DM), cardiovascular disease, and stroke (2). The pathophysiology of cardiovascular disease in MetS probably involves risk factors such as insulin resistance, chronic low-grade systemic inflammation, genetics, dietary status, and individual habits (3,4).

Abdominal fat is an active endocrine organ that generates cytokines that affect other body tissues (4). Abdominal fat releases several inflammatory markers, such as C-reactive protein (CRP), and acute-phase proteins, such as pentraxin-3 (PTX-3) (3). The level of plasma PTX-3 was inversely related to Mets in the Korean population (5). Another acute-phase protein is ferritin (6,7). Ferritin is not only a marker of iron reserves in the body but may also be a marker of inflammation (6). Abnormal cardiometabolic

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components contribute to the occurrence of endothelial dysfunction followed by blood vessel inflammation, resulting in atherosclerosis and cardiovascular disease (8). Intercellular cell adhesion molecule-1 (ICAM-1) is an endothelial dysfunction marker (8,9). Many studies have reported the relationship between MetS and inflammatory markers, but MetS occurrence varies by population, ethnicity, and sex (4,8,10). Studies on MetS conducted in females aged 50–75 years and using several inflammation (high-sensitive CRP [HsCRP], PTX-3, and ferritin) and endothelial dysfunction (ICAM-1) markers are rare (4,6,8-10). This study aimed to determine differences in the levels of inflammatory and endothelial dysfunction biomarkers between females with and without MetS aged 50–75 years.

METHODS

This cross-sectional study was conducted from January to June 2021 in the catchment area of *Puskesmas* in Mampang District, South Jakarta. The investigators enrolled 80 females aged 50–75 years with MetS and 80 non-MetS females (controls). Inclusion criteria for the MetS group were the presence of three MetS criteria, i.e., waist circumference (WC) of ≥80 cm, systolic blood pressure (SBP) level of ≥130 mmHg or diastolic blood pressure (DBP) level of ≥85 mmHg or taking antihypertensive medications; fasting blood glucose (FBG) level of ≥100 mg/dL; high-density lipoprotein (HDL) cholesterol level of <50 mg/dL; triglyceride level of ≥150 mmHg; no active infection in 2 weeks before the study, not smoking, not consuming alcohol, and providing written informed consent. Exclusion criteria for the MetS and control groups in this study comprised the administration of corticosteroids, oral anticoagulants, and hormone replacement therapy; history of malignancies; abnormal renal function. The MetS criteria employed in this study followed the revised National Cholesterol Education Programme's Adult Treatment Panel III criteria for Asians (1).

The participants were interviewed by five individuals (having at least senior high school or equivalent education) with knowledge of the aims of the study and trained in the filling of the questionnaire (including demographic characteristics, concomitant disease, smoking status, alcohol drinking status, concomitant medication usage, and anthropometrics) (Table1). The filling-in of the questionnaire was completed in 2 weeks. Following physical examination (vital signs); anthropometry; and laboratory bloodwork for lipid profile, FBG, and creatinine, participants were divided into MetS and control groups. The investigators determined the blood pressure level, body weight, height, WC, and hip circumference of participants through physical examination. Venous blood was drawn (following a 12-h fast) using a 10-mL plain vacutainer for FBG and a complete lipid profile. An aliquot of the blood sample was used to obtain serum, which was stored at –70°C for determination of PTX-3, ICAM-1, HsCRP, and ferritin levels in participants. Since differences in intraday repeatability of laboratory procedures may cause spurious differences in the results between the MetS and control groups, the concentrations of PTX-3, ICAM-1, HsCRP, and ferritin were simultaneously determined, to ensure that differences in PTX-3, ICAM-1, HsCRP, and ferritin levels were not due to laboratory errors but were true differences. The biomarkers were analysed using the following techniques: PTX-3 through enzyme-linked immunosorbent assay (ELISA) using Quantikine® ELISA Human PTX-3/TSG-14 reagents (R&D Systems, Inc., Minneapolis, USA) and Biorad model 680 microplate reader; ICAM-1 via ELISA using Quantikine® ELISA Human ICAM-1 reagent (R&D Systems, Inc., Minneapolis, USA) and Biorad model 680 microplate reader; HsCRP using immunoturbidimetry, Architect 6K26-30 reagents, and Architect c-8000 analyzer; and ferritin via chemiluminescent microparticle immunoassay using Architect 7K59 reagents and Architect i-2000 analyzer. This study was approved by the Ethics Committee, Faculty of Medicine, Universitas Trisakti (approval no. 165/KER/FK/XII/2020). Independent t-test was used to determine differences in biomarker levels between the MetS and control groups, and $p < 0.05$ were considered to indicate statistical significance.

RESULTS

The characteristics of participants with MetS and controls are summarized in Table 2. The SBP, DBP, WC, and hip circumference of participants were considerably different between the two groups (p-values of 0.001, 0.016, 0.009, and 0.006, respectively). The biochemical characteristics of participants are listed in Table 3. The MetS group showed significantly increased triglyceride and FBG and reduced HDL cholesterol levels compared with the control group. PTX-3, ferritin, and ICAM-1 level (p-values of 0.045, 0.027, and 0.004, respectively) were significantly higher in the MetS than in the control groups, whereas HsCRP levels did not indicate any significant differences. In the MetS group, the five MetS parameters presented in the order of their frequency were: WC of ≥80 cm, increased blood pressure level, HDL cholesterol level of <50 mg/dL, increased FBG level, and triglyceride level of ≥150 mg/dL.

DISCUSSION

In the present study, out of the five MetS-contributing elements, the most frequently encountered in the participants with MetS were: WC of ≥80 cm (97.5%) and increased blood pressure (91.3%), followed by HDL cholesterol concentration of <50 mg/dL (80%). The study by Sigit et al. (2) showed that the predominant MetS components in the Indonesian population were hypertension (61.3%; 56.2% in males vs. 64.6% in females) and hyperglycemia (51%; 51% in males vs. 50.9% in females), and hypertension (61.7%; 70% in males vs. 55.2% in females) and abdominal obesity (40%; 34.6% in males vs. 44.2% in females) in the Dutch population. The prevalence of abdominal obesity was approximately 57.5% in Indonesian females and 16.8% in Indonesian males (2). The aforementioned study highlighted that MetS in Indonesia was more common in females (46.2%) than in males (28%) (2). The differences between the study by Sigit et al. (2) and the current study may have occurred because participants in the current study were all females with a mean age of 59.6 ± 5.6 years in the MetS group and 59.2 ± 5.5 years in the control group, whereas Sigit et al. (2) included male and female participants, with a mean

TABLE 1. Questionnaire used during the enrollment process (English translation)

General Information	
Name:	
Address:	
Telephone/Cellphone number:	
Interviewer:	
Date of interview:	
Circle option number according to your answer to items No. 1–10 (Please include photocopy of your National Identity Card)	
1. Age (years, months):	
2. Date of birth (DD/MM/YY):	
3. Educational background	
1. None 2) Elementary School 3) Junior High School 4) Senior High School 5) Academy/Bachelor 6) Did not complete elementary school	
4. Current employment status	
1. Unemployed 2) Trader 3) Enterpreneur 4) Other	
5. Are you in menopause ?	
1. Yes 2) No	
6. If in menopause, give duration of menopause.....year (s);.....month (s)	
7. Did you have any infection in the past 2 weeks?	
1. Yes 2) No	
8. Do you have any of the following diseases or a past history of these diseases?	
a. Hypertension	1) Yes 2) No
b. Diabetes Mellitus	1) Yes 2) No
c. Kidney disease	1) Yes 2) No
d. Stroke	1) Yes 2) No
e. Cancer	1) Yes 2) No
f. Other	1) Yes 2) No
If yes, state the diagnosis	.....
9. Do you take any of the following drugs?	
a. Corticosteroids	1) Yes 2) No
b. Hormonal replacement therapy	1) Yes 2) No
c. Antihypertensive drugs	1) Yes 2) No
d. Antidiabetic drugs	1) Yes 2) No
e. Antihyperlipidemic drugs	1) Yes 2) No
f. Oral anticoagulants	1) Yes 2) No
10. Do you smoke?	1) Yes 2) No
If yes, how many cigarettes per day	.....
11. Do you consume alcoholic drinks?	1) Yes 2) No
If yes, how many glasses per day	.....

age of 52.2 ± 5.8 years in the Indonesian population (2). The prevalence of MetS increases with age, as reported in a Turkish study: 11.9% (age 20–29 years), 23.4% (age 30–39 years), 26.9% (age 40–49 years), 40.4% (age 50–59 years), 45.3% (age 60–69 years), and 26.3% (age >70 years) (11). Mehndiratta et al. (12) conducted a study on 200 women aged 45–60 years receiving ambulatory treatment in an obstetrics and gynecology department at Amritsar, Punjab, India. The study results indicated that 29% of women were found to have newly onset MetS, with an incidence of 16% in the premenopausal group and 42% in the postmenopausal group (12). MetS incidence is higher in postmenopausal women than in premenopausal women, because following menopause, the estrogen-to-testosterone ratio decreases, dilutes the vasorelaxant effects of estrogen on the vessel wall and promotes the production of vasoconstrictor factors such as endothelin which lead to metabolic culminating into MetS (12).

TABLE 2. Characteristics of study participants

Parameter	X±SD/*n* (%) MetS *n*=80	X±SD/*n* (%) Control *n*=80	*p*-value
Age (years)	59.6±5.6	59.2±5.5	0.256
Weight (kg)	60.4±10.2	55.3±8.9	0.173
Height (cm)	152.5±5.7	152.3±5.3	0.532
BMI (kg/m^2)	25.9±4.6	21.5±3.5	0.076
Pulse rate	84.9±14.2	80.6±11.9	0.060
Blood pressure level			
Systolic (mmHg)	150.5±23.0	127.6±23.7	0.000*
Diastolic (mmHg)	88.4±12.1	79.5±10.7	0.016*
Waist circumference (cm)	91.7±7.2	77.8±8.0	0.009*
Hip circumference (cm)	99.2±7.8	90.4±6.5	0.006*
Education			
None	3 (3.8)	2 (2.5)	
Elementary school	30 (37.5)	27 (33.7)	
Junior high school	21 (26.3)	20 (25)	0.785
Senior high school	19 (23.7)	26 (32.5)	
Academy/Bachelor	5 (6.2)	3 (3.8)	
Did not complete elementary school	2 (2.5)	2 (2.5)	
Employment			
Unemployed	58 (72.4)	57 (71.3)	
Trader	5 (6.3)	6 (7.5)	0.482
Entrepreneur	5 (6.3)	3 (3.7)	
Other	12 (15)	14 (17.5)	
Menopause			
Yes	72 (90)	73 (91.3)	0.348
No	8 (10)	7 (8.7)	
Duration of menopause (years)	10.11±2.3	10.7±2.1	0.753
History of diabetes mellitus	16 (20)	0 (0)	
History of hypertension	47 (58.8)	0 (0)	
Medications			
Antihypertensive	32 (40)	0 (0)	
Antidiabetic	9 (11.3)	0 (0)	
Antihyperlipidemic	12 (15)	0 (0)	

*p<0.05=significant difference (independent t-test); Chi-square test. BMI: Body mass index

TABLE 3. Biochemical and inflammatory markers

Parameter	X±SD MetS *n*=80	X±SD Non-MetS *n*=80	*p*-value
Biochemical			
Total cholesterol (mg/dL)	215.8±15.9	208.4±13.7	0.286
Triglycerides (mg/dL)	145.8±10.5	94.3±12.8	0.000*
HDL cholesterol (mg/dL)	48.8±9.8	58.9±10.5	0.000*
LDL cholesterol (mg/dL)	139.9±18.7	132.2±10.7	0.198
Fasting blood glucose (mg/dL)	124.7±13.5	88.6±9.3	0.000*
Creatinine (mg/dL)	0.77±0.2	0.79±0.3	0.686
eLFG (mL/min)	85.5±17.4	85.7±17.9	0.931
Inflammatory			
Pentraxin-3 (ng/dL)	0.81±0.20	0.72±0.19	0.045*
HsCRP (mg/L)	3.1±0.6	2.6±0.3	0.136
Ferritin (µg/L)	165.9±14.7	125.7±8.7	0.027*
ICAM-1 (ng/mL	356.6±9.9	316.8±9.5	0.004*

*p<0.05 significant difference (independent t-test). HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HsCRP: High-sensitive C-reactive protein, ICAM-1: Intercellular cell adhesion molecule-1

This study demonstrated no significant differences were found in educational level (Table 2; p = 0.785) and

employment status (Table 2; $p = 0.482$) between the MetS and control group. Most of the subjects in the two groups had an educational level of senior high school and below (MetS 91.3% vs. non-MetS 93.7%) and were not anymore employed (MetS 72.4% vs. non-MetS 71.3%). In this study, no distinction was made between senior high school and tertiary education. Research in China on 3175 respondents aged ≥45 years showed that MetS prevalence was quite high in the rural population with low income and low education (13). Stephens et al. reported that a higher education level correlates to significantly better metabolic health when compared to a lower education level and carries significantly less risk for WC, SBP, glucose and glycosylated hemoglobin, triglycerides, HDL cholesterol, and MetS (all $p < 0.05$), except for DBP, basal insulin, uric acid, low-density lipoprotein cholesterol, and total cholesterol (14).

Low-grade chronic inflammation is identified as the leading factor for the occurrence of MetS and subsequent clinical symptoms (15,16). Among the four biomarkers assessed in this study, ferritin, ICAM-1, and PTX-3, but not HsCRP, showed significant differences between the MetS and control groups (Table 3). The threshold values of HsCRP (<1, 1–3, and 3–10) indicate low, moderate, and high risk of cardiovascular disease, respectively (17). The MetS group had higher mean HsCRP levels than the control group based on these criteria. The mean HsCRP level in the MetS group was 3.1 ± 0.4 mg/L, indicating a high risk, whereas that in the control group was 2.6 ± 0.3 mg/L, indicating a moderate risk, although no significant differences were observed between the two groups. Carrero et al. (17) studied myocardial infarction (MI) survivors (17.464 participants aged >18 years) undergoing HsCRP testing for >30 days after MI and revealed that most patients with MI had increased HsCRP levels. HsCRP may be used as a prognostic factor for determining the occurrence of cardiovascular disease (17). Yilmaz et al. (18) analyzed 100 females aged 20–45 years with obesity and revealed that HsCRP, tumor necrosis factor (TNF)-α, and malondialdehyde may be used as diagnostic markers of MetS in females with obesity. Furthermore, WC is correlated with HsCRP ($r = 0.315$; $p = 0.003$) (18). The current study revealed a correlation between WC and HsCRP, both in the MetS ($r = 0.353$, $p = 0.002$; data not shown) and control ($r = 0.560$, $p = 0.003$) groups. A WC of >80 cm in females indicates the occurrence of visceral fat accumulation. Visceral fat is an endocrine organ that can secrete pro-inflammatory substances, such as leptin, adiponectin, resistin, TNF-α, and interleukin-6, which play a significant role in the occurrence of MetS (18). The study of Hong et al. in China revealed that after a follow-up period of 5 years, HsCRP was linked to MetS, but only in females. The reason why females are at higher risk for MetS than males remains unclear, but physiologically, females may have more visceral fat than males, which is associated with MetS risk (16). Four estrogens have been identified in humans: estrone, estradiol, estriol, and estetrol. Estradiol is the predominant estrogen in women during reproduction. Post-menopausal estrogen production in the ovaries is reduced therefore circulatory estrogen concentrations are also drastically reduced. After menopause, estradiol is replaced by estrone, synthesized in adipose tissue from adrenal dehydroepiandrosterone (19). The current study revealed that the HsCRP level did not significantly differ between the MetS and control groups, probably because the body mass index (BMI) of both groups was not significantly different ($p = 0.076$). A study in China revealed that BMI was correlated with HsCRP (10). In addition, 90% of our participants were in menopause, both in the MetS and control groups. Estrogen has pleiotropic effects and plays a crucial role in preserving endothelial functions (20). Estrogen increases the bioavailability of nitric oxide by promoting its synthesis and exerts direct and indirect antioxidant and anti-inflammatory effects. The decreased estrogen level in menopause causes endothelial dysfunction followed by vascular inflammation (20). Furthermore, several drugs used in the treatment of metabolic risk factors, such as statins, nicotinic acid, fibrates, angiotensin-converting enzyme inhibitors, and thiazolidinediones, have been reported to decrease CRP levels (21). Among the MetS group in the present study, 40% used anti-hypertensive drugs, 11.3% used anti-diabetics, and 15% used anti-hyperlipidemic drugs (Table 2). Silva et al. (22) reported that different anti-hypertensive drugs have different effects on inflammatory markers and markers of endothelial function. Although angiotensin-converting enzyme inhibitors and angiotensin receptor blockers do beneficially affect endothelial function and inflammation, first and second-generation beta-blockers have no such effect (22). A systematic review on the effect of statin therapy on inflammatory markers showed that statin therapy has lipid-lowering and anti-inflammatory effects (23). Forty-one participants with a BMI of 25–39.9 kg/m² and impaired glucose tolerance test were randomized to take simvastatin or metformin for 16 weeks. The study demonstrated a significant reduction in CRP and interleukin-6 concentration at the completion of the study (24).

PTX-3 is both an inflammatory marker and an acute-phase protein (25-27). Obesity and MetS are linked to chronic inflammation (27). This study revealed that PTX-3 levels were significantly higher in the MetS group than in the control group ($p = 0.045$) (Table 3). This is consistent with the study by Karakas et al., indicating that the MetS group has higher PTX-3 levels than the control group (26). Moreover, Karakas et al. found that the PTX-3 levels in the group with 5 MetS components (0.90 ± 0.06 ng/dL) were higher than in the groups with 4 MetS components (0.63 ± 0.12 ng/dL) and 3 MetS components (0.58 ± 0.11 ng/dL) (26). In our study, the mean PTX-3 levels in the MetS and control groups were 0.81 ± 0.20 and 0.72 ± 0.19 ng/dL, respectively. The mean PTX-3 level in the MetS group was higher than that reported by Karakas et al. (0.58 ± 0.11 ng/dL) with the same number of components of MetS criteria (26). The participants in our study were older than those in the study by Karakas et al. (approximately 49 years of age). Accordingly, our study participants might have had MetS for a longer period than those in the study of Karakas et al. Nevertheless, our study is in line with the study of Karakas et al. that PTX-3 level is correlated with MetS severity. Kizilgul et al. (3) stated that a number of study results related to PTX-3 level in MetS were contradictory. For instance, a study conducted on 1749 healthy Japanese participants (818 men and 931 women) in the age range of 37–87 years indicated that PTX-3 levels were lower in participants with MetS than in the non-MetS group and

that the PTX-3 levels were negatively correlated with triglyceride levels and BMI (28). Zanetti et al. (29) reported that plasma PTX-3 levels were higher in the MetS group with subclinical atherosclerosis than in the control group. Ogawa et al. (30) reported low PTX-3 and high CRP levels in males with obesity and/or MetS compared to the control group. Ogawa et al. (30) study indicate that the reduction in plasma PTX-3 may accelerate chronic inflammation and atherosclerosis in the obese and/or MetS population because of the tissue protective and antiprotective roles of PTX-3 (30). Kizilgul et al. (3) compared PTX-3 levels in patients with MetS, in patients with rheumatoid arthritis, and with healthy controls. Their results do not demonstrate an increase in the levels of PTX-3 as chronic inflammatory markers in patients with MetS (3). The symptoms of MetS are specific for each age group and population and therefore each group or population should evolve its own strategy for Mets prevention (2,25).

PTX-3, a marker of cardiovascular risk, is produced by various cells, such as adipocytes, macrophages, dendritic cells, fibroblasts, and vascular endothelial cells, and is released in response to inflammatory stimuli (26,27). The current study revealed that PTX-3 was negatively correlated with HDL cholesterol ($r = -0.253$ and $p = 0.028$) in the MetS group, whereas no significant correlation was noted in the control group (data not shown). This indicates that HDL cholesterol plays a role in inhibiting PTX-3. This is consistent with the study of Kardas et al., which showed that children with HDL cholesterol levels of <40 mg/dL have higher PTX-3 levels than those with normal HDL cholesterol levels ($p < 0.05$) (27). A study on overweight children and children with obesity indicated that the mean PTX-3 level was significantly higher in the overweight (10.23 ± 4.42 ng/mL) and obese (11.20 ± 4.12 ng/mL) groups compared to that in the control group (7.93 ± 4.35 ng/mL). In addition, PTX-3 level was linked to intima and epicardial fat thickness in overweight children. PTX-3 may be an early marker of cardiovascular risk in overweight children (31).

Ferritin is an essential protein regulating iron homeostasis in the body. Serum ferritin is used as a biomarker to determine the status of iron reserves in the body. Excessive iron accumulation may lead to different pathological conditions, such as hemochromatosis and hemosiderosis (7). In addition, serum ferritin is an acute-phase protein associated with insulin resistance. Iron accumulation interferes with pancreatic insulin synthesis and secretion and affects hepatic insulin-extracting capacity, resulting in peripheral hyperinsulinemia and impaired insulin secretion (32). Our study results revealed significant differences in serum ferritin levels between the MetS and control groups ($p = 0.027$) (Table 3). The mean ferritin level in the MetS group was significantly higher than that in the control group. Chand et al. revealed comparable results; the serum ferritin levels were higher in the MetS group than in the control group ($p < 0.0001$) (33). Our study findings are consistent with those of Shim et al. who revealed that serum ferritin was correlated with insulin resistance and abdominal obesity, both in males and females (7). Additionally, increased serum iron levels linked to an increased risk of MetS were reported in the Vietnamese population (33). Overweight individuals with high serum ferritin levels are at an increased risk of diabetes than normal individuals (10). Tofano et al. revealed that MetS components such as hyperglycemia, hypertriglyceridemia, increased blood pressure level, and increased WC were positively correlated with hyperferritinemia, whereas HDL cholesterol was negatively correlated with hyperferritinemia (6). An increased level of serum ferritin was linked to an increased risk of MetS in Chinese males but not in females (34). A Korean study revealed the same result both in males and females. The pathophysiology underlying the association between ferritin and MetS remains unknown. A possible acceptable explanation is that the increased body iron level is linked to insulin resistance, which plays an important role in the occurrence of MetS (7). Iron is a transition metal that can become highly reactive by catalyzing the formation of free radicals associated with oxidative damage to the body. Increased oxidative stress is linked to intracellular signaling and gene expression abnormalities and can result in pathological conditions, such as insulin resistance (7).

Our study results revealed significant differences in ICAM-1 level between the two groups, with a higher mean ICAM-1 level in the MetS group than in the control group ($p = 0.004$). This indicates that ICAM-1 in the MetS group is expressed to a greater extent than that in the control group. ICAM-1 is influenced by genetic polymorphisms, as indicated in the studies by Kent et al. and Zhang et al. (35,36). ICAM-1 is an adhesion molecule that plays an important role in the initiation of inflammatory processes in the vascular endothelium. ICAM-1 is usually expressed at lower levels on the surface of arterial endothelial cells. ICAM-1 expression increases when the endothelium is stimulated due to physical or chemical injury. The interaction between adhesion molecules and leukocytes influences the onset of leukocyte migration into the arterial intima. ICAM-1 plays a role in immune cell recruitment during atherosclerotic plaque formation (35). Kent et al. revealed the correlation between ICAM-1 and MetS components such as obesity, insulin resistance, and HDL cholesterol (35). Lee et al. reported that the increase in MetS score resulted in a 1.26-fold increase in the levels of endothelial dysfunction markers (such as ICAM-1, but not vascular cell adhesion molecule-1) (8).

Our study was limited by the lack of data on the duration of MetS in the participants; moreover, the recruited participants were limited to one district, such that the results cannot be generalized to the Indonesian population. Further prospective multicenter studies are needed to validate our results.

CONCLUSION

Ferritin, PTX-3, and ICAM-1 level were significantly different between the MetS and control groups. Elevated ferritin, PTX-3, and ICAM-1 level are greatly linked to increased MetS risk in females aged 50–75 years, but the same is not true for HsCRP.

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AUTHORS' CONTRIBUTIONS

Conceptualization: Pr. Data curation: Pr, RW, LTM, Me. Formal analysis: Pr, RW. Methodology: Pr, Me. Writing–original draft: Pr. Writing–review, and editing: RW, LTM, Me, RY.

STATEMENT OF INTERESTS

The authors declare that there is no conflict of interest.

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