ORIGINAL ARTICLE

Higher Circulating White Blood Cell and Lymphocyte Counts in Obese Metabolic Syndrome Patients: A Preliminary Population-based Study in Yogyakarta, Indonesia

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ABSTRACT

Introduction: Tissue and systemic chronic low-grade inflammation are associated with obesity and Metabolic Syndrome (MetS). Previous studies found that elevated levels of circulating white blood cells (WBC) are associated with the inflammation that occurs in obesity and MetS. Research shows we can prevent chronic disease progression by controlling obesity and reducing inflammation. However, the results were inconsistent between populations. This study aimed to investigate the association of WBC, lymphocytes, and the neutrophil to lymphocyte ratio (NLR) with MetS modified by the presence of obesity. **Methods:** This research was a cross-sectional study of 202 subjects that included 86 subjects who suffered from MetS. Diagnoses of MetS were based on the NCEP-ATP III modification for Asian populations. **Results:** This study found increased levels of circulating WBCs and higher NLRs in the MetS group compared to the nonMetS group, but it was not statistically significant. Among patients grouped as MetS and nonMetS based on the presence of obesity, there were statistically significant increased WBC and lymphocyte counts in the MetS-obese group compared to the MetS-non-obese group (p=0.013; p=0.049), and in the MetS-obese group compared to the Non-MetS-non-obese group (p=0.028; p=0.040), respectively. Additionally, circulating lymphocytes and WBC counts showed positive correlations with excess adiposity and increased cardiometabolic risk. **Conclusions:** Our results indicated circulating WBC and lymphocytes were associated with MetS in the presence of obesity. These findings may contribute to the strengthening of the clinical evidence that demonstrates controlling obesity can reduce inflammation and prevent chronic disease progression in patients with MetS.

Keywords: Metabolic Syndrome (MetS), Obesity, White blood cell (WBC), Lymphocyte, Chronic inflammation

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INTRODUCTION

Mortality and morbidity rates of cardiovascular diseases are positively correlated with the prevalence of Metabolic Syndrome (MetS) and its diagnostic components (1,2). The prevalence of MetS has increased worldwide, including in Indonesia (3,4). Signs of excess adiposity are observed in patients with obesity and central obesity. Although not all MetS patients are obese, a high percentage of visceral fat is often found in patients with MetS. Excess adipose tissue increases the levels of fatty acids, and products of adipocyte cell death act as antigens, which activate the body's immune response. This process induces the secretion of inflammatory cytokines, which increases the recruitment and activation of lymphocytes, monocytes, and macrophages. Inflammation occurs in both adipose tissues and the systemic circulation. Inflammation alters metabolic processes and is associated with abnormal lipid profiles and glucose levels in patients with MetS. Research shows that regulating adiposity can reduce inflammation and may reverse or prevent chronic disease progression (2,5).

Studies in animals and humans found that changes in white blood cell (WBC) counts and associated subtypes in adipose tissue and the circulation are potentially related to obesity-induced abnormalities

in the metabolism (6–9). Previous research found that circulating WBCs, lymphocytes, neutrophils, and the neutrophil to lymphocyte ratio (NLR) were independent biomarkers for the risk of obesity, insulin resistance, MetS, and cardiovascular diseases. However, the results were inconsistent between studies (10–12). To the best of our knowledge, a similar study has not been conducted in Yogyakarta, Indonesia, although obtaining measurements of circulating WBCs and its subtypes is inexpensive and available in almost all medical facilities. The biomarker assay used in this study is comparable to using C-reactive protein (CRP) as an inflammation marker related to excess adiposity and an abnormal metabolite profile. It is promising as a prognostic factor for inflammation related to excess adiposity induced metabolic abnormalities, and can potentially be used as a predictor of cardiometabolic risk and MetS (11,12). This study aimed to investigate the association of WBCs, lymphocytes, neutrophils, and the NLR with MetS and to determine any association of these biomarkers modified by the presence of obesity in MetS. This study also investigated the correlations of metabolic and anthropometric parameters related to MetS with circulating WBC, lymphocytes, neutrophils, and the NLR.

MATERIALS AND METHODS

Study design and subject recruitment

In this cross-sectional study, population screening was performed to identify patients with MetS in the province of Yogyakarta from October 2018 until March 2019. Subjects with at least three criteria for MetS were diagnosed based on the National cholesterol education program adult treatment panel (NCEP-ATP III) guidelines for the Asian population group and selected as case subjects, or patients participated as controls. Metabolic syndrome (MetS) was defined as subjects who fulfilled at least three of the following criteria: central obesity, hypertension, hyperglycemia, hypertriglycerides and low plasma high density lipoproteins (HDL) (cut off values for each criterion are described below in anthropometric, blood pressure and metabolic parameter measurements). All subjects were of Javanese ethnicity and included both males and females who were 20–70 years old. All subjects were placed in one of the following four groups: non-obese group (I), obese group (II), non-obese with MetS (III) and obese with MetS group (IV). All subjects signed informed consent forms after receiving detailed information about the purpose of this study. Subjects who were pregnant, showed symptoms of infection, had a history of cancer, or were taking antihypertension medications, lipid-lowering agents, and antidiabetics regularly for at least three months, taking antibiotics, and/or taking immunosuppression agents were excluded from this study. The protocol was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, with the reference approval number KE/FK/0761/EC/2018.

Anthropometric, blood pressure, metabolic parameter and blood count measurements

Waist circumference was measured using a calibrated tape with an anatomical marker at midcircumference between the lowest rib and anterior superior iliac spine. Central obesity was defined as a waist circumference ≥ 90 cm for men and ≥ 80 cm for women. Subjects with a Body Mass Index (BMI) higher than 30 $kg{\cdot}m^{-2}$ were classified as obese. Visceral fat was measured using a bioelectrical impedance meter (BIA, OmronR). Systolic and diastolic blood pressures were measured twice in a seated position after 5 min of rest using a calibrated sphygmomanometer. Circulating blood samples (up to 5 mL) were obtained from antecubital venous punctures following an 8 h fasting period. Subjects with systolic blood pressures ≥ 130 mmHg and/or diastolic blood pressures ≥ 85 mmHg were classified as patients with hypertension.

Plasma glucose, HDL, triglycerides, and total cholesterol were measured by colorimetric enzymatic methods adapted to an auto-analyzer (Cobas c111) following the protocols of Glucose, HDL cholesterol, Triglycerides, and Cholesterol from Roche DiagnosticsR. Hyperglycemia was defined as a fasting plasma glucose ≥ 100 $mg{\cdot}dL^{-1}$, hypertriglyceridemia was defined by fasting plasma triglyceride levels ≥ 150 $mg{\cdot}dL^{-1}$. The low-HDL group was defined as plasma HDL levels < 40 $mg{\cdot}dL^{-1}$ for men and plasma HDL levels < 50 $mg{\cdot}dL^{-1}$ for women, otherwise patients were considered to have High-HDL levels. The homeostatic model for insulin resistance (HOMA-IR) was calculated based on plasma fasting insulin ($IU{\cdot}mL^{-1}$) x plasma fasting glucose ($mmol{\cdot}L^{-1}$) divided by 22.5. The HOMA-IR was used as a biomarker for insulin resistance. Cut off values of HOMA-IR were 2.06 for males and 1.96 for females, based on our preliminary study in nondiabetic patients in our population. The atherogenic index of plasma (AIP) was log 10 of plasma triglycerides ($mmol{\cdot}L^{-1}$) divided by plasma HDL ($mmol{\cdot}L^{-1}$). The AIP was used as a biomarker for increased risk of atherosclerosis. The assessment of atherogenic risk was based on Dabiosa et al. 2003 criteria. Low risk of atherogenic has AIP < 0.11, intermediated risk of atherogenic has AIP 0.11-0.12 and increased risk of atherogenic was AIP > 0.21.

Blood peripheral samples as much as 5 mL were obtained from the antecubital vein for blood count measurement. The methods for blood count analysis were based on electric impedance used automated hematology analyzer (Sysmex KX-21NR). White blood cells, lymphocytes and neutrophils were recorded as number of cell/mm^3. The NLR was counted as the ratio of the number of neutrophils to lymphocytes in cells/mm^3.

Statistical analysis

To analyze data normality for continuous distributions, the Kolmogorov–Smirnov test was used, and not normally distributed data were transformed with log 10. Data that were not normally distributed after being transformed were presented as the median (min-max), and the Mann– Whitney test was used. Normally distributed data were presented as the mean ± standard deviation (SD). To compare the means of two groups, a Student's t-test was performed, whereas a one-way ANOVA was used to compare the means of more than two groups. A *p*-value < 0.05 indicated statistical significance.

RESULTS

This population study used a cross-sectional design and included 202 subjects who lived in Yogyakarta. Diagnoses of MetS were based on the NCEP-ATP III criteria, with a modification of central obesity criteria for Asian populations as described above in the Material and Methods section.

Although not significant, baseline subject characteristics showed that the MetS group was older, contained a higher proportion of females and had slightly different plasma fasting glucose levels. Significantly increased BMIs, waist circumference, visceral fat, plasma triglycerides, blood pressures, HOMA-IRs, and AIPs were found in the MetS group. Furthermore, significantly lower HDL levels were found in the MetS group (Table I).

We also compared WBCs, neutrophils, lymphocytes, and NLRs in the MetS and nonMetS groups. Circulating WBCs, lymphocytes, and neutrophils were higher in the MetS group, but these results were not statistically significant. NLRs were lower in the MetS group, but this result was also not statistically significant (Table I). The stratification of the MetS group based on the presence of obesity was conducted to investigate if there was any association between circulating WBCs with MetS (Table II).

Table I: Baseline subject characteristics

Characteristics	MetS (n=86)	Control (n=116)	*p* value
Age (years old)	45.27±11.72	43.95±12.24	0.442*
Gender (number of female)	48	6	0.878
BMI (kg/m^2)	29.73±4.69	24.48±4.00	<0.001*
Waist circumference (cm)	96.37±10.53	83.25±9.51	<0.001*
Visceral fat (percentage)	14.53±6.06	8.35±3.92	<0.001**
Triglyceride (mg/dL)	187.43±93.79	110.35±60.25	<0.001*
HDL (mg/dL)	36.84±6.76	41.91±9.85	<0.001*
Plasma Fasting Glucose (mg/dL)	71.30 (44.05-227.60)	71.80(41.90-224.90)	0.05**
Systolic blood pressure (mmHg)	130.0 (100.00-190.00)	110.0 (90.00-175.00)	<0.001**
Diastolic blood pressure (mmHg)	85.0 (60.00-145.00)	75.0 (60.00-110.00)	<0.001**
HOMA-IR	2.28±1.59	1.35±1.01	<0.001*
AIP	0.309 (-0.54-0.82)	0.008 (-0.51-1.10)	<0.001**
WBC (x10^3/mm^3)	7.35 (3.60-10.60)	7.10 (3.90-11.60)	0.253**
Neutrophil (x10^3/mm^3)	4.75 (1.50-7.60)	4.50 (1.10-8.60)	0.430**
Lymphocytes (x10^3/mm^3)	2.42±0.67	2.26±0.64	0.101*
NLR	2.05±0.94	2.14±0.80	0.399*

*Student t-test; **nonparametric test; *p*-value <0.05 considered significant; BMI was body mass index, HDL was high density lipoprotein, HOMA-IR was homeostatic model assessment for insulin resistance, AIP was atherogenic index of the plasma, WBC was white blood cell, NLR was neutrophil lymphocytes ratio, MetS was metabolic syndrome.

Circulating WBCs and lymphocytes were higher in the obese group with or without MetS compared to the non-obese group with or without MetS, but only the results from the comparisons to the MetS group were statistically significant. We simultaneously compared the means of the four groups and found significantly higher WBCs and lymphocytes in obese patients with MetS compared to the non-obese group. Although not statistically significant, the number of neutrophils was also higher in the obese group with or without MetS compared to the non-obese group with or without MetS. The NLRs were

Table II: Circulating WBC count profile based on metabolic syndrome and obesity

Characteristics	NonMetS			MetS			*p*-value[c]
	Group I Not obese (n = 98)	Group II Obese (n = 18)	*p*-value[a]	Group III Not obese (n = 48)	Group IV Obese (n = 38)	*p*-value[b]	
WBCs (x10^3/mm^3)	**7.00 (3.9 – 11.6)**	7.20 (3.90 – 10.20)	0.346*	**6.70 (3.60 – 10.40)**	**7.88 (4.40 – 10.60)** #	**0.013****	**0.028****
Neutrophils (x10^3/mm^3)	4.48 ± 1.31	4.83 ± 1.44	0.312*	4.42 ± 1.25	4.86 ± 1.16	0.093*	0.277*
Lymphocytes (x10^3/mm^3)	**2.23 ± 0.66**	2.42 ± 0.45	0.137*	**2.29 ± 0.62**	**2.58 ± 0.71**##	**0.049***	**0.040***
NLR	2.08 (0.80 – 5.92)	2.06 (0.39 – 3.44)	0.976	1.91 (0.71 – 8.29)	1.85 (0.86 – 5.31)	0.667**	0.574**

*parametric test; **nonparametric test; MetS, Metabolic syndrome; *p*-value < 0.05 consider as statistically significant. *p*-value[a] was comparing means of group I and group II; *p*-value[b] was comparing means of group II and group IV; *p*-value[c] was comparing means of group I, group II, group III and group IV. # statistically significant compared to group I, nonparametric test; ##statistically significant compared to group I, Bonferroni posthoc test.

lower in the MetS group with or without obesity, but this result was also not statistically significant (Table II).

Correlation analyses were performed to analyze the subjects' circulating immune cell and metabolic-adiposity profiles. WBC count was significantly positively correlated to BMI, waist circumference, visceral fat, and AIP. WBC count also exhibited a positive correlation with MetS risk and a negative correlation with HDL, but these results were not statistically significant. WBCs were positively correlated with hyper-triglycerides and insulin resistance, and these were statistically significant (Table III).

Neutrophils were significantly positively correlated with BMI and waist circumference. All other variables were not significantly correlated to neutrophils. Lymphocytes had a statistically significant correlation with all metabolic and adiposity profiles in this study. Lymphocytes showed a positive correlation with BMI, waist circumference, visceral fat, HOMA-IR, AIP, and a number of MetS risk factors. Lymphocytes also showed a negative correlation with HDL. The correlation direction was inversed regarding NLR, and there was a significant negative correlation between NLRs and triglycerides, AIPs, and MetS risk numbers (Table III).

DISCUSSION

The prevalence of MetS continues to rise globally with the increasing occurrence of obesity. Systemic and tissue inflammation occur in both conditions. Increased proinflammatory cytokines and activation of innate and adaptive cellular immune responses related to excess adipose induce metabolic disorders. Previous studies demonstrated the inflammation crosstalk between obesity and MetS, which was associated with circulating WBCs and its subtypes (8,12–13). Similar to this finding, our study found that circulating WBCs and lymphocytes were associated with MetS in the presence of obesity. Obesity causes fat to be deposited in adipose tissue and an increase in the number of proinflammatory leukocytes and immune cells, such as macrophages, T cells, B cells, neutrophils, and mast cells that can cause chronic inflammation. Increased T cells can produce potent cytokines, such as interferon-alpha, tumor-necrosis factors, and Interleukin-6 (IL-6), which can induce M1 macrophages and lead to metabolic dysfunction. In obesity, fat deposits also occur in the primary lymphoid organs (bone marrow and thymus), causing reduced integrity of lymphoid tissue, which increases the number of proinflammatory leukocytes (2,5,13).

Regardless of obesity, higher WBCs, lymphocytes, and neutrophils were found in the MetS group, but these results were not statistically significant. Stratification based on obesity showed higher WBCs, lymphocytes, and neutrophils in obese patients with or without MetS. Both may be reflective of the inflammation processes in obesity and MetS. Significantly higher WBC and lymphocyte counts were found in the MetS with obese group compared to the normal groups (non-obese and not MetS) or to the MetS non-obese group. This finding may suggest that more inflammation occurs in the MetS-obese group. Similar to the results of our study, a study in Turkey indicated that higher circulating WBC, neutrophils, and lymphocytes were found in the obese group and MetS group compared to controls, and the results increased linearly with the severity of obesity and MetS, but the study did not include an obese-MetS group (11,12). Furthermore, our research found significantly higher WBC and lymphocyte counts in the MetS-obese group compared to the MetS non-obese group, which may indicate that in the absence of obesity, patients with MetS experience less inflammation. Reduced inflammation in MetS-only patients may limit the progression of chronic diseases, such as cardiovascular diseases (5,13).

Regardless of MetS, increased levels of adiposity (BMI, waist circumference, and visceral fat percentage) exhibited positive correlations with circulating WBC

Table III: Correlation of circulating WBC count with metabolic and adiposity profile

Characteristics	WBCs (x10³/mm³)		Neutrophils (x10³/mm³)		Lymphocytes (x10³/mm³)		NLR	
	p-value	r	*p*-value	r	*p*-value	r	*p*-value	r
BMI (kg/m²)	***0.008**	**0.170**	**0.050	0.116	***<0.001**	**0.231**	*0.109	-0.087
Waist circumference (cm)	***0.006**	**0.177**	****0.041**	**0.122**	***<0.001**	**0.238**	*0.053	-0.114
Visceral fat	***0.020**	**0.144**	**0.114	0.085	***0.001**	**0.219**	*0.063	-0.108
Triglyceride (mg/dL)	**#0.003**	**0.441**	**0.314	-0.034	***<0.001**	**0.254**	***0.001**	**-0.208**
HDL (mg/dL)	*0.147	–0.074	**0.438	-0.011	***0.004**	**-0.189**	***0.035**	**0.127**
MetS risk number	*0.325	0.034	**0.207	-0.060	***0.020**	**0.151**	***0.016**	**-0.157**
HOMA-IR	**#0.018**	**0.408**	**0.307	-0.036	***0.009**	**0.167**	#0.017	0.906
AIP	***0.035**	**0.128**	**0.476	0.004	***<0.001**	**0.264**	***0.002**	**-0.203**

r = correlation coefficient; *Spearman's correlation was performed due to not normally distributed data but has a linear assumption, **Pearson correlation was performed due to normality and a linearity assumption was found. #Eta correlation due to no linear assumption between pairs of the variable. Triglyceride level was grouped to hyper-triglyceride and normal (nominal variable), and HOMA-IR was grouped to insulin resistance and normal. Eta correlation tested leucocytes and NLR as a numeric variable. One-tailed *p*-value < 0.05 considered statistically significant.

and lymphocytes. This finding may represent how abnormalities in adipose tissue contribute to systemic inflammation. Chronic adipose tissue inflammation related to obesity induces excessive immune cell recruitment, increased free fatty acids, macrophage reactive oxygen species, and other "antigens" that are produced by adipose cell death. Inflammation is mediated by the interplay between cells and components of the innate and adaptive immune system, as well as proinflammatory cytokines produced by adipose tissue. Adipose tissue inflammation also induces systemic inflammation. This study showed increased cellular markers of systemic inflammation related to excess adiposity. Increased total lymphocytes and its subtypes CD8+ lymphocytes and CD4+ Th1 lymphocytes were also found in circulation. Some studies also found increased neutrophils, but this was not as evident as the increases in lymphocytes, which may be due to a shorter transit time of neutrophils in the circulation (9,13,14). These findings may strengthen the clinical evidence that excessive adiposity biomarkers are related to chronic inflammation. Previous epidemiology research found a benefit of controlling excessive adiposity markers, showing that it might control chronic inflammation related to the progression of cardiovascular diseases (2,13).

The exact mechanism of how obesity induces cardiometabolic abnormalities related to systemic inflammation is currently unknown. The inflammation process increases insulin resistance locally in adipose tissue and systemic components mediated by proinflammatory cytokines secreted by adipose and immune cells. CD8+ lymphocytes and CD4+ Th1 lymphocytes play a major role in macrophage reprogramming and polarization to the M1 subtype. This cellular response activates inhibitors of kB (IKK) and c-Jun N-Terminal Kinase pathways, which directly impair insulin signaling. Similarly, epidemiology studies found increased circulating WBCs, neutrophils, and lymphocytes were related to insulin resistance and an increased cardiometabolic risk (10,14,16). This study also found a positive correlation between insulin resistance marked by HOMA-IR as a risk factor for diabetes mellitus with WBC and lymphocytes. Moreover, plasma triglycerides and HDL were correlated with increased lymphocyte counts, and hypertriglyceridemia was correlated with increased WBCs. These correlations may be related to insulin resistance. Insulin resistance is shown to induce elevated plasma triglycerides and lower HDL levels (17).

Atherosclerosis risk, identified using the biomarker AIP calculated as log 10 of triglycerides and HDL levels, also showed positive correlations with lymphocytes and WBC counts. The AIP which represents atherosclerosis risk, is superior to triglyceride or HDL levels alone, and can serve as a biomarker of subclinical atherosclerosis (18,19). Together, these data emphasize the role of circulating immune cells in increasing cardiometabolic risk, although an assessment of atherosclerosis was not performed. This finding showed that inflammation may contribute to metabolic dysfunction, although in this study, we could not demonstrate how this process was connected with excessive adiposity markers.

Although lymphocyte and neutrophil increases were related to adiposity and cardiometabolic risk, NLRs (another marker of inflammation) were lower in the metabolic abnormality group and showed negative correlations with triglycerides and atherosclerosis risk. This result showed that NLR in this study had an inverse correlation with the components of lipids in the blood as a risk factor for atherosclerosis. The predominant increase of lymphocytes compared to neutrophils (lower NLRs) serves as a signal for increased MetS risk more than other blood count parameters which may be related to the chronic inflammation state. The relationship between the increase of neutrophils was not as dominant as it was with increased lymphocytes, possibly because of the shorter transit time of neutrophils in circulation. These results differ from another study conducted in Turkey that showed increased NLRs were associated with increases in the severity of MetS, although one study found that the NLR was not as effective as an indicator of inflammation compared to WBC and CRP (11,12).

This study found that circulating WBCs and its subsets were associated with inflammation in the obesity group among patients with MetS, and increased cardiometabolic risks. This present study had several limitations. The cross-sectional design did not allow us to determine any direct causal relationships since it only describes the phenomena under observation. Although the circulating lymphocytes and WBC counts showed positive correlations with excess adiposity and increased cardiometabolic risk which were statistically significant, the correlation coefficient was weak, thus, becoming a limitation of our study. In the future, the small sample size should be increased, although the randomized population-based screening helped to reduce any researcher bias. Additionally, other inflammatory indicators were not used to compare with circulating WBCs and its subsets.

CONCLUSION

Circulating WBCs and lymphocytes were associated with MetS in the presence of obesity. Circulating WBCs showed positive correlations with the biomarkers of excess adiposity. Circulating lymphocytes also exhibited positive correlations with the biomarkers of excess adiposity and cardiometabolic risk. These findings may contribute to the strengthening of the clinical evidence that demonstrates controlling obesity can reduce inflammation and prevent chronic disease progression. Circulating WBCs and lymphocytes may play a role

in the crosstalk between inflammation in obesity and metabolic abnormalities in the lipid parameters.

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