Hematologic parameters as the predictors for metabolic syndrome in perimenopausal and postmenopausal women living in urban area: a preliminary report

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Abstract

Introduction: Prevalence of metabolic syndrome increases drastically during menopausal transition. Chronic inflammation is proposed as the basic pathophysiology of metabolic syndrome (MetS).

Aim of the study: To compare mean white blood cell count between perimenopausal and postmenopausal women with and without MetS and find the prevalence of MetS in this patient group.

Material and methods: A total of 140 healthy perimenopausal and postmenopausal women were interviewed and underwent anthropometric measurements, biochemical investigations for MetS and hematologic parameters. MetS was defined according to the Joint Interim Statement 2009 criteria. The outcome measures were the hematologic parameters between women with and without MetS, correlation of hematologic parameters with MetS components and optimum cutoff for MetS prediction.

Results: The mean age of participants was 50 years. 63.6% were perimenopausal and 36.4% were postmenopausal ones. The prevalence of MetS was 21.4% (95% CI: 15.0-27.9). The women with MetS had a significantly higher level of white blood cell (WBC) counts (7,466.7 and 6,514.6; $p = 0.006$) and total lymphocyte counts (2,572.0 and 2,207.7; $p = 0.003$). The optimum cutoff of WBC counts and total lymphocyte counts for prediction of metabolic syndrome was 6,750 cells/ml (sensitivity = 0.633; specificity = 0.591, $p = 0.019$) and 2,232 cells/ml (sensitivity = 0.667; specificity = 0.518, $p = 0.016$), respectively.

Conclusion: White blood cell and total lymphocyte counts were higher in perimenopausal and postmenopausal women with MetS. However, both hematologic parameters were poor predictors for MetS in peri- and postmenopausal women.

Key words: metabolic syndrome, white blood cell count, total lymphocyte count, menopause, hematologic parameters.

Introduction

In the recent years, metabolic syndrome (MetS) has been unquestionably recognized as the major predisposing cardiovascular risk factor [1] (impaired glucose tolerance, hypertension, dyslipidemia and central obesity) and other chronic conditions [2-6], all of which increase the mortality rate [7]. The prevalence of metabolic syndrome increases steeply during the menopausal transition [8-10]. This surge of prevalence was explained by a substantial increase in waist circumference and fat mass, especially visceral fat mass throughout the estrogen recessional period [6, 11, 12].

In spite of unascertained etiology of MetS, the chronic systemic inflammatory state seems to be the pivotal mechanism underlying MetS development [13] through complex pathways such as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor α (TNF-α) and interleukin (IL-6) [14], serine phosphorylation of insulin receptor substrate-1 (IRS-1) increment through activation of c-Jun *N*-terminal kinase (JNK) and IκB kinase (IKK) [15], and toll-like receptor (TLR4) signaling pathway [16]. White blood cell (WBC) count is a routinely measured marker of systemic inflammation and elevated WBC count or its subtype is intimately linked to the prevalence of MetS in previous population-base studies [17-19]. Other hematologic parameters including platelet count and hemoglobin are also associated with MetS and its components in some studies [18].

To the best of our knowledge, there is no study focusing on the association between hematologic parameters and MetS in perimenopausal and postmenopausal women. The objectives of the present study were to compare mean WBC count between perimenopausal and postmenopausal women with and without MetS, to determine the prevalence of MetS in this patient group,

to determine a correlation of hematologic parameters with MetS components, and to find a predictive value and optimum cutoff level of hematologic parameters associated with MetS.

Material and methods

The cross-sectional study was carried out in the Women Health Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, a tertiary-care university hospital. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the study protocol was approved by the Vajira Institutional Review Board.

Study design and participants

The study was conducted in perimenopausal and postmenopausal women defined according to the STRAW+10 definition [20], aged at least 40 years, living in the urban area of the capital city of Thailand, who attended health checkups at the women health clinic from September 2014 to April 2015. Participants excluded from the study were women having a history of cancer, cardiovascular disease, stroke, immunosuppressive therapy, hysterectomy, diagnosed with inflammatory disease (arthritis, inflammatory bowel disease, psoriasis, etc.), polycystic ovary syndrome, steroid or NSAIDs use, and a history of infection or invasive procedure within 6 months prior to the recruitment.

After written informed consent was obtained, all study participants were subjected to clinical and biochemical investigations. The socioeconomic data and medical history were collected, which included demographic data, lifestyle (alcohol consumption, smoking), menstrual history and family history of metabolic diseases.

The physical examinations of participants were performed including height (in cm), weight (in kg), waist circumference (in cm), and blood pressure (in mmHg). Waist circumference was measured at a level midpoint between the lower rib margin and the top of the iliac crest. Blood pressure of the participants was measured twice with a standardized mercury sphygmomanometer in a sitting position at least 60 seconds apart. The average of the two measurements was recorded. The body mass index (BMI) was then calculated and categorized into normal (BMI < 23.0 kg/m^2), overweight (BMI 23.0–29.9 kg/m^2), and obese (BMI ≥ 30.0 kg/m^2), according to the classification adopted by the World Health Organization [21].

After overnight fast, the biochemical blood tests including complete blood count, fasting blood glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were performed. The biochemical assays were conducted in the ISO 15189 certified biochemical laboratory of the Department of Clinical Pathology.

Criteria for diagnosis of metabolic syndrome

In the present study, we used the Joint Interim Statement (JIS) 2009 criteria [22]. The participants were diagnosed with metabolic syndrome if they had at least three out of five of the following factors: 1) abdominal obesity defined as waist circumference ≥ 80 cm for Asian women; 2) elevated triglycerides ≥ 150 mg/dl or drug treatment for elevated triglycerides; 3) reduced HDL-C < 50 mg/dl or drug treatment for reduced HDL-C; 4) elevated blood pressure defined as systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg or antihypertensive drug treatment; 5) elevated fasting glucose ≥ 100 mg/dl or drug treatment of elevated glucose.

Statistical analysis

Sample size was calculated using the formula for a descriptive study. When the estimated prevalence of metabolic syndrome (p) was 8% [18] and α = 0.05, a sample size of at least 127 cases was needed.

All data were analyzed by SPSS software (version 22.0). Data were presented as mean ± standard deviation (SD), number (%), or percentage (95% confidence interval – CI), as appropriate. Data comparisons were analyzed using the independent sample *t* test for continuous data and χ^2 for categorical data. Pearson's correlation coefficient was determined for the correlation between WBC, total lymphocyte count and MetS components. Receiver operating characteristic (ROC) curve analysis for diagnosing MetS was performed to obtain area under ROC curve (AUC) and optimal cutoff points of WBC and total lymphocyte count for diagnosing MetS. An optimal cutoff point was defined as a point on a ROC curve nearest to the point where both sensitivity and specificity were one. A *p* value of < 0.05 was considered statistically significant.

Results

The characteristics of 140 participants are summarized in Table I. The overall mean age was 50.0 ±7.4 years. Most participants were perimenopausal, married and multiparous. More than 60% of all participants had a healthy lifestyle; healthy foods, regular exercise, no smoking or alcohol-drinking habits (data not shown). The overall means of BMI and waist circumference were 24.0 ± 4.3 kg/m^2 and 82.1 ±9.4 cm, respectively.

The overall prevalence of MetS diagnosed by JIS 2009 criteria was 21.4% (95% CI: 15.0-27.9). The prev-

Tab. I. Characteristics of 140 participants stratified by metabolic syndrome (MetS) status

	MetS (n = 30)	Non-MetS (n = 110)	p
Age (years)	52.0 ±8.0	49.5 ±7.2	0.092*
Menopausal status, n (%)			0.009†
Perimenopause	13 (43.3)	76 (69.1)	
Postmenopause	17 (56.7)	34 (30.9)	
Alcohol consumption, n (%)	3 (10)	11 (10)	1.000†
BMI (kg/m²)	27.7 ±4.0	23.0 ±3.8	< 0.001*
Normal weight	3 (10.0)	65 (59.1)	< 0.001†
Overweight	20 (66.7)	41 (37.3)	
Obese	7 (23.3)	4 (3.6)	
Components of MetS			
Waist circumference (cm)	90.1 ± 8.6	79.9 ± 8.4	<0.001*
Triglycerides (mg/dl)	163.9 ± 89.6	83.1 ± 31.1	<0.001*
HDL-C (mg/dl)	51.3 ±14.0	61.5 ±12.9	<0.001*
Systolic BP (mmHg)	136.7 ±10.0	121.7 ±12.3	<0.001*
Diastolic BP (mmHg)	83.6 ±8.1	75.6 ±8.6	<0.001*
Fasting glucose (mg/dl)	100.1 ±7.5	93.1 ±6.9	<0.001*
Hematologic parameters			
WBC (cell/ml)	7466.7 ±2293.4	6514.6 ±1452.8	0.006*
Hb (mg/dl)	12.7 ±1.0	12.4 ±1.3	0.333*
Platelet count (cell/ml)	261700.0 ±55979.2	260709.1 ±59836.1	0.935*
Total neutrophil count (cell/ml)	4093.5 ±1884.7	3706.4 ±1196.5	0.172*
Total lymphocyte count (cell/ml)	2572.0 ±686.4	2207.7 ±557.7	0.003*

BMI – body mass index; HDL-C – high-density lipoprotein cholesterol; BP – blood pressure; WBC – white blood cell count; Hb – hemoglobin
*independent sample t-test, †χ^2

Tab. II. Pearson's correlation coefficients between white blood cell count, total lymphocyte count and components of metabolic syndrome

	WBC	Total lymphocyte count
BMI	0.290*	0.230*
Waist circumference	0.276*	0.260*
Triglycerides	0.202*	0.324*
HDL-C	−0.215*	−0.161
Systolic blood pressure	0.053	0.059
Diastolic blood pressure	0.085	0.160
Fasting glucose	0.126	0.070

WBC – white blood cell count; BMI – body mass index; HDL-C – high-density lipoprotein cholesterol
*$p < 0.05$

The hematologic parameters from the complete blood count were compared between women with and without MetS as presented in Table I. Perimenopausal and postmenopausal women with MetS had a significantly higher level of mean white blood cell count (7,466.7 ±2,293.4 and 6,514.6 ±1,452.8 in MetS and non-MetS group, respectively, p = 0.006) and total lymphocyte count (2,572.0 ±686.4 and 2,207.7 ±557.7 in MetS and non-MetS group, respectively, p = 0.003). Other hematologic parameters did not differ between perimenopausal and postmenopausal with or without MetS.

There were weak correlations between white blood cell count, total lymphocyte count and components of MetS, which are summarized in Table II. Both white blood cell count and total lymphocyte count were correlated with BMI, waist circumference and triglycerides level while HDL-C showed a weak correlation with white blood cell count only.

The ROC curve of white blood cell count and total lymphocyte count for prediction of MetS are presented in Fig. 1. Albeit the predictive performances for both hematologic parameters were poor, we proposed the optimal cutoff of 6,750 cell/ml for white blood cell count and 2,232 cell/ml for total lymphocyte count (Table III).

alence of MetS was significantly higher in postmenopausal women (33.3%, 95% CI: 20.4-46.5 in postmenopausal women and 14.6%, 95% CI: 7.3-23.1 in perimenopausal women, p = 0.009). When each diagnostic criterion was taken into account, the three most common components were abdominal obesity (57.1%), elevated blood pressure (38.6%) and elevated fasting glucose (24.3%).

Discussion

In the current study, overall prevalence of MetS was approximately 20.4%, which was higher than in a previous study in Thai women [23]. The prior study reported that prevalence of MetS was 15.9% in Thai perimenopausal and postmenopausal women attending a menopause clinic [23] and 11.7% in women attending a health checkup clinic [24]. The higher prevalence in our study might be due to that all our participants lived in the urban area, which predisposed them to lead a more sedentary lifestyle since they had higher BMI, waist circumference and alcohol consumption. The most common MetS components in our study were abdominal obesity, elevated blood pressure and elevated fasting glucose, which was also in agreement with previous studies about the most prevalent components of metabolic syndrome among postmenopausal women with MetS [9, 25, 26].

We found that perimenopausal and postmenopausal with MetS had a higher level of WBC and total lymphocyte count. Although all previous studies reported the same finding of higher levels of WBC and its subtype or being in a higher quartile of people with MetS [17-19, 24, 27-31], none of these studies focused on their association in perimenopausal and postmenopausal women. Only a WHI observational study [32] reported the level of WBC as a predictor of cardiovascular events and mortality rate in postmenopausal women. They reported that WBC count in an upper quartile was an independent predictor of coronary heart disease even if adjusted for multiple other risk factors including CRP level and total cholesterol/HDL-C ratio.

Although the mechanism of higher WBC and lymphocyte count in perimenopausal and postmenopausal women with MetS remains unclear, there are some possible explanations. The chronic inflammation appears to be a crucial mechanism for the pathophysiology of MetS [13]. During menopausal transition, the body composition changes including increased waist circumference [6, 12], fat mass, and visceral fat deposition [6, 11] contribute to reduction in circulating adiponectin [33], a collagen-like protein expressed in adipose tissue that is associated with many metabolic processes [34]. Low levels of adiponectin lead to an increase in levels of TNF-α and IL-6 from macrophages and a decrease in levels of the anti-inflammatory cytokines, IL-10 and
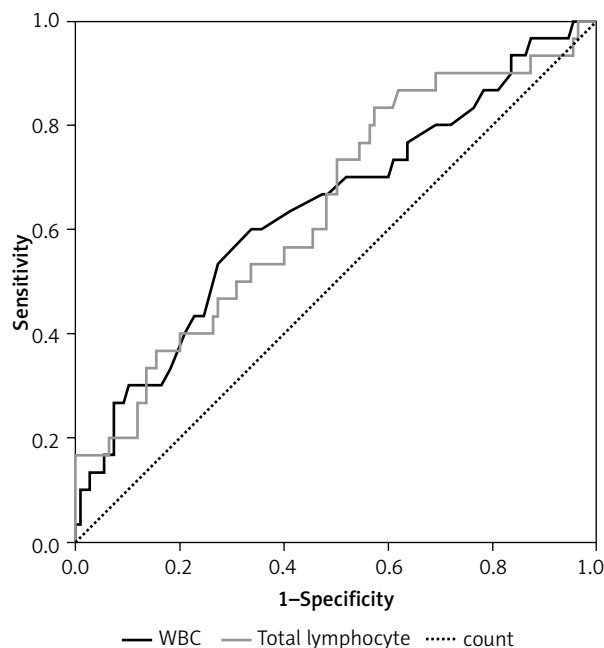

Fig. 1. ROC curve of the white blood cell count and total lymphocyte count for prediction of MetS

IL-1 receptor antagonist, thus causing a chronic inflammatory state and insulin resistance. Low levels of adiponectin also increase gluconeogenesis by inhibiting adenosine monophosphate-activated protein kinase (AMPK) and causing hyperglycemia [35]. Overall, this proinflammatory state in MetS might explain the elevation of WBC count in MetS patients. Further studies about the relationship between WBC count and serum adiponectin are needed to confirm our hypothesis.

In our study, the correlation of WBC count and total lymphocyte count with components of MetS that significantly changed during menopausal transition (waist circumference, triglycerides and HDL-C) was congruent with previous cross-sectional and longitudinal studies [19, 24, 28, 30]. This could be also explained by the inflammatory state in these patients. The inflammation, increased triglycerides, and decreased HDL-C may stem from TNF-α and IL-6, which stimulate lipolysis and increase circulating free fatty acids to the liver. This increase in free fatty acids induces hepatic triglyceride synthesis and increases very low-density lipoprotein

Tab. III. Areas under receiver operating characteristic curve (AUCs) and optimal cutoff points (OCPs) of white blood cell count and total lymphocyte count for the prediction of metabolic syndrome

	AUC (95% CI)	p	OCP	Sensitivity	Specificity
WBC (cell/ml)	0.640 (0.523-0.757)	0.019	6.750	0.633	0.591
Total lymphocyte count (cell/ml)	0.643 (0.530-0.756)	0.016	2.232	0.667	0.518

CI – confidence interval; WBC – white blood cell count

secretion from the liver, this increases hepatic triglyceride production and secretion, and thus hypertriglyceridemia [36]. Tumor necrosis factor α and IL-6 also suppress lipoprotein lipase synthesis in adipose tissue, which may contribute to hypertriglyceridemia and low HDL-cholesterol concentrations observed in individuals with visceral obesity [6, 37].

The current recommendation for the optimal cutoff point for WBC is varied according to the final diagnosis and population. We proposed an optimal cutoff point of WBC level at 6,750 cell/ml in Thai perimenopausal and postmenopausal for prediction of MetS (sensitivity 63.3% and specificity 59.1%). A previous report from Japan recommended a cutoff point at 5,000 cell/ml for the prediction of MetS (sensitivity 65% and specificity 63%) in women who attended a general medical check-up program [30]. In a WHI observational study, they recommended the level of 6,700 cell/ml for a high risk of cardiovascular disease and mortality in postmenopausal women [32]. Currently, no recommendation regarding total lymphocyte count for the prediction of MetS has been proposed. We suggest the total lymphocyte count at least 2,232 cell/ml to further investigate for MetS.

Early diagnosis and prompt treatment of MetS can prevent the morbidity and mortality from its complications [6]. In our study, WBC and total lymphocyte counts are higher in perimenopausal and postmenopausal women with MetS but the prediction power is poor. More studies are required before applying its utilities into clinical practice. Further research about the association between the adiponectin level and WBC count is also recommended which will let us better understand the role of inflammation in MetS.

To the best of our knowledge, our study is the first to demonstrate the association between WBC count and MetS in perimenopausal and postmenopausal women. However, with a cross-sectional study it is impossible to determine the direction of the association. A longitudinal study would be more appropriate for this question.

Conclusions

Metabolic syndrome is common among Thai perimenopausal and postmenopausal women living in the urban area. WBC and total lymphocyte counts were higher in perimenopausal and postmenopausal women with MetS. However, both hematologic parameters were poor predictors for MetS in this group. Further longitudinal studies are necessary to confirm the relationship between WBC, lymphocyte count and MetS in perimenopausal and postmenopausal women.

Disclosure

Authors report no conflict of interest.

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