Original Paper • CME

Platelet and White Blood Cell Counts Are Elevated in Patients With the Metabolic Syndrome

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Platelet and white blood cell counts are higher among some insulin-resistant patients and may contribute to atherothromboembolic complications. Metabolic syndrome patients are insulin resistant, often hypertensive, and at high cardiovascular disease risk, yet the relationship of platelets to the metabolic syndrome is unknown. Platelet and white blood cell counts were obtained from 135 volunteers who had measurements of blood pressure, fasting triglycerides, high-density lipoprotein cholesterol, and glucose. A body mass index >30 kg/m^2 served as a surrogate for increased waist circumference. Subjects were subdivided into three groups by the number of metabolic syndrome criteria, i.e., no metabolic syndrome risk factor (MS–0; n=40), one or two metabolic syndrome risk factors (MS1–2; n=61), and three to five metabolic syndrome risk factors (MS3–5; n=34). Platelet counts were increased significantly from 226±8 to 257±8 and 276±10 (×10^3/mm^3) in the MS–0, MS1–2, and MS3–5 groups, respectively (p<0.01), after adjustment for age, gender, ethnicity, total cholesterol, and low-density lipoprotein cholesterol. White blood cell counts were also increased across the three groups (5.4±0.2, 6.2±0.2, and 6.6±0.3 [×10^3/mm^3]; p<0.01) after multivariate adjustment. Compared with patients with zero to two metabolic syndrome risk factors, metabolic syndrome patients have higher platelet and white blood counts, which may serve as markers of a prothrombotic and proinflammatory state and contributors to atherothromboembolic risk. (J Clin Hypertens. 2005;7:705–711) ©2005 Le Jacq Ltd.

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Obesity is associated with a proinflammatory, prothrombotic state that could play a role in accelerating cardiovascular disease (CVD).[1–5] Obesity is also associated with insulin resistance, hypertension, and the metabolic syndrome; these are characterized by a clustering of cardiovascular risk factors and elevation of markers indicating a proinflammatory and prothrombotic state.[6–8] Several inflammatory markers, including C-reactive protein,[9] fibrinogen,[10] white blood cell (WBC) counts,[11–13] sialic acid,[14] and to a lesser extent factor VIII and von Willebrand factor[10,15] are positively associated with atherosclerosis and an increased incidence of coronary artery disease.

Metabolic syndrome patients have higher leukocyte counts than patients without the metabolic syndrome.[16] Higher platelet and leukocyte counts are associated with atherosclerosis and increased morbidity and mortality from CVD.[17,18] WBC counts are also higher in adults who have risk factors such as cigarette smoking and a family history of CVD than in the normal population.[19,20] Primary (essential) and secondary thrombocytosis are also linked to thrombotic and/or embolic events in the cerebral, coronary, and peripheral arterial circulation.[21,22] Other evidence suggests that platelet counts are higher and contribute to vascular events in patients with other risk factors, e.g., insulin resistance.[23–26] Thus, platelet counts emerge as another potentially

Table I. Clinical Characteristics of the Patients

Variable (n or Mean ± SEM)	No. of Metabolic Syndrome Risk Factors 0	1 or 2	3–5	*P* Value
No. of patients	40	61	34	
Gender (female/male)	20/20	34/27	22/12	0.44
Race (black/white)	14/26	30/31	23/11	<0.05
Age (yr)	34.7±1.3	36.2±1.0	38.9±1.1	<0.05
Body mass index (kg/m^2)	23.4±0.4	29.6±0.8	36.4±1.0	<0.0001
Systolic BP (mm Hg)	111.1±1.4	127.2±2.0	135.7±2.4	<0.0001
Diastolic BP (mm Hg)	72.1±1.2	83.1±1.5	90.0±1.7	<0.0001
Total cholesterol (mg/dL)	182.3±5.6	192.1±5.2	190.9±7.0	0.443
Triglycerides (mg/dL)	66.3±4.6	84.3±5.0	130.6±13.9	<0.0001
High-density lipoprotein cholesterol (mg/dL)	56.9±1.9	48.5±1.7	38.6±1.4	<0.0001
Low-density lipoprotein cholesterol (mg/dL)	112.1±4.8	127.0±4.5	126.2±5.9	<0.075
Very low-density lipoprotein cholesterol (mg/dL)	13.3±0.9	16.9±1	26.1±2.8	<0.0001
Glucose (mg/dL)	85.0±1.4	90.1±1.2	104.3±4.8	<0.0001
White blood cells (×10^3/mm^3)	5.4±0.2	6.2±0.2	6.6±0.3	<0.02
Red blood cells (×10^6/mm^3)	4.8±0.1	4.8±0.1	4.8±0.1	0.851
Hematocrit (%)	42.2±0.7	41.9±0.6	41.7±0.7	0.874
Platelets (×10^3/mm^3)	226±8	257±8	276±10	<0.001
Mean platelet volume (fL)	8.9±0.20	8.8±0.1	8.5±0.2	0.340

BP=blood pressure

useful marker of CVD risk. Although many reports have focused on platelet function and the benefits of pharmacologic intervention to alter platelet function, the relationship between platelet count and CVD risk has generated less interest.

Given the preceding information, this report examines the relationship of metabolic syndrome risk factors to platelet and leukocyte counts in volunteers with a spectrum of metabolic syndrome risk factors.

METHODS

Subjects

One hundred thirty-five volunteers were recruited by advertisement to participate in various research protocols. All subjects signed written informed consent documents approved by the Office of Research Protection and Integrity at the Medical University of South Carolina. All volunteers were nonsmokers, 21–49 years old, who underwent screening measurements to determine eligibility for participation in the full protocol. The baseline data in this report were obtained during the screening visit. Patients on medications that could affect platelet counts and/or function were excluded, including 15 women receiving hormonal birth control medications and one patient taking aspirin.

At the screening visit all volunteers had a history, physical examination, electrocardiogram (ECG), and screening laboratory tests in the fasting state. The laboratory tests included complete blood cell count, automated chemistry profile, lipid profile, and urinalysis. Women of child-bearing potential were required to have a negative urine pregnancy test before participation in this study.

Measurements. Height was measured with a standard stadiometer to the nearest 0.5 cm or 0.25 inch in subjects without shoes in the upright position. Weight was measured with a calibrated beam balance scale to the nearest 0.2 lb or 0.1 kg. Body mass index (BMI) was calculated in kg/m^2. Blood pressure (BP) was measured with a mercury sphygmomanometer after 10 minutes of rest with subjects seated. Three readings were taken in the sitting position with 2 minutes between readings. BP was determined by the average of the second and third values.

Complete Blood Cell Count. Blood was drawn from the antecubital fossa with atraumatic venipuncture into a vacutainer containing ethylenediaminetetraacetic acid. Samples were placed on the CELL-DYN 4000 System (Abbott Laboratories, Abbott Park, IL), which counts, sizes, and classifies

blood cells and platelets by flow cytometry using optical scatter/fluorescence and electrical impedance technologies as a quality check for optical platelet count. On rare occasions when measurements did not match, they were confirmed by manual count of the blood smear, and the number closest to the manual was considered the actual count. Mean platelet volume was measured by electrical impedance.

Glucose and Lipid Profile. Venous blood was drawn after 12 hours' fasting into a serum separator tube and sent for analysis of fasting glucose and lipid profile for every subject simultaneously with the platelet and WBC samples. The quantitative determination of glucose, cholesterol, triglycerides, and high-density lipoprotein (HDL) in the plasma were done on a SYNCHRON LX System (Beckman Coulter, Inc., Fullerton, CA). Glucose concentration was determined by an oxygen rate method employing the Beckman oxygen electrode.[27,28] Specific reagents were used to measure cholesterol and triglyceride concentrations by the timed end point method.[29,30] HDL was measured by a direct homogeneous assay in which a unique detergent solubilizes only the HDL particles and releases HDL cholesterol to react with cholesterol esterase and cholesterol oxidase in the presence of chromogens to produce a color product. Low-density lipoprotein (LDL) cholesterol and very LDL cholesterol were calculated from total cholesterol, HDL, and triglyceride concentrations using the Friedewald equation.[31]

Protocol. Patients reported to the General Clinical Research Center after an overnight fast for the initial screening visit. The written informed consent document was reviewed and signed. BPs were measured, and a complete physical examination and ECG were performed. Blood was drawn and sent to the laboratory. All evaluations were performed in the research center clinic in the morning between 8 a.m. and 10 a.m.

Statistical Analyses. Data are presented as mean ± SEM. Statistical analyses were conducted with SAS version 9.1 (SAS Institute Inc., Cary, NC). The chi-square test was used to analyze the categoric differences between the groups. Multiple linear regression analysis was used to assess the relationships between BMI, platelet counts, and WBC counts. Analysis of variance was used to test for significant difference in means among the three groups. Analysis of covariance was used to test for mean differences between groups, while adjusting for potential confounding variables, and p values <0.05 were considered statistically significant.

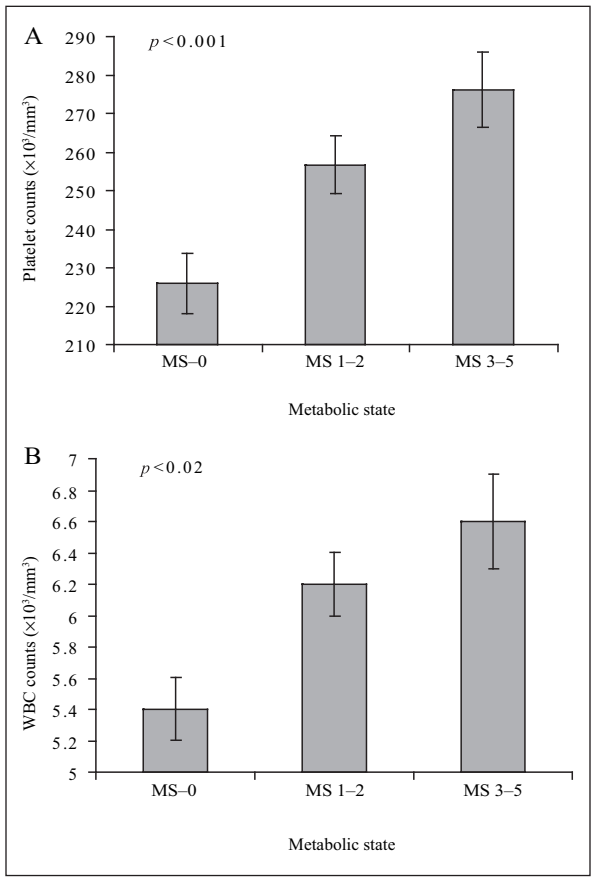

Figure. Platelet counts (A) and white blood cell (WBC) counts (B) are depicted (mean ± SEM) for the three groups of patients with no metabolic syndrome risk factors (MS–0), one or two risk factors (MS 1–2), and three to five risk factors (MS 3–5). Platelet and WBC counts increased significantly with the number of metabolic syndrome risk factors.

Table II. Metabolic Syndrome Risk Factors Present in the Study Groups With Risk Factors

	No. of Risk Factors	
Risk Factor	1 or 2 (n=61)	3–5 (n=34)
Body mass index ≥30 kg/m^2	29 (47.5)	33 (97.1)
Systolic BP ≥130 mm Hg	27 (44.3)	24 (70.6)
Diastolic BP ≥85 mm Hg	29 (47.5)	26 (76.5)
Triglycerides ≥150 mg/dL	5 (8.2)	13 (38.2)
High-density lipoprotein cholesterol		
Men: ≥40 mg/dL	13 (21.3)	9 (26.5)
Women: ≥50 mg/dL	13 (21.3)	20 (58.8)
Glucose >110 mg/dL	0 (0)	10 (29.4)

Data are listed as n (%). BP=blood pressure

RESULTS

As shown in Table I, patients were divided into three groups based on the number of metabolic syndrome criteria they met using the Adult

Table III. Multivariable Analysis of Covariance Model to Determine the Effect of the Metabolic State on Platelet and White Blood Cell Counts With Adjustment for the Variables Shown

	Platelets (×10³)		White Blood Cells (×10³)	
Variable	Coefficient	*P* Value	Coefficient	*P* Value
No. of risk factors				
0				
1 or 2	28.6	0.01	0.82	0.02
3–5	42.6	0.003	1.26	0.003
Gender				
Male	–20.8	0.10	–0.19	0.64
Female				
Race				
Black	16.5	0.12	–0.48	0.16
White				
Age	0.24	0.73	0.03	0.25
Hemoglobin	–3.02	0.49	–0.05	0.74
Total cholesterol	0.60	0.08	0.02	0.08
Low-density lipoprotein cholesterol	–0.55	0.16	–0.02	0.14

Treatment Panel III (ATP III) criteria: values for BP ≥130/85 mm Hg, fasting glucose ≥110 mg/dL, triglycerides ≥150 mg/dL, and HDL cholesterol <40 mg/dL for men and <50 mg/dL for women.[32–35] Waist circumference was not available for all subjects. Thus, a BMI >30 kg/m^2, which is a component of the World Health Organization definition of the metabolic syndrome, was used.[35] Based on previous research, ATP III waist circumference criteria are likely to be met in men and women when their BMI is ≥28.8 kg/m^2.[32,33] Patients with a BMI >30 kg/m^2 are likely to meet the ATP III waist circumference criterion for the metabolic syndrome.[35] Forty volunteers did not have any metabolic syndrome risk factors (MS–0), 61 patients had one or two risk factors (MS1–2), and 34 subjects had three or more risk factors (MS3–5) and met the modified metabolic syndrome definition.

Demographic characteristics varied across the three groups (Table I). Mean age and the proportion of African Americans increased significantly across the three groups as shown. Although the proportion of women tended to increase with the number of metabolic syndrome risk factors, the trend was not significant. As expected, the three groups showed significant differences in mean values for the five metabolic syndrome risk factors, including BMI, systolic and diastolic BP, triglycerides, HDL cholesterol, and fasting glucose. Platelet counts showed a significant stepwise increase from the MS–0 to the MS1–2 and MS3–5 groups. WBC counts showed the same significant upward trend across the three study groups. Platelet and leukocyte counts showed a significant positive correlation (r=0.30; p<0.0005); BMI correlated positively with both platelet (r=0.29; p<0.001) and WBC (r=0.26; p=0.002) counts.

The percentage of metabolic syndrome risk factors present in each of the three groups is shown in Table II. By definition, the MS–0 group had no risk factors. As expected, the MS3–5 group had a higher percentage of every metabolic syndrome risk factor than the MS1–2 group. Five metabolic syndrome patients had uncomplicated type 2 diabetes.

A multivariable analysis of covariance model was used to adjust for selected variables including age, gender, ethnicity, total cholesterol, LDL cholesterol, and hemoglobin (Table III). The stepwise increase in platelet and WBC counts across the three study groups remained significant in this model, as shown in Table III and Figures 1A and 1B.

DISCUSSION

Our study shows that platelet and WBC counts are higher in patients with than without the metabolic syndrome. Both platelet and WBC counts are positively related to the number of metabolic syndrome risk factors (Figure 1A, 1B). The relationships are independent of several non-metabolic syndrome variables. Moreover, platelet and WBC counts are directly correlated, which suggests that some factor directly or indirectly related to the metabolic syndrome may be driving the elevation of both. BMI, which is strongly related to the metabolic syndrome,[36] is positively correlated with both platelet and WBC counts.

The metabolic syndrome strongly and independently increases risk for heart disease, stroke, and chronic kidney disease.[37–39] The relationship of

the metabolic syndrome to CVD risk remains after adjustment for traditional risk factors including age, BP, total cholesterol, and LDL cholesterol.[37,38] Moreover, research cited earlier in this paper implicates platelets and leukocytes in the atherothrombotic process and related complications. Thus, elevations of these two markers, which are indicative of a proinflammatory and prothrombotic state, may contribute to the independent risk associated with the metabolic syndrome.

There are a limited number of reports that have focused on platelet number and its possible association with risk factors, inflammatory markers, and atherothrombotic complications. One study linked platelets to insulin resistance. In that study, the homeostasis model assessment index of insulin resistance (HOMA-IR) was independently predicted by BMI, glycosylated hemoglobin, platelet count, and serum triglycerides.[23] Another investigation reported an increase in total platelet counts in insulin-dependent diabetics with overt nephropathy compared with those without.[24] One report suggested platelet count and function were prognostic indicators of future vascular complications in type 1 diabetics.[25] Turakhia et al.[26] noted that higher platelet counts may be a marker of coronary or systemic inflammation, which is associated with angiographic outcomes similar to that for C-reactive protein or WBC counts.

Of potential relevance to the metabolic syndrome, platelet counts can be nutritionally modulated. Rabbits fed a high-cholesterol diet showed significant increases in platelet production and mean megakaryocyte volume. These changes were associated with the development of fatty plaques in the aorta.[40] In contrast, individuals habitually consuming a diet high in fish have suppressed platelet activity and reduced platelet counts.[41]

Platelet counts can also be modified by physical activity. Physical activity is inversely related in a dose–response fashion to platelet count and leukocyte counts, C-reactive protein, fibrinogen, blood viscosity, factor VIII and IX, von Willebrand factor, fibrin D-dimer, and tissue plasminogen activator antigen.[42] These observations suggest that platelets may be one of the transducing factors by which various metabolic and lifestyle factors affect CVD outcomes. The metabolic syndrome reflects an interplay of nutritional, physical activity, behavioral, and genetic factors that may simultaneously impact several metabolic, proinflammatory, and prothrombotic risk factors.

Obesity, insulin resistance, and diabetes are linked to higher levels of several inflammatory markers including interleukin (IL)-6, which augments hepatic production of C-reactive protein.[3–5,43–46] Administration of IL-6 to healthy dogs raises platelet counts in a dose-dependent fashion,[47] but does not alter the WBC count. Elevated levels of IL-6 and platelet counts have been reported in diabetic patients with atherosclerosis. These patients also have polyploid megakaryocytes.[48] Collectively, these data raise the possibility that IL-6 may contribute to the observed relationship between obesity (BMI), insulin resistance, diabetes and elevated platelet counts observed in numerous studies.[23,25,43,48]

Previous studies indicate that the WBC count can serve as a surrogate marker for inflammation and increased CVD risk factors and events.[11–13,16–18,20,49,50] In patients in this study, leukocyte counts showed a progressive increase from the group with no metabolic syndrome risk factors to those with one or two and three to five metabolic syndrome risk factors. WBC counts correlated positively with metabolic syndrome criteria independent of several other variables (Table III). WBC counts correlated positively with platelet counts, which may suggest that a shared mechanism drives both the elevated platelet and WBC counts in patients with this syndrome. Of note, BMI, which is strongly related to the metabolic syndrome,[37] correlated positively with both platelet and leukocyte counts. The common mechanism underlying the association of obesity, the number of metabolic syndrome factors, and elevations of both platelets and WBCs are not elucidated by our study.

CONCLUSIONS

Platelet and WBC counts are higher in patients with than without the metabolic syndrome and rise in a "dose-dependent" fashion with the number of metabolic syndrome risk factors. BMI is positively related to the metabolic syndrome and to platelet and WBC counts. Our database does not contain sufficient information to identify the variables affecting the relationship of all three factors, i.e., BMI, platelet count, and WBC count. Our findings and data from the literature, however, raise the possibility that the higher platelet and leukocyte counts in patients with the metabolic syndrome reflect and contribute to the inflammatory and atherothrombotic state in these patients. Elucidating the biologic links between these associations may enhance efforts to ameliorate metabolic syndrome-related CVD risk. The data suggest that low-dose aspirin is a reasonable recommendation for most metabolic syndrome patients.

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CME Questions

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INSTRUCTIONS FOR COMPLETING THIS FORM: Read the selected paper and answer all the questions that follow. After each question there is a series of possibly correct answers. Please select the one best answer for each and place your selection on the answer grid. **YOU MUST ALSO COMPLETE THE CME EVALUATION SECTION** and return the form within 6 months of the paper's publication to receive credit. Letters of credit will be mailed to participants biannually.

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OBJECTIVE AND TARGET AUDIENCE: All primary care physicians and cardiologists are eligible to receive credit. At the conclusion of this activity, participants should be able to: 1) summarize the important points discussed in the paper reviewed; 2) identify patients to whom the paper is relevant; 3) modify management practices as new information is learned; and 4) identify deficiencies in their knowledge base.

Please Select the One Best Answer for Each and Place Your Selection on the Answer Grid.

1. Obesity has been linked with which of the following conditions?
   A __ A proinflammatory state
   B __ A prothrombotic state
   C __ Insulin resistance
   D __ All of the above

2. Which of the following describes the aim of the study?
   A __ To examine the effects of metabolic syndrome on platelet function
   B __ To examine the relationship of metabolic syndrome to platelet and leukocyte counts
   C __ To examine the effects of metabolic syndrome to the incidence of cardiac events
   D __ To examine the effects of obesity on the incidence of metabolic syndrome

3. Which of the following statements regarding the baseline characteristics of the study population is false?
   A __ Caucasian subjects were more likely to have metabolic syndrome than African Americans
   B __ The presence of metabolic syndrome was associated with a higher systolic blood pressure
   C __ The presence of metabolic syndrome was associated with lower high-density lipoprotein cholesterol
   D __ Increasing age was associated with the presence of metabolic syndrome

4. Which of the following was the mean body mass index of patients without metabolic syndrome risk factors?
   A __ 23 kg/m^2
   B __ 25 kg/m^2
   C __ 32 kg/m^2
   D __ 39 kg/m^2

5. The results of this study demonstrated that the presence of metabolic syndrome criteria was associated with:
   A __ Decreased platelet and white blood cell counts
   B __ Increased platelet and white blood cell counts
   C __ Decreased platelet and increased white blood cell counts
   D __ Increased platelet and decreased white blood cell counts

CME Answers are available from *The Journal of Clinical Hypertension* page at www.lejacq.com

CME Answer Grid

Answer the questions from the previous page by selecting the best choice of A, B, C, or D

Questions: 1.__ 2.__ 3.__ 4.__ 5.__

CME Evaluation

	Agree				Disagree
1. My knowledge was enhanced by this activity.	1.__	2.__	3.__	4.__	5.__
2. The activity helped to clarify issues specific to hypertensive patients.	1.__	2.__	3.__	4.__	5.__
3. The information obtained from this exercise will have an impact on my care of patients.	1.__	2.__	3.__	4.__	5.__
4. The format of the exercise was useful.	1.__	2.__	3.__	4.__	5.__

5. Suggestions for future topics:

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Re: Jesri A, Okonofua EC, Egan BM. Platelet and white blood cell counts are elevated in patients with the metabolic syndrome. *J Clin Hypertens (Greenwich)*. 2005;7:705–711.

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