Associations between White Blood Cell Count and Features of the Metabolic Syndrome in Japanese Male Office Workers

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Abstract: We assessed the association of white blood cell (WBC) count with different components of the metabolic syndrome (MS) in 5275 Japanese male office workers aged 23–59 years. There was a significantly crude correlation between WBC count and body mass index, systolic and diastolic blood pressures, total cholesterol, high-density lipoprotein cholesterol (negative), triglycerides, fasting plasma glucose, and uric acid (all P<0.001). After controlling for potential confounding factors, the adjusted means of WBC count were significantly higher in subjects with each feature of the MS (obesity, hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol levels, hypertriglyceridemia, high fasting plasma glucose levels, and hyperuricemia) (all P<0.005). The adjusted WBC count increments in subjects with 1, 2, 3, 4, and ≥5 features of the MS were 0.28, 0.45, 0.68, 0.76, and 1.40×10⁹ cells/l, respectively, compared with the subjects without features of the MS (P for trend<0.001). The adjusted means of WBC count increased significantly with the increasing number of features of the MS in both non-smokers and smokers (both P<0.001). These data indicate a strong association between WBC count and a number of disorders characterizing the MS independent of cigarette smoking among Japanese men.

Key words: White blood cell count, Metabolic syndrome, Cross-sectional study, Japanese men

The metabolic syndrome (MS) is characterized by insulin resistance accompanied by the cluster of a number of risk factors for coronary heart disease (CHD) (i.e. obesity, glucose metabolism disturbances, abnormal lipids, and high blood pressure)¹. Although both hereditary and environmental factors contribute to the development of the MS, little is known about the underlying pathogenic mechanisms. However, a central role has been attributed to the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6, supported by the fact that both are produced in substantial amounts by human adipose tissue²–³. Both cytokines impair stimulated glucose uptake in a variety of cells, and their concentrations are raised in subjects with type 2 diabetes, particularly in those with features of the insulin resistance. The lipid pattern of high triglycerides and low high-density lipoprotein (HDL) cholesterol is a feature of inflammation and, more specifically, TNF-α⁴. Inflammation may contribute to vascular complications of hypertension by increasing microvascular capillary resistance, release of vasoconstrictor substances, and initiation of platelet aggregation⁵–⁷. Epidemiological evidence is accumulating that increased, albeit normal, white blood cell (WBC) counts correlate well with CHD risk factors, subclinical atherosclerosis, and the occurrence of CHD⁸–⁹. The significance of the association between WBC count and CHD is not clear among Japanese, nor is there

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much information available concerning the relationship between WBC count and other risk factors for CHD. In this report on a cross-sectional study based on annual health examinations at the workplace, we examined the association of WBC count with components of the MS in Japanese male office workers, with special reference to clustered features of the MS.

A survey to evaluate the association between WBC count and features of the MS was conducted in May 1996 among employees of A Corporation, which is one of the biggest building contractors in Japan. The surveillance population in May 1996 consisted of 5275 Japanese male office workers aged 23–59 years. The participation rate was 99.6%, and there were no acutely ill subjects. The survey included medical history; a questionnaire on alcohol intake and smoking; physical examination; anthropometric measurements; blood pressure measurement; and collection of blood samples for laboratory analysis. The participants were asked to fast for at least 8 hours and to avoid heavy physical activity for more than 2 hours before the examinations. Medical history and history of use of prescription drugs were assessed by the examining physicians. Data on alcohol intake and cigarette smoking were obtained by interview. An interviewer assessed the usual weekly intake of alcohol in units of ‘go’ (a traditional Japanese unit of measurement, by volume, corresponding to 23 g of ethanol), which were converted to grams of ethanol per day. One go is 180 ml of Sake (Japanese rice wine), and it corresponds to one bottle (663 ml) of beer, two single shots (75 ml) of whisky, or two glasses (180 ml) of wine. The questionnaire asked about smoking habits (never, past, or current smoker); past or current smokers were asked about the number of cigarettes smoked daily and the duration of smoking in years. In this study, past and never smokers were combined, and the number of cigarettes smoked daily was used in the analysis. Body mass index (BMI) was used as a measure of overall obesity and was calculated as body weight/height$^2$ (kg/m$^2$). Blood pressures (BPs) were measured by trained observers using standard mercury sphygmomanometers on the right arm of seated participants who had rested for 5 minutes. While the participant was fasting, blood samples were drawn from an antecubital vein. Serum total cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose, and uric acid were measured with Olympus AU-5200 equipment (Olympus Japan Co, Ltd., Tokyo, Japan) at FALCO Biosystems Tokyo Ltd. (Tokyo, Japan). WBC counts were determined by using a Sysmex E-4000 autoanalyzer (Toa Medical Electronics Co, Ltd., Tokyo, Japan).

Characteristics of the MS were defined by the following cutoff limits$^{10-12}$: BMI $\geq 25$ kg/m$^2$, systolic BP $\geq 140$ mm Hg, diastolic BP $\geq 90$ mm Hg, total cholesterol $\geq 5.69$ mmol/l (220 mg/dl), HDL cholesterol $< 1.03$ mmol/l (40 mg/dl), triglycerides $\geq 1.69$ mmol/l (150 mg/dl), fasting plasma glucose $\geq 6.1$ mmol/l (110 mg/dl), and uric acid $\geq 416$ µmol/l (7.0 mg/dl). Subjects were considered to have the respective features of the MS if they had medication for hypertension, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, or hyperuricemia. Hypertension was also defined as systolic BP $\geq 140$ mmHg and/or diastolic BP $\geq 90$ mmHg or receipt of antihypertensive medications.

As for analytical procedures, Spearman’s correlation analyses were performed between values for WBC count and components of the MS. Mean values of WBC count were calculated across categorized features of the MS, and all mean values were adjusted for age (years), cigarette smoking (cigarettes/day), alcohol consumption (g/day of ethanol), and the remaining components of the MS (BMI [kg/m$^2$], systolic BP [mm Hg], total cholesterol [mmol/l], HDL cholesterol [mmol/l], triglycerides [mmol/l], fasting plasma glucose [mmol/l], and uric acid [µmol/l]) by means of a multiple linear regression model. Subjects with a different number of components of the MS were grouped into six subgroups (graded from 0 through ≥ 5). Means of WBC count were then calculated for each cluster by means of a multiple linear regression model, with adjustment for age, cigarette smoking, and alcohol consumption. All tests were performed at a nominal 5% level and were computed using SPSS software, version 10.0J for Windows.

Table 1 shows the distribution of selected variables and Spearman’s rank correlation coefficients with WBC count among 5275 Japanese male office workers. There was a statistically significant positive correlation between WBC count and age, BMI, systolic BP, diastolic BP, total cholesterol, triglycerides, fasting plasma glucose, uric acid, and the number of cigarettes smoked per day, and a significant negative correlation of WBC count with HDL cholesterol. The strongest correlation ($r=0.426$) was observed between WBC count and the number of cigarettes smoked per day.

Table 2 shows the adjusted means and differences of WBC count for categorized components of the MS. After controlling for age, smoking, alcohol intake, and all other components of the MS, the adjusted means were higher in subjects with a BMI $\geq 25$ kg/m$^2$, systolic BP $\geq 140$ mm Hg or medication for hypertension, diastolic BP $\geq 90$ mm Hg or medication for hypertension, total cholesterol $\geq 5.69$ mmol/l or medication for dyslipidemia, HDL cholesterol $< 1.03$ mmol/l, triglycerides $\geq 1.69$ mmol/l or medication for
dyslipidemia, fasting plasma glucose ≥ 6.1 mmol/l or medication for diabetes, and uric acid ≥ 416 µmol/l or medication for hyperuricemia.

Table 3 shows the adjusted means and differences of WBC count for clustered components of the MS: obesity, hypertension, hypercholesterolemia, low HDL cholesterol levels, hypertriglyceridemia, high fasting plasma glucose levels, and hyperuricemia. Only 37.6% of the total population subjects were free of all seven disorders, and 6.9% had more than four features of the MS. Compared with the subjects
with the presence of 0 features of the MS, the WBC count increments in subjects grouped according to the presence of 1, 2, 3, 4, and ≥ 5 features of the MS were 0.28, 0.45, 0.68, 0.76, and 1.40 × 10^9 cells/l, respectively, with a statistically highly significant trend (P<0.001).

To assess the effect of cigarette smoking on the association between WBC count and clustered features of the MS, the adjusted means and differences of WBC count for clustered components of the MS were also calculated according to smoking status (data not shown). Among non-/ex-smokers, compared with the subjects without features of the MS (mean adjusted for age and alcohol intake, 5.59 × 10^9 cells/l), the WBC count increments in subjects grouped according to the presence of 1, 2, 3, 4, and ≥ 5 features of the MS were 0.31, 0.56, 0.76, 0.85, and 1.28 × 10^9 cells/l (P for trend < 0.001). Among current smokers, the respective WBC count increments compared with the subjects without features of the MS (mean adjusted for age, cigarette smoking, and alcohol intake, 6.96 × 10^9 cells/l) were 0.27, 0.37, 0.65, 0.72, and 1.53 × 10^9 cells/l (P for trend < 0.001). These findings suggest that a higher WBC count is related to a more atherogenic profile independent of cigarette smoking. While traditionally used as an indication of current infection, a high WBC count could serve as a predictor of future CHD and thus may be an important addition to risk assessment at annual health examinations at the workplace. Furthermore, a change in WBC count may be valuable in assessing changes in risk factors for CHD.

The mechanism of how WBC count increases the risk of the MS, however, remains to be elucidated. IL-6 has been shown to be released by adipose tissue, and this release is greater in obese subjects. Furthermore, IL-6 increases postprandially, in parallel to glucose and insulin levels in the interstitial fluid of subcutaneous adipose tissue. TNF-α produces insulin resistance by influencing the function of insulin receptor and alters β-cell function of free-fatty-acid production. Moreover, inflammation may alter the endothelial function and rheological properties with an increased tendency to adhere to vascular endothelium, and may result in capillary leukocytosis and subsequent increased vascular resistance. Because WBCs are increased by cytokines, elevated, albeit normal, WBC counts could be due to the presence of a subclinical inflammatory reaction, and may contribute to the development of the MS. However, the cross-sectional study design lacks information on the time sequence of events and, thus, does not permit identification of causal relationships. Further studies should be needed to clarify whether WBC count, although within the normal range, contributes to the development of the MS.

In conclusion, our data indicate that WBC count is strongly associated with the number of disorders characterizing the MS. Although the WBC count is one of the most commonly performed clinical laboratory tests, much remains to be learned about its value as a predictor rather than merely an indicator of disease.

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