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# Association of white blood cell count with metabolic syndrome in patients undergoing peritoneal dialysis

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**Abstract**

Metabolic syndrome is associated with an increased risk of diabetes and cardiovascular disease. Although some data suggest that the prevalence of metabolic syndrome is higher in patients undergoing peritoneal dialysis (PD), the factors related to this increased risk are not well elucidated. We therefore examined whether peripheral white blood cell (WBC) count is correlated with the risk of metabolic syndrome in nondiabetic PD patients. We enrolled 104 nondiabetic PD patients without current infections or chronic inflammatory diseases. Complete blood cell count, anthropometry, blood pressure, fasting glucose, insulin, and lipid profiles were measured. *Metabolic syndrome* was defined in accordance with the National Cholesterol Education Program (Adult Treatment Panel III) criteria. Metabolic syndrome was present in 49 patients (47.1%). Patients with metabolic syndrome had a higher WBC count and high-sensitivity C-reactive protein level. As the number of metabolic syndrome components increased, WBC count increased significantly. White blood cell count was significantly positively correlated with body mass index, insulin, homeostasis model assessment of insulin resistance, and triglyceride and negatively correlated with high-density lipoprotein cholesterol. The risk of metabolic syndrome increased significantly with a higher WBC count, resulting in an adjusted odds ratio of 1.65 (per $10^3/\mu$L increase, $P = .002$). These findings demonstrate that metabolic syndrome is prevalent among nondiabetic PD patients and that WBC count is strongly associated with metabolic syndrome and its components.


## 1. Introduction

*Metabolic syndrome* is defined as the coexistence of risk factors that include high blood pressure (BP), elevated triglycerides (TG), low high-density lipoprotein (HDL) concentrations, impaired glucose tolerance, and excess abdominal fat. Metabolic syndrome and each of its components are well-known risk factors for cardiovascular disease and type 2 diabetes mellitus [1].

Chronic low-grade inflammation has been proposed to be related to the development of both insulin resistance and atherogenesis [2]. Significant associations between inflammation and type 2 diabetes mellitus, central fat accumulation, insulin resistance, and dyslipidemia have been described [3], supporting the notion that inflammation is closely related to lipid and glucose metabolism. One hypothesis regarding the relationship between inflammation and insulin resistance states that chronic inflammation induces obesity and glucose intolerance. Another concept is that metabolic disturbances are proinflammatory and by themselves stimulate the inflammatory process [4].

Inflammatory markers such as C-reactive protein (CRP) have been found to be associated with metabolic disturbances in the general population and in patients undergoing hemodialysis [5,6]. Given that white blood cell (WBC) count is a conventional and simple measure of systemic inflammation, reports have previously demonstrated the relationship between WBC count and metabolic syndrome in the general population [7]. However, the association between WBC count and metabolic syndrome in patients with end-stage renal disease (ESRD) has rarely been explored. In this study, therefore, we investigated the relationship between WBC count and metabolic syndrome in nondiabetic ESRD patients

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undergoing peritoneal dialysis (PD), who are vulnerable to hyperglycemia and weight gain due to excessive glucose absorbed from the dialysate [8,9].

## 2. Subjects and methods

### 2.1. Patient population

This study is a cross-sectional observational study of 104 ESRD patients undergoing PD. Patients were recruited from a single Korean dialysis center and were followed up at Yonsei University Health System in Seoul, Korea. We excluded patients who were younger than 18 years, who had maintained PD for fewer than 3 months, who had overt infections during the last 3 months before entry or within 1 month after the enrollment, or who had a history of malignancy or other chronic inflammatory disease such as rheumatoid arthritis or systemic lupus erythematosus. To reduce confounding factors of glucose and lipid metabolism, diabetic patients were excluded.

Demographic data were obtained by a senior nursing clinician. Height and body weight were measured at the time of blood sampling. Body mass index (BMI) was calculated as weight divided by height squared. Systolic and diastolic blood pressures (SBP and DBP) were measured by nursing staff using standard mercury sphygmomanometers on the right arm of seated participants who had rested for at least 5 minutes. To simulate the actual dialysis condition, all patients had a full abdomen at the time of blood sampling. Blood samples for laboratory measurements were drawn from the antecubital vein after the first 2 hours of PD exchange with 1.5% dextrose dialysate in an overnight fasting state. The preceding overnight dwell was regulated to 1.5% dextrose dialysate to minimize and standardize the effect of glucose load. Informed consent was obtained by all participants before study entry.

### 2.2. Laboratory measurements

Plasma was separated from blood within 30 minutes and stored at −70°C until analysis. Fasting glucose was measured by the glucose oxidase method; and insulin concentration, by immunoradiometric assay (RIABEAD II kit; Abbott, Japan; intraassay coefficient of variation, 1.2%-1.9%; interassay coefficient of variation, 1.4%-3.3%). Serum total cholesterol, HDL cholesterol, and TG concentrations were measured by an autoanalyzer with enzymatic colorimetric method (Hitachi 7150; Hitachi, Tokyo, Japan); and serum albumin levels, by the photometric bromocresol green complex method using a Hitachi 917 (Roche Diagnostics, Indianapolis, IN). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. High-sensitivity CRP (hsCRP) levels were measured using a BN II analyzer (Dade Behring; Newark, DE) by a latex-enhanced immunonephelometric method. Total WBC count was determined by an auto-analyzer (ADIVA 120; Bayer, Leverkusen, Germany).

### 2.3. Metabolic syndrome and estimation of insulin resistance

*Metabolic syndrome* was diagnosed using the National Cholesterol Education Program (Adult Treatment Panel [ATP] III) criteria [10], which define it as the presence of 3 or more of the following criteria: (1) SBP of at least 130 mm Hg and/or DBP of at least 85 mm Hg, (2) serum TG of at least 150 mg/dL, (3) serum HDL cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women, (4) fasting plasma glucose of at least 110 mg/dL, and (5) abdominal obesity. *Abdominal obesity* was defined based on BMI rather than on waist circumference measures. Participants with a BMI of at least 25 $kg/m^2$ were classified as having central obesity according to the World Health Organization Western Pacific Regional Office BMI criteria [11]. The modified ATP III definition used has been previously validated to determine metabolic syndrome better than the WHO criteria among Koreans [12].

Insulin resistance was calculated by the homeostasis model assessment (HOMA-IR) using the following formula:

$$\text{HOMA}-\text{IR} = [\text{fasting insulin (in microunits per milliliter)} \times \text{fasting serum glucose (in millimoles per liter)}/22.5].$$

### 2.4. Statistical analysis

Statistical analysis was performed using SPSS software for Windows, version 13.0 (SPSS, Chicago, IL). All data were expressed as mean ± SD. Because of the log-normally distributed values of insulin, TG, hsCRP, and HOMA-IR, their natural log values were used for analysis. Geometric means for all log-normally distributed continuous variables were calculated and reported with 95% confidence intervals (CIs). Because dialysis duration was also not normally distributed, median values with ranges were reported. To compare differences between patients with and without metabolic syndrome, Student *t* test or Mann-Whitney *U* test was used for continuous variables and the $\chi^2$ test was used for categorical variables. White blood cell counts present across the numbers of metabolic syndrome components were compared by the *P* value for trend test. Pearson correlation analysis was performed to estimate the correlation between WBC count and other variables. Odds ratios (ORs) of having metabolic syndrome with increasing WBC count and hsCRP level were calculated by logistic regression. Confounders for adjustment included age, male sex, and a history of smoking. In addition, WBC count and hsCRP concentrations were adjusted for each other. Receiver operating characteristic (ROC) analysis was conducted to determine the power of WBC count in diagnosing metabolic syndrome. Area under the curve was calculated for WBC count and hsCRP levels. A *P* value less than .05 was considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

Baseline patient characteristics are listed in Table 1. The mean age was 51.6 ± 13.2 years, 47 patients (45.2%) were male, and the mean BMI was 24.1 ± 3.2 kg/m$^2$. The median continuous ambulatory PD duration was 83.6 (6.7-210.4) months, and 79 patients (76.0%) were on erythropoietin treatment. The mean fasting glucose levels were 92.1 ± 14.4 mg/dL, and 22 patients had fasting glucose levels greater than 100 mg/dL. All patients were prescribed continuous ambulatory PD with a daily dialysate volume of 8 L.

### 3.2. Comparison between patients with and without metabolic syndrome

Based on the presence of metabolic syndrome, patients were divided into 2 groups. Metabolic syndrome was present in 49 patients (47.1%). Body mass index (22.8 ± 2.7 vs 25.4 ± 3.1 kg/m$^2$, $P < .001$), fasting glucose (87.4 ± 11.9 vs 97.5 ± 15.2 mg/dL, $P < .001$), HOMA-IR (1.2, 95% CI: 1.1-1.7 vs 2.4, 95% CI: 1.9-3.2, $P < .001$), and TG levels (98.5 mg/dL, 95% CI: 89.6-122.5 vs 183.5 mg/dL, 95% CI: 150.3-219.2, $P < .001$) were significantly higher, whereas HDL cholesterol levels (49.2 ± 12.4 vs 39.7 ± 11.1 mg/dL, $P < .001$) were significantly lower in patients with metabolic syndrome. In contrast, there were no differences in SBP (147.4 ± 22.8 vs 147.4 ± 16.6 mm Hg, $P = .98$), DBP (85.9 ± 8.0 vs 88.4 ± 8.4 mm Hg, $P = .13$), and the proportion of patients with smoking history (25.5% vs 36.7%, $P = .29$) or the proportion of current smokers (16.3% vs 10.9%, $P = .57$) between the 2 groups. The total dose of erythropoietin given was comparable between patients with and without metabolic syndrome (5265.3 ± 3334.0 vs 5309.1 ± 3447.3 U/wk, $P = .95$).

White blood cell count (5715.1 ± 1546.3 vs 7132.7 ± 1534.2/μL, $P < .001$), absolute neutrophil count (ANC) (3568.6 ± 1130.2 vs 4632.0 ± 1411.9/μL, $P < .001$), lymphocyte count (1312.5 ± 460.2 vs 1662.0 ± 640.2/μL, $P = .002$), and monocyte count (301.6 ± 144.4 vs 397.5 ± 198.9/μL, $P = .006$) were significantly higher in the metabolic syndrome group, whereas there were no differences in eosinophil (331.4 ± 277.7 vs 375.4 ± 323.1/μL, $P = .46$) and basophil counts (33.6 ± 24.1 vs 38.9 ± 19.1/μL, $P = .21$) between the 2 groups. High-sensitivity CRP concentrations (0.78 mg/dL, 95% CI: 0.54-1.14 vs 1.66 mg/dL, 95% CI: 1.13-2.43, $P = .01$) were also significantly higher in patients with metabolic syndrome (Table 2).

### 3.3. WBC count according to the number of metabolic syndrome components

When the subjects were divided into 6 groups according to the number of metabolic syndrome components, WBC

Table 1
Demographic and baseline clinical data of study participants (N = 104)

| | |
|---|---|
| Age (y) | 51.6 ± 13.2 |
| Sex (male/female) | 47/57 |
| Smoking history (ever, %) | 32 (30.8) |
| BMI (kg/m$^2$) | 24.1 ± 3.2 |
| Duration of PD (mo) | 83.6 (6.7-210.4) |
| SBP (mm Hg) | 147.4 ± 19.9 |
| DBP (mm Hg) | 88.0 ± 13.0 |
| Primary kidney disease | |
| Hypertension | 25 (24.0%) |
| Glomerulonephritis | 39 (37.5%) |
| Others | 10 (9.6%) |
| Unknown | 30 (28.8%) |
| Fasting glucose (mg/dL) | 92.1 ± 14.4 |
| Insulin (μU/mL) | 7.5 (6.9-9.7) |
| HOMA-IR | 1.7 (1.6-2.3) |
| WBC count (/μL) | 6382.7 ± 1703.3 |
| Hematocrit (%) | 30.6 ± 5.3 |
| BUN (mg/dL) | 60.2 ± 17.9 |
| Creatinine (mg/dL) | 13.0 ± 3.3 |
| Albumin (g/dL) | 3.5 ± 0.4 |
| hsCRP (mg/dL) | 1.12 (0.85-1.47) |
| Total cholesterol (mg/dL) | 190.9 ± 37.9 |
| TG (mg/dL) | 132.0 (124.6-164.7) |
| HDL cholesterol (mg/dL) | 44.6 ± 12.7 |
| LDL cholesterol (mg/dL) | 112.9 ± 35.6 |
| Calcium (mg/dL) | 9.4 ± 1.0 |
| Phosphate (mg/dL) | 4.8 ± 1.2 |

Data are expressed as mean ± SD or geometric mean (95% CI); median value (range) is expressed for duration of PD. BUN indicates blood urea nitrogen.

Table 2
Comparison of clinical and biochemical variables in patients with and without metabolic syndrome

| | Without MS (n = 55) | With MS (n = 49) |
|---|---|---|
| Age (y) | 50.4 ± 10.4 | 53.0 ± 10.2 |
| Sex (male/female) | 29/26 | 18/31 |
| Smoking | | |
| Ever (%) | 14 (25.5) | 18 (36.7) |
| Current (%) | 6 (10.9) | 8 (16.3) |
| BMI (kg/m$^2$) | 22.8 ± 2.7 | 25.4 ± 3.1* |
| Duration of PD (mo) | 83.6 (19.1-210.4) | 84.0 (6.7-163.8) |
| SBP (mm Hg) | 147.4 ± 22.8 | 147.4 ± 16.6 |
| DBP (mm Hg) | 85.9 ± 8.0 | 88.4 ± 8.4 |
| Fasting glucose (mg/dL) | 87.4 ± 11.9 | 97.5 ± 15.2* |
| Insulin (μU/mL) | 5.8 (4.8-7.5) | 10.2 (8.1-13.0)* |
| HOMA-IR | 1.2 (1.1-1.7) | 2.4 (1.9-3.2)* |
| WBC count (/μL) | 5715.1 ± 1546.3 | 7132.7 ± 1534.2* |
| ANC (/μL) | 3568.6 ± 1130.2 | 4632.0 ± 1411.9* |
| ALC (/μL) | 1312.5 ± 460.2 | 1662.0 ± 640.2* |
| AMC (/μL) | 301.6 ± 144.4 | 397.5 ± 198.9* |
| AEC (/μL) | 331.4 ± 277.7 | 375.4 ± 323.1 |
| ABC (/μL) | 33.6 ± 24.1 | 38.9 ± 19.1 |
| hsCRP (mg/dL) | 0.78 (0.54-1.14) | 1.66 (1.13-2.43)* |
| Total cholesterol (mg/dL) | 184.0 ± 39.7 | 198.4 ± 34.8 |
| TG (mg/dL) | 98.5 (89.6-122.5) | 183.5 (150.3-219.2)* |
| HDL cholesterol (mg/dL) | 49.2 ± 12.4 | 39.7 ± 11.1* |
| LDL cholesterol (mg/dL) | 115.2 ± 31.6 | 111.3 ± 38.5 |
| Erythropoietin (U/wk) | 5309.1 ± 3447.3 | 5265.3 ± 3334.0 |

Data are expressed as mean ± SD or geometric mean (95% CI); median value (range) is expressed for duration of PD. MS indicates metabolic syndrome; ALC, absolute lymphocyte count; AEC, absolute eosinophil count; ABC, absolute basophil count.

* $P < .05$ vs group without MS.

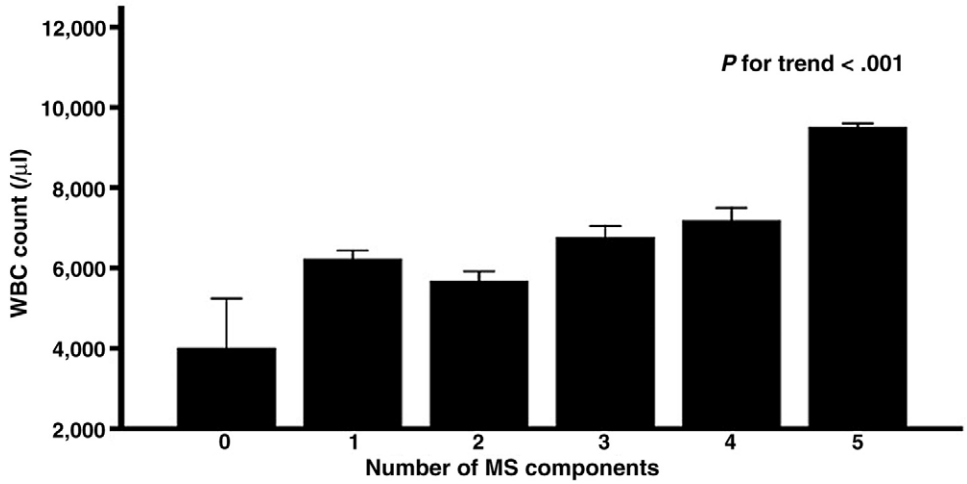


Fig. 1. White blood cell count according to the number of metabolic syndrome components. Each bar shows the mean and its standard error. White blood cell counts increased in parallel with the number of metabolic syndrome components ($P$ for trend < .001).

count increased significantly as the number of components increased ($P$ for trend < .001, Fig. 1).

### 3.4. Correlation between WBC count and metabolic syndrome components

There were significant positive correlations between WBC count and BMI ($r$ = 0.25, $P$ = .01), insulin concentration ($r$ = 0.36, $P$ < .001), HOMA-IR ($r$ = 0.36, $P$ < .001), and TG level ($r$ = 0.33, $P$ = .001). In contrast, WBC count was negatively correlated with HDL cholesterol concentration ($r$ = −0.36, $P$ < .001). There were no significant correlations between WBC count and SBP ($r$ = −0.09, $P$ = .35), DBP ($r$ = −0.03, $P$ = .82), duration of PD ($r$ = 0.11, $P$ = .26), fasting glucose levels ($r$ = 0.17, $P$ = .08), and the total dose of erythropoietin given ($r$ = 0.13, $P$ = .89). When further analyses were performed with differential WBC counts, ANC positively correlated with BMI ($r$ = 0.27, $P$ = .01), HOMA-IR ($r$ = 0.23, $P$ = .02), and TG levels ($r$ = 0.27, $P$ = .01) and negatively correlated with HDL cholesterol concentrations ($r$ = −0.36, $P$ < .001). Absolute monocyte counts (AMCs) also had a direct association with BMI ($r$ = 0.26, $P$ = .01) and HOMA-IR ($r$ = 0.20, $P$ = .04), whereas there was a positive association between lymphocyte counts and serum albumin levels ($r$ = 0.27, $P$ = .01) (Table 3).

Table 3
Univariate relations between WBC, neutrophil, lymphocyte, monocyte, and eosinophil counts with selected anthropometric and metabolic characteristics

| | WBC | ANC | ALC | AMC | AEC |
|---|---|---|---|---|---|
| Age (y) | 0.05 | 0.06 | 0.04 | 0.29† | 0.06 |
| BMI (kg/m$^2$) | 0.25* | 0.27* | 0.15 | 0.26* | −0.13 |
| Duration of PD (mo) | 0.11 | 0.07 | −0.09 | 0.06 | 0.06 |
| SBP (mm Hg) | −0.09 | −0.07 | −0.07 | −0.01 | 0.02 |
| DBP (mm Hg) | −0.03 | −0.12 | 0.08 | −0.04 | 0.28 |
| Fasting glucose (mg/dL) | 0.17 | 0.18 | 0.11 | 0.29† | −0.08 |
| Insulin (μU/mL) | 0.36† | 0.24* | 0.29 | 0.18 | 0.06 |
| HOMA-IR | 0.36† | 0.23* | 0.28† | 0.20* | 0.04 |
| Albumin (g/dL) | 0.05 | −0.06 | 0.27* | −0.02 | 0.03 |
| hsCRP (mg/dL) | 0.33* | 0.40† | −0.10 | 0.15 | 0.06 |
| Total cholesterol (mg/dL) | 0.05 | 0.08 | 0.12 | −0.03 | −0.07 |
| TG (mg/dL) | 0.33† | 0.27* | 0.18 | 0.03 | 0.08 |
| HDL cholesterol (mg/dL) | −0.36† | −0.36† | −0.01 | 0.01 | −0.09 |
| LDL cholesterol (mg/dL) | 0.001 | 0.06 | 0.001 | −0.14 | −0.18 |

* $P$ < .05.
† $P$ < .01.

### 3.5. WBC count as an independent factor of metabolic syndrome

Multivariate analysis revealed that both WBC count (OR: 1.80, 95% CI: 1.34-2.41, $P$ < .001) and hsCRP level (OR: 1.10, 95% CI: 1.03-1.18, $P$ = .008) were significant independent factors associated with metabolic syndrome, even after adjusting for age, sex, and smoking history (adjusted WBC count OR: 1.65, 95% CI: 1.20-2.28, $P$ = .002; hsCRP level OR: 1.11, 95% CI: 1.02-1.20, $P$ = .01) (Table 4). Interestingly, when values were further adjusted for hsCRP level, WBC count remained an independent factor associated with metabolic syndrome (OR: 1.58, 95% CI: 1.13-2.20, $P$ = .01); conversely, the significance of hsCRP level disappeared with adjustment for WBC count (OR: 1.10, 95% CI: 0.98-1.17, $P$ = .15). White blood cell count

Table 4
WBC count, hsCRP, and their relative importance to metabolic syndrome

| | WBC (per $10^3$/μL increase) | | hsCRP (per $10^{-1}$-mg/dL increase) | |
|---|---|---|---|---|
| | OR | $P$ value | OR | $P$ value |
| Crude | 1.80 (1.34-2.41) | <.001 | 1.10 (1.03-1.18) | .008 |
| Model 1 | 1.65 (1.20-2.28) | .002 | 1.11 (1.02-1.20) | .01 |
| Model 2 | 1.58 (1.13-2.20) | .01 | 1.10 (0.98-1.17) | .15 |

Model 1: adjusted for age, sex, and smoking history; model 2: plus adjustment for above risk factors, white blood cell count, and hsCRP concentrations were adjusted for each.

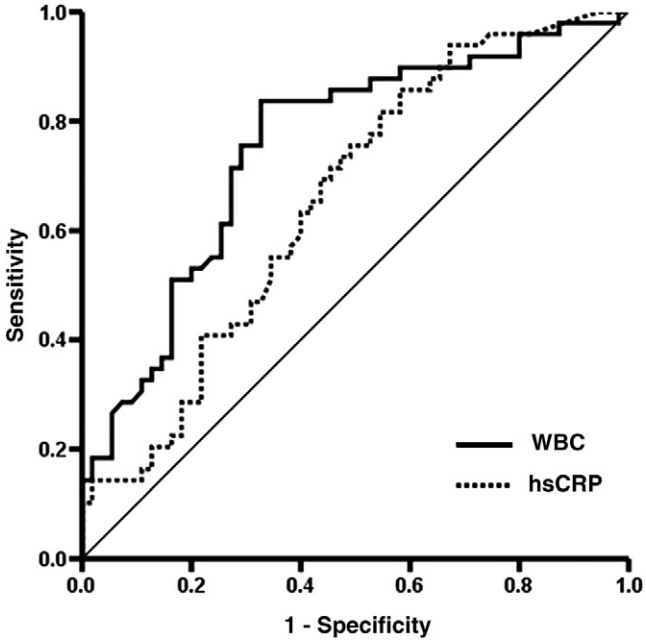


Fig. 2. Receiver operating characteristic curve for WBC and hsCRP. White blood cell provided higher diagnostic accuracy for metabolic syndrome, with the area under the ROC curve for WBC being 75.3% ($P < .001$) and that for hsCRP being 65.6% ($P = .006$).

provided a higher diagnostic accuracy for metabolic syndrome compared with hsCRP levels (Fig. 2), where the area under the ROC curve was 75.3% for WBC count and 65.6% for hsCRP levels ($P = .006$). The cutoff value of WBC count greater than $6 \times 10^3/\mu L$ provided a sensitivity of 84% and specificity of 67% to diagnose metabolic syndrome.

## 4. Discussion

This study demonstrated that peripheral total WBC count, even when within the reference range, is closely related to metabolic syndrome. In addition, the results of the present study show that WBC is independently associated with metabolic syndrome in nondiabetic PD patients even after controlling for age, sex, smoking history, and hsCRP level.

There has recently been a striking increase in the prevalence of metabolic syndrome in both developed and developing countries [13]. The prevalence of metabolic syndrome has been reported to be 20% to 30% in the general population and even higher in patients with certain diseases [14]. Because metabolic syndrome is not only a cause of chronic kidney disease, but also a consequence of impaired renal function, the prevalence of metabolic syndrome is higher in patients with ESRD [15,16]. In this study, we found that 47.1% of nondiabetic PD patients had metabolic syndrome, which was comparable with a report by Johnson et al [15] (53.1%), although their study enrolled both diabetic and nondiabetic PD patients. Recently, however, Jiang et al [17] found a higher prevalence of metabolic syndrome (69.2%) in nondiabetic Chinese PD patients than our study. The difference in the diagnostic criteria of metabolic syndrome used in each study may contribute to these disparities.

It has been previously suggested that the glucose absorbed from the dialysate results in hyperglycemia and weight gain in PD patients [9]. In addition, several studies have shown that dyslipidemia is aggravated after PD commencement and that lipid levels increase along with the duration of PD treatment [18]. In the present study, however, PD duration was not a factor associated with metabolic syndrome. Because the median PD duration of our subjects was more than twice as long than in previous studies, we infer that the influence of PD duration on metabolic syndrome may become weak when the PD duration surpasses a certain length of time. On the other hand, we found that HDL cholesterol levels were low in patients both with and without metabolic syndrome. Because previous study has shown that glucose load is associated with HDL cholesterol levels in the general population [19], we surmise that low HDL cholesterol levels in PD patients were partly attributed to the glucose absorbed from the dialysate.

Cardiovascular disease is the leading cause of morbidity and mortality in patients undergoing dialysis [20]. Because accumulating evidence has shown that metabolic syndrome, inflammation, and atherosclerosis are closely related [21], early detection of metabolic syndrome and elucidation of its independent factors in ESRD patients would be a cost-effective strategy to prevent cardiovascular disease. Numerous studies have demonstrated that inflammatory markers such as CRP and fibrinogen are associated with metabolic syndrome as well as cardiovascular mortality [22]. White blood cell count is another index representing systemic inflammation whose measurement is inexpensive, reliable, and routinely ordered in clinics and health surveillance settings. Since the early 1970s, WBC counts have been found to be related to the development of cardiovascular disease and metabolic syndrome in both the general population and in ESRD patients [23-25]. Hoffman et al [23] showed that the value of WBC count in predicting cardiovascular disease was similar to serum cholesterol and BP. Moreover, recent studies have shown that WBC count was associated with metabolic syndrome in adults and children receiving routine health examinations [7,26]. Furthermore, circulating macrophage levels have been shown to correlate with fat mass and to predict outcome in patients with chronic kidney disease [27]. In this study, we found that WBC count was a significant independent factor associated with metabolic syndrome in nondiabetic PD patients. There were significant correlations between WBC count, TG level, and insulin resistance. These findings suggest that WBC count may reflect a disordered state of lipid and glucose metabolism in PD patients and that WBC count measurement could be a simple way to assess the

presence of metabolic syndrome in nondiabetic ESRD patients undergoing PD.

What is the underlying mechanism of the relationship between leukocytosis and metabolic syndrome? Advanced glycation end products and reactive oxygen species have been reported to activate leukocytes [28,29]. In addition, leptin, an adipocytokine, has been shown to stimulate leukocyte proliferation and differentiation as well as to induce erythropoiesis possibly by direct bone marrow stimulation [30,31]. Recently, circulating mononuclear cells in obese subjects, in which insulin receptor phosphorylation is suppressed, have also been reported to be in a proinflammatory state [32,33]. On the contrary, leukocytes express cytokines related to glucose homeostasis and lipid metabolism such as adenosine triphosphate–binding cassette transporter A1, resistin, and visfatin [34,35]. These findings suggest that leukocytosis may both contribute to and result from metabolic syndrome.

C-reactive protein, a well-known inflammatory marker, has been postulated as an independent risk factor of cardiovascular morbidity and mortality in both the general population and ESRD patients [2,36]. In addition, Frőhlich et al [5] demonstrated a clear association between CRP and metabolic syndrome in the general population. However, the relationship between CRP and metabolic syndrome has been rarely studied in ESRD patients. The results of the present study show that hsCRP is closely associated with metabolic syndrome even in nondiabetic PD patients. Interestingly, the significant association between hsCRP and metabolic syndrome becomes weak after adjusting for WBC count, whereas WBC count remained an independent predictor of metabolic syndrome after hsCRP adjustment. These findings suggest that, although both WBC count and hsCRP are measured to reflect systemic inflammation, WBC count is a more independent factor associated with metabolic syndrome. We suppose that this discrepant effect of WBC count and hsCRP may be attributed to the fact that, whereas the increase in WBC count is a cause as well as the result of obesity, elevated CRP level is only a consequence of adiposity [37,38].

One of the limitations of this study is defining metabolic syndrome in PD patients by using the modified criteria. Although the guideline of the National Cholesterol Education Program ATP III is generally used in routine medical practice, a modified version, which substitutes BMI for waist circumference to ascertain abdominal obesity, has also been proposed and has been applied to patients with different physical conditions by several investigators [17,39]. However, data validating the concordance of these 2 methods in PD patients are insufficient. Another is the cross-sectional design, which makes it hard to assess the effect of leukocytosis on the development of metabolic syndrome. Further prospective studies are needed to confirm whether WBC count is a useful predictor of metabolic syndrome, cardiovascular morbidity, and overall mortality in nondiabetic PD patients.

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## References

[1] Haffner SM, Valdez RA, Hazuda HP, et al. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 1992;41: 715-22.
[2] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.
[3] Ohshita K, Yamane K, Hanafusa M, et al. Elevated white blood cell count in subjects with impaired glucose tolerance. Diabetes Care 2004; 27:491-6.
[4] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793-801.
[5] Frohlich M, Imhof A, Berg G, et al. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. Diabetes Care 2000;23:1835-9.
[6] Jofre R, Rodriguez-Benitez P, Lopez-Gomez JM, et al. Inflammatory syndrome in patients on hemodialysis. J Am Soc Nephrol 2006;17: S274-80.
[7] Lohsoonthorn V, Dhanamun B, Williams MA. Prevalence of metabolic syndrome and its relationship to white blood cell count in a population of Thai men and women receiving routine health examinations. Am J Hypertens 2006;19:339-45.
[8] Jolly S, Chatatalsingh C, Bargman J, et al. Excessive weight gain during peritoneal dialysis. Int J Artif Organs 2001;24:197-202.
[9] Szeto CC, Chow KM, Kwan BC, et al. New-onset hyperglycemia in nondiabetic Chinese patients started on peritoneal dialysis. Am J Kidney Dis 2007;49:524-32.
[10] Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
[11] Anuurad E, Shiwaku K, Nogi A, et al. The new BMI criteria for Asians by the Regional Office for the Western Pacific region of who are suitable for screening of overweight to prevent metabolic syndrome in elder Japanese workers. J Occup Health 2003;45:335-43.
[12] Shiwaku K, Nogi A, Kitajima K, et al. Prevalence of the metabolic syndrome using the modified ATP III definitions for workers in Japan, Korea and Mongolia. J Occup Health 2005;47:126-35.
[13] Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among US adults. Diabetes Care 2004;27: 2444-9.
[14] Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 2008;28:629-36.
[15] Johnson DW, Armstrong K, Campbell SB, et al. Metabolic syndrome in severe chronic kidney disease: prevalence, predictors, prognostic significance and effects of risk factor modification. Nephrology (Carlton) 2007;12:391-8.
[16] Peralta CA, Kurella M, Lo JC, et al. The metabolic syndrome and chronic kidney disease. Curr Opin Nephrol Hypertens 2006;15: 361-5.
[17] Jiang N, Qian J, Lin A, et al. Initiation of glucose-based peritoneal dialysis is associated with increased prevalence of metabolic syndrome in non-diabetic patients with end-stage renal disease. Blood Purif 2008; 26:423-8.

[18] Breckenridge WC, Roncari DA, Khanna R, et al. The influence of continuous ambulatory peritoneal dialysis on plasma lipoproteins. Atherosclerosis 1982;45:249-58.
[19] Ford ES, Liu S. Glycemic index and serum high-density lipoprotein cholesterol concentration among US adults. Arch Intern Med 2001; 161:572-6.
[20] Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the united states medicare population, 1998 to 1999. J Am Soc Nephrol 2005;16: 489-95.
[21] Ridker PM, Buring JE, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.
[22] Dandona P, Aljada A, Chaudhuri A, et al. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005;111:1448-54.
[23] Hoffman M, Blum A, Baruch R, et al. Leukocytes and coronary heart disease. Atherosclerosis 2004;172:1-6.
[24] Reddan DN, Klassen PS, Szczech LA, et al. White blood cells as a novel mortality predictor in haemodialysis patients. Nephrol Dial Transplant 2003;18:1167-73.
[25] Friedman GD, Klatsky AL, Siegelaub AB. The leukocyte count as a predictor of myocardial infarction. N Engl J Med 1974;290:1275-8.
[26] Hsieh CH, Pei D, Kuo SW, et al. Correlation between white blood cell count and metabolic syndrome in adolescence. Pediatr Int 2007;49: 827-32.
[27] Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.
[28] Pertynska-Marczewska M, Kiriakidis S, Wait R, et al. Advanced glycation end products upregulate angiogenic and pro-inflammatory cytokine production in human monocyte/macrophages. Cytokine 2004;28:35-47.
[29] Shurtz-Swirski R, Sela S, Herskovits AT, et al. Involvement of peripheral polymorphonuclear leukocytes in oxidative stress and inflammation in type 2 diabetic patients. Diabetes Care 2001;24: 104-10.
[30] Gainsford T, Willson TA, Metcalf D, et al. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. Proc Natl Acad Sci U S A 1996;93:14564-8.
[31] Axelsson J, Qureshi AR, Heimburger O, et al. Body fat mass and serum leptin levels influence epoetin sensitivity in patients with ESRD. Am J Kidney Dis 2005;46:628-34.
[32] Ghanim H, Aljada A, Daoud N, et al. Role of inflammatory mediators in the suppression of insulin receptor phosphorylation in circulating mononuclear cells of obese subjects. Diabetologia 2007;50:278-85.
[33] Ghanim H, Aljada A, Hofmeyer D, et al. Circulating mononuclear cells in the obese are in a proinflammatory state. Circulation 2004;110: 1564-71.
[34] Kielar D, Dietmaier W, Langmann T, et al. Rapid quantification of human ABCA1 mRNA in various cell types and tissues by real-time reverse transcription-PCR. Clin Chem 2001;47:2089-97.
[35] Lago F, Dieguez C, Gomez-Reino J, et al. The emerging role of adipokines as mediators of inflammation and immune responses. Cytokine Growth Factor Rev 2007;18:313-25.
[36] Zimmermann J, Herrlinger S, Pruy A, et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999;55:648-58.
[37] Das UN. Is obesity an inflammatory condition? Nutrition 2001;17: 953-66.
[38] Yudkin JS, Stehouwer CD, Emeis JJ, et al. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972-8.
[39] Cheal KL, Abbasi F, Lamendola C, et al. Relationship to insulin resistance of the Adult Treatment Panel III diagnostic criteria for identification of the metabolic syndrome. Diabetes 2004;53:1195-200.