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A white blood cell count in the normal concentration range is independently related to cardiorespiratory fitness in apparently healthy Korean men

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Abstract

Despite the documented health benefits of physical activity, the mechanism whereby physical activity prevents cardiovascular disease is incompletely understood. In the present study, we investigated the relationship between white blood cell (WBC) count and cardiorespiratory fitness ($\dot{V}O_2$max) after adjusting for several well-known cardiovascular risk factors. Subjects who visited our health promotion center for a medical checkup and treadmill test (n = 8241; age: median, 48 years; range, 16-79 years) were classified into 3 groups based on their WBC counts (group 1, 2200-5300 μL, n = 2823; group 2, 5301-6500 μL, n = 2709; group 3, 6501-10 000 μL, n = 2709). After adjusting for age, body mass index, body fat percentage, smoking history, systolic blood pressure, diastolic blood pressure, serum lipid profile, and fasting plasma glucose, $\dot{V}O_2$max still showed a significant association with WBC count (partial $r = -0.11$, $P < .001$). In logistic regression analyses, subjects in the highest WBC tertile showed lower $\dot{V}O_2$max compared with those in the lowest WBC tertile after adjusting for age and cardiovascular risk factors (odds ratio, 0.42; 95% confidence interval, 0.36-0.49 for the highest $\dot{V}O_2$max tertile). These results suggest that a WBC count in the normal concentration range is independently related to cardiorespiratory fitness in Korean men.

1. Introduction

Although the health benefits of physical activity are well established, the mechanism whereby physical activity prevents cardiovascular disease is incompletely understood. It has been reported that risk factors such as hypertension, obesity, dyslipidemia, and insulin resistance could respond favorably to moderate levels of physical activity, thereby could protect against cardiovascular disease [1-3]. However, it is uncertain whether the beneficial effects of physical activity are independent of the previously mentioned cardiovascular risk factors.

Increasing evidence indicates that atherosclerosis is associated with an inflammatory process [4-7], and markers of inflammation have a predictive value for the risk of future cardiovascular events [8,9]. A recent meta-analysis revealed moderate but significant associations between markers of inflammation and coronary heart disease [10]. A number of prospective epidemiologic studies have shown that the leukocyte count is a good predictor of atherosclerosis [11-17], and leukocyte counts are positively associated with increased cardiovascular mortality, mainly from coronary heart disease and ischemic stroke [18-21]. Moreover, it is believed that physical activity could modify the inflammatory process, and cross-sectional studies on physical activity and physical fitness have shown inverse associations with inflammatory markers [22-27]. Cardiorespiratory fitness, as assessed by maximal exercise testing, was found to be a better predictor of health outcome than self-reported physical activity [28]. In addition, cardiorespiratory fitness is an objective laboratory measurement that reduces the misclassification bias associated with self-reported measures. In this study, we investigated the relationship between white blood cell (WBC) count

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and cardiorespiratory fitness after adjusting for several well-known cardiovascular risk factors.

2. Methods

2.1. Subjects

The medical records of 15 277 subjects who visited our health promotion center for a medical checkup and treadmill testing between 2001 and 2003 were investigated. Because most of the subjects who participated in treadmill testing were men (men, 12 696; women, 2531), only male subjects were included in this study. Subjects meeting any of the following criteria were excluded: a positive test for hepatitis C virus antibody (n = 108), a positive test for hepatitis B virus surface antigen (n = 663), a history of current antidiabetic/antihypertensive/antilipid medication (n = 3084), a history of heart failure/chronic obstructive pulmonary disease (n = 1154), or a WBC count higher than 10 000 cells/μL (n = 327). After excluding those who met the previously mentioned criteria, the medical records of 8241 men (age: median, 48 years; range, 16-79 years) were investigated. Because routine medical checkups are not covered by the Korean medical insurance system, we suspect that most of our study subjects were members of the upper-middle economic class. The subjects were classified into 3 groups according to their WBC counts (group 1, 2200-5300 cells/μL, n = 2823; group 2, 5301-6500 cells/μL, n = 2709; group 3, 6501-10 000 cells/μL, n = 2709). Diabetes was defined as fasting plasma glucose (FPG) 126 mg/dL or higher, impaired fasting glucose (IFG) as $\geq$110 and less than 126 mg/dL, hypertension as a systolic blood pressure (SBP) of 140 mm Hg or greater and/or a diastolic blood pressure (DBP) 90 mm Hg or greater, and dyslipidemia as a serum low-density lipoprotein cholesterol (LDL-C) 160 mg/dL or greater and/or triglyceride 160 mg/dL or greater and/or high-density lipoprotein cholesterol (HDL-C) 45 mg/dL or less. This study was approved by the internal review board of Samsung Medical Center, and an informed consent was obtained for each subject.

2.2. Assay methods

Height and weight were measured with subjects wearing light clothing without shoes in the morning, and blood pressure was measured using a mercury sphygmomanometer on the right arm with subjects in a sitting position after a 5-minute rest. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Information on lifestyle factors including cigarette smoking was obtained by trained nurses. Blood samples were obtained in the morning after an overnight fast. Plasma glucose was measured in duplicate by the hexokinase method using an autoanalyzer (Hitachi, Tokyo, Japan), which had an interassay coefficient of variation of 1.6%. Standard liver function test, total cholesterol, HDL-C, LDL-C, and triglyceride were measured using an autoanalyzer (Hitachi), as were WBC counts (Sysmex, Kobe, Japan). Hepatitis B virus surface antigen was measured using a commercially available immunoradiometric assay (Riakey, Koyang, Korea), as was hepatitis C virus antibody (Riakey). Body fat percentage was measured by bioelectrical impedance analysis (InBody 3.0, Biospace, Seoul, Korea) [29,30].

2.3. Measurement of $\dot{V}O_2max$

Subjects performed symptom-limited graded exercise tests on a treadmill, and the Bruce protocol was used to determine peak oxygen uptake values. During the tests, expired gases were collected through a 1-way valve and analyzed by breath-by-breath analysis. The period over which the oxygen consumption values were averaged was 20 seconds. The highest 20-second average was taken as the $\dot{V}O_2$max. Oxygen and carbon dioxide analyzers were calibrated before and after each test using known gas mixtures. Peak oxygen uptake (mg/kg per minute) was defined as the highest value recorded during test. Twelve-lead electrocardiogram and automated blood pressure were continuously recorded. The initial speed and grade were 1.7 mph and 10%, respectively, and the workload was progressed every 3 minutes by increasing the speed by 0.8 mph and the grade by 2% until any of the following criteria was met: voluntary exhaustion, respiratory exchange ratio greater than 1.10, achievement of an age-predicted maximal heart rate, a rating of perceived exertion of greater than 17 (very hard), or patients' request to stop because of dyspnea or fatigue.

2.4. Statistical analysis

Data are expressed as means $\pm$ 1 SD. Analysis of variance and least significant difference (LSD) post hoc analysis or the χ^2 test was used to compare variables among tertile groups. To determine the presence of relationships between WBC count and the other variables, bivariate and partial correlation analyses were performed. Logistic regression analysis was used to calculate odds ratios for diabetes, hypertension, dyslipidemia, obesity, smoking history, and $\dot{V}O_2$max for the highest WBC tertile vs the lowest WBC tertile. Statistical analyses were performed using SPSS/PC$^+$ software (SPSS, Inc, Chicago, Ill). Differences were considered statistically significant at a P level of less than .05.

3. Results

3.1. Univariate analyses between WBC counts and other variables

The clinical characteristics of study subjects and the corresponding WBC counts are presented in Table 1. Body mass index, body fat percentage, SBP, DBP, serum LDL-C, and triglyceride increased with increasing WBC count. Age, serum HDL-C, and $\dot{V}O_2$max values decreased with increasing WBC count, whereas the frequencies of obesity,

Table 1
Clinical characteristics of the study subjects according to WBC count

	Serum WBC (/μL)			
	2200-5300 (n = 2823)	5301-6500 (n = 2709)	6501-10000 (n = 2709)	*P* for trend
Age (y)	48.7 ± 8.0	48.1 ± 8.4	47.4 ± 8.4	<.001
BMI (kg/m^2)	24.0 ± 2.4	24.6 ± 2.6	24.6 ± 2.7	<.001
Total body fat %	20.7 ± 4.4	21.9 ± 4.6	22.1 ± 4.7	<.001
Overweight/obesity (%)	31.8/1.1	38.6/2.3	40.0/2.9	<.001
SBP (mm Hg)	117.0 ± 14.6	118.7 ± 14.9	118.7 ± 15.1	<.001
DBP (mm Hg)	74.4 ± 10.2	75.2 ± 10.2	75.2 ± 10.3	.002
Hypertension (%)	16.8	19.6	19.9	.005
LDL-C (mg/dL)	131.5 ± 29.7	136.3 ± 31.7	137.832.2	<.001
Triglyceride (mg/dL)	124.9 ± 71.0	149.4 ± 82.0	171.3 ± 97.9	<.001
HDL-C (mg/dL)	50.4 ± 11.9	48.1 ± 10.8	46.4 ± 11.3	<.001
Dyslipidemia (%)	45.8	54.7	61.5	<.001
FPG (mg/dL)	95.6 ± 12.0	96.3 ± 14.0	96.2 ± 16.9	NS
IFG/diabetes (%)	6.9/1.6	7.5/2.4	7.8/3.7	<.001
WBC (/μL)	4575 ± 538	5905 ± 339	7651 ± 877	<.001
Current smoking (%)	23.9	36.7	56.2	<.001
Alcohol intake ≥360 g/wk (%)	62.2	61.7	62.0	NS
College or university graduation (%)	57.6	58.7	56.4	NS
Household income ≥US$40000/y (%)	55.4	55.0	53.8	NS
$\dot{V}O_2$max (mg/kg per min)	35.5 ± 5.4	34.4 ± 5.4	33.6 ± 5.2	<.001

Data are means ± SD or percentages. Overweight, 25 kg/m^2 less than or equal to BMI <30; obese, BMI ≥30; hypertension, SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg; dyslipidemia, LDL-C ≥160 mg/dL and/or triglyceride ≥160 mg/dL and/or HDL-C <45 mg/dL; IFG, 110 less than or equal to FPG <126 mg/dL; diabetes, FPG >126 mg/dL. NS indicates not significant.

hypertension, dyslipidemia, and current smoking increased with increasing WBC count. Although no significant difference in FPG levels was observed among the 3 groups, the frequencies of IFG and diabetes increased with increasing WBC count. The frequencies of heavy alcohol drinking (≥360 g/wk), educational background, and household incomes were not different among the 3 groups.

3.2. Bivariate and partial correlations between WBC counts and other variables

Table 2 shows bivariate correlation coefficients between WBC counts and the other variables. For these analyses, $\dot{V}O_2$max, age, and serum HDL-C showed significant negative associations with WBC count. In addition, SBP, DBP, BMI, body fat percentage, serum LDL-C, and triglyceride showed significant positive associations with WBC count. Of note, body fat percentage showed a stronger positive association than BMI. No significant association was found between FPG and WBC count. Table 3 shows a partial correlation between WBC count and $\dot{V}O_2$max. After adjusting for age, BMI, body fat percentage, a smoking history, SBP, DBP, serum lipid profile, and FPG, we found that $\dot{V}O_2$max remained significantly associated with WBC count (partial $r = -0.113$, $P < .001$).

3.3. Logistic regression analyses

In this analysis, covariates were age as continuous variable, obesity, dyslipidemia, diabetes, hypertension, current smoking, and tertiles of $\dot{V}O_2$max. The odds ratios (95% confidence interval) for obesity (BMI ≥30 kg/m^2), dyslipidemia, diabetes, hypertension, and current smoking, in the highest WBC tertile vs the lowest WBC tertile, were 1.962 (1.255-3.069), 1.652 (1.471-1.855), 1.921 (1.311-2.814), 1.439 (1.239-1.671), and 3.895 (3.450-4.398), respectively. The odds ratios (95% confidence interval) for the second vs the highest $\dot{V}O_2$max tertile and for the highest vs the lowest WBC tertile were 0.614 (0.532-0.708) and 0.418 (0.359-0.487), respectively.

Table 2
Bivariate correlations between WBC count and other variables

Variable	*r*	*P*
$\dot{V}O_2$max	−0.154	<.01
Age	−0.077	<.01
SBP	0.043	<.01
DBP	0.035	<.01
BMI	0.097	<.01
Total body fat %	0.132	<.01
LDL-C	0.087	<.01
Triglyceride	0.217	<.01
HDL-C	−0.162	<.01
FPG	0.014	NS

Table 3
Partial correlations between WBC count and $\dot{V}O_2$max

	Partial *r*	*P*
Unadjusted	−0.154	<.001
Adjusted for age	−0.196	<.001
Adjusted for BMI	−0.141	<.001
Adjusted for total body fat %	−0.123	<.001
Adjusted for smoking history	−0.146	<.001
Model 1	−0.137	<.001
Model 2	−0.113	<.001

Model 1, adjusted for age, BMI, total body fat percentage, and smoking history. Model 2, adjusted for SBP, DBP, LDL-C, triglyceride, HDL-C, FPG, and the variables shown in model 1.

4. Discussion

The primary finding of this cross-sectional study was of an inverse association between WBC count and cardiorespiratory fitness, and the latter of which is independent of known cardiovascular risk factors in apparently healthy Korean men. Lee et al [21] reported that an elevated leukocyte count is directly associated with increased incidence of coronary heart disease and ischemic stroke, and mortality from cardiovascular disease. Recently, Tong et al [31] observed that elevated leukocyte count, even within the reference range, is associated with macrovascular and microvascular complications in type 2 diabetes. Although some studies have reported an association between inflammatory markers and cardiovascular fitness [22,23], few have examined the association between WBC count and cardiorespiratory fitness [24,32]. Moreover, almost all studies on this topic have been conducted in elderly subjects or subjects with cardiovascular risk factors [25-27].

Perhaps regular exercise modifies the several well-known cardiovascular risk factors, for example, obesity, dyslipidemia, dysglycemia, or hypertension [1-3], and it is likely that subjects who exercise regularly tend to have a lifestyle favoring good health. In view of the fact that WBC count is a well-established marker of subclinical inflammation [11-21,31], our results imply that greater physical fitness has a beneficial effect by reducing subclinical inflammation and that this benefit is caused by a mechanism independent of the traditional cardiovascular risk factors. Inflammatory cytokines may offer a potential mechanism as tumor necrosis factor α and interleukin 6 are known to be released from adipose tissue [33,34]. Moreover, this release is augmented by increased sympathetic stimulation, which is down-regulated by regular physical activity [35]. Several longitudinal studies showed that exercise training could lower the parameters of inflammation. Smith et al [36] found that a 6-month exercise program reduced tumor necrosis factor α. Tsukui et al [37] reported that exercise training in 29 obese women reduced tumor necrosis factor α with only modest weight loss. Mattusch et al [38] found that 9 months of marathon training reduced C-reactive protein. However, Rawson et al [39], in their longitudinal study, found that BMI, but not previous-year or current physical activity via 24-hour recall, predicted highly sensitive C-reactive protein. Considering that the current study was a cross-sectional design, direct comparison of results is not possible. In subgroup analyses of this study, $\dot{V}O_2$max still showed a significant association with WBC count in lean/normal-weight group (BMI <25 kg/m^2, partial $r = -0.104$, $P < .001$) and overweight/obese group (BMI >25 kg/m^2, partial $r = -0.111$, $P < .001$) after adjusting for age, BMI, body fat percentage, smoking history, SBP, DBP, serum lipid profile, and FPG. Future prospective studies should be conducted to address this issue.

Our study has some limitations that should be mentioned. Because it is a non–population-based study and all study subjects participated in a health examination program voluntarily, it is limited in terms of relevancy of these results in the general population. Major conditions that might affect WBC counts, such as hepatitis C, hepatitis B, a history of current antidiabetic/antihypertensive/antilipid medications, and a history of heart failure/chronic obstructive pulmonary disease, were excluded. Therefore, because the main focus of this study was to determine whether the association between WBC count and physical fitness is independent of known cardiovascular risk factors, we do not believe that this selection bias affected the validity of our results. Moreover, no difference in social factors (ie, heavy alcohol drinking, educational backgrounds, and household income) was observed in the study groups, which should lessen concerns of selection bias. Information about herbal supplements/other nonprescription medications and dietary habit was not available in this study. Furthermore, we used only WBC count as a parameter of subclinical inflammation because we did not have any data about other parameters, for example, highly sensitive C-reactive protein, interleukins, and tumor necrosis factor α. In view of the consistent finding of a negative association between WBC count and cardiorespiratory fitness, we anticipate that similar results would have been obtained for other inflammatory markers. One of the important limitations is that this was a cross-sectional study. This cross-sectional design restricted the power of our analyses and therefore limited the conclusions that could be drawn. The correlation coefficient between leukocyte counts and $\dot{V}O_2$max was not so strong. Therefore, we should consider the possibility that the statistical significance of the data was due primarily to the high numbers of subjects. The presence of difference from a physiological perspective remains to be clarified in another study. Accepting the above, this study suggests a negative association between subclinical inflammation and cardiorespiratory fitness, which is independent of the traditional cardiovascular risk factors examined, and demonstrates a need to determine the mechanism involved.

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