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Original

Total and Differential White Blood Cell Counts, Fasting Insulin Concentrations, and Components of Metabolic Syndrome in Japanese Men and Women: the Kurihashi Lifestyle Cohort Study

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We examined the cross-sectional association between fasting insulin, metabolic syndrome (MetS), and total and differential white blood cell (WBC) counts in Japanese men and women. Middle-aged and apparently healthy subjects (1,910 men, 849 women) who participated in a general health check-up were included. The International Diabetes Federation definition was adopted to identify subjects with MetS. The prevalence of MetS was 12.4% among men and 10.4% among women. Multivariate logistic regression model showed that men and women in the highest quartile of total WBC counts had a 2.26-fold and 2.71-fold increased risk of MetS, respectively, compared to those in the lowest quartile. Similarly, men and women in the highest quartile of neutrophil count had a 2.17-fold and 4.08-fold increased risk of MetS, respectively, compared to those in the lowest quartile of neutrophil count. Lymphocyte count was an independent risk factor for MetS only in men. These associations were all independent of the fasting insulin. Our data suggests that MetS relates to total and differential WBC counts, independent from fasting insulin in both sexes. However, it is unknown whether sex differences in the association between MetS and WBC subtypes relate to sex differences in incident cardiovascular diseases and diabetes.

Key Words: white blood cell count, insulin, metabolic syndrome

Introduction

Recently, evidence has shown that chronic inflammation is an important factor associated with the progression of atherosclerosis[1] and insulin resistance[2]. White blood cell (WBC) count is a well-known objective biological marker of acute infection, tissue damage, and other systemic inflammatory conditions. Several studies have shown that increased WBC counts are associated with components of metabolic syndrome (MetS)[3], type 2 diabetes mellitus (DM)[4], and coronary heart disease[5]. Some Japanese studies have also shown a significant association between WBC counts and MetS[6~9]. Thus, the WBC count may be a powerful predictor of several atherosclerotic diseases. Regarding WBC subtypes, recent studies suggest that elevated neutrophil or granulocyte counts may be the strongest predictor of carotid arteriosclerosis, coronary heart disease (CHD), and cardiovascular disease (CVD) mortality[10~12]. However, few studies have investigated the relationship between MetS and differential WBC count[13~15].

MetS, which comprises various metabolic disorders, is a known risk factor for CVD and DM[16][17]. Insulin sensitivity is closely related to MetS[18], CVD[19], and DM[20]. However, little is known regarding the relationship between WBC subtypes and MetS via insulin resistance. Thus, the aim of this study was to assess the relationship between total and differential WBC counts and MetS and to test whether this relationship was independent of insulin concentrations in Japanese men and women.

Subjects and Methods

Study subjects

From February 2006 to January 2007, Saitama-ken Saiseikai Kurihashi (SSK) Hospital conducted a health check-up program in which 3,825 subjects aged 30-76 years participated and were followed up in the Kurihashi Lifestyle Cohort Study. Subjects were excluded if they had DM, CVD, cancer, asthma, or certain infectious diseases or if they were under pharmacological treatment for hypertension or dyslipidemia. Moreover, 234 subjects with abnormal WBC counts ($\geq 10 \times 10^9$ cells/L or $< 4.0 \times 10^9$ cells/L), indicative of an infectious disease or pathological state of leucopenia, were later excluded from the study. The remaining 2,759 subjects were included in the study.

Data collection

The general health check-up examination procedure at SSK Hospital included biochemical laboratory tests and a self-administered questionnaire regarding smoking status, physical activities during leisure time, medical history, alcohol habits, and in women, menopausal status. Smoking status was classified into three categories (never, past, and current smoker). Physical activity status during leisure time was classified as sedentary, occasionally, or active. Alcohol habits were divided into three categories (never, occasionally, and regularly). The height, weight, blood pressure, and waist circumference (WC) of all subjects were measured. Body height was measured to the nearest 0.1 cm with the subject standing without shoes. The subjects were requested to wear light indoor clothes before the body weight was measured to the nearest 0.1 kg. Blood pressure was measured in a sitting position after 5 min of rest by using an automatic sphygmomanometer. WC was measured to the nearest 0.1 cm at the navel level at the end of the expiration of a normal breath and with the subject in a standing position. Blood samples were collected in the morning after a 10-h fast. Fasting plasma glucose (FPG) (glucose oxidase method), triglyceride (enzymatic method), and high-density lipoprotein cholesterol (HDL-C) (direct method) levels and WBC counts (Kinetic WBC optical count, CELL-DYN, Abbott Japan) were measured at the hospital laboratory. Insulin concentration was measured by an immunoradiometric assay at a commercial laboratory.

Statistical analysis

Statistical analyses were performed and reported separately for men and women. MetS was defined using International Diabetes Federation (IDF) criteria. To investigate the possible relationship between anthropometric measurements, metabolic activities, and lifestyle characteristics and WBC counts, data were divided into quartiles of WBC counts. The equality of means of each variable across quartiles of WBC counts was tested by analysis of variance (ANOVA). The chi-squared test was used to compare the proportions. Subjects with different numbers of MetS components were divided into six groups by numbers 0-5. The components of MetS included central obesity, high fasting glucose levels, high triglyceride levels, low HDL-C levels, and high blood pressure. Means of total WBC counts and WBC subtypes were calculated for each group and groups with and without MetS by means of a multiple linear regression model. The multivariate adjusted odds ratios and their 95% confidence intervals associated with the presence of MetS were calculated for each quartile category of total WBC and WBC subtype counts by using logistic regression models. In the multivariate model, age (continuous), physical activity during leisure time (categorical), alcohol habits (categorical), smoking status (categorical), fasting insulin concentration, and (in women only) menopause status (categorical) were included as confounding factors.

Statistical Package for Social Sciences (SPSS) for Windows (version 14.0, Chicago, IL, USA) was used for all statistical analyses. All reported p values are two-tailed, and $p < 0.05$ was considered statistically significant. The study was approved by the Institutional Review Board of SSK Hospital, and informed consent was obtained from the study participants.

Results

Anthropometric, metabolic, and lifestyle characteristics in relation to WBC counts

The classical CVD risk factors deteriorated with increasing WBC counts in both men and women,

Table 1 Relationships between anthropometric measurements, metabolic activity and lifestyle characteristics, and quartiles of white blood cell counts (/μl)

Men	Quartile 1 (n=478) ≤4.98	Quartile 2 (n=481) 4.99-5.71	Quartile 3 (n=474) 5.72-6.59	Quartile 4 (n=477) ≥6.70	p value
Age (years)	51 ± 9	51 ± 8	50 ± 9	50 ± 8	0.039
Body mass index (kg/m^2)	22.9 ± 2.7	23.6 ± 2.9	23.9 ± 3.0	24.2 ± 3.4	<0.001
Waist circumference (cm)	83.1 ± 7.3	84.8 ± 7.7	86.0 ± 7.8	86.6 ± 8.3	<0.001
Systolic blood pressure (mmHg)	123 ±15	125 ± 15	127 ±16	125 ± 18	0.018
Diastolic blood pressure (mmHg)	78 ±12	79 ± 12	81 ±13	80 ± 13	0.001
High-density lipoprotein cholesterol (mg/dl)	60 ±15	56 ± 15	53 ±14	50 ± 13	<0.001
Triglyceride (mg/dl)	100 ±61	123 ±118	133 ±86	147 ±108	<0.001
Fasting plasma glucose (mg/dl)	94 ±11	94 ± 12	95 ±14	95 ± 15	0.687
Fasting insulin (μU/ml)	5.62 ± 3.20	6.58 ± 4.30	6.77 ± 3.82	7.48 ± 4.57	<0.001
Alcohol intake regularly (%)	42.6	45.7	44.7	43.7	0.799
Current smoker (%)	21.5	36.4	47.0	65.6	<0.001
Physically active during leisure time (%)	22.1	19.9	17.4	12.9	<0.001
Metabolic syndrome (%)	5.9	10.0	15.4	18.2	<0.001
Women	Quartile 1 (n=216) ≤4.46	Quartile 2 (n=210) 4.47-5.07	Quartile 3 (n=211) 5.08-5.85	Quartile 4 (n=212) ≥5.86	p value
Age (years)	51 ± 8	52 ± 8	50 ± 8	49 ± 7	0.037
Body mass index (kg/m^2)	21.8 ± 3.0	22.3 ± 2.9	22.5 ± 3.1	23.1 ± 3.5	<0.001
Waist circumference (cm)	78.4 ± 8.8	80.4 ± 8.1	80.1 ± 8.5	81.8 ± 9.4	<0.001
Systolic blood pressure (mmHg)	120 ±16	121 ±15	122 ±17	120 ±17	0.421
Diastolic blood pressure (mmHg)	72 ±11	72 ±12	74 ±12	72 ±12	0.267
High-density lipoprotein cholesterol (mg/dl)	70 ±15	68 ±15	67 ±16	62 ±14	<0.001
Triglyceride (mg/dl)	79 ±46	87 ±39	95 ±51	102 ±47	<0.001
Fasting plasma glucose (mg/dl)	89 ±10	89 ± 9	89 ± 9	90 ±13	0.135
Fasting insulin (μU/ml)	4.86 ± 2.51	5.50 ± 2.88	5.90 ± 3.24	6.37 ± 3.77	<0.001
Alcohol intake regularly (%)	13.2	13.9	11.3	14.9	0.709
Current smoker (%)	8.8	7.1	10.0	17.9	0.009
Physically active during leisure time (%)	14.5	19.0	13.9	15.2	0.447
Menopause (%)	46.9	51.7	50.5	43.2	0.304
Metabolic syndrome (%)	5.1	7.6	12.8	16.0	0.001

Variables are the mean ± SD for continuous variables and percentages of subjects for categorical variables.
p values were for the equality of quartile group means determined by ANOVA.
Chi-squared tests of independence were tested between alcohol habits, smoking status, physical activity, and menopausal status and quartile groups.

except for FPG and alcohol habits in men and blood pressure, FPG, alcohol habits, physical activity at leisure time, and menopause in women (Table 1). Fasting insulin concentrations and the prevalence of MetS increased with increase of total WBC counts in both sexes.

Total and differential WBC counts and MetS

The overall prevalence of MetS was 12.4% in men and 10.4% in women. Total WBC and neutrophil counts increased with increasing numbers of components of MetS, after adjusting for confounding factors in both men and women (Table 2). In men, total WBC, neutrophil, lymphocyte, eosinophil, and basophil counts were elevated in subjects with MetS. In women, total WBC, neutrophil, and lymphocyte counts were elevated in subjects with MetS (Table 2).

According to the multivariate logistic regression model, total WBC and neutrophil counts showed statistically significant linear positive relationships with MetS in both men and women (p for linear trend = 0.004 and 0.022 and 0.046 and 0.045, respectively), and the lymphocyte count showed a statistically significant linear positive relationship with MetS in men (p for trend = 0.01) (Table 3). However, fasting insulin concentrations were not independent risk factors for total and differential WBC counts in men and women. Men in the highest quartiles of to-

Table 2 Adjusted means of total and differential white blood cell counts for clustered components of metabolic syndrome

Men								
Number of components	n	%	Total WBC (/μl)	Neutrophil (/μl)	Lymphocyte (/μl)	Monocyte (/μl)	Eosinophil (/μl)	Basophil (/μl)
0	555	29.1	5,525±1,331	3,114± 882	1,844± 599	240±157	148±148	22±2
1	619	32.4	5,707±1,230	3,278± 870	1,871± 592	248±159	153±138	23±2
2	413	21.6	5,887±1,280	3,356± 928	1,967± 646	263±166	148±132	22±2
3	230	12.0	6,292±1,316	3,535± 879	2,069± 639	283±171	176±158	26±2
4	79	4.1	6,240±1,212	3,673± 966	2,113± 573	274±171	178±218	27±2
5	14	0.7	6,514±1,128	3,488±1,166	2,292±1,099	252±179	223±282	21±2
	Trend		<0.001	0.005	0.110	0.053	0.062	0.062
non-MetS	1,674	87.6	5,723±1,290	3,249± 897	1,894± 610	250±161	151±143	22±2
MetS	236	12.4	6,282±1,281	3,597± 899	2,097± 669	280±170	184±173	27±2
	Trend		<0.001	0.002	0.003	0.077	0.004	0.002
Women								
Number of components	n	%	Total WBC (/μl)	Neutrophil (/μl)	Lymphocyte (/μl)	Monocyte (/μl)	Eosinophil (/μl)	Basophil (/μl)
0	283	33.3	4,804±1,069	2,679± 686	1,674±588	199±129	132±141	21±2
1	288	33.9	5,013±1,027	2,871± 770	1,631±477	192±129	121±123	21±2
2	184	21.7	5,242±1,176	2,961± 760	1,670±567	219±115	148±142	23±2
3	71	8.4	5,461±1,208	3,251± 837	1,757±547	194±128	124±136	22±2
4	18	2.1	5,832±1,165	3,434±1,074	1,827±478	240±133	158±139	23±2
5	5	0.6	5,822±1,066	2,919± 361	2,488±978	266±133	300±360	22±2
			0.012	0.045	0.230	0.152	0.057	0.832
non-MetS	761	89.6	4,995±1,086	2,831± 740	1,655±536	201±126	131±135	21±2
MetS	88	10.4	5,561±1,218	3,267± 881	1,839±607	210±123	142±157	22±2
			0.018	0.017	0.030	0.541	0.933	0.813

WBC, white blood cell; MetS, metabolic syndrome.

Components of MetS: central obesity, high blood pressure, high triglyceride, low high-density lipoprotein cholesterol, and high fasting plasma glucose.

Variables are the means±SD.

Adjusted for age, smoking status, alcohol intake, physical activity during leisure time, fasting insulin concentration in both men and women, and in women only, menopausal status.

tal WBC, neutrophil, and lymphocyte counts had a 2.26-, 2.17-, and 2.32-fold increased risk for MetS, respectively, relative to men in the lowest quartiles of those counts, and this finding was independent of the fasting insulin concentration. Women in the highest quartiles of total WBC and neutrophil counts had a 2.71- and 4.08-fold increased risk for MetS, respectively, relative to women in the lowest quartiles of those counts (Table 3).

Discussion

Recent studies have shown that chronic inflammation is associated with the progression of atherosclerosis[1] and insulin resistance[2]. Insulin resistance plays an important role in the progression of MetS, CVD and DM[18)~20)]. In our study, fasting insulin concentrations were not independently related to total and differential WBC counts in both sexes. However, the significant relation between IDF-MetS and total WBC and neutrophil counts in both sexes and lymphocyte count in men were significantly independent from confounding factors including fasting insulin concentrations. Thus, IDF-MetS seems to be an insulin independent inflammatory condition leading to atherosclerotic diseases. However, it was unknown to what extent the sex difference in the effect of IDF-MetS on WBC subtypes relates to the sex difference in incident CVD and DM.

Previous cross-sectional studies have shown an association between total WBC counts and MetS in subjects from Japan. Nagasawa et al. reported an association between WBC counts and MetS by using body mass index (BMI) as an obesity criterion instead of WC in men but not in women[6]. However, fasting insulin concentrations were not significantly

Table 3 Odds ratios with the 95% confidence intervals for MetS according to the quartiles of total and differential WBC counts

		Men Odds ratio (95% confidence interval)	Women Odds ratio (95% confidence interval)
Total WBC	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.28 (0.72-2.29)	1.22 (0.51-2.95)
	Quartile 3	2.26 (1.29-3.93)	1.97 (0.86-4.49)
	Quartile 4	2.26 (1.30-3.96)	2.71 (1.20-6.10)
	p for trend	0.004	0.046
Neutrophil	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.28 (0.70-2.35)	2.84 (0.81-9.95)
	Quartile 3	1.94 (1.10-3.43)	3.43 (0.99-11.76)
	Quartile 4	2.17 (1.23-3.82)	4.08 (1.19-13.95)
	p for trend	0.022	0.045
Lymphocyte	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.22 (0.68-2.21)	0.98 (0.34-2.82)
	Quartile 3	1.63 (0.93-2.87)	1.41 (0.54-3.65)
	Quartile 4	2.32 (1.33-4.04)	2.04 (0.83-5.05)
	p for trend	0.010	0.332
Monocyte	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.16 (0.68-1.98)	1.17 (0.61-2.23)
	Quartile 3	1.55 (0.93-2.59)	1.19 (0.62-2.27)
	Quartile 4	1.68 (0.99-2.83)	1.34 (0.72-2.52)
	p for trend	0.172	0.838
Eosinophil	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.59 (0.95-2.66)	1.06 (0.54-2.08)
	Quartile 3	1.63 (0.97-2.74)	1.13 (0.58-2.20)
	Quartile 4	1.93 (1.16-3.22)	1.87 (1.01-3.45)
	p for trend	0.091	0.130
Basophil	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.32 (0.78-2.25)	1.01 (0.53-1.92)
	Quartile 3	1.86 (1.12-3.08)	1.07 (0.56-2.03)
	Quartile 4	2.03 (1.23-3.36)	1.36 (0.73-2.52)
	p for trend	0.022	0.724

WBC, white blood cell; MetS, metabolic syndrome.
Adjusted for age, smoking status, alcohol intake, physical activity during leisure time, fasting insulin concentration in both men and women, and only in women, menopausal status.

related to WBC count in this study. Their finding was partly accordance with our result. Ishizaka et al reported that high WBC counts are independent risk factors for MetS, after adjusting for age and total cholesterol in both men and women; however, BMI was used for the diagnosis of MetS in women because WC data were not available[7][8]. Oda et al reported that the prevalence of MetS increased through the quartiles of WBC counts in Japanese men and women[9]. This was accordance with our result. In our study, IDF-MetS was a significant, positive, and an independent risk factor for total and differential WBC counts. To our knowledge, this is the first study, using complete data of defined MetS and after adjusting for confounding factors related to lifestyle in Japanese men and women, to show a positive association between total WBC counts and MetS in both sexes. The MetS may directly increase WBC counts, since MetS comprises abdominal obesity which cause insulin resistance.

A few studies have analyzed an association between WBC subtype counts and components of

MetS. Kim et al showed that the numbers of total WBCs, neutrophils, and lymphocytes were elevated in men with MetS but not in women[13]. Another large study from Korea suggested that total and all differential WBC counts were associated with the presence of MetS[14] in men and women. One Japanese study showed that total WBC and lymphocyte counts were elevated with clustered features of MetS[15] only in men. The reasons for differences between these findings and the present data are unclear, but possible reasons include differences in sample size, age distribution, and adjustment of different confounding factors. Recent prospective studies have shown an association between total and differential WBC counts and CVD, IFG, DM, and all-cause mortality[4)10)~12)]. To our knowledge, however, no studies have analyzed impact of WBC counts on various end points independent from insulin concentrations. Further prospective studies are needed to clarify the role of total and differential WBC counts, MetS, and insulin in the development of atherosclerotic diseases.

There is a sex difference in the progression of DM and CVD[21]. A similar sex difference has been reported in total and differential WBC counts[22)23)]. In our study, lymphocyte count was not an independent risk factor for MetS in women. The reason for this is unclear. However, the number of women in our study was less than half of that of men, and thus, our findings in women might be weakened by the sample size. There may be environmental sex differences in lifestyle such as smoking status and physical activity. In our study, men include a higher proportion of smokers and physically active persons during leisure time than women. A female sex hormone, estrogen, may protect from atherosclerosis by decreasing the inflammatory cell adhesion[24], since we have adjusted for menopausal status in the current study.

Despite the mounting evidence of associations between total and differential WBC counts and the risk of MetS, explanatory biological mechanisms remain unclear. Vascular endothelial cells are activated by the presence of atherosclerotic risk factors, such as hypertension, dyslipidemia, and hyperglycemia, thus promoting increased production and release of proinflammatory cytokines and chemokines. Proinflammatory T cell cytokines, interleukin-2 (IL-2) and interferon-γ, were found in atherosclerotic lesion, which demonstrates the presence of Th1-type T cell response[25]. Thus, the atherosclerotic lesion contains large numbers of T lymphocytes. Additionally, proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6, which are secreted from adipose tissue, are known to increase WBC counts[26]. TNF-α is a potent stimulator of IL-6 production, and IL-6 stimulates neutrophils directly[27]. Leptin, which is also released from adipocytes, activates neutrophils via the induction of TNF-α[28]. Moreover, it has been reported that adipose tissue secretes IL-8 and monocyte chemoattractant protein-1, which contribute to the migration of granulocytes and activated T lymphocytes[29]. Thus, human adipose tissue, which is a major concept of MetS, could play an important role in increasing total and differential WBC counts.

There were several limitations in our study. Firstly, this study had a cross-sectional design, thus a temporal relationship between total and differential WBC counts and MetS could not be established. Secondly, though the hyperinsulinemic-euglycemic clamp is the standard technique to measure insulin sensitivity, we used the fasting insulin concentration as a surrogate measure of insulin resistance. As our subjects were participants in general health check-ups, it was impossible to perform such expensive, invasive, and long-sustained examinations. Thirdly, the questionnaire of physical activity, alcohol consumption, and smoking status was self-reported and not validated. Fourthly, high-sensitivity C-reactive protein (hs-CRP) is superior to WBC as an inflammatory component of MetS[30]. However, data of hs-CRP was not available because it was expensive whereas WBC was a stable, well-standardized, and inexpensive marker of routine health care data. Further researches are needed to examine the relation between inflammation and MetS using more sensitive marker. In addition to the limitations, our study has some major advantages. Firstly, we excluded subjects whose WBC

counts exceeded 10×10^9 cells/L or were lower than 4×10^9 cells/L, thus we examined subjects whose WBC counts were within the normal range. Secondly, to avoid systematic bias, we were extremely careful in data collection. We excluded subjects who had previous medical histories of diseases associated with low-grade inflammation. Thirdly, we adjusted for many confounding factors considered to have influence on MetS and insulin resistance in our data analysis.

In conclusion, IDF-MetS relates to inflammatory condition, increased total and differential WBC counts, independent from fasting insulin concentrations in both sexes. However, it is a future challenge to examine to what extent sex differences in the association between MetS and WBC subtypes relates to sex differences in the incident atherosclerotic diseases including CVD and DM.

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総白血球数とその分画，空腹時インスリン，メタボリックシンドロームの関係

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日本人において，総白血球数とその分画，インスリン，メタボリックシンドロームの関係を横断的に検討した．対象は，埼玉県済生会栗橋病院の人間ドックを受診した日本人男女（男性 1,910 人，女性 849 人）で，慢性的に炎症を引き起こす可能性のある疾患の既往歴や糖尿病，高血圧，脂質異常症の内服がなく，白血球数が正常範囲内の者である．メタボリックシンドロームの診断には国際糖尿病連合の診断基準を用いた．メタボリックシンドロームの有病率は，男性で 12.4%，女性で 10.4% であった．男女とも，白血球数の増加に従い，肥満度や心血管危険因子は悪化し空腹時インスリン値は上昇した．また，空腹時インスリン値を含む交絡因子で補正後の総白血球数，好中球数は，メタボリックシンドロームの構成因子数の増加に従い増加した．空腹時インスリン値を含む多因子補正後のロジスティック回帰分析では，総白血球数の 4 分位において，最上位群では最下位群と比較し男女それぞれ，メタボリックシンドロームの相対危険度が 2.26 倍，2.71 倍であった．同様に，好中球数の 4 分位において，最上位群では最下位群と比較し男女それぞれ，メタボリックシンドロームの相対危険度が 2.17 倍，4.08 倍であった．また，男性でのみ，リンパ球数はメタボリックシンドロームの独立した危険因子であった．本横断研究において，メタボリックシンドロームはインスリンから独立した炎症状態（総白血球数とその分画）を示唆していた．しかし本関係には男女差があり，この点が心血管疾患や糖尿病の発症の性差にどの程度関連しているのかは不明であり，今後の検討課題である．