Elevated White Blood Cell Count in Subjects With Impaired Glucose Tolerance

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OBJECTIVE — Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) differ in their risk of all-cause and cardiovascular mortality, but previous cross-sectional studies have suggested little difference in their levels of lipids or blood pressure. We compared the white blood cell (WBC) count between subjects with IFG and IGT.

RESEARCH DESIGN AND METHODS — The subjects were 4,720 nondiabetic Japanese men aged 24–84 years. Based on the 75-g oral glucose tolerance test, the subjects were classified into the following four groups: normal fasting glucose/normal glucose tolerance (n = 3,753), isolated IFG (n = 290), isolated IGT (n = 476), and IFG/IGT (n = 201). We compared the WBC count among the four groups and investigated variables that showed a significant association with the WBC count.

RESULTS — The isolated IGT group had a significantly higher WBC count than the isolated IFG group (6,530 vs. 6,210/mm^3, $P < 0.05$). By stepwise analyses, age, triglycerides, HDL cholesterol, fasting insulin, and 2-h postchallenge plasma glucose (PG) showed an independent association with the WBC count (adjusted R^2 = 0.057). In the analysis stratified by smoking status, the WBC count was independently associated with 2-h PG and triglycerides, irrespective of smoking status.

CONCLUSIONS — Individuals with isolated IGT had a significantly higher WBC count than those with isolated IFG. The WBC count was associated with 2-h PG and various components of the metabolic syndrome.

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An elevated white blood cell (WBC) count is a predictor of cardiovascular mortality independent of the effects of smoking and other traditional risk factors (1–3). Even within the normal range, the WBC count is positively and independently associated with mortality from coronary heart disease (2). There is also a significant positive association between the WBC count and the severity of carotid atherosclerosis (4). Inflammation contributes to vascular injury, atherogenesis, and thrombosis (5,6). A WBC, which is activated by cytokines, especially interleukin (IL)-6 and IL-8 (7), may serve as an important marker of these processes (8,9). WBCs contribute to blood viscosity, release products that induce plaque rupture and thrombus formation (9), and have a role in endothelial dysfunction (10).

Impaired glucose tolerance (IGT) is often associated with the metabolic syndrome and is an established risk factor for cardiovascular disease (11,12). In contrast, the prognostic significance of impaired fasting glucose (IFG) for macrovascular complications is still unclear (11–14). Although previous cross-sectional studies (15–18) have suggested little difference between IFG and IGT with respect to lipids or blood pressure, IGT is more closely associated with the risk of all-cause and cardiovascular mortality than IFG (11,12). We hypothesized that some other difference may exist between individuals with IFG and IGT regarding the cardiovascular risk profile. To address this question, we evaluated differences between subjects with IFG and IGT using the WBC count as a marker of subclinical inflammation and investigated the variables that showed a correlation with WBC count.

RESEARCH DESIGN AND METHODS

— The subjects included 4,720 nondiabetic men aged 24–84 years who consecutively visited the Nippon Telegraph and Telephone West Corporation Chugoku Health Administration Center for general health examinations from 1992–2002. After an overnight fast, fasting blood samples were obtained and a 75-g oral glucose tolerance test (OGTT) was performed as described previously (19). Subjects with either a fasting plasma glucose (FPG) ≥7.0 mmol/l or a 2-h postchallenge glucose (PG) level ≥11.1 mmol/l (n = 434) were defined as having diabetes and excluded from analysis. Subjects who had cardiovascular disease, liver dysfunction (aspartate transaminase ≥100 units/l, alanine transaminase ≥100 units/l, or γ-glutamyltranspeptidase ≥300 units/l), renal dysfunction (creatinine >106 μmol/l), or a history of gastrectomy were also excluded. Subjects

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Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL, interleukin; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, postchallenge glucose; WBC, white blood cell.

Table 1—*The mean WBC count by smoking status*

	Never smokers	Former smokers	Current smokers
n	1,515	954	2,251
WBC (per mm^3)*	5,530 (3,500–8,750)	5,690 (3,600–8,990)†	7,030 (4,440–11,120)†‡

The WBC count was $\log_{10}$ transformed before statistical testing. *Geometric means (95% CI) are shown; †$P < 0.05$ vs. never smokers; ‡$P < 0.05$ vs. former smokers.

with acute infection were excluded on the basis of interview, physical examination, urinalysis, and chest roentgenograms. This study was approved by the local ethics committee.

The WBC count was determined using a Coulter STKS hematology analyzer (Coulter, Miami, FL). Triglyceride level was measured by an enzymatic method, and HDL cholesterol was measured by a precipitation method. LDL cholesterol was calculated using Friedewald's formula (20). Fasting insulin was measured by an enzyme immunoassay (Dainabot, Tokyo, Japan) with the intra-assay coefficient of variation at 3.1–4.4%. Based on the 75-g OGTT, the nondiabetic subjects were classified into four groups: normal fasting glucose (NFG)/normal glucose tolerance (NGT) (FPG <6.1 mmol/l and 2-h PG <7.8 mmol/l), $n = 3,753$; isolated IFG (FPG between 6.1 and 7.0 mmol/l and 2-h PG <7.8 mmol/l), $n = 290$; isolated IGT (FPG <6.1 mmol/l and 2-h PG between 7.8 and 11.1 mmol/l), $n = 476$; and IFG/IGT (FPG between 6.1 and 7.0 mmol/and 2-h PG between 7.8 and 11.1 mmol/l), $n = 201$. Blood pressure was measured by a mercury sphygmomanometer after 5 min of rest. The subjects also completed a medical history that included questions about smoking, and the smoking status was classified as "never," "former," and "current."

The mean values of the WBC count and other clinical factors were compared among the four groups. Comparison of smoking status among the groups was carried out using the χ^2 test for independence. Differences among the groups were tested by ANOVA. Pearson's correlation coefficients were calculated to determine whether a significant relationship existed between the WBC count and other clinical factors by smoking status because smoking is associated with an increase in the WBC count (21) and the mean WBC count was related to smoking status in our study population (Table 1). Furthermore, stepwise multiple regression analyses were performed to assess the independent relationship between the WBC count and variables that showed significant associations. WBC count, triglycerides, and insulin levels were $\log_{10}$ transformed before statistical testing. Data were analyzed using SAS version 8.0 (SAS, Cary, NC).

RESULTS — Subjects with isolated IFG had significantly higher BMI, systolic and diastolic blood pressure, triglycerides, fasting insulin, FPG, and 2-h PG values compared with those of the NFG/NGT group, but there was no difference in WBC count (Table 2). Subjects with isolated IGT had significantly higher BMI, systolic and diastolic blood pressure, triglycerides, LDL cholesterol, fasting insulin, FPG, and 2-h PG levels, as well as lower HDL cholesterol levels, than the NFG/NGT group. In addition, they had a higher WBC count than those in the NFG/NGT group. Compared with subjects with isolated IFG, subjects with isolated IGT had significantly higher triglyceride and 2-h PG levels and lower HDL cholesterol and FPG levels. Moreover, the isolated IGT group had a higher WBC count than the isolated IFG group (6,530 vs. 6,210/mm^3, $P < 0.05$). Adjustment for age and smoking status did not affect the significance of these differences (Table 3). After adjustment for BMI in addition to age and smoking status, the difference in the WBC count between the two groups was still significant (6,320 vs. 6,090 mm^3, $P < 0.05$). However, after additional adjustment for triglycerides, the difference between these groups was no longer significant (6,280 vs. 6,090/mm^3, $P = 0.06$). There were no significant differences of clinical factors between the isolated IGT and IFG/IGT groups, except for BMI, fasting insulin, FPG, and 2-h PG (Table 2).

The WBC count showed a significant relationship with age, triglycerides, HDL

Table 2—*The mean WBC count and clinical factors*

	NFG/NGT	Isolated IFG	Isolated IGT	IFG/IGT
n	3,753	290	476	201
Age (years)	49.6 ± 5.6	51.3 ± 5.6*	50.2 ± 5.6*†	50.9 ± 5.6*
Smoking status (former/current) (%)‡	19.2/48.4	23.8/41.7	24.0/46.8	25.4/45.8
WBC (per mm^3)§	6,190 (3,720–10,320)	6,210 (3,730–10,340)	6,530 (3,920–10,890)*†	6,580 (3,950–10,950)*†
BMI (kg/m^2)	23.4 ± 2.8	24.2 ± 2.8*	24.4 ± 2.8*	24.9 ± 2.8*†‖
Systolic blood pressure (mmHg)	112 ± 16	117 ± 16*	118 ± 16*	119 ± 16*
Diastolic blood pressure (mmHg)	72 ± 11	75 ± 11*	76 ± 11*	77 ± 11*
Triglycerides (mmol/l)§	1.51 (0.60–3.84)	1.68 (0.66–4.26)*	1.83 (0.72–4.63)*†	1.92 (0.76–4.88)*†
HDL cholesterol (mmol/l)	1.45 ± 0.38	1.44 ± 0.38	1.35 ± 0.38*†	1.35 ± 0.38*†
LDL cholesterol (mmol/l)	3.01 ± 0.78	3.03 ± 0.78	3.11 ± 0.79*	3.10 ± 0.78
Fasting insulin (pmol/l)§	34 (12–98)	39 (14–112)*	41 (15–117)*	46 (16–129)*†‖
FPG (mmol/l)	5.3 ± 0.4	6.3 ± 0.4*	5.5 ± 0.4*†	6.4 ± 0.4*†‖
2-h PG (mmol/l)	5.9 ± 1.0	6.4 ± 1.0*	8.7 ± 1.0*†	9.1 ± 1.0*†‖

Data are means ± SD. The WBC count, triglycerides, and insulin levels were $\log_{10}$ transformed before statistical testing. *$P < 0.05$ vs. NFG/NGT group; †$P < 0.05$ vs. isolated IFG group; ‡P value for the χ^2 test is 0.020; §Geometric means (95% CI) are shown; ‖$P < 0.05$ vs. isolated IGT group.

Table 3—*The mean WBC count and clinical factors adjusted for age and smoking status*

	NFG/NGT	Isolated IFG	Isolated IGT	IFG/IGT
WBC (per mm^3)*	6,000 (3,710–9,690)	6,110 (3,880–9,620)	6,340 (3,990–10,060)†‡	6,410 (4,060–10,120)†‡
BMI (kg/m^2)	23.5 ± 2.9	24.3 ± 2.7†	24.5 ± 2.8†	25.0 ± 2.8†‡§
Systolic blood pressure (mmHg)	113 ± 17	117 ± 16†	118 ± 16†	119 ± 16†
Diastolic blood pressure (mmHg)	73 ± 12	75 ± 11†	76 ± 11†	77 ± 11†
Triglycerides (mmol/l)*	1.50 (0.56–4.01)	1.69 (0.66–4.32)†	1.81 (0.74–4.48)†‡	1.92 (0.77–4.77)†‡§
HDL cholesterol (mmol/l)	1.46 ± 0.40	1.45 ± 0.37	1.37 ± 0.38†‡	1.37 ± 0.37†‡
LDL cholesterol (mmol/l)	3.02 ± 0.82	3.02 ± 0.78	3.11 ± 0.79†	3.10 ± 0.78
Fasting insulin (pmol/l)*	35 (12–106)	40 (15–111)†	42 (15–115)†	47 (16–132)†‡
FPG (mmol/l)	5.3 ± 0.4	6.3 ± 0.4†	5.5 ± 0.4†‡	6.4 ± 0.4†‡§
2-h PG (mmol/l)	5.9 ± 1.0	6.4 ± 1.0†	8.7 ± 1.0†‡	9.1 ± 1.0†‡§

Data are means ± SD. The WBC count, triglycerides, and insulin levels were $\log_{10}$ transformed before statistical testing. *Geometric means (95% CI) are shown; †$P < 0.05$ vs. NFG/NGT group; ‡$P < 0.05$ vs. isolated IFG group; §$P < 0.05$ vs. isolated IGT group.

and LDL cholesterol, fasting insulin, and 2-h PG in the overall study population (Table 4). In stratified analysis, the WBC count showed a significant relationship with BMI, systolic blood pressure, triglycerides, HDL and LDL cholesterol, 2-h PG, and fasting insulin, irrespective of smoking status. In addition, the relationship between the WBC count and diastolic blood pressure was significant in never and former smokers. The WBC count was also significantly correlated with FPG in former and current smokers. By stepwise multiple regression analysis (Table 5), age, triglycerides, HDL cholesterol, fasting insulin, and 2-h PG showed an independent association with the WBC count in the overall study population (adjusted $R^2 = 0.057$). In never smokers, 2-h PG, fasting insulin, triglycerides, and LDL cholesterol were independently associated with WBC count (adjusted $R^2 = 0.058$), and the addition of any of the other parameters did not improve the model. In former smokers, 2-h PG, fasting insulin, and triglycerides showed a significant association with the WBC count (adjusted $R^2 = 0.057$), whereas 2-h PG, triglycerides, LDL cholesterol, and BMI were significantly associated with the WBC count in current smokers (adjusted $R^2 = 0.046$).

CONCLUSIONS — To our knowledge, this is the first report to show a significant difference in the WBC count between subjects with isolated IFG and those with isolated IGT. We also found that the WBC count was correlated with various components of the metabolic syndrome, including BMI, blood pressure, fasting insulin, HDL and LDL cholesterol, and triglycerides. By stepwise multiple regression analyses, the WBC count was independently related to 2-h PG and triglycerides, irrespective of the smoking status.

Our subjects with isolated IGT had significantly higher triglyceride levels and WBC counts, as well as lower HDL cholesterol levels, than the subjects with isolated IFG (Tables 2 and 3). To clarify the difference in the cardiovascular risk profile between individuals with isolated IFG and isolated IGT, previous studies have compared various clinical factors, including lipid levels and blood pressure in Caucasians (17,18) or Asian people (15,16), but little difference has been found. In the Japanese, it was also previously reported (16) that the isolated IFG group and isolated IGT group had similar cardiovascular risk factors. As far as we know, although subclinical inflammation plays an important role in vascular injury and atherosclerosis, there have been no assessments of the differences of inflammatory markers between IFG and IGT. Increased subclinical inflammation may be one of the reasons for the elevated cardiovascular risk in subjects with IGT. Our data are in agreement with the recently

Table 4—*Relationship between log_{10} WBC and various clinical factors*

	Overall		Never smokers (n = 1,515)		Former smokers (n = 954)		Current smokers (n= 2,251)	
	r	P	r	P	r	P	r	P
Age	−0.05	0.0008	NS		NS		NS	
BMI	NS		0.09	0.0008	0.13	<0.0001	0.05	0.02
Systolic blood pressure	NS		0.06	0.02	0.09	0.007	0.05	0.02
Diastolic blood pressure	NS		0.08	0.002	0.09	0.007	NS	
Triglycerides	0.22	<0.0001	0.17	<0.0001	0.21	<0.0001	0.19	<0.0001
HDL cholesterol	−0.18	<0.0001	−0.11	<0.0001	−0.15	<0.0001	−0.12	<0.0001
LDL cholesterol	0.06	0.0001	0.11	<0.0001	0.08	0.02	0.09	<0.0001
Fasting insulin	0.07	<0.0001	0.21	<0.0001	0.17	<0.0001	0.07	0.0005
FPG	NS		NS		0.10	0.002	0.06	0.004
2-h PG	0.10	<0.0001	0.12	<0.0001	0.15	<0.0001	0.10	<0.0001

The WBC count, triglycerides, and insulin levels were $\log_{10}$ transformed before statistical testing. NS, not significant.

Table 5—*Stepwise multiple regression analyses with log_{10} WBC as the dependent variable*

	Overall		Never smokers (n = 1,515)		Former smokers (n = 954)		Current smokers (n = 2,251)	
	β	SE	β	SE	β	SE	β	SE
Age	−0.00072*	0.00028	—		—		—	
BMI	—		NS		NS		−0.00026†	0.00087
Systolic blood pressure	—		NS		NS		NS	
Diastolic blood pressure	—		NS		NS		—	
Triglycerides	0.091†	0.0095	0.036†	0.013	0.058†	0.018	0.093†	0.013
HDL cholesterol	−0.030†	0.0047	NS		NS		NS	
LDL cholesterol	NS		0.0075*	0.0031	NS		0.0080†	0.0029
Fasting insulin	−0.018*	0.0075	0.064†	0.011	0.035*	0.014	NS	
FPG	—		—		NS		NS	
2-h PG	0.0046†	0.0012	0.0047†	0.0018	0.0051*	0.0021	0.0064†	0.0016

The WBC count, triglycerides, and insulin levels were log_{10} transformed before statistical testing. NS, the variable was not accepted as significant for stepwise analysis; —, the variable was not considered because no univariate correlation was found; *$P < 0.05$; †$P < 0.01$.

published results of large prospective cohort studies (11,12) demonstrating a higher risk of cardiovascular disease and death in subjects with IGT than in those with IFG.

We found that the WBC count was increased in isolated IGT subjects, but not in IFG subjects (Tables 2 and 3). Moreover, the WBC count was independently related to 2-h PG regardless of smoking status (Table 5). Festa et al. (22) have reported that the C-reactive protein level is more strongly associated with PG than with fasting glucose in nondiabetic subjects. IL-6 increases postprandially, which is in parallel with glucose (23). Hyperglycemic spikes have more influence on plasma tumor necrosis factor-α, IL-6, and IL-18 concentrations than continuous hyperglycemia (24). Glucose causes significant production of IL-8, a potent chemoattractant that may be responsible for recruitment of neutrophils, by human endothelial cells (25). In addition, IL-8 concentration is increased after an OGTT in nondiabetic subjects (26,27). WBCs increase after a meal (28) or glucose challenge with a significant increase of the plasma IL-8 level (7). The elevated WBC count in our isolated IGT group may reflect such postprandial inflammatory changes.

The WBC count was associated with various clinical factors, including BMI, blood pressure, fasting insulin, HDL and LDL cholesterol, and triglycerides (Table 4). In addition, fasting insulin was independently associated with WBC count in never and former smokers (Table 5). It was previously reported that the WBC count was related to insulin resistance (29) and to components of the metabolic syndrome (30). Our results are consistent with these studies. The circulating IL-6 level was also associated with fasting insulin and blood pressure (31). Because insulin reduces the mediation of acute-phase response by IL-6 (32), insulin resistance could lead to higher concentrations of inflammatory markers. These data may support the hypothesis that subclinical inflammation is a component of the metabolic syndrome (33).

We found that the WBC count was independently related to not only 2-h PG but also lipoproteins (Table 5). The relationship between the WBC count and lipoproteins may be indirect and mediated via other pathogenetic factors, such as body fat or insulin resistance. However, a direct effect of triglycerides on WBCs is not necessarily excluded. We found that the difference in the WBC count between the isolated IFG group and isolated IGT group did not reach statistical significance after adjustment for triglycerides in addition to age and smoking status. According to recent studies, the increment of triglyceride level after a fat load is paralleled by the increment of WBCs (34), and triglycerides have been shown to directly activate neutrophils (35).

The WBC count was not correlated with BMI and systolic blood pressure in the overall study population, although the relationship was significant in all of the subgroups stratified by smoking status (Table 4). Current smokers had significantly lower BMI and systolic blood pressure levels than never and former smokers, whereas the range of the WBC count in current smokers was higher and wider than that of never and former smokers (Table 1). Therefore, the results for the overall population differed from those obtained by stratified analysis. Stepwise regression analyses yielded adjusted R^2 values of 0.046–0.058 ($P < 0.0001$). Although these values mean that there is a significant association, the low R^2 values indicate that other factors must also have an influence on WBC count.

The present study had several limitations. First, we did not assess C-reactive protein, which is a more specific marker of inflammation and has attracted attention as a strong predictor of cardiovascular events. We assessed WBC count rather than other inflammatory markers because the WBC count is one of the most common laboratory tests. Further studies of other inflammatory markers are required to confirm the differences between subjects with IGT and those with IFG. Second, we examined 4,720 Japanese men in this study. Cardiovascular risk as well as the prevalence of IGT and IFG is influenced by the sex and ethnicity of the study population. Therefore, further data obtained by comparing cardiovascular risk factors between IFG and IGT from a variety of populations are desirable. Third, our results suggest that chronic subclinical inflammation may be one mechanism contributing to the excess risk of subjects with IGT. However, a cross-sectional study cannot provide information on the causal relationship between the WBC count and excess cardiovascular risk in subjects with IGT,

so this needs to be elucidated in future prospective studies.

In summary, our subjects with IGT had a higher WBC count than those with IFG. The WBC count was associated with various components of the metabolic syndrome and was independently related to 2-h PG and triglycerides. Increased subclinical inflammation may contribute to the elevated cardiovascular risk in subjects with IGT.

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