

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/mm³, $P < 0.05$). 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 μ mol/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.

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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 log₁₀ 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/l and 2-h PG between 7.8 and 11.1 mmol/l), n = 201. Blood pressure was measured by a mercury sphygmomanom-

eter 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 log₁₀ 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/mm³, 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 mm³, P < 0.05). However, after additional adjustment for triglycerides, the difference between these groups was no longer significant (6,280 vs. 6,090/mm³, 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 log₁₀ 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 log₁₀ 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 R² = 0.057). In never smokers, 2-h PG, fasting insulin, triglycerides, and LDL cholesterol were independently associated with WBC count (adjusted R² = 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 R² = 0.057), whereas 2-h PG, triglycerides, LDL cholesterol, and BMI were significantly associated with the WBC count in current smokers (adjusted R² = 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 log₁₀ 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 log₁₀ transformed before statistical testing. NS, not significant.

Table 5—Stepwise multiple regression analyses with log₁₀ 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 log₁₀ 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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References

- Brown DW, Giles WH, Croft JB: White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. *J Clin Epidemiol* 54:316–322, 2001
- Weijenberg MP, Feskens EJ, Kromhout D: White blood cell count and the risk of coronary heart disease and all-cause mortality in elderly men. *Arterioscler Thromb Vasc Biol* 16:499–503, 1996
- Gillum RF, Ingram DD, Makuc DM: White blood cell count, coronary heart disease, and death: the NHANES I Epidemiologic Follow-up Study. *Am Heart J* 125:855–863, 1993
- Elkind MS, Cheng J, Boden-Albala B, Paik MC, Sacco RL: Elevated white blood cell count and carotid plaque thickness: the Northern Manhattan Stroke Study. *Stroke* 32:842–849, 2001
- Mehta JL, Saldeen TG, Rand K: Interactive role of infection, inflammation and traditional risk factors in atherosclerosis and coronary artery disease. *J Am Coll Cardiol* 31:1217–1225, 1998
- Ross R: Atherosclerosis—an inflammatory disease. *N Engl J Med* 340:115–126, 1999
- Van Oostrom AJ, Sijmonsma TP, Verseyden C, Jansen EH, De Koning EJ, Rabelink TJ, Castro Cabezas M: Postprandial recruitment of neutrophils may contribute to endothelial dysfunction. *J Lipid Res* 44:576–583, 2003
- de Servi S, Ricevuti G, Mazzone A, Ghio S, Zito A, Raffaghello S, Specchia G: Granulocyte function in coronary artery disease. *Am J Cardiol* 68:64B–68B, 1991
- Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA: Leukocytes and the risk of ischemic diseases. *JAMA* 257:2318–2324, 1987
- Murohara T, Buerke M, Lefer AM: Polymorphonuclear leukocyte-induced vasoconstriction and endothelial dysfunction: role of selectins. *Arterioscler Thromb* 14:1509–1519, 1994
- Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A: Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Funagata Diabetes Study. *Diabetes Care* 22:920–924, 1999
- DECODE Study Group, European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 161:397–404, 2001
- Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Bonadonna R, Muggeo M: Plasma glucose within the normal range is not associated with carotid atherosclerosis: prospective results in subjects with normal glucose tolerance from the Bruneck Study. *Diabetes Care* 22:1339–1346, 1999
- De Michele M, Panico S, Celentano E, Covetti G, Intriери M, Zarrilli F, Sacchetti L, Tang R, Bond MG, Rubba P: Association of impaired glucose homeostasis with preclinical carotid atherosclerosis in women: impact of the new American Diabetes Association criteria. *Metabolism* 51:52–56, 2002
- Lim SC, Tai ES, Tan BY, Chew SK, Tan CE: Cardiovascular risk profile in individuals with borderline glycemia: the effect of the 1997 American Diabetes Association diagnostic criteria and the 1998 World Health Organization Provisional Report. *Diabetes Care* 23:278–282, 2000
- DECODA Study Group, International Diabetes Epidemiology Group: Cardiovascular risk profile assessment in glucose-intolerant Asian individuals: an evaluation of the World Health Organization two-step strategy: the DECODA Study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia). *Diabet Med* 19:549–557, 2002
- H Larsson, G Berglund, F Lindgarde, B Ahren: Comparison of ADA and WHO criteria for diagnosis of diabetes and glucose intolerance (Letter). *Diabetologia* 41:1124–1125, 1998
- Metcalf PA, Scragg RK: Comparison of WHO and ADA criteria for diagnosis of glucose status in adults. *Diabetes Res Clin Pract* 49:169–180, 2000
- Ozaki K, Okubo M, Mori H, Mito K, Hara H, Kohno N: Decreased insulin secretion and dyslipidemia coexist in subjects with impaired fasting glucose. *Diabetes Res Clin Pract* 55:159–164, 2002
- Friedewald WT, Levy RI, Fredrickson D: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
- Corre F, Lellouch J, Schwartz D: Smoking and leucocyte-counts: results of an epidemiological survey. *Lancet* 2:632–634, 1971
- Festa A, D'Agostino R Jr, Tracy RP, Haffner SM: C-reactive protein is more strongly related to post-glucose load glucose than to fasting glucose in non-diabetic subjects: the Insulin Resistance Atherosclerosis Study. *Diabet Med* 19:939–943, 2002
- Nappo F, Esposito K, Cioffi M, Giugliano G, Molinari AM, Paolisso G, Marfella R, Giugliano D: Postprandial endothelial activation in healthy subjects and in type 2 diabetic patients: role of fat and carbohydrate meals. *J Am Coll Cardiol* 39:1145–1150, 2002
- Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliari L, Ceriello A, Giugliano D: Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 106:2067–2072, 2002
- Srinivasan S, Yeh M, Danziger EC, Hatley ME, Riggan AE, Leitinger N, Berliner JA, Hedrick CC: Glucose regulates monocyte adhesion through endothelial production of interleukin-8. *Circ Res* 92:371–377, 2003
- Straczkowski M, Dzienis-Straczkowska S, Stepien A, Kowalska I, Szelachowska M, Kinalska I: Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-alpha system. *J Clin Endocrinol Metab* 87:4602–4606, 2002
- Straczkowski M, Kowalska I, Nikolajuk A, Dzienis-Straczkowska S, Szelachowska M, Kinalska I: Plasma interleukin 8 concentrations in obese subjects with impaired glucose tolerance. *Cardiovasc Diabetol* 2:5, 2003
- Hansen K, Sickelmann F, Pietrowsky R, Fehm HL, Born J: Systemic immune changes following meal intake in humans. *Am J Physiol* 273:R548–R553, 1997
- Temelkova-Kurktschiev T, Siebert G, Bergmann S, Henkel E, Koehler C, Jaross W, Hanefeld M: Subclinical inflammation is strongly related to insulin resistance but not to impaired insulin secretion in a high risk population for diabetes. *Metabolism* 51:743–749, 2002
- Nakanishi N, Sato M, Shirai K, Nakajima K, Murakami S, Takatorige T, Suzuki K, Tataru K: Associations between white blood cell count and features of the metabolic syndrome in Japanese male office workers. *Ind Health* 40:273–277, 2002
- Fernandez-Real JM, Vayreda M, Richart C, Gutierrez C, Broch M, Vendrell J, Ricart W: Circulating interleukin 6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. *J Clin Endocrinol Metab* 86:1154–1159,

- 2001
32. Campos SP, Baumann H: Insulin is a prominent modulator of the cytokine-stimulated expression of acute-phase plasma protein genes. *Mol Cell Biol* 12:1789–1797, 1992
33. Festa A, D'Agostino R Jr, Howard G, Mykanen L, Tracy RP, Haffner SM: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 102:42–47, 2000
34. Van Oostrom AJ, Sijmonsma TP, Rabelink TJ, Van Asbeck BS, Cabezas MC: Postprandial leukocyte increase in healthy subjects. *Metabolism* 52:199–202, 2003
35. Wanten G, van Emst-De Vries S, Naber T, Willems P: Nutritional lipid emulsions modulate cellular signaling and activation of human neutrophils. *J Lipid Res* 42:428–436, 2001