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ORIGINAL ARTICLE

Relationships between C-reactive protein, white blood cell count, and insulin resistance in a Chinese population

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Abstract This study is to clarify whether C-reactive protein (CRP) and white blood cell (WBC) count influence insulin homeostasis to the same degree. Serum CRP and peripheral WBC were measured in 739 subjects with normal glucose regulation, 512 with impaired glucose regulation, and 502 newly diagnosed diabetic patients. Levels of insulin resistance (IR) were assessed using the index of homeostasis model (HOMA-IR). Serum CRP and WBC were significantly correlated with HOMA-IR and risk factors of IR. Relative risks of IR for each 1-SD increase of Ln (CRP) and Ln (WBC) were 1.28 (1.10–1.47) and 1.15 (1.01–1.31), respectively after adjustment for age, sex, obesity measurements, and other traditional risk factors. Additional adjustment for WBC slightly attenuated the association between CRP and IR [1.25 (1.08–1.45); $P = 0.003$] whereas adjustment for CRP substantially attenuated the association of WBC with IR toward null ($P = 0.134$). Moreover, individuals with both high levels of CRP and WBC were at higher risks of IR than those with high CRP or WBC alone. Both CRP and WBC were significantly associated with risks of IR. CRP might be a more effective biomarker in terms of the association with IR.

Keywords C-reactive protein · White blood cell count · Insulin resistance

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Introduction

Insulin resistance (IR) is the primary defect in both initiation and progression of type 2 diabetes. Recently, it has been demonstrated that IR is associated with a state of chronic low-grade inflammation [1, 2]. Mediators released from cells of the immune system as well as from adipose tissue are critically involved in this process [3]. The inflammation is activated by mediators including white blood cell (WBC), C-reactive protein (CRP), interleukin (IL)-6 and plasminogen activator inhibitor-1, etc. [4–6].

Recent studies demonstrated that both CRP and WBC were significantly correlated with IR cross sectionally and predicted the development of type 2 diabetes prospectively [7–11]. They were elevated in diabetic patients and decreased after treatments [12]. It was also reported that increased CRP and WBC were associated with arterial stiffness and incident coronary artery diseases among diabetic patients [13, 14]. However, it remains unclear whether CRP and WBC influence insulin homeostasis to the same degree.

In this study, we investigated and compared the associations of CRP and WBC with IR in a Chinese population aged 40 years and above.

Results

General characteristics

The characteristics of the study population by different glycaemic status were summarized in Table 1. Except for sex distribution and percentages of current smokers and alcohol consumers, characteristics were significantly different among groups. Subjects with impaired glucose regulation (IGR) or type 2 diabetes generally had more

Table 1 Clinical and biochemical characteristics of study participants by glycaemic status

Characteristics	NGR	IGR	Type 2 diabetes	*P* value
Number of subjects	739	512	502	
Female (%)	63.2	63.3	58.6	0.19
Age (years)	61.3 ± 9.9	63.5 ± 9.0	62.8 ± 9.3	<0.001
Current smoking (%)	20.0	18.8	24.3	0.07
Alcohol consumption (%)	13.5	12.3	15.9	0.23
BMI (kg/m^2)	24.2 ± 3.1	25.5 ± 3.2	26.4 ± 3.7	<0.001
WHR	0.87 ± 0.06	0.88 ± 0.06	0.90 ± 0.06	<0.001
SBP (mmHg)	136 ± 20	145 ± 21	148 ± 22	<0.001
DBP (mmHg)	79 ± 10	83 ± 10	84 ± 11	<0.001
TG (mmol/l)	1.14 (0.80–1.63)	1.46 (1.01–2.12)	1.71 (1.19–2.43)	<0.001
TC (mmol/l)	4.80 ± 0.84	4.96 ± 0.90	5.07 ± 1.15	<0.001
HDL (mmol/l)	1.47 (1.25–1.73)	1.37 (1.16–1.61)	1.28 (1.08–1.51)	<0.001
LDL (mmol/l)	2.71 ± 0.68	2.81 ± 0.73	2.85 ± 0.83	0.002
FPG (mmol/l)	5.32 ± 0.48	5.97 ± 0.55	7.91 ± 2.07	<0.001
2 h PPG (mmol/l)	6.11 ± 0.99	8.49 ± 1.42	14.23 ± 4.50	<0.001
FINS (mIU/l)	4.30 (2.10–7.60)	5.90 (2.80–10.98)	7.85 (3.50–14.43)	<0.001
HOMA-IR	0.99 (0.51–1.81)	1.52 (0.76–2.89)	2.67 (1.23–5.06)	<0.001
FBCI	0.84 (0.41–1.44)	0.97 (0.46–1.84)	1.01 (0.45–1.92)	0.001
CRP (mg/l)	1.70 (0.70–3.50)	2.60 (1.30–5.40)	3.10 (1.50–6.03)	<0.001
WBC ($\times 10^9$/l)	5.40 (4.60–6.40)	5.90 (5.00–6.90)	6.00 (5.20–7.20)	<0.001

Data were means ± S.D. or medians (interquartile range) for skewed variables or proportions for categorical variables

BMI body mass index, *WHR* waist-to-hip ratio, *TG* triglycerides, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HOMA-IR* homeostasis model assessment of insulin resistance, *FBCI* fasting β-cell function index, *FPG* fasting plasma glucose, *PPG* post-load plasma glucose, *FINS* fasting insulin

adverse risk profiles than those with normal glucose regulation (NGR), such as higher body mass index (BMI) and waist-to-hip ratio (WHR), higher blood pressure, more disturbed lipid metabolism, increased concentrations of fasting insulin and fasting β-cell secretion.

CRP levels in type 2 diabetes were significantly higher than those in NGR ($P < 0.001$). Meanwhile, CRP concentrations in IGR group were also significantly higher than those in NGR group ($P < 0.001$). After adjustment for a wide range of covariates, these findings did not materially change (Fig. 1a). With regard to WBC count in different groups, similar results were obtained (Fig. 1b).

Correlations between CRP, WBC and risk factors of insulin resistance

CRP concentrations and WBC count were closely related ($r = 0.202$, $P < 0.001$), and they both were positively and significantly correlated with the index of homeostasis model assessment of IR (HOMA-IR) ($r = 0.232$, $P < 0.001$; $r = 0.127$, $P < 0.001$, respectively). Correlations between CRP, WBC, and anthropometric and metabolic risk factors for IR are shown in Table 2. CRP and WBC were positively correlated with BMI, WHR, blood pressure, triglycerides, total cholesterol, low-density lipoprotein (LDL), and glucose levels.

Comparisons of associations between CRP and WBC with insulin resistance

After adjustment for age, sex, obesity measurements and other traditional risk factors, the risk of IR was higher among individuals with high CRP than those with low CRP [odds ratio (OR) 1.28, 95% confidence interval (95% CI) 1.10–1.47; $P = 0.001$] and higher among subjects with high WBC than low WBC (OR 1.15, 95% CI 1.01–1.31; $P = 0.040$). The significance remained for association between CRP and IR after further adjustment for WBC (OR 1.25, 95% CI 1.08–1.45; $P = 0.003$). In contrast, higher WBC levels were no longer associated with higher risks of IR after additional controlling for CRP concentrations (Table 3).

Combined effect of CRP and WBC on risks of insulin resistance

Participants with high values of both CRP and WBC tended to be older, were more likely to be current smokers,

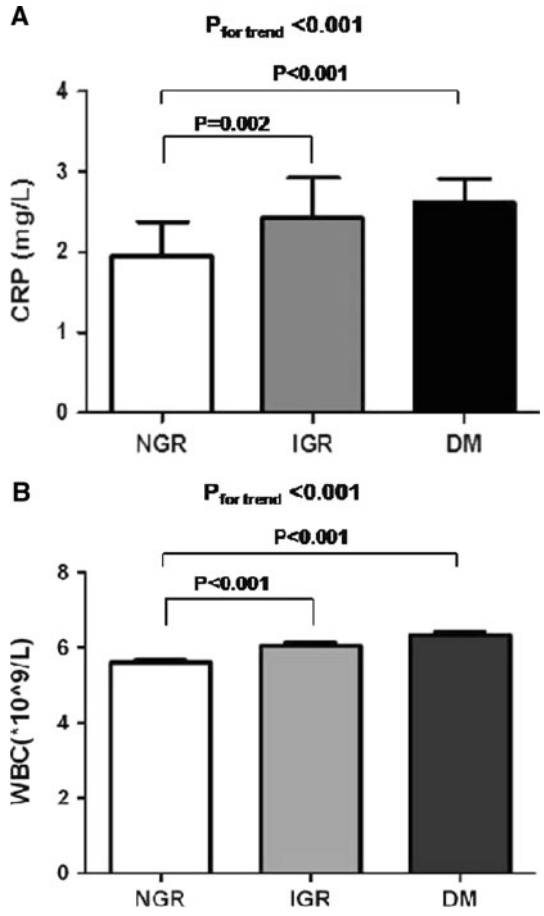

Fig. 1 CRP levels (**a**) and WBC count (**b**) in three groups (NGR, IGR, and type 2 diabetes) after adjustment for age, sex, current smoking and alcohol consumption, BMI, WHR, systolic and diastolic blood pressure, and serum lipid levels (TC, TG, HDL, and LDL). Abbreviations: *CRP* C-reactive protein, *WBC* white blood cell, *NGR* normal glucose regulation, *IGR* impaired glucose regulation, and *DM* diabetes mellitus

had significantly higher BMI and WHR, higher blood pressure, higher fasting and post-load glucose levels, higher concentrations of triglycerides and LDL, and lower high-density lipoprotein (HDL) than those with low CRP and low WBC levels (all $P < 0.05$; Table 4).

Furthermore, participants with both high CRP and high WBC levels had significantly increased values of HOMA-IR compared with those having low CRP and low WBC ($P < 0.001$). Subjects with high CRP and low WBC also had a higher HOMA-IR than those with low CRP and low WBC ($P < 0.01$), whereas no significant difference was found between participants with low CRP and high WBC and those with low CRP and low WBC (Table 4). Furthermore, risks of IR increased across the four groups in different adjusting models. The ORs were 1.00, 1.26, 2.20, and 2.49 for groups of low CRP low WBC, low CRP high WBC, high CRP low WBC, and high CPR high WBC, respectively, after adjustment for other IR risk factors (P value for trend = 0.039; Table 5).

Table 2 Correlations between CRP, WBC, and risk factors of insulin resistance

Variables	CRP	WBC
CRP (mg/l)	–	$r = 0.202$; $P < 0.001$
WBC ($\times 10^9$/l)	$r = 0.202$; $P < 0.001$	–
Age (years)	$r = 0.195$; $P < 0.001$	$r = -0.003$; $P = 0.885$
BMI (kg/m^2)	$r = 0.317$; $P < 0.001$	$r = 0.160$; $P < 0.001$
WHR	$r = 0.245$; $P < 0.001$	$r = 0.134$; $P < 0.001$
SBP (mmHg)	$r = 0.196$; $P < 0.001$	$r = 0.128$; $P < 0.001$
DBP (mmHg)	$r = 0.097$; $P < 0.001$	$r = 0.115$; $P < 0.001$
TG (mmol/l)	$r = 0.190$; $P < 0.001$	$r = 0.193$; $P < 0.001$
TC (mmol/l)	$r = 0.102$; $P < 0.001$	$r = 0.092$; $P < 0.001$
HDL (mmol/l)	$r = -0.158$; $P < 0.001$	$r = -0.198$; $P < 0.001$
LDL (mmol/l)	$r = 0.103$; $P < 0.001$	$r = 0.061$; $P = 0.011$
FPG (mmol/l)	$r = 0.149$; $P < 0.001$	$r = 0.109$; $P < 0.001$
2 h PPG (mmol/l)	$r = 0.217$; $P < 0.001$	$r = 0.143$; $P < 0.001$

BMI body mass index, *WHR* waist-to-hip ratio, *TG* triglycerides, *TC* total cholesterol, *LDL* low-density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *PPG* post-load plasma glucose

Table 3 Risks of insulin resistance with each 1-SD increase of Ln (CRP) or Ln (WBC)

Model	OR (95% CI)	P value
Ln (CRP) (model A)	1.66 (1.47–1.88)	<0.001
Ln (CRP) (model B)	1.28 (1.10–1.47)	0.001
Ln (CRP) (model C)	1.25 (1.08–1.45)	0.003
Ln (WBC) (model A)	1.36 (1.21–1.52)	<0.001
Ln (WBC) (model B)	1.15 (1.01–1.31)	0.040
Ln (WBC) (model D)	1.11 (0.97–1.27)	0.134

Model A adjusted for age and sex, *Model B* additionally adjusted for current smoking, alcohol consumption, BMI, WHR, SBP, DBP, and serum lipid levels (TC, TG, HDL, and LDL) based on model A, *Model C* additionally adjusted for WBC count based on model B, and *Model D* additionally adjusted for CRP levels based on model B

Discussion

In this study, we confirmed the associations of CRP and WBC with IR in a Chinese population aged 40 years and above. The major findings of our study were: (1) CRP and WBC levels were increased significantly across groups with different glycaemic status, i.e., from NGR, IGR to type 2 diabetes. They were also significantly associated with HOMA-IR and risk factors of IR, such as BMI for general obesity, WHR for abdominal fat accumulation and adverse lipid profile; (2) Increases in CRP levels and WBC count were both associated with higher risks of IR independent of other established risk factors. However, high CRP levels were independently associated with IR after adjustment for WBC, whereas elevated WBC count was no

Table 4 Characteristics of study participants by combined CRP and WBC levels

Characteristics	Low CRP low WBC[a]	Low CRP high WBC	High CRP low WBC	High CRP high WBC
Number of subjects	171	58	73	126
Female (%)	69.0	46.6†	64.4	58.7
Age (years)	61.1 ± 9.7	57.7 ± 8.1*	64.1 ± 9.6*	64.6 ± 8.7†
Current smoking (%)	11.1	34.5†	26.0*	27.8‡
Alcohol consumption (%)	8.8	19.0	19.2*	11.9
BMI (kg/m^2)	23.0 ± 2.9	23.9 ± 3.0*	26.0 ± 3.7‡	26.8 ± 3.5‡
WHR	0.85 ± 0.05	0.86 ± 0.06	0.88 ± 0.06‡	0.91 ± 0.06‡
SBP (mmHg)	133 ± 20	134 ± 19	141 ± 24†	148 ± 21‡
DBP (mmHg)	78 ± 10	79 ± 10	81 ± 13	83 ± 11‡
TG (mmol/l)	1.09 (0.73–1.57)	1.17 (0.82–1.66)	1.24 (0.84–1.69)	1.61 (1.06–2.40)†
TC (mmol/l)	4.83 ± 0.95	4.57 ± 0.81	4.75 ± 0.93	5.04 ± 0.92
HDL (mmol/l)	1.58 (1.27−1.86)	1.45 (1.18−1.63)†	1.48 (1.02−1.78)	1.26 (1.04−1.42)‡
LDL (mmol/l)	2.67 ± 0.73	2.47 ± 0.75	2.70 ± 0.73	2.92 ± 0.75†
FPG (mmol/l)	5.77 ± 1.28	5.97 ± 1.43	6.37 ± 1.82†	6.78 ± 2.10‡
2 h PPG (mmol/l)	7.31 ± 3.06	8.59 ± 3.53†	9.29 ± 4.33‡	10.74 ± 4.53‡
HOMA-IR	0.97 (0.51-1.78)	1.36 (0.42–2.09)	1.65 (0.75–3.19)†	2.25 (1.18–4.00)‡

Data were means ± S.D. or medians (interquartile range) for skewed variables or proportions for categorical variables

BMI body mass index, *WHR* waist-to-hip ratio, *TG* triglycerides, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HOMA-IR* homeostasis model assessment of insulin resistance

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$

[a] Low CRP low WBC served as the reference group

Table 5 Risks of insulin resistance by combined CRP and WBC levels

Model	Low CRP high WBC		High CRP low WBC		High CRP high WBC		*P* value for trend
	OR[a] (95% CI)	*P* value	OR[a] (95% CI)	*P* value	OR[a] (95% CI)	*P* value	
Model A	1.42 (0.56–3.57)	0.458	2.88 (1.38–6.05)	0.005	6.04 (3.21–11.37)	<0.001	<0.001
Model B	1.41 (0.54–3.67)	0.479	2.96 (1.34–6.54)	0.007	6.15 (3.07–12.33)	<0.001	<0.001
Model C	1.26 (0.45–3.54)	0.666	2.20 (0.85–5.68)	0.105	2.49 (1.06–5.90)	0.037	0.039

Model A adjusted for age and sex, *Model B* additionally adjusted for current smoking, alcohol consumption, SBP and DBP based on model A, and *Model C* additionally adjusted for BMI, WHR, and serum lipid levels (TC, TG, HDL, and LDL) based on model B

[a] Low CRP low WBC served as the reference group

longer associated with IR after adjustment for CRP; (3) Subjects with increased concentrations of both CRP and WBC had the most unfavorable metabolic profile compared with those having low CRP and/or low WBC, including HOMA-IR. The combination of high CRP and high WBC was associated with the highest risks of IR.

Previous studies have reported an association between CRP and IR and between WBC and IR, respectively. Only a few have, however, evaluated the effects of CRP and its interaction with WBC on the risks of IR. Also, there are few data available regarding which biomarker is superior when it comes to associations with IR. Except from those findings that both CRP and WBC were correlated with HOMA-IR and various risk factors of IR and that CRP and WBC were both independent risk factors for IR, which were consistent with several previous studies [15–18], we also found that the role of CRP in IR might be more significant than that of WBC. Moreover, an even better association with IR was obtained when both CRP and WBC were considered. Individuals with high levels of both CRP and WBC were at higher risks of IR than those with high levels of CRP or WBC alone.

The mechanism that could explain the associations of CRP and WBC with IR has not yet been fully clarified. Stimuli would result in cytokine hypersecretion and eventually lead to IR and diabetes in genetically or metabolically predisposed individuals. Cytokines, mainly including IL-1, IL-6, and tumor necrosis factor (TNF)-α, also exert major stimulatory effects on hepatic synthesis of acute-phase proteins such as CRP [19]. On the other hand, decreased insulin sensitivity may lead to enhanced CRP expression by counteracting the physiological effect of

insulin on hepatic acute-phase protein synthesis [20, 21]. Some studies have shown that IL-6, a potent WBC differentiation factor that is produced mostly in adipose tissue, is associated with IR [22]. Hormones are another possible link between WBC and insulin sensitivity. Varieties of hormones have receptors on the surface of WBCs and have been shown to play a role in their production and maturation. Some of them, such as insulin, cortisol, and sex hormones, are also associated with IR.

The explanation for the finding that the association with IR was stronger for CRP than WBC was that the way WBC count influenced IR might be a part of the way that CRP level did. Another explanation might be that CRP level indicated the body status for a longer time than WBC. Therefore, CRP was a more effective biomarker for the metabolic status and potential low-grade inflammatory state than WBC.

Several limitations of our study had also to be acknowledged. First, although our study subjects were originated from an epidemiological study, it should not be regarded as a randomly selected sample from the general population due to the fact that only those who agreed to participate were enrolled in this study. Possible selection bias could not be ruled out. Second, we used the index of homeostasis model for the assessment of IR rather than a more precise measurement such as the euglycaemic clamp. However, studies showed that HOMA-IR is a well-validated measurement for IR in epidemiological studies and well correlated with reference techniques (0.58–0.88). Third, a cross-sectional study cannot provide information on a causal relationship. Therefore, longitudinal studies are warranted to further clarify the associations of CRP and WBC with IR.

On the basis of our results, although both CRP levels and WBC count were significantly associated with risks of IR, CRP might be a more effective biomarker than WBC. Increased levels of both CRP and WBC indicated the highest risk for IR more accurately than one of them alone.

Materials and methods

Study subjects

We performed a two-step blood glucose survey in 2004–2005 in a population selected from an urban community of Shanghai, which has been reported previously [23–25]. In brief, we first invited all registered permanent residents aged 40–80 years in Youyi community to participate in a screening examination, which included a fasting capillary blood glucose test. After exclusion of subjects with diagnosed diabetes, we classified the screened participants into three groups according to their capillary glucose concentrations: 7.0 mmol/l or above, 5.6–6.9 mmol/l, or below 5.6 mmol/l. We selected randomly a sex- and age-matched sample from these three groups for further investigation, which included questionnaire interview, collecting information on lifestyle, medical history and medications, anthropometric measurements, a 75-g oral glucose tolerance test (OGTT), and blood and urine sampling. A total of 9,219 subjects (27% of the registered permanent residents) participated in the first step of our survey, among whom, 2,297 were selected and 1,835 (the retention rate, 80%) eventually participated in the second step of the survey. Eighty-two subjects were excluded from this analysis due to missing information on fasting plasma glucose (FPG) or 2-h post-load plasma glucose (PPG) ($n = 35$), serum CRP concentration ($n = 8$), or WBC count ($n = 39$). Thus, 1,753 subjects were finally included in this analysis, and reclassified as NGR ($n = 739$), IGR ($n = 512$), and newly diagnosed type 2 diabetes ($n = 502$), determined by OGTT according to the 1999 WHO criteria.

The Institutional Review Board of Rui-Jin Hospital approved the study protocol. Informed consent was obtained from each participant.

Clinical and biochemical measurements

The body height, body weight, and waist and hip circumferences were measured by the same physicians who completed training. BMI was calculated using the formula of weight/height^2 (kg/m^2). Blood pressure was measured at the non-dominant arm with an automated electronic device (OMRON Model1 Plus, Omron Company, Kyoto, Japan) three times consecutively with 1-min interval after at least 5 min rest in the seated position. The mean of the three times was used for analysis. Plasma glucose concentrations and serum triglycerides, total cholesterol, HDL, and LDL were measured using an autoanalyzer (Beckman CX-7 Biochemical Autoanalyser, Brea, CA). WBC count was determined using an automated cell counter. Serum CRP concentration was measured using highly sensitive competitive immunoassay (antigens and antibodies from BioCheck, Foster City, CA). The intra-and inter-assay coefficients of variation for CRP concentration were 4.4 and 3.3%, respectively. Serum insulin concentration was measured by a radioimmunoassay (Sangon Company, Shanghai, China). HOMA-IR and fasting β-cell function index (FBCI) were then calculated according to the formulas: HOMA-IR = fasting insulin concentration (mIU/l) $\times$ FPG concentration (mmol/l)/22.5 and FBCI = fasting insulin concentration (mIU/l)/FPG concentration (mmol/l). All the tests were conducted in the same laboratory.

Statistical analysis

We used SAS version 8.1 (SAS Institute, Cary, NC) for database management and statistical analysis. Data were presented as means ± S.D. or medians (interquartile range). Distributions of serum triglycerides, HDL, fasting insulin, HOMA-IR, CRP, and WBC levels were skewed; therefore, logarithmically transformed values were used. Analysis of variance (ANOVA) or χ^2 tests were applied to compare variables among groups with different glycaemic status. Pearson's correlation coefficients were calculated to determine whether a significant relationship existed among CRP, WBC, and relevant risk factors of IR. Multiple logistic regression analyses were performed to assess the independent relationship of CRP and WBC with IR, which was defined as HOMA-IR above its 75th percentile.

Furthermore, we defined CRP concentrations as "high" if they fell in the highest quartile in our population (≥4.8 mg/l) and as "low" with those in the lowest quartile (<1.0 mg/l). The same definition was applied to WBC count (highest quartile $\geq 6.80 \times 10^9$/l, lowest quartile $< 4.90 \times 10^9$/l). The study population was then reclassified into four groups: low CRP and low WBC, low CRP and high WBC, high CRP and low WBC, and high CRP and high WBC. Using the group of low CRP and low WBC as the reference, risks of IR in the other three groups were evaluated using logistic regression analyses.

All the statistical tests were two-tailed, and a P value <0.05 was considered statistically significant.

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References

1. G. Hotamisligil, Inflammation and metabolic disorders. Nature **444**, 860–867 (2006)
2. K. Wellen, G. Hotamisligil, Inflammation, stress and diabetes. J. Clin. Invest. **115**, 1111–1119 (2005)
3. E. Rosen, B. Spiegelman, Adipocytes as regulators of energy balance and glucose homeostasis. Nature **444**, 847–853 (2006)
4. J. Yudkin, I. Juhan-Vague, E. Hawe, S. Humphries, G. di Minno, M. Margaglione, E. Tremoli, T. Kooistra, P. Morange, P. Lundman, V. Mohamed-Ali, A. Hamsten, HIFMECH Study Group, Low-grade inflammation may play a role in the etiology of the metabolic syndrome in patients with coronary heart disease: the HIFMECH study. Metabolism **53**, 852–857 (2004)
5. R. Retnakaran, A. Hanley, P. Connelly, S. Harris, B. Zinman, Elevated C-reactive protein in Native Canadian children: an ominous early complication of childhood obesity. Diabetes Obes. Metab. **8**, 483–491 (2006)
6. A. Festa, R. D'Agostino Jr., R. Tracy, Elevated levels of acute phase proteins and plasminogen activator inhibitor-1 (PAI-1) predict the development of type 2 diabetes mellitus: the Insulin Resistance Atherosclerosis Study (IRAS). Diabetes **51**, 1131–1137 (2002)
7. G. Yuan, L. Zhou, J. Tang, Y. Yang, W. Gu, F. Li, J. Hong, Y. Gu, X. Li, G. Ning, M. Chen, Serum CRP levels are equally elevated in newly diagnosed type 2 diabetes and impaired glucose tolerance and related to adiponectin levels and insulin sensitivity. Diabetes Res. Clin. Pract. **72**, 244–250 (2006)
8. T. Temelkova-Kurktschiev, G. Siegert, S. Bergmann, E. Henkel, C. Koehler, W. Jaross, M. Hanefeld, 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)
9. B. Vozarova, C. Weyer, R. Lindsay, R. Pratley, C. Bogardus, P. Tataranni, High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes **51**, 455–461 (2002)
10. N. Nakanishi, H. Yoshida, Y. Matsuo, K. Suzuki, K. Tatara, White blood-cell count and the risk of impaired fasting glucose or type II diabetes in middle-aged Japanese men. Diabetologia **45**, 42–48 (2002)
11. P. Tong, K. Lee, W. So, M. Ng, W. Chan, M. Lo, N. Chan, J. Chan, White blood cell count is associated with macro- and microvascular complications in Chinese patients with type 2 diabetes. Diabetes Care **27**, 216–222 (2004)
12. R. Farah, R. Shurtz-Swirski, O. Lapin, Intensification of oxidative stress and inflammation in type 2 diabetes despite antihyperglycemic treatment. Cardiovasc. Diabetol. **7**, 20 (2008)
13. J. Tian, Y. Yang, Q. Cheng, H. Huang, R. Li, G. Jiang, S. Liu, X. Li, G. Ning, Association of WBC count and glucose metabolism among Chinese population aged 40 years and over. Diabetes Res. Clin. Pract. **82**, 132–138 (2008)
14. I. Wakabayashi, H. Masuda, Association of acute-phase reactants with arterial stiffness in patients with type 2 diabetes mellitus. Clin. Chim. Acta **365**, 230–235 (2006)
15. M. Mendall, P. Patel, L. Ballam, D. Strachan, T. Northfield, C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ **312**, 1061–1065 (1996)
16. J. Yudkin, C. Stehouwer, J. Emeis, S. Coppack, C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction. Arterioscler. Thromb. Vasc. Biol. **19**, 972–978 (1999)
17. M. Desai, D. Dalal, R. Santos, J. Carvalho, K. Nasir, R. Blumenthal, Association of body mass index, metabolic syndrome, and leukocyte count. Am. J. Cardiol. **97**, 835–838 (2006)
18. V. Lohsoonthorn, B. Dhanamun, M. Williams, 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. **19**, 339–345 (2006)
19. I. Kushner, Regulation of the acute phase response by cytokines. Perspect. Biol. Med. **36**, 611–622 (1993)
20. S. Campos, H. Baumann, Insulin is a prominent modulator of the cytokine-stimulated expression of acute-phase plasma protein genes. Mol. Cell. Biol. **12**, 1789–1797 (1992)
21. A. Festa, R. Agostion Jr., G. Howard, Chronic subclinical inflammation as part of the Insulin Resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRSA). Circulation **120**, 42–47 (2000)
22. J. Fernandez-Real, M. Vayreda, C. Richart, C. Gutierrez, M. Broch, J. Vendrell, W. Ricart, Circulating interleukin 6 levels,

blood pressure, and insulin sensitivity in apparently healthy men and women. J. Clin. Endocrinol. Metab. **86**, 1154–1159 (2001)
23. X. Li, M. Xu, J. Wang, X. Wang, Y. Huang, Q. Cheng, H. Huang, R. Li, J. Xiang, J. Tan, M. Dai, G. Ning, Serum C-reactive protein (CRP) and microalbuminuria in relation to fasting and 2-h postload plasma glucose in a Chinese population. Clin. Endocrinol. **70**, 691–697 (2009)
24. J. Xiang, X. Li, M. Xu, J. Hong, Y. Huang, J. Tan, X. Lu, M. Dai, B. Yu, G. Ning, Zinc Transporter-8 gene (SLC30A8) is associated with type 2 diabetes in Chinese. J. Clin. Endocrinol. Metab. **93**, 4107–4112 (2008)
25. M. Xu, X. Li, J. Wang, X. Wang, Y. Huang, Q. Cheng, H. Huang, R. Li, J. Xiang, J. Tan, M. Dai, G. Ning, Retinol-binding protein 4 is associated with impaired glucose regulation and microalbuminuria in a Chinese population. Diabetologia **52**, 1511–1519 (2009)