

Association of Insulin Resistance and Hematologic Parameters: Study of a Middle-aged and Elderly Chinese Population in Taiwan

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Background: Chronic inflammation is a common feature related to changes in hematologic parameters in insulin resistance. The aims of this study were to explore the relationship between hematologic parameters and insulin resistance, and to establish a gerontologic profile for following studies.

Methods: Residents aged over 40 years in 3 major townships in I-Lan County participating in the Adult Health Examination were invited for the study. Diagnosis of diabetes mellitus (DM) was done according to American Diabetes Association criteria. Insulin resistance was measured by homeostasis model assessment (HOMA-IR), and subjects with the highest tertile of HOMA-IR were defined as being insulin resistant. Hematologic parameters including white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, and platelet count were measured for comparisons.

Results: A total of 857 subjects (mean age, 64.6 ± 11.2 years; male/female, 373/484) participated in this study. Their mean body mass index (BMI) was 24.5 ± 3.7 kg/m², and 42.4% of them were obese and 21.8% were overweight. The overall prevalence of DM was 15.4% (7.7% were previously diagnosed and 7.7% were newly diagnosed), and impaired fasting glucose was 7.2%. Trend analyses confirmed that age, BMI, HOMA-IR, WBC and platelet counts were significantly increased as glycemic metabolism exacerbated ($p = 0.007$, < 0.001 , < 0.001 , < 0.001 and 0.025 , respectively). Compared with insulin-sensitive subjects, insulin-resistant subjects were more likely to be females (70.2% vs. 49.7%, $p < 0.001$), and had significantly higher BMI (26.2 ± 3.9 kg/m² vs. 23.7 ± 3.3 kg/m², $p < 0.001$), HOMA-IR (3.6 ± 3.5 vs. 0.7 ± 0.3, $p < 0.001$), WBC count (6686.9 ± 1889.2/mm³ vs. 5942.9 ± 1740.4/mm³, $p < 0.001$), and platelet count (243.5 ± 70.9 × 10³/mm³ vs. 231.0 ± 62.2 × 10³/mm³, $p = 0.011$), but not age (64.5 ± 11.0 years vs. 64.6 ± 11.4 years, $p = 0.93$) or RBC count (4.6 ± 0.6 M/mm³ vs. 4.6 ± 0.6 M/mm³, $p = 0.76$). When age and sex were controlled, HOMA-IR significantly correlated with WBC count ($\gamma = 0.23$, $p < 0.001$) and platelet count ($\gamma = 0.09$, $p = 0.007$). However, by multiple logistic regression, female gender, overweight and obesity, and elevated WBC count were all found to be independent risk factors of insulin resistance, but age, RBC and platelet counts were not.

Conclusion: Elevated WBC count but not RBC count was significantly associated with insulin resistance and glycemic metabolism. The relationship between platelet count and insulin resistance deserves further investigations. [*J Chin Med Assoc* 2006;69(6):248–253]

Key Words: blood platelet count, diabetes mellitus, hemoglobin, insulin resistance, white blood cell count

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Introduction

Clustering of multiple cardiovascular risk factors such as hypertension, central obesity, dyslipidemia, and dysglycemia is a fundamental phenomenon of insulin resistance.¹⁻³ Hyperinsulinemia, the most important characteristic of insulin resistance, is also considered to be a cardiovascular risk factor.^{4,5} Microscopically, chronic inflammation features insulin resistance, and is closely related to diabetes mellitus (DM) and atherosclerosis.⁶ This chronic inflammatory state is also associated with elevations in the levels of various cytokines and changes in hematologic parameters.⁷ Leukocytosis and erythropoiesis are the 2 most commonly observed phenomena, and leukocytosis is secondary to interleukin (IL)-6 secretion and erythropoiesis is stimulated by insulin independent of erythropoietin.^{8,9}

Elevated white blood cell (WBC) count and red blood cell (RBC) count have been proposed as the diagnostic feature of metabolic syndrome.^{10,11} Several epidemiologic studies have indicated a close relationship between WBC count plus RBC count and components of metabolic syndrome.¹²⁻¹⁴ Although a number of studies have confirmed the associations of hematologic parameters with insulin resistance, studies performed by direct measurement of insulin resistance rather than its surrogates are relatively scarce. The gold standard to evaluate insulin resistance is the glucose clamp method, but it is impractical for large-scale community-based studies. The homeostasis model assessment (HOMA) can successfully overcome the difficulties,¹⁵ and thus has been validated extensively.^{16,17} The major purpose of this study was to explore the relationships between insulin resistance and hematologic parameters among the middle-aged and elderly Chinese in Taiwan, and to establish a baseline gerontologic profile for future studies.

Methods

Study subjects

From January 2000 to December 2000, we conducted a community-based study focused on insulin resistance in 3 major townships in I-Lan County (Tou-Cheng, Tonshan, and Sanhsing). Residents aged over 40 years undertaking adult health examinations at local health stations were invited to participate in this study.¹⁸ The whole study was approved by the ethics committee of Taipei Veterans General Hospital. Subjects with apparent pulmonary, hepatic and renal malignancies, infectious disorders, immunologic or

hematologic diseases with WBC count $> 15,000/\text{mm}^3$, and platelet count $> 500,000/\text{mm}^3$ were excluded from the study. Moreover, subjects who were on steroids, immunosuppressants, hemodialysis, or erythropoietin therapy during the study were also excluded.

Physical and laboratory examinations

Three well-trained physicians took the medical history and performed a physical examination for each subject. Study nurses took anthropometric measurements for each subject and drew blood samples for further laboratory tests. All the research staff were trained for a week before the study regarding interview skill, standardized measurements of body height and body weight, standard procedures for blood sampling, centrifuging and serum preservation. Body weight was recorded with subjects wearing light indoor clothes and no shoes, graduating to 0.1 kg. Body height was measured by a standard scale to 0.5 cm. Body mass index (BMI) was expressed as the body weight (in kilograms) divided by the square of the body length (in meters). All subjects were on an overnight fast for more than 10 hours before blood sampling. Fasting plasma glucose (FPG) levels were measured by an automatic analyzer (Hitachi Model 736; Hitachi, Tokyo, Japan), and measurement of fasting serum insulin (FI) levels was performed by radioimmunoassay (Diagnostic Product Corp, Los Angeles, CA, USA). Complete blood counts including WBC, RBC, hemoglobin, and platelets were performed by automatic counting (Coulters STKS; Beckman Coulter Inc, Fullerton, CA, USA).

Diagnosis of DM, obesity and insulin resistance

For the purposes of international comparison, obesity was defined according to the recommendations of the World Health Organization-International Obesity Task Force (WHO-IOTF). Obesity was classified as $\text{BMI} > 25 \text{ kg/m}^2$, and overweight was defined when $23 < \text{BMI} \leq 25$.¹⁹ Diagnosis of DM was made according to the criteria of the American Diabetes Association in 1997, i.e. DM was diagnosed when $\text{FPG} > 125 \text{ mg/dL}$ on 2 different occasions.²⁰ Impaired fasting glucose (IFG) was defined as $110 < \text{FPG} \leq 125 \text{ mg/dL}$. Those whose FPG levels were $\leq 110 \text{ mg/dL}$ were referred to as having normal fasting glucose. HOMA-IR was expressed as $\text{FPG (in mmol/L)} \times \text{FI (in mU/L)} / 22.5$,¹⁸ and those subjects with the highest tertile of the HOMA-IR were defined as insulin-resistant.

Statistical analysis

Data in the text and tables were expressed as mean \pm standard deviation. Results compared between groups were analyzed by χ^2 test, Student *t* test, Mann–Whitney *U* test or one-way ANOVA analysis (SPSS version 13.0; SPSS Inc, Chicago, IL, USA) when appropriate. *Post hoc* test (Tukey's HSD test) was done when a significant *F* value was identified in one-way ANOVA. Trend analysis of various variables between different glycemic statuses was done by one-way ANOVA as well. Partial Spearman's correlations (adjusting for age, sex, and BMI) with insulin resistance (HOMA-IR) for various hematologic parameters were estimated. Blood counts were divided into quartiles to evaluate the relative risk of insulin resistance by multivariate logistic regression with the dependent variable of insulin-resistant state, age and sex as the covariates, and obesity, WBC count, RBC count, and platelet count as the independent variables. For all tests, results with $p < 0.05$ (two-tailed) were considered statistically significant.

Results

Demographic data of study subjects

A total of 857 subjects (mean age, 64.6 ± 11.2 years; male/female, 373/484) participated in this study. The mean BMI of study subjects was 24.5 ± 3.7 kg/m²; 21.8% were overweight and 42.4% were obese. The overall prevalence of DM was 15.4% (7.7% were previously diagnosed and 7.7% were newly diagnosed). IFG was 7.2, and 77.4% of study subjects maintained normal fasting glucose. The hematologic parameters were as follows: mean WBC count, 6190.3 ± 1824.2 /mm³; mean RBC count, 4.6 ± 0.6 M/mm³; mean hemoglobin concentration, 13.2 ± 1.7 g/dL; mean

platelet count, $235.2 \pm 65.5 \times 10^3$ /mm³. In this study, females were significantly younger (63.1 ± 10.9 years *vs.* 66.5 ± 11.3 years, $p < 0.001$) and had higher BMI than males (25.0 ± 3.8 kg/m² *vs.* 23.9 ± 3.5 kg/m², $p < 0.001$). However, the prevalence of DM was not significantly different between females and males (16.7 *vs.* 13.7%, $p = 0.21$).

Comparisons between subjects in different glycemic status

Comparing subjects in different glycemic status, we found that age, BMI, WBC count, platelet count, and HOMA-IR were significantly different by one-way ANOVA (Table 1). *Post hoc* analysis revealed that significances were mainly derived from DM. By one-way ANOVA trend analysis, we found that age, BMI, HOMA-IR, WBC count, and platelet count increased significantly as glycemic metabolism exacerbated ($p = 0.007$, < 0.001 , < 0.001 , < 0.001 and 0.025 , respectively). By using Spearman's rank correlation, glycemic status was found to be correlated with age ($\gamma = 0.09$, $p = 0.01$), BMI ($\gamma = 0.18$, $p < 0.001$), HOMA-IR ($\gamma = 0.45$, $p < 0.001$), WBC count ($\gamma = 0.19$, $p < 0.001$) and platelet count ($\gamma = 0.09$, $p = 0.008$). Compared with subjects who were previously diagnosed with DM, newly diagnosed DM subjects had similar BMI (25.5 ± 3.8 kg/m² *vs.* 26.4 ± 3.4 kg/m², $p = 0.15$), HOMA-IR (4.4 ± 5.5 *vs.* 4.2 ± 3.9 , $p = 0.78$), WBC count (7068.3 ± 1990.8 /mm³ *vs.* 6790.4 ± 1898.8 /mm³, $p = 0.41$), RBC count (4.6 ± 0.6 M/mm³ *vs.* 4.6 ± 0.6 M/mm³, $p = 0.86$), hemoglobin (13.1 ± 1.5 g/dL *vs.* 13.5 ± 1.7 g/dL, $p = 0.13$) and platelet count (245.2 ± 65.3 *vs.* 243.2 ± 72.3 , $p = 0.87$). However, subjects with newly diagnosed DM were somewhat older (68.6 ± 10.5 years *vs.* 65.2 ± 9.1 years, $p = 0.048$) and more predominantly males (47.0% *vs.* 30.3%, $p = 0.05$).

Table 1. Demographic data, hematologic parameters and insulin resistance among subjects with different glycemic statuses

	Normal fasting glucose	Impaired fasting glucose	Diabetes mellitus	<i>p</i>
Case number	663	62	132	
Age (yr)	64.0 ± 11.5	66.0 ± 9.9	66.9 ± 9.9	0.015
Male (%)	44.6	41.9	38.6	0.431
BMI (kg/m ²)	24.2 ± 3.8	24.6 ± 2.9	26.0 ± 3.6	< 0.001
HOMA-IR	1.1 ± 1.2	1.9 ± 1.6	4.3 ± 4.8	< 0.001
WBC count (/mm ³)	$6,024.6 \pm 1,753.3$	$6,388.9 \pm 1,924.9$	$6,929.4 \pm 1,942.9$	< 0.001
RBC count (M/mm ³)	4.6 ± 0.6	4.5 ± 0.5	4.6 ± 0.5	0.408
Hemoglobin (g/dL)	13.2 ± 1.7	13.3 ± 1.6	13.3 ± 1.6	0.817
Platelet count (10 ³ /mm ³)	232.2 ± 64.3	247.9 ± 68.4	244.2 ± 68.6	0.044

BMI = body mass index; HOMA-IR = insulin resistance expressed by homeostasis model assessment; WBC = white blood cell, RBC = red blood cell.

Hematologic parameters and insulin resistance

The mean HOMA-IR of the study subjects was 1.7 ± 2.5 , and the cutoff for insulin resistance was 1.35 as defined. Compared with insulin-sensitive subjects, insulin-resistant subjects were more likely to be females (70.2% vs. 49.7%, $p < 0.001$), and have significantly higher BMI ($26.2 \pm 3.9 \text{ kg/m}^2$ vs. $23.7 \pm 3.3 \text{ kg/m}^2$, $p < 0.001$), HOMA-IR (3.6 ± 3.5 vs. 0.7 ± 0.3 , $p < 0.001$), WBC count ($6,686.9 \pm 1,889.2/\text{mm}^3$ vs. $5,942.9 \pm 1,740.4/\text{mm}^3$, $p < 0.001$), and platelet count ($243.5 \pm 70.9 \times 10^3/\text{mm}^3$ vs. $231.0 \pm 62.2 \times 10^3/\text{mm}^3$, $p = 0.011$). However, age (64.5 ± 11.0 years vs. 64.6 ± 11.4 years, $p = 0.93$) and RBC count ($4.6 \pm 0.6 \text{ M/mm}^3$ vs. $4.6 \pm 0.6 \text{ M/mm}^3$, $p = 0.76$) were similar in both groups. When age and sex were controlled, HOMA-IR was significantly correlated with WBC count ($\gamma = 0.23$, $p < 0.001$) and platelet count ($\gamma = 0.09$, $p = 0.007$). By multivariate logistic regression, we found that female gender, overweight and obesity, and elevated WBC count were all independent risk factors of insulin resistance, but age, RBC count or platelet count were not (Table 2).

Discussion

Insulin resistance is a condition in which target cells are unable to respond to ordinary circulating levels of insulin, and is frequently associated with a number of pathologic conditions, including obesity, type 2 DM, cardiovascular diseases, and chronic inflammations.²¹ The interrelationship between insulin resistance and

inflammatory activity is like a vicious cycle. IL-6, a cytokine generated from adipose tissue, is significantly elevated in obese individuals and thereby stimulates WBC.²² Reduced IL-6-mediated acute-phase responses among insulin-resistant subjects lead to higher concentrations of inflammatory markers,²³ and activated WBC enhances atherosclerotic process and vascular injury.²⁴ Furthermore, insulin resistance and/or hyperinsulinemia also enhance erythropoiesis independent of erythropoietin.^{25,26}

In addition to the associations with cardiovascular risk factors or insulin resistance, elevated WBC and RBC counts are also linked to the risk of myocardial infarction, coronary mortality, and ischemic stroke.¹²⁻¹⁴ Integration of hematologic parameters into the diagnosis of metabolic syndrome is recommended owing to these discoveries.^{10,11,27} However, not all of these associations were found by using direct measurements of insulin resistance and that possibly limits the interpretations because of the complex interrelationship among all these risk factors. In this current study, insulin resistance was measured by HOMA-IR, an extensively validated tool to quantify insulin resistance. The association of WBC count with insulin resistance was very significant in this study, but an association of RBC count with insulin resistance was not found. Instead, platelet count was significantly correlated with HOMA-IR, although it was not an independent risk factor of insulin resistance in multivariate logistic regression.

Physiologically, insulin decreases platelet aggregability through reduction of responses to ADP and thrombin.²⁸ The anti-aggregatory ability to insulin is reduced in obese insulin-resistant subjects.²⁹

Table 2. Independent risk factors for insulin-resistant state among middle-aged and elderly subjects by multivariate logistic regression

	OR (95% CI)	<i>p</i>
Sex		
Male	1.0	
Female	2.69 (1.86–3.89)	< 0.001
Obesity		
Normal weight ($18.5 \leq \text{BMI} < 23 \text{ kg/m}^2$)	1.0	
Overweight ($23 \leq \text{BMI} < 25 \text{ kg/m}^2$)	2.72 (1.82–4.01)	< 0.001
Obesity ($\text{BMI} \geq 25 \text{ kg/m}^2$)	4.09 (2.78–6.02)	< 0.001
White blood cell count (/mm ³)		
< 4,960	1.0	
4,960–5,900	1.33 (0.87–2.03)	0.19
> 5,900–7,190	2.33 (1.47–3.68)	< 0.001
> 7,190	3.44 (2.11–5.59)	< 0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index.

Therefore, hyperactivity of platelet function and overconsumption of platelets resulting from the underlying prothrombotic condition are common in insulin-resistant or diabetic subjects.^{30,31} However, this study found a progressive increase of platelet count as insulin resistance or glycemic status progressed. In 2003, Taniguchi et al³² reported that increased platelet count may independently predict insulin resistance among nonobese Japanese type 2 DM patients. Although the precise mechanism for this phenomenon is unclear, our discovery is partly compatible with this observation. Strong associations of platelet count and insulin resistance as in Taniguchi et al's report was not found in this study, but the relationship between insulin resistance and platelet count deserves further investigations.

In conclusion, elevated WBC count was significantly associated with insulin resistance among the middle-aged and elderly in selected townships in Taiwan. However, an association between RBC count and insulin resistance was not observed. The significant but weak association between platelet count and insulin resistance found in this study deserves further detailed investigations.

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