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Association of homeostasis model assessment of insulin resistance, adiponectin, and low-grade inflammation with the course of the metabolic syndrome

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ABSTRACT

Objective: We examined the association between insulin resistance (IR), adiponectin, and inflammation markers and the development of metabolic syndrome (MetS). Furthermore, we aimed to establish the relationship between IR, serum adiponectin, and parameters of chronic inflammation.

Methods: MetS was assessed in 1628 Kazakh participants (768 men; 860 women) in Xinjiang, Northwestern China.

Results: Adiponectin, homeostasis model assessment of IR (HOMA-IR), interleukin-6 (IL-6), and C-reactive protein (CRP) remained significantly associated with MetS after further adjustment for sex, age, smoking status, low-density lipoprotein cholesterol, total cholesterol, and high-density lipoprotein cholesterol. Moreover, HOMA-IR, IL-6, and CRP increased concurrently with an increased number of MetS components, and an inverse trend between adiponectin and increased number of MetS components was found. The median of IL-6 and CRP increased with HOMA-IR from the lowest to the highest quartile. In contrast, the median of adiponectin remarkably decreased with HOMA-IR from the lowest to the highest quartile ($P < 0.001$). According to multiple linear regression analysis, adiponectin, CRP, and IL-6 also showed a significant association with HOMA-IR.

Conclusion: We strengthen the notion that HOMA-IR, adiponectin, and inflammatory markers can predict the course of MetS. Furthermore, our results suggest that a chronic state of inflammation and decreased serum adiponectin might be associated with IR.

Introduction

The metabolic syndrome (MetS), which is considered as a cluster of metabolic abnormalities leading to increased risk of cardiovascular disease and type 2 diabetes mellitus [1–3], has become a global public health problem affecting all nations and races [4].

Low-grade chronic inflammation [5], insulin resistance (IR) [6,7], and hypoadiponectinemia [8,9] are important factors that may be involved in the potential mechanisms of MetS. However, studies concerning the relationships between IR, adiponectin, and inflammation markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are limited, especially in community-dwelling populations.

Low-level chronic inflammation mediates many pathogenic mechanisms responsible for the association between MetS components, which is considered to be a common background of IR [10]. CRP is a useful inflammation marker [8,11]. Elevated CRP levels are related to the increased expression and release of IL-6 by adipose tissue [12]. IL-6 is a proinflammatory cytokine that can stimulate the production of CRP in the liver. Circulating IL-6 and CRP levels are strong independent predictors for future cardiovascular events [13].

The accumulated evidence indicates that IR is another key pathogenic factor for MetS. It is generally believed that elevated blood pressure, dyslipidemia, and impaired glucose tolerance are caused by IR [9,14]. IR is often associated with increased adipose tissue mass. Adipose tissue is no longer viewed as a passive organ for triacylglycerol storage, and in fact, adipocytes are active endocrine-secreting cells that release adipokines including IL-6, visfatin, adiponectin, leptin, and tumor necrosis factor-α [15,16]. Adiponectin, the most abundant adipokine found in circulation, has insulin-sensitizing [9,17], anti-inflammatory [18,19], and anti-dyslipidemic activities [20]. Decreased serum

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CRP, C-reactive protein; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; OR, odds ratio; TC, total cholesterol.

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adiponectin is associated with most MetS component and hence with MetS [21,22].

In this community-based study, we examined the association between IR, adiponectin, and inflammation markers with the development of MetS. Furthermore, we aimed to establish the relationships between IR, serum adiponectin, and parameters of chronic inflammation.

Materials and methods

Ethics statement

The Institutional Ethics Review Board (IERB) of the First Affiliated Hospital of Shihezi University School of Medicine approved the study (IERB No. SHZ2009LL05). Standard university hospital guidelines including informed consent, voluntary participation, confidentiality, and anonymity were followed. All participants provided written informed consent before participation.

Settings and participants

The study sample consisted of 1628 participants (860 women and 768 men) who resided in villages in Xinyuan County, Xinjiang, inhabited by Kazakhs who engage in grazing as an occupation. Exclusion criteria included acute illness within the previous 2 weeks, currently taking medication, cancer, and pregnancy. The study was conducted between May 2009 and May 2013.

Anthropometric measurements and laboratory tests

Each participant was interviewed using a structured questionnaire to collect general and demographic information (age and sex) as well as cigarette smoking history (never smoked, ex-smoker, or current smoker). Waist circumference (cm) was measured midway between the lower rib and iliac crest. Weight (kg) and height (m) were measured with the participants in light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2) and expressed as kg/m^2. Casual blood pressure (BP) was measured 3 times after a 5-min rest in the sitting position using a mercury sphygmomanometer, and an average of 3 measurements was used for analyses. After the physical examination, a blood sample was drawn from the cubital vein in the morning after an overnight fast and placed in a tube containing heparin sodium. The blood was centrifuged at 2000 rpm for 10 min, and plasma was then separated and stored at −70 °C until analysis. Total cholesterol (TC), triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG) levels were measured using a biochemical autoanalyzer (Olympus AU 2700; Olympus Diagnostics, Hamburg, Germany) in the clinical laboratory at the First Affiliated Hospital of Shihezi University School of Medicine.

Circulating IL-6 and adiponectin levels were determined using ELISA kits (Shanghai Westang Bio-Tech Co. Ltd., Shanghai, China; and Phoenix Pharmaceuticals Inc., Belmont, CA, USA, respectively). CRP was determined by immunonephelometry with a kit was purchased from Beijing Leadman Bio-Tech Co. Ltd., Beijing, China; Insulin level was measured by radioimmunoassay. The HOMA-IR index was calculated as follows: fasting insulin (μIU/mL) × FBG (mM) / 22.5 [23].

Definition of MetS

MetS was defined using the International Diabetes Federation criteria [24], which include central obesity (Chinese population waist circumference cutoffs of ≥90 cm in men or ≥80 cm in women [25]) plus any 2 of the following 4 factors: elevated triglyceride level (>150 mg/dL or 1.69 mmol/L), reduced HDL-C (<40 mg/dL or 1.04 mmol/Lin men; <50 mg/dL or 1.29 mmol/L in women), elevated systolic BP (≥130 mm Hg) or diastolic BP (≥85 mm Hg), and elevated FBG (≥100 mg/dL).

Statistical analysis

Continuous variables are presented as mean ± standard deviation for clinical characteristics or median (interquartile range) for IL-6, CRP, adiponectin, and fasting insulin levels. These variables were compared using unpaired *t* tests or Mann–Whitney *U* tests. Multivariable logistic regression analysis with MetS as the dichotomous dependent variable was conducted to determine the association between adiponectin, HOMA-IR, IL-6, CRP, and MetS, while adjusting for potentially confounding variables such as sex, age, BMI, smoking status, and LDL-C, TC, and HDL-C levels. The resulting odds ratios (ORs) and 95% confidence intervals (CIs) are reported. The participants were divided into 4 groups according to the quartiles of HOMA-IR, variables were compared by ANOVA and χ^2 test among these quartiles, respectively. Multiple linear regression analysis was performed with HOMA-IR as the dependent variable and other factors of MetS as the independent variables. All analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Differences with a P value <0.05 were considered statistically significant.

Results

The characteristics of the study population are shown in Table 1. MetS prevalence was 34.38% for men and 31.05% for women. The serum insulin level, HOMA-IR, and most anthropometric characteristics were significantly greater in men than in women ($P < 0.001$). In contrast, HDL-C and adiponectin levels were remarkably lower in men than in women. CRP, IL-6, and TC showed no significant differences between men and women.

The adjusted ORs (95% CIs) for the logistic regression analyses are shown in Table 2. The ORs of MetS as a dependent variable, the multivariable adjusted OR (95% CI) of MetS with the highest quartile compared with that of a lower quartile of markers showed that adiponectin, HOMA-IR, IL-6, and CRP were significantly associated with MetS. In model III, adjusted for sex, age, smoking status, LDL-C, TC, and HDL-C, adiponectin (OR, 0.30; 95% CI, 0.19–0.46), HOMA-IR (OR, 3.82; 95% CI, 2.42–6.04), IL-6 (OR, 4.10; 95% CI, 2.62–6.43), and

Table 1
Clinical characteristics of the study population.

Parameters	Men (n = 768)	Women (n = 860)	*P*
Age (years)	43.03 ± 12.75	46.48 ± 13.47	<0.001
Waist circumference (cm)	87.28 ± 11.69	81.82 ± 11.32	<0.001
BMI (kg/m^2)	25.00 ± 4.12	24.09 ± 4.14	<0.001
Systolic BP (mm Hg)	132.93 ± 22.80	129.47 ± 24.03	<0.001
Diastolic BP (mm Hg)	85.31 ± 13.29	82.85 ± 13.88	0.003
Current smoker (n [%])	600 (78.13)	445 (51.74)	<0.001
Total cholesterol (mM)	4.35 ± 1.11	4.27 ± 1.17	0.149
Triglyceride (mM)	1.37 ± 0.99	1.13 ± 0.66	<0.001
HDL cholesterol (mM)	1.40 ± 0.48	1.51 ± 0.47	<0.001
LDL cholesterol (mM)	2.31 ± 0.81	2.20 ± 0.76	0.003
FBG (mg/dL)	4.85 ± 1.26	4.57 ± 1.04	<0.001
Insulin (μIU/dL)	12.90 (7.70–15.90)	11.30 (7.35–16.20)	0.546
HOMA-IR	2.48 (1.51–3.48)	2.17 (1.42–3.58)	0.055
Adiponectin (ng/ml)	5.34 (3.45–6.33)	6.70 (4.99–8.34)	<0.001
CRP (ng/ml)	1.70 (1.10–2.50)	1.60 (1.10–2.30)	0.081
IL-6 (pg/ml)	1.08 (0.20–1.75)	0.96 (0.19–1.76)	0.289
Metabolic syndrome (%)	34.38	31.05	0.153

Values are expressed as means ± SD or number (%), if not stated otherwise. Median values of adiponectin, fasting insulin, IL-6, CRP, and HOMA-IR are presented (lower quartile-upper quartile).

Abbreviations: SD, standard deviation; BMI, body mass index; TG, triglyceride; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; and IL-6, interleukin-6.