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Association of serum ferritin levels with metabolic syndrome and insulin resistance in a Chinese population

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ABSTRACT

Aims: Increased iron is associated with type 2 diabetes, dyslipidemia, and high blood pressure. Therefore, serum ferritin may be a suitable biomarker to detect metabolic syndrome (MetS). We investigated the relationship between serum ferritin, and the prevalence of MetS and insulin resistance (IR).
Methods: This cross-sectional study assessed 2,786 Chinese participants, aged 25–75 years. MetS was defined using the 2006 International Diabetes Federation guidelines. IR was assessed with homeostasis model assessment estimated IR (HOMA-IR). Regression analysis was used to estimate the association between serum ferritin and the prevalence of MetS and IR.
Results: MetS prevalence within each serum ferritin quartile (Q1-4) was 31.7%, 37.1%, 43.6%, and 55.4%, respectively in men ($P < 0.001$), and 30.1%, 34.8%, 48.2%, and 66.9%, respectively in women ($P < 0.001$). Increased serum ferritin correlated with the number of MetS components ($P < 0.001$). The odds ratio for MetS in the ferritin Q4 group was 1.95 (1.39–2.73) for men and 1.66(1.12–2.47) for women, compared with Q1. Serum ferritin correlated positively with HOMA-IR in men (regression coefficient: 0.058, $P = 0.009$) and women (regression coefficient: 0.082, $P = 0.001$).
Conclusion: MetS prevalence increased with elevated serum ferritin levels, and serum ferritin levels were independently associated with MetS and IR.

1. Introduction

Iron plays an important role in maintaining normal physiological processes in the human body, including oxygen transportation and storage, and the synthesis of cytochromes and a variety of metalloenzymes (Heeney & Andrews, 2004). As approximately 30% of iron in the body is stored in the form of serum ferritin and hemosiderin, serum ferritin levels reflect the iron storage conditions of healthy individuals (Cook, Flowers, & Skikne, 2003). Inflammation and dietary factors can also affect serum ferritin levels (Leonard, 2014).

Metabolic syndrome (MetS) is a group of metabolic conditions that present clinically as a combination of central obesity, insulin resistance (IR), hypertension, high triglyceride(TG) levels, low high-density lipoprotein cholesterol (HDL-C) levels, a decline in glucose tolerance, or type 2 diabetes mellitus (Scheen, Luyckx, & Lefebvre, 2006). Previous studies have indicated that for each additional condition that is involved in MetS, morbidity and mortality from cardiovascular disease and cancer increases (Giudice, 2014; Onat, 2010).

Previous studies of healthy populations have shown that elevated serum ferritin levels are associated with an increased risk of high blood pressure (BP) (Kim, 2012), type 2 diabetes (Jiang, 2004), dyslipidemia (Han, 2014), and MetS (Sun, 2008; Tang, 2015; Vari, 2007). However, there has been limited research assessing the relationship between serum ferritin and MetS in the Chinese population. A study of the general Chinese population showed that elevated serum ferritin levels were an independent risk factor for MetS, and other studies have shown that elevated ferritin levels may be associated with IR (Liu, 2015). Importantly, these studies did not consider the effects of IR as a confounding factor in the relationship between serum ferritin levels and MetS, and most did not consider the potential effects of dietary factors and inflammation.

In this study, we use epidemiological data from the Pinggu district of Beijing, China to investigate the association between serum ferritin levels and the prevalence of MetS and IR.

Conflicts of interest: None.

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2. Materials and methods

2.1. Subjects

A cross-sectional, population based study was conducted in the Pinggu district of Beijing, China from March 2012 to May 2013. Stratified random two-stage cluster sampling was used to recruit participants. Five rural towns and one street were randomly selected. Five villages and seven neighborhood communities were then randomly drawn from these areas. We randomly selected between 173 and 900 residents, aged 25–74 years, who had lived in Pinggu for at least five years, from each village or resident committee to participate. The sample was stratified according to the age and sex distribution of Pinggu. A total of 5004 individuals (2504 from the rural towns and 2500 from the streets; 2499 men and 2505 women) were invited to participate. The overall response rate was 66.9% (n = 3350). Stratified response rates were 75.4% for residents living in rural towns and 58.4% for those living in the street, and were 64.1% for men and 69.7% for women. Participants were excluded if they had a known history of liver disease, an aminotransferase level greater than three times the normal range, an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, or if they had missing data on weight, body mass index (BMI), white blood cell count (WBC), or hemoglobin A1c (HbA1c). Participants with a known history of diabetes were also excluded, as lifestyle interventions and medications are known to affect insulin and serum ferritin levels. Participants with a known history of chronic or acute inflammatory disease or atherosclerosis were also excluded. The final study population consisted of 2786 individuals. All participants provided written informed consent, and the study was approved by the Ethics and Human Subject Committee of Peking University People's Hospital.

2.2. Data collection and variable definitions

Data were collected by at interviews conducted by trained physicians using a standardized questionnaire. The questionnaire included questions about demographic characteristics (e.g., age, ethnicity, occupation, and education); lifestyle characteristics (e.g., smoking status, alcohol intake, tea intake, and physical activity); health status and medical history; family history of diabetes and related chronic diseases; diet; psychology and life stress; and knowledge of diseases related to MetS. A family history of related chronic disease was defined as a history of one of the following diseases in parents, children, or siblings: hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, stroke, chronic kidney disease, hyperuricemia or gout, obesity, or cancer. Dietary questions included time, location, frequency, and quantity of meals. Frequency of pork consumption was defined as 0 when consumed less than seven times per week, or 1 when consumed more than seven times per week. Health questions for women included history of menstruation and pregnancy.

Height and weight were measured using a pre-calibrated height–weight scale with subjects standing barefoot and wearing light clothing. Waist circumference (WC) was measured at the mid-point between the lower rib margin and the iliac crest. BP was measured three times after 10 min resting in a seated position, and the mean of these three readings was used for analysis. BMI was calculated as weight (kg) divided by height squared (m^2). Education was divided into two categories: college education and higher, or lower than college education. Smoking status was also divided into two categories: current smokers who smoked every day, or non-smokers, which included former smokers, occasional smokers, and those who had never smoked.

2.3. Clinical and laboratory measurements

Study participants were instructed to eat an unrestricted diet for at least three days, followed by an overnight fast of 10–12 hours before examination. An oral glucose tolerance test (OGTT) was performed in the morning after fasting. Blood samples were collected before glucose ingestion and two hours after a 75 g anhydrous glucose load.

Plasma glucose was measured using a hexokinase method. HbA1c was measured by high-pressure liquid chromatography (ADAMS A1c HA-8160; Arkray, Inc., Kyoto, Japan). The HbA1c assay was Diabetes Control and Complications Trial aligned. The intra-assay coefficient of variation (CV) for HbA1c was 0.78%. The inter-assay CV for HbA1c was 1.31% at a mean value of 4.74%, and 1.37% at a mean value of 9.12%. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (SCr), uric acid (UA),total cholesterol (TC), TG, WBC, HbA1c,HDL-C, and low-density lipoprotein cholesterol (LDL-C) were measured in fasting blood samples using an automated biochemical instrument(Coulter UniCel DxC 800, Beckman, Miami, FL, USA). Urine albumin and creatinine were measured in spot urine samples using a immunoturbidimetric assay and Jaffe's assay(COBAS C311, Roche Diagnostics, Tokyo, Japan), respectively. Serum ferritin was measured with a solid-phase, two-site chemiluminescent immunometric assay (IMMULITE 2000 system, Siemens, Flanders, NJ, USA). Urinary albumin to creatinine ratio (ACR) was calculated from the urine sample results. Neutrophil to lymphocyte (N/L) ratio was calculated by dividing counts of neutrophils by lymphocytes.

2.4. Definitions

MetS was defined based on the 2006 International Diabetes Federation definition (Scheen et al., 2006). MetS was defined as the diagnosis of central obesity (WC greater than 90 cm in men and 80 cm in women), plus any two of the following four factors: (1) TG levels ≥1.7 mmol/L, (2) HDL <1.03 mmol/L in men or <1.29 mmol/L in women,(3) systolic BP ≥130 mmHg and diastolic BP ≥85 mmHg,(4)fasting blood glucose (FBG) ≥5.6 mmol/L, or previous diagnosis with type 2 diabetes mellitus.

MetS components included WC, TG levels, HDL-C, BP, and FBG levels. Subjects were divided into three groups according to the number of MetS components: group 1(<3 components), group 2 (3–4 components), and group 3(>4 components).

2.5. Statistical analysis

Data were expressed as means and standard deviations, or medians and interquartile ranges for continuous variables, and percentages for categorical variables.

One-way ANOVAs and chi-square tests were used to analyze statistical differences among the study participant's characteristics in relation to serum ferritin quartile (Q1-4) groups. General linear models were used to assess the association between serum ferritin levels and the number of MetS components. Estimates of serum ferritin levels were adjusted for age, ALT, SCr, WBC count, and HbA1c. Binary logistic regression models were used to compute odds ratios (ORs) for MetS according to serum ferritin quartiles. Multiple linear regression models were used to analyze the association between serum ferritin levels and homeostasis model assessment estimated IR (HOMA-IR).

Statistical analysis was performed using SPSS for windows 17.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided with a statistical significance level set at $P < 0.05$.

3. Results

3.1. General patient characteristics

In both men and women, increased levels of serum ferritin corresponded with increases in age, MetS incidence, BMI, WC, HOMA-IR, FBG, fasting insulin, HbA1c, UA, ALT, AST, WBC, TC, and TG levels. Increased serum ferritin levels also significantly correlated

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