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Plasma CTRP-3 concentrations in Chinese patients with obesity and type II diabetes negatively correlate with insulin resistance

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KEYWORDS:
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BACKGROUND: To analyze the association between the plasma C1q/TNF-related protein-3 (CTRP-3) concentrations, obesity, and type II diabetes in the Chinese population.

METHODS: The plasma CTRP-3 concentrations were analyzed in 174 Chinese subjects with obesity (n = 43), type II diabetes (n = 41), obesity combined with type II diabetes (n = 45), and healthy subjects (n = 45), as were various clinical parameters of obesity-related metabolic disorders and adipokines.

RESULTS: The plasma CTRP-3 concentrations were significantly lower in patients with obesity and type II diabetes than in healthy subjects ($P < .01$). Obese type II diabetic patients had the lowest CTRP-3 concentrations. Correlation analysis revealed that the plasma CTRP-3 concentrations were significantly negatively correlated with body mass index, waist circumferences, fasting plasma glucose, 2 h plasma glucose, hemoglobin A1c, triglyceride, fasting insulin, homeostasis model assessment for insulin resistance, and interleukin 6 levels and were positively correlated with high-density lipoprotein cholesterol level (all $P < .01$). Multiple linear regression analysis showed that hemoglobin A1c ($\beta = -0.232$, $P = .023$), triglyceride ($\beta = -0.147$, $P = .040$), and homeostasis model assessment for insulin resistance ($\beta = -0.172$, $P = .031$) were independently correlated with circulating CTRP-3. Multivariate logistic regression analysis revealed that plasma CTRP-3 concentrations were significantly correlated with obesity, even after adjusting for glucose metabolic factors.

CONCLUSIONS: Chinese patients with obesity and type II diabetes have significantly lower plasma CTRP-3 concentrations than healthy subjects do, and plasma CTRP-3 is strongly associated with glucose and lipid metabolism, chronic inflammation, and insulin resistance.

Introduction

Obesity is associated with adverse alterations in adipose tissue that can lead to metabolic dysregulation. These adverse alterations include the accumulation of inflammatory macrophages leading to the activation of inflammation pathways, increased adipose tissue dysfunction, and increased ectopic fat deposition. These alterations are pivotal in the development of insulin resistance, type II diabetes

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mellitus (T2DM), and other metabolic dysfunctions.[1] Therefore, a more complete understanding of the adipocytokines involved in the pathogenesis of obesity is crucial.

C1q/TNF-related proteins (CTRPs), originally introduced by Harvey Lodish,[2] are a highly conserved family that share homology with adiponectin. There are 15 members in the CTRP family (CTRP-1–15) with different structures and functions.[3] CTRP-3, also known as CORS-26, cartducin, and cartonectin, is highly expressed and secreted by mesenteric adipose tissue in humans and by mature human and murine adipocytes.[3,4] Yi et al[5] found that CTRP-3 could improve cardiac function and revascularization in mice. Kopp et al[6] reported that CTRP-3 inhibited lipopolysaccharide (LPS)-induced interleukin (IL)-6 and tumor necrosis factor (TNF) release in human monocytes and that anti-inflammatory effect of CTRP-3 was restricted to monocytes from healthy subjects and was completely lost in T2DM patients. Murayama et al[7] demonstrated that C1qtnf3$^{-/-}$ mice were susceptible to collagen-induced arthritis and had enhanced inflammatory cytokine production. This result indicates that CTRP-3 is a potent anti-inflammatory adipokine. Obesity is considered a state of chronic low-grade systemic inflammation. However, to the best of our knowledge, no data about circulating CTRP-3 concentrations in obese humans have been reported.

Peterson et al[8] reported that recombinant CTRP-3 administration significantly lowered glucose levels in mice. However, the circulating concentration of CTRP-3 in diabetic patients remains controversial. Choi et al[9] reported that the circulating levels of CTRP-3 were increased in patients with prediabetes and T2DM, yet Ban B et al[10] found that the circulating CTRP-3 levels were lower in newly diagnosed T2DM patients. We therefore developed an enzyme-linked immunosorbent assay (ELISA) to assess the circulating CTRP-3 concentrations in blood samples from a Chinese population with diverse body mass index (BMI) and glucose tolerance levels.

Methods

Subjects

Eighty-six patients with newly diagnosed T2DM and 88 subjects with normal glucose tolerance (NGT) were recruited in this study, and the age of the subjects ranged from 40 to 75 years. In all 174 subjects, 75g oral glucose tolerance test was performed, all of the T2DM patients were newly diagnosed and had not received any antidiabetes treatments including diet, exercise, and medications. The diagnoses of T2DM were based on the diagnostic criteria of World Health Organization in 1999, and then, according to the World Health Organization Western Pacific Region diagnostic criteria (2000)[11] that defined obesity as BMI $\geq$25 kg/m^2. All subjects were divided into 4 subgroups: NGT-normal weight (NGT-NW), NGT-obesity (NGT-OB), T2DM-NW, and T2DM-OB subgroups.

Exclusion criteria

(1) Smoking and drinking history;
(2) Acute and chronic complications of diabetes;
(3) Stage II hypertension (resting blood pressure (BP) $\geq$160/100 mm Hg), history of cardiovascular disease (myocardial infarction, unstable angina, stroke, peripheral artery disease, or cardiovascular revascularization);
(4) Acute and chronic inflammatory diseases as determined by clinical symptom of infection, or blood leukocyte $>7 \times 10^9$/L, or those taking medications that could affect their inflammatory status within 3 months;
(5) Hepatic or renal disease and systemic corticosteroid treatment;
(6) Women who were currently pregnant and breastfeeding were also excluded from this study.

The study was approved by the Ethical Committee of the First Affiliated Hospital of Chongqing Medical University. Signed informed consents were obtained from all participants in this study.

Study measurements

Clinical evaluation of subjects

Standardized protocols were used to measure height, body weight, waist and hip circumferences, and BP in all subjects. Height and waist and hip circumferences were measured to minimum recorded unit 0.1 cm, body weight was measured to an accuracy of $\pm$0.2 kg, and BP was measured twice with a standard mercury manometer with the subjects seated and was used for the second measurement. BMI and waist-to-hip ratio (WHR) were calculated.

Overnight fasting blood samples were collected for the determination of fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), fasting insulin (FINS), triglyceride (TG), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, liver and kidney function. Blood samples were also collected after 2 h of a 75g oral glucose tolerance test for determining the 2 h plasma glucose (2hPG). All the blood samples were separated within 1 h, and then, frozen at -80°C until used in this study, all within 3-mo period. Glucose was assayed by glucose oxidase method. HbA1c was measured by isoelectric focusing. FINS was measured in serum by radio immunoassay using human insulin as standard (Linco, St Charles, MO). Lipid profiles and liver and kidney functions were detected by biochemical auto analyzer (Beckman CX-7 Biochemical Autoanalyser, Brea, CA).

Assessment of plasma CTRP-3 and IL-6 levels

Plasma CTRP-3 and IL-6 levels were determined by commercial ELISA kits according to the manufacturers' instructions (Human ELISA kit, Uscn Life Science Inc, Wuhan, China). All samples were run in duplicate and