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The association between serum ferritin levels and the risk of new-onset type 2 diabetes mellitus: A 10-year follow-up of the Chinese Multi-Provincial Cohort Study

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ABSTRACT

Aims: To investigate the association of serum ferritin levels and ferritin level changes with the 10-year risk of new-onset type 2 diabetes mellitus (T2DM).

Methods: Among 2359 subjects without T2DM at baseline in 2002, 1956 subjects were re-examined in 2007, and 1660 subjects were invited to be re-examined in 2012. Serum ferritin (ng/ml) levels were measured by latex-enhanced turbidimetric immunoassay. Five-year serum ferritin changes were categorized into four groups using the median as the cut-off point. Multivariate logistic regression was performed to examine the independent association of serum ferritin levels and 5-year ferritin level changes with 10-year new-onset T2DM.

Results: At the 10-year follow-up, 205 (12.3%) subjects had developed new-onset T2DM. After adjusting for traditional risk factors and high-sensitivity C-reactive protein, 10-year new-onset T2DM risk was significantly increased in subjects in the highest tertile of baseline serum ferritin levels [odds ratio (OR) = 1.80, 95% confidence interval (CI): 1.17–2.79] and in subjects with high serum ferritin levels in both 2002 and 2007 (OR = 1.54, 95% CI: 1.01–2.34). After adjusting for baseline fasting blood glucose, the effect was attenuated and became borderline or non-significant.

Conclusions: Serum ferritin levels and ferritin level changes were associated with 10-year new-onset T2DM risk in the Chinese population, whereas the independent effect awaits validation from studies with larger sample sizes.

1. Introduction

Diabetes is an important cause of mortality, morbidity and health-system costs globally [1,2]. The most recent national survey in 2010 reported that the prevalence of diabetes was 11.6%, representing an estimated 113.9 million adults in China with diabetes [3]. Therefore, identification of the risk factors associated with diabetes is important for

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understanding the etiology and preventing the disease. Previous studies have found that individuals with pathologic iron overload often subsequently develop type 2 diabetes mellitus (T2DM), but the underlying pathophysiology is not completely understood [4,5]. A possible mechanism may involve elevated iron body stores resulting in raised intra-hepatic oxidative stress level and hepatic fibrosis, which may impair insulin extraction and insulin ability to suppress glucose production [6].

Ferritin is an iron-storage protein, in which the shell of a globular apoferritin holds a micelle of iron inside. As a key protein regulating iron homeostasis, serum ferritin is the standard marker for non-invasive evaluation of iron stores and is widely used in clinical practice [7]. To date, several prospective studies have investigated the association between serum ferritin levels and T2DM [8–19], and observed a significant positive association in a meta-analysis published recently [20]. However, the majority of those studies did not adjust for baseline glucose level, and the evidence from Asian population is scarce [8,19]. Therefore, the association between serum ferritin levels and the risk of new-onset T2DM among Chinese people remains unclear. Hence, we performed a large-scale prospective cohort study to evaluate the effects of serum ferritin levels and 5-year ferritin level changes on incident T2DM in a middle-aged Chinese community population.

2. Subjects, materials and methods

2.1. Subjects

Study subjects were recruited from the Chinese Multi-Provincial Cohort Study - Beijing Project, which is a prospective cohort study carried out in two communities in Beijing [21]. Briefly, 2829 subjects, aged 40–74 years, completed examinations on demographic characteristics and traditional risk factors in 2002. After excluding those with T2DM, defined as fasting blood glucose (FBG) $\geq$7.0 mmol/L or with a clinical diagnosis at baseline, and those without blood samples at baseline, 1956 subjects were re-examined in 2007. In addition, 1660 subjects were invited to be re-examined in 2012. Written informed consent was obtained from all subjects. The protocol was approved by the Ethics Committee of Beijing An Zhen Hospital, Capital Medical University.

2.2. Clinical and laboratory measurements

All three surveys (2002, 2007 and 2012) were conducted based on the same protocol for risk factor surveys [22]. A standardized questionnaire was used to collect information, including demographic characteristics, personal medical history, medical therapy, smoking status, alcohol consumption and physical activities. Heights, weights and blood pressure (BP) levels were measured during physical examination. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Metabolic syndrome (MetS) was defined based on the Joint Scientific Statement declared in 2009 as presence of any three of the following five risk factors: (1) waist circumference $\geq$85 cm for men and 80 cm for women (for Chinese patients); (2) elevated triglyceride (TG) level: at least 1.7 mmol/L or specific treatment for these lipid abnormalities; (3) reduced high density lipoprotein-cholesterol (HDL-C): less than 1.03 mmol/L in men and 1.29 mmol/L in women, or specific treatment for these lipid abnormalities; (4) elevated blood pressure: at least 130 mmHg systolic BP (SBP) or 85 mmHg diastolic BP (DBP) or treatment of previously diagnosed hypertension; (5) FBG at least 5.6 mmol/L or previously diagnosed T2DM [23]. Survey method details were described previously [21].

Overnight fasting venous blood samples were collected for laboratory measurements. Total cholesterol (TC), TG, low density lipoprotein-cholesterol (LDL-C), HDL-C and FBG levels were measured by enzymatic method (TC, TG and FBG) or homogeneous assay (LDL-C and HDL-C) on fresh samples collected on the day of survey. The remaining samples were stored at −80 °C without repeated freeze-thaw cycles to minimize any degradation. Alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and fasting insulin levels were measured in 2008 by kinetic colorimetry and chemiluminescent microparticle immunoassay in 900 subjects who came from one of the two communities. Homeostasis model of insulin resistance (HOMA-IR) was calculated from FBG and fasting insulin as: FBG (mmol/L) $\times$ fasting insulin (U/L)/22.5. Serum ferritin and high-sensitivity C-reactive protein (hs-CRP) levels were measured in 2015 on an automatic biochemical analyzer (Hitachi 7180, Hitachi, Japan) using a latex-enhanced immunoturbidimetric assay (Denka Seiken, Ltd).

2.3. Definition of incident T2DM

Incident cases of T2DM were determined as FBG $\geq$ 7.0 mmol/L at re-examination [24] or with a clinical diagnosis or died for T2DM during follow-up. A total of 152 new cases of T2DM were found in the 2007 re-examination, 204 new cases were found in the 2012 re-examination. One subject did not take part in the re-examinations in 2007 or 2012 but died of T2DM in 2008 (Fig. 1).

2.4. Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD) and compared by independent *t*-test if normally distributed or expressed as median (interquartile ranges, IQR) and compared by Wilcoxon rank sum test. Categorical variables were expressed as proportions (%) and compared by χ^2 test. After adjusting for confounding variables, including age, sex, TG, BMI, MetS, hs-CRP, SBP, use of BP lowering drugs, statin use, family history of diabetes and FBG, multivariate logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of the baseline serum ferritin tertiles for 5-year and 10-year incident T2DM risks. In addition, we also analyzed the association between changes in serum ferritin levels between 2002 and 2007 and risk of 10-year incident T2DM (2002–2012). Changes in serum ferritin levels were divided into four categories using the median ferritin level as the cut-off point: low serum ferritin in both 2002 and 2007; low serum ferritin in 2002 but high in 2007; high serum ferritin