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Hepcidin and iron metabolism associated with cardiometabolic risk factors in children: A case–control study

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Abstract *Background and aims:* Iron metabolism plays a crucial role in the development of cardiometabolic disease; however, the association between cardiometabolic risk factors (CMRFs) and hepcidin as well as other iron parameters remains unclear in children. The aims of this study were to compare the circulating hepcidin levels and iron metabolism between children with and without CMRFs and to investigate the association between those iron parameters and CMRFs.
Methods and results: A case–control study was conducted among 1126 children aged 7–14 years in the case group ($n = 563$) with CMRFs and the healthy control group ($n = 563$). Iron parameters, lipids, and anthropometric characteristics were evaluated. The information on demographics, diet, and physical activities was either children reported or parent reported. Compared with the healthy controls, children with CMRFs had higher levels of hepcidin and lower levels of serum iron, transferrin, and soluble transferrin receptor (sTfR; $P < 0.001$). Besides, the odds ratios (ORs) for low levels of high-density lipoprotein (HDL) were 2.03, 0.21, and 0.33 in children with higher hepcidin, transferrin, and sTfR levels ($P < 0.05$). Furthermore, ORs for cardiometabolic risk were 0.50 (95% confidence interval (CI): 0.30–0.85, $P < 0.05$), 0.22 (95% CI: 0.12, 0.42, $P < 0.01$) and 0.19 (95% CI: 0.10, 0.36, $P < 0.01$) in children with higher serum iron, transferrin, and sTfR levels, respectively.
Conclusion: The levels of hepcidin were higher, while those of iron, transferrin, and sTfR were lower in children with CMRF. Hepcidin was positively associated with the risk of low HDL levels, whereas transferrin and sTfR levels negatively correlated with the risk of low HDL levels. In addition, serum iron, transferrin, and sTfR levels were negatively associated with cardiometabolic risk.

Introduction

A series of studies have clearly documented that metabolic risk factors, such as obesity, hypertension, insulin resistance, and dyslipidemia, are closely associated with the onset of cardiovascular diseases (CVDs). Metabolic syndrome (MetS) was usually applied to describe the clustering of cardiometabolic risk factors and was defined as central adiposity, dyslipidemia, impaired glucose metabolism, and elevated blood pressure [1]. The prevalence of

Abbreviations: BMI, body mass index; *CI*, confidence interval; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; Fe, serum iron; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; *OR*, odds ratio; SBP, systolic blood pressure; sTfR, soluble transferrin receptor; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

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MetS in adolescents had sharply increased from 4.1% to 10% over the past decades according to the National Health and Nutrition Examination Survey data in the USA [2,3]. In China, a survey conducted in six cities showed that the prevalence of MetS in children and adolescents was 2.5% [4]. These two studies revealed that the proportion of children with at least one metabolic risk factor was even higher in the USA (73.2%) and China (25%). MetS and its risk factors in adolescents would accelerate and aggravate early atherosclerotic vascular changes, leading to an increasing risk of CVDs in adulthood [5]. Given the ascending prevalence and known adverse consequences of MetS, the prevention of the syndrome and its related cardiometabolic risk factors in childhood remain urgent public health priorities.

A large number of studies have shown that iron metabolism plays a crucial role in the development of cardiometabolic disorders, such as MetS, type 2 diabetes, atherosclerosis, and consequent CVDs [6]. Previous epidemiological studies reported that the hepcidin levels, the key regulator of iron metabolism, increased in children and adults with obesity and type 2 diabetes [7,8]. Another study conducted in adults with MetS demonstrated that higher hepcidin levels were associated with the increasing number of metabolic risk factors [9]. However, whether the same situation exists in children remains unclear. Other iron metabolic parameters, such as serum iron, ferritin, transferrin, and soluble transferrin receptor (sTfR), have also been reported to be associated with MetS and its components in adults [10–13]. Nevertheless, the relationships between cardiometabolic risk factors and multiple iron metabolic parameters, including hepcidin, transferrin, and sTfR, are less well studied in children, which are necessary to be explored.

Several studies carried out in in vitro cell lines have further indicated that hepcidin might contribute to iron-induced atherosclerosis [14]. It is well known that the atherosclerotic process is closely relevant to dyslipidemia. However, the associations between the lipid profile and hepcidin as well as other iron metabolic parameters are still unclear in children. Considering these factors, this study aimed to investigate the status of hepcidin and other iron parameters, such as serum iron, ferritin, transferrin, and sTfR, in children with and without cardiometabolic risk factors and to explore the associations between these iron parameters and the cardiometabolic risk factors, especially the adverse lipid profile.

Methods

Study population

The present study included children aged 7–14 years, who were enrolled from a large epidemiological study conducted in Guangzhou, South China, in 2014. Firstly, five elementary schools and four secondary schools were selected via multistage cluster sampling. Secondly, we chose subjects with the available anthropometric, lipid profile, and fasting serum glucose data, and then divided them into case and control groups according to the inclusive and exclusive criteria. The case group involved individuals with at least one MetS component according to the criteria published by Cook et al. [15] The control group included individuals without any MetS component, who were randomly matched by age and gender (1:1 pair-wise matching). Both groups excluded individuals with genetic syndromes, endocrine diseases, or psychiatric disorders. In addition, individuals who would graduate within a year (in grades 6 and 9) were not enrolled due to their stressful courses. Eventually 1126 adolescents were included in the present study.

This study was approved by the Ethical Committee of the Peking University. Signed informed consents were given by parents or other legal guardians of the participants.

Anthropometric measurement

All the participants were subjected to anthropometric measurements, namely height, weight, waist circumference, hip circumference, and blood pressure, which were performed by the same group of experienced clinicians and nurses (no more than four observers for each item). Height was measured to the nearest 0.1 cm using a fixed stadiometer (Yilian TZG, Jiangsu, PRC). Weight was measured to the nearest 0.1 kg using a lever scale (Hengxing RGT-140, Jiangsu, PRC). Waist circumference and hip circumference were measured to the nearest 0.1 cm using a flexible tape in the standing position at the end of a gentle respiration, taking the umbilical scar and the largest point of outer hip as the reference, respectively. Blood pressure was measured on the upper right arm in the seated position using a mercury sphygmomanometer (Yutu XJ1ID, Shanghai, PRC) with at least a 10-min rest before the measurement. The first and the fifth Korotkoff sounds were used for representing the systolic and diastolic blood pressure. These anthropometric measurements were digitally measured twice for each subject and the average values were calculated. Inter- and intra-observer reliability were >0.94 and > 0.96, respectively. The body mass index (BMI) was calculated as weight (kg)/(height (m)) [2], and the waist-to-hip ratio (WHR) was calculated as waist circumference (cm)/hip circumference (cm).

Questionnaire assessment

The self-reported questionnaires were developed on the basis of previously tested and validated questions, including questions of demography, sleep duration, physical activities (vigorous-intensity activities, moderate-intensity activities, and walking and sedentary behaviors) and diet (sugar-sweetened beverage consumption and snacking habits). For sleep duration, participants were asked, “How many hours do you sleep per day?” Sleep duration per day was categorized into four groups (<7.0, 7–9, 9–11, and >11 h/day). For physical activities, the participants were asked the following questions: “How