Archives of Medical Research 46 (2015) 507–513

Archives of Medical Research

PRELIMINARY REPORT

Circulating Hepcidin Is Independently Associated with Systolic Blood Pressure in Apparently Healthy Individuals

Milton Fabian Suárez-Ortegón,[a,b] Alejandra Arbeláez,[b,c] Mildrey Mosquera,[b,c] José Maria Moreno-Navarrete,[d] Cecilia Aguilar-Plata,[b,c] and José Manuel Fernández-Real[d]

[a]*Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK*
[b]*Nutrition Group,* [c]*Physiological Sciences Department, Universidad del Valle, Cali, Colombia*
[d]*Department of Diabetes, Endocrinology and Nutrition, Institut d'Investigació Biomèdica de Girona (IdIBGi), CIBEROBN (CB06/03/010) and Instituto de Salud Carlos III (ISCIII), Girona, Spain*

Received for publication April 21, 2015; accepted July 31, 2015 (ARCMED-D-15-00261).

Background and Aims. Few studies have described the association between hepcidin levels and cardiometabolic risk in the general population and more so by considering robust adjustment for confounding factors. Therefore, the aim of the present study was to investigate the associations between circulating hepcidin and anthropometric, biochemical and vascular variables related to cardiometabolic risk in healthy individuals adjusting for relevant covariates.

Methods. Two-hundred thirty nine individuals (20–65 years old) were included in this cross-sectional study. Outcome variables were fasting glucose, triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, waist circumference, systolic and diastolic blood pressures, and the Framingham risk score. Multivariate linear regression and ANCOVA analyses including covariates of body mass index (BMI), menopausal status, physical inactivity, alcohol intake, insulin resistance, subclinical/chronic inflammation, ferritin and soluble transferrin receptors were used to describe the associations between hepcidin and cardiometabolic risk markers.

Results. In adjusted linear regression analyses, there was no significant association in men. In women, a relationship between hepcidin and triglycerides became significant after adjustments ($p < 0.05$). By comparing quartiles of hepcidin levels, systolic blood pressure values in men were significantly higher in the upper quartile of hepcidin vs. the rest of quartiles independently of BMI, chronic inflammation, insulin resistance and other iron markers (ANCOVA, $p < 0.05$). There were no significant independent associations with the Framingham risk score (total points).

Conclusion. We found a threshold effect of hepcidin levels on systolic blood pressure specifically in men. Further larger studies and experimental research are required to investigate possible mechanisms for the relationship between hepcidin metabolism and vascular function.

Key Words: Hepcidin, Blood pressure, Cardiovascular risk, Insulin resistance.

Introduction

Because possible differences by gender in iron status were postulated as a potential explanation for difference in cardiovascular risk between men and women, iron parameters have been evaluated as potential modifiable factors in the general population in the last two decades (1,2). Body iron stores measured as circulating ferritin levels have been

Address reprint requests to: Milton Fabian Suárez-Ortegón, Centre for Population Health Sciences, College of Medicine and Veterinary Medicine, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, United Kingdom; Phone: +44 (0) 131 650 3237; FAX: +44 (0) 131 650 6909 and; E-mail: Milton.Suarez@ed.ac.uk; or José Manuel Fernández-Real, Section of Diabetes, Endocrinology and Nutrition, Hospital of Girona "Dr Josep Trueta", Carretera de França s/n, 17007 Girona, Spain; Phone: +34 972 94 02 00; FAX: +34 972 94 02 70; E-mail: jmfreal@idibgi.org

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2015.07.007

found associated with increased risk of type 2 diabetes and metabolic alterations related to cardiovascular risk, but the causal relationship is still inconclusive (3−5).

The exploration of new markers of iron metabolism regarding cardiometabolic risk supposes a further step in the characterization of this relationship. The relationship of hepcidin with cardiometabolic risk has been scarcely investigated. Hepcidin is a peptide produced mainly by the liver in response to increased plasma or tissue iron to homeostatically downregulate its absorption by binding and inactivating intestinal ferroportin (6). Given the potential pleiotropic effects of hepcidin (7), it is important to assess the effect of covariates regarding theoretical relationships with variables of cardiometabolic risk. In the limited studies conducted to date, robust multivariate analyses have not been performed and therefore it is not clear whether the associations with cardiometabolic risk would be similar to those observed with ferritin and whether the associations are independent of insulin resistance, inflammation and/or adiposity. Therefore, the aim of the present study was to investigate whether variables related to cardiometabolic risk were associated with circulating hepcidin in healthy individuals after adjusting for important confounding variables.

Materials and Methods

Subjects

The study population consisted of 239 volunteers (20−65 years old) from the staff of a hospital, a university, a governmental health department and a supermarket chain in Cali, Colombia and who responded to advertisements describing our study. In order to obtain healthy subjects and to avoid bias in estimating variables related to cardiometabolic risk and iron parameters, the following exclusion criteria were considered: clinically significant liver diseases, neurologic or endocrine systems, cardiometabolic diseases (hypertension, history of stroke, myocardial infarction, or type 2 diabetes) or other major systemic disease; smoking; blood transfusion or iron therapies during the previous 6 months; long-term multivitamin or vitamin supplements consumption (two or more days/week); hypolipidemic or oral hypoglycemic drugs; current evidence of acute or chronic inflammatory or infective diseases; and history of disturbances in iron balance (e.g., hemosiderosis from any cause, hemolytic anemia, iron deficiency). The Universidad del Valle Research Ethics Committee approved the study and all participants gave written informed consent.

Clinical Measurements

Blood pressure was measured using digital sphygmomanometers with an appropriately sized cuff in a sitting position after a 15-min rest. The measurement was repeated after 5 min. The mean of the two measurements was used in the statistical analyses. Body weight and height were measured using standard techniques and instruments and body mass index (BMI) was calculated as weight in kg/height in m^2. Waist circumference (WC) was measured from the midpoint between the lateral iliac crest and the lowest rib using a flexible steel tape measure. A survey to record personal data and lifestyle habits were recorded by trained interviewers.

Biochemical Measurements

After 8 h fasting, blood was obtained and serum and plasma samples were stored at −80°C until subsequent analyses. Fasting glucose, triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-C) were determined by using enzymatic-colorimetric assays (Biosystems Inc., Spain). Low-density lipoprotein cholesterol (LDL-C) levels were calculated according to the Friedewald equation: total cholesterol-(HDL-C + (triglycerides/5)) (8). Serum ferritin and high sensitivity C-reactive protein (CRP) were measured using turbidimetry (Biosystems Inc.). Fasting insulin was measured using chemiluminiscence. Levels of hepcidin and soluble transferrin receptor (sTfR) were measured using a double monoclonal sandwich enzyme immunoassay (DRG® Hepcidin 25 [Bioactive] ELISA [EIA-5258, DRG International, Inc., Mountainside, NJ]; and Human sTfR ELISA [RD194011100, Heidelberg, Germany], respectively). Intra- and interassay coefficients of variation were <5.5%. HOMA-IR (Homeostatic Model Assessment-Insulin Resistance) was calculated as (insulin mU/mL × [glucose mg-dL]/405) (9).

Framingham Risk Score

The Framingham risk score was calculated according to the points-based system (10). Sub-total points derived from variables of age, total cholesterol and HDL-C and systolic blood pressure were used obtain the total points. In this calculation, there were no sub-total points derived from smoking because this was an exclusion criterion of the study. Equivalent 10-year risk was derived from the values of total points (10).

Statistical Analysis

All analyses were conducted in each gender and the study variables were described as means and standard deviation or median and interquartile range according to distribution of the variables. Differences were estimated via Student t test or Mann−Whitney U test. Because 12 subjects had values of hepcidin below the detection limit, the value assigned for these cases for descriptive purposes was the same value of detection limit (0.35 μg/mL). Multivariate linear regression analysis was conducted to evaluate and adjust the associations of hepcidin with cardiometabolic