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The incidental relationship between serum ferritin levels and hypertension ☆

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ABSTRACT

Background and objective: Although several studies have shown an association between ferritin level and hypertension, only a few studies have investigated the longitudinal relationship between them. Thus, we evaluated the incidental risk for hypertension according to baseline ferritin level.

Patients and methods: A total of 7104 healthy Korean men matched by a propensity score, who had participated in a medical health check-up program in 2005, were followed up from 2005 to 2010. They were divided into four groups according to baseline serum ferritin level (first quartile–fourth quartile). The incidence of hypertension was compared among the four groups, and the Cox-proportional hazard model was used to assess whether the development of hypertension was associated with higher baseline serum ferritin level.

Results: A total of 1252 (17.6%) cases had newly developed hypertension during the 26,339.5 person-years of follow-up between 2006 and 2010. The adjusted hazard ratios (HRs) (95% confidence intervals, CIs) for incident hypertension were 1.00 (reference), 1.09 (0.91–1.30), 1.21 (1.01–1.45) and 1.28 (1.07–1.52), respectively (P for trend = 0.003) through the quartiles of serum ferritin levels, respectively, after adjusting for multiple confounders. For the log-transformed serum ferritin levels as a continuous variable, adjusted HRs and 95% CIs for HTN were 1.15 (1.02–1.29).

Conclusions: Elevated serum ferritin level was independently associated with the incidental risk for hypertension in Korean men. This finding suggests the value of elevated ferritin level as an early predictor of hypertension.

1. Introduction

High blood pressure is one of the most common risk factors for ischemic heart disease, stroke, hypertensive heart disease, and renal failure [1]. Hypertension (HTN) ranked third as a global and regional disease burden and has been verified as the top risk factor for mortality [1]. Overall, 26.4% of the world's adult population had HTN in 2000, and this prevalence is likely to increase to 29.2% by 2025 [2]. Thus, prevention and prediction of HTN are essential for decreasing the global disease burden and cardiovascular mortality.

The health risk posed by iron overload has been attracting much interest with the discovery that the C282Y mutation in the *HFE* gene is involved in hereditary hemochromatosis [3]. Serum ferritin level is a highly sensitive parameter used to evaluate body iron status [4]. Several studies have investigated the association between elevated serum ferritin and prevalence and risk for HTN [5–7]. However, clinical evidence remains limited for a concrete etiological association between high serum ferritin level and incident HTN because only one study has analyzed the temporal relationship between elevated serum ferritin and development of HTN [7]. Therefore, we conducted this study to assess the effect of elevated serum ferritin level on the future risk of HTN.

Abbreviations: HTN, hypertension; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; TIBC, total iron binding capacity.

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2. Participants and methods

2.1. Study design

A prospective cohort study was conducted to examine the association between serum ferritin levels and the development of HTN in Korean men participating in a medical health check-up program at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. The study methods and explanation of the medical health check-up program were described in detail in our previous study [8].

2.2. Study population

A total of 43,604 men (age, 30–59 yr), who had visited the Health Promotion Center at Kangbuk Samsung Hospital for a medical check-up in 2005, participated in this study. Among the 43,604 participants, 13,264 were excluded based on the following exclusion criteria that could influence HTN or serum ferritin level: 2120 had a positive serologic marker for hepatitis B surface antigen (HBs Ag); 41 had a positive serologic marker for hepatitis C virus antibody (HCV Ab); 47 had ultrasonographically detected liver cirrhosis; 400 had ultrasonographically detected chronic hepatic diseases; 1491 had a history of blood transfusion; 29 were regarded as probably having hemochromatosis based on abnormal serum ferritin level > 800 ng/mL; 193 had a history of malignancy; 210 had a history of cardiovascular disease; 2990 were receiving lipid-lowering medications; 11 had no baseline HTN information in 2005; and 8139 had baseline HTN at the initial examination. Because some participants had more than one exclusion criteria, the total number of men who were eligible for the study was 30,340. We further excluded 6872 participants who did not attend any follow-up visits between 2006 and 2010. Without the follow-up visit, we could not identify the development of HTN or calculate the individual person year. Among the 23,468 participants, 6043 were excluded, because they have missing values for covariate information. Among the 17,425 participants, 7104 participants were included in the final analysis after matching in a 1:1 ratio by a propensity score.

The total follow-up period was 26,339.5 person-years, and the average follow-up period was 3.71 (standard deviation [SD], 1.35) person-years. Ethics approvals for this study protocol and analysis of the data were obtained from the institutional review board of Kangbuk Samsung Hospital. The informed consent requirement was exempted because we only retrospectively accessed a de-identified database for analytical purposes.

2.3. Clinical and laboratory measurements

Study data included a medical history, a physical examination, information provided by a questionnaire, anthropometric measurements and laboratory measurements. The medical history and the history of drug prescription were assessed by the examining physicians. All the participants were asked to respond to a questionnaire on health-related behavior. Questions about alcohol intake included the frequency of alcohol consumption on a weekly basis and the usual amount that was consumed on a daily basis (≥20 g/day). We considered persons reporting that they smoked at that time to be current smokers. In addition, the participants were asked about their weekly frequency of physical activity, such as jogging, bicycling, and swimming that lasted long enough to produce perspiration (≥1 time/week). Diabetes mellitus was defined as fasting serum glucose of at least 126 mg/dL or current use of blood glucose-lowering agents.

Systolic and diastolic blood pressure (BP) was measured with a standardized mercury sphygmomanometer after at least 5 min of seated rest using the Hypertension Detection and Follow-Up Protocol. According to the JNC-7 guidelines, HTN was defined as a systolic BP of at least 140 mm Hg or a diastolic BP at least 90 mm Hg, or current use of antihypertensive agents [9]. The development of HTN was assessed from the annual records of all participants and defined as blood pressure (BP) ≥ 140/90 mm Hg. Also, participants who had a history of HTN or currently used antihypertensive medication based on the self-report questionnaire at each visit were considered to have developed HTN.

Anthropometric measurements and procedures for obtaining the blood samples were described in detail elsewhere [8]. Serum levels of ferritin, iron and total iron binding capacity (TIBC) were measured by electrochemiluminescence immunoassay using a Modular E170 analyzer (Roche Diagnostics, Basel, Switzerland). The clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories.

2.4. Propensity-score models

The highest three quartiles of baseline serum ferritin level were matched to the lowest quartile to balance the major covariates which was associated with the development of hypertension by using a propensity score. Multiple logistic regression was used to estimate propensity scores of highest three quartiles of baseline serum ferritin level on the lowest quartile level of serum ferritin level as the reference group after adjustments for the major covariates. Highest three quartile levels of serum ferritin level were matched with the reference group (1st quartile level of serum ferritin level) using a propensity score with a caliper method using SAS macro program (%PSMatching). The caliper was set as a 0.0004 to match the propensity score and the matching ratio was 1:1.

Additional detailed information about propensity score matching is available in the Supplementary Appendix.

2.5. Statistical analyses

Data were expressed as means ± (standard deviation) or medians (interquartile range) for continuous variables and percentages of the number for categorical variables.

The one-way ANOVA and χ^2-test were used to analyze the statistical differences among the characteristics of the study participants at the time of enrollment in relation to the quartile groups of serum ferritin levels.

The distributions of continuous variables were evaluated, and log transformations were used in the analysis as required. For incident HTN cases, because we couldn't know the exact time for the development of HTN, the time of HTN was assumed to be the midpoint between the baseline visit (2005) and the visit at which HTN was first detected. The person years were calculated as the sump of follow-up times for the baseline until an assumed time of HTN development or until the final examination of each individual.

To evaluate the associations of baseline serum ferritin levels and incident HTN, we used Cox-proportional hazard models stratified by matched pairs to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident HTN comparing the highest 3 quartiles of baseline fasting serum ferritin vs the lowest quartile. Cox-proportional hazard models were adjusted for the multiple confounding factors. In the multivariate models, we included variables that might confound the relationship between serum ferritin and incident HTN, which include: age, body mass index (BMI), white blood cell (WBC), low-density lipoprotein (LDL) cholesterol, log(hsCRP), homeostasis model assessment of insulin resistance (HOMA-IR), estimated glomerular filtration rate (eGFR), total iron binding capacity (TIBC), smoking status, alcohol intake, regular exercise and type 2 diabetes mellitus. For the linear trends of risk, the number of quartiles was used as a continuous variable and tested on each model. We also conducted the sensitivity analysis, after serum ferritin was log-transformed as a continuous variable to assess the robustness of associations with the risk of HTN.