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Incidental risk for diabetes according to serum ferritin concentration in Korean men

Sunyong Kim [a,1], Sung Keun Park [a,b,1], Jae-Hong Ryoo [b,*], Joong-Myung Choi [b], Hyun Pyo Hong [c], Jai Hyung Park [d], Young Ju Suh [e], Young-Sang Byoun [f]

[a] Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[b] Departments of Preventive Medicine, School of Medicine, Kyung Hee University, Seoul, Republic of Korea
[c] Department of Radiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[d] Department of Orthopaedic Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, Republic of Korea
[e] Institute of Clinical Research, School of Medicine, Inha University, Incheon, Republic of Korea
[f] Departments of Internal Medicine, Bucheon Daesung Hospital, Gyeonggi-do, Republic of Korea

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ABSTRACT

Background: Despite accumulating evidence suggesting the clinical association between serum ferritin concentrations and diabetes, it is not clearly identified in other ethnic groups besides western population. This study analyzed a longitudinal relationship between serum ferritin concentration and the risk for diabetes in non-diabetic Korean men.
Methods: This study was composed of a cohort of 30,002 non-diabetic Korean men who participated in medical health check-up program in 2005. They were divided into 4 groups according to their baseline ferritin concentrations (first quartile–fourth quartile) and monitored until 2010. Their incidences and hazard ratios of diabetes were compared among 4 groups according to their baseline ferritin concentrations.
Results: While 2655 cases of diabetes newly developed during follow-up, incidence of diabetes increased proportionally to the baseline serum ferritin concentrations. In Cox-proportional hazard model, hazard ratios for diabetes also independently increased according to the baseline serum ferritin concentrations [quartile 1: 1.00 (reference), quartile 2: 1.00 (0.87–1.12), quartile 3: 1.13 (1.00–1.29), quartile 4: 1.18 (1.04–1.34), respectively].
Conclusions: Increased ferritin concentration was associated with increased risk for diabetes in Korean men. These findings suggest the clinical significance of serum ferritin concentration in the development diabetes.

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1. Introduction

Diabetes is a challenging worldwide public-health burden because of its high prevalence and concomitant risks of various complications [1,2]. In 2013, 382 million people, or 8.3% of worldwide adults, are estimated to have diabetes and 592 million people, or 8.8% of adults are predicted to have diabetes by 2035, if these trends continue [3]. Patients with diabetes have higher risk of developing neurological, peripheral vascular, cardiovascular, renal, metabolic and other various chronic complications compared with individuals without diabetes [1,4]. The burden of diabetes might be laid on the economy in the form of increased medical expenses and indirect costs from absenteeism of work, reduced productivity [1,4]. Therefore, early detection and

management of high-risk individuals is crucial to prevent numerous complications of diabetes, thereby, to potentially improve social and economic effect of diabetes.

The iron overload as a risk factor of health has been attracting concerns with the discovery of the C282Y mutation of the HFE gene which is associated with hereditary hemochromatosis [5]. There have been increasing concerns with regard to the association between the increased serum ferritin and prevalence and risk of diabetes [6–25].

Nonetheless, evidences are still lacking to support a concrete temporal relationship between high concentration of serum ferritin and incident diabetes, especially for Asian population. This study design was based on the hypothesis that the BMI change rate might affect the future development of hypertension.

2. Methods

2.1. Study design

A prospective cohort study was conducted to examine the association between serum ferritin concentrations and the development of

diabetes 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 have been described in detail previously [26].

2.2. Study population

A total of 46,787 men who had visited Health Promotion Center at Kangbuk Samsung Hospital for a medical check-up in 2005 participated in this study. Among the 46,787 participants, 6668 men were excluded based on the following exclusion criteria that might influence diabetes or serum ferritin concentration: 2226 had a positive serologic marker for hepatitis B surface antigen (HBsAg); 71 had a positive serologic marker for hepatitis C virus antibody (HCVAb); 51 had ultrasonographically detected liver cirrhosis; 445 had ultrasonographically detected chronic liver diseases; 1694 had a past history of blood transfusion; 33 were regarded as probably having hemochromatosis based on abnormal values of serum ferritin >800 ng/ml; 239 had a past history of a malignancy; 324 had a past history of cardiovascular disease; 53 had no information of baseline diabetes in 2005 and 2524 had a baseline diabetes at initial examinations. Because some participants had >1 exclusion criteria, the total number of men who were eligible for the study was 40,119. We further excluded 10,117 participants who did not attend any follow-up visit between 2006 and 2010. Without the follow-up visit, we could not identify the development of diabetes and also could not calculate the individual person year. Accordingly, 30,002 participants were included in the final analysis and were observed for the development of diabetes. The total follow-up period was 112,398.3 person year and average follow-up period was 3.75 (SD 1.39) person year. Ethics approvals for the study protocol and analysis of the data were obtained from the institutional review board of Kangbuk Samsung Hospital. The informed consent requirement was exempted by the Institutional Review Board because researchers only accessed retrospectively a de-identified database for analysis 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).

The development of diabetes was assessed from the annual records of all participants and defined as fasting serum glucose ≥126 mg/dl or HbA1c ≥6.5% [27]. Participants who had a history of diabetes mellitus, or were undergoing treatment with anti-diabetic agents based on the self-administered questionnaire at each visit, were considered diabetes. Hypertension was defined as having blood pressure (BP) ≥140/90 mm Hg or on antihypertensive medication, at their initial examinations. Trained nurses obtained sitting BP concentrations with a standard mercury sphygmomanometer. The first and fifth Korotkoff sounds were utilized to estimate the systolic and diastolic BP.

Blood samples were collected after more than 12 h of fasting and were drawn from an antecubital vein. Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT) were measured using Bayer Reagent Packs (Bayer HealthCare, Tarrytown, NY) on an automated

chemistry analyzer (ADVIA 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Insulin concentrations were measured with immunoradiometric assays (Biosource). Insulin resistance was calculated with the homeostasis model assessment of insulin resistance (HOMA-IR) as described by Matthews et al.: fasting serum insulin (uU/ml) × fasting serum glucose (mmol/l)/22.5 [28]. HbA1c was measured by immunoturbidimetric assay with a Cobra Integra 800 automatic analyzer (Roche Diagnostics). The serum creatinine (SCr) concentration was measured by means of the alkaline picrate (Jaffe) method. Kidney function was measured with estimated glomerular filtration rate (eGFR), which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: eGFR = $141 \times \min(SCr/K, 1)^a \times \max(SCr/K, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [female] × 1.159 [Black], where SCr is serum creatinine, K is 0.7 for females and 0.9 for males, a is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/K or 1 and max indicates the maximum of SCr/K or 1 [29].

The fasting serum glucose was measured with the hexokinase method. Total cholesterol and triglyceride were measured with enzymatic colorimetric tests, low-density lipoprotein (LDL) cholesterol was measured with the homogeneous enzymatic colorimetric test, and high-density lipoprotein (HDL) cholesterol was measured with the selective inhibition method (Bayer Diagnostics). Serum concentrations of ferritin, iron and total iron binding capacity (TIBC) were measured by electrochemiluminescence immunoassay using Modular E170 analyzer (Roche Diagnostics). The clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Height and weight were measured after an overnight fast with the shoeless participants wearing a lightweight hospital gown.

2.4. 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 concentrations. The distributions of continuous variables were evaluated, and log transformations were used in the analysis as required.

For incident diabetes cases, the time of diabetes occurrence was assumed to be the midpoint between the visit at which diabetes was first detected and the baseline visit (2005). The person years were calculated as the sum of follow-up times from the baseline until an assumed time of diabetes development or until the final examination of each individual.

To evaluate the associations of baseline serum ferritin concentrations and incident diabetes, we used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for incident diabetes 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 diabetes, which include: age, BMI, WBC, total cholesterol, Log (HOMA-IR), eGFR, TIBC, smoking status, alcohol intake, regular exercise and hypertension. For the linear trends of risk, the number of quartiles was used as a continuous variable and tested on each model.

To test the validity of the Cox-proportional hazard models, we checked the proportional hazard assumption. The proportional hazard assumption was assessed by log-minus-log survival function and found to be graphically unviolated. P values <0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS Windows ver 18.0.