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Associations between hemoglobin concentrations and the development of incidental metabolic syndrome or nonalcoholic fatty liver disease

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ABSTRACT

Aims: Hemoglobin (Hb) is known to be associated with both nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome (MS). We evaluated the relationship between serum Hb levels and the development of MS or NAFLD.
Methods: A retrospective cohort study was conducted. We recruited participants who underwent abdominal ultrasonography and blood samplings in both 2005 and 2010.
Results: Graded independent relationships were observed between higher Hb levels and the incidence of MS and NAFLD. After adjusting for age, body mass index, and fasting glucose, high-density lipoprotein cholesterol and triglyceride levels, the risk of developing MS was significantly higher according to the Hb quartiles in men (*P* for trend = 0.027). The adjusted odds ratio (OR) and 95% confidence intervals (CIs) for the highest Hb quartile was 1.81 (1.06–3.10) for women and 1.43 (1.00–2.05) for men. The risk of developing NAFLD was also significantly higher according to the Hb quartiles in men (*P* for trend = 0.03). The adjusted OR and 95% CI for the highest Hb quartile was 1.18 (0.73–1.91) in women and 1.76 (1.16–2.66) in men.
Conclusions: The risk of developing either MS or NAFLD was significantly associated with serum Hb levels in men. These findings have implications in the clinical availability of serum Hb as a predictor of MS and NAFLD.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the leading form of chronic liver disease, with a prevalence of up to 20–30% in the general population [1,2]. NAFLD is closely related to risk factors for cardiovascular diseases, including central obesity, dyslipidemia, hypertension and glucose intolerance, all of which are components of metabolic syndrome (MS) [3,4]. Because the central pathogenesis of NAFLD development is insulin resistance, NAFLD is regarded as a hepatic feature of MS [5], and close associations have been found between NAFLD and MS [6–8]. Moreover, NAFLD has been considered a potential precursor of MS. Previous meta-analysis and systematic review showed that the presence of NAFLD may be a risk factor for development of MS, indicating a strong determinant for the future development of MS [9–13].

Hemoglobin (Hb) is a blood parameter that is simple and inexpensive to evaluate, and hemoglobin levels are closely associated with iron levels. Previous studies have revealed a relationship between increased iron levels and the severity and progression of NAFLD [14–16]. A recent study showed that increased blood hematocrit levels are significantly associated with fibrosis in biopsy-diagnosed NAFLD patients [17]. However, serum ferritin levels lack the diagnostic accuracy for assessing liver fibrosis in NAFLD [18] and phlebotomy does not invariably benefit NAFLD due to inconsistent data [19,20]. Hb has been used as an important risk factor for NAFLD, even in subjects without MS and in lean subjects with NAFLD [21,22]. Consistently, the association between Hb concentration and MS has been reported [16,23]. In a Taiwanese

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Chinese population study, increased red and white blood cell counts were significantly associated with various components of MS [24]. Recently, a population-based study reported that Hb concentrations were associated with an increased risk of incidental MS in men [25].

Because NAFLD and MS are intimately linked and share insulin resistance as a pathogenic mechanism, we hypothesized that increased Hb level contribute to the initial development of both NAFLD and MS. Therefore, we evaluated the relationship between serum Hb levels and the development of MS or NAFLD.

2. Patients and methods

2.1. Study population

We analyzed data from a previously described cohort [26]. Briefly, subjects who underwent abdominal ultrasonography (US) and blood samplings at the Seoul National University Hospital Gangnam Healthcare Center, Seoul, Korea for routine health check-ups in both 2005 and 2010 were initially included in this cohort. Subjects with significant alcohol intake (> 20 g/day for males and >10 g/day for females) were excluded (n = 754). We also excluded 184 individuals who were positive for the hepatitis B virus and 44 subjects who were positive for the hepatitis C virus. Additionally, 89 subjects for whom any information was missing were excluded from the study. This study was approved by the Institutional Review Board of the Seoul National University Hospital and the requirement for informed consent was waived.

2.2. Clinical and, laboratory assessments

Each subject completed a routine previous medical history questionnaire and underwent an anthropometric assessment in addition to laboratory and radiological tests on the same day. Body weight and height were measured using a digital scale. Body mass index (BMI) was calculated as the weight/height (kg/m^2) ratio. Waist circumference was measured by a well-trained person at the midpoint between the lower costal margin and the anterior superior iliac crest. Systolic and diastolic blood pressure were measured twice, and the mean values were reported. After a 12-h fast, blood samples were collected from the antecubital vein of each individual. Hb levels were quantified using an automated blood cell counter (ADVIA 2120, Bayer, NY, USA). The laboratory evaluations included assessments of serum alanine aminotransferase (ALT), total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and fasting glucose levels, as well as the presence of hepatitis B surface antigen and antibody to the hepatitis C virus.

2.3. Definitions

Diabetes mellitus was defined as either a fasting serum glucose ≥126 mg/dL or the use of anti-diabetic medication. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or the use of anti-hypertensive medication. Regarding smoking status, each patient was categorized as a nonsmoker, former smoker or current smoker [27].

MS was diagnosed when three or more of the following five components were present, based on the modified National Cholesterol Education Program Adult Treatment Panel III [28]. (1) Central obesity [defined as a waist circumference >90 cm (men) or >80 cm (women) according to the Regional Office for the Western Pacific Region of the World Health Organization criteria]; (2) triglyceride levels ≥150 mg/dL (3) HDL-cholesterol levels <40 mg/dL (men) or <50 mg/dL (women); (4) fasting glucose levels ≥100 mg/dL or the use of anti-diabetic medications; and (5) blood pressure ≥130/85 mmHg or the use of anti-hypertensive medications.

A diagnosis of NAFLD was based on findings determined by experienced radiologists using ultrasonography (Acusion, Sequoia 512, Siemens, Mountain View, CA). The radiologists were unaware of any relevant clinical information. The sonographic features of a fatty liver included the following: bright echoes in the liver, high hepatorenal echo contrast, or deep attenuation and impaired visualization of the diaphragm and marked vascular blurring [29]. The follow-up hepatic sonography was based on the same protocol and performed using the same equipment that was used at baseline.

2.4. Statistical analysis

The Hb quartiles were determined based on the values observed in this cohort. Because hemoglobin levels differ significantly by sex, hemoglobin quartiles were categorized separately by gender as follows: for women, Q1: ≤126, Q2: 126–132, Q3: 132–139, and Q4: ≥139 g/L; for men, Q1: ≤148, Q2: 148–154, Q3: 154–161, and Q4: ≥161 g/L. Comparisons of continuous variables between the two groups were performed using Student's *t*-test, and categorical variables were compared using chi-square test or Fisher's exact tests. Variables that were statistically significant in the univariate analysis and known risk factors were included in a multiple logistic regression model to identify independent predictors of NAFLD and MS. All statistical analyses were performed using SPSS 22.0 (SPSS Inc.; Chicago, IL, USA). *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

First, we evaluated the development of MS according to serum Hb levels. Among the 3473 subjects enrolled, 840 (24.1%) were excluded because of pre-existing MS. A total of 2722 subjects were included in the final analysis (Fig. 1). The mean age of these participants was 47.6 ± 9.6 years old and 50.8% were male. The mean Hb level was 132.1 g/L in women and 154.5 g/L in men. Table 1 shows the clinical and biochemical characteristics of the study population in relation to the serum Hb quartiles. The mean ALT values and the risk of developing MS after 5 years were significantly higher in the 4th quartile in both sexes ($p < 0.001$ and $p = 0.003$ in women and $p < 0.001$ and $p = 0.046$ in men, respectively).

Second, we evaluated the development of NAFLD according to serum Hb levels. Among the 3473 subjects who were initially enrolled, 1168 (33.6%) were excluded because of pre-existing NAFLD, and a total of 2216 subjects were included in the final analysis (Fig. 1). The mean age of these participants was 48.1 ± 9.6 years old, and 43.1% were male. Table 2 shows the baseline characteristics of the study population according to the serum Hb quartiles. The mean values of ALT, and the risk of developing NAFLD after 5 years were significantly higher in the 4th quartile in both sexes. ($p < 0.001$ and $p = 0.041$ in women and $p < 0.001$ and $p < 0.001$ in men, respectively).

3.2. Development of MS and NAFLD

During the 5 year follow-up period from 2005 to 2010, 585 (21.5%) cases of incidental MS developed. Fig. 2 shows the proportion of incidental MS cases according to the Hb quartiles. The percentage of incidental MS gradually increased in accordance with the Hb quartiles of the participants in both sexes: 8.1%, 11.0%, 13.7% and 17.3% in women and 27.5%, 26.1%, 32.4% and 34.7% in men in Q1, Q2, Q3, and Q4, respectively (Fig. 2). Table 3 shows the risk of developing MS according to the Hb quartiles. After adjusting for age, BMI, and fasting glucose, HDL-cholesterol and triglyceride levels, the risk of developing MS significantly increased as the Hb quartile

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