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Change in serum albumin concentration is inversely and independently associated with risk of incident metabolic syndrome

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ABSTRACT

Background. Low serum albumin concentration is associated with a high risk of morbidity and mortality from cardiovascular diseases. However, high serum albumin level appears to be linked to metabolic syndrome (MetS). This study aimed to dissect the relative contributions of baseline and change in serum albumin concentration to the risk of incident metabolic syndrome.

Methods. This was a 5-year (63,060 person-years) retrospective longitudinal study of 12,567 participants without metabolic syndrome, diabetes, or cardiovascular disease who were enrolled in a health screening program. The risk of developing MetS was analyzed according to baseline and change in serum albumin concentration.

Results. A total of 2582 incident cases of metabolic syndrome developed. The hazard ratio (HR) for incident MetS increased with increasing quartile of baseline serum albumin level compared with those in the lowest quartile, in a fully adjusted model (p for trend = 0.013). The HRs [95% confidence intervals (CIs)] of incident MetS comparing the second, third, and fourth quartiles to the first quartile of change in serum albumin level were 0.478 (0.421–0.544), 0.353 (0.307–0.405), and 0.262 (0.224–0.305) in the fully adjusted model, respectively (p for trend <0.001). Percent change in serum albumin concentration inversely correlated with percent change in serum level of high-sensitivity C-reactive protein ($r = -3.5444$, $p < 0.001$).

Abbreviations: ALT, alanine aminotransferase; ANOVA, analysis of variance; BMI, body-mass index; CI, confidence interval; CVD, cardiovascular diseases; DBP, diastolic blood pressure; DCCT, Diabetes Control and Complication Trial; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index for insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; MetS, metabolic syndrome; NGSP, National Glycohemoglobin Standardization Program; ROS, reactive oxygen spiecies; SBP, systolic blood pressure; TG, triglycerides; VIF, variance inflation factor.

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Conclusions. Although a higher baseline level of serum albumin was linked to increased risk of incident metabolic syndrome, increase in serum albumin concentration might be a protective factor against the risk of MetS.

1. Introduction

Because of its abundance in the body, albumin is considered a major antioxidant [1]. A large proportion of the antioxidant activity in human serum is attributable to human serum albumin, including >70% of the free radical-trapping activity in serum [2,3]. Augmented albumin concentrations at local inflammation sites have also been shown to have potent antioxidant activity [4]. Serum albumin exerts antioxidant activity by limiting reactive oxygen species (ROS) production via binding to ligands, such as metal ions and fatty acids, and by scavenging ROS through free radical-trapping activity. Several methionine residues and the cysteine-34 residue are involved in antioxidant activity [1]. Albumin is considered a sacrificial antioxidant because it has a high turnover rate and no recycling pathway; damage to albumin also does not directly affect cellular function.

Low serum albumin concentration has been consistently suggested to be associated with a higher risk of morbidity and mortality from cardiovascular diseases (CVDs) [5–9]. Moreover, a decrease in serum albumin concentration within normal range, rather than chronic low serum albumin level, has been suggested to be a risk factor of incident CVDs [9]. Aside from the association between low serum albumin concentration and malnutrition, these observations have been additionally supported by the indirect and sacrificial antioxidant properties of albumin [4,10–14]. In addition, beyond the well-known role of albumin as a negative acute-phase protein, the concentration of albumin also falls during chronic inflammatory processes, making a decrease in albumin an indicator of increased risk of CVD caused by chronic inflammation [15–17].

On the other hand, several cross-sectional studies have reported that high serum albumin is linked to conventional risk factors for atherosclerosis, such as obesity, insulin resistance, and metabolic syndrome, which are all indicators of over-nutrition [18–20]. These cross-sectional studies focused on the role of serum albumin as an indicator of over-nutrition. However, an increasing body of evidence suggests that obesity is associated with adipose tissue inflammation and that the inflammatory processes in accumulated adipose tissue may be an early initiator of metabolic syndrome [21,22]. Although chronic ROS production may contribute to both the onset and the progression of insulin resistance [21,23,24], dynamic changes in serum albumin level before the development of metabolic syndrome have not been examined via longitudinal analysis. Moreover, longitudinal analysis of high-sensitivity C-reactive protein (hs-CRP) was not performed in previous studies [18–20], which thus limited the information that could be obtained regarding inflammatory status.

Therefore, this study sought to examine the relative contributions of baseline serum albumin concentration and change in serum albumin concentration to the risk of incident metabolic syndrome via longitudinal analysis of a cohort in which serial hs-CRP data were available in all study subjects.

2. Materials and Methods

2.1. Study Population and Design

This retrospective longitudinal study included adults aged ≥20 years who participated in a medical health check-up program at the Health Promotion Center of Samsung Medical Center, Seoul, Korea. Using an electrical medical record system, we extracted clinical data, including anthropometric data, laboratory data, medical history, and smoking status, of subjects who had at least four follow-up visits between January 2006 and December 2012 (n = 25,170). Individuals who met any of the following criteria were excluded from the study: diagnosed with metabolic syndrome (n = 2603), hypertension (n = 4251), or diabetes mellitus (n = 1805) at baseline; established CVD at baseline (n = 744); on statin therapy (n = 805); missing waist circumference data at baseline (n = 3285); estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease (MDRD) equation, <60 ml/min per 1.73m^2 at baseline (n = 240); elevated total bilirubin or liver enzymes (n = 504); seropositivity for HBs antigens (n = 1065) or anti-HCV antibodies (n = 232); missing waist circumference during the follow-up period (n = 1108); and development of metabolic syndrome at the first follow-up visit (n = 2968). The remaining 12,567 subjects were included in this study. The observation period was the interval between the date of the first examination and the date of diagnosis of metabolic syndrome or the date of the last visit.

This study was approved by the Institutional Review Board of Samsung Medical Center and was carried out in accordance with recommendations of the Declaration of Helsinki.

2.2. Definitions

Metabolic syndrome was defined according to the harmonized criteria by the related federations [25]. People with three or more of the following criteria were classified as having metabolic syndrome: 1) waist circumference ≥90 cm in men or ≥80 cm in women; 2) triglycerides (TG) ≥150 mg/dl; 3) high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men or <50 mg/dl in women; 4) elevated blood pressure (systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DBP) ≥85 mmHg) or use of anti-hypertensive medications; or 5) fasting plasma glucose (FPG) ≥100 mg/dl or receiving treatment for diabetes.

Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or use of anti-hypertensive medications. Diabetes mellitus was diagnosed as FPG ≥126 mg/dL, HbA1c ≥6.5%, or use of anti-diabetes medications.

Changes in albumin, hs-CRP, and body mass index (BMI) were obtained by subtracting the baseline level from the final level (measured at the end of follow-up) in subjects without