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Association between vitamin D status and asymmetric dimethylarginine (ADMA) concentration in the Korean elderly population

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ABSTRACT

Objectives: Vitamin D deficiency has been reported to be associated with the risk of cardiovascular disease. We investigated the relationship between vitamin D status and asymmetric dimethylarginine (ADMA) concentration, a marker of endothelial dysfunction, in the Korean elderly population.

Study design: A cross-sectional study was conducted on 269 men and 382 women (mean age, 71.6 years) enrolled in the Korean Social Life, Health, and Aging Project (KSHAP), a population-based longitudinal study of health determinants in elderly Koreans. We stratified patients by vitamin D status into three groups according to serum 25-hydroxyvitamin D [25(OH)D] level: sufficient (≥30 ng/mL, n = 25), insufficient (10- < 30 ng/mL, n = 516), and deficient (< 10 ng/mL, n = 110). To measure endothelial dysfunction, ADMA concentration was assayed by high-performance liquid chromatography. The association between 25(OH)D status and ADMA concentration was analyzed by multiple linear regression models.

Results: The mean ADMA concentration was significantly higher in the insufficient 25(OH)D group (0.665 μmol/L, p = 0.001) and the deficient 25(OH)D group (0.734 μmol/L, p < 0.001) compared with the sufficient 25(OH)D group (0.589 μmol/L). Even after adjusting for sex, age, body mass index, blood pressure, diabetes mellitus, total and HDL cholesterol, estimated glomerular filtration rate (eGFR), smoking status, and drinking status, ADMA concentrations were higher in the insufficient group (β = 0.0742 μmol/L, p = 0.001) and the deficient group (β = 0.1417 μmol/L, p < 0.001) compared than in the sufficient group. In a sex-stratified analysis, 25(OH)D deficiency was associated with higher ADMA levels in both women (p < 0.001) and men (p = 0.007), while 25(OH)D deficiency was associated with higher ADMA levels in women (p < 0.001) but not in men (p = 0.631).

Conclusion: Our findings suggest that low serum 25(OH)D level may be associated with endothelial dysfunction in elderly Korean people.

1. Introduction

Vitamin D deficiency is prevalent in elderly people, consistent with the finding that aging reduces the production of vitamin D by the skin [1,2]. Although vitamin D deficiency is not considered to be a traditional cardiovascular risk factor [3], increasing evidence supports an association between low vitamin D concentration and increased risk of cardiovascular diseases [4,5]. Cardiovascular risk factors, including high blood pressure and abnormal blood lipid levels, can contribute to the development of endothelial dysfunction [3]. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide (NO) synthase [6]. Reduced levels of NO impair endothelium-dependent vasodilation, leading to endothelial dysfunction [7]. Based on previous studies, we hypothesized that vitamin D deficiency would accelerate endothelial dysfunction and increase blood ADMA concentration in elderly people. However, the relationship between vitamin D and serum ADMA concentration has not been rigorously studied. Thus, we investigated the association between vitamin D status and ADMA concentration in the Korean elderly population.

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2. Methods

2.1. Study population

We used data from the Korean Social Life, Health, and Aging Project (KSHAP), which was initiated in 2011. The KSHAP study recruited individuals aged 60 years or older and their spouses living in a rural township of Ganghwa Island, South Korea. From December 2011 to July 2012, 814 of the enrolled 860 community-dwelling adults (response rate, 94.7%) participated in the study and completed the questionnaire surveys [8]. The KSHAP-Health Examination (KSHAP-HE) cohort was a subcohort of 698 people who underwent additional health examinations at a public health center (n = 533) or at home (n = 165) between December 2011 and January 2012 [9]. In this study, among the 698 participants who completed the KSHAP-HE, 47 were excluded for lacking data such as serum 25-hydroxyvitamin D {25(OH)D} or ADMA plasma concentration (n = 22), body mass index (BMI), or glomerular filtration rate (GFR) (n = 25). Therefore, a total of 651 participants (269 men and 382 women) were included in the current study. All participants provided written informed consent.

2.2. Measurements

All participants were interviewed by trained personnel using standardized questionnaire surveys according to a predefined protocol. The standardized questionnaire was used to obtain socio-demographic characteristics such as age, education, marital status, and health behaviors. Health behavior-related questions dealt with medical history, smoking habits, and drinking habits.

We measured each participant's height and weight in the morning while he/she wore light indoor clothing but no shoes. Standing height was measured to the nearest 0.1 cm with a stadiometer, and body weight was measured to the nearest 0.1 kg with a digital scale. Body mass index (BMI) was calculated as body weight divided by squared height (kg/m^2). Blood pressure was measured twice using an automatic sphygmomanometer (Dinamap 1846 SX/P; GE Healthcare, Waukesha, WI, USA) after participants rested for at least 5 min in a seated position. If the two measurements differed by 10 mmHg or more, additional measurements were performed after 5 min. We used the average of the last two measurements in this study.

Blood samples were drawn after at least 8 h of fasting. Fasting concentrations of blood glucose, BUN, and creatinine were measured using a colorimetry-based method (ADVIA1800 Auto Analyzer, Siemens Medical Sol., Deerfield, IL, USA). Fasting insulin concentration was measured using an immunoradiometric assay (SR-300, Stratec, Germany). Diabetes was defined as fasting glucose ≥ 126 mg/dL or current treatment using antidiabetic drugs. Total cholesterol, HDL cholesterol, and triglyceride concentrations were measured by enzymatic methods (ADVIA1800 Auto Analyzer, Siemens Medical Sol., Deerfield, IL, USA).

Serum 25(OH)D was measured by a chemiluminescence immunoassay (CLIA) (Liaison, Diasorin, Germany). We used the LIAISON 25 OH Vitamin D TOTAL Assay. The CLIA is a direct competitive assay that measures the quantity of total 25(OH)D within serum. In order to compare the associations between 25(OH)D and ADMA concentration according to different vitamin D characteristics, patients were classified into one of the three following vitamin D groups according to serum 25(OH)D level: (1) deficient, serum 25(OH)D < 10 ng/mL; (2) insufficient, 10 ≤serum 25(OH)D < 30 ng/mL; and (3) sufficient, serum 25(OH)D ≥30 ng/mL [10]. In addition, ADMA plasma concentration was assayed by an enzyme-linked immunosorbent assay (Spectramax190, Molecular Devices, USA).

2.3. Statistical analysis

We compared the general and clinical characteristics of the three 25(OH)D subgroups. Continuous variables that followed a normal distribution are expressed as mean and standard deviation, whereas skewed variables are described as median and interquartile range. Categorical variables are expressed as numbers and percentages. Characteristic differences among 25(OH)D statuses were analyzed using analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables. We also used the general linear models with contrast coefficients for linear trend test for continuous variables. The Cochran-Armitage test was performed for linear trend for categorical variables. Fasting blood glucose and insulin values were log-transformed for parametric analysis because they were skewed to the right. Correlation between serum 25(OH)D concentration and ADMA concentration was assessed by Spearman's coefficients. To evaluate independent associations between 25(OH)D status (including 25(OH)D level) and ADMA plasma concentration, we carried out multiple linear regression analyses in an unadjusted model and two adjusted models. Model 1 was adjusted for sex and age, whereas Model 2 was adjusted for sex, age, body mass index, blood pressure, diabetes mellitus, total cholesterol, HDL cholesterol, eGFR, smoking status, and drinking status. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA), and statistical significance was defined as a two-sided p value less than 0.05.

3. Results

The demographic and clinical characteristics of the study participants are shown in Table 1. The mean 25(OH)D concentration was 16.5 ng/mL (men, 17.7 ng/mL; women, 15.6 ng/mL). Regarding vitamin D status, 16.9% of the participants were vitamin D-deficient and another 79.3% were vitamin D-insufficient. The mean ADMA concentration was significantly higher in people with insufficient vitamin D (0.665 μmol/L, $p < 0.001$) and deficient vitamin D (0.734 μmol/L, $p < 0.001$) compared to people with sufficient vitamin D (0.589 μmol/L). None of the other variables examined showed a significant difference between the vitamin D status groups.

Fig. 1 shows scatter plots of 25(OH)D concentrations and ADMA concentrations and also displays Spearman's coefficients describing the correlations. Overall, the 25(OH)D concentration was significantly and negatively correlated with ADMA concentration with both simple and partial correlations after controlling for sex and age. Furthermore, in both men and women, the 25(OH)D concentration showed a significant inverse correlation with ADMA level, both before and after adjusting for age.

Table 2 presents the associations between serum ADMA concentration and categorical 25(OH)D status from multiple linear regression analyses. Overall, the ADMA concentrations in the insufficient and deficient 25(OH)D groups were significantly higher than those in the sufficient 25(OH)D group in the unadjusted model and in the sex and age-adjusted model. Even after adjusting for sex, age, body mass index, blood pressure, diabetes mellitus, total and HDL cholesterol, eGFR, smoking status, and drinking status, ADMA concentrations were still higher in the insufficient and deficient 25(OH)D groups compared to the sufficient 25(OH)D group. In a sex-stratified analysis, the significant association of deficient 25(OH)D and higher ADMAconcentration was also present in both women and men, both before and after multiple adjustments. However, the ADMA concentrations in the insufficient 25(OH)D group were significantly higher in women but not in men. This result was obtained both before and after multiple adjustments.

Furthermore, Table 3 shows that ADMA level significantly increased according to a 10 ng/mL decrease of 25(OH)D, both overall and in both sexes. This result was obtained both before and after adjusting for sex and age. Moreover, after multiple adjustments for potential confounders, the association between serum ADMA level and continuous 25(OH)D level did not change.