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Serum vaspin levels are positively associated with carotid atherosclerosis in a general population

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ABSTRACT

Objectives: Vaspin is a novel adipocytokine with potential insulin-sensitizing properties. Insulin resistance (IR) plays a role in the development and progression of atherosclerosis. However, the relationship between serum vaspin levels and atherosclerosis remains unknown. Therefore, we investigated whether vaspin was correlated with carotid intima-media thickness (c-IMT).
Methods: Data for fasting vaspin levels of 201 subjects (78 men and 123 women aged over 40 years) were obtained from a general population in Japan. We obtained anthropometric parameters and blood chemistries, and calculated homeostasis model assessment-IR (HOMA-IR) index. C-IMT was measured by B-mode ultrasonography. The mean values of each parameter by tertiles of vaspin were compared with analysis of variance, and the associations of vaspin with IR and c-IMT were evaluated by multiple stepwise regression analysis.
Results: Univariate analysis revealed that vaspin levels were positively correlated with BMI, insulin, HOMA-IR index, estimated glomerular filtration rate (eGFR), c-IMT and hypertensive medication. Multiple stepwise regression analysis revealed that HOMA-IR index, c-IMT and eGFR were significantly and independently associated with vaspin. We performed multivariate analyses with c-IMT as the dependent variable. Age, hypertensive medication and vaspin were significant for c-IMT. Moreover, a mediation analysis demonstrated that vaspin was significantly related to c-IMT, independently of IR.
Conclusions: The present study not only confirmed the previous finding of the positive association of vaspin with IR but also demonstrated that serum vaspin level was positively associated with c-IMT, independently of IR in a general population. Our results may suggest a role of vaspin in atherosclerosis in humans.

1. Introduction

Vaspin was first identified from visceral adipose tissues of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of type 2 diabetes mellitus with obesity and insulin resistance (IR) [1]. It is one of the visceral adipose tissue-derived adipocytokines, which belongs to the family of serine protease inhibitor (serpin) [2]. Adipose tissue expression of vaspin was significantly increased when obesity peaked in OLETF rats and administration of vaspin to obese mice improved glucose tolerance and insulin sensitivity [1]. Thereafter, many in vitro and in vivo animal studies demonstrated insulin-sensitizing capacity of vaspin [3–5].

In humans, vaspin appears to have insulin-sensitizing properties [6] as well. Some clinical studies regarding regulation of human vaspin have shown that serum levels are positively associated with IR [7,8] and the values are decreased following weight reduction and short-term intensive lifestyle modification [9], and restrictive

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bariatric surgery and laparoscopic Roux-en-Y gastric bypass (RYGB) surgery [10,11]. Thus, observations of animal and human studies suggest that vaspin could be a novel adipocytokine with an insulin-sensitizing property.

Recently, it has been considered that vaspin may possess anti-atherosclerotic properties. However, there have been a few data available for the association of vaspin with atherosclerosis [12,13]. Accordingly, we investigated whether serum vaspin levels were correlated with intima-media thickness of the carotid artery, a marker of subclinical atherosclerosis in a general population.

2. Methods

2.1. Study population

A total of 226 subjects (86 men and 140 women) aged over 40 years received a population-based health examination in a fishing community in southwestern Japan, Uku town, in 2008. This town is an isolated island in Sasebo city, located in Nagasaki prefecture, and the total population is about 3700. Of these, we excluded 25 subjects whose vaspin data were missing or who rejected the blood tests. Consequently, 201 subjects (78 men and 123 women) were enrolled in this study.

2.2. Data collection

Height and weight were measured, and body mass index (BMI) was calculated as weight (kg) divided by the square of height (square meters) as an index of the presence or absence of obesity. Waist circumference was measured at the level of the umbilicus in a standing position. Blood pressure (BP) was measured twice with the subjects in the sitting (first) and supine (second) position. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurements. The second BP with the fifth phase diastolic pressure was used for analysis. Blood was drawn from the antecubital vein for determinations of lipid profiles (high-density lipoprotein cholesterol [HDL-cholesterol], low-density lipoprotein cholesterol [LDL-cholesterol] and triglycerides), creatinine, uric acid (UA), fasting plasma glucose (FPG), insulin, glycated hemoglobin A1c [HbA1c (NGSP)] and serum vaspin levels in a morning after 12-h fasting. Fasting blood samples were centrifuged within 1 h after the collection. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation modified with a Japanese coefficient [14]. Serum vaspin levels were measured with an enzyme-linked immunosorbent assay (ELISA) system [1]. Intra- and inter-assay coefficients of variation of vaspin in a commercially available laboratory (AdipoGen Inc. Incheon, Korea) were 2.8% and 6.1%, respectively.

HOMA-IR index was calculated from FPG and insulin levels [FPG (mg/dl) × insulin (μU/ml)/405] as a marker of IR. Subjects with type 2 diabetes mellitus were defined as those with FPG ≥126 mg/dl or HbA1c ≥6.5%, or those taking oral hypoglycemic agents and receiving insulin injection. c-IMT of the common carotid artery was determined by using duplex ultrasonography (Sonosite "TITAN", ALOKA) with a 10-MHz transducer in the supine position. Longitudinal B-mode images at the diastolic phase of the cardiac cycle were recorded by a single trained technician who was blinded to the subjects' background. We measured the only far wall of c-IMT. The images were magnified and measured on the screen, and printed with a high-resolution line recorder (LSR-100A, Toshiba). We measured c-IMT according to the originally described method published in Circulation. Briefly, the c-IMT defined by Pignoli et al. [15,16] was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. The first line represented the lumen–intimal interface; the collagen-containing upper layer of the tunica adventitia formed the second line. At each longitudinal projection, the site of the greatest thickness, including plaque, was sought along the arterial walls nearest the skin and farthest from the skin from the common carotid artery to the internal carotid artery. Three determinations of c-IMT of one artery were conducted at the site of the greatest thickness and at 2 other points, 1 cm upstream and 1 cm downstream from this site. The averaged value among the 6 IMTs (3 from the left and 3 from the right) was used as the representative value for each individual.

The mayor and the welfare section of Uku town approved this study. The ethical committee of Kurume University also approved this study. All participants gave informed consent.

2.3. Statistical analysis

Because of skewed distributions, the natural logarithmic (ln) transformations were performed for triglycerides, insulin, HOMA-IR and vaspin. Log-transformed values were reconverted to anti-logarithm forms in the tables. The medications for hypertension, dyslipidemia, and type 2 diabetes mellitus were coded as dummy variables. First, we performed multivariate analyses with vaspin as a dependent variable, and then with the c-IMT as a dependent variable. Finally, we performed a mediation analysis by creating a structural equation model to see whether vaspin was directly related to c-IMT. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the SAS system (Release 9.3, SAS Institute, Cary, NC).

3. Results

Characteristics of the subjects stratified by tertiles of vaspin are shown in Table 1. BMI ($p < 0.05$), insulin ($p < 0.05$), HOMA-IR ($p < 0.01$), c-IMT ($p < 0.05$) and hypertensive medication ($p < 0.05$) were positively associated with serum vaspin level, whereas eGFR ($p < 0.05$) was inversely associated. Characteristics of the subjects stratified by tertiles of c-IMT are shown in Table 2. Age ($p < 0.001$), vaspin ($p < 0.05$) and hypertensive medication ($p < 0.001$) were positively associated with c-IMT, whereas eGFR ($p < 0.01$) was inversely associated.

Multiple stepwise regression analysis revealed that serum vaspin level was significantly and independently associated with eGFR ($p < 0.01$; inversely), HOMA-IR ($p < 0.05$) and c-IMT ($p < 0.05$) (Table 3a). Multiple stepwise regression analysis also revealed that c-IMT was significantly and independently associated with age ($p < 0.001$), hypertensive medication ($p < 0.01$) and vaspin ($p < 0.05$) (Table 3b).

The result of the mediation analysis is presented in Table 4 with path diagram in the Fig. 1. We found that HOMA-IR was not related to c-IMT, and vaspin was directly related to c-IMT although vaspin was related to both c-IMT and HOMA-IR.

4. Discussion

In this cross-sectional cohort study in a general population, multiple stepwise regression analysis revealed that serum vaspin levels were significantly and independently associated with HOMA-IR index and c-IMT, markers of IR and carotid atherosclerosis, respectively. Moreover, a mediation analysis demonstrated that vaspin was directly related to c-IMT, independently of IR.

4.1. Vaspin and insulin resistance

Our results are consistent with previous studies showing a close association of serum vaspin level with IR [6,17,18] in humans.