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Relationships of elevated levels of serum hepatic enzymes and alcohol intake with arterial stiffness in men

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ABSTRACT

Objective: The present study aimed to evaluate the relationships between elevated serum levels of hepatic enzymes and arterial stiffness and to investigate whether alcohol intake had a modifying effect on these relationships in Japanese men. **Methods**: A total of 647 eligible men aged 35–69 years who underwent measurement of brachial-ankle pulse wave velocity (baPWV) as an index of arterial stiffness were evaluated. Information on their lifestyle characteristics were obtained from a structured self-administered questionnaire. Serum biochemical factors, including alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), were determined. The serum ALT and GGT levels were divided into tertiles, and their associations with baPWV values were evaluated using general linear models adjusted for potential confounding factors. The interaction effects between serum hepatic enzymes and alcohol intake on baPWV were further evaluated. **Results**: Elevated serum ALT and GGT levels were proportionally associated with increased baPWV after adjusting for the multivariable covariates (*P* values for trend, 0.004 and 0.003, respectively). Further analyses revealed that the proportional associations between serum levels of hepatic enzymes and baPWV were striking in the subjects without alcohol intake but not in those with alcohol intake. The interaction effect between serum GGT level and alcohol intake on baPWV was significant (*P* for interaction, 0.042). **Conclusion**: These results demonstrate that elevated serum ALT and GGT levels are associated with increased arterial stiffness, independent of the classical atherosclerotic risk factors in Japanese men, and that the association of elevated serum GGT level with arterial stiffness differs according to alcohol intake.

1. Introduction

Considering that cardiovascular disease is a leading cause of death in developed countries, early detection cardiovascular damage is important to prevent mortality and morbidity from cardiovascular disease. Arterial atherosclerotic changes mainly contribute to the pathogenesis of cardiovascular disease, and increased arterial stiffness is demonstrated to be associated with atherosclerosis. Arterial stiffness can be assessed by measuring pulse wave velocity (PWV). Brachial-ankle PWV (baPWV) measurement is convenient, reproducible, relatively quick, and well correlated with carotid-femoral PWV, which is an established index for assessing aortic stiffness [1]. Therefore, baPWV measurement is widely used in screening for arterial stiffness in Asian countries. A considerable number of reports have suggested that elevated serum levels of aminotransferase (ALT) and gamma-glutamyl transferase (GGT), biomarkers for liver injury or dysfunction, are associated with the development of metabolic syndrome and type 2 diabetes, which are high-risk conditions for cardiovascular diseases [2–5]. Elevations in serum ALT and GGT levels have been further shown to predict cardiovascular diseases and events in prospective studies independent of conventional cardiovascular risk factors [6–8]. However, detailed reports about the relationships between serum elevated levels of hepatic enzymes and arterial stiffness are few. Because higher circulating levels of hepatic enzymes, especially GGT, are also used as indexes of alcohol consumption, alcohol intake might have a modifying effect on the relationships between serum levels of hepatic enzymes and arterial stiffness. The present study evaluated the relationships of elevated serum ALT and GGT levels with arterial stiffness in Japanese men. In addition, whether alcohol intake had a modifying effect on the relationships was further evaluated.

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2. Materials and methods

2.1. Study subjects

A total of 710 men aged 35–69 years who were enrolled in the baseline survey of a prospective cohort study in Tokushima Prefecture, Japan, between November 2009 and June 2012 and in whom baPWV was measured at the baseline survey were included in this cross-sectional study. The subjects were workers, and most of them were office workers and not shift workers. This study was performed as part of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study, a prospective cohort study [9]. Briefly, the J-MICC Study aims to examine the relationships of lifestyle and genetic factors as well as their interactions with lifestyle-related diseases. All the participants in the J-MICC Study provided written informed consent prior to participation. The respective ethics committees of Nagoya University School of Medicine (the affiliation of the former principal investigator, Nobuyuki Hamajima), Aichi Cancer Center (the affiliation of the current principal investigator, Hideo Tanaka), and the University of Tokushima Graduate School all approved the study protocol.

2.2. Questionnaire

Information on individual medical histories and lifestyle characteristics over the past year was obtained through a structured self-administered questionnaire. All the responses were reviewed by trained staff at the time of the survey. Leisure-time exercise was estimated on the basis of the International Physical Activity Questionnaire [10]. Exercise was divided into 3 levels as follows: light (e.g., walking and hiking), moderate (e.g., light jogging and swimming), and vigorous (e.g., marathon running and competitive sports). The degrees of leisure-time exercise for the 3 levels were expressed as metabolic equivalent (MET)-hours/week (MET level × hours of activity × events per week) and summed. In this estimation, light, moderate, and vigorous exercises were assigned with 3.4, 7.0, and 10.0 METs, respectively.

Diet was evaluated using a validated short food frequency questionnaire (FFQ) in the baseline survey of the J-MICC Study [11–14]. This FFQ included questions about the dietary intake of 47 varieties of foods and beverages over the past year. Information about the intake frequencies and amounts of the 3 staple foods (i.e., rice, bread, and noodles) consumed at breakfast, lunch, and dinner was obtained. The volumes and frequencies of the consumption of alcoholic beverages including sake, beer, *shochu* (a Japanese distilled beverage), *chuhai* (a sweetened beverage mixed with *shochu*), whiskey, and wine, were obtained. Only the intake frequency was determined for the other 43 foods and beverages. Daily intakes of total energy and ethanol were calculated using a program developed by the Department of Public Health, Nagoya City University School of Medicine [11,12].

2.3. Measurements

baPWV was measured using a waveform analyzer (model BP-203RPE III; Colin, Co. Ltd., Komaki, Japan), as described previously [15]. Briefly, the subject was examined while resting in the supine position in an air-conditioned room. Extremity blood pressure was measured using an oscillometric method, and the ankle brachial index (ABI) was automatically calculated. baPWV was calculated through a time-phase analysis between the right brachial artery pressure and volume waveforms at both ankles. To reduce inter-observer variation, all the baPWV measurements were performed by a single researcher throughout the study. Individual baPWV and ABI data were expressed as the means of the bilateral baPWV and ABI, respectively.

Body mass index was calculated as weight (kg) divided by height (m) squared. Venous blood was aspirated from each participant, and serum was separated within 3 h and stored at −80 °C. Biochemical factors, including ALT, GGT, highly sensitive C-reactive protein (hs-CRP), and lipids in the stored sera, were measured at an external laboratory (BML Inc., Tokyo, Japan).

2.4. Statistical analyses

Among the 710 men initially included in this cross-sectional study, we excluded 39 who had a history of ischemic heart disease ($n = 16$), stroke ($n = 14$), hepatitis B ($n = 9$), hepatitis C ($n = 3$), cirrhosis ($n = 1$), or hepatic cancer ($n = 1$). Some of the men had a history of overlapping diseases. We also excluded 4 men who had a low right or left ABI (ABI $\leq$ 0.9), which suggested peripheral arterial occlusive disease. We further excluded 5 subjects whose estimated daily total energy intake was extremely high (>4000 kcal/day) or low (<1000 kcal/day) and who were taking calcium or vitamin D supplements, which are thought to affect arterial stiffness. After excluding an additional 15 subjects who had no data on serum lipid or hepatic enzymes or any factors included in the multivariate models, a total of 647 men were included in the analyses.

The serum ALT and GGT levels were divided into tertiles so that the numbers of subjects in the 3 categories were almost equal; the lowest category was used as the referent. Continuous variables were expressed as mean ± SD or median values (25th percentile, 75th percentile). Categorical variables were expressed as numbers (%). The analysis of variance, Kruskal–Wallis test, Fisher exact test, and general linear models were used to compare the baseline and clinical characteristics between the tertile categories of serum ALT and GGT levels and between the alcohol consumption categories, where appropriate. General linear models were used to evaluate the relationships of elevated serum ALT and GGT levels with baPWV after adjusting for the following covariates: 1) age (continuous) and systolic blood pressure (<120, 120 to <130, 130 to <140, 140 to <160, or ≥160 mm Hg, without medical treatment or antihypertensive agent use), which are recognized as being very closely associated with arterial stiffness (model 1); and 2) age, systolic blood pressure, body mass index (kg/m2, quartiles), smoking habit (current, past, or never), alcohol intake (current or others), exercise (MET-hours/week, quartiles), hypercholesterolemia (≥220 mg/dL or receiving medical treatment, no/yes) low high-density lipoprotein (HDL) cholesterol (<40 mg/dL, no/yes), elevated triglyceride levels (≥150 mg/dL, no/yes), diabetes (receiving medical treatment, no/yes), and daily energy intake (kcal/day, quartiles; model 2). Tests for trends were performed by assigning the ordinal categorical variables of 1, 2, and 3 for each tertile category of serum ALT and GGT levels. We further evaluated the combined associations of serum hepatic enzymes (tertiles) and alcohol intake (current drinking, no/yes) with baPWV using similar general linear models to assess whether alcohol intake had a modifying effect on the relationship between serum ALT or GGT level and arterial stiffness. In these analyses, a combined category of the lowest tertile of ALT or GGT levels and non-alcohol intake was used as the referent. Interaction terms of the 2 exposure variables (serum ALT or GGT level, continuous, log-transformed; alcohol intake, dichotomous) were created and included in the models to assess statistical interactions. We additionally evaluated the associations of alcohol consumption with serum GGT levels and baPWV values using general linear models.

All the calculations and statistical tests were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). All the statistical