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Original article

Oxidative stress is associated with increased arterial stiffness in middle-aged and elderly community-dwelling persons

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ABSTRACT

Background/Purpose: Oxidative stress is thought to be involved in the development of vascular dysfunction. Arterial stiffness is one of the most significant manifestations of aging and vascular disease. We investigated whether increased malondialdehyde-modified low-density lipoprotein (MDA-LDL), which is responsible for oxidative stress, was associated with increased arterial stiffness, independent of confounders of cardiovascular disease.

Methods: The participants comprised 10 men aged 70 ± 7 years (range, 61–82 years) and 86 women aged 67 ± 7 years (range, 53–81 years). Peripheral arterial stiffness was evaluated by the mean of the right and left brachial to ankle pulse wave velocity (baPWV).

Results and conclusion: Both right and left baPWV values of Tertile-2 (61–81 U/L) and Tertile-3 (82–218 U/L) categorized by tertiles of the MDA-LDL level were significantly higher than those of Tertile-1 (34–60 U/L; $p = 0.022$ and $p = 0.018$, respectively). The multivariate-adjusted baPWV increased significantly from the lowest to the highest MDA-LDL group. Both baPWV values of Tertile-2 (61–81 U/L) and Tertile-3 (82–218 U/L) were significantly higher than those of Tertile-1 (34–60 U/L) ($p = 0.044$ and $p = 0.044$, respectively). To further investigate whether MDA-LDL can explain baPWV levels independent of other known confounding factors, multiple linear regression analyses for baPWV were conducted, which showed that MDA-LDL levels ($\beta = 0.164$, $p = 0.037$) were independently and significantly associated with baPWV as well as gender, age, and presence of raised blood pressure. In addition, we found that a slightly high–normal MDA-LDL level within a normal range is significantly associated with a higher baPWV. MDA-LDL levels are associated with an increased risk of arterial stiffness in community-dwelling persons.

1. Introduction

In humans, oxidative stress is thought to be involved in the development of vascular dysfunction[1] and has been implicated in the pathogenesis of aging, atherosclerosis,[2] heart failure,[3] myocardial infarction,[4] diabetes,[5] hypertension,[6] and hypercholesterolemia.[7] Thus, increased oxidative modification of low-density lipoprotein (ox-LDL) as one indication of oxidative stress is also significantly associated with lipid levels as well as blood pressure and fasting plasma glucose (FPG), and is also a well-known risk marker in the initiation and progression of cardiovascular disease (CVD).[8]

Arterial stiffness, one of the most significant manifestations of aging, vascular disease, and hypertension, is altered primarily in association with increased collagen content, alterations of extracellular matrix protein (arteriosclerosis), and smooth muscle cell.[9,10] Arterial stiffness can be relatively simple and noninvasively assessed by measuring pulse wave velocity (PWV),[10] and the assessment by brachial–ankle PWV (baPWV) has recently been proposed in Japan.[11,12] Many studies have demonstrated that increased baPWV is useful for discriminating middle-aged patients with CVD[12,13] and mortality.[14] Thus, increased baPWV may be one

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important explanation linking the relationship between ox-LDL and CVD. The exact mechanisms underlying arterial stiffness, however, remain unknown.

We investigated whether increased ox-LDL was associated with increased arterial stiffness by measuring baPWV, and whether this association is independent of gender, body mass index, and other confounders of CVD. For this, we used cross-sectional data from middle-aged and elderly community-dwelling persons.

2. Methods

2.1. Participants

The present study was designed as part of the Nomura study.[15] The study population was selected through a community-based annual check-up process from the Nomura Health and Welfare Center in a rural town located in Ehime prefecture, Japan. Participants were enrolled in the study by public health nurses at the health and welfare center. Physical activity level, information on medical history, present conditions, and medications of the candidates were obtained through interviews. Those with CVDs or any other major illnesses that could affect the laboratory test results were excluded. All individuals aged 53–82 years with a clinically documented diagnosis of hypertension, dyslipidemia, Type 2 diabetes, obesity, or any combination thereof were identified from the case records. The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Ehime University School of Medicine, Ehime, Japan (UMIN000010611), with written informed consent obtained from each participant.

2.2. Evaluation of risk factors

Information on demographic characteristics and risk factors was collected using the clinical files at baseline. Body mass index was calculated by dividing weight (in kilograms) by the square of the height (in meters). We measured blood pressure with an appropriate-sized cuff on the right upper arm of the participants in a sedentary position using an automatic oscillometric blood pressure recorder while they were seated after having rested for at least 5 minutes. The mean of two consecutive measurements was used for the analysis. Triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and FPG were measured during an overnight fast of > 11 hours. Serum malondialdehyde-modified low-density lipoprotein (MDA-LDL), which produces ox-LDL, was measured using an enzyme-linked immunosorbent assay. Estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) equations modified by a Japanese coefficient ($eGFR_{CKDEPI}$): male—Cr $\leq$0.9 mg/dL, $141 \times (Cr/0.9)^{-0.411} \times 0.993^{age} \times 0.813$, and Cr >0.9 mg/dL, $141 \times (Cr/0.9)^{-1.209} \times 0.993^{age} \times 0.813$; female, Cr $\leq$0.7 mg/dL, $144 \times (Cr/0.7)^{-0.329} \times 0.993^{age} \times 0.813$, and Cr >0.7 mg/dL, $144 \times (Cr/0.7)^{-1.209} \times 0.993^{age} \times 0.813$.[16] Histories of the use of antihypertensive, antidyslipidemic, and antidiabetic medications were also evaluated. Raised blood pressure was defined as systolic blood pressure $\geq$ 130 mmHg and/or diastolic blood pressure $\geq$ 85 mmHg, and/or the current treatment for hypertension; elevated FPG was defined as an FPG level of $\geq$ 100 mg/dL or the current treatment for diabetes mellitus.

2.3. Measurement of baPWV

PWV was measured using an automatic waveform analyzer (PWV/ABI; Colin, Co., Ltd, Komaki, Japan). All individuals were examined after resting in the supine position for at least 5 minutes, as described previously.[17] This device records a phonocardiogram, an electrocardiogram, a volume pulse form, and arterial blood pressure at the left and right brachial arteries and ankles. Values of baPWV were calculated using time-phase analysis between the right brachial artery pressure and the volume waveforms at both ankles. The distance between the right brachium and the ankle was estimated based on the participant's height. We used the mean of the right and left baPWVs as a marker of arterial stiffness.

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 (SPSS Japan, Inc., Tokyo, Japan). Data are presented as the mean ± standard deviation unless otherwise specified, and for parameters with a non-normal distribution (TG, MDA-LDL, and baPWV), the data are shown as median (interquartile range) values. In all analyses, parameters with a non-normal distribution were used after log transformation. In these analyses, the participants were divided into three categories based on the tertiles of the MDA-LDL level (Tertile-1, 34–60 U/L; Tertile-2, 61–81 U/L; and Tertile-3, 82–218 U/L), and differences among the groups were analyzed by Student *t* test for continuous variables or χ^2 test for categorical variables. Pearson's partial correlations, after adjusting for gender and age, were calculated in order to characterize the associations between various characteristics and baPWV because the levels increased with gender and age.[17] Multiple linear regression analysis was used to evaluate the contribution of each confounding factor to baPWV. Analysis of covariance (ANCOVA) was performed using a general linear model approach to determine the association between the confounding factors and baPWV in these analyses; baPWV was the dependent variable, the three categories of MDA-LDL levels were the fixed factors, and significantly confounding factors were added as covariates. A p value < 0.05 was considered significant.

3. Results

3.1. Characteristics of various confounding factors of participants categorized by tertiles of MDA-LDL level

Table 1 shows the characteristics of the participants categorized by tertiles of the MDA-LDL level. The participants comprised 10 men aged 70 ± 7 years (range, 61–82 years) and 86 women aged 67 ± 7 years (range, 53–81 years). Systolic blood pressure, diastolic blood pressure, TG, and LDL-C were significantly higher in the higher MDA-LDL group, but high-density lipoprotein cholesterol was significantly lower.

3.2. Gender- and age-adjusted PWV of participants categorized by tertiles of MDA-LDL level

As shown in Table 2, both right and left baPWV values of Tertile-2 (61–81 U/L) and Tertile-3 (82–218 U/L) were significantly higher than those of Tertile-1 (34–60 U/L).

3.3. Multivariate-adjusted baPWV of participants categorized by MDA-LDL level

Figure 1 shows the multivariate-adjusted baPWV of participants categorized by tertiles of the MDA-LDL level. BaPWV was adjusted for gender, age, and presence of raised blood pressure. The multivariate-adjusted baPWV increased significantly from the lowest to the highest MDA-LDL group categorized by tertiles of the MDA-LDL level. Both baPWV values of Tertile-2 (61–81 U/L) and