Original Article

Determinants of plasma homocysteine levels and carotid intima-media thickness in Japanese

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Although hyperhomocysteinemia is considered to be a key risk factor for atherosclerosis, especially in Western countries, its role in the Asian population is still controversial. In this study, we evaluated the determinants of homocysteine and carotid intima-media thickness, a clinical marker for the detection of atherosclerosis, in Japanese. In 289 Japanese adults (age 37-86 yrs), we screened plasma total homocysteine by high performance liquid chromatography and evaluated maximum carotid intima-media thickness by ultrasound. Other blood chemistry values were also measured. Total homocysteine levels were higher in men than in women and increased with age. In multiple regression analysis, adjusted for age and sex, serum creatinine was a powerful determinant of homocysteine (β=3.3, p<0.01). Maximum carotid intima-media thickness was higher in men than in women and increased with age. When adjusted for age and sex, systolic blood pressure was independently correlated with maximum carotid intima-media thickness (β=0.001, p<0.01). Our current results support previous findings that in addition to age and sex, serum creatinine and systolic blood pressure are independent determinants of homocysteine and carotid intima-media thickness, respectively.

Key Words: atherosclerosis, cardiovascular diseases (CVD), carotid intima-media thickness (CIMT), folate, homocysteine (HCY), Asia

INTRODUCTION

Cardiovascular diseases (CVD) are a major public health problem in affluent countries, including Japan. In 2004, 15.7% (159,490) of all deaths in Japan were due to coronary heart disease, and 12.5% (129,009) were due to cerebrovascular accidents. Classically, high blood pressure, an unfavorable lipid profile, and smoking explain the majority of CVD cases. Especially in Japan, high salt intake is a considered to be a major risk factor. However, identification of other risk factors is important for implementation of an effective preventive strategy, including education.

Homocysteine (HCY) is a putatively atherothrombotic sulfur-containing amino acid produced during methionine metabolism.[1] Mildly to severely elevated plasma concentrations of HCY are positively associated with an increased risk of atherosclerosis, independent of traditional vascular disease risk factors.[2,3] It has been proposed that a C to T substitution at 677 in the methylenetetrahydrofolate reductase (MTHFR) gene (MTHFR c.677C>T (A222V)), which encodes a key enzyme in the remethylation cycle, relatively increases HCY in subjects with the TT genotype.[4,5]

Besides the MTHFR genotype, it is known that supplementation of folate (alone or in combination with vitamin B12) effectively reduces HCY concentration in normal subjects.[6,7] In order to reduce the risk of hyperhomocysteinemia and subsequently of CVD, further identification of HCY determinants is important.

High-resolution B-mode ultrasonography provides a non-invasive method to quantify arterial wall thickening and atherosclerosis progression. Selhub et al. performed a cross-sectional study of elderly subjects from the Framingham Heart Study and concluded that high plasma HCY concentrations and low concentrations of folate and vitamin B6, through their role in HCY metabolism, are associated with an increased risk of extracranial carotid-artery stenosis in the elderly.[8] Furthermore, an increased carotid intima-media thickness (CIMT) has been shown to be a strong predictor of cardiovascular morbidity and mortality in longitudinal studies.[9,10] Linnebank et al. recently analyzed the association between HCY metabolism and CIMT in patients who experienced vascular events and concluded that elevated HCY levels were causally involved in cerebrovascular disease.[11]

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In the general population, the association between tHCY and CIMT was recently reviewed, and it was reported to be often weak or absent.[3] Interestingly, in cross-sectional studies, it was reported that tHCY was not associated with CIMT in European countries such as the U.K., in the African Caribbean population, or in French or Dutch populations,[12,13] while two Japanese studies showed a definite correlation between the two factors.[14,15] These results suggest that ethnic background may affect the association between nutritional factors such as HCY and the development of atherosclerosis.

In this study, we analyzed the determinants of HCY and CIMT to elucidate their potential roles as risk factors for the development of atherosclerosis in the Japanese population for implementation of an effective preventive strategy for CVD.

MATERIALS AND METHODS

Prior to this study, ethical approval was obtained from the special committee of Nagasaki University (project registration number 0406220063). The study was conducted in April to May 2005, during a medical screening program for the general population living in the town of Obama (total population was 11,571 in 2003), Nagasaki Prefecture, Japan. The data was collected by the staff of Nagasaki University, in cooperation with that of the town of Obama. Among 839 subjects who participated in the medical screening program during this period, 310 agreed to participate in our study, and written informed consent was obtained from each study participant before the study. Since participants with an apparent past or present history of cerebral infarction (n=10) or hemorrhage (n=2) or ischemic heart disease (n=9) were excluded from the study, we included 289 subjects for analysis (195 women and 94 men; age range, 37 to 86 years). The median ages of the study participants were 61 (51-68) years in women and 66 (57-70) years in men, respectively ($p<0.05$).

The subjects' medical history, current use of alcohol (yes or no), and current smoking (yes or no) were classified by questionnaire. Height and weight were measured, and body mass index (BMI; kilograms per meter squared) was calculated as an index of obesity. The median BMI was 22.8 (21.0-24.9) for women and 23.9 (22.1-25.6) for men. Systolic and diastolic blood pressures (SBP and DBP, respectively) were recorded at rest.

After fasting blood samples were obtained, serum and plasma were collected and kept at -20ºC until assay. Serum lipids (total cholesterol and HDL-cholesterol), glycosylated hemoglobin $A1_c$ (HbA1c), and creatinine were measured. LDL-cholesterol was calculated by the Friedewald formula.[16] Plasma folate and highly sensitive C-reactive protein (hs-CRP) concentrations were measured using the chemiluminescent immunoassay method and the N-Latex CRP II method (Dade Behring, Tokyo, Japan), respectively. The lower limit of detection for hs-CRP was 0.0001 mg/L. Plasma total HCY concentrations were measured using high-performance liquid chromatography with fluorescence detection.[17]

Measurement of CIMT by ultrasonography of the left and right common carotid arteries was performed using LOGIQ Book XP with a 10-MHz linear array transducer (GE Medical Systems, USA). Subjects were examined in the supine position. On a longitudinal 2-dimensional ultrasonographic image of the carotid artery, the far wall of the carotid artery is displayed as 2 bright white lines separated by a hypoechoic space. The distance from the leading edge of the first bright line (lumen-intima interface) to the leading edge of the second bright line (media-adventitia interface) was identified as the CIMT. Images obtained were stored on the ultrasound equipment's hard disk and analyzed by the software Intima Scope® (MEDIA CROSS, Tokyo, Japan). Averages of left and right maximum CIMT were calculated and used in the analysis.

Obtained results are expressed as the median (25th-75th percentile). Differences between women and men were evaluated using the Mann-Whitney U test. Multiple linear regression analysis was performed for the identification of determinants of tHCY levels and CIMT, adjusted for age and sex. A probability value of less than 0.05 was considered as significant. All statistical analyses were performed with SPSS 14.0® (SPSS Japan Inc., Tokyo, Japan).

Table 1. Multiple linear regression analysis for determinants of plasma tHCY levels adjusted for age and sex. The regression coefficient (β) is the average amount that the dependent variable increases when the independent variable increases one unit and other variables are held constant. 95% confidence interval (CI) represents the plus/minus range around the observed sample regression coefficients. If the coefficient interval includes 0, then there is no significant linear relationship.

Variables	β	95% CI	*p*
Body mass index, kg/m^2	0.007	-0.10, 0.11	0.89
Systolic blood pressure, mmHg	0.009	-0.009, 0.026	0.34
Diastolic blood pressure, mmHg	0.003	-0.027, 0.033	0.86
Folate, ng/ml	0.019	-0.049, 0.088	0.58
Total cholesterol, mg/dL	0	-0.010, 0.010	0.99
HDL-cholesterol, mg/dL	-0.014	-0.035, 0.007	0.20
LDL cholesterol, mg/dL	0.003	-0.008,0.014	0.62
Creatinine, mg/dL	3.3	0.98, 5.6	<0.01
hs-CRP, mg/L	0.32	-0.39, 1.0	0.37
HbA1c, %	-0.17	-0.71, 0.36	0.53
Alcohol intake, %yes	0.038	-0.61, 0.75	0.84
Current smoking, % yes	0.39	-0.78, 1.6	0.51
Maximum CIMT, mm	0.75	-1.5, 3.1	0.52

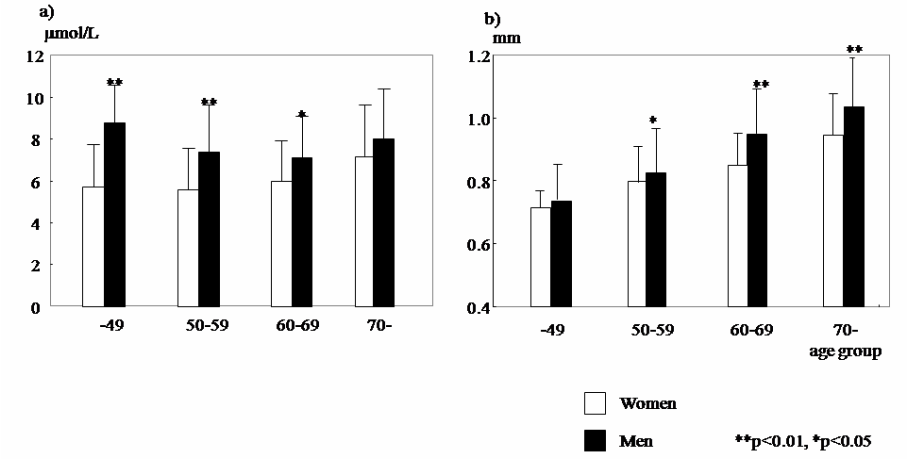

Figure 1. a) Mean plasma HCY levels and b) maximum CIMT stratified by age group in women and men.

RESULTS

Figure 1a) shows mean plasma tHCY levels stratified by age groups in women and men. Especially in women, plasma tHCY levels increased with age, and they were significantly higher in men than in women. These results indicate that age and sex are major determinants of plasma tHCY concentrations.

Pearson correlation analysis showed that tHCY levels were significantly correlated with maximum CIMT (r=0.17), current smoking (r=0.12), current drinking of alcohol (r=0.11), SBP (r=0.17), HDL-cholesterol (r=-0.16), and creatinine (r=0.31). When multiple regression analysis was performed, adjusted for age and sex, only serum creatinine was significantly related to tHCY level (β=0.23, p<0.01, Table 1). Plasma folate was not significantly related with tHCY levels (β=0.019, p=0.58).

Figure 1b) shows mean CIMT levels stratified by age groups in women and men. CIMT values increased with age, and they were greater in men than in women, especially those beyond their sixties. The rate of thickening in women was 0.006 mm/year, whereas that of men was 0.008 mm/year. These results indicate that age and sex are also major determinants of CIMT.

Pearson correlation analysis showed that maximum CIMT values were significantly associated with tHCY (r=0.17), SBP (r=0.36), DBP (r=0.15), creatinine (r=0.21), and HDL-cholesterol (r=-0.20). CIMT significantly correlated with HCY in women (r=0.22, p<0.01) but not in men (r=0.01, p=0.90). In multiple regression analysis, adjusted for age and sex, only systolic blood pressure was significantly related to maximum CIMT (β=0.001, p<0.01, Table 2).

DISCUSSION

Our current study showed that age and sex are the major determinants of plasma tHCY in the Japanese population, which is consistent with previous reports.[18-20] As shown in Figure 1a**)**, plasma tHCY increased with age in women, but no clear relationship was observed in men. This may be partially influenced by the change of muscle volume in each generation of men, since the formation of muscle is associated with the simultaneous formation of HCY in connection with creatine/creatinine synthesis.[21] Our study demonstrated that creatinine was an independent determinant of HCY. Besides acting as a marker of renal function, creatinine reflects the muscle activity of an individual, since creatinine is a metabolic product of creatine, and this conversion is related to muscle activity.[21] This suggests that individual muscle activity is also a key determinant of tHCY concentration.

Our current results show that age is the major determinant of CIMT in Japanese. In a previous study, Homma et al. screened CIMT in healthy Japanese people ranging from young adults to centenarians (n=319) and observed a linear increase in CIMT with age.[22] This increase was found for each decade of life, and the mean rate of thickening was estimated at 0.009 mm/year. In our study, the rate of CIMT thickening in women was 0.006 mm/year, whereas that of men was 0.008 mm/year. This difference in thickening rate may be caused by the influence of sex

Table 2. Multiple linear regression analysis for determinants of maximum CIMT adjusted for age and sex.

Variables	β	95% CI	p
Body mass index, kg/m^2	-0.001	-0.006, 0.004	0.75
Systolic blood pressure, mmHg	0.001	0, 0.002	<0.01
Diastolic blood pressure, mmHg	0.001	-0.001, 0.002	0.35
Folate, ng/ml	-0.001	-0.005,0.001	0.12
Total cholesterol, mg/dL	0	0.001, 0.002	0.82
HDL cholesterol, mg/dL	-0.001	-0.002, 0	0.17
LDL cholesterol, mg/dL	0	0,0.001	0.33
Creatinine, mg/dL	-0.042	-0.16, 0.076	0.48
tHCY, μmol/L	0.002	-0.004, 0.008	0.52
hs-CRP, mg/L	-0.004	-0.040, 0.032	0.82
HbA1c, %	0.006	-0.021, 0.033	0.65
Alcohol intake, % yes	0	-0.034, 0.035	0.99
Current smoking, % yes	0.013	-0.047, 0.072	0.67

hormones and the ratio of smoking and other factors, and it may result in the sex difference in CIMT.

Our current study showed that SBP is an independent determinant of CIMT in Japanese. This suggests the importance of blood pressure control in the Japanese population to prevent the future development of atherosclerosis.

The association between peripheral blood pressure and CIMT is controversial. Adachi et al. showed that SBP was significantly related to CIMT, adjusted by sex and age,[14] whereas Tanaka et al. suggested that CIMT increases with age in healthy men in the absence of elevation of peripheral SBP.[23] This may be due to the differences in the target populations, since the subjects in the former study were Japanese, whereas the latter were probably American. The discrepancy between the findings of these two studies suggests that blood pressure may play different roles in the development of atherosclerosis in people of different ethnic backgrounds.

In this study, we could not identify any other factors that related with CIMT, except for age, sex, and SBP. Adachi et al reported that in the Japanese general population, HDL-cholesterol was inversely correlated with CIMT.[14] This discrepancy with our findings might be caused by t confounders such as the intake of statins and other drugs, since we did not consider the drug intake of study participants. Also, we did not evaluate LDL-cholesterol by direct measurement, but rather by calculation of the Friedewald formula, which might have caused the lack of association between LDL-cholesterol and CIMT.

Also CIMT was not significantly correlated with HCY in this study. Durga et al. recently reviewed the relationship between hyperhomocysteinemia and CIMT and concluded that the association between tHCY and CIMT in the general population is often weak or absent.[3] Furthermore, Linnebank et al. reported that CIMT was significantly predicted by age, sex, creatinine levels, lipoprotein(a) levels, pack-years of smoking, the presence of hypertension, and the presence of diabetes mellitus but not by HCY concentrations, which suggests that HCY might not be an independent predictor/risk factor for increased CIMT as sign of atherosclerosis.[11] Since other valuables confound, HCY may not be an independent predictor/risk factor for increased CIMT as sign of atherosclerosis.

The present study has several limitations. Our sample size was relatively small for analysis, and results in this study could not identify any alternative determinants of HCY and CIMT. We did not include the evaluation of Lp(a) in this study. Also, we could not evaluate the degree of alcohol intake and smoking, which might have been responsible for their lack of association with HCY and CIMT. Furthermore, ewe did not find plasma folate to be an independent determinant of HCY, which is inconsistent with previous studies. Although we cannot say why there is this lack of association, immediately prior ingestion might have affected folate concentration in an unrepresentative way.

Recently, Durga et al. reported that erythrocyte folate status, rather than serum and plasma folate, was inversely associated with CIMT, and concluded that low folate concentrations, independent of hyperhomocysteinemia, may promote atherogenesis in men and postmenopausal women.[25] Since erythrocyte folate is thought to reflect liver stores of folate, this suggests that low concentrations of folate for a long period of time may promote atherosclerosis. These authors showed that the association between folate deficiency and increased CIMT was independent of CRP and postulated that the greater risk of vascular disease morbidity and mortality associated with low concentrations of folate and increased HCY may originate from possible pathogenic effects on the coagulation or inflammation systems. Although Japan has been considered to be a "folate-sufficient area," recent Westernized food choices may cause a relative folate deficiency in Japanese. Further evaluation of this issue will be valuable for identification of HCY and CIMT determinants in Japanese.

In conclusion, we determined that in addition to age and sex, serum creatinine and systolic blood pressure are independent determinants of tHCY and CIMT, respectively. Further approaches, including genotype/phenotype evaluation of related genes, such as MTHFR, will be needed as effective prevention strategies against atherosclerosis are reviewed.

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AUTHOR DISCLOSURES

Noboru Takamura, Yasuyo Abe, Mio Nakazato, Takahiro Maeda, Mitsuhiro Wada3, Kenichiro Nakashima, Yosuke Kusano and Kiyoshi Aoyagi, no conflicts of interest.

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Original Article

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日本人血漿中的同半胱胺酸量與頸動脈中內膜層厚度的決定因子

雖然高同半胱胺酸血症被認為是動脈硬化的關鍵危險因子，尤指西方國家，但它在亞洲族群中的角色尚未有定論。本研究我們評估日本人同半胱胺酸及頸動脈中內膜層厚度（一個動脈硬化臨床標記）之決定因子。我們以高效能液相層析儀分析 289 名日本成年人(年齡 37-86 歲)血漿總同半胱胺酸，並用超音波評估頸動脈中內膜層厚度最大值。同時評估其他血液生化值。總同半胱胺酸量男性高與女性，並且隨著年齡增加。在多元迴歸分析，校正年齡及性別後，血清肌酸酐是同半胱胺酸(β=3.3，p<0.01)有力的決定因子。頸動脈中內膜層厚度最大值男性高於女性，且隨著年齡增加。當校正年齡及性別後，收縮壓與頸動脈中內膜層最大值具有獨立相關性(β=0.001，p<0.01)。我們目前的結果支持之前的發現，亦即除了年齡及性別外，血清肌酸酐與收縮壓分別為同半胱胺酸及頸動脈中內層厚度的決定因子。

關鍵字：動脈硬化、心血管疾病(CVD)、頸動脈中內膜層厚度(CIMT)、葉酸、同半胱胺酸(HCY)、亞洲。