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Higher serum uric acid is associated with increased arterial stiffness in Japanese individuals

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Abstract

Hyperuricemia is postulated to be a risk factor for atherosclerotic diseases, although whether it is independent of classical atherogenic risk factors is controversial. The automatic computer-assisted measurement of brachial-ankle pulse wave velocity (baPWV) is a valid and reproducible method by which to assess arterial stiffness, a potential surrogate marker of early atherosclerosis. By analyzing cross-sectional data from 982 individuals who underwent health screening, we have investigated whether serum uric acid is associated with high baPWV, which was determined as the highest quartile of baPWV values, in a sex-specific manner. Multivariate analysis showed that the odds ratios (95% CI) of the highest baPWV quartile across the sex-specific quartiles of serum uric acid were 1.0, 2.80 (0.93–8.40), 2.13 (0.74–6.19), and 2.76 (1.01–7.55) in women, and 1.0, 1.10 (0.55–2.20), 1.97 (1.04–3.75), and 2.24 (1.10–4.56) in men after adjusting for age, total and HDL-cholesterol, BMI, systolic blood pressure, triglycerides, fasting glucose and smoking status. The association between uric acid and high baPWV was observed in both subjects with metabolic syndrome and those without. These data suggest that in both genders, serum uric acid level is associated with increased baPWV, a marker of arterial stiffness, and is in part independent of other conventional risk factors for atherosclerosis and metabolic syndrome.

Keywords: Aortic stiffness; Pulse wave velocity; Metabolic syndrome; Multivariate analysis

1. Introduction

Aortic pulse wave velocity (PWV) and augmentation index are indices of arterial stiffness, and are a predictor for cardiovascular diseases, stroke, and cognitive impairment [1–3]. Recent studies have shown that brachial-ankle PWV (baPWV), which can be measured fairly reproducibly by an automated device [4], well correlates well with aortic stiffness determined by an invasive method [5]. Because of their non-invasive nature, both baPWV measurements and carotid artery ultrasonography are used to assess arteriosclerosis during health screening. Several risk factors for increased PWV have been reported, including raised C-reactive protein (CRP) levels [6], menopause [7], and increased vascular calcification observed in patients with end-stage renal disease (ESRD) [8].

Several previous studies have suggested that hyperuricemia is a risk factor for cardiovascular diseases [9,10]. Hyperuricemia increases the risk for metabolic syndrome, which has reported to be a risk factor for cardiovascular disease [11,12]. Therefore, it is possible that observed association between uric acid (UA) and atherosclerotic disease may be in part attributed to the link between hyperuricemia and metabolic syndrome. On the other hand, however, recent stud-

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ies also suggested that association between serum UA and death from cardiovascular disease and that between serum UA and carotid plaque may be independent of variables related to metabolic syndrome [13,14].

It has recently been reported that metabolic syndrome is a strong risk factor for increased baPWV [15]. Thus, in the present study, we have investigated whether serum UA is associated with increased baPWV, and the independency of this association from metabolic syndrome as well as classical risk factors.

2. Methods

2.1. Study subjects

The study was approved by The Ethical Committee of Mitsui Memorial Hospital. A total of 982 (women, 297, and men, 695) subjects aged between 23 and 87 (mean 59.2) years, who underwent health screening targeted towards atherosclerosis between April 2003 and March 2005 at our institute participated in the study. In Japan, regular health check-ups for employees are legally mandated, and all or most of the costs of the screening are usually paid by the company to which they belong or by each subject. At our institute, several types of health screening program are available, and the current one is termed atherosclerosis-screening course. The choice of which course to be chosen is dependent on the decision of individuals and/or the companies to which they belong. Among 982 enrolled subjects (mean age, 59 yr), 89 (9.0%) were taking anti-hyperlipidemic, 36 (3.7%) were taking anti-diabetic, and 166 (16.9%) were taking antihypertensive drugs. These percentages were significantly greater than those in the subjects who underwent 'ordinary' heath screening course during this study period (mean age, 52 yr, anti-hyperlipidemic drugs, 4.1%; anti-diabetic drugs, 2.2%; anti-hypertensive drugs, 10.0%). Therefore, it could be said that there might have been some selection bias for participants planning atherosclerosis-screening course. However, this was never either the decision or the recommendation of any attending physician.

2.2. Laboratory data

Serum levels of TC, HDL-C, and TG were determined enzymatically. Serum UA was measured by the uricase-peroxidase method, haemoglobin A_{1C} was determined by the latex agglutination immunoassay, and serum total bilirubin was measured by the bilirubin oxidase method.

The mean UA level was found to be significantly lower in women (4.7 ± 0.9 mg/dL) than in men (6.1 ± 1.2 mg/dL, $P < 0.0001$). Therefore, sex-specific quartiles of serum UA were used. The median (range) UA values of 3.6 (2.1–4.0), 4.3 (4.1–4.6), 5.0 (4.7–5.3) and 5.9 (5.4–8.0) mg/L were used for women, and 4.6 (2.9–5.2), 5.7 (5.3–6.0), 6.5 (6.1–6.9) and 7.8 (7.0–11.0) mg/L were used for men (Table 1).

2.3. Criteria for metabolic syndrome

Diagnosis of metabolic syndrome was made according to the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III), with body mass index (BMI) used as a surrogate for waist circumference [16]. Metabolic syndrome was diagnosed when three or more of following components were present. (1) triglyceride levels $\geq$150 mg/dL, (2) HDL-C levels $<$40 mg/dL in men or $<$50 mg/dL in women, (3) fasting plasma glucose levels $\geq$110 mg/dL, or taking an antidiabetic medication, (4) systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mm Hg or taking an antihypertensive medication, or (5) BMI >25 kg/m^2.

2.4. Measurement of baPWV and ankle-brachial pressure index (ABI)

baPWV was assessed by using a fully automatic device (form® PWV/ABI, model BP-203RPE II, COLIN Medical Technology Co. Ltd., Komaki, Japan) as described elsewhere [5]. Due to its automated nature, the applied this method has been shown to possess high inter- and intra-observer reproducibility [5,17,18]. High baPWV was defined as the highest quartile of the values among the study subjects, which was equal to or more than 1594 cm/s in women and 1721 cm/s in men. Ankle-brachial pressure index (ABI), a simple marker of peripheral arterial stenosis was measured simultaneously with baPWV measurement. To test inter- and intra-observer reproducibility, three observers measured baPWV of three subjects at the four different time points. Pearson's correlation coefficients of intraobserver and intraobserver reproducibility were $r = 0.984$ and $r = 0.970$, respectively, indicating that baPWV measurement using an automatic device was fairly reproducible as has been reported elsewhere [5].

2.5. Carotid ultrasonography

Carotid artery status was studied and analyzed as described previously [19]. In brief, it was examined by high resolution B-mode ultrasonography, using an instrument (Sonolayer SSA270A, Toshiba, Japan) equipped with a 7.5 MHz transducer (PLF-703ST, Toshiba). The carotid arteries were examined bilaterally at the levels of the common carotid, the bifurcation, and the internal carotid arteries from transverse and longitudinal orientations by trained sonographers. The intima-media thickness was measured using a computer-assisted method by experienced sonographers who were unaware of the subjects' clinical and laboratory findings. Plaque was defined as a clearly isolated focal thickening of the intima-media layer with thickness of $\geq$1.3 mm at the common or internal carotid artery or the carotid bulb.

In the current study population, carotid plaque was positive in 39% (116/297) of women and 52% (338/655) of men, values that were significantly greater than that we have reported before (16% (440/2671) of women, and 29%

Table 1
Baseline characteristics

Variables	Quartiles of serum uric acid				*P*-value
	1	2	3	4	
Women					
Uric acid range (median), mg/dL	2.1–4.0 (3.7)	4.1–4.6 (4.3)	4.7–5.3 (5.0)	5.4–8.0 (5.7)	
Number of subjects	76	70	78	73	
Age, years	60 ± 11	60 ± 10	58 ± 12	63 ± 10	0.062
Body mass index, kg/m^2	21.4 ± 2.6	21.5 ± 3.0	21.7 ± 2.6	23.3 ± 3.7	0.0001
Systolic blood pressure, mmHg	118 ± 22	119 ± 22	122 ± 18	137 ± 23	<0.0001
Diastolic blood pressure, mmHg	71 ± 12	73 ± 13	74 ± 111	83 ± 12	<0.0001
Heart rate, bpm	65 ± 8	64 ± 8	66 ± 11	67 ± 9	0.33
Laboratory data					
Uric acid, mg/dL	3.6 ± 0.5	4.3 ± 0.2	5.0 ± 0.2	5.9 ± 0.6	<0.0001
Total bilirubin, mg/dL	0.76 ± 0.27	0.76 ± 0.22	0.76 ± 0.26	0.80 ± 0.25	0.63
Creatinine, mg/dL	0.62 ± 0.10	0.61 ± 0.09	0.64 ± 0.10	0.69 ± 0.10	<0.0001
gamma-GTP, IU/L	23.3 ± 14.5	26.8 ± 17.4	28.1 ± 19.1	30.0 ± 31.4	0.27
C-reactive protein, mg/dL	0.08 ± 0.17	0.21 ± 0.96	0.10 ± 0.16	0.17 ± 0.25	0.38
Serum lipid data					
Total cholesterol, mg/dL	222 ± 31	216 ± 33	220 ± 38	235 ± 29	0.0062
HDL-cholesterol, mg/dL	72 ± 14	70 ± 21	69 ± 15	68 ± 17	0.46
Triglycerides, mg/dL	82 ± 34	81 ± 33	90 ± 51	107 ± 49	0.0009
Glucose metabolisms					
Fasting glucose, mg/dL	91 ± 18	91 ± 10	95 ± 21	94 ± 10	0.22
Haemoglobin A1C, %	5.10 ± 0.66	5.15 ± 0.38	5.19 ± 0.60	5.23 ± 0.46	0.52
Smoking status					
Non-smokers (%)	66 (87)	63 (90)	66 (85)	64 (88)	0.87
Former smokers (%)	4(5)	4(6)	7(9)	6(8)	
Current smokers (%)	6(8)	3(4)	5(6)	3(4)	
Men					
Uric acid range (median), mg/dL	2.9–5.2 (4.7)	5.3–6.0 (5.7)	6.1–6.9 (6.5)	7.0–11.0 (7.7)	
Number of subjects	159	162	177	157	
Age, years	60 ± 10	58 ± 11	60 ± 10	56 ± 11	0.0002
Body mass index, kg/m^2	23.2 ± 2.8	24.2 ± 2.9	24.2 ± 2.8	25.1 ± 2.7	<0.0001
Systolic blood pressure, mmHg	127 ± 21	131 ± 21	131 ± 18	133 ± 20	0.07
Diastolic blood pressure, mmHg	78 ± 12	82 ± 13	82 ± 11	83 ± 11	0.0021
Heart rate, bpm	64 ± 11	64 ± 9	65 ± 9	64 ± 8	0.76
Laboratory data					
Uric acid, mg/dL	4.6 ± 0.6	5.7 ± 0.2	6.5 ± 0.3	7.8 ± 0.7	<0.0001
Total bilirubin, mg/dL	0.89 ± 0.29	0.92 ± 0.37	0.90 ± 0.30	0.87 ± 0.32	0.59
Creatinine, mg/dL	0.83 ± 0.12	0.88 ± 0.13	0.88 ± 0.12	0.94 ± 0.18	<0.0001
gamma-GTP, IU/L	46.0 ± 36.4	49.8 ± 38.5	64.1 ± 74.8	79.0 ± 86.0	<0.0001
C-reactive protein, mg/dL	0.24 ± 1.39	0.18 ± 0.20	0.19 ± 0.44	0.19 ± 0.40	0.6
Serum lipid data					
Total cholesterol, mg/dL	205 ± 30	208 ± 35	208 ± 32	212 ± 30	0.34
HDL-cholesterol, mg/dL	57 ± 13	55 ± 12	54 ± 13	53 ± 14	0.015
Triglycerides, mg/dL	124 ± 82	129 ± 64	154 ± 234	165 ± 93	0.022
Glucose metabolisms					
Fasting glucose, mg/dL	105 ± 23	107 ± 31	104 ± 18	103 ± 20	0.53
Haemoglobin A1C, %	5.56 ± 0.84	5.46 ± 0.92	5.41 ± 0.64	5.33 ± 0.60	0.058
Smoking status					
Non-smokers (%)	43 (27)	47 (29)	48 (27)	46 (29)	0.57
Former smokers (%)	72 (45)	59 (36)	82 (46)	64 (41)	
Current smokers (%)	44 (28)	56 (35)	47 (27)	48 (30)	

(1607/5473) of men) [14]. This difference was partly because the mean age was greater than in our previous study (57 ± 11 yr in women, and 57 ± 11 yr in men in the previous study; and 60 ± 11 yr in women and 59 ± 11 yr in men in the current study).

2.6. Statistical analysis

The data in this study were analyzed by the χ^2-test, ANOVA with a Bonferroni post hoc test, and multivariate logistic regression analysis using computer software,

StatView ver. 5.0 (SAS Institute, NC, USA). A value of $p < 0.05$ was taken to be statistically significant. Results are expressed as the mean ± S.D. unless stated otherwise.

3. Results

3.1. Baseline characteristics

The age of the enrolled subjects ranged from 23 to 87 yr (women, 25–85 yr; men, 23–87 yr) with a mean age of 59.2 ± 10.8 yr (women, 60.2 ± 10.8 yr; men, 58.8 ± 10.8 yr). The mean age did not significantly differ among each UA quartile group in women. In men, by contrast, the mean age in the fourth quartile was less than that in the first quartile ($P = 0.0001$) (Table 1). Of the 982 subjects, an ABI value of <0.95 was obtained in only 13 subjects (1.3%).

3.2. Relationship between UA and PWV

Pearson's correlation coefficients for the relationship between UA and baPWV were 0.19 ($P = 0.0033$) in women and 0.033 (P = NS) in men. The mean baPWV value was 1549 ± 342 in men, which was significantly higher than in women (1447 ± 315, $P < 0.0001$). The sex-specific interquartile cut off points for baPWV were 1207, 1370, and 1594 cm/s in women, and those of 1311, 1493, 1721 cm/s in men. Thus, the high baPWV was defined as equal to or more than 1594 cm/s in women and 1721 cm/s in men.

The prevalence of the high baPWV in the first, second, third, and fourth UA quartiles in each gender is shown in Fig. 1. When multivariate analysis was performed after adjusting for gender, age, TC, BMI, systolic blood pressure, HDL-C, triglycerides, fasting glucose and smoking status, the association between UA and high baPWV was statistically significant, and statistical significance was maintained after subdividing subjects according to their gender (Table 2).

In this model, the odds ratios (95% CI) of the other covariates were as follows. In women, age (per 1 yr), 1.13 (1.08–1.19), $P < 0.0001$, TC (per 1 mg/dL), 1.01 (1.00–1.02), $P = 0.075$; former smoking, 1.07 (0.24–4.82), $P = 0.93$; current smoking, 5.67 (0.79–40.41), $P = 0.084$; BMI (per 1 kg/m^2), 0.95 (0.84–1.08), $P = 0.43$; systolic blood pressure (per 1 mmHg), 1.05 (1.03–1.08), $P < 0.0001$; HDL-C

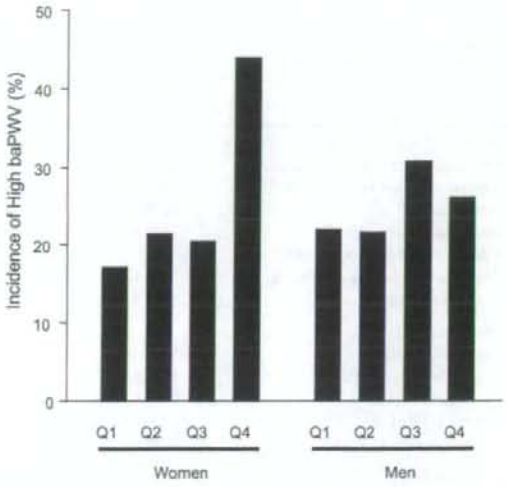

Fig. 1. Incidence of high baPWV according to the UA quartile and gender.

(per 1 mg/dL), 1.00 (0.97–1.01), $P = 0.79$; triglycerides (per 1 mg/dL), 1.00, (CI 1.00–1.01), $P = 0.30$; fasting glucose (per 1 mg/dL), 1.01 (0.99–1.02), $P = 0.57$. In men, age (per 1 yr), 1.18 (1.14–1.22), $P < 0.0001$, TC (per 1 mg/dL), 1.00 (0.99–1.01), $P = 0.82$; former smoking, 1.77 (0.97–3.22), $P = 0.61$; current smoking, 1.74 (0.88–3.46), $P = 0.11$; BMI (per 1 kg/m^2), 0.98 (0.89–1.08), $P = 0.68$; systolic blood pressure (per 1 mmHg), 1.05 (1.04–1.06), $P < 0.001$; HDL-C (per 1 mg/dL), 1.01 (0.99–1.03), $P = 0.18$; triglycerides (per 1 mg/dL), 1.00 (1.00–1.00), $P = 0.27$; fasting glucose (per 1 mg/dL), 1.01 (0.99–1.02), $P = 0.37$.

Serum creatinine showed graded increase according to the UA levels in both genders (Table 1). After further adjustment for serum creatinine level, mode of association between serum UA quartile and high baPWV did not greatly changed; odds ratios (95% CI) for the first, second, third, and fourth UA quartiles were 1.0 (reference), 2.81 (0.93–8.46, $P = 0.066$), 2.22 (0.76–6.49, $P = 0.15$), and 2.97 (1.05–8.39, $P = 0.040$), respectively, in women, and 1.0 (reference), 1.19 (0.58–2.42, $P = 0.64$), 2.13 (1.11–4.09, $P = 0.024$), and 2.63 (1.26–5.50, $P = 0.010$), respectively, in men.

We also assessed whether increased CRP levels, white blood cell count, and serum bilirubin levels were associated with increased baPWV using the above-described

Table 2
Multivariate analysis assessing the association between UA and high baPWV

	Quartiles of serum uric acid			
	Q1	Q2	Q3	Q4
Whole	1 (reference)	1.41 (0.78–2.51)	2.00 (1.17–3.43)*	2.40 (1.36–4.26)**
Women	1 (reference)	2.80 (0.93–8.40)	2.13 (0.74–6.19)	2.76 (1.01–7.55)*
Men	1 (reference)	1.10 (0.55–2.20)	1.97 (1.04–3.75)*	2.24 (1.10–4.56)*

Age, sex (for whole), BMI, systolic blood pressure, TC, HDL-C, triglycerides, fasting glucose, and smoking status were used as covariates.
* $P < 0.05$.
** $P < 0.01$ versus the lowest quartile (reference).

factors as covariates. For the high baPWV, the odds ratio of increased CRP levels (per 1 mg/dL) was 1.13 (95% CI 1.08–1.19, $P<0.0001$) in women and 1.79 (95% CI 0.99–3.24, $P=0.056$) in men; that of the white blood cell count (per $1 \times 10^3/\mu L$) was 0.98 (95%CI 0.74–1.29, $P=0.86$) in women and 1.08 (95% CI 0.90–1.29, $P=0.42$) in men; and those of serum bilirubin levels (per 1 mg/dL) were 1.98 (95%CI 0.46–8.60, $P=0.36$) in women and 0.61 (95%CI 0.29–1.29, $P=0.20$) in men.

3.3. Effect of metabolic syndrome on the association between UA and baPWV

Out of 952 subjects, 159 (17%) were found to have metabolic syndrome (16/297 (5.4%) in women, 143/655 (21.8%) in men). After adjusting for gender, age, TC, and smoking status, serum UA level was found to be associated with metabolic syndrome with an odds ratio of 1.32 (95% CI 1.14–1.53, $P=0.0003$, per 1 mg/dL increase) which was in agreement with previous findings [20]. In addition, after adjusting for gender, age, TC, and smoking status, metabolic syndrome was associated with the high baPWV with an odds ratio of 2.43 (95% CI 1.55–3.83, $P=0.0001$).

Thus we next investigated the association between UA and baPWV according to the status of metabolic syndrome. After adjusting for gender, age, TC, BMI, systolic blood pressure, HDL-C, triglycerides, fasting glucose and smoking status, the odds ratio (95% CI) of the first, second, third, and fourth UA quartiles for the high baPWV was 1.0 (reference), 1.19 (0.62–2.27, $P=0.60$), 1.86 (1.01–1.32, $P=0.047$), and 2.02 (1.04–3.90, $P=0.037$), respectively, in subjects without metabolic syndrome, and 1.0 (reference), 3.34 (0.74–14.9, $P=0.11$), 3.36 (0.83–13.61, $P=0.089$), and 4.52 (1.09–18.72, $P=0.038$), respectively, in the subjects with metabolic syndrome.

3.4. Relationship between carotid plaque, carotid intima-media thickening, and baPWV

The incidence of carotid plaque in subjects with and without high baPWV were 49/76 (64%) and 67/221 (30%), respectively, in women ($P<0.0001$), and 117/165 (71%) and 221/490 (45%), respectively, in men ($P<0.0001$). After adjusting for age, BMI, systolic blood pressure, TC, HDL-C, triglycerides, fasting glucose and smoking status, the odds ratio (95% CI) of the first, second, third, and fourth baPWV quartiles for the carotid plaque was 1.0 (reference), 1.69 (0.72–3.95, $P=0.23$), 1.23 (0.49–3.06, $P=0.66$), and 3.00 (1.07–8.39, $P=0.037$), respectively, in women, and 1.0 (reference), 1.42 (0.87–2.31, $P=0.16$), 1.70 (1.00–2.90, $P=0.052$), and 1.96 (1.03–3.75, $P=0.041$), respectively, in men.

The incidence of carotid intima-media thickening in subjects with and without high baPWV were 28/76 (37%) and 18/221 (8%), respectively, in women ($P<0.0001$), and 47/165 (28%) and 60/490 (12%), respectively, in men ($P<0.0001$). After adjusting for age, BMI, systolic blood pressure, TC, HDL-C, triglycerides, fasting glucose and smoking status, the odds ratio (95% CI) of the first, second, third, and fourth baPWV quartiles for the carotid intima-media thickening was 1.0 (reference), 4.49 (0.51–39.45, $P=0.17$), 4.35 (0.50–38.14, $P=0.18$), and 10.76 (1.20–96.59, $P=0.034$), respectively, in women, and 1.0 (reference), 1.37 (0.52–3.66, $P=0.52$), 2.93 (1.17–7.32, $P=0.022$), and 1.97 (0.71–5.47 −3.75, $P=0.19$), respectively, in men.

When compared to the lower three baPWV quartiles, high baPWV was associated with carotid plaque with odds ratio (95% CI) of 2.24 (1.10–4.48, $P=0.025$) in women, and 1.26 (0.79–2.20, $P=0.92$) in men, and associated with intima-media thickening with odds ratio (95% CI) of 2.67 (1.17–6.07, $P=0.019$) in women, and 0.83 (0.47–1.46, $P=0.51$) in men, after adjusting for above-mentioned variables.

4. Discussion

In the present study, by analyzing the subjects undergoing health screening test, we found that serum UA levels showed a graded association with the incidence of high baPWV, which was determined as ≥1594 cm/s in women and ≥1721 cm/s in men, and that this association was independent of other confounding atherogenic risk factors. A high baPWV value, as determined by these cut-off points may have clinical significance, because baPWV over 1400 cm/s and that over 1600 cm/s have been shown to be useful to predictors for cardiovascular diseases as assessed by the Framingham risk score [21] and for mild cardiac diastolic dysfunction [22], respectively, in the general population. It has been reported that both increased baPWV and hyperuricemia are associated with an increased incidence of some pathophysiological conditions, such as ischemic heart disease [9,23], poor prognosis in patients with coronary artery disease [10,24], and heart failure [22,25].

Non-invasive aortic stiffness measurement is postulated to be a surrogate marker of early atherosclerosis. An automated computer-assisted baPWV measurement facilitates a valid and reproducible assessment of arterial stiffness that is closely associated with invasive measurements of aortic stiffness [5]. Not surprisingly, carotid atherosclerosis and PWV have been shown to be related to each other in several previous studies [22,26,27], as well as in the current one. It might be considered that screening of both baPWV may not provide any information additional to carotid ultrasonographic evaluation. However, PWV may not be significantly associated with carotid atherosclerosis in certain cases [28,29], and a combination of carotid atherosclerosis and PWV may have a more power for detecting atherosclerotic diseases than PWV alone [27]. In addition, besides being an indicator of atherosclerosis, arterial stiffness itself may be involved in the process of atherosclerosis [30]. These data support the utility

of baPWV measurements in the setting of a general health screening test.

Although baPWV is easily performed, caution should be taken because the accuracy of the baPWV value obtained is diminished when the ABI is less than 0.95 due to the peripheral artery stenosis [31]. In the current study, however, only 1.3% subjects were found to have an ABI of less than 0.95, which supports the validity of using the baPWV measurement in our study. This finding also supports the notion that the baPWV measurement is more useful for participants undergoing general health screening than for those who are known to have severe atherosclerotic diseases.

In the current study, we have shown that serum UA levels is associated with metabolic syndrome, in agreement with our previous findings [14]. Together with a report from another group [32], our current study shows that metabolic syndrome is a risk factor for increased baPWV. Thus, the link between serum UA levels and increased PWV might be mediated by the metabolic syndrome. We found here, however, that an association between serum UA levels and baPWV could be observed in both subjects with metabolic syndrome and in those without, suggesting that this association is in part independent of metabolic syndrome. We have previously shown that serum UA is associated with carotid plaque that is independent of other confounding atherogenic risk factors [14]. In that study, we found that metabolic syndrome was found to be a risk factor for carotid plaque and that UA was associated with carotid plaque in a metabolic syndrome-independent manner. Thus, the overall relationship between serum UA and high baPWV is similar to that between serum UA and carotid plaque.

In the current study, we showed that association between serum UA and high baPWV was at least in part independent of conventional risk factors for atherosclerosis. What is the possible underlying mechanism that links between hyperuricemia and arterial stiffening? It has been reported that UA promotes vascular smooth muscle proliferation and upregulates the expression of platelet-derived growth factor [33] and monocyte chemoattractant protein-1 [34]. Hypoxanthine is converted to uric acid via xanthine. This reaction can be catalyzed by xanthine hydrogenase and xanthine oxidase, the latter of which produce uric acid and superoxide. Thus, it is possible that, in certain diseased conditions, hyperuricemia is accompanied by the increased production of reactive oxygen species [35], which may result the modulation of vascular contractility [36]. Consistent with this notion that allopurinol, a xanthine oxidase inhibitor, not only reduced the serum UA levels but also improved vascular endothelial function in patients with chronic heart failure [37]. Another possible explanation is that hyperuricemia may induce endothelial dysfunction by decreasing the production of nitric oxide in the vascular endothelial cells [38]. Although these mechanisms may underlie the hyperuricemia-associated arterial stiffening, it should be kept in mind that whether the relationship between serum UA and increased arterial stiffness is circumstantial or causal cannot be determined by this cross-sectional study.

In conclusion, by analyzing the data of individuals who had undergone general health screening that was targeted towards screening for atherosclerosis, we have found that serum UA is associated with baPWV, and thus increased arterial stiffness. Although serum UA is associated with an incidence of metabolic syndrome, association between serum UA and baPWV is, in part, independent of metabolic syndrome.

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Association between serum albumin, carotid atherosclerosis, and metabolic syndrome in Japanese individuals

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Abstract

Serum albumin is a maker of nutritional status and possesses antioxidative properties. Here, we have sought to investigate the mode of association between serum albumin levels, metabolic syndrome, and carotid atherosclerosis by analyzing the data of the cross-sectional data from 8143 individuals who underwent general health screening test. After adjusting for age, total cholesterol, and smoking status, the highest quartile of serum albumin (≥4.7 g/dL) was associated with increased prevalence of metabolic syndrome with an odds ratio of 1.80 (95% CI 1.41–2.23, $P < 0.0001$) in women, and 1.60 (95% CI 1.44–1.78, $P < 0.0001$) in men, when compared to the lowest serum albumin quartile (<4.3 g/dL). By contrast, when compared with the lowest quartile, the highest quartile of serum albumin was associated with reduced prevalence of carotid plaque with an odds ratio of 0.62 (95% CI 0.42–0.91, $P < 0.001$) in women, and 0.76 (95% CI 0.62–0.93, $P < 0.01$) in men, and for carotid intima-media thickening with an odds ratio of 0.57 (95% CI 0.35–0.94, $P < 0.05$) in women, and 0.71 (95% CI 0.55–0.92, $P < 0.01$) in men. Our data showed that higher serum albumin was inversely associated with the prevalence of early carotid atherosclerosis, although it was positively associated with the prevalence of metabolic syndrome. Whether these observations are in part explained by the antioxidative properties of albumin requires further investigation.

Keywords: Metabolic syndrome; Carotid atherosclerosis; Ultrasonography; Albumin; Antioxidants

1. Introduction

Serum albumin level is known to be reduced in various diseased conditions, such as malnutrition, inflammatory states, and liver diseases [1]. It has been shown that lower levels of serum albumin are associated with increased risk of cardiovascular mortality [2,3] and carotid atherosclerosis [4,5]. On the other hand, serum albumin levels show positive association with some of the coronary risk factors, such as body mass index (BMI), blood pressure, and lipid profiles [6–9], although these associations cannot distort the association between low serum albumin levels and cardiovascular disease.

It has recently been suggested that there may be an inverse association between circulating antioxidants, such as Vitamin C and carotenoids, and metabolic syndrome [10]. In the serum, albumin as well as bilirubin and uric acid represent major plasma antioxidant components. In the previous study, we reported negative association between serum bilirubin and metabolic syndrome and positive association between serum uric acid and metabolic syndrome [11]. Serum albumin may be associated positively with several atherogenic risk factors [6]; however, little has been known about the mode of association between serum albumin and metabolic syndrome. Thus, in the present study, we have investigated the mode of association between serum albumin, carotid

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atherosclerosis, and metabolic syndrome by analyzing the cross-sectional data from individuals undergoing general heath screening.

2. Methods

2.1. Study subjects

The study was approved by The Ethical Committee of Mitsui Memorial Hospital. Between September 1994 and December 2003, 49,331 (16,868 women, 32,463 men) subjects aged 20 years old or older underwent a general health screen. Of the 49,331 subjects, 8143 subjects (2671 women, 5472 men) underwent health screening course including carotid ultrasonography, and were enrolled in the present study. In Japan, regular health check-ups for employees are legally mandated, and all or most of the costs of the screening are usually paid by the company to which they belong or by each subject. There are several courses, with different costs, in our health screening. Some courses include carotid ultrasonography, but some do not. Therefore, the study subjects were not considered to be a random selection from the whole subjects who underwent general health screening during the study period; however, which course to be chosen was not recommended by the physicians or health care participants. The interquartile cut off points of serum albumin, 4.3, 4.5, and 4.7 g/dL, were used in both genders. Cigarette smoking outcome data were collected in a structured questionnaire.

2.2. Laboratory data

Blood samples were taken from our subjects after an overnight fast. Serum albumin was measured by Bromcresol Green (BCG) dye-binding method and inter-assay coefficient of variation was 0.6%. Serum levels of total cholesterol (TC), HDL-cholesterol (HDL-C), and triglycerides were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method, haemoglobin A_{1C} was determined using the latex agglutination immunoassay, and bilirubin was determined by the vanadium oxide method. Plasma glucose was measured by hexokinase method and serum insulin was measured by enzyme immunoassay.

The data of basal insulin levels were available in 6338 subjects (2026 women, 4312 men), and homeostasis model assessment insulin resistance (HOMA-IR) was calculated in these individuals according to the following formula: HOMA-IR = [fasting immunoreactive insulin (IRI; μU/mL) × FPG (mg/dL)]/405.

When converting from mg/dL to mmol/L or mg/dL to μmol/L, following conversion factors would be used: uric acid, 59.48 (mg/dL to μmol/L); bilirubin, 17.10 (mg/dL to μmol/L); TC, 0.0259 (mg/dL to mmol/L); HDL-C, 0.0259 (mg/dL to mmol/L); triglycerides, 0.0113 (mg/dL to mmol/L); and glucose, 0.0555 (mg/dL to mmol/L).

2.3. Carotid ultrasonography

Carotid artery status was studied and analyzed as described previously [11]. In brief, this was examined by high resolution B-mode ultrasonography, using a machine (Sonolayer SSA270A, Toshiba, Japan) equipped with a 7.5 MHz transducer (PLF-703ST, Toshiba). The carotid arteries were examined bilaterally at the levels of the common carotid, the bifurcation, and the internal carotid arteries from transverse and longitudinal orientations by trained sonographers. The intima-media thickness was measured using a computer-assisted method by experienced sonographers who were unaware of the subjects' clinical and laboratory findings. Plaque was defined as a clearly isolated focal thickening of the intima-media layer with thickness of ≥1.3 mm at the common or internal carotid artery or the carotid bulb. Carotid intima-media wall thickening was said to occur when the intima-media thickness which was measured at the far wall of the distal 10 mm of the common carotid artery was ≥1.0mm.

2.4. Criteria for metabolic syndrome

Diagnosis of metabolic syndrome was made according to the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) [12] with BMI used as a surrogate for waist circumference as has been done in previous other studies, because waist circumference was not available in this study sample. The five thresholds used were: (1) triglyceride levels ≥150 mg/dL (1.69 mmol/L), (2) HDL-C levels <40 mg/dL (1.04 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, (3) fasting plasma glucose levels ≥110 mg/dL (6.1 mmol/L), or taking an antidiabetic medication, (4) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or taking an antihypertensive medication, and (5) body mass index (BMI) ≥25 kg/m^2. These five parameters were designated 'metabolic syndrome risk factor components' in the current study. Metabolic syndrome was diagnosed when three or more of these components were present.

2.5. Statistical analysis

The data in this study were analyzed by the χ^2-test, ANOVA with a Bonferroni post hoc test, and multivariate logistic regression analysis using computer software, StatView ver. 5.0 (SAS Institute, NC, USA). A value of $P < 0.05$ was taken to be statistically significant. Results are expressed as the mean ± S.D. unless stated otherwise.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the study subjects are given in Table 1. The age of the enrolled subjects ranged from 22

Table 1
Baseline characteristics

Variables	Quartiles of serum albumin				*P*-value
	1	2	3	4	
Women					
Albumin range (g/dL)	3.3–4.2	4.3–4.4	4.5–4.6	4.7–5.4	
No. of subjects	639	826	735	471	
Age (years)	59 ± 11	56 ± 10	56 ± 10	55 ± 10	<0.0001
Body mass index (kg/m^2)	21.9 ± 3.3	21.9 ± 3.1	22.0 ± 3.0	21.7 ± 3.2	0.57
Systolic BP (mmHg)	119 ± 21	120 ± 19	122 ± 21	126 ± 23	<0.0001
Diastolic BP (mmHg)	73 ± 11	73 ± 11	75 ± 12	77 ± 13	<0.0001
Laboratory data					
White blood cells (×10^3/μL)	5.0 ± 1.3	4.9 ± 1.3	5.0 ± 1.3	5.1 ± 1.3	0.045
Hemoglobin (g/dL)	12.8 ± 1.2	13.1 ± 1.0	13.3 ± 1.0	13.6 ± 1.0	<0.0001
Platelet count (×10^4/μL)	23.0 ± 5.7	23.2 ± 5.2	23.7 ± 5.3	23.7 ± 5.6	0.036
Total protein (g/dL)	7.0 ± 0.4	7.2 ± 0.4	7.5 ± 0.3	7.8 ± 0.4	<0.0001
Albumin (g/dL)	4.1 ± 0.1	4.4 ± 0.1	4.5 ± 0.1	4.8 ± 0.1	<0.0001
AST (IU/L)	25.4 ± 36.4	22.4 ± 8.7	22.6 ± 6.6	24.5 ± 11.6	0.0075
Uric acid (mg/dL)	4.6 ± 1.0	4.7 ± 1.0	4.7 ± 1.0	4.8 ± 1.1	0.027
Total bilirubin (mg/dL)	0.7 ± 0.3	0.8 ± 0.3	0.8 ± 0.2	0.9 ± 0.3	<0.0001
γ-GTP (IU/L)	28.5 ± 33.9	28.1 ± 39.0	29.4 ± 24.8	39.1 ± 64.8	<0.0001
CRP > 0.4 mg/dL (%)	7	4	3	3	0.0001
Serum lipid data					
Total cholesterol (mg/dL)	206 ± 33	215 ± 35	221 ± 36	228 ± 36	<0.0001
HDL-cholesterol (mg/dL)	68 ± 15	70 ± 17	70 ± 18	71 ± 18	0.050
Triglycerides (mg/dL)	90 ± 51	94 ± 61	101 ± 70	102 ± 75	0.0028
Glucose metabolism					
Fasting glucose (mg/dL)	91 ± 19	90 ± 13	93 ± 16	95 ± 17	<0.0001
Haemoglobin A_{1C} (%)	5.2 ± 0.6	5.1 ± 0.4	5.2 ± 0.6	5.1 ± 06	0.0013
Smoking status					
Non-smokers (%)	85	84	86	83	0.40
Former smokers (%)	5	5	4	7	
Current smokers (%)	10	11	11	11	
Men					
Albumin range (g/dL)	2.3–4.2	4.3–4.4	4.5–4.6	4.7–5.6	
No. of subjects	1002	1521	1601	1348	
Age (years)	61 ± 10	58 ± 10	56 ± 10	53 ± 10	<0.0001
Body mass index (kg/m^2)	23.7 ± 2.7	24.0 ± 2.9	24.0 ± 2.7	24.0 ± 2.8	0.014
Systolic BP (mmHg)	126 ± 19	127 ± 19	128 ± 19	130 ± 19	<0.0001
Diastolic BP (mmHg)	78 ± 11	79 ± 11	80 ± 12	81 ± 12	<0.0001
Laboratory data					
White blood cells (×10^3/μL)	5.7 ± 1.6	5.6 ± 1.5	5.8 ± 1.6	5.8 ± 1.5	0.0003
Hemoglobin (g/dL)	14.5 ± 1.2	14.9 ± 1.0	15.1 ± 1.0	15.3 ± 1.0	<0.0001
Platelet count (×10^4/μL)	21.5 ± 5.0	22.1 ± 4.9	22.5 ± 4.9	22.6 ± 5.3	<0.0001
Total protein (g/dL)	7.0 ± 0.4	7.2 ± 0.3	7.4 ± 0.3	7.7 ± 0.3	<0.0001
Albumin (g/dL)	4.1 ± 0.1	4.4 ± 0.1	4.5 ± 0.1	4.8 ± 0.1	<0.0001
AST (IU/L)	25.0 ± 13.8	25.9 ± 13.4	25.7 ± 10.2	27.6 ± 12.9	<0.0001
Uric acid (mg/dL)	5.9 ± 1.2	6.1 ± 1.2	6.2 ± 1.2	6.4 ± 1.3	<0.0001
Total bilirubin (mg/dL)	0.8 ± 0.3	0.8 ± 0.3	0.9 ± 0.3	1.0 ± 0.4	<0.0001
γ-GTP (IU/L)	54.3 ± 63.2	61.2 ± 68.0	64.6 ± 64.1	74.2 ± 67.0	<0.0001
CRP > 0.4 mg/dL (%)	10	7	5	5	<0.0001
Serum lipid data					
Total cholesterol (mg/dL)	198 ± 35	201 ± 30	208 ± 31	213 ± 33	<0.0001
HDL-cholesterol (mg/dL)	56 ± 17	56 ± 15	55 ± 14	54 ± 15	0.0003
Triglycerides (mg/dL)	132 ± 131	136 ± 90	151 ± 106	164 ± 149	<0.0001
Glucose metabolism					
Fasting glucose (mg/dL)	100 ± 24	100 ± 21	101 ± 21	102 ± 22	0.021
Haemoglobin A_{1C} (%)	5.5 ± 0.9	5.4 ± 0.7	5.4 ± 0.7	5.3 ± 0.8	<0.0001
Smoking status					
Non-smokers (%)	29	33	28	33	0.0031
Former smokers (%)	32	33	35	33	
Current smokers (%)	39	35	37	33	

BP and CRP indicate blood pressure and C-reactive protein, respectively.

Table 2
Serum albumin quartiles and risk for metabolic syndrome

Quartiles of albumin	Whole odds ratio (95% CI)	Women odds ratio (95% CI)	Men odds ratio (95% CI)
Q1	1 (reference)	1 (reference)	1 (reference)
Q2	1.17 (0.96–1.42)	1.16 (0.72–1.86)	1.17 (0.94–1.45)
Q3	1.30 (1.07–1.58)§	2.19 (1.40–3.42)*	1.14 (0.92–1.42)
Q4	1.54 (1.26–1.89)†	1.74 (1.05–2.91)‡	1.47 (1.17–1.84)*

Age, sex (for whole), total cholesterol, and smoking status were used as covariates. ‡$P<0.05$; §$P<0.01$; *$P<0.001$; †$P<0.0001$ vs. the lowest quartile (reference).

to 88 years (women, 22–87 years; men, 21–88 years) with a mean age of 56.6 ± 10.5 years (women, 56.4 ± 10.4 years; men, 56.7 ± 10.6 years). The mean age either in the second, third, and fourth quartiles was less than that in the first quartile ($P<0.0001$) in both genders. The mean serum albumin level was 4.4 ± 0.3 g/dL in women, and 4.5 ± 0.3 g/dL in men. Only 0.3% (9/2671) of the female and 0.1% (8/5472) of the male subjects had serum albumin levels of less than the lowest normal value, which is 3.7 g/dL. Pearson's correlation coefficients for the relationship between serum albumin and each variable were as follows (women/men): age, −0.13/−0.278; BMI, 0.00/0.05; systolic blood pressure, 0.12/0.08; diastolic blood pressure, 0.14/0.10; total bilirubin 0.20/0.21; uric acid, 0.06/0.11; TC, 0.22/0.17; triglycerides, 0.08/0.11; HDL-C, 0.06/−0.06; plasma glucose, 0.091/0.05; and hemoglobin A1C, −0.05/−0.08. A value of $P<0.001$ was obtained for all of these correlations except for BMI (n.s.), HDL-C ($P<0.01$), and hemoglobin A1C ($P<0.05$) in women. In both genders, albumin level in the former smoker (women, 4.5 ± 0.3 g/dL; men, 4.4 ± 0.2 g/dL) and in current smokers (women, 4.5 ± 0.3 g/dL; men, 4.4 ± 0.2 g/dL) did not significantly differ from that in the never smokers (women, 4.5 ± 0.3 g/dL; men, 4.4 ± 0.2 g/dL).

3.2. Prevalence of metabolic syndrome

When compared with the individuals in the lowest albumin quartile, HOMA-IR was significantly greater in the subjects in the highest quartile ($P<0.01$) in women, and in those in any higher quartiles ($P<0.001$) in men (Fig. 1A). In addition, prevalence of metabolic syndrome in the second to fourth quartiles of serum albumin was greater than that in the lowest quartile (Fig. 1B). After adjustment for age, TC, and smoking status, logistic regression analysis showed that individuals in the highest quartile, in men and those in the highest and the second highest quartiles, in women of serum albumin had a

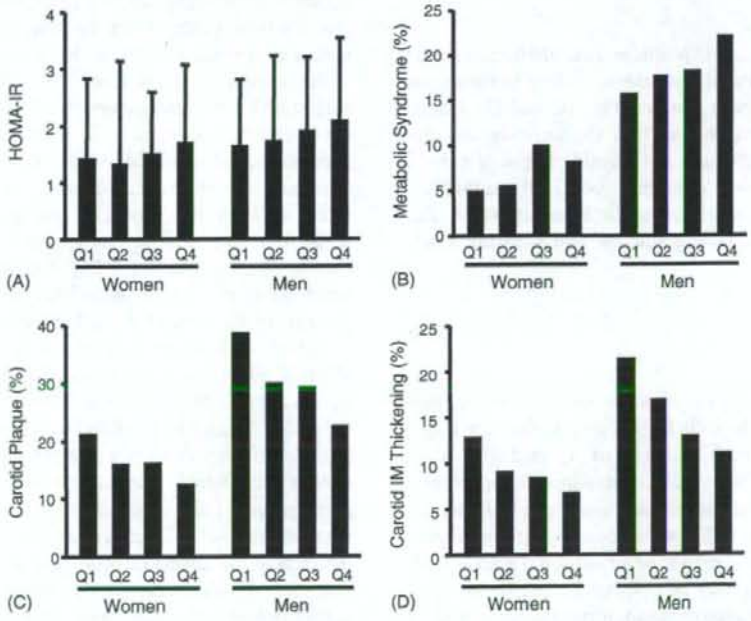

Fig. 1. (A) HOMA-IR of each gender according to the serum albumin quartile and gender. (B) Prevalence of metabolic syndrome according to the serum albumin quartile and gender. (C) Prevalence of carotid plaque according to the serum albumin quartile and gender. (D) Prevalence of intima-media (IM) thickening according to the serum albumin quartile and gender.

Table 3
Serum albumin quartiles and risk for carotid plaque and intima-media thickening

Quartiles of albumin	Whole odds ratio (95% CI)	Women odds ratio (95% CI)	Men odds ratio (95% CI)
For carotid plaque			
Q1	1 (reference)	1 (reference)	1 (reference)
Q2	0.82 (0.70–0.96)‡	0.82 (0.61–1.09)	0.82 (0.68–0.99)*
Q3	0.91 (0.78–1.07)	0.84 (0.62–1.14)	0.94 (0.78–1.14)
Q4	0.72 (0.60–0.89)*	0.62 (0.42–0.91)*	0.76 (0.62–0.93)§
For carotid intima-media thickening			
Q1	1 (reference)	1 (reference)	1 (reference)
Q2	0.88 (0.73–1.01)	0.81 (0.56–1.18)	0.90 (0.72–1.13)
Q3	0.73 (0.60–0.89)§	0.73 (0.49–1.09)	0.73 (0.58–0.92)§
Q4	0.68 (0.54–0.85)*	0.57 (0.35–0.94)‡	0.71 (0.55–0.92)§

Age, sex (for whole), BMI, systolic blood pressure, total cholesterol, HDL-cholesterol, triglycerides, fasting glucose, and smoking status were used as covariates.
‡$P<0.05$; §$P<0.01$; *$P<0.001$ vs. the lowest quartile (reference).

significantly greater prevalence of metabolic syndrome when compared to the individuals in the lowest quartile in each gender (Table 2). Serum albumin levels (g/dL) of women who had zero ($n=1365$), one ($n=791$), two ($n=329$), three ($n=130$), four ($n=46$), and five ($n=10$) risk factor components were 4.41 ± 0.24, 4.42 ± 0.27, 4.46 ± 0.27, 4.54 ± 0.27, and 4.46 ± 0.17, respectively. Serum albumin levels (g/dL) of men who had zero ($n=1405$), one ($n=1790$), two (n = 1271), three ($n=703$), four ($n=270$), and five ($n=33$) risk factor components were 4.44 ± 0.25, 4.47 ± 0.25, 4.50 ± 0.26, 4.53 ± 0.26, and 4.53 ± 0.28, respectively.

3.3. Prevalence of carotid plaque and intima-media thickening

The prevalence of carotid plaque and carotid intima-media thickening showed graded decrease according to the serum albumin quartiles in both genders (Fig. 1C and D). Logistic regression analysis showed that the negative association between serum albumin and carotid plaque or carotid intima-media thickening remained statistically significant after adjusting for age, BMI, systolic blood pressure, TC, HDL-C, triglycerides, fasting glucose, and smoking status (Table 3).

4. Discussion

In the present study, we demonstrated two major findings. First, individuals with higher serum albumin had a significantly reduced odds ratio for early carotid atherosclerosis (carotid plaque and carotid intima-media thickening). Second, individuals with higher serum albumin had a significantly increased odds ratio for metabolic syndrome. Serum albumin levels are considered to be a nutritional marker [13]. Serum albumin levels may be reduced in various diseased conditions, such as malnutrition and inflammatory states [1], and, on the contrary, they may be increased in the individuals with increased total body fat [6]. Although serum albumin levels may be modulated in response to the nutritional status, they may not be much reduced until near terminal starvation in otherwise healthy individuals [14], and thus, they lay within relatively narrow range in general populations [3,15].

It has been shown that lower levels of serum albumin are associated with increased risk of all-cause and cardiovascular mortality [2]. Djoussé et al. have reported that lower serum albumin concentrations are associated with an increased risk of coronary disease in both genders by analyzing the data from participants of the Framingham Offspring Study [3]. It still remains unclear whether the prognostic value of low albumin simply reflects inflammation/nutrition status or if there is an independent effect of albumin. However, there are several possible mechanisms that explain inverse association between serum albumin and cardiovascular disease. First, serum albumin may retard the atherogenesis by its antioxidative properties [16,17], as ROS may play a crucial role in the atherosclerotic process [18]. This possibility may be supported by the observations that oral intake or plasma levels of certain antioxidants, such as Vitamins C and E, and β-carotene, are associated with a reduced risk of coronary artery disease and carotid atherosclerosis [20–23]. Furthermore, we have also shown an inverse association between serum bilirubin, another endogenous antioxidant [19], and carotid atherosclerosis [11,20]. Second, subjects with low serum albumin levels are more likely to be cigarette smokers [15,21]. In the present study, however, this possibility may be rather unlikely, as negative association between serum albumin and carotid atherosclerosis remained statistically significant in both genders even after the adjustment of smoking status. Third, low albumin levels may reflect activation of proinflammatory cytokines and ongoing subclinical inflammation [22], which plays a crucial role in the process of atherogenesis [23]. Consistent with this idea was the finding that positive CRP, defined as CRP > 0.4 mg/dL, was most frequent in the lowest quartile of serum albumin in the current study. Finally, albumin may act as an anti-inflammatory agent towards endothelial cells [24].

Interestingly, Saito et al. have reported the positive associations of serum albumin with BMI, blood pressure, and lipid profiles after adjusting for gender and age in rural residents

[6]. Similarly, by analyzing the cross-sectional data from individual without a history of coronary heart disease, Danesh et al. have reported that serum albumin levels were positively associated with low-density lipoprotein cholesterol, triglycerides, and blood pressure [7]. Several other studies have also shown that serum albumin was associated with blood pressure and lipid profiles [8,9]. In addition to these observations, we have shown that serum albumin was positively associated with metabolic syndrome and insulin resistance, estimated by HOMA-IR, which are risk factors for carotid atherosclerosis that were independent of conventional atherogenic risk factors [25], in the current study, for the first time to out best knowledge. As serum albumin is considered to be cardioprotective, irrespective of its association with several atherogenic risk factors, several underlying mechanisms have been proposed in previous studies as mentioned above; however, so far, there is no direct evidence.

Although diet restriction may be effective in reducing subcutaneous and visceral fat, and in improving insulin sensitivity, it might also decrease serum albumin levels [26]. It may be questioned whether or not caloric restriction [27], especially when accompanied by the reduction of serum albumin levels, acts favorably in terms of protection of atherosclerotic diseases. Although we cannot answer this question from the current study, this should be investigated in future prospective studies.

Our study does have some limitations. First, as described in Section 2, only individuals who underwent health screening including carotid ultrasonography were selected as the study population; therefore, the study subjects were not considered to be a random selection from the whole subjects who underwent general health screening during the study period. Second, due to the cross-sectional nature of the current study, we are not able to conclude the causal or resultant relationship between serum albumin and metabolic syndrome or carotid atherosclerosis. Third, although serum albumin is postulated to possess antioxidant properties, there are other known circulating antioxidants, such as Vitamins A, C, and E; retinyl esters; and carotenoids. Association between some of these circulating antioxidants and metabolic syndrome were suggested as described above [10]; however, we did not use these factors as covariates. Finally, neither did we adjust the results for physical activity, which may also affect the prevalence of metabolic syndrome [28]. These possible confounding factors should be taken into consideration in future studies.

In conclusion, by analyzing cross-sectional data from individuals undergoing general health screening including carotid ultrasonography, we have demonstrated that higher serum albumin is associated with reduced prevalence of carotid atherosclerosis, whereas it is associated with increased prevalence of metabolic syndrome. Our data may provide evidence that negative association between serum albumin and atherosclerotic disease may not be explained by the hemodynamic and metabolic abnormalities that comprise the components of metabolic syndrome.

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Original Article

Is Metabolic Syndrome a Risk Factor for Carotid Atherosclerosis in Normotensive and Prehypertensive Individuals?

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Aim: We have investigated whether metabolic syndrome is a risk factor for carotid atherosclerosis also in normotensive or prehypertensive individuals.
Methods: We analyzed the data from 851 subjects who had a blood pressure of less than 140/90 mmHg and were not taking antihypertensive medication. Metabolic syndrome was defined according to three different criteria: Japan criteria (Japan-MetS); those of the National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATPIII) (NCEP-MetS); and modified NCEP-ATPIII criteria in which body mass index was used as a surrogate for waist circumference (modified NCEP-MetS).
Results: Japan-MetS, NCEP-MetS, and modified NCEP-MetS were found, respectively, in 1%, 4%, and 4%, of women, and in 10%, 5%, and 9%, of men. After the adjustment for gender and age, the association between MetS and carotid atherosclerosis did not reach statistical significance.
Conclusion: Although the number of enrolled subjects was relatively small, these data may further support the importance of controlling blood pressure within the optimal range for the purpose of preventing atherosclerosis in individuals with metabolic syndrome.

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Key words; Metabolic syndrome, Carotid artery, Normotension, Prehypertension

Introduction

Metabolic syndrome (MetS), which is thought to be linked with insulin resistance, is a risk factor for cardiovascular disease[1] and stroke[2]. We have previously shown that MetS is a risk factor for carotid atherosclerosis in those undergoing general health screening[3]. Several other studies have shown an association between atherosclerotic diseases and MetS in individuals of different race and ethnicity, although these studies may have used different, or slightly modified, diagnostic criteria for MetS, such as those proposed by the World Health Organization (WHO)[4], the National Cholesterol Education Program (NCEP)[5], or those used in our country[6]. Although these criteria vary in some components, they all share several conventional atherogenic risk factors as diagnostic criteria[7-9], including impaired glucose metabolism, hypertension, and dyslipidemia.

Individuals with prominent hemodynamic and metabolic abnormalities can readily be recognized and managed by health care providers. Thus, it might be questioned whether, by using the concept of MetS, we can identify individuals at higher risk for atherosclerotic complications among those with only mild hemodynamic and/or metabolic abnormalities. We found that hypertension is the most common component of metabolic syndrome and the greatest contributor to carotid arteriosclerosis in individuals who had undergone general health screening[10]. Recently, we investigated data from subjects with normotension or prehypertension, who underwent general health screening between September 1994 and December 2003, and found that MetS might not be an independent risk factor for carotid atherosclerosis in such a population[11]. As waist circum-

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ference (WC) data were not available in that study, however, body mass index (BMI) was used as a surrogate for waist circumference for the diagnosis of MetS. As WC has recently become a routine measurement during general health screening at our institute, here we re-analyzed whether MetS, as diagnosed by Japan and NCEP criteria, is a risk factor for carotid atherosclerosis in normotensive or prehypertensive individuals.

Methods

Study Subjects

The study was approved by The Ethical Committee of Mitsui Memorial Hospital. Between October 2005 and June 2006, 1323 subjects underwent general health screening including carotid ultrasonography, measurement of other metabolic markers, and waist circumference necessary to assess the presence or absence of MetS at the Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital. Among them 851 (342 women, 509 men), who were not taking anti-hypertensive medications, were found to have a systolic blood pressure (SBP) of less than 140 mmHg and a diastolic blood pressure (DBP) of less than 90 mmHg, and were enrolled in the current study. Data on basal insulin levels were available for all subjects enrolled, and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated in these individuals according to the following formula: HOMA-IR = fasting immunoreactive insulin (μU/mL) × fasting plasma glucose (FPG, mg/dL))/405[12]. Normotension or prehypertension was defined according to the criteria of JNC 7[13], unless otherwise stated.

Definition of Metabolic Syndrome

For the diagnosis of MetS, we used three different criteria.

(1) Definition and diagnostic criteria of MetS in Japan[6] (Japan-MetS).

Waist circumference (WC) ≧90 cm in women or ≧85 cm in men plus two or more of the following: HDL cholesterol (HDL-C) <40 mg/dL or triglycerides (TG) ≧150 mg/dL; SBP ≧130 mmHg or DBP ≧85 mmHg; FPG ≧110 mg/dL.

(2) MetS diagnosed by NCEP ATP-Ⅲ criteria[5] (NCEP-MetS).

Subjects with three or more of the following five components were considered to have MetS: TG levels ≧150 mg/dL; HDL-C levels <40 mg/dL in men or <50 mg/dL in women; FPG ≧110 mg/dL; SBP ≧130 mmHg or DBP ≧85 mmHg; waist circumference >102 cm in men and >88 cm in women.

(3) MetS diagnosed by NCEP ATP-Ⅲ criteria using BMI criteria as a surrogate for the WC criterion (modified NCEP-MetS).

In these criteria, BMI ≧25.0 kg/m^2 was used as a surrogate of the WC criterion in NCEP-ATPⅢ criteria.

Of the 851 study subjects, 11 (1%) were taking anti-diabetic medicine, and were considered to fulfill the FPG criterion.

Carotid Ultrasonography

Carotid artery status was assessed using a high-resolution B-mode ultrasonography instrument (Sonolayer SSA270A, Toshiba, Japan) equipped with a 7.5 MHz transducer (PLF-703ST, Toshiba). In the current study, we diagnosed carotid plaque according to the criteria of the Society for the Study of Early Atherosclerosis; these criteria differ from those used in several previous studies[3], where carotid plaque was defined as clearly isolated focal thickening of the intima-media layer with a thickness of ≧1.3 mm. Here, we defined carotid plaque by a portion of the artery with an intima-media complex thickness of ≧1.1 mm[14] with a focal protrusion or point(s) of inflexion. The difference in the prevalence of carotid plaque in health screening participants between the current and previous studies[3] may be due to the difference in criteria used to diagnose carotid plaque. On the other hand, carotid wall intima-media thickening was said to be present when intima-media thickness, measured at the far wall of the distal 10 mm of the common carotid artery, was ≧1.0 mm[3].

Statistical Analysis

The data in this study were analyzed by the χ^2 test, unpaired t test, and multivariate logistic regression analysis using computer software, StatView ver. 5.0. A value of $p<0.05$ was taken as significant. The results are expressed as the mean ± SD.

Results

Prevalence of MetS Defined by Three Diagnostic Criteria

The age of the subjects ranged from 25 to 91 years (women, 25-91 years; men, 29-89 years) (**Table 1**). Japan-MetS, NCEP-MetS, and modified NCEP-MetS were found, respectively, in 4 (1%), 14 (4%), and 13 (4%) women, and in 49 (10%), 24 (5%), and 47 (9%) men. The prevalence and overlap of MetS defined by these criteria are shown in **Fig. 1**. In the study population, 767 (90.1%) individuals were found to be free from MetS, as defined by any of the three criteria. HOMA-IR in individuals with or without Japan-MetS

Table 1. Baseline characteristics and laboratory data

Variables	Women (n=342)	Men (n=509)
Age, years	55.9±11.0	56.9±10.8
Body mass index, kg/m^2	21.2±2.9	23.6±2.6
Waist circumferrence, cm	77.2±9.2	85.7±7.3
Systolic blood pressure, mmHg	114±13	118±12
Diastolic blood pressure, mmHg	71±9	76±8
Normotension (%)	219 (64)	237 (47)
Prehypertension (%)	123 (36)	272 (53)
Laboratory data		
Total cholesterol, mg/dL	223±34	210±33
HDL-cholesterol, mg/dL	70±16	56±14
Triglycerides, mg/dL	84±43	127±93
Uric acid, mg/dL	4.5±0.9	6.2±1.1
Fasting glucose, mg/dL	90±12	99±18
Hemoglobin A1C, %	5.2±0.5	5.4±0.6
HOMA-IR	1.2±0.8	1.6±1.0
Smoking status		
Never (%)	297 (87)	161 (32)
Former (%)	20 (6)	215 (42)
Current (%)	25 (7)	133 (26)

was, respectively, 4.0±2.5 or 1.2±0.7 (p<0.0001) in women, and 2.4±1.5 or 1.5±0.9, respectively, (p<0.0001) in men. HOMA-IR in individuals with or without NCEP-MetS was, respectively, 2.7±1.6 or 1.2±0.7 (p<0.0001) in women, and 2.8±1.6 or 1.67±1.06 (p<0.0001) in men. HOMA-IR in individuals with or without modified NCEP-MetS was, respectively, 2.7±1.7 and 1.2±0.7 (p<0.0001) in women, and 2.6±1.6 and 1.5±0.90 (p<0.0001) in men. The characteristics and laboratory data of individuals who had metabolic syndrome defined by either criterion are described in **Table 2**.

In the whole study population, 674 individuals (284 women, 390 men) had a BP of <130/85 mmHg, and in this subpopulation, the prevalence of Japan-MetS, NCEP-MetS, and modified NCEP-MetS was found to be, respectively, 0 (0%), 5 (2%), and 4 (1%) in women, and 9 (2%), 7 (2%), and 14 (4%) in men. In addition, in 456 normotensive individuals (219 women, 237 men) (i.e., individuals with a BP of <120/80 mmHg), the prevalence of Japan-MetS, NCEP-MetS, and modified NCEP-MetS was found to be, respectively, 0 (0%), 5 (2%), and 4 (2%), respectively, in women, and 5 (2%), 3 (1%), and 4 (2%), respectively, in men.

Relation between Carotid Plaque and MetS

Carotid plaque was found in 145 (42%) of the 342 women and 295 (58%) of the 509 men. HOMA-IR in individuals with or without carotid plaque was, respectively, 1.3±0.8 or 1.2±0.8 (p=0.44) in women, and 1.6±1.0 or 1.7±1.1 (p=0.45) in men. When individuals with fasting glucose of ≧140 mg/dL (2 in women and 17 in men) were excluded from this analysis, HOMA-IR in individuals with or without carotid plaque was, respectively, 1.3±0.7 or 1.2±0.7 (p=0.35) in women, and 1.5±0.8 or 1.7±1.1 (p=0.12) in men.

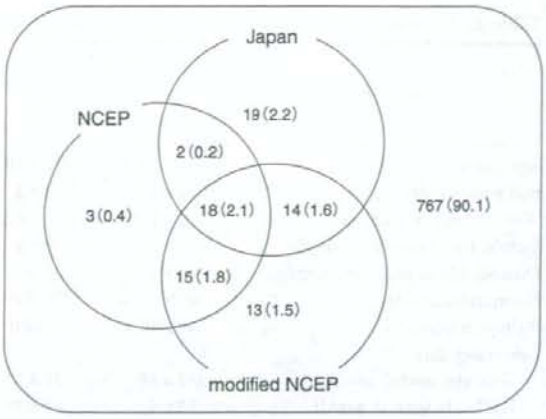

Fig. 1. Venn diagram showing the three target populations. Percentages are shown in parentheses.

After adjustment for gender and age, logistic regression analysis showed that the association between MetS defined by the three different criteria and carotid plaque did not reach statistical significance. After further adjustment for smoking status and SBP, the odds ratio for carotid plaque was decreased and, again, MetS as defined by any of the three criteria was not found to be associated with carotid plaque (**Table 3**).

Relation between Carotid Intima-Media Thickening and MetS

Carotid intima-media thickening was found in 20/342 (5.8%) women and 61/509 (12.0%) men. After adjustment for gender and age, logistic regression analysis showed that the odds ratio of MetS defined by the three different criteria for carotid intima-media thickening was as follows: Japan-MetS, 1.63 (95% CI 0.69-3.84. p=0.27); NCEP-MetS, 1.25 (95% CI 0.42-3.78, p=0.69); and modified NCEP-MetS, 0.94 (95% CI 0.35-2.58, p=0.92). After further adjustment for smoking status and SBP, the odds ratio for carotid plaque was decreased and, again, MetS as defined by any of the three criteria was not found to be associated

Table 2. Clinical characteristics and laboratory data of individuals who were positive for metabolic syndrome

Variables	Japan-Mets		NCEP-Mets		modified NCEP-Mets	
	Women (n=4)	Men (n=49)	Women (n=14)	Men (n=24)	Women (n=13)	Men (n=47)
Age, years	65.3±13.5	56.2±10.1	59.6±10.1	56.7±8.5	56.0±11.0	55.3±10.1
Bod y mass index, kg/m^2	24.2±1.6	25.2±2.4	24.5±2.3	25.6±3.1	25.8±2.4	26.0±2.4
Waist circumferrence, cm	92.3±1.7	91.0±6.2	89.5±3.9	90.8±9.2	88.5±3.8	91.3±7.4
Systolic blood pressure, mmHg	134±2	130±8	126±11	127±11	128±10	129±9
Diastolic blood pressure, mmHg	84±4	81±5	77±8	79±9	79±7	80±7
Normotension (%)	0 (0)	5 (10)	5 (36)	3 (13)	4 (31)	5 (11)
Prehypertension (%)	4 (100)	44 (90)	9 (64)	21 (88)	9 (69)	42 (89)
Laboratory data						
Total cholesterol, mg/dL	231±16	211±37	226±29	215±34	214±29	211±38
HDL- cholesterol, mg/dL	55±5	47±11	51±9	42±8	50±10	42±8
Triglycerides, mg/dL	129±51	229±149	180±76	252±115	165±66	249±145
Uric acid, mg/dL	4.5±1.2	6.5±1.2	5.0±1.0	6.6±1.5	5.1±0.9	6.6±1.3
Fasting glucose, mg/dL	115±26	117±35	104±16	116±17	104±16	107±17
Hemoglobin A1C, %	5.8±1.1	5.9±1.0	5.5±0.8	6.0±0.7	5.4±0.8	5.6±0.7
HOMA-IR	4.0±2.5	2.4±1.5	2.7±1.6	2.8±1.6	2.7±1.7	2.6±1.6
Smoking status						
Never (%)	4 (100)	11 (22)	11 (79)	8 (33)	11 (85)	15 (32)
Former (%)	0 (0)	16 (33)	1 (7)	9 (38)	1 (8)	18 (38)
Current (%)	0 (0)	22 (45)	2 (14)	7 (29)	1 (8)	14 (30)

Table 3. Odds ratio for carotid plaque

Variables	Odds raio (95% CI)	p value
Japan-MetS		
Adjusted for sex, age	1.62 (0.84-3.11)	0.15
Adjusted for sex, age, SBP, smoking status	1.22 (0.62-2.39)	0.57
NCEP-MetS		
Adjusted for sex, age	1.73 (0.82-3.65)	0.15
Adjusted for sex, age, SBP, smoking status	1.42 (0.67-3.01)	0.36
modified NCEP-MetS		
Adjusted for sex, age	1.52 (0.84-2.74)	0.75
Adjusted for sex, age, SBP, smoking status	1.19 (0.65-2.20)	0.57

with carotid plaque: Japan-MetS, odds ratio 1.27 (95% CI 0.51-3.17. p=0.60); NCEP-MetS, 0.97 (95% CI 0.31-3.00, p=0.96); and modified NCEP-MetS, 0.68 (95% CI 0.24-1.89, p=0.45).

Discussion

In the present study, we found that, in individuals with normotension or prehypertension, the prevalence of Japan-MetS, NCEP-MetS, and modified NCEP-MetS was, respectively, 1%, 4%, and 4% in women, and 10%, 5% and 9% in men. MetS defined by Japan-MetS, NCEP-MetS, or modified NCEP-MetS was not found to be statistically significantly associated with carotid plaque after adjustment for age and gender. This statistical non-significance remained after further adjustment for smoking status and systolic blood pressure.

In a previous report, we showed that MetS was associated with carotid plaque, which was independent of other conventional atherogenic risk factors[3]. On the other hand, we found that MetS may not be a risk factor for carotid atherosclerosis in individuals with normotension or prehypertension[11]. In those previous studies, for the diagnosis of MetS, we used NCEP-ATPⅢ criteria with BMI as a surrogate for WC, designated here as modified NCEP-MetS. In the current study, we extended the concept that there is no association between MetS and carotid atherosclerosis even when using other diagnostic criteria including the WC component. Although the results obtained are in agreement with those of a previous report[11], several points need careful consideration.

First, the number of subjects enrolled was not large in the current study, which may weaken the statistical

power. For example, although not statistically significant, the odds ratio of Japan-MetS for carotid plaque after adjustment for sex and age (1.62) was almost comparable to the odds ratio (1.72) of modified NCEP-MetS for carotid plaque after adjusting for sex, age, total cholesterol levels, and smoking status found previously in health screening participants[15]. Thus, we should re-evaluate these observations in future studies after increasing the number of subjects enrolled. We should also investigate whether the association between MetS, as defined by the Japan criteria or by the NCEP-ATPⅢ criteria, and carotid atherosclerosis remains statistically significant after further adjustment for other traditional cardiovascular risk factors and/or each component of MetS.

Second, in the current study, we used a different definition of carotid plaque from that used in our previous study, where carotid plaque was defined as clearly isolated focal thickening of the intima-media layer with a thickness of ≧1.3 mm at the common or internal carotid artery or the carotid bulb[11]. In the current study, by contrast, carotid plaque was diagnosed when maximal intima-media thickness was ≧1.1 mm. It may be expected that the prevalence of carotid atherosclerosis would substantially differ according to the criteria used: in individuals with normotension or prehypertension, carotid plaque was found in 42% of women (mean age 56 years) and 58% of men (mean age 57 years) in the current study, and in 13% of women (mean age 55 years) and 24% of men (mean age 55 years) in the previous study[11].

In the current study, the prevalence of Japan-MetS in men was more than 8-fold that in women. This marked difference is in agreement with a recent study reported by another group, in which the prevalence of Japan-MetS in the general Japanese population was found to be 1.7% (mean age 46±1 years) in women and 12.1% (mean age 46±0 years) in men[16]. We have found that in studies using NCEP criteria, the prevalence of MetS (NCEP-MetS) is much closer between genders, which may also be in agreement with studies analyzing the Japanese population[16-19]. When comparing the prevalence of MetS reported in various studies, however, it should be noted that diagnostic criteria with certain minor modifications may have been used in various studies.

We have previously reported that hypertension is the most frequent component of modified NCEP-MetS and the greatest contributor to carotid atherosclerosis among its risk factor components[10]. Mancia *et al.* reported in a population-based study in San Marino that the prevalence of MetS was 24% in hypertensive subjects, whereas it was as little as 4% in subjects with optimal, normal, or high-normal BP[20]. Similarly, during the current study period, we found that the prevalence of Japan-MetS in the whole study population who had undergone carotid ultrasonography was 3% in women and 22% in men (Ishizaka Y, unpublished data); in addition, in the current study, which targeted individuals with optimal, normal, or high normal BP, it was 1% in women and 10% in men. Furthermore, when individuals with a BP ≧130/85 mmHg were removed from our analysis (corresponding to optimal or normal BP according to JNC Ⅵ classification[21]), the prevalence of Japan-MetS was 0% in women and 2% in men. Kanauchi *et al.* analyzed the prevalence of MetS, as diagnosed by NCEP-MetS with a modified WC criterion, in individuals who were not taking anti-hypertensive medication, and found it to be 10%, 19%, and 36% in those with normotension, prehypertension, and hypertension, respectively[22]. These data collectively indicate that the prevalence of MetS, regardless of the diagnostic criteria used, is substantially lower in individuals whose BP is in the preferable range.

In summary, we analyzed individuals who underwent general health screening including carotid ultrasonography, and found that Japan-MetS, NCEP-MetS, or modified NCEP-MetS was not a predictor for carotid atherosclerosis in normotensive or prehypertensive individuals after adjusting for sex and age. Our data suggest that maintaining BP within the optimal range is crucial for reducing the risk for both metabolic syndrome and carotid atherosclerosis. As our study involved a relatively small study population, further investigation should be performed after increasing the size of the study population in the future.

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