Table 2 Association between potential confounding variables and DHEA-S tertiles in women

Characteristic	DHEA-S tertiles T1 <1.17 μmol/L (<43 μg/dL), *n* = 33	 T2 1.17–1.49 μmol/L (43–55 μg/dL), *n* = 32	 T3 >1.49 μnmol/L (>55 μg/dL), *n* = 32	*P*-value
Age, years	83 ± 6	82 ± 6	80 ± 6	0.08
Nutritional parameters				
Body mass index, kg/m^2	22.3 ± 2.7	22.5 ± 3.2	23.7 ± 2.7	0.31
Hemoglobin, g/dL	12.6 ± 1.4	12.6 ± 1.2	13.1 ± 1.1	0.16
Albumin, g/dL	4.1 ± 0.3	4.2 ± 0.3	4.3 ± 0.2	0.18
Total cholesterol, mg/dL	205 ± 30	204 ± 35	205 ± 35	0.99
Prevalent diseases, *n* (%)				
Hypertension	10 (30)	14 (44)	15 (47)	0.47
Heart disease	4 (12)	7 (22)	8 (25)	0.46
Stroke	5 (15)	4 (13)	6 (19)	0.79
Diabetes mellitus	5 (15)	4 (13)	5 (16)	0.90
Osteoarthropathy	8 (24)	11 (34)	13 (40)	0.47
Lung disease	3 (9)	2 (6)	2 (6)	0.56
Other chronic diseases	17 (52)	19 (59)	18 (56)	0.90
Functional parameters				
Barthel Index	90 ± 7	93 ± 8	95 ± 8	0.04
HDS-R	23 ± 6	22 ± 7	25 ± 5	0.39
Vitality Index	9.2 ± 1.4	9.1 ± 2.2	8.8 ± 2.9	0.35
GDS	6.8 ± 2.6	5.9 ± 3.4	6.9 ± 3.3	0.16
Sex hormone levels				
DHEA-S, μmol/L	0.8 ± 0.2	1.3 ± 0.1	2.0 ± 0.3	<0.01
(μg/dL)	30 ± 7	49 ± 4	73 ± 12	
Testosterone, nmol/L	1.2 ± 0.6	1.2 ± 0.6	1.3 ± 0.5	0.81
(ng/dL)	35 ± 17	36 ± 17	37 ± 13	
Estradiol, pmol/L	56 ± 32	57 ± 37	67 ± 46	0.41
(pg/mL)	15.3 ± 8.6	15.5 ± 10.2	18.3 ± 12.5	

Values are shown as mean (standard deviation). Differences between the groups were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

circulatory system (HR = 13.1, 95% CI = 2.39–72.3, $P < 0.01$), while there was no association with deaths from non-circulatory causes (HR = 0.93, 95% CI = 0.86–1.02, $P = 0.14$).

Discussion

In this small prospective study of Japanese elderly who were receiving care in facilities, a low testosterone level was associated with mortality in men independent of multiple risk factors and pre-existing health conditions. In addition, a low DHEA-S level in older women was related to increased mortality. In contrast, DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Recent prospective cohort studies in Western countries have yielded inconsistent findings about the use of a low total testosterone level as a predictor of all-cause and cardiovascular mortality in middle-aged to older men.[4,5,38,39] In the two studies that found no significant prediction of mortality,[38,39] the populations were younger (mean or median ages were in the early 50s), testosterone levels were higher and mortality rates were lower (11.6 and 15.4/1000 person-years, respectively) compared to those in studies that found positive results. In the present study, although the sample size was small, the subjects were frail and older than those in any previously reported studies, with a relatively small age range and higher mortality rate. Therefore, the relation between testosterone level and mortality might have been easier to detect in our study than in other studies with healthy middle-aged and older men.

There could be several mechanisms by which endogenous testosterone affects mortality in men. Although the number of subjects was too small to perform cause-specific analysis in the present study, other studies have reported that a low testosterone level predicted increased risk of death due to CVD.[4,5] Further, in addition to the relation to muscle strength, physical performance and ADL,[10–12,21] some but not all reports have

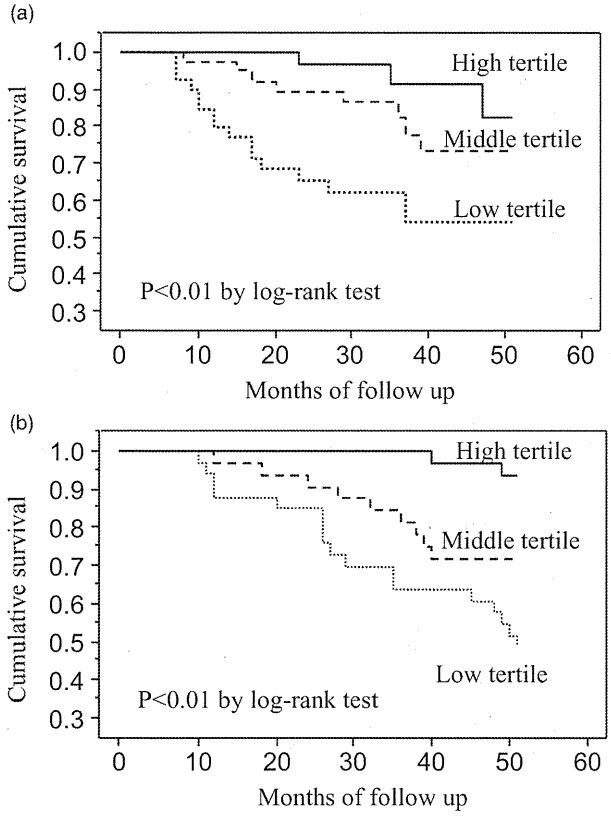

Figure 1 (a) Survival curves by tertile group of plasma testosterone level in men. (b) Survival curves by tertile group of plasma dehydroepiandrosterone sulfate level in women.

demonstrated an association between low testosterone level in older men and risk of a fall or fracture and frailty.[12–14,20] It is noteworthy that in the 10 men who died of respiratory infection, four had a history of a fall and fracture, which resulted in worse disability. Accordingly, a low testosterone level may contribute to frailty, which influences men's susceptibility to illness and falls and the capability to recover from disease or fractures, and thereby affects mortality.

Other than aging, systemic illness can result in decreased testosterone levels; therefore, low testosterone levels in older men could be attributable to acute and chronic diseases,[40] and the possible reverse causality should be considered. To evaluate this possibility, we excluded the first 12 months of observation and still found that in 12–52 months of observation, men in the low testosterone tertile had a greater risk of mortality from all causes than those in higher tertiles. We carefully excluded subjects with critical diseases and conditions at baseline, although our subjects were old with multiple chronic diseases, and it is difficult to exclude the possibility that men with subclinical critical conditions might have been included. Moreover, at baseline, there was a significant difference in functional status (ADL and cognition) and nutritional parameters (serum albumin and hemoglobin levels) between testosterone tertiles, as reported previously;[21] thus, our results need to be confirmed in a cohort with no difference in these factors between testosterone groups to exclude the influence of these biases on mortality. Also, it needs to be explored whether low testosterone in older men plays a pathogenic role, such as affecting the immune system, developing physical frailty and depression, or simply serves as a marker for biological vulnerability and poor prognosis. Long-term studies also need to test whether testosterone treatment should yield clinically significant improvements in mortality in appropriately selected older men, with consistent symptoms and signs and unequivocally low serum testosterone levels.

Low DHEA-S has been associated with increased all-cause and cardiovascular mortality in older men;[26,27,41] however, no association was found in the present study. Because DHEA(-S) is an inactive prohormone and we and others have found an association between testosterone and mortality,[3–8] it is suggested that testosterone could be a stronger predictor of mortality in older men.

On the other hand, a low DHEA-S level in older women was associated with a poor prognosis after adjusting for multiple factors related to mortality. Other previous reports showed an inconsistent relationship between DHEA-S level and mortality in older women,[29–31] possibly due to differences in the cohorts including age, DHEA-S level, heterogeneity of health status and mortality rate, and the method of statistical analysis used to demonstrate the relationship, regression models with linear/non-linear assumption.

Previous studies support a potential physiological role of DHEA-S, which could contribute to reduced mortality, an anti-inflammatory action and immune regulatory activity.[42] However, there are still many unanswered questions regarding DHEA's role in aging, and there is insufficient evidence to support DHEA replacement for increasing longevity in older women. It also needs to be explored whether the DHEA-S level contributes to mortality or is merely a biomarker of the underlying health condition of older women.

Our study has some limitations. First, the sample size was too small to reach a clear conclusion with strong statistical power, thus limiting the precision of the estimates, which is reflected in the broad range of HR for mortality. Second, the results are based on single measurements of sex hormones, which do not allow assessment of changes in levels over time; therefore, they may overestimate or underestimate the association between hormone levels and mortality. Third, we did not measure estradiol levels in men, although it would have been helpful to see whether the effects of testosterone on mortality are mediated by testosterone itself or by aromatization to estradiol in older men. Finally, active forms of testosterone such as bioavailable and

Table 3 Hazard ratios for low tertile 1 vs tertiles 2–3 of plasma sex hormone levels for all-cause mortality in men and women

	Unadjusted	Model 1	Model 2
Men (n = 117)			
HR of low testosterone for mortality	3.83 (1.74–8.40)**	3.71 (1.54–8.04)**	3.27 (1.24–12.91)*
Excluding first-year deaths (n = 108)	3.81 (1.53–6.93)**	3.49 (1.14–7.39)**	3.08 (1.11–13.62)*
Excluding deaths from cancer (n = 113)	4.18 (1.77–9.86)**	4.03 (1.70–9.58)**	5.02 (1.51–15.41)*
Women (N = 97)			
HR of low DHEA-S for mortality	3.77 (1.77–8.07)**	3.86 (1.79–8.32)**	4.42 (1.51–12.90)*
Excluding first-year deaths (n = 95)	3.38 (1.55–7.37)**	3.43 (1.56–9.54)**	3.58 (1.12–11.46)*
Excluding deaths from cancer (n = 92)	3.82 (1.69–8.60)**	3.55 (1.54–8.19)**	3.92 (1.28–11.98)*

*P < 0.05; **P < 0.01 vs reference group (tertile 2–3). Values are expressed as HR (95% CI). Model 1, adjusted for age; Model 2, adjusted for age, nutritional parameters, functional parameters and prevalent disease. DHEA-S, dehydroepiandrosterone sulfate; HR, hazards ratio.

calculated free testosterone were not measured, because a direct assay of bioavailable testosterone or an assay of sex hormone binding globulin, which is necessary for free testosterone calculation, is not available in Japan. However, because most of the above-mentioned previous reports have shown an association of total testosterone with mortality, the fundamental findings might not have differed if active forms of testosterone had been analyzed.

In conclusion, a low testosterone level in men and a low DHEA-S level in women are associated with increased mortality risk, independent of multiple risk factors and several pre-existing health conditions in disabled elderly. To our knowledge, the present study is the first that showed testosterone as a predictor of mortality in Asian men. Also, this is the first study that investigated frail or disabled older persons receiving care at facilities. Our results imply the clinical importance of measuring plasma androgen levels even in disabled elderly to estimate their prognosis.

Acknowledgments

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ORIGINAL ARTICLE

Relationship between interleukin-6 and cerebral deep white matter and periventricular hyperintensity in elderly women

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Aim: We evaluated the relationships between serum levels of high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 with the severity of leukoaraiosis.

Methods: One hundred and thirty-seven elderly women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were enrolled in this study. Leukoaraiosis was assessed by periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score.

Results: Serum log IL-6 level correlated with PVH and DWMH scores, but hsCRP did not. By multinomial logistic analysis, IL-6 was significantly related to DWMH score, independent of age and systolic blood pressure.

Conclusion: IL-6 is presumably an important marker of leukoaraiosis, as is the case with silent cerebral infarction. **Geriatr Gerontol Int 2011; 11: ••–••.**

Keywords: interleukin-6, leukoaraiosis, white matter hyperintensity.

Introduction

Leukoaraiosis, an isointense lesion on T_1-weighted images and hyperintense lesion on T_2-weighted images of magnetic resonance imaging (MRI), is considered to be a type of ischemic change in the brain on the basis of decreased blood flow in the area of leukoaraiosis.[1] In addition, leukoaraiosis is likely to have a relationship with vascular risk factors such as hypertension and diabetes.[2] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of the geriatric syndromes such as dementia, gait disturbance and functional disability.[3–5] Hence, leukoaraiosis is regarded as a significant brain lesion linking vascular risk factors and the occurrence of geriatric syndromes. Previous research on leukoaraiosis showed that women tended to have more white matter lesions than men,[6] and progression of deep white matter hyperintensity (DWMH) lesion was grater in women than men.[7] Furthermore, Gouw *et al.* showed that leukoaraiosis tended to develop greater in women than men and lacunes were vice versa.[8] Recently, many studies have focused on the relationships between brain ischemia and inflammation. Above all, Hoshi *et al.* demonstrated that serum high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 levels correlated with silent brain infarction.[9] They suggested an involvement of inflammation in cerebral infarction. However, few studies have examined the relationships between inflammatory markers and other cerebral ischemic changes such as leukoaraiosis.Therefore, we investigated whether serum levels of hsCRP and IL-6 have a relationship with leukoaraiosis in elderly women.

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Methods

Patients

One hundred and thirty-seven women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were included in this study. This study was approved by the Ethics Committee of Kyorin University School of Medicine. Accordingly, written informed consent was obtained from all patients.

MRI

Magnetic resonance imaging (MRI) was performed on 1.5-T scanners (Toshiba Medical Systems, Tochigi, Japan). T_1-weighted images (repetition time [TR] = 496 msec, echo time [TE] = 12 msec), T_2-weighted images (TR = 4280 msec, TE = 105 msec) and fluid attenuated inversion recovery-weighted images (TR = 8000 msec, TE = 105 msec, 5 mm slice thickness) were obtained in the axial planes.

Periventricular hyperintensity and DWMH Score

Leukoaraiosis was classified as periventricular hyperintensity (PVH) adjacent to the lateral ventricle, and DWMH located in the deep white matter apart from the lateral ventricles. PVH was evaluated in six regions in three slices. Each region was rated as five grades (0–4) according to the systematic quantification method developed by Junque *et al.*[3] The sum of all grades in the six regions was defined as the PVH score (range 0–40).[4] DWMH was evaluated in the frontal, temporal, parietal and occipital lobes and in the basal ganglia in both hemispheres. Each lesion was rated as three grades according to the diameter, as described by de Groot *et al.*[5] The sum of all grades in five regions in both hemispheres was defined as the DWMH score.[4]

Laboratory tests

Blood samples were obtained in the morning after an overnight fast. Serum levels of hsCRP and IL-6 were measured using nephelometry and enzyme-linked immunosorbent assay, respectively. The intra-assay coefficients of variation for the measurements of hsCRP and IL-6 were 1.3% and 2.9%, respectively.

Statistical analysis

Because the distribution of hsCRP and IL-6 levels appeared to be left-skewed, they were normalized by logarithmic transformation. We used Spearman's ρ to investigate correlations between parameters and PVH score or DWMH score. Also, to test independently the effect of the inflammatory markers associated with the severity of leukoaraiosis, multinomial logistic regression analysis was performed with the grade of PVH (tertiles of PVH score) or DWMH (tertiles of DWMH score) as the dependent variable; and hsCRP or IL-6, together with age and systolic blood pressure (SBP) as independent variables. $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS ver. 17.0.

Results

The characteristics of the study subjects are shown in Table 1. They were non-obese normolipidemic elderly persons, however, SBP was elevated. The distribution of PVH score and DWMH score of these subjects were 1–24 and 0–209, respectively. In Spearman's correlation coefficient, IL-6 correlated with PVH score ($\rho = 0.340$, $P \leq 0.05$) and DWMH score ($\rho = 0.299$, $P \leq 0.05$) (Fig. 1), whereas hsCRP showed no relation to PVH score or DWMH score (Table 2). PVH score and DWMH score also correlated with age and SBP. When log IL-6 and log hsCRP were grouped by tertile (see legend to Fig. 2), it was found that the average PVH score and DWMH score were higher in the highest tertile of IL-6 level than in the lowest tertile according to the Kruskal–Wallis test (Fig. 2a,b). On the other hand, this increment was not found in hsCRP (Fig. 2c,d).

Because leukoaraiosis can be observed on MRI even in normal elderly persons,[10] and hypertension is known to be a risk factor for leukoaraiosis,[11] we performed multinomial logistic regression analysis using PVH or DWMH severity (tertiles of PVH and DWMH score) as the dependent variable, and age, SBP and inflammatory

Table 1 Clinical characteristics of study subjects (women, $n = 137$)

Age (years)	76 ± 7
BMI (kg/m^2)	20.8 ± 3.3
SBP (mmHg)	142 ± 26
DBP (mmHg)	80 ± 14
PVH score (points)	8.2 ± 4.0
DWMH score (points)	61.4 ± 51.0
Total cholesterol (mmol/L)	5.38 ± 0.91
HDL cholesterol (mmol/L)	1.50 ± 0.36
LDL cholesterol (mmol/L)	3.23 ± 0.65
Triglyceride (mmol/L)	1.08 ± 0.46
Log IL-6 (ng/L)	0.35 ± 0.46
Log hsCRP (μg/L)	2.58 ± 0.58

All parameters are expressed as mean ± standard deviation. IL-6 and CRP are shown as log transformed. BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; PVH, periventricular hyperintensity; SBP, systolic blood pressure.

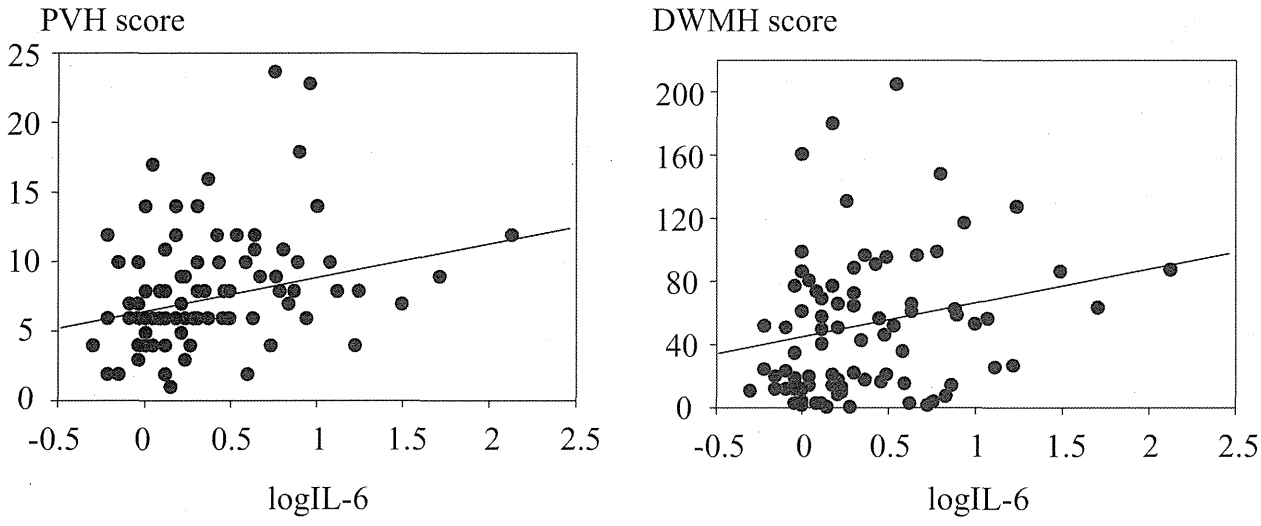

Figure 1 Relations between periventricular hyperintensity (PVH) score and log interleukin (IL)-6 (left panel; $\rho = 0.340$, $P \leq 0.05$, $n = 137$), and deep white matter hyperintensity (DWMH) score and log IL-6 (right panel; $\rho = 0.299$, $P \leq 0.05$, $n = 137$).

Table 2 Spearman's correlation coefficient between leukoaraiosis and parameters

	PVH score		DWMH score	
	ρ	*P*	ρ	*P*
Age	0.411	<0.001	0.271	0.002
BMI	−0.156	0.085	−0.124	0.179
SBP	0.215	0.014	0.232	0.009
Total cholesterol	−0.128	0.192	−0.149	0.134
HDL cholesterol	−0.053	0.595	−0.205	0.041
LDL cholesterol	−0.093	0.349	−0.025	0.802
Triglyceride	−0.014	0.885	0.080	0.421
Smoke	0.337	0.005	0.443	0.000
Log IL-6	0.340	0.002	0.299	0.006
Log hsCRP	−0.018	0.867	0.019	0.855

BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; PVH, periventricular hyperintensity; SBP, systolic blood pressure.

markers as independent variables. As shown in Table 3, it was confirmed that the level of IL-6 was significantly associated with the progression of PVH grade (from lowest to middle and middle to highest) and DWMH score (from middle to highest). However, this trend was not found in hsCRP.

Discussion

In this study, we showed relationships between IL-6 and PVH score and IL-6 and DWMH score. It is assumed that IL-6 has an association with cerebral ischemic changes such as leukoaraiosis as well as silent brain infarction.[9] Additionally, PVH and DWMH were correlated with IL-6, but not with hsCRP. With respect to this point, Schmidt *et al.* suggested that CRP is a marker of active carotid atherosclerosis, but not of a small vessel disease-related brain lesion.[12] On the other hand, it is envisaged that elevated hsCRP levels generally reflect large vessel atherosclerosis. Because leukoaraiosis is regarded as one of the brain changes caused by small vessel disease, our results support the idea of Schmidt *et al.*

Interleukin-6 is one of the principal acute-phase reactants, playing a significant role in the activation of the coagulation–fibrinolysis system. On the other hand, leukoaraiosis has been associated with a hypercoagulable condition. Endothelium-derived adhesion molecules have been reported to be elevated in patients with great leukoaraiosis or lacunar infarcts. Leukocyte-mediated injury of the small vessels and ensuing upregulation of endothelial adhesion molecules are implicated in the pathogenesis of leukoaraiosis.[13]

The Rotterdam Scan Study showed that higher hsCRP levels were associated with presence and progression of leukoaraiosis after adjustment for cardiovascular risk factors and carotid atherosclerosis.[14] The subjects in the Rotterdam Scan Study were a population-based cohort ($n = 1033$), while the subjects in the present study were outpatients in the memory clinic ($n = 137$). In this respect, the difference in characteristics and numbers of the subjects may have given rise to the different results in terms of hsCRP in the present study and the Rotterdam Scan Study.

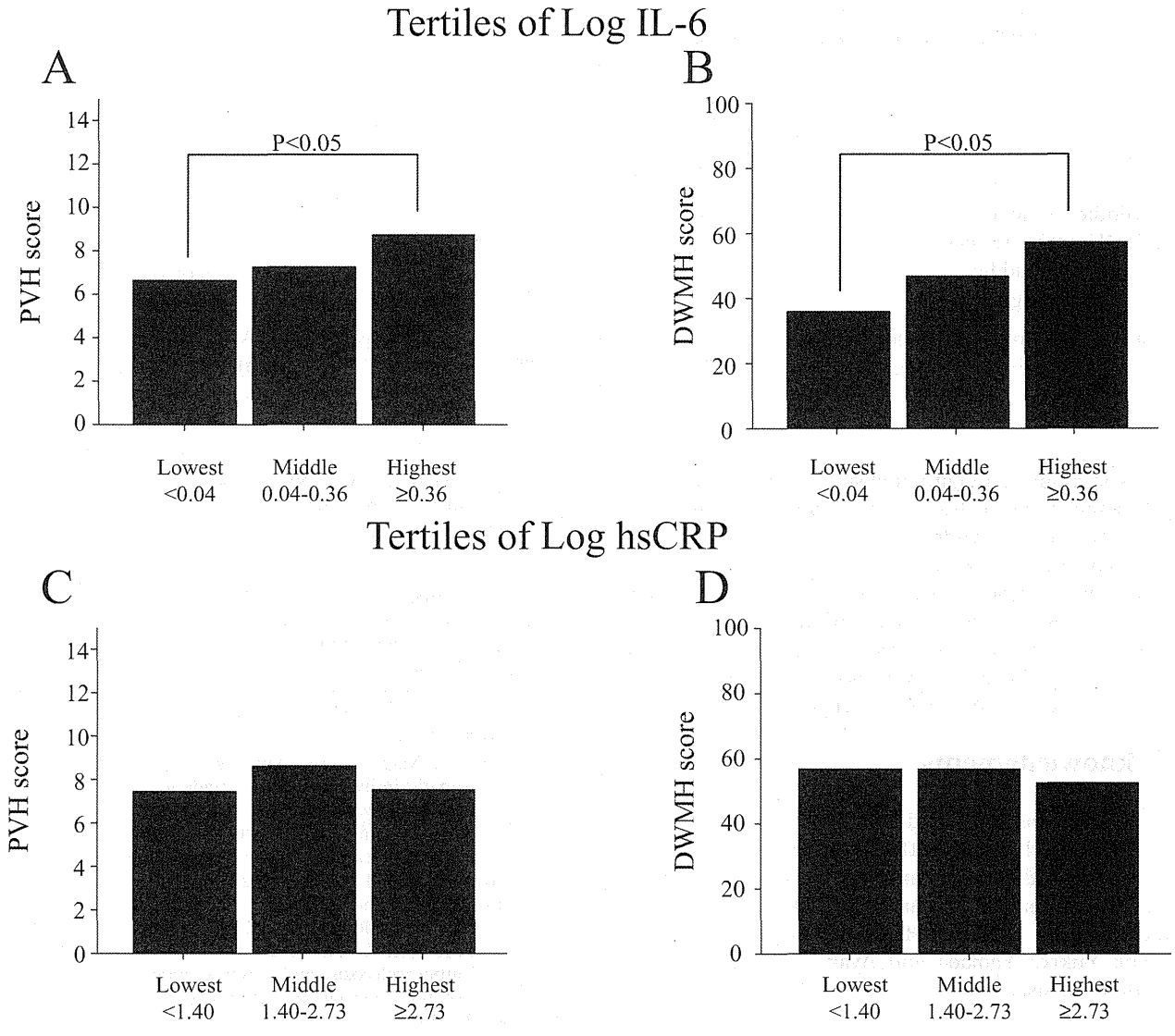

Figure 2 Average of periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score by tertile of interleukin (IL)-6 (a,b) and tertile of high-sensitivity C-reactive protein (hsCRP) (c,d). Log IL-6 tertile; lowest, <0.04 pg/mL, $n = 55$, 73.4 ± 7 1 years old (y/o); middle, 0.04–0.36 pg/mL, $n = 38$, 76.9 ± 6.8 y/o; highest, ≥0.36 pg/mL, $n = 44$, 79.5 ± 5.3 y/o. Log hsCRP; lowest, <1.40 ng/mL, $n = 44$, 73.9 ± 7.0 y/o; middle, 1.40–2.73 ng/mL, $n = 46$, 77.6 ± 7.1 y/o; highest, ≥2 73 ng/mL, $n = 41$, 77.8 ± 6.3 y/o.

In the Framingham Heart Study, no association was found between hsCRP and leukoaraiosis on MRI.[15] In the Cardiovascular Health Study, hsCRP level was modestly associated with semi-quantified leukoaraiosis volume, but the effect attenuated after excluding prevalent cerebrovascular and coronary disease cases.[13] In addition, Wright *et al.* was not able to find an association between hsCRP and leukoaraiosis volume.[16] Together, the relationships between leukoaraiosis and hsCRP varied depending upon different reports. This may come from the difference in study subjects and analytical methods. Further investigation is necessary to hold more definite opinion about which inflammatory biomarker represents the presence and development of leukoaraiosis.

Several lines of evidence suggest a relationship between IL-6 and symptoms of the geriatric syndromes, unique features of common health problems associated with poor morbidity in elderly people, such as dementia,[17] functional disability[18] and frailty.[19] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of geriatric syndromes such as dementia, falls, gait disturbance and functional disability.[3–5] Therefore, IL-6 may be an important biomarker linking the severity of leukoaraiosis to the geriatric syndromes. Because the present study is

Table 3 Associations between inflammation markers and the severity of leukoaraiosis according to tertiles (PVH score or DWMH score) adjusting for age and systolic blood pressure (logistic regression analysis)

	Log hsCRP, μg/L Odds ratio (95% CI)	Log IL-6, ng/L Odds ratio (95% CI)
PVH grade (tertiles)		
Lowest to middle	1.84 (0.78–4.31)	5.80 (1.43–23.60)
Middle to highest	0.39 (0.12–1.32)	4.39 (1.02–18.85)
DWMH grade (tertiles)		
Lowest to middle	0.81 (0.333–1.99)	3.18 (0.78–12.95)
Middle to highest	1.25 (0.48–3.29)	7.85 (1.69–36.38)

Grade of leukoaraiosis according to tertiles of PVH score or DWMH score. CI, confidence interval; DWMH, deep white matter hyperintensity; IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein; PVH, periventricular hyperintensity.

cross-sectional, a longitudinal study would corroborate the associations of IL-6 with leukoaraiosis, and IL-6 with the geriatric syndromes.

In conclusion, we demonstrated that IL-6 level is significantly associated with the severity of PVH and DWMH lesions. The results of the present study, together with the previous studies, suggest that IL-6 is an important marker of the progression of cerebral ischemic disease, linking to the presence of geriatric syndromes.

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COMMISSION REPORT

Survey on geriatricians' experiences of adverse drug reactions caused by potentially inappropriate medications: Commission report of the Japan Geriatrics Society

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Aim: The Japan Geriatrics Society (JGS) developed the guidelines for medical treatment and its safety in the elderly and the list of potentially inappropriate medication use, a Japanese version of the Beers list, in 2005. The JGS working group in collaboration with the Japan Broadcasting Corporation conducted the survey to geriatricians to investigate their experiences of adverse drug reactions (ADR) caused by potentially inappropriate medications.

Methods: In September 2008, the survey mails were sent to all the JGS certified geriatricians ($n = 1492$). The questionnaire consisted of 1 year of experiences of ADR of any type, past experiences of ADR by the use of antipsychotic benzamides, hypnotic benzodiazepines, digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and additional drugs, and their attitudes to reduce the dose/number of drugs for the prevention of ADR.

Results: A total of 425 geriatricians responded (response rate 29%). Seventy-two percent experienced ADR within 1 year. Past experiences of ADR were reported by 79% for antipsychotic benzamides, 86% for hypnotic benzodiazepines, 70% for digoxin and 37% for vitamin D_3. Free responses included frequent ADR by non-steroidal anti-inflammatory, antihypertensive, antiplatelet, anti-arrhythmic, antidiabetic and antidepressant drugs. Reduction of drugs for ADR prevention was attempted by 93%.

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Conclusion: This survey showed that most geriatricians experience ADR and take preventive measures for ADR. The results can be used for education and the development of new guidelines. **Geriatr Gerontol Int 2011; 11: 3–7.**

Keywords: adverse drug reactions, Beers list, geriatrician, polypharmacy, side-effect.

Introduction

Adverse drug reactions (ADR) are more frequent and severe in the elderly than in young adults. A recent systematic review[1] of prospective observational studies reported that 10.7% of hospital admissions were associated with ADR in elderly patients, while 6.3% were so in young adults. Surveys performed in acute care hospitals in Japan also showed that inpatients aged 70 years or older were 1.5-fold more likely to develop ADR than those under 60 years of age,[2] and that the ADR incidence among elderly inpatients was 6–15%.[3] It has been reported from Western countries that ADR occur in more than 10% of outpatients or nursing home residents.[4]

Although many factors relate to the high ADR incidence in the elderly, overdoses resulting from age-related changes of pharmacokinetics/pharmacodynamics and polypharmacy may be of critical importance.[2–4] Because the evidence for the elderly is limited, practical guidelines to medical treatment and its safety are required in the field of geriatric medicine.

The Japan Geriatrics Society (JGS) has conducted educational activities through scientific sessions and official journals to reduce ADR. As part of activities, the ad hoc committee "Working group on guidelines for medical treatment and its safety in the elderly" was set up in 2003, and the JGS guidelines for medical treatment and its safety in the elderly were published in 2005.[5] In the guidelines, the list of medications that should be prescribed with special attention to elderly patients was reported and was put on the JGS website. This list, a Japanese version of the Beers list,[6,7] consists of 45 drugs or drug classes that may be harmful or less efficient, thus potentially inappropriate for elderly patients, and can be applied to reduce ADR and polypharmacy in clinical settings of geriatric medicine and nursing-care facilities.[5]

Although the mass media expressed an interest in these activities, the JGS should increasingly accumulate the evidence and make a proposal on pharmacotherapy of the elderly for public education. For this purpose, the JGS working group in collaboration with the Japan Broadcasting Corporation (NHK) conducted the survey to JGS certified geriatricians to investigate their experiences of ADR caused by potentially inappropriate medications. This commission report of the working group shows the survey results.

Methods

Mailing and collection of the questionnaire

In September 2008, the questionnaire was mailed by the NHK to all the JGS certified geriatricians (n = 1492) who appeared on the JGS website. In the cover letter, a brief introduction including the background and aim of the survey was described, followed by the statement that this survey was carried out in collaboration with the NHK and the JGS working group. The JGS version of the Beers list (Table 1 and detailed explanation) was included in the mail for options of additional drugs. The responder was asked to return the questionnaire to the NHK by fax without his/her name.

Questionnaire item

The questionnaire consisted of 1-year experiences of ADR of any type (yes/no question), past experiences (frequent, occasional or none) of ADR by the use of antipsychotic benzamides (sulpiride, sultopride), hypnotic benzodiazepines (flurazepam, haloxazolam, quazepam, triaxolam), digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and free additions, and their attitudes to reduce the dose/number of drugs for the prevention of ADR (yes/no question). In addition, free comments on the problems and approaches related to pharmacotherapy in the elderly were asked. The above four classes of drugs were chosen from the JGS version of the Beers list (Table 1) because these drugs were considered frequently prescribed to elderly patients.

Statistical analysis

The data are shown as the number and the percent of subjects. The χ^2-test was performed to analyze the associations between ADR experiences.

Results

A total of 425 geriatricians responded, resulting in a response rate of 28.5%. The response rate would have been 29.1% if the 30 subjects to whom the mails were not successfully delivered were excluded.

The summary of the results is shown in Table 2. Seventy percent of the geriatricians reported

Table 1 List of medications that should be prescribed with special attention to elderly patients (JGS version of the Beers list)

Class	Drug (generic name)
Antihypertensive (central sympathetic blocking agents)	Methyldopa
	Clonidine
Antihypertensive (rauwolfia)	Reserpine
Antihypertensive (short-acting calcium channel blockers)	Nifedipine
Vasodilator	Isoxsuprine
Cardiac glycoside	Digoxin (≥0.15 mg/day)
Anti-arrhythmic	Disopyramide
	Amiodarone
Antiplatelet	Ticlopidine
Hypnotic (barbiturates)	Pentobarbital
	Amobarbital
	Barbital
	Chlorpromazine, promethazine, phenobarbital
Hypnotic (benzodiazepines)	Flurazepam
	Haloxazolam
	Quazepam
	Triaxolam
Anxiolytic (benzodiazepines)	Chlordiazepoxide, diazepam
Antidepressants	Tricyclic (amitriptyline, imipramine, clomipramine)
	Maprotiline
Antipsychotic (phenothiazines)	Thioridazine, chlorpromazine, levomepromazine
Antipsychotic (butyrophenones)	Haloperidol, timiperone, bromperidol
Antipsychotic (benzamides)	Sulpride, sultopride
Anti-parkinsonian	Trihexyphenidyl
Antiepileptic	Phenobarbital
	Phenytoin
Narcotic analgesic	Pentazocine
Non-steroidal anti-inflammatory	Indometacin
	Diclofenac sodium, naproxen, piroxicam
Irritant laxative	Caster oil
Skeletal muscle relaxant	Methocarbamol
Soothing muscle relaxant	Oxybutynin
Intestinal antispasmodic	Butylscopolamine
	Propantheline
Anti-emetic	Metoclopramide
	Domperidone
Androgen	Methyltestosterone
Estrogen	Estrogens
Thyroid hormone	Dried thyroid
Hypoglycemics (1st-generation sulfonyl urea)	Chlorpropamide
	Acetohexamide
Hypoglycemics (biguanides)	Metformin
	Buformine
Iron	Fe (≥300 mg/day)
Vitamin D	Alfacalcidol (≥1.0 μg/day)

Doses in the parentheses are applicable for digoxin, Fe and alfacalcidol. This list with detailed explanation such as trade names and alternative drugs was enclosed in the questionnaire.

experiences of ADR within a year, even though non-responders ($n = 7$) were included in those without experience. Regarding past experiences of ADR, approximately a quarter of the geriatricians reported frequent ADR experiences by antipsychotic benzamides and hypnotic benzodiazepines. Seventy to eighty percent frequently or occasionally experienced ADR by these two classes of drugs and by digoxin, and

Table 2 Geriatricians' experiences of adverse drug reactions (ADR) and their attitudes to reduce drugs for the prevention of ADR ($n = 425$)

1. One-year experiences of ADR of any type ($n = 418$)			71.5%
2. Past experiences of ADR by use of the following drugs			
	Frequent	Occasional	Frequent + Occasional
(i) Antipsychotic benzamides ($n = 381$) (sulpiride, sultopride)	93 (24.4%)	207 (54.3%)	300 (78.7%)
(ii) Hypnotic benzodiazepines ($n = 386$) (flurazepam, haloxazolam, quazepam, triaxolam)	93 (24.1%)	241 (62.4%)	334 (86.5%)
(iii) Digoxin (≥0.15 mg/day) ($n = 382$)	33 8.6%)	234 61.3%)	267 69.9%)
(iv) Vitamin D_3 ($n = 373$) (alfacalcidol ≥1.0 μg/day)	14 (3.7%)	125 (33.5%)	139 (37.3%)
3. Past experiences of ADR (free responses; $n = 240$)			
Class of drugs	Frequent	Occasional	Frequent + Occasional
(i) Non-steroidal anti-inflammatory	60	34	94
(ii) Antihypertensive	19	27	46
(iii) Antiplatelet	17	21	38
(iv) Antidiabetic	19	15	34
(v) Anti-arrhythmic	13	17	30
(vi) Antidepressant	15	10	25
(vii) Anti-Parkinson	9	12	21
(viii) Warfarin	6	7	13
4. Reduction of the dose/number of drugs for the prevention of ADR ($n = 417$)			93.0%

Data in the parentheses indicate the number of responses to each questionnaire item. Each value indicates the number of cases and the percentage. Free responses to past experiences of ADR show the classes of drugs with more than 10 cases.

nearly 40% by vitamin D_3. Interestingly, the χ-square test showed that 1-year experiences of ADR of any type were significantly associated with ADR experiences by each of the four classes of drugs (data not shown), suggesting that some geriatricians frequently experience ADR of various types, and others do not. Free responses ($n = 240$) included common ADR by non-steroidal anti-inflammatory drugs; 25% of the responders reported frequent ADR and 39% reported frequent or occasional ADR. More than 90% of the geriatricians reported that they reduced the dose and number of drugs for the prevention of ADR.

Free comments on the problems and approaches related to pharmacotherapy in the elderly were summarized as follows: (i) lack of understanding about drug metabolism and ADR by doctors and patients, and need for their education; (ii) training of geriatricians who understand medical treatment in the elderly and are able to align prescriptions in a comprehensive manner; (iii) medication errors and a lack of prescription information derived from multi-consultations are problematic, thus a medication management and interdisciplinary collaboration system must be established; and (iv) because a medical fee system in which an easy medication is profitable rather than attentive listening may cause polypharmacy, guidelines and a new medical system to block this pathway should be created.

Discussion

In this questionnaire survey, although the mails were sent from the NHK, approximately 30% of the JGS certified geriatricians responded, expressing their high interest in medical treatment in the elderly. Seventy percent of them reported ADR experiences within a year, while more than 90% attempted to reduce the dose and number of drugs for the prevention of ADR.

Although most geriatricians reported ADR experiences, the prevalence should be carefully interpreted. First, sampling bias and overestimation are possible, because geriatricians who experienced more ADR and were conscious of ADR might have responded more actively. Second, there is a problem in reliability of ADR, because judgments of ADR including causality and severity may vary between geriatricians, and ADR experiences were dependent on memory rather than records. The questionnaire item concerning the frequency of ADR for individual drugs was also ambiguous. Because the frequency of ADR is related to the frequency of prescriptions, free responses included many common medications for elderly patients, such as non-steroidal anti-inflammatory drugs and antihypertensive drugs.

As described above, this survey was not designed to determine the incidence of ADR per patient or drug. The aim was to accumulate the opinions of JGS certified

geriatricians about ADR and pharmacotherapy, thus the results may have reflected their awareness of the issues. Taken together, it is reasonable that antipsychotic benzamides, hypnotic benzodiazepines and digoxin (≥0.15 mg/day) are included in the JGS version of the Beers list, because 70–80% of geriatricians reported ADR experiences by these drugs. This questionnaire also asked about ADR by vitamin D, which was not included in the lists of potentially inappropriate medications in Western countries.[6–8] Vitamin D_3 (alfacalcidol ≥1.0 μg/day) was included in the JGS list, because this class of drugs are frequently and carelessly used at high doses with calcium preparations for treatment of osteoporosis, leading to hypercalcemia. The result that 37% experienced vitamin D-related ADR justified the inclusion of vitamin D in the list. Regarding additional classes of drugs with more than 10 responses, some drugs of all classes but warfarin were also included in the JGS list. Each drug with many responses should be considered for inclusion when the list is updated.

It is not surprising but important that 93% of geriatricians reduced drugs for the prevention of ADR. This may be a result of educational activities by the JGS and may represent advanced performance of JGS certified geriatricians. Educational efforts and public information to reduce ADR should be strengthened.

The data are not available about what percentage of patients received interventions for drug reduction. We reanalyzed the data of the ADR survey conducted in five university hospitals,[3] and found that the number of drugs were decreased in 20% of inpatients ($n = 1002$) during hospital stay, although the reason for drug reduction is unknown. The investigation of five long-term care facilities[9] showed that one or more drugs were discontinued after admission in 40% of 581 patients on medications. It is noteworthy that the numbers of drugs included in the 1997 version of the Beers list[6] were decreased by 33% (from 61 to 41 cases) in this investigation, even though these drugs were not selectively discontinued. In the future, prospective studies to survey the frequency of drug reduction per patient for ADR prevention, and interventional studies, preferably randomized controlled trials, to investigate the efficacy of drug review/reduction using the JGS version of the Beers list needs to be performed.

Finally, free comments should be appreciated. Various problems and proposals raised from clinical practice are reasonable and were summarized as described in the results section. Other comments included the issue of drug dependency or fear of some patients, effectiveness-biased advertisements by pharmaceutical companies and disease-specific guidelines neglecting the individual difference, leading to the high ADR incidence and inappropriate medication management in elderly patients. Based on the results and comments obtained from this survey, the JGS and geriatricians should promote researches and accumulate the evidence concerning pharmacotherapy in the elderly to develop new guidelines and advance educational activities.

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COMMENTARY

Strict *vs.* mild blood pressure control in the elderly

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Elderly hypertensive patients, particularly those aged 75 years or above, should be carefully treated because they are at higher risk for both cardiovascular and adverse drug events than younger patients. A number of trials showed the efficacy of lowering systolic blood pressure (SBP) to some extent in the elderly with SBP > 160 mm Hg irrespective of drug classes. Recently, the Hypertension in the Very Elderly Trial[1] demonstrated the benefits of antihypertensive treatment even in patients over the age of 80 years with SBP ⩾160 mm Hg. In this study, the target SBP was <150 mm Hg with the achieved SBP of 144 mm Hg after the mean follow-up period of 2 years. These results rationalize to consider that SBP should be maintained below 150 mm Hg in elderly patients including those over 75 years old.

It is still controversial whether SBP should be lowered below 140 mm Hg in elderly patients, although epidemiological studies and the meta-analysis of 147 randomized trials[2] suggest a proportional reduction in cardiovascular events according to BP level. In fact, no previous trials have achieved SBP <140 mm Hg. Conversely, excessive BP lowering in the elderly may cause adverse reactions, such as light-headedness and falls, and has been associated with the J-curve phenomenon.[3]

The Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS) was the first study that was specially designed to compare the strict (<140 mm Hg) with the mild (140–159 mm Hg) target of SBP for 2 years in the elderly aged 65–85 years. Principal results of JATOS by intention-to-treat analysis revealed that the outcomes were similar between the strict and mild treatment groups.[4] However, a large amount of subjects failed to achieve the target SBP, resulting in a weak statistical power of JATOS.

In this issue of *Hypertension Research*, Rakugi *et al.*[5] reported a per-protocol analysis of JATOS to evaluate the outcomes among the target SBP-achieved subjects. In JATOS, 54% (1192 of 2212 subjects) in the strict treatment group and 69% (1531 of 2206 subjects) in the mild treatment group achieved their target SBPs by use of efonidipine, a long-acting calcium antagonist, as the first-line drug. Although average SBP and DBP were different by 14.3 and 4.3 mm Hg, respectively, the incidence of the primary end points, a composite of cardiovascular disease and renal failure, was similar between the two groups. There was no difference in each of end point components or the incidence of adverse events between the strict target-achieved group and the mild target-achieved group.

These results are consistent with the principal intention-to-treat analysis of JATOS[4] and with the recently published Valsartan in Elderly Isolated Systolic Hypertension (VALISH) Study[6] as well. VALISH study compared the strict (<140 mm Hg) with the moderate (140–149 mm Hg) target of SBP for ⩾2 years in 3260 hypertensive patients aged 70–84 years on valsartan-based treatment. Both intention-to-treat and per-protocol analyses showed that a composite of end points and adverse events were similar between the two groups.[6] By contrast, an Italian study[7] demonstrated that the aggressive target of SBP <130 mm Hg (achieved SBP of 131.9 mm Hg) was superior to the less aggressive target of SBP <140 mm Hg (achieved SBP of 135.6 mm Hg) in non-diabetic hypertensive patients. Reduced end points of this study, however, were left ventricular hypertrophy, coronary revascularization and new-onset atrial fibrillation, most of which were not included in JATOS and VALISH study. In addition, the subjects were younger (⩾55 years of age, mean age of 67 years) than those of JATOS and VALISH, and the event rate was remarkably higher than those of the two Japanese studies. The summary of the three studies is shown in Table 1. These points along with ethnicity may explain the difference in the main results.

Finally, what should we do in clinical practice? Although JATOS targeted SBP <140 *vs.* 140–159 mm Hg, it may be commonly accepted that SBP should be kept <150 mm Hg in the elderly as HYVET showed.[1] This view can be strengthened by the finding of JATOS that target-unachieved patients had worse prognosis than target-achieved patients, despite the study groups.[5] Then, should we reduce SBP below 140 mm Hg or maintain SBP between 140 and 150 mm Hg in elderly patients? At present, no clinical trial has confirmed the benefits of lowering SBP below 140 mm Hg in the elderly. Obviously, however, cardiovascular disease risk is higher in elderly patients than younger ones. Accordingly, one might expect the benefits of reducing SBP <140 mm Hg or lower, which have been shown in younger populations such as Cardio-Sis.[7] Statistical power might have been insufficient in JATOS and VALISH to detect a small difference between the groups, if present. Furthermore, targeting SBP <140 mm Hg was not associated with the increase in adverse events in JATOS and VALISH. Taken together, strict control of SBP <140 mm Hg may be of little clinical importance for the prevention of cardiovascular and renal events in the elderly. This may not be applicable to patients with cardiovascular disease or non-Asian populations. Conversely, it may not be necessary to withdraw antihypertensive therapy once SBP is safely maintained below 140 mm Hg. Pending future trials and meta-analyses determining the optimal SBP level for elderly patients,

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Table 1 Summary of JATOS, VALISH and Cardio-Sis that were specifically designed to compare the target systolic blood pressure (SBP)

Study	*Age range (mean)*	*Inclusion SBP*	*Target SBP*	*Achieved SBP*	*Event rate/1000 patient-years*[a]
JATOS	65–85 (74) years	>160 mm Hg	<140 mm Hg *vs.* 140–159 mm Hg	136 mm Hg *vs.* 146 mm Hg	22.6 *vs.* 22.7
				Per-protocol	Per-protocol
				132 mm Hg *vs.* 147 mm Hg	11.1 *vs.* 13.2
VALISH	70–84 (76) years	⩾160 mm Hg	<140 mm Hg *vs.* 140–149 mm Hg	137 mm Hg *vs.* 142 mm Hg	10.6 *vs.* 12.0
Cardio-Sis	55– (67) years	⩾150 mm Hg	<130 mm Hg *vs.* <140 mm Hg	132 mm Hg *vs.* 136 mm Hg	25.4 *vs.* 51.4

[a]Event rates of composite cardiovascular end points are shown as those of the primary outcomes for JATOS[4,5] and VALISH,[6] and that of the secondary outcome for Cardio-Sis.[7]

we should follow the JSH 2009 guidelines[8] that are compatible with the above-mentioned points.

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Visceral Fat Accumulation and Metabolic Risk Factor Clustering in Older Adults

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OBJECTIVES: To examine the relationship between visceral fat area (VFA) evaluated using computed tomography (CT) scans and the number of metabolic risk factors in older adults.

DESIGN: Cross-sectional study

SETTING: A community clinic in Tokyo, Japan.

PARTICIPANTS: Two hundred eighteen individuals aged 65 and older without impairments in activities of daily living who underwent geriatric health examination (63 men, mean age 74.5 ± 7.1; 155 women, mean age 75.3 ± 6.7).

MEASUREMENTS: VFA was obtained from a cross-sectional image at umbilical level in the supine position using CT scanning. Metabolic syndrome components except waist circumference were measured using the criteria of the International Diabetes Federation.

RESULTS: There was a positive correlation between VFA and number of metabolic risk factors in men and women. Multiple regression analysis demonstrated that only VFA was significantly correlated with number of risk factors in men, whereas age and VFA were significantly correlated in women; body mass index was not correlated with number of metabolic risk factors in men or women. Dyslipidemia and high blood glucose were associated with higher VFA, but high blood pressure was not. There was a negative correlation between VFA and serum adiponectin level and a positive correlation between VFA and homeostasis model assessment of insulin resistance.

CONCLUSION: Visceral fat accumulation is associated with metabolic risk factor clustering even in the elderly population. These results have clinical implications for the management of obesity in older adults. **J Am Geriatr Soc 58:1658–1663, 2010.**

Key words: visceral fat; metabolic syndrome; elderly; BMI

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Several lines of evidence have suggested that visceral fat accumulation is associated with metabolic abnormalities such as high blood pressure (BP), high serum triglycerides, low serum high-density lipoprotein cholesterol (HDL-C), and high blood glucose through insulin resistance and abnormal secretion of adipocytokines.[1–4] Thus, visceral fat obesity has been established as a cause of cardiovascular disease,[5,6] although most of the subjects of studies delineating the relationship between visceral fat accumulation and metabolic abnormalities have consisted of middle-aged adults.[7–9] Therefore, the clinical significance of visceral fat accumulation in older adults is unclear in relation to metabolic abnormalities.

Aging is generally associated with a relative increase in visceral fat mass.[10,11] This is considered to be mainly due to decreased basal metabolism caused by loss of muscle mass, low physical activity, and an increase in carbohydrate intake.

Nevertheless, the prevalence of each metabolic syndrome component increases with age, and accordingly, elderly patients tend to have a higher number of metabolic abnormalities than other adults,[12–14] although it remains to be determined whether metabolic risk factor clustering, which is often observed in older adults, is attributable to visceral fat accumulation. It was assumed that visceral fat might affect this increase in the number of metabolic abnormalities with aging, through insulin resistance and abnormal secretion of adipocytokines. Thus, this study was conducted to clarify the relationship between visceral fat area (VFA) precisely evaluated using abdominal computed tomography (CT) scanning and the number of metabolic risk factors in an elderly sample.

METHODS

Subjects

Subjects who voluntarily participated in geriatric health examination were recruited at a community clinic from September 1 to November 30, 2005. Two hundred seventy-two subjects aged 65 and older who had no impairments in

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activities of daily living and consented to this study were selected.

Medical history and information on medications and smoking status were obtained from all subjects. Body weight, height, and waist circumference were measured, and BP was measured in the sitting position. Body mass index (BMI) was calculated (weight/height^2, kg/m^2). Venous blood samples were collected in the early morning after a 12-hour fast.

People with a history of cancer or gastrointestinal tract surgery; under treatment for endocrine disease or heart failure; taking pioglitazone, metformin, insulin, alpha-blockers, beta-blockers, beta-stimulators, or hormone therapy (including glucocorticoids); and with serum albumin of 3.0 g/dL or lower, serum creatinine greater than 1.5 mg/dL, or blood hemoglobin of 10.0 g/dL or lower were excluded because such factors as abnormal fat metabolism and insulin resistance might have affected them, leaving 218 subjects to be enrolled in this study.

The ethics committee of Abe Clinic approved this study, and written informed consent was obtained from all subjects.

VFA Measurement

VFA was obtained from a cross-sectional image at the umbilical level in the supine position using CT scanning (X Vision Scanner, Toshiba Medical Systems, Tokyo, Japan) and calculated using commercially available software (Fat Scan, N2 System, Osaka, Japan).

Definition of Metabolic Risk Factors

Components of the metabolic syndrome except waist circumference were defined using the criteria of the International Diabetes Federation (IDF): systolic BP (SBP) of 130 mmHg, greater or diastolic BP (DBP) of 85 mmHg or greater, or treatment with antihypertensive drug; fasting serum triglyceride level of 150 mg/dL or greater or treatment with fibrate; serum HDL-C level less than 40 mg/dL in men and less than 50 mg/dL in women; fasting plasma glucose of 100 mg/dL or greater or treatment with an antidiabetic drug.[15]

Homeostasis Model Assessment of Insulin Resistance and Serum Adiponectin Level

Homeostasis model assessment of insulin resistance (HOMA-IR), calculated as fasting insulin level (μIU/mL) × early morning fasting blood glucose level (mg/dL)/405, was evaluated to determine degree of insulin resistance.[16,17] Subjects with diabetes mellitus were excluded from HOMA-IR calculation because of a lack of reliability of their data.

Serum level of adiponectin was measured using an enzyme-linked immunosorbent assay (Human Adiponectin ELISA Kit, Otsuka, Tokyo, Japan).

Statistical Analysis

The subjects were divided into four groups according to individual calculated VFA values in men and women. High BP, high triglycerides, low HDL-C, and high blood glucose were used as metabolic risk factors. The number of metabolic risk factors was calculated as their sum (0–4). Data were expressed as means ± standard deviations or standard errors. The statistical significance of differences was assessed using unpaired *t*-tests for two groups and analysis of variance for three or more groups, followed by the Fisher protected least significant difference test to compare each group. Multiple regression analysis was performed to determine independent factors for the number of metabolic risk factors. The correlation of VFA with HOMA-IR or serum adiponectin level was analyzed using the Pearson correlation coefficient.

$P<.05$ was considered significant. Statistical analysis was performed using Stat View software (version 5.0, SAS Institute, Inc., Cary, NC).

RESULTS

Clinical characteristics of the subjects are depicted in Table 1. Mean VFA in men was significantly higher than in women, although BMI (kg/m^2) was comparable. The prevalence of subjects with high BP was 79.4% in men and 78.7% in women, including 46.8% in men and 43.2% in

Table 1. Clinical Characteristics of Study Population

Characteristic	Men (n = 63)	Women (n = 155)
Age, mean ± SD (range)	74.5 ± 7.1 (65–93)	75.3 ± 6.7 (65–92)
Body mass index, kg/m^2, mean ± SD (range)	22.9 ± 2.8 (15.4–29.4)	22.5 ± 3.3 (15.9–33.4)
Waist circumference, cm, mean ± SD (range)	86.6 ± 8.3 (63.0–104.3)	83.7 ± 11.0 (54.0–111.0)
Visceral fat area, cm^2, mean ± SD (range)	134.8 ± 53.0 (33.2–258.3)	91.2 ± 44.8* (17.5–240.5)
Components of metabolic syndrome, n (%)†		
High blood pressure	50 (79.4)	122 (78.7)
High serum triglycerides	8 (12.7)	15 (9.7)
Low HDL-C	9 (14.3)	33 (21.3)
High blood glucose	21 (33.3)	42 (27.1)
Smoking status, n (%)		
Current	14 (22.6)	8 (5.2)
Former	24 (38.7)	4 (2.6)
Never	24 (38.7)	143 (92.6)
Past history, n (%)		
Cerebral infarction	5 (8.1)	5 (3.2)
Ischemic heart disease	1 (1.6)	6 (3.9)
Medications, n (%)		
Antihypertensive drugs	29 (46.8)	67 (43.2)
Fibrates	0 (0.0)	3 (1.9)
Statins	7 (11.3)	38 (24.5)
Antidiabetic drugs	4 (6.5)	2 (1.3)

* $P<.001$ vs men.

† Components of the metabolic syndrome were diagnosed according to the definition of the International Diabetes Federation: high blood pressure = systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or treatment with antihypertensive drug; high serum triglycerides = fasting serum triglyceride level ≥150 mg/dL or treatment with fibrates; low high-density lipoprotein cholesterol (HDL-C) = serum HDL-C level <40 mg/dL in men and <50 mg/dL in women; high blood glucose = fasting plasma glucose ≥100 mg/dL or treatment with antidiabetic drugs.

SD = standard deviation.

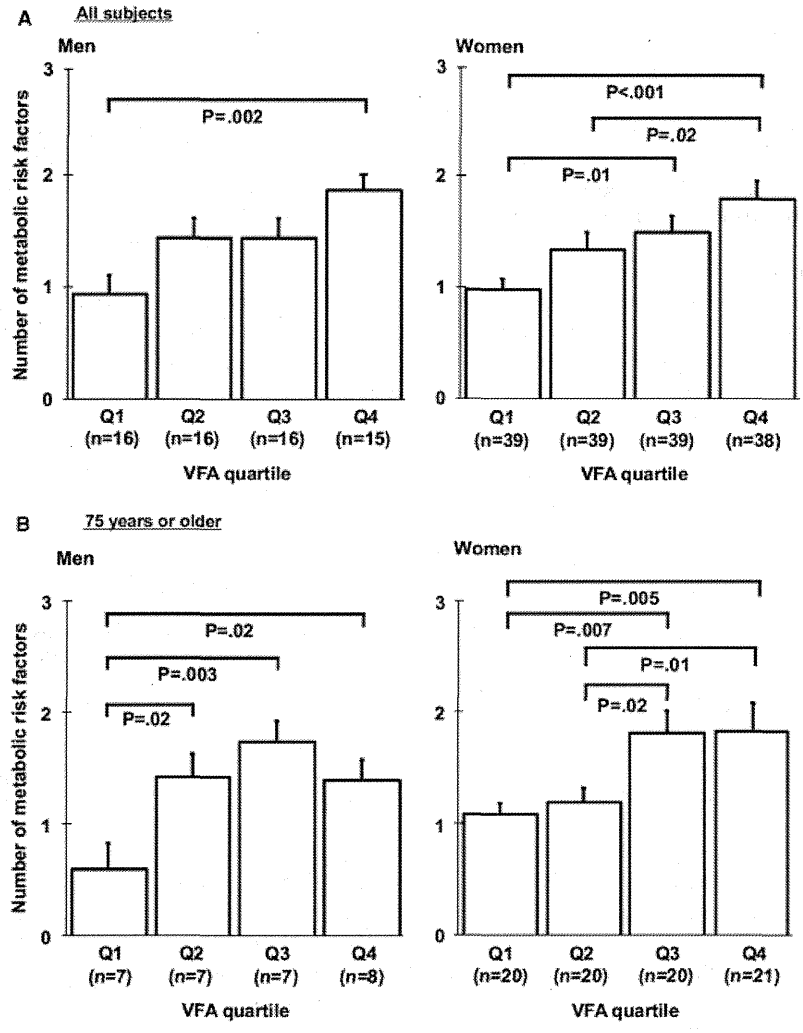

Figure 1. Number of metabolic risk factors according to quartile (Q) of visceral fat area (VFA) in all subjects (A) and subjects aged 75 and older (B). Metabolic risk factors include high blood pressure, high serum triglycerides, low serum high-density lipoprotein cholesterol, and high blood glucose. Data are expressed as means ± standard errors.

women receiving antihypertensive treatment. The prevalence of subjects who had never smoked was markedly higher in women (92.6%) than in men (38.7%).

Figure 1A shows the relationship between VFA and number of metabolic risk factors. The number of risk factors was greater with larger VFA values in men and women. This positive relationship was also observed in subjects aged 75 and older, especially in women (Figure 1B).

Next, multiple regression analysis was performed to detect independent factors for number of metabolic risk factors, using age, VFA, and BMI as independent variables. In men, VFA and in women, VFA and age were positively correlated with number of risk factors (Table 2). BMI was not correlated with number of metabolic risk factors in men or women. Moreover, when waist circumference was added in this multiple regression analysis, VFA was significantly correlated with number of metabolic risk factors in men and women ($P = .02$; data not shown). Waist circumference was not correlated with number of metabolic risk factors in men or women ($P = .85$ in men, $P = .08$ in women; data not shown).

Table 2. Multiple Regression Analysis with Number of Metabolic Risk Factors

Independent Variable	Coefficient (Standard Error)	Standardized Coefficient	*P*-Value
Men*			
Age	0.012 (0.014)	0.10	.39
VFA	0.006 (0.002)	0.39	.01
BMI	0.055 (0.047)	0.18	.25
Women†			
Age	0.027 (0.011)	0.19	.01
VFA	0.007 (0.002)	0.33	.001
BMI	0.010 (0.028)	0.04	.72

*Correlation coefficient (R) = 0.515, coefficient of determination (R^2) = 0.265, $P < .001$.

†$R = 0.393$, $R^2 = 0.154$, $P < .001$.

VFA = visceral fat area; BMI = body mass index.

Metabolic risk factors indicate components of the metabolic syndrome except abdominal obesity according to the definition of the International Diabetes Federation.

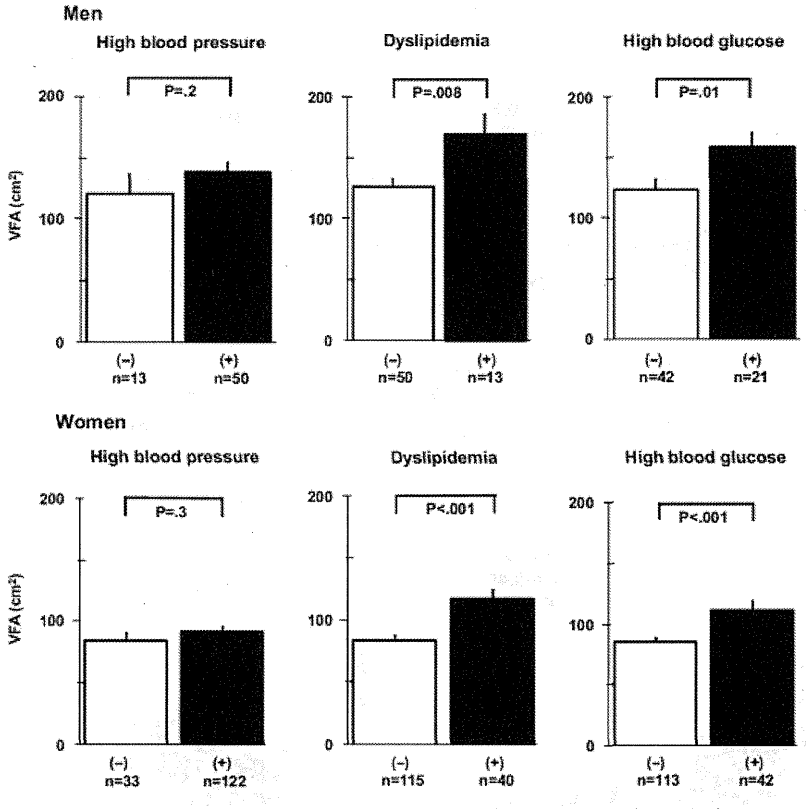

Figure 2. Visceral fat area (VFA) in the absence (–) and presence (+) of each metabolic risk factor. Dyslipidemia includes high triglycerides, low high-density lipoprotein cholesterol, or both. Data are expressed as means ± standard errors.

The relationship between each metabolic risk factor and VFA in elderly subjects was examined. As shown in Figure 2, men and women with dyslipidemia (high triglycerides, low HDL-C, or both) had a significantly greater mean VFA than those without dyslipidemia. Similar results were observed in subjects with and without high blood glucose, although there was no significant difference in VFA between subjects with and without high BP. Changing the cutoff values to 140/90 mmHg from 130/85 mmHg in this analysis made no difference in the results ($P = .25$ in men, $P = .41$ in women; data not shown). A simple regression analysis between VFA and SBP or DBP in subjects not receiving antihypertensive treatment showed no correlation (SBP: $P = .51$ in men, $P = .72$ in women; DBP: $P = .81$ in men, $P = .11$ in women; data not shown).

Finally, a significant negative correlation was observed between VFA and serum adiponectin and a positive correlation between VFA and HOMA-IR in men and women (Figure 3).

DISCUSSION

VFA is associated with metabolic abnormalities, as previously shown in studies of middle-aged populations.[7–9] This association was still observed after adjustment for age and BMI, suggesting that visceral fat accumulation might be a strong risk factor for the metabolic syndrome even in older adults. This association was observed even in subjects aged 75 and older, and VFA was correlated with components of the metabolic syndrome even in subjects who on average had a normal BMI.

Nevertheless, in multiple regression analysis, BMI was not correlated with number of metabolic risk factors in men or women. These results suggest that, for the evaluation of metabolic abnormalities in older adults, VFA is more useful than BMI because BMI in older adults might reflect not only visceral fat mass, but also lower muscle mass and intercellular fluid associated with aging. Thus, because of a reduction of muscle mass with aging, studies that use only BMI would underestimate the health effect of body fatness. Moreover, even if waist circumference was added in this multiple regression analysis, VFA was significantly correlated with number of metabolic risk factors in men and women, but waist circumference was not, suggesting that VFA rather than waist circumference may strongly predict metabolic abnormalities. Data from the Diabetes Prevention Program Research Group showed that visceral adipose tissue predicted the development of type 2 diabetes mellitus better than BMI or waist circumference, but analyses were not limited to older adults (only 20% were ≥60).[18] Thus, it would be important to assess the value of VFA prospectively in predicting the worsening of metabolic risk factors and age-related diseases (e.g., diabetes mellitus and cardiovascular disease).

A strength of this study is the precise assessment of visceral fat according to CT scanning instead of the generally used waist circumference for assessment of abdominal obesity. In many clinical studies, large waist circumference, representing visceral fat accumulation, has been reported to