



## 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<sub>1</sub>-weighted images and hyperintense lesion on T<sub>2</sub>-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.<sup>1</sup> In addition, leukoaraiosis is likely to have a relationship with vascular risk factors such as hypertension and diabetes.<sup>2</sup> 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.<sup>3-5</sup> 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,<sup>6</sup> and progression of deep white matter hyperintensity (DWMH) lesion was greater in women than men.<sup>7</sup> Furthermore, Gouw *et al.* showed that leukoaraiosis tended to develop greater in women than men and lacunes were vice versa.<sup>8</sup> 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.<sup>9</sup> 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<sub>1</sub>-weighted images (repetition time [TR] = 496 msec, echo time [TE] = 12 msec), T<sub>2</sub>-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.*<sup>3</sup> The sum of all grades in the six regions was defined as the PVH score (range 0–40).<sup>4</sup> 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.*<sup>5</sup> The sum of all grades in five regions in both hemispheres was defined as the DWMH score.<sup>4</sup>

### 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  $\rho$  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

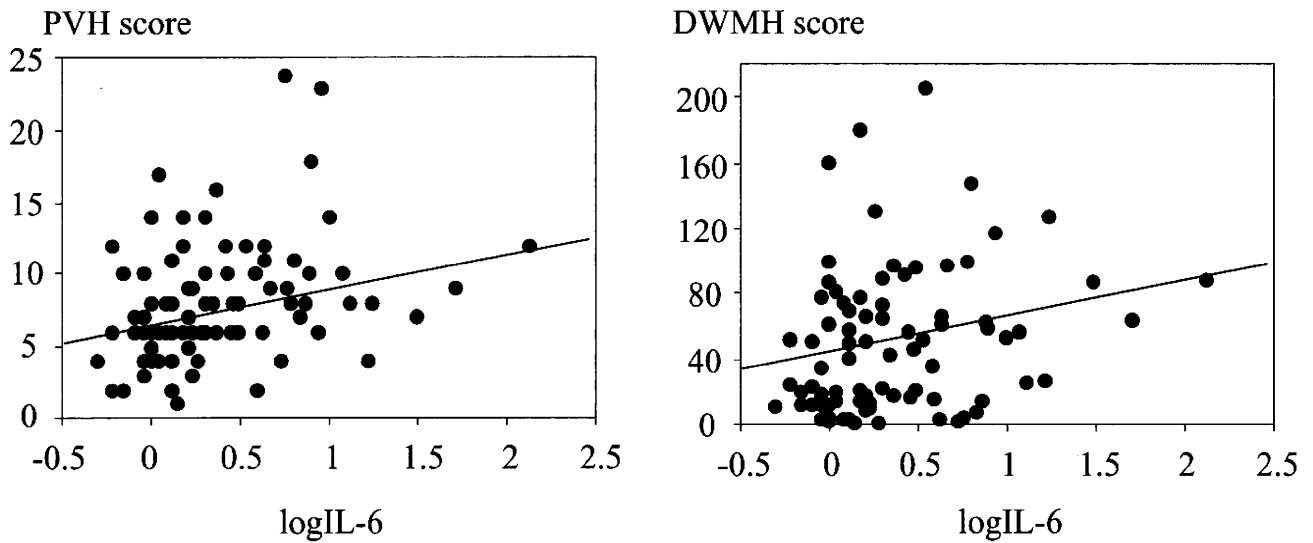
The characteristics of the study subjects are shown in Table 1. They were non-obese normolipidemic elderly persons, however, SBP was elevated. The distribution of PVH score and DWMH score of these subjects were 1–24 and 0–209, respectively. In Spearman's correlation coefficient, IL-6 correlated with 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,<sup>10</sup> and hypertension is known to be a risk factor for leukoaraiosis,<sup>11</sup> 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 <sup>2</sup> )	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	
	$\rho$	$P$	$\rho$	$P$
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.

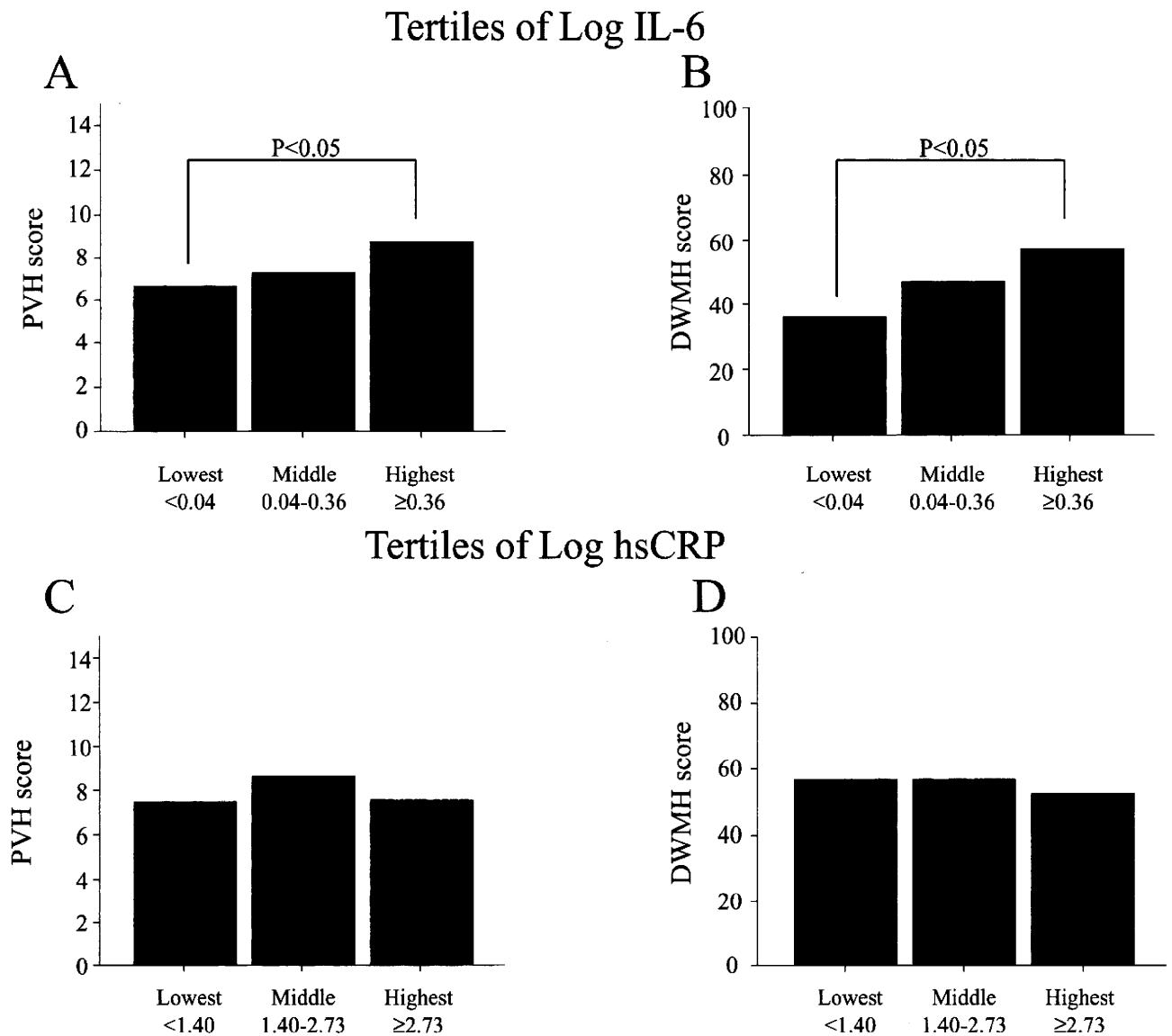
## Discussion

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.<sup>9</sup> 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.<sup>12</sup> 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.<sup>13</sup>

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.<sup>14</sup> 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,  $n = 55$ ,  $73.4 \pm 7.1$  years old (y/o); middle, 0.04–0.36 pg/mL,  $n = 38$ ,  $76.9 \pm 6.8$  y/o; highest,  $\geq 0.36$  pg/mL,  $n = 44$ ,  $79.5 \pm 5.3$  y/o. Log hsCRP; lowest, <1.40 ng/mL,  $n = 44$ ,  $73.9 \pm 7.0$  y/o; middle, 1.40–2.73 ng/mL,  $n = 46$ ,  $77.6 \pm 7.1$  y/o; highest,  $\geq 2.73$  ng/mL,  $n = 41$ ,  $77.8 \pm 6.3$  y/o.

In the Framingham Heart Study, no association was found between hsCRP and leukoaraiosis on MRI.<sup>15</sup> 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.<sup>13</sup> In addition, Wright *et al.* was not able to find an association between hsCRP and leukoaraiosis volume.<sup>16</sup> 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,<sup>17</sup> functional disability<sup>18</sup> and frailty.<sup>19</sup> 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.<sup>3-5</sup> 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.

## Acknowledgments

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## References

- Oishi M, Mochizuki Y. Regional cerebral blood flow and cerebrospinal fluid glutamate in leukoaraiosis. *J Neurol* 1998; **245**: 777–780.
- Munoz DG. Leukoaraiosis and ischemia: beyond the myth. *Stroke* 2006; **37**: 1348–1349.
- Junque C, Pujol J, Vendrell P *et al*. Leuko-araiosis on magnetic resonance imaging and speed of mental processing. *Arch Neurol* 1990; **47**: 151–156.
- Sonohara K, Kozaki K, Akishita M *et al*. White matter lesions as a feature of cognitive impairment, low vitality, and other symptoms of the geriatric syndrome in the elderly. *Geriatr Gerontol Int* 2008; **8**: 93–100.
- de Groot JC, de Leeuw FE, Oudkerk M *et al*. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol* 2000; **47**: 145–151.
- de Leeuw FE, de Groot JC, Achten E *et al*. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry* 2001; **70**: 9–14.
- van den Heuvel DM, Admiraal-Behloul F, ten Dam VH *et al*. Different progression rates for deep white matter hyperintensities in elderly men and women. *Neurology* 2004; **63**: 1699–1701.
- Gouw AA, van der Flier WM, Fazekas F *et al*. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. *Stroke* 2008; **39**: 1414–1420.
- Hoshi T, Kitagawa K, Yamagami H *et al*. Relations of serum high-sensitivity C-reactive protein and interleukin-6 levels with silent brain infarction. *Stroke* 2005; **36**: 768–772.
- Fazekas F. Magnetic resonance signal abnormalities in asymptomatic individuals: their incidence and functional correlates. *Eur Neurol* 1989; **29**: 164–168.
- Basile AM, Pantoni L, Pracucci G *et al*. Age, hypertension, and lacunar stroke are the major determinants of the severity of age-related white matter changes. The LADIS (Leukoaraiosis and Disability in the Elderly) Study. *Cerebrovasc Dis* 2006; **21**: 315–322.
- Schmidt R, Schmidt H, Pichler M *et al*. C-reactive protein, carotid atherosclerosis, and cerebral small-vessel disease: results of the Austrian Stroke Prevention Study. *Stroke* 2006; **37**: 2910–2916.
- Fornage M, Chiang YA, O'Meara ES *et al*. Biomarkers of inflammation and MRI-defined small vessel disease of the brain: the cardiovascular health study. *Stroke* 2008; **39**: 1952–1959.
- van Dijk EJ, Prins ND, Vermeer SE *et al*. C-reactive protein and cerebral small-vessel disease: the Rotterdam Scan Study. *Circulation* 2005; **112**: 900–905.
- Jefferson AL, Massaro JM, Wolf PA *et al*. Inflammatory biomarkers are associated with total brain volume: the Framingham Heart Study. *Neurology* 2007; **68**: 1032–1038.
- Wright CB, Moon Y, Paik MC *et al*. Inflammatory biomarkers of vascular risk as correlates of leukoaraiosis. *Stroke* 2009; **40**: 3466–3471.
- Dziedzic T. Systemic inflammatory markers and risk of dementia. *Am J Alzheimers Dis Other Demen* 2006; **21**: 258–262.
- Ferrucci L, Harris TB, Guralnik JM *et al*. Serum IL-6 level and the development of disability in older persons. *J Am Geriatric Soc* 1999; **47**: 639–646.
- Leng S, Chaves P, Koenig K, Walston J. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *J Am Geriatric Soc* 2002; **50**: 1268–1271.



## 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 ( $\geq 0.15$  mg/day), vitamin D<sub>3</sub> (alfacalcidol  $\geq 1.0$   $\mu$ g/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<sub>3</sub>. 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<sup>1</sup> 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,<sup>2</sup> and that the ADR incidence among elderly inpatients was 6–15%.<sup>3</sup> It has been reported from Western countries that ADR occur in more than 10% of outpatients or nursing home residents.<sup>4</sup>

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.<sup>2–4</sup> 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.<sup>5</sup> 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,<sup>6,7</sup> 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.<sup>5</sup>

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, triazolam), digoxin ( $\geq 0.15$  mg/day), vitamin D<sub>3</sub> (alfacalcidol  $\geq 1.0$   $\mu$ g/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  $\chi^2$ -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 ( $\geq 0.15$ mg/day)
Anti-arrhythmic	Disopyramide Amiodarone
Antiplatelet	Ticlopidine
Hypnotic (barbiturates)	Pentobarbital Amobarbital Barbital Chlorpromazine, promethazine, phenobarbital
Hypnotic (benzodiazepines)	Flurazepam Haloxazolam Quazepam Triazolam
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 ( $\geq 300$ mg/day)
Vitamin D	Alfacalcidol ( $\geq 1.0$ $\mu$ g/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 ( <i>n</i> = 418)	71.5%		
2. Past experiences of ADR by use of the following drugs			
	Frequent	Occasional	Frequent + Occasional
(i) Antipsychotic benzamides ( <i>n</i> = 381) (sulpiride, sultopride)	93 (24.4%)	207 (54.3%)	300 (78.7%)
(ii) Hypnotic benzodiazepines ( <i>n</i> = 386) (flurazepam, haloxazolam, quazepam, triazolam)	93 (24.1%)	241 (62.4%)	334 (86.5%)
(iii) Digoxin ( $\geq 0.15$ mg/day) ( <i>n</i> = 382)	33 (8.6%)	234 (61.3%)	267 (69.9%)
(iv) Vitamin D <sub>3</sub> ( <i>n</i> = 373) (alfacalcidol $\geq 1.0$ $\mu$ g/day)	14 (3.7%)	125 (33.5%)	139 (37.3%)
3. Past experiences of ADR (free responses; <i>n</i> = 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 ( <i>n</i> = 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<sub>3</sub>. Interestingly, the  $\chi$ -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 ( $\geq 0.15$  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.<sup>6–8</sup> Vitamin D<sub>3</sub> (alfacalcidol  $\geq 1.0$   $\mu$ g/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,<sup>3</sup> 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<sup>9</sup> 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<sup>6</sup> 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.

## Acknowledgments

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## References

- 1 Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother* 2008; **42**: 1017–1025.
- 2 Toba K, Akishita M, Mizuno Y *et al*. Adverse drug reaction in the elderly. *Jpn J Geriatr* 1999; **36**: 181–185.
- 3 Arai H, Akishita M, Teramoto S *et al*. Incidence of adverse drug reactions in geriatric units of university hospitals. *Geriatr Gerontol Int* 2005; **5**: 293–297.
- 4 Rothschild JM, Bates DW, Leape LL. Preventable medical injuries in older patients. *Arch Intern Med* 2000; **160**: 2717–2728.
- 5 The Japan Geriatrics Society. *Guidelines for Medical Treatment and Its Safety in the Elderly 2005*. Tokyo: Medical View, 2005 (in Japanese).
- 6 Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; **157**: 1531–1536.
- 7 Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003; **163**: 2716–2724.
- 8 McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *CMAJ* 1997; **156**: 385–391.
- 9 Mita Y, Akishita M, Tanaka K *et al*. Improvement of inappropriate prescribing and adverse drug withdrawal events after admission to long-term care facilities. *Geriatr Gerontol Int* 2004; **4**: 146–150.



## 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<sup>1</sup> demonstrated the benefits of antihypertensive treatment even in patients over the age of 80 years with SBP  $\geq$  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<sup>2</sup> 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.<sup>3</sup>

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.<sup>4</sup> 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.*<sup>5</sup> 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<sup>4</sup> and with the recently published Valsartan in Elderly Isolated Systolic Hypertension (VALISH) Study<sup>6</sup> as well. VALISH study compared the strict (< 140 mm Hg) with the moderate (140–149 mm Hg) target of SBP for  $\geq$  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.<sup>6</sup> By contrast, an Italian study<sup>7</sup> 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 ( $\geq$  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.<sup>1</sup> 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.<sup>5</sup> 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.<sup>7</sup> 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 <sup>a</sup>
JATOS	65–85 (74) years	> 160 mm Hg	< 140 mm Hg vs. 140–159 mm Hg	136 mm Hg vs. 146 mm Hg Per-protocol 132 mm Hg vs. 147 mm Hg	22.6 vs. 22.7 Per-protocol 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

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

we should follow the JSH 2009 guidelines<sup>8</sup> that are compatible with the above-mentioned points.

1 Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpiitt CJ, HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**: 1887–1898.

2 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *Br Med J* 2009; **338**: b1665.

3 Ogihara T. Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension (The PATE-Hypertension Study) in Japan. *Am J Hypertens* 2000; **13**: 461–467.

4 JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res* 2008; **31**: 2115–2127.

5 Rakugi H, Ogihara T, Goto Y, Ishii M, on behalf of the JATOS Study Group. Comparison of strict- and mild-blood pressure control in elderly hypertensive patients: a per-protocol analysis of JATOS. *Hypertens Res* 2010; **33**: 1124–1128.

6 Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, Imai Y, Kikuchi K, Ito S, Eto T, Kimura G, Imaizumi T, Takishita S, Ueshima H, for the Valsartan in Elderly Isolated Systolic Hypertension Study Group. Target blood pressure for treatment of isolated systolic hypertension in the elderly. Valsartan in Elderly Isolated

Systolic Hypertension Study. *Hypertension* 2010; **56**: 196–202.

7 Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, Mureddu G, Pede S, Maggioni AP, Lucci D, Reboldi G. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet* 2009; **374**: 525–533.

8 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H, Japanese Society of Hypertension Committee. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.

# 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  $74.5 \pm 7.1$ ; 155 women, mean age  $75.3 \pm 6.7$ ).

**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.<sup>1–4</sup> Thus, visceral fat obesity has been established as a cause of cardiovascular disease,<sup>5,6</sup> although most of the subjects of studies delineating the relationship between visceral fat accumulation and metabolic abnormalities have consisted of middle-aged adults.<sup>7–9</sup> 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.<sup>10,11</sup> 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,<sup>12–14</sup> 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

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<sup>2</sup>, kg/m<sup>2</sup>). 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.<sup>15</sup>

#### 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.<sup>16,17</sup> 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<sup>2</sup>) 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

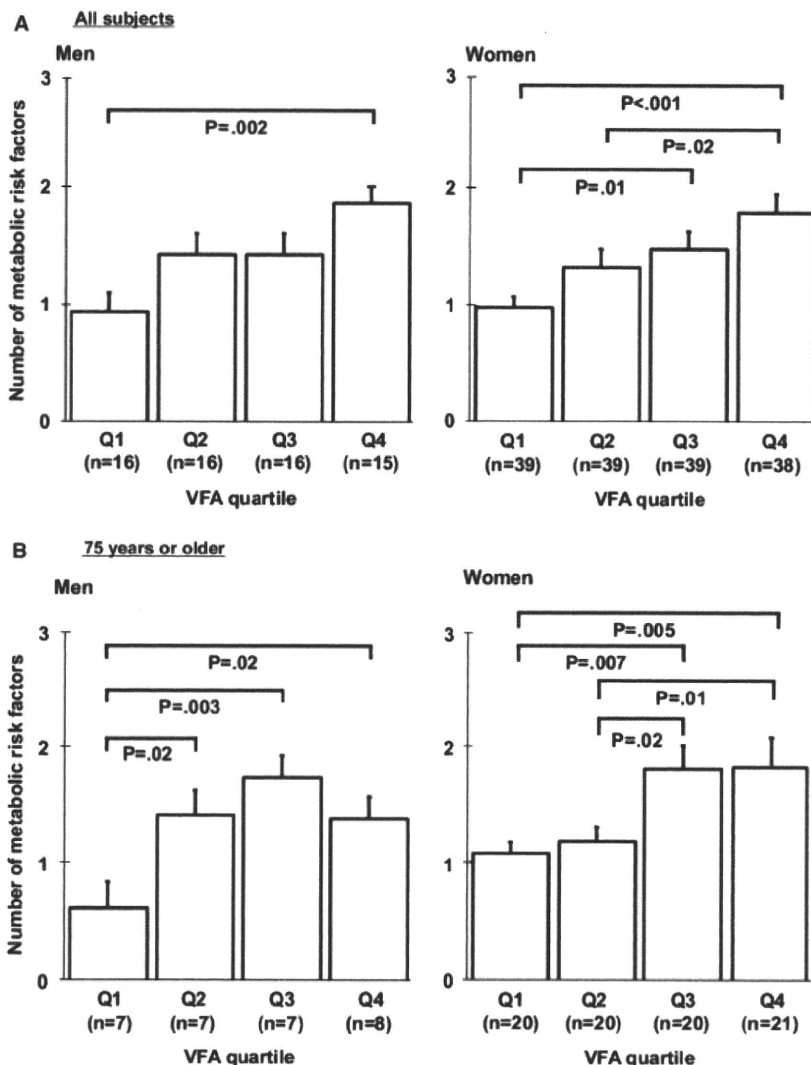
Table 1. Clinical Characteristics of Study Population

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 <sup>2</sup> , 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 <sup>2</sup> , mean ± SD (range)	134.8 ± 53.0 (33.2–258.3)	91.2 ± 44.8* (17.5–240.5)
Components of metabolic syndrome, n (%) <sup>†</sup>		
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.

<sup>†</sup> 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
<b>Men*</b>			
Age	0.012 (0.014)	0.10	.39
VFA	0.006 (0.002)	0.39	.01
BMI	0.055 (0.047)	0.18	.25
<b>Women†</b>			
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.

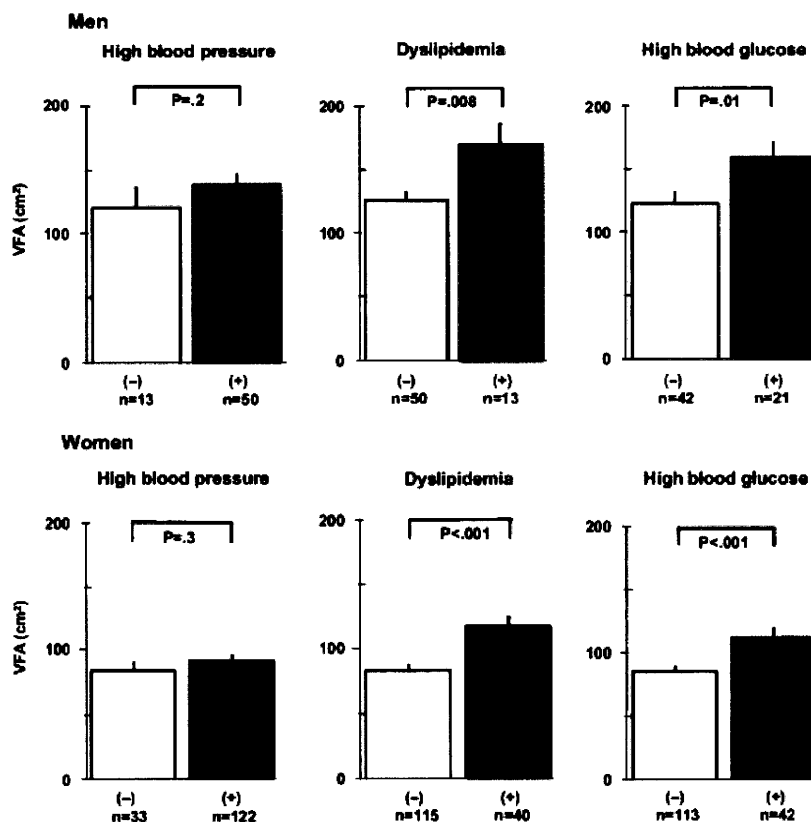


Figure 2. Visceral fat area (VFA) in the absence (–) and presence (+) of each metabolic risk factor. Dyslipidemia includes high triglycerides, low high-density lipoprotein cholesterol, or both. Data are expressed as means  $\pm$  standard errors.

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

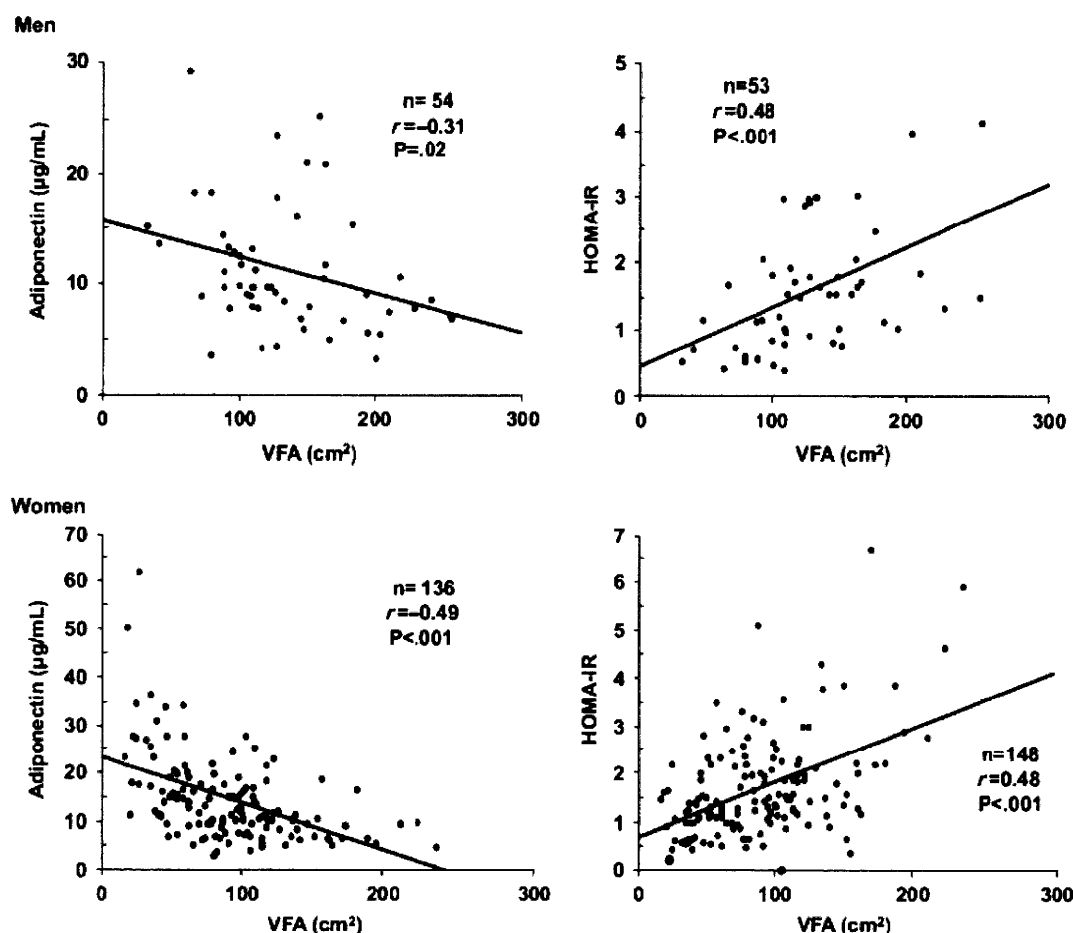
VFA is associated with metabolic abnormalities, as previously shown in studies of middle-aged populations.<sup>7–9</sup> This association was still observed after adjustment for age and BMI, suggesting that visceral fat accumulation might be a strong risk factor for the metabolic syndrome even in older 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  $\geq 60$ ).<sup>18</sup> 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





**Figure 3.** Correlation between visceral fat area (VFA) and serum adiponectin in all subjects and homeostasis model assessment of insulin resistance (HOMA-IR) in older men and women without diabetes mellitus. There was a significant negative correlation between VFA and serum adiponectin and a positive correlation between VFA and HOMA-IR in men and women.  $r$  = correlation coefficient.

be associated with greater cardiovascular disease and mortality.<sup>19–21</sup> As the mechanism of this association, it has been proposed that visceral fat accumulation is associated with metabolic abnormalities through insulin resistance and abnormal secretion of adipocytokines.<sup>22,23</sup> This study confirmed that visceral fat accumulation was negatively correlated with serum adiponectin level and positively correlated with insulin resistance as estimated by HOMA-IR in older adults. These findings suggest that older adults with visceral fat accumulation might tend to show metabolic abnormalities through decreased secretion of adiponectin and exacerbation of insulin resistance, similar to middle-aged adults with abdominal obesity.

No association was observed between high BP and VFA. Although the high rate (nearly 80%) of high BP may have affected this result, an additional analysis of this study showed no association between VFA and high BP using a modified cutoff value (140/90 mmHg). Moreover, the simple regression analysis showed no correlation between VFA and SBP or DBP in subjects not receiving antihypertensive treatment. These results suggest that factors other than visceral fat accumulation, such as sclerosis of blood vessels and enhancement of salt sensitivity, both of which are associated with aging, might affect BP in older adults. To the

contrary, impaired energy metabolism (e.g., high blood glucose and dyslipidemia) was closely associated with visceral fat accumulation.

It has been reported that weight-reduction therapy using diet, exercise, or both is efficacious in terms of improvement of insulin resistance and dyslipidemia even in older adults.<sup>24,25</sup> Thus, taking together the results of this study and these reports, it appears that the beneficial effects of weight-reduction therapy for older adults even with normal BMI might result from a reduction of visceral fat mass and subsequent improvement in energy metabolism. However, severe dietary therapy for weight reduction is difficult to achieve in elderly patients and has potential risks of causing micronutrient deficiencies,<sup>26–28</sup> generalized weakness, and loss of lean body mass.

There are some limitations of this study. First, because of exclusion criteria, the results of this study might not be generalizable to the general elderly population. Second, this study did not determine the effects of other body parameters such as subcutaneous fat and nonfat mass on metabolic abnormalities. Third, with the cross-sectional design, causal relationships cannot be established between VFA and metabolic risk factors. Finally, it remains to be determined whether metabolic syndrome in older adults

contributes to cardiovascular events or mortality.<sup>29,30</sup> Confirmation by a large prospective study with precise assessment, such as CT scanning, will be needed to determine whether visceral fat accumulation in older adults directly contributes to cardiovascular events or mortality.

In conclusion, this study suggests that visceral fat accumulation is associated with metabolic risk factor clustering even in older adults with normal BMI. These results provide important insight into the management of metabolic abnormalities in older adults.

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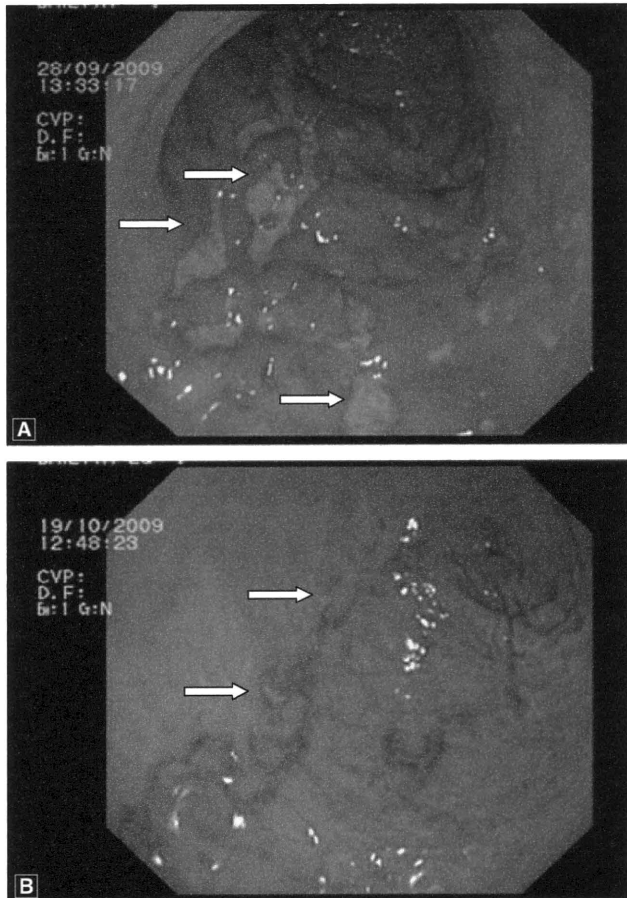
The authors do not have any conflict of interest with a company whose products or services are directly related to the subject matter of the manuscript.

**Author Contributions:** Study concept and design: Kazushi Nomura, Masato Eto, Masahiro Akishita, Yasuyoshi Ouchi. Acquisition of subjects and data: Kazushi Nomura, Taro Kojima, Tetsuro Nakamura, Masahiro Akishita. Analysis and interpretation of data: Kazushi Nomura, Masato Eto, Sumito Ogawa, Katsuya Iijima, Atsushi Araki, Masahiro Akishita, Yasuyoshi Ouchi. Preparation of manuscript: Kazushi Nomura, Masato Eto.

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## REFERENCES

- Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: The paradox between visceral and subcutaneous fat. *Curr Diabetes Rev* 2006;2:367–373.
- Carr DB, Utzschneider KM, Hull RL et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes* 2004;53:2087–2094.
- Pouliot MC, Despres JP, Lemieux S et al. Waist circumference and abdominal sagittal diameter: Best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;73:460–468.
- Anderson PJ, Critchley JAJH, Chan JCN et al. Factor analysis of the metabolic syndrome: Obesity vs insulin resistance as the central abnormality. *Int J Obes* 2001;25:1782.
- Rexrode KM, Carey VJ, Hennekens CH et al. Abdominal adiposity and coronary heart disease in women. *JAMA* 1998;280:1843–1848.
- Nakamura T, Tokunga K, Shimomura I et al. Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 1994;107:239–246.
- Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity New criteria for 'obesity disease' in Japan. *Circ J* 2002;66:987–992.
- Chiba Y, Saitoh S, Takagi S et al. Relationship between visceral fat and cardiovascular disease risk factors: The Tanno and Sobetsu Study. *Hypertens Res* 2007;30:229–236.
- Ribeiro-Filho FF, Faria AN, Kohlmann O Jr et al. Ultrasonography for the evaluation of visceral fat and cardiovascular risk. *Hypertension* 2001;38:713–717.
- Cefalu WT, Wang ZQ, Werbel S et al. Contribution of visceral fat mass to the insulin resistance of aging. *Metabolism* 1995;44:954–959.
- Kuk JL, Lee S, Heymsfield SB et al. Waist circumference and abdominal adipose tissue distribution: Influence of age and sex. *Am J Clin Nutr* 2005;81:1330–1334.
- Harris MI, Flegal KM, Cowie CC et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 1998;21:518–524.
- Burt VL, Whelton P, Roccella EJ et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995;25:305–313.
- Park YW, Zhu S, Palaniappan L et al. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 2003;163:427–436.
- Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetes Med* 2006;23:469–480.
- Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004;27:1487–1495.
- Matthews DR, Hosker JP, Rudenski AS et al. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419.
- Bray GA, Jablonski KA, Fujimoto WY et al. Relation of central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. *Am J Clin Nutr* 2008;87:1212–1218.
- Zhang C, Rexrode KM, van Dam RM et al. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: Sixteen years of follow-up in US women. *Circulation* 2008;117:1658–1667.
- Yusuf S, Hawken S, Ounpuu S et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: A case-control study. *Lancet* 2005;366:1640–1649.
- Balkau B, Deanfield JE, Després JP et al. International Day for the Evaluation of Abdominal Obesity (IDEA): A study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation* 2007;116:1942–1951.
- Nagaretani H, Nakamura T, Funahashi T et al. Visceral fat is a major contributor for multiple risk factor clustering in Japanese men with impaired glucose tolerance. *Diabetes Care* 2001;24:2127–2133.
- Côté M, Mauriège P, Bergeron J et al. Adiponectinemia in visceral obesity: Impact on glucose tolerance and plasma lipoprotein and lipid levels in men. *J Clin Endocrinol Metab* 2005;90:1434–1439.
- McTigue KM, Hess R, Ziouras J. Obesity in older adults: A systematic review of the evidence for diagnosis and treatment. *Obesity* 2006;14:1485–1497.
- Crandall J, Schade D, Ma Y et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci* 2006;61A:1075–1081.
- de Groot CP, van den Broek T, van Staveren W. Energy intake and micronutrient intake in elderly Europeans: Seeking the minimum requirement in the SENECA study. *Age Ageing* 1999;28:469–474.
- Meunier N, O'Connor JM, Maiani G et al. Importance of zinc in the elderly: The ZENITH study. *Eur J Clin Nutr* 2005;59:1–4.
- Davies S, McLaren Howard J, Hunnisett A et al. Age-related decreases in chromium levels in 51,665 hair, sweat, and serum samples from 40,872 patients—implications for the prevention of cardiovascular disease and type II diabetes mellitus. *Metabolism* 1997;46:469–473.
- Maggi S, Noale M, Gallina P et al. Metabolic syndrome, diabetes, and cardiovascular disease in an elderly Caucasian cohort: The Italian Longitudinal Study on Aging. *J Gerontol A Biol Sci Med Sci* 2006;61:505–510.
- Hildrum B, Mykletun A, Dahl AA et al. Metabolic syndrome and risk of mortality in middle-aged versus elderly individuals: The Nord-Trøndelag Health Study (HUNT). *Diabetologia* 2009;52:583–590.



**Figure 1.** (A) Ulcerations in the left colon (arrows), seen on the first colonoscopy. (B) Colonoscopy after antiviral treatment, ulcerations are in phase of remission (arrows).

## DISCUSSION

CMV colitis is a rare cause of diarrhea in older adults; it is more commonly seen in people who are immunosuppressed (with the human immunodeficiency virus or after bone marrow transplant), in whom it is often due to a virus reactivation, or in patients with preexisting inflammatory bowel disease.<sup>4</sup> Nevertheless, although it may be considered an invasive diagnostic test in a frail elderly patient, a sigmoidoscopy with biopsy should be considered as a necessary investigation if culture-negative diarrhea persists. Although some cases of CMV colitis are described in immunocompetent patients, when a diagnosis of CMV colitis is made, screening to exclude the presence of concomitant immunomodulating conditions or inflammatory bowel disease is necessary. In the clinical history of this patient, different coexisting immune-modulating conditions (diabetes mellitus, previous HCV infection, probable essential thrombocythemia) can be identified.

Most cases of CMV infection described in the literature are limited to the left colon, but the infection could theoretically involve all of the digestive tract. In this case, an ulceration was also found in the bulbar duodenum; because the ulcer was bloody, histology was not done, so it was not possible to confirm whether it was a location of CMV infection. Anyway, in a meta-analysis, in which the authors identified 44 cases of CMV bowel infection in immunocompetent patients, the extent of disease was not an independent predictor of survival.<sup>3</sup>

No conclusive statement regarding the need for specific antiviral treatment can be made from the available data in the literature. Although patients with no associated comorbidities seem to have a good rate of spontaneous remission, a trend for higher mortality has been reported in patients aged 55 and older and in patients with diseases affecting immune responses,<sup>3</sup> with a mortality rate of 31.8% in patients aged 55 and older. The patient in the current case belongs to this latter group at high risk of mortality, so it was thought that the antiviral treatment was mandatory. Nevertheless, randomized controlled trials are needed for a more-conclusive answer about antiviral treatment in immunocompetent patients suffering from severe CMV infection.

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**Author Contributions:** Margherita Azzini contributed to the collection of clinical data and the preparation of manuscript. Claudia Bozzini wrote the manuscript. Claudio Bellamoli contributed to the collection of clinical data and reviewed the manuscript.

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## REFERENCES

- Rafailidis PI, Mourtzoukou EG, Varbobitis IC et al. Severe cytomegalovirus infection in apparently immunocompetent patients: A systematic review. *Virology* 2008;5:47.
- Lockwood MR, Liddle J, Kitsanta P. Cytomegalovirus colitis—an unusual cause for diarrhoea in an elderly woman. *Age Ageing* 2006;35:198–200.
- Galiatsatos P, Shrier I, Lamoureux E et al. Meta-analysis of outcome of Cytomegalovirus colitis in immunocompetent hosts. *Digestive Dis Sci* 2005;50:609–616.
- Julka K, Surawicz CM. Cytomegalovirus in inflammatory bowel disease: Time for another look? *Gastroenterology* 2009;137:1163–1166.

## EFFECTS OF TESTOSTERONE IN OLDER MEN WITH MILD-TO-MODERATE COGNITIVE IMPAIRMENT

*To the Editor:* Some population-based studies have found that endogenous testosterone levels are associated with general cognitive function,<sup>1,2</sup> and it has also been reported that testosterone levels are associated with physical and psychological functions, including cognition, in disabled older men,<sup>3</sup> but there have been few studies evaluating the effects of testosterone supplementation in men with cognitive impairment, and the results were inconsistent.<sup>4–7</sup> Thus, additional information is needed for frail or disabled older men with cognitive impairment as the targets of testosterone supplementation. Here, a pilot study to investigate the effect of oral testosterone supplementation for 6 months on

Table 1. Changes in Functional Parameters According to Treatment Group

Functional Parameters	Mean $\pm$ Standard Deviation						P-Value
	Testosterone			Control			
	Baseline	3 Months	6 Months	Baseline	3 Months	6 Months	
Mini-Mental State Examination	20.2 $\pm$ 4.5	21.8 $\pm$ 4.7	22.6 $\pm$ 6.5*	21.9 $\pm$ 5.3	22.0 $\pm$ 4.6	22.0 $\pm$ 4.1	.03
Hasegawa Dementia Scale, Revised	17.6 $\pm$ 5.9	18.2 $\pm$ 7.1	20.6 $\pm$ 7.3*	19.6 $\pm$ 5.6	20.1 $\pm$ 7.0	18.8 $\pm$ 7.7	.02
Barthel Index	91 $\pm$ 12	89 $\pm$ 17	91 $\pm$ 15	92 $\pm$ 10	91 $\pm$ 10	92 $\pm$ 7	.70
Vitality Index	9.0 $\pm$ 0.9	9.3 $\pm$ 0.9	7.9 $\pm$ 1.3	9.0 $\pm$ 1.0	9.4 $\pm$ 1.0	9.4 $\pm$ 0.9	.35

P-values are based on repeated-measures analysis of variance comparing the 6-month change between the groups.

\* $P < .05$  compared with baseline.

cognitive function in Japanese older men with mild to moderate cognitive decline is reported.

Eleven men with cognitive impairment, mean age  $81 \pm 6$ , receiving long-term care, were assigned to take oral testosterone undecanoate 40 mg daily for 6 months after a breakfast containing 15 to 20 g of fat. The control group of 13 men matched for age and cognitive function were followed without testosterone treatment. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) and Hasegawa Dementia Scale, Revised (HDS-R) at baseline and at 3 and 6 months. Plasma hormone levels were also measured. The institutional review board approved the study protocol, and all participants or their families gave written informed consent.

At baseline, mean total and free testosterone levels, calculated using the Vermeulen equation,<sup>8</sup> were  $14 \pm 4$  nmol/L and  $246 \pm 47$  pmol/L, respectively. There were no significant differences between the groups in age, length of education, nutritional parameters, functional parameters, or plasma hormone levels. Fasting plasma testosterone levels in the morning did not change significantly during the study, whereas the post-dose levels increased up to  $30 \pm 8$  nmol/L 6 hours after testosterone administration, as reported previously.<sup>9</sup> The changes in functional parameters in each group from baseline to 6 months are shown in Table 1. At 3 months, subjects who received testosterone treatment showed a nonsignificant increase in MMSE and HDS-R scores, whereas at 6 months, cognitive scores were significantly greater than at baseline. In the control group, both cognitive scores remained unchanged. The difference between the groups was significant at 6 months. Prostate-specific antigen and liver function were unchanged, and no adverse effects were observed.

No significant changes were observed in basic activities of daily living (ADL) and ADL-related vitality in either group (Table 1), possibly because these scores were preserved in most subjects at baseline; the Barthel Index and Vitality Index<sup>10</sup> were  $91 \pm 10$  (full score = 100) and  $9.0 \pm 1.0$  (full score = 10), respectively.

This preliminary study needs to be confirmed in a randomized controlled trial with a large sample size. Nevertheless, these results indicate the effects of testosterone treatment on cognitive function in frail elderly men.

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