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.

Acknowledgments

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COMMENTARY

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

Masahiro Akishita

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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

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.

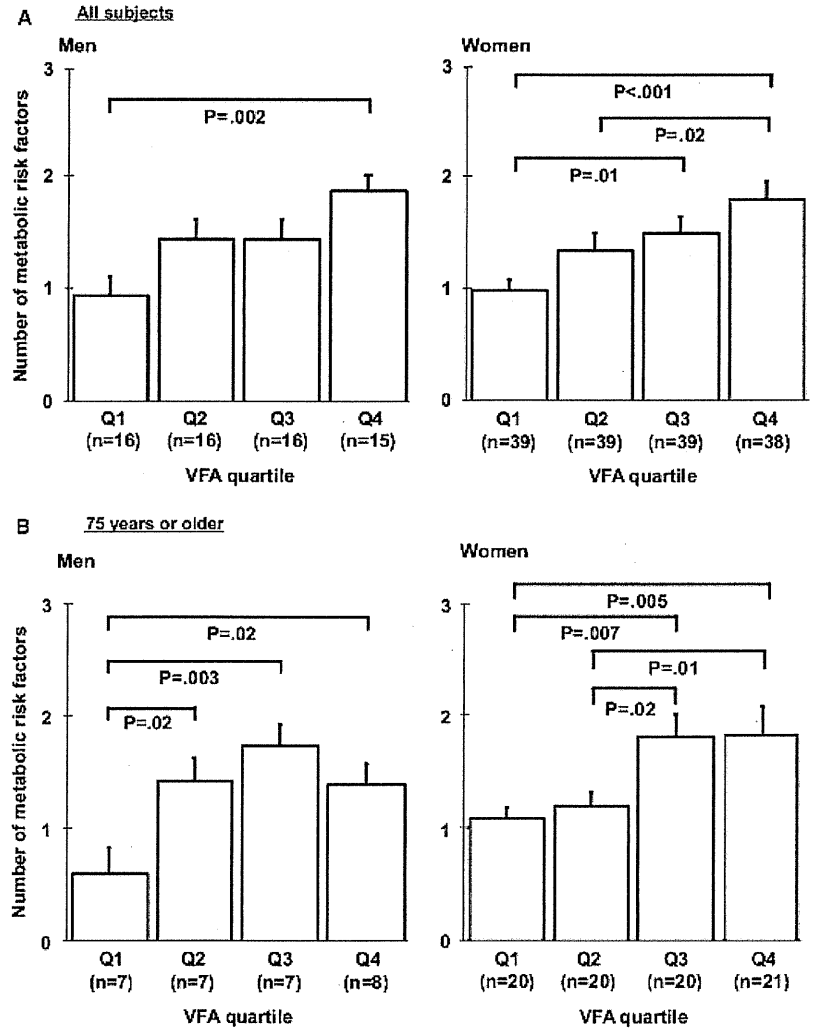

Figure 1. Number of metabolic risk factors according to quartile (Q) of visceral fat area (VFA) in all subjects (A) and subjects aged 75 and older (B). Metabolic risk factors include high blood pressure, high serum triglycerides, low serum high-density lipoprotein cholesterol, and high blood glucose.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

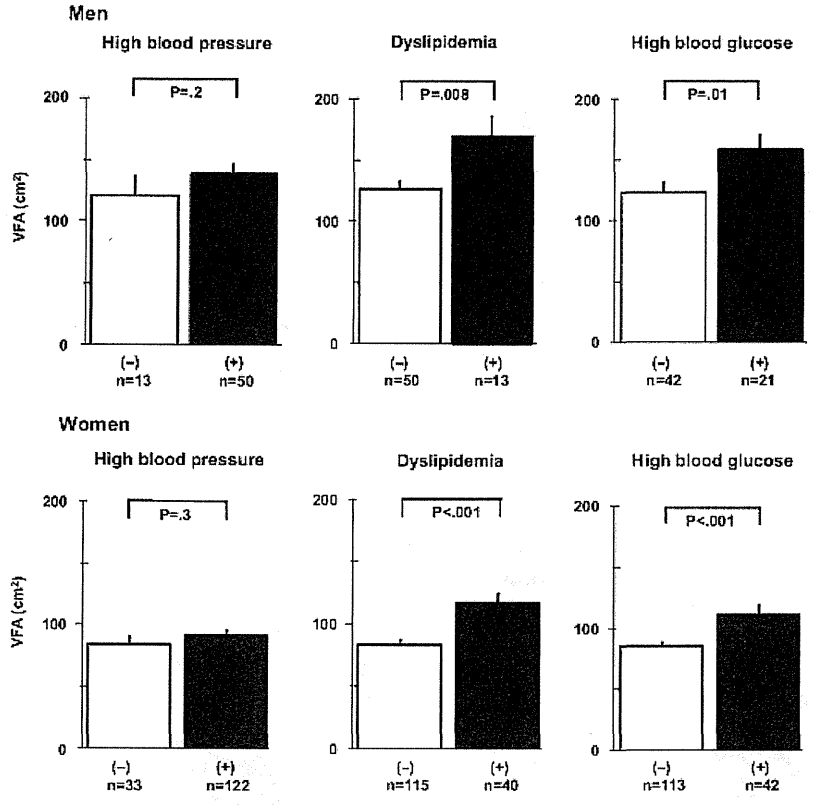

Figure 2. Visceral fat area (VFA) in the absence (–) and presence (+) of each metabolic risk factor. Dyslipidemia includes high triglycerides, low high-density lipoprotein cholesterol, or both. Data are expressed as means ± standard errors.

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

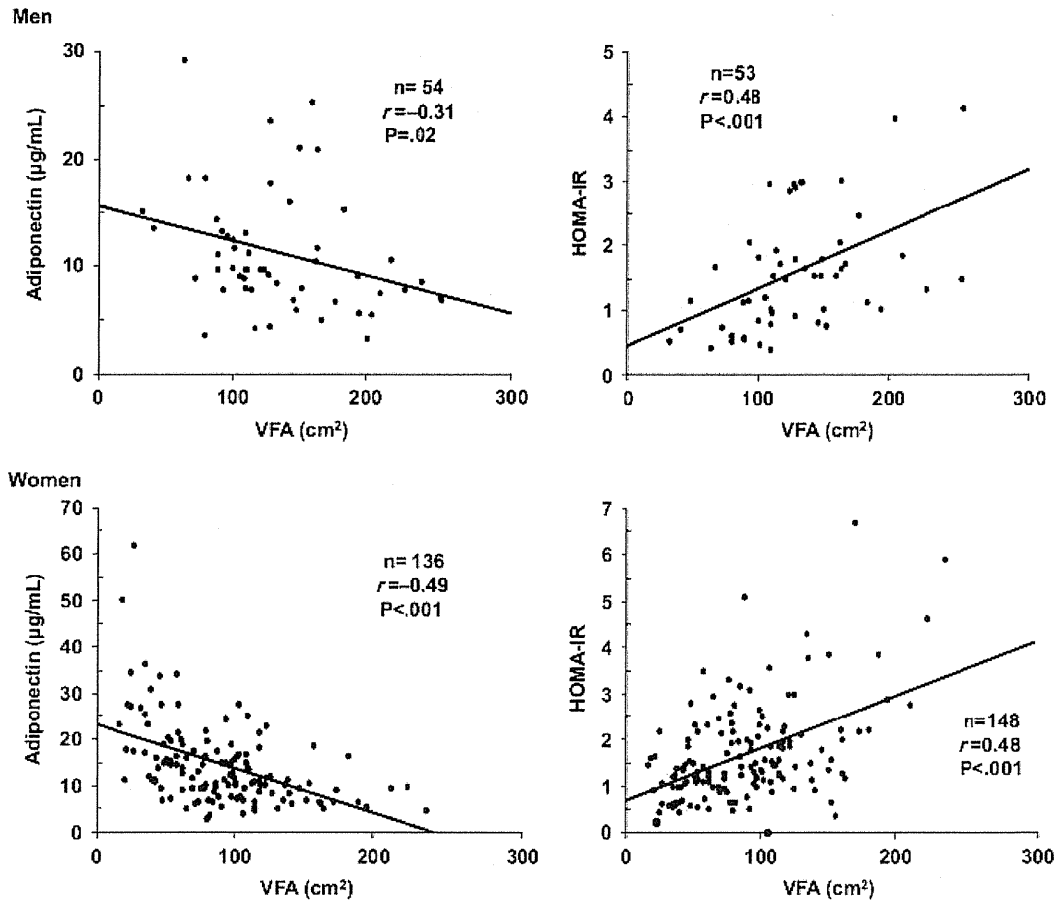

Figure 3. Correlation between visceral fat area (VFA) and serum adiponectin in all subjects and homeostasis model assessment of insulin resistance (HOMA-IR) in older men and women without diabetes mellitus. There was a significant negative correlation between VFA and serum adiponectin and a positive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

be associated with greater cardiovascular disease and mortality.[19–21] 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.[22,23] 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.[24,25] 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,[26–28] 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.[29,30] 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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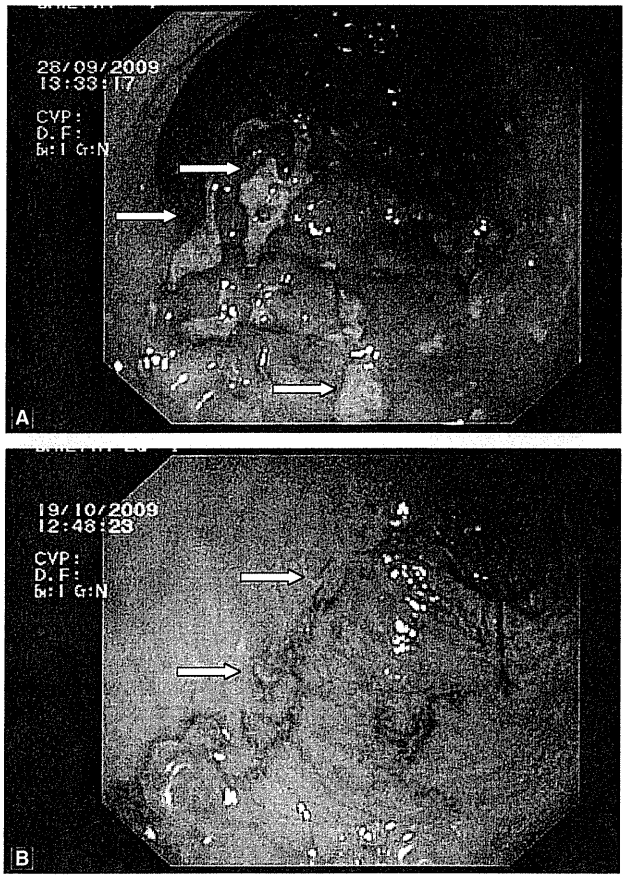

Figure 1. (A) Ulcerations in the left colon (arrows), seen on the first colonoscopy. (B) Colonoscopy after antiviral treatment, ulcerations are in phase of remission (arrows).

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.[4] 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.[3]

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,[3] 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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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,[1,2] and it has also been reported that testosterone levels are associated with physical and psychological functions, including cognition, in disabled older men,[3] but there have been few studies evaluating the effects of testosterone supplementation in men with cognitive impairment, and the results were inconsistent.[4–7] 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 ± Standard Deviation								P-Value
	Testosterone				Control				
	Baseline	3 Months	6 Months	Difference: 0 to 6 Months	Baseline	3 Months	6 Months	Difference: 0 to 6 Months	
Mini-Mental State Examination	20.2 ± 4.5	21.8 ± 4.7	22.6 ± 6.5*	2.4 ± 3.1	21.9 ± 5.3	22.0 ± 4.6	22.0 ± 4.1	0.1 ± 2.7	.03
Hasegawa Dementia Scale, Revised	17.6 ± 5.9	18.2 ± 7.1	20.6 ± 7.3*	3.0 ± 4.3	19.6 ± 5.6	20.1 ± 7.0	18.8 ± 7.7	−0.8 ± 2.3	.02
Barthel Index	91 ± 12	89 ± 17	91 ± 15	0.5 ± 7.1	92 ± 10	91 ± 10	92 ± 7	0.4 ± 7.6	.70
Vitality Index	9.0 ± 0.9	9.3 ± 0.9	7.9 ± 1.3	−1.1 ± 1.0	9.0 ± 1.0	9.4 ± 1.0	9.4 ± 0.9	0.4 ± 1.0	.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 ± 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,[8] were 14 ± 4 nmol/L and 246 ± 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 ± 8 nmol/L 6 hours after testosterone administration, as reported previously.[9] 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[10] were 91 ± 10 (full score = 100) and 9.0 ± 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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A CASE OF SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED RAPID EYE MOVEMENT BEHAVIOR DISORDER

To the Editor: Rapid eye movement (REM) sleep behavior disorder (RBD) is often seen in older patients and is characterized by a loss of normal skeletal muscle atonia during REM sleep.[1,2] As a result, the disease manifests as nocturnal motor activity consistent with the enactment of dream content, for example grabbing the bed partner in response to a dream about falling from a cliff. RBD often results in injury to the patient, bed partner, or both.[1,2]

In perhaps up to two-thirds of cases, RBD is associated with neurodegenerative disorders, most notably the alpha-synucleinopathies (Parkinson's disease, Lewy body disease, multiple systems atrophy), often antedating other manifestations of these disorders by many years.[1–4] Other cases seem to be idiopathic, although it has been suggested that various medications, notably selective serotonin reuptake inhibitors (SSRI) and other antidepressants, may commonly induce RBD.[1,4,5] In spite of this assertion, there have been few supporting case reports.[5,6] The authors recently cared for a man who clearly developed RBD as a result of SSRI treatment; the use of the SSRI for posttraumatic stress disorder (PTSD) complicated the clinical picture.

CASE REPORT

An 87-year-old male World War II veteran had been treated for PTSD with associated nightmares but no nocturnal motor activity with bupropion and lorazepam. Past medical history was significant only for essential hypertension. In 1998, after many years of treatment, sertraline was added because of increasing symptoms. Within 6 months of adding sertraline, the patient developed frequent nocturnal motor behavior consistent with the content of his dreams and nightmares, for example punching and choking his wife in the context of a dream about being in a fight. As a result, he and his wife had suffered lacerations and contusions. Other behaviors included running out of his bedroom or running into a window. Upon awakening, he was able to recall portions of the dreams but was unaware of the motor behaviors.

Trials of temazepam, zolpidem, and trazodone were ineffective in improving these behaviors. Ultimately, a diagnosis of RBD was made based on the clinical presentation. Clonazepam 1 mg at bedtime was added, which resulted in a moderate decrease in the frequency of the nocturnal motor activity, from nightly to two or three times per week. After 3 months, sertraline was slowly tapered and discontinued, which resulted in a complete cessation of all nocturnal motor behavior. He remained free of nocturnal motor activity for 5 months, until sertraline was inadvertently restarted after the loss of his wife. Within 1 month of restarting sertraline, the nocturnal motor behavior returned. There has thus far been no evidence of dementia or of parkinsonism.

This patient's clinical presentation was typical of RBD; unfortunately, his and his wife's injuries were also typical. It seems clear that his RBD was SSRI induced; it developed after sertraline was started, did not definitively improve until it was stopped, and recurred after it was inadvertently restarted, and there was no evidence of parkinsonism or dementia over the previous 12 years. Although there are few published cases of SSRI-induced overt RBD, increased electromyography activity during REM sleep has been demonstrated in patients taking SSRIs. (None of the patients were being treated for PTSD.)[7]

The relationship between RBD and PTSD is complex and not fully investigated. There is clinical and polysomnographic evidence of greater motor activity during REM sleep in patients with PTSD,[8] and greater prevalence of RBD was noted in a cohort of patients with PTSD.[9] SSRIs are effective for PTSD-related nightmares[10] but may cause RBD, clonazepam is effective for RBD[1,2,4] but not for PTSD-related nightmares,[10] and RBD is not associated with the typical diurnal symptoms of PTSD. In spite of his long history of PTSD and related nightmares, this patient had never exhibited any significant motor activity during sleep until the SSRI was started.

RBD is relatively common in geriatric practice and should be explored in any patient with nocturnal injuries or motor activity. RBD responds well to treatment, generally with clonazepam. Discontinuation of SSRIs or changing to

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Effects of dehydroepiandrosterone supplementation on cognitive function and activities of daily living in older women with mild to moderate cognitive impairment

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Aim: There is little evidence that dehydroepiandrosterone (DHEA) has beneficial effects on physical and psychological functions in older women. We investigated the effect of DHEA supplementation on cognitive function and ADL in older women with cognitive impairment.

Methods: A total of 27 women aged 65–90 years (mean ± standard deviation, 83 ± 6) with mild to moderate cognitive impairment (Mini-Mental State Examination, MMSE; 10–28/30 points), receiving long-term care at a facility in Japan were enrolled. Twelve women were assigned to receive DHEA 25 mg/day p.o. for 6 months. The control group ($n = 15$) matched for age and cognitive function was followed without hormone replacement. Cognitive function was assessed by MMSE and Hasegawa Dementia Scale-Revised (HDS-R), and basic activities of daily living (ADL) by Barthel Index at baseline, 3 and 6 months. Plasma hormone levels including testosterone, DHEA, DHEA-sulfate and estradiol were also followed up.

Results: After 6 months, DHEA treatment significantly increased plasma testosterone, DHEA and DHEA-sulfate levels by 2–3-fold but not estradiol level compared to baseline. DHEA administration increased cognitive scores and maintained basic ADL score, while cognition and basic ADL deteriorated in the control group (6-month change in DHEA group vs control group; MMSE, +0.6 ± 3.2 vs −2.1 ± 2.2, $P < 0.05$; HDS-R, +2.8 ± 2.8 vs −0.3 ± 4.1, $P < 0.05$; Barthel Index, +3.7 ± 7.1 vs −2.7 ± 4.6, $P = 0.05$). Among the cognitive domains, DHEA treatment improved verbal fluency ($P < 0.05$).

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Conclusion: DHEA supplementation in older women with cognitive impairment may have beneficial effects on cognitive function and ADL. **Geriatr Gerontol Int 2010; 10: 280–287.**

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Introduction

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are the most abundant circulating steroids mainly produced by the adrenal zona reticularis in both sexes.[1] Their circulating levels decline with advancing age,[1–4] and there has been growing public interest in DHEA supplementation to prevent age-associated physical and cognitive impairment. DHEA is considered a crucial precursor of human sex steroid biosynthesis, and to exert indirect androgenic and estrogenic effects following conversion into smaller amounts of testosterone and estradiol.[5,6] While this conversion contributes to a part of testosterone production in men, its role may be much more significant in postmenopausal women whose ovarian production of androgen and estrogen has waned. Importantly, postmenopausal women with intact ovaries continue to produce androgens; DHEA(-S), testosterone and androstenedione, while their production of estradiol is minimal.[7] However, the role of androgens in older women's health is not fully understood.

Clinical trials of the effects of estrogen replacement therapy on cognitive function have shown a lack of efficacy in postmenopausal women initiating hormone replacement therapy after the age of 65 years.[8,9] On the other hand, previous reports have suggested that DHEA may have neuroprotective effects, and the age-associated DHEA(-S) decline is associated with cognitive impairment in older women.[2,10–12] One longitudinal study observed lower DHEA-S levels in patients who subsequently developed Alzheimer's disease.[13] However, controlled trials with DHEA supplementation have failed to show beneficial effects on cognition in healthy middle-aged to older women.[14–16] In these studies, the participants were limited to those who did not have cognitive impairment; therefore, it is reasonable to hypothesize that DHEA supplementation may be effective in much older women with cognitive decline as well as lower DHEA levels.

Dehydroepiandrosterone deficiency is also considered to be involved in the development of physical frailty.[17] Clinical experience with DHEA supplementation in older women is limited, and the few clinical trials examining its effect on physical function and activity of daily living (ADL) have yielded inconsistent results.[18–20] Evidence is lacking for much older women in whom physical impairment becomes more apparent and is accompanied by an age-associated DHEA decline. In our previous study, plasma DHEA and DHEA-S levels, but not estradiol level, were independently related to higher basic ADL in older women aged 70–93 years with functional decline receiving long-term care.[21] We hypothesized that in older women, DHEA replacement could be effective for the age-related decline of physical as well as psychological function.

This study therefore examined the effect of relatively low-dose (25 mg daily) p.o. DHEA supplementation for 6 months on cognitive function and ADL in older women with cognitive impairment.

Methods

Subjects and study design

In this open, non-randomized controlled study, 27 women aged 65 years or older who attended a health service facility for the elderly (a facility that provides nursing care and rehabilitation services to elderly people with disability, Mahoroba-no-Sato, located in Nagano Prefecture, Japan) were enrolled. The participants were in a chronic stable condition and receiving Long-term Care Insurance service either for admission to the facility or day-care services. The principal inclusion criteria were mild to moderate cognitive decline; both Mini-Mental State Examination (MMSE)[22] and Hasegawa Dementia Scale-Revised (HDS-R)[23] scores were between 10 and 28. The subjects were diagnosed as having a mild cognitive impairment[24] or Alzheimer's disease according to the Diagnostic and Statistical Manual of Mental Disorders IV.[25] The participants had never been treated with hormone replacement therapy, and plasma DHEA-S concentration was less than 3.0 μmol/L. The exclusion criteria were history of stroke, extremely low ADL status (Barthel Index[26] <50), malnutrition (serum albumin <3.5 mg/dL), malignancy, acute inflammation (fever, white blood cell count >10 000/μL, or other signs of infection within 4 weeks before enrollment) and overt endocrine diseases, because these diseases may affect both plasma sex hormone levels and functions. None of the subjects were taking a cholinesterase inhibitor (donepezil hydrochloride) or glucocorticoid, opiate or hormone supplement.

Twelve women were assigned to receive DHEA capsule (25 mg/day, Athena Clinics International,

Honolulu, HI, USA) and 15 women were followed up without any additive medication. Medications that could influence cognitive function and plasma hormone levels were not changed during the study period. Outcome measures were cognitive function, ADL, plasma hormone levels, blood cell counts, blood chemical parameters and subjective adverse events. They were assessed at baseline, and after 3 and 6 months. The institutional review board of Mahoroba-no-Sato approved the study protocol, and all participants or their families gave written informed consent.

Hormone measurements

Blood samples were obtained from the participants in the morning after an overnight fast, and plasma hormone levels in addition to blood cell counts and blood chemical parameters were determined by a commercial laboratory (Health Sciences Research Institute, Yokohama, Japan). DHEA and DHEA-S were assayed using sensitive radioimmunoassays with minimum detection limits of 0.04 ng/mL (0.14 nmol/L) and 2.0 μg/dL (0.05 μmol/L), respectively. Total testosterone and estradiol were assayed using chemiluminescent immunoassays with minimum detection limits of 7 ng/dL (0.2 nmol/L) and 4 pg/mL (14.7 pmol/L), respectively. The intra-assay coefficients of variation for these measurements were less than 5%.

Cognitive function

Trained examiners administered two standardized cognitive function tests, MMSE[22] and HDS-R,[23] to assess multiple, diverse aspects of cognitive function at baseline and at the 3- and 6-month visits. Both scores range 0–30, with higher scores indicating better performance. HDS-R includes questions about the subject's age, orientation, immediate recall, serial subtraction of 7 s, reciting digits backward, recalling three words, recalling five objects and word fluency (generating names of vegetables). MMSE evaluates five aspects of cognition: (i) orientation; (ii) registration; (iii) attention and calculation; (iv) recall; and (v) comprehension of spoken language (naming objects, spoken language ability, following commands). MMSE, but not HDS-R, includes four performance tests: (i) three-stage command; (ii) reading and following a command; (iii) writing; and (iv) construction drawing). Based on the results of HDS-R and MMSE, we evaluated seven cognitive domains (points) as follows: (i) orientation (10); (ii) verbal memory (9); (iii) attention and calculation (5); (iv) visual memory (5); (v) spoken-language comprehension (9); (vi) verbal fluency (5); and (vii) performance (7).

Other functional parameters and anthropometric measures

Trained nurses and physical therapists visited the participants at the facility and performed the assessments. Basic ADL was assessed by Barthel Index,[26] mood by Geriatric Depression Scale (GDS, 15 items),[27] and ADL-related vitality by Vitality Index (10-point scale). [28] Higher GDS scores indicate a more marked self-reported depressive status, while higher Vitality Index scores indicate greater willingness.

Adverse events

Information regarding adverse events was obtained by questioning or examining the subjects. At each visit during the treatment period, all new complaints and symptoms were recorded. The safety of DHEA supplementation was assessed from the symptoms and by measuring blood chemical parameters including liver and kidney function, electrolyte levels and hematological parameters. Preexisting complaints or symptoms that increased in intensity or frequency during the treatment period also were examined.

Statistical analysis

Data were analyzed using SPSS statistical software ver. 17.0. Changes in outcome measures at 3 and 6 months were calculated by comparing the values at baseline with those at each measurement. Within each group, the significance of the change from baseline to 6 months was tested using paired Student's *t*-test. Repeated-measures ANOVA was used to test the statistical significance of the effects of DHEA versus control. Significance tests were two-sided, with an α-level of 0.05.

Results

Hormone changes and adverse effects

Characteristics and hormone levels at baseline according to treatment groups are shown in Table 1. There were no significant differences between the DHEA group and the control group in age, length of education, nutritional parameters, functional parameters and plasma hormone levels. DHEA supplementation was well tolerated, with high adherence, and there were no detectable adverse events and none of the subjects dropped out during the study. Measures of liver function, kidney function, electrolyte levels and hemoglobin level were not significantly altered by treatment with DHEA (data not shown). Body mass index remained unchanged in both groups.

Subjects in the DHEA group showed a significant increase from baseline to 3 and 6 months in levels of

Table 1 Participant characteristics at baseline

	DHEA	Control
No. of subjects	12	15
Age, years	82 ± 6 (69–90)	83 ± 6 (65–89)
Education, years	8 ± 2	8 ± 2
Nutritional parameters		
Body mass index, kg/m^2	22.0 ± 2.4 (18.8–26.4)	22.4 ± 3.2 (17.6–27.1)
Albumin, g/dL	4.4 ± 0.3 (3.7–4.9)	4.3 ± 3.2 (3.8–4.7)
Total cholesterol, mg/dL	227 ± 39 (166–294)	203 ± 22 (173–250)
Functional parameters		
MMSE	24.0 ± 4.2 (18–28)	23.4 ± 4.4 (14–28)
HDS-R	19.9 ± 5.8 (10–28)	21.7 ± 5.6 (10–28)
Barthel Index	89.6 ± 9.4 (55–100)	89.7 ± 6.4 (75–100)
Vitality Index	9.8 ± 0.6 (8–10)	9.9 ± 0.3 (9–10)
GDS	7.0 ± 4.4 (1–15)	7.0 ± 4.0 (1–13)
Hormones		
DHEA-S, μmol/L	1.8 ± 0.6 (0.7–2.4)	1.6 ± 0.8 (0.3–2.9)
DHEA, nmol/L	7.6 ± 4.7 (2.4–19.1)	6.6 ± 3.1 (2.1–11.5)
Testosterone, nmol/L	1.4 ± 0.4 (0.9–2.3)	1.3 ± 0.9 (0.2–3.8)
Estradiol, pmol/L	88 ± 52 (15–187)	70 ± 26 (45–115)

Values are shown as mean ± standard deviation (range). HDS-R, Hasegawa Dementia Scale-Revised; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; DHEA-S, dehydroepiandrosterone sulfate; DHEA, dehydroepiandrosterone. There was no significant difference in each parameter between the groups.

circulating DHEA, DHEA-S and testosterone, with levels reaching approximately 2–3-fold higher than those at baseline, whereas the increase in estradiol level was not significant (Table 2). Subjects in the control group showed no significant change in hormone levels.

Changes in cognitive function and ADL

The changes in functional parameters in each group from baseline to 6 months are shown in Table 2. After 6 months, mean HDS-R score significantly improved in the DHEA group while it remained unchanged in the control group. Mean MMSE score significantly declined in the control group while it remained unchanged in the DHEA group. As a result, significant differences were found in these scores between the groups. DHEA treatment maintained Barthel Index score, whereas the score deteriorated significantly during 6 months in the control group, although the between-group difference at 6 months was not statistically significant. Regarding the components of Barthel Index, in the control group, the sum score of mobility deteriorated significantly after 6 months compared to baseline, while no significant change was observed in the sum score of self care (Table 3). Neither Vitality Index nor GDS changed significantly in both groups.

Table 4 shows the cognitive domain scores at baseline and at 3- and 6-month follow up. Among the seven cognitive domains, DHEA treatment improved verbal fluency ($P < 0.05$), resulting in a significant difference at 6 months between the groups. Verbal memory showed a non-significant trend towards improvement in the DHEA group. Performance test scores significantly declined over time in both groups. There were no differences between the groups in the scores of orientation, attention and calculation, visual memory and spoken-language comprehension.

Discussion

Daily administration of DHEA 25 mg for 6 months in elderly women with mild to moderate cognitive impairment improved cognitive function and maintained basic ADL, compared to the control group. Among the cognitive domains, DHEA significantly improved verbal fluency. At baseline, DHEA and DHEA-S levels were lower than those reported in healthy postmenopausal women in both groups,[2,4] and DHEA treatment increased DHEA, DHEA-S and testosterone levels by 2–3-fold to the mid-normal range for premenopausal

Table 2 Changes in hormone levels and functional parameters by treatment group

	DHEA				Control				*P*
	Baseline	3 months	6 months	0–6-month difference	Baseline	3 months	6 months	0–6-month difference	
Hormones									
DHEA-S, μmol/L	1.8 ± 0.6	4.5 ± 1.3*	5.6 ± 2.9*	3.8 ± 2.8	1.6 ± 0.8	1.8 ± 1.0	1.7 ± 0.8	–0.02 ± 0.4	<0.01
DHEA, nmol/L	7.6 ± 4.7	12.2 ± 4.8*	13.7 ± 7.7*	6.1 ± 8.2	6.6 ± 3.1	7.3 ± 3.7	7.4 ± 4.5	0.9 ± 2.8	0.04
Testosterone, nmol/L	1.4 ± 0.4	2.3 ± 0.7*	2.3 ± 0.8*	0.9 ± 0.8	1.4 ± 0.7	1.4 ± 0.7	1.6 ± 0.8	0.2 ± 0.5	<0.01
Estradiol, pmol/L	88 ± 52	92 ± 48	101 ± 37	13 ± 51	70 ± 26	68 ± 20	67 ± 42	–4.0 ± 38	0.17
Functional parameters									
MMSE	24.0 ± 4.2	24.1 ± 4.6	24.6 ± 4.3	0.6 ± 3.2	23.4 ± 4.4	23.1 ± 5.4	21.3 ± 5.0**	–2.1 ± 2.2	0.04
HDS-R	19.9 ± 5.8	20.5 ± 7.3	22.7 ± 6.3**	2.8 ± 2.8	21.7 ± 5.6	22.1 ± 5.6	21.3 ± 6.4	–0.3 ± 4.1	0.04
Barthel Index	89.6 ± 9.4	92.7 ± 6.5	93.3 ± 6.8	3.7 ± 7.1	89.7 ± 6.4	86.9 ± 7.2	87.0 ± 6.7*	–2.7 ± 4.6	0.04
Vitality Index	9.8 ± 0.6	9.7 ± 0.5	9.7 ± 0.7	–0.1 ± 1.0	9.9 ± 0.3	9.8 ± 0.5	9.7 ± 1.0	–0.3 ± 1.0	0.80
GDS	7.0 ± 4.4	6.2 ± 3.4	6.6 ± 3.7	–0.4 ± 1.7	7.0 ± 4.0	8.3 ± 3.9	7.5 ± 3.5	0.5 ± 3.3	0.60

Values are shown as mean ± standard deviation (range). *P*-values are for repeated-measure ANOVA over all three time points. DHEA, dehydroepiandrosterone; HDS-R, Hasegawa Dementia Scale-Revised; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; DHEA-S, dehydroepiandrosterone sulfate; DHEA, dehydroepiandrosterone. $^{**}P < 0.01$ compared to baseline, $^{*}P < 0.05$ compared to baseline.

women.[2] No detectable adverse effects were observed throughout the study.

According to the previous trials, DHEA supplementation of 50 mg or more daily does not provide beneficial effects on cognition in healthy middle-aged to elderly women without cognitive impairment.[14–16] However, in a small-scale randomized double-blind placebo-controlled study, DHEA transiently improved cognition (after 3 months) in subjects with Alzheimer's disease while the improvement was not significant at 6 months.[29] Preliminary analysis of the small number of subjects in the present study suggested that DHEA treatment was no less effective in subjects with low baseline cognitive function than those with higher cognitive function (data not shown). Whether the effects of DHEA might be influenced by baseline cognitive function should be further investigated.

It is noteworthy that the 6-month effect of donepezil hydrochloride (5 or 10 mg), the only cholinesterase inhibitor used in Japan, in patients with Alzheimer's disease ranged from no change to less than 1 point improvement in MMSE score,[29–33] which is not so different from the effect of DHEA observed in the present study.

In the present study, not only the participants' cognitive function was impaired, but baseline plasma DHEA(-S) level was also low compared to that in postmenopausal or perimenopausal women.[2,4,10] Regarding DHEA-S levels, according to a report in which healthy pre- and postmenopausal women were studied, DHEA-S levels in women aged 35–44 years and 45–55 years were as follows: 4.31 ± 2.11, 3.90 (mean ± standard deviation) and 3.42 ± 2.01 μmol/L.[2] In this study, DHEA-S was measured using chemiluminescent enzyme immunometric assay; although the measurements by this method and those by radioimmunoassay have been reported to be comparable. In our study, DHEA treatment increased DHEA-S levels to the mid-normal range for premenopausal women.[2] Also, the subjects with lower baseline DHEA-S levels showed non-significant trend towards more improvement in cognitive scores (data not shown). Thus, future studies are needed to explore whether the effects of DHEA might be influenced by baseline DHEA levels.

Because the DHEA receptor has not been identified, DHEA may act after conversion to testosterone and subsequently estradiol through estrogen receptors and androgen receptors, both of which are found in the hippocampus and frontal lobes and subserve verbal memory and working memory in women.[34,35] Further, hippocampal volume and perfusion have been shown to correlate with serum DHEA-S level in demented patients.[36,37] It has also been suggested that estrogenic and androgenic derivatives of DHEA might have different effects on cognitive functions.[38] However, the mechanism by which DHEA improves cognitive

Table 3 Changes in mobility and self-care scores in Barthel Index during the study

Domains (points)	Mean ± SD Baseline	3 months	6 months	Change (0–6 months)	*P*
Mobility (55)					
DHEA	46.9 ± 9.2	48.2 ± 6.0	49.2 ± 5.2	2.3 ± 5.4	0.01
Control	47.5 ± 5.4	46.2 ± 5.5	45.0 ± 4.3*	−3.7 ± 3.9	
Self care (45)					
DHEA	42.7 ± 6.1	44.5 ± 1.5	43.1 ± 2.5	0.4 ± 6.9	0.96
Control	41.8 ± 4.2	42.5 ± 3.4	41.2 ± 4.3	0.7 ± 3.2	

Mobility is the sum score of five domains: (i) transfer (moving from a bed to a wheelchair and back); (ii) walking on a level surface; (iii) propelling a wheel chair; (iv) ascending and descending stairs; and (v) bathing and toilet use. Self care includes feeding, grooming, dressing, bowels and bladder. *P*-values are for repeated-measure ANOVA over all three time points. $^{*}P < 0.05$ compared to baseline. SD, standard deviation.

Table 4 Changes in cognitive domain scores during study

Domains (points)	Mean ± SD Baseline	3 months	6 months	Change (0–6 months)	*P*
Orientation (10)					
DHEA	8.3 ± 1.9	8.0 ± 2.7	7.5 ± 3.0	−0.1 ± 1.2	0.28
Control	8.3 ± 1.9	8.0 ± 2.8	7.5 ± 2.9	−0.7 ± 1.7	
Verbal memory (9)					
DHEA	5.7 ± 2.1	6.5 ± 2.3	6.7 ± 2.5†	1.0 ± 1.9	0.79
Control	6.5 ± 1.7	7.5 ± 1.8	7.0 ± 1.9	0.5 ± 1.7	
Attention and calculation (5)					
DHEA	2.3 ± 1.9	2.8 ± 2.0	2.7 ± 1.8	0 ± 2.3	0.79
Control	2.0 ± 1.7	1.9 ± 1.2	1.8 ± 1.5	−0.5 ± 1.4	
Visual memory (5)					
DHEA	3.6 ± 0.9	3.6 ± 1.3	3.8 ± 1.2	0.3 ± 1.1	0.91
Control	3.6 ± 1.3	3.9 ± 0.9	3.9 ± 1.0	0.5 ± 1.1	
Language comprehension (9)					
DHEA	8.5 ± 0.8	7.8 ± 2.5	8.7 ± 0.7	0.1 ± 0.3	0.12
Control	8.5 ± 0.8	8.5 ± 0.8	8.4 ± 1.1	−0.1 ± 0.9	
Verbal fluency (5)					
DHEA	2.8 ± 3.3	2.5 ± 2.0	4.3 ± 1.1*	1.5 ± 1.7	0.01
Control	3.2 ± 1.9	3.8 ± 1.6	3.3 ± 1.9	0.1 ± 2.1	
Performance (7)					
DHEA	5.7 ± 0.7	5.5 ± 0.7	4.8 ± 0.4**	−0.8 ± 0.6	0.36
Control	5.6 ± 0.6	5.1 ± 0.6	4.5 ± 0.9**	−1.1 ± 0.8	

Change refers to score change during 0–6 months for each parameter in each treatment group. *P*-values are for repeated-measure ANOVA over all three time points. DHEA, dehydroepiandrosterone. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{\dagger}P < 0.1$ vs baseline. SD, standard deviation.

function is unknown. In the present study, plasma estradiol level was not significantly increased after DHEA treatment, implying that its beneficial effects on cognition might be androgen-dependent. Unfortunately, free testosterone levels were not measured, because they were considered to be undetectable in many cases in older women. In addition, sex hormone-binding globulin (SHBG) measurement was not available; however, it has been reported that DHEA 50 mg treatment for 3 months in postmenopausal women did not significantly change SHBG levels,[39] suggesting that the change in SHBG-bound hormone levels after DHEA treatment might be minimal. Given the local aromatization of androgen to estradiol in the brain, the effect of DHEA on cognition might be indirect, complex and heterogeneous. The molecular mechanism underlying the association