Vitamin D Deficiency in Elderly Women in Nursing Homes: Investigation with Consideration of Decreased Activation Function from the Kidneys

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OBJECTIVES: To determine the approximate percentage of women in nursing homes who have vitamin D deficiency and to investigate whether, in assessing vitamin D status in elderly women, there are problems with measuring only 25 hydroxy-vitamin D_3 ($25(OH)D_3$) and whether decreased vitamin D activation as a result of poor renal function needs to be considered.

DESIGN: Cross-sectional study.

SETTING: Forty-eight nursing homes in Japan.

PARTICIPANTS: Four hundred three women with a mean age of 86.5 living in nursing homes who had participated in a clinical trial for hip protectors and were not bedridden.

MEASUREMENTS: At the start of the trial, in addition to general biochemical data, $25(OH)D_3$, 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$), intact parathyroid hormone (intact PTH), calcium (Ca), phosphorus (P), bone alkaline phosphate (BAP), cross-linked *N*-telopeptide of type I collagen (NTx), and osteocalcin were measured in participants' blood, and statistical analysis was performed.

RESULTS: $25(OH)D_3$, which is thought to reflect vitamin D status in the body, was surveyed and found to have a mean value of 16.7 ng/mL. $25(OH)D_3$ was less than 16 ng/mL in 49.1% of all participants. Creatinine clearance (CCr) was less than 30 mL/min in 20.1% of participants. Participants with serum $25(OH)D_3$ less than 16 ng/mL and CCr less than 30 mL/min had significantly higher levels of intact PTH and serum NTx. Participants with a CCr less than 30 mL/min had significantly lower levels of $1,25(OH)_2D_3$.

CONCLUSION: Frail elderly adults living in nursing homes with poor renal function had lower $1,25(OH)_2D_3$ and higher intact PTH levels and were thus thought to have poorer vitamin D activating capacity. Supplementation with cholecalciferol may be insufficient in people who have poor renal function. **J Am Geriatr Soc 60:251–255, 2012.**

Key words: 25-hydroxy-vitamin D_3; 1,25-dihydroxy-vitamin D_3; nursing homes

The importance of vitamin D for bones has been indicated in previous studies.[1,2] Frail elderly adults with limited ability to perform activities of daily living (ADL) who enter a nursing home are at high risk for low vitamin D as a result of poor nutrition and lack of sunlight. Vitamin D deficiency is an important risk factor for osteoporosis and fractures from falls in elderly adults.[3–5] When assessing serum 25 hydroxy-vitamin D_3 ($25(OH)D_3$) levels to define vitamin D deficiency, many reports have adopted a cutoff of 20 ng/mL.[6–8] It has also been reported that individuals with hip fracture or those with a history of falls have low $25(OH)D_3$ levels.[9,10] Secondary hyperparathyroidism from poor renal function in elderly adults must also not be overlooked.[11] The group that is probably at the highest risk of falls and fractures is elderly women living in nursing homes who are not completely bedridden but have a mobility level of at least being able to move about in a wheelchair with assistance. The participants in this study were such a group of people, who had previously participated in a fracture prevention trial using hip protectors.[12] Vitamin D levels, renal function, and the relationship between the two were investigated in these women, and the approximate percentage of these nursing home residents who needed supplemental vitamin D was considered.

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METHODS

Participants were 403 women aged 70 and older (range: 70–103) who lived in 48 nursing homes from whom consent was obtained for participation in a fracture prevention trial using hip protectors.[12] They had a mobility level of at least being able to move about in a wheelchair with assistance. A history of bilateral hip fracture was a condition for exclusion. Written informed consent was obtained from all participants. The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study. Blood was collected from participants as the 48 nursing homes in the southern part of central Japan were visited in turn between January 2005 and May 2008. At the start of the trial, in addition to general biochemical data, 25(OH)D_3, 1,25-dihydroxy-vitamin D_3 (1,25$(OH)_2D_3$), intact parathyroid hormone (PTH), calcium (Ca), phosphorus (P), bone alkaline phosphate (BAP), cross-linked *N*-telopeptide of type I collagen (NTx), and osteocalcin were measured using participants' blood, and statistical analysis was performed. 25(OH)D_3 was measured using the radioimmunoassay double antibody method. Frail elderly adults have little muscle, and even if creatinine (Cr) is in the normal range, it cannot be concluded that renal function is normal. For a simpler assessment of renal function, we estimated Cr clearance (CCr) with adjustments for age and body weight using the widely adopted Cockcroft-Gault formula.[13]

Statistical Analyses

SPSS (version 17.0, SPSS, Inc., Chicago, IL) was used in the statistical analysis. Adjustment was made for age as a control variable in partial correlation. Two-tailed significance probability <.05 was taken to be significant. The Student *t*-test was used to test for differences between the mean values of the two groups, with $P < .05$ taken to indicate significance. The Bonferroni test was used to compare the mean values in the groups, using a general linear model adjusted for age. $P < .05$ was taken to indicate a significant difference.

RESULTS

Participants were aged 70 were to 103 (mean 86.5). Mean 25(OH)D_3 level, which is an indicator of vitamin D level, was low (16.7 ng/mL). The mean values for the following tests were: 1,25$(OH)_2D_3$, 44.4 ± 17.5 pg/mL; intact PTH, 57.4 ± 38.7 pg/mL; BAP, 32.4 ± 13.2 U/L; osteocalcin, 7.8 ± 3.8 ng/mL; and NTx, 17.6 ± 9.7 nmol bone collagen equivalent/L. The percentile distribution in the 25(OH)D_3 distribution is shown in Figure 1. When 25(OH)D_3 concentration of less than 20 ng/mL was taken to indicate vitamin D deficiency, 78.1% of participants were found to be vitamin D deficient.

To further investigate 25(OH)D_3, the partial correlation was first examined adjusted for age. There were significant positive correlations between 25(OH)D_3 and 1,25$(OH)_2D_3$ (correlation coefficient (r) = 0.149, $P = .003$), albumin ($r = 0.185$, $P < .001$), total cholesterol ($r = 0.165$, $P = .001$), blood urea nitrogen ($r = 0.116$, $P = .02$), Ca ($r = 0.153$, $P = .002$), and P ($r = 0.100$, $P = .04$). Significant negative correlations were shown with serum NTx ($r = -0.153$, $P = .002$) and intact PTH ($r = -0.178$, $P < .001$). It was then decided to further investigate intact PTH, which had shown a high correlation. Mean intact PTH levels in the group with a serum 25$(OH)D_3$ concentration less than 12.0 ng/mL, 12.0 to 15.9 ng/mL, and 16.0 ng/mL or higher were 72.3 pg/mL, 60.4 pg/mL, and 51.1 pg/mL, respectively. Mean intact PTH level was significantly higher in participants with a serum 25(OH)D_3 concentration less than 12.0 ng/mL ($P < .001$) and 12.0 to 15.9 ng/mL ($P = .02$) than in those with a concentration of 16.0 ng/mL or higher. Participants younger than 85 were then compared with those aged 85 and older to determine whether the various data differed depending on age (Table 1). Significant differences were seen in 25(OH)D_3, 1,25$(OH)_2D_3$, and intact PTH. Because 1,25$(OH)_2D_3$, a form of activated vitamin D, also decreases with age, it was decided to investigate 1,25$(OH)_2D_3$. First, in the age-adjusted partial correlation, 1,25$(OH)_2D_3$ showed the strongest negative correlation with Cr ($r = -0.323$, $P < .001$). This finding suggests that renal function strongly affects 1,25$(OH)_2D_3$. The relationship between 1,25$(OH)_2D_3$ concentration and estimated CCr is shown in Table 2. 1,25$(OH)_2D_3$ concentration was significantly lower in participants with CCr less than 30 mL/min. Similarly, intact PTH concentration was significantly higher in participants with CCr less than 30 mL/min, in whom 1,25$(OH)_2D_3$ concentration was significantly lower (Table 2). A tendency was seen for 25(OH)D_3 levels to be higher with lower CCr, and a significant difference was seen between groups with CCr of less than 30 and 45 mL/min or greater ($P < .05$, general linear model Bonferroni test). To improve understanding of how participants were distributed according to 25(OH)D_3 concentration and CCr value, they were divided into four groups with 25(OH)D_3 concentrations of less than 16 and 16 ng/mL and greater and CCr of less than 30 and 30 mL/min and greater. Concentrations of 1,25$(OH)_2D_3$, intact PTH, and serum NTx of the groups were then compared (Table 3). Of 198 participants with 25(OH)D_3 concentrations of less than 16 ng/mL, 36 (18.4%) had poor renal function (CCr < 30 mL/min), and of 205 participants with

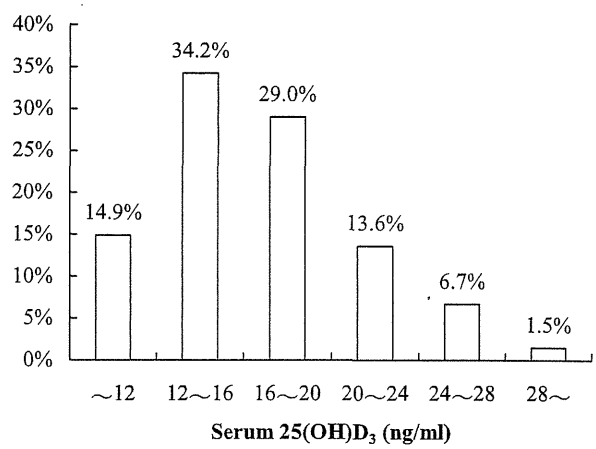

Figure 1. Percentile distribution of serum 25 hydroxy-vitamin D_3 (25(OH)D_3) concentrations. 25(OH)D_3 level was < 20 ng/mL in 78.1% and < 16 ng/mL in approximately half.

Table 1. Comparison of Mean Data Values According to Age

Characteristic	Normal Range	Mean ± Standard Deviation <85 (n = 139)	Mean ± Standard Deviation ≥85 (n = 264)	*P*-Value
Age	—	79.1 ± 3.8	90.4 ± 3.7	<.001
Height, cm	—	145.2 ± 7.5	142.8 ± 7.2	.003
Weight, kg	—	44.1 ± 8.3	41.6 ± 7.5	.003
Body mass index, kg/m^2	—	20.7 ± 4.4	20.0 ± 3.3	.28
25 hydroxy-vitamin D_3, ng/mL	—	17.5 ± 4.9	16.3 ± 4.7	.01
1,25-dihydroxy-vitamin D_3, pg/mL	20–60	47.5 ± 18.1	42.7 ± 16.9	.008
Intact parathyroid hormone, pg/mL	10–65	51.6 ± 27.4	60.4 ± 43.2	.03
Albumin, g/dL	3.9–4.9	3.9 ± 0.3	3.9 ± 0.4	.01
Total protein, g/dL	6.5–8.2	6.9 ± 0.5	6.9 ± 0.5	.26
Total cholesterol, mg/dL	120–220	207.6 ± 38.0	195.9 ± 36.3	.003
Blood urea nitrogen, mg/dL	8–20	17.8 ± 6.5	18.7 ± 7.7	.25
Creatinine, mg/dL	0.5–0.8	0.66 ± 0.3	0.72 ± 0.4	.13
Creatinine clearance (Cockcroft-Gault formula), mL/min	—	55.2 ± 18.6	38.9 ± 12.7	<.001
Glomerular filtration rate (modified diet in renal disease formula), mL/min	—	73.9 ± 25.0	65.4 ± 22.1	.001
Calcium, mg/dL	8.7–10.1	8.8 ± 0.4	8.8 ± 0.5	.25
Phosphorus, mg/dL	2.5–4.5	3.6 ± 0.4	3.6 ± 0.5	.21
Aspartate aminotransferase, U/L	10–40	19.2 ± 6.2	19.7 ± 6.2	.39
Alanine aminotransferase, U/L	5–45	13.2 ± 7.5	11.5 ± 6.0	.02

Table 2. Comparison of 1,25-Dihydroxy-Vitamin D_3 ($1,25(OH)_2D_3$), Intact Parathyroid Hormone (PTH), and 25 Hydroxy-Vitamin D_3 ($25(OH)D_3$) Concentrations According to Creatinine Clearance (CCr)

CCr, mL/min	Mean (Standard Error) $1,25(OH)_2D_3$, pg/mL	Intact PTH, pg/mL	25 Hydroxy-Vitamin D_3, ng/mL
<30.0 (n = 82)	33.0 (1.9)*	80.1 (4.3)*	17.9 (5.2)
30.0–44.9 (n = 160)	45.8 (1.3)	52.7 (3.0)	17.0 (4.9)
≥45 (n = 161)	48.8 (1.4)	50.5 (3.2)	15.9 (4.4)

* $P < .05$, general linear model Bonferroni test.

Table 3. Comparison of 1,25-Dihydroxy-Vitamin D_3 ($1,25(OH)_2D_3$), Intact Parathyroid Hormone (PTH), and Cross-Linked *N*-Telopeptide of Type I Collagen (NTx) Concentrations According to Creatinine Clearance (CCr) and 25 Hydroxy-Vitamin D_3 ($25(OH)D_3$) Concentration

CCr, mL/min	Mean (Standard Error) $25(OH)D_3$, ng/mL <16	$25(OH)D_3$, ng/mL ≥16
<30		
$1,25(OH)_2D_3$, pg/mL	29.0 (2.7)*	36.3 (2.5)*
Intact PTH, pg/mL	104.8 (6.1)*	60.7 (5.4)
NTx, nmolBCE/L	28.3 (1.6)*	18.9 (1.4)
≥30		
$1,25(OH)_2D_3$, pg/mL	45.2 (1.2)	49.3 (1.3)
Intact PTH, pg/mL	55.1 (2.8)	48.1 (2.9)
NTx, nmolBCE/L	17.1 (0.7)	15.3 (0.7)

$1,25(OH)_2D_3$ levels were significantly lower in participants with CCr lower than 30 mL/min than those with CCr of 30 mL/min and higher. Mean intact PTH and NTx concentrations in participants with CCr lower than 30 mL/min and $25(OH)D_3$ of less than 16 ng/mL were significantly higher than in the other participants.

* $P < .05$, general linear Bonferroni test.

$25(OH)D_3$ concentrations of 16 ng/mL and higher, 45 (22.0%) had poor renal function. These percentages were approximately the same, but concentrations of intact PTH and NTx were significantly higher in the group with $25(OH)D_3$ of less than 16 ng/mL and CCr of less than 30 mL/min. In addition, in the group with CCr of less than 30 mL/min, $1,25(OH)_2D_3$ concentration was significantly lower than in the group with CCr of 30 mL/min and higher, regardless of $25(OH)D_3$ concentration.

DISCUSSION

Table 4 summarizes the reports on $25(OH)D_3$ concentration in elderly cohorts.[14–20] A comparison of reports in which participants were living in institutions and reports in which participants were living independently revealed lower levels of $25(OH)D_3$ in residents of institutions, who are thought to have greater difficulty with activities of daily living. Experts have proposed that $25(HO)D_3$ concentrations of 20 to 32 ng/mL, or roughly 30 ng/mL, are the minimum necessary concentration to prevent fractures.[21] A recent meta-analysis also reported that concentrations of 75 to 100 nmol/L balanced the benefits and risks of the health of elderly people.[22] Many studies take PTH to be an indicator of the cutoff value for $25(OH)D_3$ concentration.[6–8] When PTH is taken as an indicator, a $25(OH)D_3$ concentration of 20 ng/mL is taken as the cutoff

Table 4. Past Reports of 25 Hydroxy-Vitamin D_3 (25 $(OH)D_3$) Levels in Elderly Cohorts

Study Participants	n	Age, Mean	25(OH)D_3, ng/mL, Mean	References
Nursing home (Japan)	133	84.6	11.9	14
Nursing home or housebound (United States)	116	81	12.6	15
Nursing home (this study, Japan)	425	86.4	16.8	—
Nursing home (United States)	35	74	17.4	16
Independent women (Canada)	186	73	15.6	17
Independent women (France)	440	80	17.0	18
Community-dwelling elderly women (Japan)	2,007	75.4	24.2	19
Independent women (United States)	500	71	29.6	20

in many reports.[6–8] In the participants in this study, 78.1% had 25(OH)D_3 levels less than 20 ng/mL. Another study reported that 25(OH)D_3 of 20 ng/mL and greater is needed when intact PTH is taken as the indicator and that 28 ng/mL and greater is needed when bone density in the femoral neck is taken as the indicator.[6] From the present results, the cutoff value for 25(OH)D_3 as an indicator of intact PTH was thought to be 16 ng/mL; 49.1% of participants had 25(OH)D_3 of less than 16 ng/mL (Figure 1). In general, people with poor renal function have lower levels of 1,25$(OH)_2D_3$, an activated form of vitamin D, as a result of poor vitamin D activating capacity. Moreover, secondary hyperparathyroidism from poor renal function is not unusual in elderly people.[11] In the present results as well, there was a strong negative correlation between 1,25 $(OH)_2D_3$ and CCr ($r = -0.323$, $P < .001$), which suggests that renal function strongly affects 1,25$(OH)_2D_3$. As shown in Table 2, intact PTH levels were significantly higher and 1,25$(OH)_2D_3$ significantly lower with a CCr of less than 30 mL/min. From this it can be conjectured that vitamin D activation in the kidneys may decrease in cases of secondary hyperparathyroidism from poor renal function. In addition, as shown in Table 3, the percentage of people with poor renal function (CCr < 30 mL/min) was nearly the same in participants with 25(OH)D_3 levels greater and less than 16 ng/mL. Women with such vitamin D activating capacity made up 20.1% of all participants, although according to guidelines published in the United States in 2003[23] for bone metabolism disorders in individuals with chronic kidney disease, if PTH is measured and found to be high in people undergoing dialysis and those with chronic renal failure with less than 60% renal function, it is recommended that serum 25(OH)D_3 be measured and vitamin D_2 be administered if it is less than 30 ng/mL. Considering these guidelines, a greater number of people would probably be judged to have poor renal function, although there are limitations to this investigation. All CCr values were derived through calculation, not from actual measurements of CCr or glomerular filtration rate (GFR). Cystatin C was not measured either. The Cockcroft-Gault formula was first used to calculate CCr, but the Modification of Diet in Renal Disease (MDRD) formula[24] was also used to investigate CCr. The correlation between CCr calculated using the Cockcroft-Gault formula and GFR calculated using the MDRD formula was high ($r = 0.769$, $P < .001$). Moreover, in the group with GFR of less than 50 mL/min (n = 84, 20.8%), a significant difference, similar to that in the results obtained with the Cockcroft-Gaults formula, was seen. Thus, although CCr obtained from calculations is not ideal, it seems to be reliable. In addition, intact PTH level may be a useful indicator in establishing a cutoff value for 25(OH) D_3 in frail elderly adults such as the present participants. Moreover, because plainly higher intact PTH levels were shown in participants with poor vitamin D activation in the kidneys, intact PTH may have an important role in considering vitamin D supplementation in frail elderly adults. Many experts recommend vitamin D supplementation with cholecalciferol when 25(OH)D_3 level drops below 30 to 32 ng/mL. A recent Institute of Medicine report[25] recommends supplementation when 25(OH)D_3 is less than 20 ng/mL, but it does not specifically address frail elderly adults. Vitamin D is not activated efficiently even with cholecalciferol supplementation in frail elderly adults, such as the present participants, who seem to have poor activation of vitamin D. Theoretically, therefore, it would seem that supplementation with a form of activated vitamin D such as paricalcitol or alfacalcidol may be beneficial in the case of frail elderly adults with poor renal function.

CONCLUSION

In this study, 25(OH)D_3 levels were found to be low in women living in nursing homes who were at least able to move about in a wheelchair with assistance. Approximately 50% to 80% of participants were thought to be vitamin D deficient, although this depends somewhat on the cutoff value used for 25(OH)D_3. In addition, approximately 20% of all participants were thought to have decreased vitamin D activating capacity in the kidneys. Such poor vitamin D activation capacity in the kidneys was present in a similar 20% of people whose 25(OH)D_3 level was above the cutoff level (16 ng/mL). An unexpectedly large number of women in nursing homes thus had poor vitamin D activation secondary to poor renal function. For vitamin D supplementation, therefore, it may be necessary to make a comprehensive judgment with measurements of intact PTH and CCr or GFR and 1,25 $(OH)_2D_3$ rather than cholecalciferol supplementation based simply on 25$(OH)_3$ level.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Relationship between Atrophy of the Medial Temporal Areas and Cognitive Functions in Elderly Adults with Mild Cognitive Impairment

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Key Words
Entorhinal cortex · VSRAD · Voxel-based morphometry · Wechsler Memory Scale · Stroop test

Abstract
Aim: The current study sought to determine which types of cognitive function are related to atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) in elderly adults. ***Methods:*** The subjects were 96 elderly adults (mean age 75.3 years) with mild cognitive impairment. Subjects underwent Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II), Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backword (DSB), digit symbol-coding (DSC), Stroop Color and Word Test-Interference List (SCWT-IL) as well as magnetic resonance imaging (MRI) and were divided into elderly adults without or with mild to moderate MTA-ERC atrophy, and those with severe atrophy. ***Results:*** In all subjects, MTA-ERC atrophy showed significant relationships with age (r = 0.43), education (r = –0.25), WMS-R, LM I (r = –0.21), DSC (r = –0.32), and SCWT-IL (r = 0.32). The mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and age (r = 0.34), DSC (r = –0.28), and SCWT-IL (r = 0.25). In contrast, in the severe atrophy group, MTA-ERC atrophy was correlated significantly with RCF-3 min (r = –0.70) and RCF-30 min (r = –0.74). The linear regression model included demographic variables and cognitive tests; two variables to survive the step-wise analysis were age (β = 0.374) and SCWT-IL (β = 0.247) in all subjects. Age (β = 0.301), and RCF-30 min (β = –0.521) and age (β = 0.460) remained as a significant variable in the mild to moderate atrophy and severe atrophy groups, respectively. ***Conclusion:*** Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and a decline in the RCF test may suggest severe MTA-ERC atrophy in elderly adults with MCI.

Introduction

There is increasing evidence for baseline structural magnetic resonance imaging (MRI) correlates of cognitive impairment in elderly adults exhibiting mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1–4]. To date, the most reliable and well-documented finding is an association between impaired memory ability

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and medial temporal lobe atrophy, which is particularly robust in the hippocampus and entorhinal cortex (ERC) [5]. Several studies have reported that hippocampal and ERC atrophy can predict conversion to AD [6–9], as well as memory decline in MCI and AD [10, 11]. Although memory deficits constitute the hallmark feature of MCI, many patients exhibit deficits in other cognitive domains, such as mild anomia [12, 13], reductions in semantic fluency [14] and executive dysfunction, characterized by impaired working memory, inhibition, set-shifting, and phonemic fluency [15, 16]. The pathological hallmarks of AD (e.g. neurofibrillary tangles and senile plaques) have been found in the ERC in the earliest phase of disease, leading to an overall neuronal loss of 32% compared with control subjects [17]. An MRI investigation of the ERC reported a 37% decrease in patients who went on to develop AD, in comparison with control subjects [18]. These findings indicate that a strong relationship exists between in vivo measures of ERC atrophy in the early stages of AD.

The region of interest (ROI) method and more automated methods such as voxel-based morphometry (VBM) are the most common MR analysis techniques used for examining brain atrophy. Automated analytical methods such as VBM enable objective examination of anatomical group differences in controls, MCI patients, and AD patients across the whole brain. With this statistical parametric mapping technique, researchers are able to evaluate group differences in gray matter, white matter, and cerebrospinal fluid (CSF) volume with high spatial resolution. Whole-brain VBM has the important advantage of not requiring a priori assumptions about the size, location, or shape of the brain ROI(s). Furthermore, VBM allows the quantification of brain changes that are not easily revealed by visual inspection, such as atrophy that is not fully encompassed by sulcal boundaries between structures.

Recent research has led to the development of a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which enables the examination of atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) using VBM [19–21]. The VSRAD has been shown to achieve high accuracy (87.8%) in discriminating patients in the very early stages of AD with MCI from normal control subjects using Z-scores [21]. Atrophy of the MTA-ERC was indicated by VSRAD to exhibit a clear functional relationship with blood flow changes in the hippocampus, thalamus and temporal lobe, which were suggested to be closely related to interregional anatomical and physiological connections [22]. In cognitive function, Nagata et al. [23] reported that Z-scores of the VSRAD was associated with executive function, although there was no relationship between Z-scores and memory function which was assessed by the Mini-Mental State Examination (MMSE) in the amnestic MCI and early AD patients. These authors suggested that detailed examination such as the Wechsler Memory Scale was required to reveal the relationship between MTA atrophy and memory function. Moreover, it is currently unclear which aspects of cognitive function including memory and executive function are related to the atrophy of the MTA-ERC identified by VSRAD in elderly adults with MCI.

In the current study, we measured volumetric MRI and performance in a range of cognitive domains, including logical memory, visual memory, working memory, processing speed, and executive function in elderly adults with MCI. Overall, we sought to determine which aspects of cognitive performance were associated with MTA-ERC atrophy in elderly adults with MCI.

Methods

Subjects

Subjects in this study were recruited from two volunteer databases (n = 1,543), which included elderly individuals (65 years and over) selected either by random sampling, or when they attended a medical check-up in Obu, Japan. 528 prospective subjects with a Clinical Dementia Rating (CDR) of 0.5, or who complained of memory impairment, were recruited in the first eligibility assessments. 165 subjects responded to the second eligibility assessments, and 125 out of 165 subjects completed the neuropsychological tests which included language and memory tests, attention and executive function tests, clinical diagnosis, activities of daily living (ADL), educational level, and MRI scanning. Out of 125 subjects, 25 were excluded and the remaining 100 subjects met definition of MCI using Petersen criteria [24]. All MCI subjects had objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. Final classification of subjects was based on the above factors and consensus of a team of neuroscientists. Exclusion criteria included CDR 0, or 1–3, a history of neurological, psychiatric, and cardiac disorders or other severe health issues, use of donepezil, impairments in basic ADL, and participation in other research projects. 96 elderly adults remained after these exclusions (mean age 75.3 ± 6.8 years, range 65–93, men n = 48, 50%), and were included in the final analysis. Table 1 shows the characteristics of the subjects.

The purpose, nature, and potential risks of the experiments were fully explained to subjects. All subjects gave written, informed consent before participating in the study. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology.

Table 1. Characteristics of subjects (mean ± SD)

Age, years	75.3 ± 6.8
Male, %	50
Education, years	10.6 ± 2.5
Body mass index	23.0 ± 3.1
Cognitive functions	
MMSE, points	26.5 ± 2.5
WMS-R, LM I, points	14.4 ± 7.1
WMS-R, LM II, points	10.0 ± 7.4
RCF-3 min, points	15.5 ± 6.3
RCF-30 min, points	14.9 ± 6.7
DSB, points	5.2 ± 1.6
DSC, points	46.1 ± 15.9
SCWT-IL, s	21.1 ± 17.2
Medication, yes, %	
Hypertension	44.8
Heart disease	5.2
Diabetes mellitus or hyperlipidemia	20.9
Total number ± SD	2.3 ± 2.1

WMS-R, LM = Wechsler Memory Scale-Revised, Logical Memory; RCF = Rey complex figure retention test; DSB = digit span backward; DSC = digit symbol coding; SCWT-IL = Stroop Color and Word Test-Interference List.

MRI

MRI was performed with a 1.5-T system (Magnetom Avanto; Siemens, Germany). Three-dimensional volumetric acquisition with a T_1-weighted gradient echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time 1,700 ms, echo time 4.0 ms, flip angle 15°, acquisition matrix 256 × 256, 1.3 mm slice thickness).

The MRI images acquired from the subjects were formatted to gapless, transaxial images, followed by extraction of the gray matter images using SPM2. Anatomical standardization was used to fit each individual brain to the standard template MRIs in the common coordinate system of the MNI T_1 MRI template [25, 26]. The segmented gray matter images were then subjected to affine and non-linear standardization using a template of prior gray matter.

The anatomically standardized gray matter images were then smoothed again using an isotropic Gaussian kernel 12 mm in full width at half maximum, to determine the partial volume effect and create a spectrum of gray matter intensities. Gray matter intensities were equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensity was considered equivalent to gray matter concentration. We compared the gray matter image of each patient with the mean and standard deviation (SD) of gray matter images of healthy volunteers using voxel-by-voxel Z-score analysis. In the final step, the Z-score was calculated according to the following equation: (Z-score = ((control mean) – (individual value))/control SD). The Z-score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z-scores indicated clearer MTA-ERC atrophy.

Cognitive Tests

Speech therapists conducted all of the memory tests, and a speech therapist recalculated all of the results. The Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II) [27], Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backward (DSB) and digit symbol-coding (DSC) subset of the Wechsler Adult Intelligence Scale III [28], and Stroop Color and Word Test-Interference List (SCWT-IL) [29] were included as cognitive tests.

Modified versions of the logical memory subtest from the WMS-R and RCF were used to assess logical and visual memory ability, respectively. In the WMS-R, two short stories (story a and b) were read aloud to the subject, who was instructed to recall details of the stories immediately (LM I) and after 30 min (LM II) [27]. We calculated the total score, i.e. sum score of story a and b, of WMS-R in LM I and LM II. In the RCF, subjects were requested to copy the RCF figure (construction ability) and reproduce it after 3- and 30-min delays. One rater independently scored the RCF using the system described by Osterrieth and Rey [30] and translated by Corwin and Bylsma [31]. DSB and DSC were used to assess working memory and processing speed, respectively. DSB required subjects to repeat a series of verbally presented digits of increasing length in backward order. In the DSC, subjects copied symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant drew the symbol under the corresponding number. The score of DSC was the number of correct symbols drawn within 120 s. In the SCWT-IL as a test of executive function, subjects were presented with a series of color words. Our test version consisted of two subtasks. The first subtask showed color words in random order (red, blue, yellow, green) printed in black ink. The second subtask contains color words printed in an incongruous ink color, for example, the word *yellow* printed in red ink. The subjects were instructed to read the words and name the ink color of the printed words as quickly and as accurately as possible in the two subsequent subtasks. The score was measured as the total time taken to complete the task with 24 words [32]. The time limit to complete a subtask was set at 120 s. An interference measure was calculated by subtracting the average time needed to complete the first subtask from the time needed to complete the second subtask.

Analysis

The relationships between atrophy of the MTA-ERC and cognitive measurements were examined with Pearson correlations. The independent associations between MTA-ERC atrophy and cognitive ability with each demographic (i.e. sex, age, and educational level) and diagnosis (aMCI and non-aMCI) variables were tested using a linear regression model with a step-wise analysis. To examine differences in MTA-ERC atrophy level, subjects were divided into the following two groups according to the Z-score: (1) mild to moderate atrophy group (Z-score: 0–1.99) and (2) severe atrophy group (Z-score: 2.00 and over) in the MTA-ERC, according to the results of the VSRAD [23]. Pearson correlations and the linear regression model with a step-wise analysis were used to examine the relationships between MTA-ERC atrophy and cognitive tests in each group. SPSS 18.0 software (SPSS Inc., Chicago, Ill., USA) was used for all data management and statistical analysis. The statistical threshold was set at a $p < 0.05$.

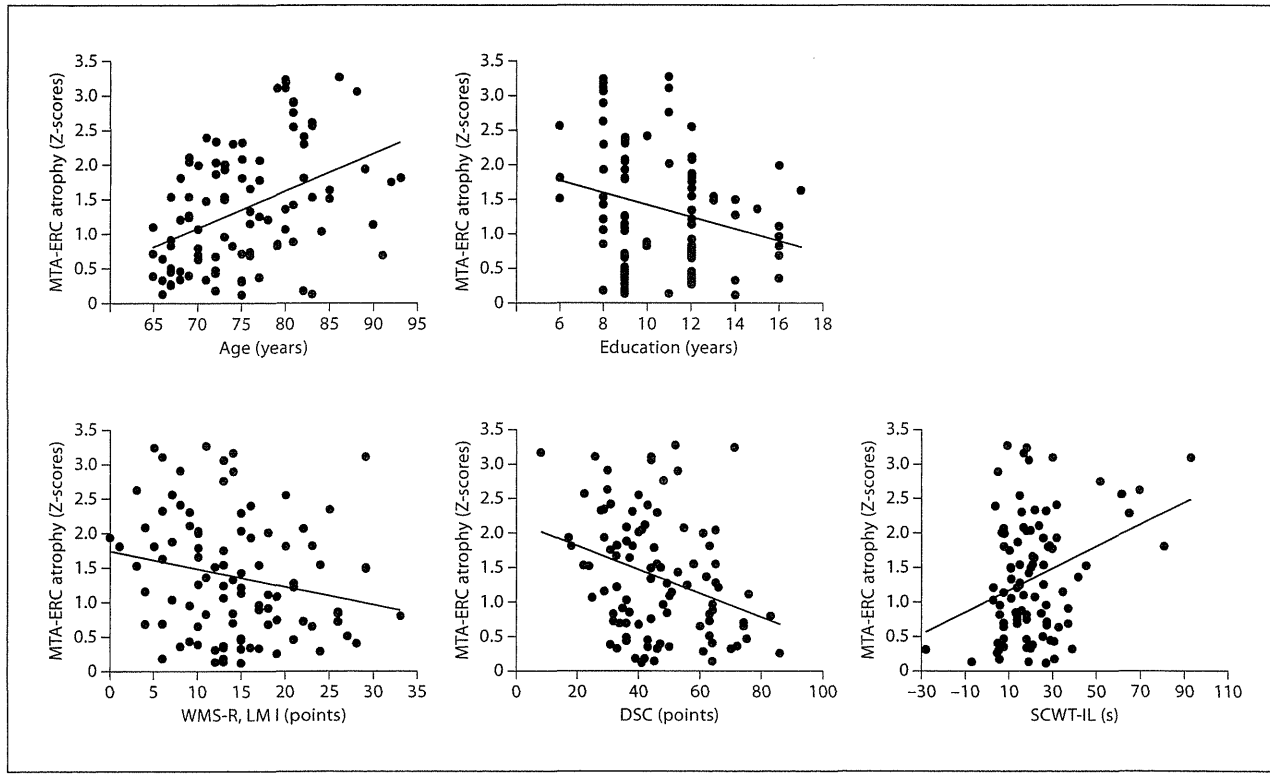

Fig. 1. Relationship between the Z-score of MTA-ERC and age, education, and cognitive test scores. MTA-ERC atrophy was correlated significantly with age ($r = 0.43$, $p < 0.001$), educational level ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$).

Table 2. Pearson correlation coefficients between MTA-ERC atrophy and age, educational level, and cognitive measurements

	All subjects (n = 96)		Mild to moderate atrophy group (n = 72)		Severe atrophy group (n = 24)	
	r	p value	r	p value	r	p value
Age	0.43	**<0.001**	0.34	**0.003**	0.71	**<0.001**
Education	−0.25	**0.012**	0.01	0.921	−0.26	0.224
WMS-R, LM I	−0.21	**0.040**	−0.17	0.155	−0.06	0.774
WMS-R, LM II	−0.09	0.370	0.03	0.812	−0.22	0.308
RCF-3 min	−0.16	0.119	−0.10	0.396	−0.70	**<0.001**
RCF-30 min	−0.13	0.201	−0.11	0.386	−0.74	**<0.001**
DSB	−0.15	0.134	−0.12	0.298	−0.14	0.511
DSC	−0.32	**0.002**	−0.28	**0.016**	−0.05	0.825
SCWT-IL	0.32	**0.002**	0.25	**0.031**	0.18	0.404

For abbreviations, see table 1.

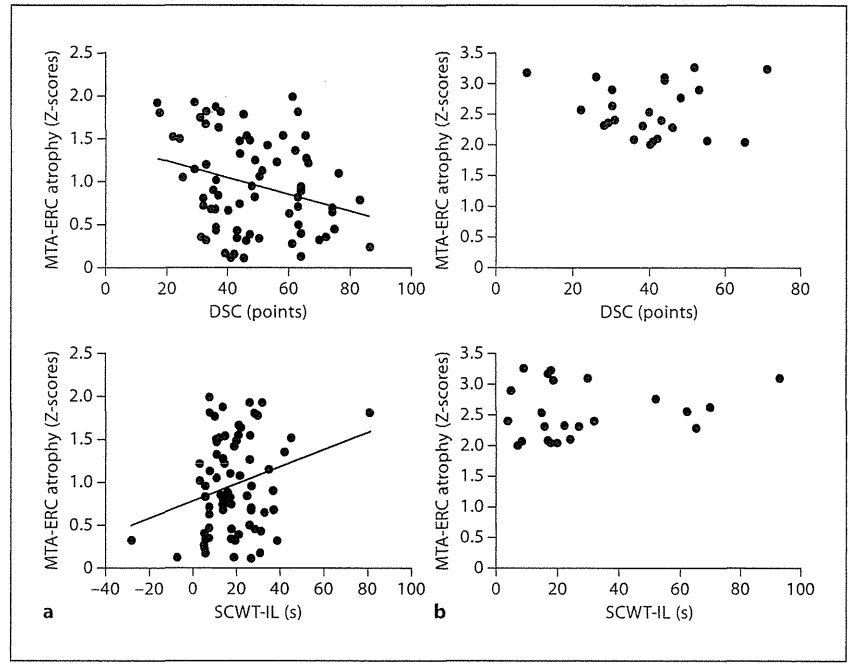

Fig. 2. Relationship between the Z-score of MTA-ERC and processing speed and executive function in the mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and DSC and the lower panel shows scatter plots between MTA-ERC atrophy and SCWT-IL. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with DSC ($r = -0.28$, $p = 0.016$) and SCWT-IL ($r = 0.25$, $p = 0.031$) in the mild and moderate atrophy group.

Table 3. Multivariate regression analysis between MTA-ERC atrophy and age, educational level, and cognitive measurements

	β	t value	p value	R^2
All subjects				
Age	0.374	4.0	<0.001	0.236
SCWT-IL	0.247	2.6	0.01	
Mild to moderate atrophy group				
Age	0.301	2.6	0.011	0.091
Severe atrophy group				
RCF-30 min	−0.521	−3.8	0.001	0.706
Age	0.460	3.4	0.003	

For abbreviations, see table 1.

Results

In all subjects, Z-score showed significant relationships with age ($r = 0.43$, $p < 0.001$), education ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$) (fig. 1; table 2). There were no significant relationships between Z-score and WMS-R, LM II, RCF-3 min, RCF-30 min, and DSB (table 2). In linear regression model, two variables to survive the step-wise analysis were age ($\beta = 0.374$, $p < 0.001$) and SCWT-IL ($\beta = 0.247$, $p < 0.010$) (table 3).

Of the 96 MCI elderly adults tested, the mild to moderate atrophy and severe atrophy groups included 72 (75%) and 24 (25%) subjects, respectively. In the Pearson correlation analysis, the mild to moderate atrophy group showed significant relationships between Z-score and age ($r = 0.34$, $p = 0.003$), DSC ($r = -0.28$, $p = 0.016$), and SCWT-IL ($r = 0.25$, $p = 0.031$) (fig. 2; table 2). In contrast, Z-scores were correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group (fig. 3; table 2).

A multivariate regression model indicated that age ($\beta = 0.301$, $p = 0.011$) remained as the only significant variable in the mild to moderate atrophy group (table 3). DSC and SCWT-IL did not reach significance in this group. In the severe atrophy group, two variables to survive the step-wise analysis were RCF-30 min ($\beta = -0.521$, $p = 0.001$) and age ($\beta = 0.460$, $p = 0.003$) (table 3).

Discussion

It is well established that structures in the medial temporal lobe, particularly the hippocampus and ERC, are essential for normal memory function [33]. There is evi-

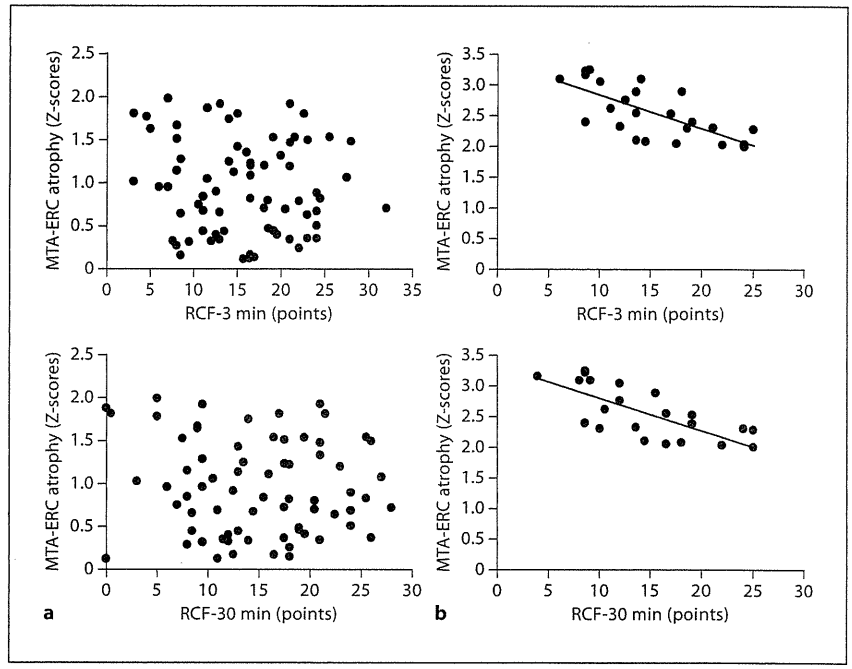

Fig. 3. Relationship between the Z-score of MTA-ERC and Rey complex figure retention test in mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and RCF-3 min and the lower panel shows scatter plots between MTA-ERC atrophy and RCF-30 min. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group.

dence that these brain regions are substantially affected by disease in the early stages of AD [34, 35], in accord with the finding that memory impairment is the earliest symptom of disease in most AD patients. The ERC is part of a critical pathway in the neural system underlying memory. Zola-Morgan et al. [36] reported that this area receives afferents from widespread association and limbic areas, projects to the dentate gyrus of the hippocampal formation, receives afferents from the hippocampus, and sends afferents back to association neocortex. An epidemiological study reported that ERC atrophy was greater than hippocampal atrophy in patients suffering from MCI [35]. However, the two measures were found not to differ in AD, suggesting that the ERC atrophies before the hippocampus in incipient AD [37]. An autopsy study of early AD patients reported neurofibrillary tangles in the ERC before evidence of hippocampal involvement [35]. Thus, volumetric MRI analysis of the MTA included ERC may be a sensitive predictor to identify AD conversion and decline of neuropsychological performances in MCI elderly adults.

In the current study, 25% of elderly adults with MCI exhibited severe atrophy in the MTA-ERC. The VSRAD analysis revealed that Z-scores indicating probable AD and amnestic MCI patients averaged 1.94 ± 1.24 (ranging from 0 to 4.69) [22]. Subjects exhibiting MTA-ERC atrophy as well as probable AD were included in the present MCI study. Numerous imaging studies have reported a correlation between increasing age and decreasing brain volume [38–42]. This decline in brain volume may be due to a non-linear acceleration in rates of atrophy after 70 years of age [43]. In the current study, 72 subjects (75%) were 70 years and over. Thus, the brain volume of our sample may have been affected by advancing age. In fact, we found significant relationships between age and MTA-ERC atrophy in MCI elderly adults. Similar findings were revealed in the relationship between MTA-ERC atrophy and educational level. Educational level was also a potential confounding factor of the prevalence and risk of dementia [44–46]. Educational level is thought to construct cognitive reserve, which modifies the relationship between brain atrophy and cognitive decline [47].

In the cognitive tests, WMS-R, LM I, DSC, and SCWT-IL showed significant correlations with MTA-ERC atrophy in univariate regression analysis. However, a multivariate regression model that included age and educational level revealed that MTA-ERC atrophy, i.e. high Z-score of VSRAD, was related only to SCWT-IL score in all subjects. Functional neuroimaging studies during executive tasks suggest that dorsolateral prefrontal cortex is responsible for maintenance of task demands and preparatory deployment of attention, and anterior cingulate

cortex is responsible for monitoring performance in order to detect cognitive and behavioral conditions with potential negative outcomes, and triggering dorsolateral prefrontal cortex to increase attention or change behavior [48–52]. A volumetric MRI study showed that there was an association between left hemisphere dorsolateral prefrontal cortex and anterior cingulate cortex atrophy and poorer attentional control accuracy. In the right hemisphere, atrophy of the temporal-parietal junction and ventrolateral and dorsolateral prefrontal cortices were associated with slower response times during attentional control on accurate trials [53]. This evidence from neuroimaging studies suggests that an executive deficit was caused by brain disorders in widespread regions that included prefrontal cortex, parietal lobe, and cingulate cortex. Neuropathological studies have shown that axonal pathology is strongly associated with cognitive impairment [54], and MCI patients may have increased white matter diffusivity in frontal and temporal regions [55]. The disruption of neural networks between the anterior and posterior cerebral areas, known as disconnection syndrome, during the initial stage of AD and MCI causes executive dysfunction, including changes in inhibition control [56–58]. Atrophy of the MTA is correlated with the degree of dementia and also with the extent of temporoparietal hypometabolism; both results are assumed to reflect changes in cerebral connectivity, especially between the MTA and the neocortex [59–61]. AD patients, as well as older adults with MCI, have shown selective disruption of default network intrinsic connectivity, most prominently in connectivity between the precuneus/posterior cingulate and medial temporal lobe regions [58, 61–64]. In diffusion tensor imaging study, the cingulum fibers, which connect the posterior cingulate gyrus and the hippocampus, may be compromised in the early stage of AD [65]. In recent years, Grambaite et al. [66] reported that frontal and temporal white matter diffusivity changes in the posterior cingulate region as well as the anterior cingulate region in MCI patients who had attention and executive dysfunctions. Reciprocal connections between the dorsolateral frontal cortex and anterior cingulate cortex [67–70] are part of a frontolimbic network [71, 72]. In the present study, MCI subjects showed a relationship between Z-score of the VSRAD and cognitive tests, especially tests of executive function. This relationship may be affected by not only MTA-ERC atrophy but also disconnectivity among MTA, temporoparietal, anterior cingulate, and prefrontal regions.

In a sub-analysis dividing subjects into two groups, the mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and DSC and SCWT-IL. The multivariate analysis on the mild to moderate atrophy group did not sustain the statement that DSC and SCWT-IL performances may be a reliable indicator of MTA-ERC atrophy in MCI patients. Increasing age is related closely with decreasing brain volume [38–42]. In fact, age remains the only significant variable indicating that its relative weight is too high and deletes the association between Z-scores and DSC and SCWT-IL observed in univariate models. In contrast, MTA-ERC atrophy was related closely to RCF-3 min and RCF-30 min in the severe atrophy group. In the multivariate regression model, MTA-ERC was associated independently with visual memory adjusted for age, educational level, and other cognitive functions. For the right temporal lobe there is some evidence that damage specifically in temporomesial structures may be the cause of impairments in nonverbal memory functions. Patients with hippocampal damage showed preoperatively [73] and postoperatively [74] impaired visual memory performance, whereas patients without hippocampal damage exhibited no deficiencies in visual memory. In line with previous operative studies, our results from MCI elderly adults with severe atrophy suggest a special involvement of MTA in visual memory performance. However, the VSRAD system was developed to measure the total atrophy in the bilateral parahippocampal gyrus and ERC. Thus, the association between visual memory and right hippocampal volume reduction should be investigated in the future.

It should be noted that this study may have been limited by a restricted sample. In addition, we did not include an analysis of genetic factors. Because genetic and physical factors such as apolipoprotein E genotype [75] and head size [76] may impact on neurodegenerative disorders and brain volume, analyzing genetic factors may extend the current results. Fitness level may have also acted as a confounding factor. Many studies have reported that physical activity can reduce the likelihood of the development of cognitive decline over time [77, 78]. Higher levels of fitness related to increased physical activity have been associated with enhanced neuronal survival in response to brain insult [79, 80], increased vascularization [81], and elevation of growth factors in areas important for memory [82]. More detailed analysis adjusting for these confounding variables will be required to further elucidate the relationship between MTA-ERC atrophy and memory function.

Overall, the present findings revealed that MTA-ERC atrophy was associated with age, educational level, and executive function, whereas no significant relationship

was found between MTA-ERC atrophy and memory tests in elderly subjects with MCI. This included the adults who had mild to moderate atrophy in MTA-ERC. In contrast, there was a significant relationship between MTA-ERC atrophy and visual memory test scores in elderly adults with severe MTA-ERC atrophy. These results suggest that executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy. A decline of visual memory function suggested severe MTA-ERC atrophy in elderly adults with MCI. Future research needs to determine the relationships between cognitive functions and brain atrophy except MTA-ERC in elderly adults with MCI.

Take Home Message

(1) MTA-ERC atrophy was significantly related to age, educational level, and executive function in elderly subjects with MCI.
(2) The subjects with severe MTA-ERC atrophy showed significant relationships between MTA-ERC atrophy and a decline in visual memory score.
(3) Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and decline in the RCF test suggests severe MTA-ERC atrophy in elderly adults with MCI.

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地域在住中高年者の微量ミネラルおよびビオチンの摂取量

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資　料

地域在住中高年者の微量ミネラルおよびビオチンの摂取量

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要旨：日本食品標準成分表が5年ぶりに改訂され，ヨウ素，セレン，クロム，モリブデン，ビオチン含有量が新たに収載された。これらの栄養素は平成12年から使用されている「第六次改定日本人の栄養所要量食事摂取基準」に言及がありながら，これまでの食品成分表には収載されていなかった。そのため，日本人の摂取量に関する報告が乏しい。そこで本研究では，無作為抽出された地域在住中高年者（40-89歳，男性1,065人，女性1,050人）を対象とした3日間の食事記録調査に基づき，ヨウ素，セレン，クロム，モリブデンおよびビオチン摂取量を算出した。また性別に5歳刻みの年代群別に1日平均摂取量を算出し，分布を示した。地域在住中高年者のヨウ素，セレン，クロム，モリブデン，ビオチン摂取量の中央値は男性で151.0μg/日，50.1μg/日，6.3μg/日，175.8μg/日，27.3μg/日，女性で117.5μg/日，42.9μg/日，5.3μg/日，132.4μg/日，23.8μg/日であった。

キーワード：ヨウ素，セレン，クロム，モリブデン，ビオチン

平成22年11月，文部科学省により日本食品標準成分表が5年ぶりに改訂され，日本食品標準成分表2010（以下，食品成分表2010）[1]が公表された。収載食品数は五訂増補日本食品標準成分表[2]と変わらず1,878食品だが，成分項目にヨウ素，セレン，クロム，モリブデン，ビオチン，アミノ酸組成から算出したたんぱく質量，トリアシルグリセロール当量の7種が拡充され基本栄養素が50種に増えた。その中のヨウ素，セレン，クロム，モリブデンの微量ミネラルとビオチンは，平成12年（2000年）に公表された第六次改定日本人の栄養所要量[3]の食事摂取基準において，生体の機能維持に必要との考えに基づき摂取基準が策定されているものの[4]，これまでの食品成分表にはこれらの値は収載されていなかった。そのため，わが国の一般地域住民での摂取量に関する報告も乏しく，日本人の食事摂取基準［2010年版］[5]においても，基準値の策定にあたっては，海外での調査結果を主に参照したことが明記されている。

今回の食品成分表2010で，これらの栄養素は498食品について掲載されており，これは収載食品全体の26.5%である。部分的なデータベースであるが，日本の一般住民を対象とした大規模栄養調査において摂取量や分布を明らかにすることは，今後の摂取基準策定や食品成分表の充実に有用であり，公衆栄養上，重要であると考える。

そこで本研究では，新しく公表された食品成分表2010を用いて，地域在住中高年者におけるヨウ素，セレン，クロム，モリブデンおよびビオチンの摂取量を，性別，5歳刻みの年代別に算出し報告することとした。

方　法

1. 対　象

対象者は「独立行政法人国立長寿医療研究センター・老化に関する長期縦断疫学研究（National Institute for Longevity Sciences-Longitudinal Study of Aging：NILS-LSA）」[6]の第6次調査（2008-2010年）に参加した地域在住中高年者である。NILS-LSAは，年齢および性別で層化無作為抽出された地域在住中高年者（愛知県大府市または同県東浦町在住，初回調査時年齢40-79歳）を対象とした縦断的コホート調査である。本研究では下記の食事調査を完成した2,115名（40-89歳，男性：1,065名，女性：1,050名）を対象とした。

なおNILS-LSAは，国立長寿医療研究センター倫理委員会で承認を得ており，参加対象者に事前に説明会を行い，参加者全員に文書での同意を得て行われている。

2. 調査項目および解析

食事調査は，写真撮影を併用した休日1日を含む連続した3日間の食事秤量記録調査（3DR）[7]を用いた。食品

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成分表2010[1]を用いて，ヨウ素，セレン，クロム，モリブデンおよびビオチンの1日摂取量を算出し，それぞれ1階級あたり1–100 μg/日でヒストグラムを性別に作成した（図1-5）。さらに，性別の5歳刻みの年代群別摂取量より5，25，50（中央値），75，95パーセンタイル値を求め，食事摂取基準［2010年版］の推定平均必要量（EAR），推奨量（RDA），目安量（AI），目標量（DG），耐容上限量（UL）と比較した（表2-6）。

BMI（kg/m^2）は，身長，体重の測定値より算出した。喫煙の有無，自覚的健康度については自記式質問票を用いて調査し，基本的な栄養摂取量とアルコールの1日平均摂取量は3日間の食事記録調査（3DR）から算出した。

統計解析にはSAS 9.1.3を用いた。対象者特性の性差は，カテゴリー変数についてはχ^2検定，連続変数についてはWilcoxon検定を用いて検討した。有意水準は5%とした。

結　　果

1. 対象者特性

対象者の特性を表1に示した。基本的な栄養素およびヨウ素，セレン，クロム，モリブデンおよびビオチンの1日平均摂取量はすべて男性で有意に多く摂取されていた（$p<0.0001$）。

表1　対象者特性

		男性（$n=1065$）	女性（$n=1050$）	p[a]
年齢	n, %			0.6251
40–44歳		134, 12.6%	144, 13.7%	
45–49歳		95, 8.9%	103, 9.8%	
50–54歳		104, 9.8%	97, 9.2%	
55–59歳		147, 13.8%	137, 13.0%	
60–64歳		139, 13.1%	138, 13.1%	
65–69歳		128, 12.0%	119, 11.3%	
70–74歳		133, 12.5%	125, 11.9%	
75–79歳		113, 10.6%	109, 10.4%	
80歳以上		72, 6.8%	78, 7.4%	
自覚的健康度	n, %			0.0543
非常に良い		65, 6.1%	44, 4.2%	
良い		320, 30.1%	302, 28.8%	
普通		615, 57.8%	634, 60.4%	
悪い		63, 5.9%	68, 6.5%	
非常に悪い		2, 0.2%	2, 0.2%	
喫煙の有無	n, %			<0.0001
現在吸っている		235, 20.1%	46, 4.4%	
やめた		524, 49.2%	60, 5.7%	
以前から吸わない		306, 28.7%	944, 89.9%	
アルコール摂取量	g/日	15.1±19.5	3.0±7.9	<0.0001
BMI	kg/m^2	23.1±2.7	22.3±3.3	<0.0001
栄養素摂取量				
エネルギー	kcal/日	2198±390	1798±313	<0.0001
たんぱく質	g/日	81.0±15.9	68.1±13.1	<0.0001
動物性たんぱく質	g/日	43.1±13.3	35.4±10.7	<0.0001
脂質	g/日	58.6±16.6	52.1±14.6	<0.0001
動物性脂質	g/日	29.6±11.3	25.3±9.9	<0.0001
炭水化物	g/日	303.0±62.0	255.6±50.1	<0.0001
ナトリウム	g/日	4.6±1.0	3.8±0.8	<0.0001
ヨウ素	μg/日	889.6±2011.7	687.6±2184.0	<0.0001
セレン	μg/日	53.6±24.4	44.8±18.6	<0.0001
クロム	μg/日	6.5±2.3	5.6±2.2	<0.0001
モリブデン	μg/日	185.3±66.3	139.3±48.2	<0.0001
ビオチン	μg/日	29.4±12.9	25.4±10.5	<0.0001

[a] カテゴリー変数についてはχ^2検定，連続変数についてはWilcoxon検定を用いて検討した。

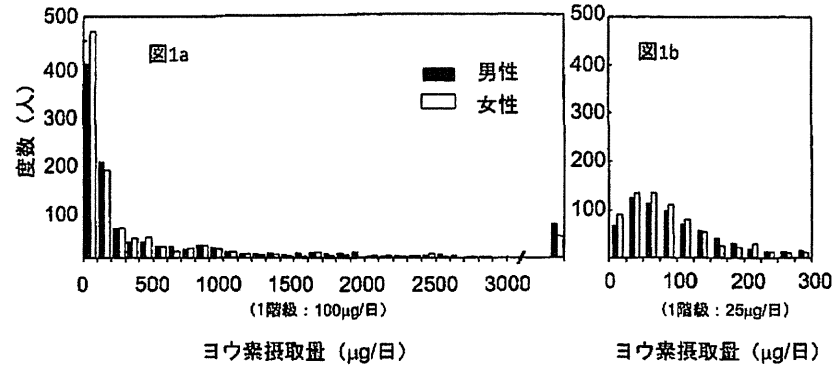

図1　a. ヨウ素摂取量の全体のヒストグラム（μg/日），b. 0-300μg/ 日範囲のヨウ素摂取量のヒストグラム（μg/ 日）

表2　中高年者における性・年代群別ヨウ素摂取量の各パーセンタイル値と食事摂取基準値

	食事摂取基準（2010年版）								パーセンタイル値				
	EAR	RDA	AI	DG	UL	*n*	Mean	SD	5	25	50	75	95
男性（*n*＝1065）													
40-44歳	95	130	—	—	2200	134	582 ± 1715		16	54	108	364	2338
45-49歳	95	130	—	—	2200	95	462 ± 929		21	67	118	388	2470
50-54歳	95	130	—	—	2200	104	659 ± 1464		16	55	117	651	2572
55-59歳	95	130	—	—	2200	147	1017 ± 2279		25	61	150	705	4330
60-64歳	95	130	—	—	2200	139	734 ± 1582		22	69	152	850	3163
65-69歳	95	130	—	—	2200	128	753 ± 1217		23	70	172	1027	3181
70-74歳	95	130	—	—	2200	133	1409 ± 2969		22	78	220	1501	8051
75-79歳	95	130	—	—	2200	113	1134 ± 2440		26	79	250	953	6489
80歳以上	95	130	—	—	2200	72	1301 ± 2348		19	98	271	1075	6666
総数	—	—	—	—	—	1065	890 ± 2012		22	66	151	799	3956
女性（*n*＝1050）													
40-44歳	95	130	—	—	2200	144	441 ± 1081		19	41	79	317	2352
45-49歳	95	130	—	—	2200	103	368 ± 739		19	55	113	306	1617
50-54歳	95	130	—	—	2200	97	546 ± 1333		15	49	97	222	4038
55-59歳	95	130	—	—	2200	137	1018 ± 4016		20	54	112	440	5022
60-64歳	95	130	—	—	2200	138	721 ± 1600		18	61	136	653	3479
65-69歳	95	130	—	—	2200	119	655 ± 1420		23	62	128	566	3671
70-74歳	95	130	—	—	2200	125	786 ± 2302		20	61	138	462	3078
75-79歳	95	130	—	—	2200	109	623 ± 1195		24	68	139	571	2859
80歳以上	95	130	—	—	2200	78	1084 ± 3543		18	75	168	649	3307
総数	—	—	—	—	—	1050	688 ± 2184		19	58	118	480	3167

EAR：推定平均必要量，RDA：推奨量，AI：目安量，DG：目標量，UL：耐容上限量，Mean：1日平均摂取量，SD：標準偏差

2. ヨ ウ 素

ヨウ素摂取量は，幅広く分布していたため，図1aには全体の分布を確認出来るように1階級100 μg/日あたりの度数分布を示し，図1bには最頻値の0-300 μg/日の範囲を1階級25 μg/日で示した。男女ともに50-75 μg/日付近にピークのある非常に右裾に長い尾を引いた分布であることが特徴であった（図1）。3,000 μg/日を超える者は男性で77名（7.2%），女性で56名（5.3%）であった。表2より，食事摂取基準の推奨量と本研究対象者での中央値はほぼ同等であり，女性の45-49歳を除いたすべての群で，95パーセンタイル値が耐容上限値を上回っていた。

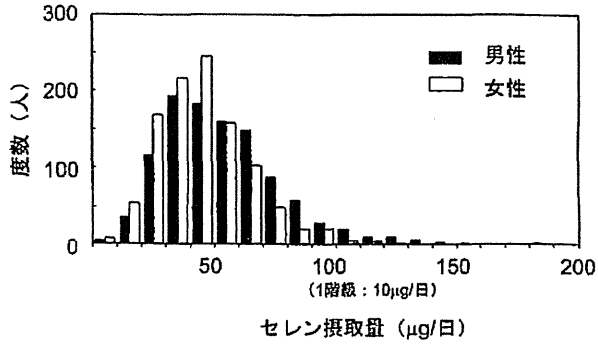

図2　セレン摂取量のヒストグラム（μg/日）

表3 中高年者における性・年代群別セレン摂取量の各パーセンタイル値と食事摂取基準値

	食事摂取基準（2010年版）					パーセンタイル値						
	EAR	RDA	AI	DG	UL	*n*	Mean SD	5	25	50	75	95
男性（*n*＝1065）												
40–44歳	25	30	—	—	300	134	51.4±26.3	20.3	34.5	44.6	64.1	103.0
45–49歳	25	30	—	—	300	95	50.1±24.0	21.5	31.6	45.0	69.9	91.0
50–54歳	25	30	—	—	280	104	55.5±27.5	22.3	39.5	50.0	65.6	100.0
55–59歳	25	30	—	—	280	147	54.1±22.7	23.1	37.4	50.9	68.8	99.0
60–64歳	25	30	—	—	280	139	57.3±23.0	27.0	40.5	56.1	68.0	103.9
65–69歳	25	30	—	—	280	128	58.0±26.8	24.6	35.1	53.7	74.4	104.0
70–74歳	25	30	—	—	260	133	50.6±21.6	19.3	32.0	51.2	65.9	83.9
75–79歳	25	30	—	—	260	113	50.3±20.9	19.2	33.8	47.2	64.1	86.2
80歳以上	25	30	—	—	260	72	54.3±26.9	20.3	33.9	47.1	70.9	111.0
総数	—	—	—	—	—	1065	53.6±24.4	21.7	35.2	50.1	66.9	97.9
女性（*n*＝1050）												
40–44歳	20	25	—	—	230	144	42.1±16.9	16.4	29.0	42.9	52.4	72.2
45–49歳	20	25	—	—	230	103	41.7±16.3	17.5	31.1	42.2	48.5	72.2
50–54歳	20	25	—	—	230	97	47.9±20.9	16.3	34.1	45.0	58.7	89.5
55–59歳	20	25	—	—	230	137	46.4±16.8	24.0	34.8	43.6	54.4	80.4
60–64歳	20	25	—	—	230	138	48.7±19.5	21.0	35.2	45.5	63.6	86.7
65–69歳	20	25	—	—	230	119	45.8±18.2	19.1	31.7	44.8	59.2	73.0
70–74歳	20	25	—	—	210	125	44.7±19.4	19.4	31.6	40.7	56.6	75.8
75–79歳	20	25	—	—	210	109	44.5±19.6	19.2	30.5	42.3	55.8	80.2
80歳以上	20	25	—	—	210	78	39.6±18.7	15.8	25.9	35.9	50.0	74.3
総数	—	—	—	—	—	1050	44.8±18.6	19.2	31.5	42.9	55.1	78.9

EAR：推定平均必要量，RDA：推奨量，AI：目安量，DG：目標量，UL：耐容上限量，Mean：1日平均摂取量，SD：標準偏差

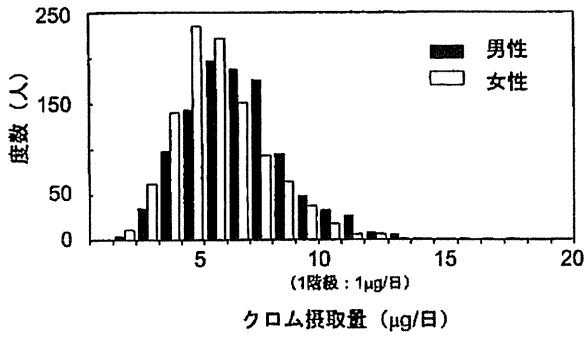

図3 クロム摂取量のヒストグラム（μg/日）

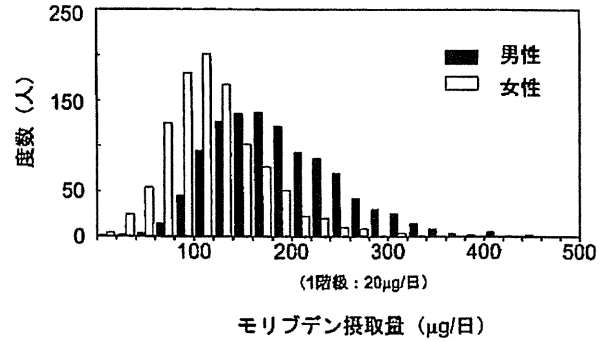

図4 モリブデン摂取量のヒストグラム（μg/日）

3. セ レ ン

セレン摂取量は，男性で30 μg/日付近にピークのある右裾広がりの分布であった。女性は50 μg/日付近にピークのある右裾広がりの分布であった（図2）。食事摂取基準の推奨量に対して中央値では1.5–1.8倍量であり，95パーセンタイル値は耐容上限値の0.3倍であった（表3）。

4. ク ロ ム

クロム摂取量は，男性で6 μg/日付近にピークがあり，女性は5 μg/日付近にピークのある右裾広がりの分布であった（図3）。食事摂取基準の推奨量と比べると中央値で0.15倍量であった。95パーセンタイル値でも推奨量の0.24–0.3倍であった（表4）。

5. モリブデン

モリブデン摂取量は，男性で160–180 μg/日付近にピークがあり，女性は100–120 μg/日付近にピークのある右裾広がりの分布であった（図4）。食事摂取基準の推奨量と比べると5パーセンタイル値で2倍以上摂取されていた。95パーセンタイル値では耐容上限量の約0.5倍であった（表5）。

6. ビ オ チ ン

ビオチン摂取量は，男性で25–30 μg/日付近にピークがあり，女性は20–25 μg/日付近にピークのある右裾広がりの分布であった（図5）。食事摂取基準の目安量と比べると中央値で半量しか摂れておらず，95パーセンタイル値でも男性の60–64歳群を除いたすべての群で目安量を下回った（表6）。