ORIGINAL ARTICLE

Association between cognitive decline and decreased serum osteocalcin levels in community-dwelling older people

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Abstract

Many reports show that low bone mineral density and osteoporosis are associated with cognitive impairment and Alzheimer's disease in older women. In addition, bone-related substances such as osteocalcin (OC) and insulin-like growth factor 1 (IGF-1) affect cognitive function. In this study, the aim was to clarify the relationship between changes in cognitive function and changes in serum OC, IGF-1, and albumin levels in community-dwelling older people. The participants were 76 healthy older people living in Japan. They participated in a weekly, local government-supported exercise class for 13 weeks. The Mini-Mental State Examination (MMSE) was used to evaluate cognitive function. Twenty-two participants (28.9%) had decreased MMSE scores at the 13th week. Correlation analysis showed that ΔOC correlated with ΔMMSE score. On analysis of covariance adjusted for baseline values, the cognitive decline group had a significantly greater decrease in OC levels than the no cognitive decline group. The participants with increased ΔOC had lower odds of cognitive decline at the 13th week on logistic regression analysis. These results suggest that there may be a relationship between decreases in serum OC levels and cognitive decline in community-dwelling older people.

Key words: *cognitive function, osteocalcin, older people*

INTRODUCTION

The prevention of dementia and musculoskeletal disease is an important issue in Japan, as the older population continues to grow. Many reports show that low bone mineral density (BMD) and osteoporosis are associated with cognitive impairment and Alzheimer's disease (AD) in older women (Lui, 2003; Tan, 2005; Zhou, 2011; Lee, 2012; Sohrabi, 2015).

Bone remodeling is performed continuously through osteoblastic bone formation and osteoclastic bone resorption. Osteocalcin (OC) is secreted by bone osteoblasts and used as a biomarker of the osteogenic process (Guntur, 2012). In recent years, OC has been linked to cognition, via its binding to the Gpr158receptor, which is abundant in neurons in the hippocampus CA3 region, a memory center of the brain (Khrimian, 2017a). OC-deficient mice have been shown to have small hippocampus volume and low memory capacity (Oury, 2013). On the other hand, insulin-like growth factor 1 (IGF-1) has been reported to promote cell survival in the hippocampus, suppress apoptosis, and stimulate neurogenesis; it is also abundant in bone matrix and increases bone formation (Lee, 2009). IGF-1 has been reported to suppress deposition of brain amyloid beta and abnormal tau phosphorylation associated with AD (Hong, 1997). Hippocampal neurogenesis is reduced and spatial learning is impaired in mice with reduced IGF-1 levels and in IGF-1 gene-deficient mice (Llorens-Martín, 2010).

The positive effect of improved cognitive function can generally be seen with exercise interventions conducted for healthy older people and those with mild cognitive impairment (Angevaren, 2008; Smith 2010; Nagamatsu, 2012; Suzuki, 2012). In humans, aerobic exercise and combined aerobic and aerobic-resistance training have been found to increase serum IGF-1 and OC levels, respectively (Lester, 2009; Cetinkaya, 2013; Alghadir, 2014).

The above results suggest that bone-related substances may be involved in cognitive function. However, there is no report on the relationship between changes in cognitive function and changes in these biomarkers in humans. The aim was to clarify the relationship between changes in cognitive function

and changes in OC and IGF-1 levels in community-dwelling older people.

METHODS

Participants

The present study was conducted in Kaizuka city, Osaka Prefecture, Japan, between January and April 2019. The inclusion criteria were as follows: 1) age ≥ 60 years; 2) living independently at home; and 3) not having a cardiac pacemaker. In total, 76 participants (mean age [standard deviation], 74.7 [5.4] years; range, 63–91 years) were included in the analysis. The Ethics Committee of Osaka Kawasaki Rehabilitation University approved this study (Reference No. OKRU30-A016), and the study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before the study began.

Exercise class

All participants took part in a local government-supported exercise class that was conducted once a week (1 h per session) for 13 weeks by a certified physical therapist. The contents of the class included 15 min of intellectual tasks and 45 min of exercise tasks, such as soft gymnastics and light dancing. Various measurements were taken twice before participation (baseline) and after 13 weeks.

Measurement variables

Body composition parameters were measured using an InBody 270 bioelectrical impedance analysis (BIA) device (InBody, Tokyo, Japan) at 20 and 1000 kHz while the participants were wearing normal indoor clothing without socks or shoes. All participants were instructed to grasp the handles of the BIA device and stand on electrodes contacting the bottoms of their feet. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Calcaneus BMD was evaluated by quantitative ultrasound (i.e., the speed of sound [SOS] of the calcaneus) and expressed as the percent of Young Adult Mean of the SOS (%YAM) using an ultrasound bone densitometer (AOS-100SA, Hitachi, Tokyo, Japan).

Evaluation of cognitive function

Cognitive function was assessed using the Japanese version of the Mini-Mental State Examination (MMSE) (Folstein, 1975). Changes in cognitive function were calculated by subtracting the MMSE score at the 13th week from the MMSE score at baseline. The no cognitive decline group included participants whose MMSE scores differed < 0 between the baseline and the 13th week. The cognitive decline group included participants whose MMSE score differed > 0 between the baseline and the 13th week.

Blood examination

Blood samples were taken between 10:00 AM and 3:00 PM. All participants fasted 2 hours before blood collection. The following were measured at baseline and the 13th week: OC, IGF-1, and albumin levels. Albumin was used as a nutritional marker. Blood analyses were performed at a laboratory within 24 h of being taken (Japan Clinical Laboratories, Inc., Kyoto, Japan). OC was measured by electrochemiluminescence immunoassay, IGF-1 by immuno radio metric assay, and albumin by nephelometry.

Questionnaire

A self-completed questionnaire regarding education history and medical history of hypertension, diabetes mellitus, hyperlipidemia, Parkinson's disease, AD, cerebrovascular dementia, stroke, osteoporosis, and depression was used.

Statistical analysis

To compare numerical values between the cognitive decline group and the no cognitive decline group, the normality of their distributions and homogeneity of variance were tested prior to comparison across groups. Student's *t*-test was used when assumptions of a normal distribution and homogeneity of variance were fulfilled in both groups, and Welch's *t*-test was used when the assumption of a normal distribution, but not that of homogeneity of variance, was met. The Wilcoxon signed-rank test was used when data were not normally distributed. The X^2 test was used to compare disease prevalence between the cognitive decline group and the no cognitive decline group. Pearson product-moment correlation analysis was conducted to clarify the correlation between each measurement and ΔMMSE score. Analysis of covariance (ANCOVA) was used to compare the Δvalue between cognitive groups after adjustment for baseline values. The independent variable was the group, and the dependent variables were the Δvalues. The odds ratios (ORs) of cognitive decline for ΔOC were calculated using logistic regression analysis. Logistic regression Model 1 was adjusted for sex, Model 2 was adjusted for sex and BMI, and Model 3 was adjusted for sex and osteoporosis status. All statistical

analyses were conducted using JMP 11 (SAS Institute, Cary, NC). Values of $p < 0.05$ were considered significant. All p values are presented along with 95% confidence intervals (CIs) for the two-sided analyses.

RESULTS

Characteristics of study participants

Table 1 shows participants' characteristics and medical histories. The BMI was significantly higher in the cognitive decline group than in the no cognitive decline group ($p = 0.022$).

Correlation of measurements with changes in the cognition score

Pearson product-moment correlation analysis showed that none of the values at baseline was correlated with ΔMMSE score. Among the Δvalues, only ΔOC correlated with ΔMMSE score ($r = 0.286$, $p = 0.012$) (Table 2).

Comparisons of changes in the cognitive decline and no cognitive decline groups

Twenty-two participants (28.9%) had cognitive decline based on a decreased MMSE score at the 13th week compared with baseline. To compare the Δvalue between the groups, ANCOVA was used after adjusting for baseline values. Compared with the cognitive decline group, the no cognitive decline group showed a significantly greater increase in the OC level ($F = 5.252$, $p = 0.025$) (Figure 1) (Table 3).

Odds ratios for changes in biomarkers in participants with cognitive decline

Table 4 shows the ORs for changes in biomarkers in the cognitive decline group as assessed by logistic regression analysis adjusted for sex (Model 1), for sex and BMI at baseline (Model 2), and for sex and osteoporosis status at baseline (Model 3). All results showed that participants with increased ΔOC values had significantly lower odds of cognitive decline at the 13th week (OR = 0.731, CI = 0.556-0.960, $p = 0.013$;

Table 1. Characteristics of study participants at baseline

	Total (n=76)	Cognitive decline group (n=22)	No cognitive decline group (n=54)	p value
Male (%)	16 (21.05)	6 (27.27)	10 (18.52)	0.404[¶]
Age (years)	74.74 (5.36)	74.77 (6.05)	74.72 (5.11)	0.971[†]
Education history (years)	12.16 (2.37)	12.36 (0.51)	12.07 (0.32)	0.063[†]
MMSE score	28.84 (1.45)	29.18 (1.30)	28.70 (1.500)	0.111[§]
BMI (kg/m^2)	22.77 (2.97)	23.99 (2.91)	22.27 (2.87)	**0.022**[†]
SMI (kg/m^2)	5.98 (0.93)	6.17 (1.04)	5.90 (0.88)	0.243[†]
BMD (%YAM)	86.64 (10.69)	88.73 (14.10)	85.80 (8.97)	0.752[§]
OC (ng/ml)	16.52 (6.68)	16.28 (5.51)	16.61 (7.15)	0.845[†]
IGF-1 (ng/ml)	94.88 (29.43)	98.68 (30.65)	93.33 (29.07)	0.476[†]
Albumin (g/dl)	4.33 (0.21)	4.35 (0.17)	4.32 (0.22)	0.659[†]
Hypertension	34 (44.74%)	9 (40.91%)	25 (46.30%)	0.512[¶]
Diabetes mellitus	4 (5.26%)	1 (4.55%)	3 (5.56%)	0.856[¶]
Hyperlipidemia	21 (27.63%)	3 (13.64%)	18 (33.33%)	0.068[¶]
Parkinson's disease	0 (0%)	0 (0%)	0 (0%)	-
Alzheimer's disease	0 (0%)	0 (0%)	0 (0%)	-
Cerebrovascular dementia	0 (0%)	0 (0%)	0 (0%)	-
Stroke	2 (20.63%)	0 (0%)	2 (3.70%)	0.239[¶]
Osteoporosis	19 (2.63%)	3 (13.64%)	16 (29.63%)	0.128[¶]
Depression	2 (2.63%)	0 (0%)	2 (3.70%)	0.239[¶]

Notes: Data are presented as mean (standard deviation) or as prevalence (percentage). Bold type indicates significant difference. [†]Student's t-test, [‡]Welch's t-test, [§]Wilcoxon signed-rank test, [¶]χ^2 test between males and females.
Abbreviations: BMI, body mass index; SMI, smooth muscle mass index; BMD, bone mineral density; OC, osteocalcin; IGF-1, insulin-like growth factor-1.

Table 2. Correlation of measurements with change in cognition score

Variable	Pearson's correlation coefficient (*r*)	*p* value
Age[#]	0.049	0.677
BMI[#]	-0.102	0.381
SMI[#]	-0.023	0.844
BMD[#]	-0.052	0.658
OC[#]	0.090	0.437
IGF-1[#]	0.042	0.717
Albumin[#]	0.006	0.956
ΔBMI	0.118	0.308
ΔSMI	-0.043	0.710
ΔBMD	-0.047	0.688
ΔOC	0.286	**0.012**
ΔIGF-1	-0.117	0.315
ΔAlbumin	-0.083	0.477

Notes: Bold type indicates significant difference. [#]Value at baseline.
Abbreviations: Δ, change from baseline to the 13th week; BMI, body mass index; SMI, smooth muscle mass index; BMD, bone mineral density; OC, osteocalcin; IGF-1, insulin-like growth factor-1.

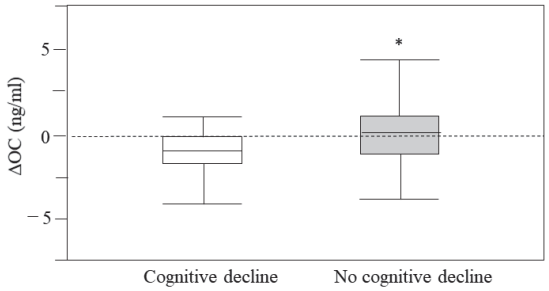

Figure 1. The serum ΔOC levels in the cognitive decline group and the no cognitive decline group. The box plot shows the median, lower, and upper quartiles and the minimum and maximum values. Δ, change from baseline to the 13th week; OC, osteocalcin. *$p < 0.05$ vs. cognitive decline group.

Table 3. Comparison of changed biomarkers by cognitive group

	Cognitive decline group (*n*=22)		No cognitive decline group (*n*=54)		ANCOVA[†]	
	Mean	95% CI	Mean	95% CI	*F*	*p* value
ΔBMI (kg/m^2)	-0.418	-0.727, -0.110	-0.148	-0.260, -0.036	1.459	0.231
ΔSMI (kg/m^2)	0.077	0.013, 0.141	0.096	0.048, 0.145	0.071	0.790
ΔBMD (%YAM)	-2.409	-4.038, -0.781	-1.778	-2.880, -0.675	0.017	0.896
ΔOC (ng/ml)	-1.177	-1.913, -0.442	0.230	-0.493, 0.959	5.252	**0.025**
ΔIGF-1 (ng/ml)	-3.910	-11.687, 3.740	-7.060	-11.439, -2.672	1.790	0.185
ΔAlbumin (g/dl)	-0.277	-0.340, -0.215	-0.324	-0.388, -0.260	1.300	0.258

Notes: Bold type indicates significant difference. [†]Analysis of covariance (ANCOVA) was used after adjustment for baseline values.
Abbreviations: Δ, change from baseline to the 13th week; OC, osteocalcin; IGF-1, insulin-like growth factor-1; CI, confidence interval

Table 4. Odds ratios of amounts of change of osteocalcin for cognitive decline

				Model 1			Model 2			Model 3		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
ΔOC (ng/ml)	0.731	0.556, 0.960	**0.013**	0.734	0.557, 0.967	**0.015**	0.725	0.547, 0.963	**0.014**	0.746	0.567, 0.983	**0.021**

Logistic regression analysis was used.
Notes: Bold type indicates significant difference.
Model 1: Adjusted for sex.
Model 2: Adjusted for sex and BMI at baseline.
Model 3: Adjusted for sex and osteoporosis status at baseline.
Abbreviations: Δ, change from baseline to the 13th week; OC, osteocalcin; CI, confidence interval.

Model 1: OR = 0.734, CI = 0.557-0.967, p = 0.015; Model 2: OR = 0.725, CI = 0.547-0.963, p = 0.014; Model 3: OR = 0.746, CI = 0.567-0.983, p = 0.021).

DISCUSSION

In the present study, the relationships between OC, IGF-1, and albumin levels and cognitive function were investigated in community-dwelling older people who participated in an exercise class once a week for 13 weeks. Compared with the no cognitive decline group, the cognitive decline group showed a significantly larger decrease in OC levels. The participants with increased ΔOC values had significantly lower odds of cognitive decline at the 13th week by ANCOVA adjusted for sex (Model 1), for sex and BMI at baseline (Model 2), and for sex and osteoporosis status at baseline (Model 3). These results suggest that there is a relationship between the amount of change in OC levels and the change in cognitive function.

Training that combines aerobic and resistance exercises has been reported to increase blood OC levels (Lester, 2009; Alghadir, 2014). However, in the present study, not all participants who continued weekly exercise for 13 weeks had elevated OC levels. This may also be affected by individual differences in exercise intensity and activities of daily living.

In the present study, OC levels were higher in women (M =17.24 [SD = 6.96] ng/ml) than in men (M = 13.80 [SD = 4.77] ng/ml), which is consistent with a previous report (Yoshimura, 2011). Of the participants in this study, 25.0% (19 of 76) had osteoporosis. Therapeutic agents for osteoporosis such as parathyroid hormone 1-34 and vitamin K_2 have been reported to affect serum OC levels (Shiraki, 2009; Nakamura, 2012). However, the cognitive decline group showed a significantly greater decrease in OC levels by ANCOVA adjusted for sex and osteoporosis status at baseline (Model 3), implying that these drug treatments for osteoporosis do not affect OC levels. Furthermore, the cause of the change in the OC value during the 13 weeks is not clear, but it is presumed that the difference in lifestyle including the amount of exercise has an effect.

The OCs produced by osteoblasts are γ-carboxylated at 3 residues and become GlaOC with a strong affinity to bone and the extracellular matrix; the low pH of the bone resorption zone by osteoclasts leads to decarboxylated GlaOC, which becomes GluOC and is then released into the blood (Wajih, 2004). There have been several reports on the relationship between OC and cognition. A study using OC knockout mice showed that GluOC not only participates in sugar and lipid metabolism, but also in the development of brain structures such as the hippocampus in embryonic development (Lee, 2007). In adult OC knock-out mice, an increase in anxious behavior and impairments in learning and memory were observed. In terms of the mechanism of OC in the brain, Oury (2013) reported that GluOC passes through the blood-brain barrier and acts on neurons of the brain stem, thalamus, and hypothalamus to promote the expression of genes involved in the synthesis of monoamine neurotransmitters, such as serotonin and dopamine, and then suppresses the expression of gamma-aminobutyric acid (GABA). Furthermore, in aged mice, OC was reported to produce brain-derived neurotrophic factor (BDNF), which is known to have an impact on direct hippocampal-dependent memory (Khrimian, 2017b). These results strongly support the present results.

There is a report that IGF-1, an endocrine hormone, is a key regulator of skeletal muscle development and also contributes to synaptic plasticity and the neural mechanisms necessary for learning and memory through blood-brain-barrier transport (Dyer, 2016). In older people with low IGF-1 levels, the relative risk of mild cognitive impairment is high, and blood IGF-1

levels are reduced in patients with familial AD (Mustafa, 1999). In studies of middle-aged and older people without AD, participants with high serum levels of IGF-1 showed less cognitive decline, a larger total brain volume, and lower risk for developing AD than those with low serum levels of IGF-1(Mustafa, 1999; Kalmijn, 2000; Westwood, 2014; Al-Delaimy, 2009). Furthermore, IGF-1 levels and cognitive function have been shown to be positively correlated in men, but not in women (Al-Delaimy, 2009). In the present study, no relationship was found between IGF-1 concentrations or changes in IGF-1 concentrations and cognitive impairment. Like OC, this may be due to differences in the race, lifestyle, and number of participants compared with previous studies. The level of OC decreases sharply before 30 and 50 years of age in women and men, respectively (Mera, 2016).

According to Yoshimura's report, mean change rates for serum total OC decreased 0.95% per year in men aged 70-79 years and 1.73% per year in women aged 70-79 years (Yoshimura, 2011). These results suggest that maintaining OC concentrations, which decrease with age, may be important for maintaining cognitive function.

In conclusion, there is a potential relationship between decreases in serum OC levels and cognitive decline in community-dwelling older Japanese people. Increasing OC levels may protect against cognitive decline.

LIMITATIONS AND FUTURE RESEARCH

The present study had several limitations. First, the sample size (n = 76) was small. Therefore, additional research with a larger sample is needed. Second, participants in the present study were all Japanese people; thus caution is required when generalizing the results to other populations. Third, comorbid diseases that could affect cognitive function, such as vitamin D depletion and hypothyroidism, were not examined. Future studies that include this information are needed. Fourth, since this was a cross-sectional study, and the data obtained only showed changes over 13 weeks, it is necessary to clarify the changes over a longer period, including elucidation of the reason for the change in OC values.

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