Serum levels of albumin-amyloid β complex in patients with depression

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ABSTRACT

Objectives: *Epidemiological studies have demonstrated that suffering from depression may be a risk for Alzheimer's disease (AD). As a possible biological mechanism underlying the transition from depression to AD, it has been speculated that pathological changes in amyloid β (Aβ) metabolism are involved. To further understand the peripheral kinetics of amyloid in patients with depression, we investigated serum levels of free Aβ and albumin-bound Aβ.*

Method: *A total of 70 inpatients with DSM-IV major depressive disorder (MDD) and 81 healthy individuals (the comparison group) were recruited between June 2012 and February 2014. Serum Aβ40 and Aβ42 levels, Aβ40/Aβ42 ratio and serum levels of albumin-Aβ complexes (SLAAC) were compared between the comparison group and patients in two age groups comprising younger (<60 years) and elderly (≥60 years) people.*

Results: *The SLAAC was decreased in older patients with MDD, but not in younger patients. The serum-free Aβ40/Aβ42 ratio was higher in patients with depression, even in younger patients.*

Conclusion: *Our findings suggest that free Aβ and the albumin-bound Aβ reflect a different serum amyloid kinetics in depression. We speculate that serum-free Aβ reflects changes in amyloid metabolism in patients suffering from depression, and albumin-bound Aβ reflects AD pathology and may be a potential predictor of the prodromal stage of AD.*

INTRODUCTION

Although epidemiological studies have demonstrated that depression may increase the risk for dementia, including Alzheimer's disease (AD) (1-3), the biological mechanisms underlying the transition from depression to AD are still unclear. Recently, pathological changes in amyloid metabolism in some patients with depression have been speculated upon as a possible mechanism (4-6). The neuropathology of the AD brain is characterized by the presence of extracellular senile plaques and intracellular neurofibrillary tangles; these changes precede the occurrence of clinical symptoms by many years (7,8). The major component of senile plaques is amyloid β protein (Aβ). Aβ has two major isoforms of 40 (Aβ40) or 42 (Aβ42) amino acids, and the Aβ42 peptide is deposited in the earlier stages of AD than Aβ40 (9). In cerebrospinal fluid (CSF), the levels of Aβ42 are reduced in patients with AD and in those with mild cognitive impairment (MCI) (10, 11), suggesting an association with selective deposition of Aβ42 in the brain. Studies measuring the plasma or serum levels of free Aβ in patients with AD have been contradictory (12-15). It has been reported that the large majority (approximately 89%) of Aβ is bound to albumin and very little free Aβ is in the blood under normal physiological conditions (16). We previously investigated serum levels of albumin-Aβ complexes (SLAAC) in patients with AD and in healthy individuals, and found that low SLAAC were associated with an increased prevalence of AD (OR 0.27; 95% CI 0.14–0.51) (17). In addition, decreased SLAAC were associated with decreased levels of Aβ42 in CSF and increased levels of phosphorylated tau (p-tau) in CSF, suggesting that SLAAC reflect AD

progression.

The results of studies investigating plasma and serum Aβ levels in patients with depression have also been contradictory (18-24). We recently evaluated serum Aβ40 and Aβ42 levels in a large number of patients who were stringently diagnosed as having major depressive disorder (MDD) and healthy controls (5). In that study, we found that the serum Aβ40/Aβ42 ratio was significantly higher in patients with MDD than the healthy group even in the younger age group, suggesting that Aβ metabolism may be affected in depression. Moreover, we investigated associations between cerebrovascular changes, serum Aβ and age of onset in patients with MDD (25). The results showed that cerebrovascular changes positively correlated with age at onset and the Aβ40/Aβ42 ratio negatively correlated with the age at onset. These findings suggested possible mechanisms for the transition from depression to AD. However, as mentioned above, most Aβ is bound to albumin in the blood. Thus, evaluation of both free Aβ and albumin-bound Aβ is needed to understand the peripheral kinetics of amyloid in patients with depression.

The aim of the present study was to investigate whether SLAAC may be altered in patients with MDD and whether any change is also seen in younger patients.

METHODS

Participants

A total of 79 inpatients with depression were recruited from Juntendo Koshigaya Hospital, Saitama, Japan, between Jun 2012 and Feb 2014, as part of the Juntendo University Mood Disorder

Project (JUMP). The study protocols were approved by the Medical Ethics Committee of Juntendo University and Juntendo Koshigaya Hospital. All participants provided written informed consent prior to participation.

Among the depressed participants, only patients who met the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) criteria for MDD were enrolled. Patients who had a history of other psychiatric disorders, including severe or acute medical illnesses, neurological disorders, or use of drugs that may cause depression, were excluded. Patients who had clinical evidence of dementia or with Mini-Mental State Examination (MMSE) (26) scores <24 were excluded. Nine patients were excluded by these criteria. Finally, 70 cognitively intact patients with MDD (19 men, 51 women; mean age, 56.3 years; range, 20–81 years) were enrolled in this study. Depressive symptoms were assessed using the Hamilton Rating Scale for Depression (HAM-D) (27). Age at the onset of the first depressive episode, the number of depressive episodes, and total duration of treatment by medication were confirmed via medical records. All patients were on antidepressant medication at the time of the study. The doses of antidepressants were converted to an equivalent dose of imipramine (28). Four patients were taking lithium, three patients were taking anticonvulsants, 21 patients were taking antipsychotics including sulpiride and 30 patients were taking benzodiazepines.

A total of 81 healthy participants (22 men, 59 women; mean age, 56.6 years; range, 18–78 years) were recruited from the general population as the comparison group. Participants in the comparison

group were confirmed to have no history of depression, dementia or other neuropsychiatric disease, and MMSE scores >24. All healthy participants were working at least part-time.

Serum Aβ40 and Aβ42 measurements

We have collected and stored serum samples for the JUMP study and serum Aβ40 and Aβ42 levels were measured in these as described in a previous report (5). Fasting blood samples were drawn into serum separator tubes containing separator gel and were centrifuged immediately (Venoject II® Termo Co., Ltd. Tokyo, Japan). Serum samples were stored at −80 °C until use. A sandwich Aβ enzyme-linked immunosorbent assay kit was used (Wako, Osaka, Japan). The Aβ(1-40) kit uses the BAN50 monoclonal antibody, which specifically detects the N-terminal portion of human Aβ(1-16), and the BA27 monoclonal antibody, which detects the C-terminal portion of Aβ(1-40). The Aβ(1-42) kit uses BAN50 and the BC05 monoclonal antibody, which detects the C-terminal portion of Aβ(1-42). The sensitivity was 0.019 pmol/L (dynamic range: 1.0-100 pmol/L) for Aβ40 and 0.06 pmol/L (dynamic range: 0.1-20 pmol/L) for Aβ42. The intra-assay coefficients of variation (CVs) were 4.8% at a mean of 14.2 pmol/L, 4.25% at a mean of 36.0 pmol/L, and 3.6% at a mean of 75.5 pmol/L for Aβ40, and 0.8% at a mean of 3.2 pmol/L, 0.8% at a mean of 7.4 pmol/L, and 1.0% at a mean of 16.4 pmol/L for Aβ42. The inter-assay CVs were 3.2% at a mean of 14.8 pmol/L, 1.1% at a mean of 33.6 pmol/L, and 2.5% at a mean of 75.7 pmol/L for Aβ40, and 8.3% at a mean of 3.2 pmol/L, 11.3% at a mean of 7.1 pmol/L, and 5.8% at a mean of

16.4 pmol/L for Aβ42.

Serum levels of albumin-Aβ complexes (SLAAC) measurements

SLAAC were measured according to our previous report (17), including immunoprecipitation to prove the existence of albumin-Aβ complexes. Albumin-Aβ complexes were probed with a purified anti-human albumin polyclonal antibody, followed by horseradish peroxidase (HRP)-labeled secondary antibody and the chemiluminescent substrate. Signals were visualized using a LAS-3000 luminescent image analyzer (Fujifilm, Tokyo, Japan). Densitometric measurements were carried out using Fotodyne visionary documentation system (Fotodyne, Hartland, WI, USA). We measured the SLAAC using a specific sandwich ELISA that uses an anti-human Aβ N-terminal monoclonal antibody (BAN50) and an anti-human albumin purified polyclonal antibody. The intra- and interassay coefficients of variability was 5.1% and 13.8%, respectively. A standard curve for the ELISA from our previous study was used (17). The detection limit in serum was as low as 2.5 mg/mL equivalent to albumin preparation. The concentration of albumin-Aβ complexes below the lower detection limit were set to zero.

Other biological measurements

APOE phenotypes for all samples were determined by isoelectric focusing carried out at SRL, Tokyo, Japan (29). Serum total protein (TP), albumin (Alb), albumin/globulin ratio (A/G), asparatate

aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cre), total cholesterol (T-Cho) and triglycerides (TG) levels were measured at the laboratory of Juntendo Koshigaya Hospital.

Data analysis

For statistical analyses, age, education, MMSE score, and serum TP, Alb, A/G, AST, ALT, Cre, T-Cho and TG were compared between MDD and the comparison group using the two-tailed unpaired Student's t test. When variables violated the parametric test assumptions, we verified the results using nonparametric tests. Since there were no appreciable differences, we present only the parametric results. The χ^2 test was used to compare the variables of sex and ApoE4 phenotype. Serum Aβ40, Aβ42 levels, and the Aβ40/Aβ42 ratio and SLAAC were compared using the Mann-Whitney *U* test; median values were used for variables with skewed distributions (5, 24, 30). The relationships between age at onset and HAM-D score and serum Aβ indices were assessed using Spearman's rank correlation coefficient. To compare the serum levels of free Aβ and SLAAC between younger and elderly subjects, we divided both MDD patients and the comparison group into two age groups (younger, <60 years and elderly, ≥60 years) as done in previous studies (6, 18). A 2 (age group; younger vs. elderly) × 2 (diagnosis; MDD vs. comparison group) analysis of variance (ANOVA) was used for the two age-group comparisons. Multiple regression analyses were conducted using SLAAC as the dependent variable, and age, sex, age at onset, HAM-D total score at admission, the number of depressive episodes, total doses of antidepressant (equivalent dose of

imipramine), TP and Alb as independent variables. Free Aβ40 and Aβ42 levels, Aβ40/Aβ42 ratios, SLAAC were transformed to $\log_{10}$ for 2 × 2 ANOVA and multiple regression analysis because of the skewed distribution of these variables. A significance level of $p < 0.05$ was used. Statistical procedures were performed using the Japanese version of IBM SPSS Statistics for Windows, Version 21.0 (SPSS Japan, Tokyo, Japan).

RESULTS

Demographics and clinical features

The socio-demographic and clinical information of the MDD group and the comparison group are shown in Table 1. Age, sex, education, serum levels of AST, ALT, Cre, T-Cho, TG, MMSE score or ApoE4 frequencies were not significantly different between the two groups. TP, Alb and A/G were significantly lower in the MDD group than the comparison group (Table 1). HAM-D scores were not correlated with the serum Aβ indices, and the serum Aβ40/Aβ42 ratio was significantly negatively correlated with age at onset ($n=70$, $r = -0.27$, $p = 0.035$). There were no differences in serum Aβ40 levels between the two groups. However, serum Aβ42 levels were significantly lower and the Aβ40/Aβ42 ratio was significantly higher in the MDD group compared with the comparison group (Table 1). Although SLAAC were significantly lower in the MDD group than the comparison group (Table 1).

When the subjects were divided into two age groups by a cut-off of 60 years of age, age, sex,

MMSE scores, and ApoE4 frequencies were not significantly different between the MDD and comparison groups, in both age groups (Table 2). However, Alb serum levels were lower in the MDD group than the comparison group in both younger (Student's t Test, df = 65, $p < 0.001$) and elderly (Student's t Test, df = 81, $p < 0.001$) groups (Table 2). In the elderly MDD group, we also analyzed the data for late-onset MDD patients (LOMDD: defined as patients with an onset of the first depressive episode at age 60 or after; Table 2). The results of 2 × 2 ANOVA are show in Table 3. For serum levels of free Aβ, there was no significant main effect of age-group and diagnosis on Aβ40. Although there was no significant main effect of age-group, the main effect of diagnosis was significant for the serum levels of Aβ42 and Aβ40/Aβ42 ratio (Table 3). This indicates lower Aβ42 and a higher Aβ40/Aβ42 ratio in the MDD group than the comparison group regardless of age-group. For albumin-Aβ complexes, a significant main effect of diagnosis on SLAAC was seen, and interaction of age-group and diagnosis was significant both on SLAAC (Table 3). SLAAC was significantly lower in the elderly MDD group than the elderly comparison group; however, these differences were not seen in the younger groups. When the 2 × 2 ANOVA was reanalyzed substituting LOMDD for elderly MDD, the results were similar to the previous data (not shown).

Multiple regression analysis showed that age, sex, age at onset, HAM-D score, number of depressive episodes, total dose of antidepressant, serum levels of TP and Alb did not influence SLAAC (Table 4).

DISCUSSION

A main finding of the present study is that SLAAC is decreased in elderly patients with major depression. This decrease was not seen in younger patients. On the other hand, the serum-free Aβ40/Aβ42 ratio was higher in patients with depression even in younger patients.

Although several reports have evaluated blood levels of free Aβ40 and Aβ42 in older patients with depression, the results have been inconsistent. Pomara and Murali Doraiswamy (20) reported higher plasma Aβ42 levels in 47 elderly patients with MDD compare to 35 healthy individuals. Moon et al(19) also reported higher levels of plasma Aβ42 in elderly with depressive symptoms in 123 community-dwelling elderly. In contrast, several reports have demonstrated a decreased Aβ42 and higher Aβ40/Aβ42 ratio in elderly depressives (5, 18, 21-25). Qiu and Sun et al.(24) evaluated plasma Aβ in 995 homebound elderly and reported lower plasma Aβ42 levels and a higher Aβ40/Aβ42 ratio in depressive individuals, and they suggested that depressive individuals with a higher Aβ40/Aβ42 ratio may have preclinical and/or early stage AD. Moreover, Pomara et al. reported lower levels of Aβ42 in elderly patients with depression, even in CSF (31). We recently evaluated serum Aβ40 and Aβ42 levels in 193 patients who were stringently diagnosed as having MDD and 413 healthy participants and compared Aβ40/Aβ42 ratio among three age groups (5). In that study, we found that the serum Aβ40/Aβ42 ratio was significantly higher in patients with MDD than the comparison group in the elderly, middle-aged and even in the younger group (age < 40 years). From those results, we suggested that Aβ metabolism may be affected in depression. In

support of this suggestion, we also demonstrated a negative correlation between serum Aβ40/Aβ42 ratio and age at onset, suggesting that the earlier onset of depression may have a more serious abnormality in Aβ metabolism (25). In the present study, our previous result has almost been reproduced. A hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis, which is well described in MDD (32, 33), is also observed in AD and results in increased glucocorticoid levels in blood and CSF(34-38). Several studies have demonstrated that glucocorticoid administration increases Aβ pathology in a model mouse of AD (39), and chronic glucocorticoid administration decreased plasma Aβ42 levels in a macaque (40). From these previous reports, serum-free Aβ may reflect a change of amyloid metabolism as a result of depression.

However, SLAAC were decreased only in elderly patients with depression. This result was similar to our previous result in patients with AD (17). In that study, SLAAC were significantly lower in the AD group ($p < 0.0001$), and the decreased SLAAC were associated with decreased CSF levels of Aβ42 ($r = 0.38$, $p = 0.022$) and increased CSF levels of phosphorylated tau ($r = -0.43$, $p = 0.009$). From these previous and present results, SLAAC may associate with AD pathology, and elderly patients with depression who exhibit a low SLAAC may be in a prodromal stage of AD. In our present study, serum levels of albumin were lower in MDD patients than the comparison group. This may be caused by a decrease in appetite as a symptom of MDD and may influence the SLAAC results. Therefore, we performed multiple regression analysis to reveal the influence of albumin levels to the SLAAC, and the result showed that serum albumin levels did not influence SLAAC.

This suggests that the decreased serum albumin level is unlikely to be a major factor influencing our result of decreased SLAAC levels. Aβ is bound and transported with albumin in human plasma (16), and this interaction is involved in Aβ aggregation and deposition into insoluble amyloid fibrils (41-45). In addition, serum levels of free Aβ did not link with SLAAC. It has been reported that serum albumin is modified by several factors including oxidation or glycation (46, 47). The decreased SLAAC shown in patients with AD and some elderly patients with depression may not be associated with levels of free Aβ, but may be caused by the decreased Aβ binding ability of serum albumin in these patients.

There are several limitations to the present study. First, all patients with MDD in this study were on medication and receiving several types of psychotropic drugs mainly antidepressants. It has been reported that antidepressants, including selective serotonin reuptake inhibitors, influence brain amyloid (48). Some drugs bind with proteins including albumin in the blood, and this may possibly to influence the results of SLAAC analysis. Although a different result of SLAAC was shown between the younger and elderly groups, the type of drugs and dose of antidepressants were not different between these patients groups (data not shown). Moreover, dose of antidepressant was not associated with SLAAC (Table 4). Accordingly, medication is unlikely to be a major factor that influences the result of SLAAC measurement. However, further study investigating only drug naïve patients should be undertaken in order to avoid influences by medications completely. Second, to understand the peripheral kinetics of amyloid in patients with depression in more detail, CSF levels

of Aβ should be evaluated. Although several studies have demonstrated a relationship between CSF and blood levels of Aβ, results have been inconsistent (17, 49-52). A lack of CSF data may also be considered a limitation. Third, we hypothesized that an alteration in Aβ metabolism in depression may be influenced by HPA axis activity. However, our study did not include any measure of HPA axis activity and this, including glucocorticoid levels, should be evaluated in future studies. Fourth, it has been reported that the production of Aβ may be regulated by the sleep/wake cycle, which can be affected by depression (53-55). However, in our study we did not have enough information about insomnia or sleep deprivation, particularly in the comparison group, to be able to assess this. Moreover, platelets are a major source of peripheral Aβ, and their activity may be associated with MDD. Pomara et al. hypothesized that increased platelet activity may be a mechanism for Aβ abnormalities in MDD (56). A lack of clinical information and biological data may also be considered as a limitation in our study. Fifth, it is known that APOE phenotyping is less accurate than APOE genotyping, so the determination of APOE status by phenotyping may also be a limitation here. Finally, this study was cross-sectional in nature. Thus we cannot attribute the result of Aβ to AD pathology conclusively. Further study including a large number of subjects and prospective longitudinal observation would be needed to confirm our suggestions.

Conclusion

The serum levels of albumin-Aβ complexes were decreased in elderly patients with major

depression, and free Aβ40/Aβ42 ratios were increased both in elderly and younger patients. These findings suggest that free Aβ and albumin-bound Aβ reflect different amyloid kinetics in the serum of depressed individuals. It may be speculated that serum-free Aβ reflects changes in amyloid metabolism affected by suffering from depression, and albumin-bound Aβ reflects AD pathologies as a potential predictor of the prodromal stage of AD.

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Table 1. Demographic and Comparison Data of MDD and Comparison Group

	All Subjects		
	MDD (n = 70) Mean (SD)	Comparison (n = 81) Mean (SD)	*P Value*
Age (Years)	56.3 (14.5)	56.6 (15.0)	0.88[a]
Sex (M/F)	19/51	22/59	0.57[b]
Education (Years)	13.0 (2.2)	12.4 (2.9)	0.19[a]
TP (g/dL)	6.6 (0.4)	7.2 (0.5)	< 0.001[a]
Alb (g/dL)	3.9 (0.3)	4.3 (0.4)	< 0.001[a]
A/G	1.4 (0.2)	1.6 (0.3)	0.002[a]
AST (U/L)	23.5 (23.5)	23.0 (11.3)	0.84[a]
ALT (U/L)	16.5 (22.5)	17.5 (11.0)	0.76[a]
Cre (mg/dL)	0.7 (0.2)	0.7 (0.1)	0.22[a]
T-Cho (mg/dL)	190.4 (40.7)	198.7 (36.5)	0.20[a]
TG (mg/dL)	127.7 (92.6)	129.8 (83.3)	0.89[a]
Ham-D score	20.7 (9.3)	-	-
Age at Onset	49.7 (15.0)	-	-
Number of Depressive Episodes	2.2 (1.9)	-	-
Total Duration of Medication (M)	38.0 (83.5)	-	-
Total Dose of Antidepressant (mg) [d]	125.5 (93.5)	-	-
MMSE	27.4 (2.0)	27.7 (1.9)	0.45[a]
ApoE4 N/total (%)	13/70 (18.6)	23/81 (28.4)	0.15[b]
	median (Q1-Q3)	**median (Q1-Q3)**	***P Value***
Aβ40 (pmol/L)	23.4 (14.4-36.6)	22.4 (15.6-27.8)	0.25[c]
Aβ42 (pmol/L)	1.7 (1.0-3.3)	2.2 (1.6-4.2)	0.02[c]
Aβ40/Aβ42 ratio	12.7 (8.2-17.8)	8.7 (6.2-12.1)	0.001[c]
Alb-Aβ Complex (mg/mL)	116.5 (59.0-196.9)	158.9 (94.5-232.3)	0.007[c]
Alb-Aβ Complex / Alb	29.4 (14.6-52.9)	35.2 (20.6-51.2)	0.1[c]

[a] Student's *t*-Test (df=149), [b] χ2Test (df=1), [c] Mann-Whitney *U* Test, [d] Antidepresants were converted into imipramine doses.

MDD: Major Depressive Disorder, TP: total protein, Alb: albumin, A/G: albumin/globulin ratio, AST: asparatate aminotransferase, ALT: alanine aminotransferase, Cre: creatine, T-Cho: total cholesterol, TG: triglyceride, HAM-D: Hamilton rating scale of depression, MMSE: Mini-Mental State Examination, ApoE4: apolipoprotein ε4 carrier, Aβ: amyloid β protein, Q: quartile

Table 2. Demographic and Comparison Data in Each Age Groups

	Younger (< 60 y)		Elderly (≥ 60y)	
	MDD (n = 33)	Comparison (n = 35)	MDD (n = 37) / LOMDD (n=16)	Comparison (n = 46)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (Years)	43.6 (9.9)	42.6 (12.1)	67.6 (5.9) / 70.1 (4.7)[c]	67.1 (5.1)
Sex (M/F)	12/21	10/25	7/30 / 4/12	12/34
MMSE	28.3 (1.7)	28.5 (1.5)	26.6 (1.9) / 26.1 (1.9)	27.0 (1.8)
ApoE4 N/total (%)	6/33 (18.2)	7/35 (20)	8/37 (21.6) / 3/16 (18.8)	16/46 (34.8)
Alb	4.0 (0.3)	4.4 (0.5)[b]	3.8 (0.3) / 3.7 (0.3)[c]	4.2 (0.3)[b]
	median (Q1-Q3)	median (Q1-Q3)	median (Q1-Q3)	median (Q1-Q3)
Aβ40 (pmol/L)	25.7 (18.3-35.5)	19.0 (14.1-24.4)	21.2 (13.6-40.0) / 20.7 (11.9-42.3)	24.6 (17.4-34.4)
Aβ42 (pmol/L)	1.7 (1.0-4.1)	2.1 (1.4-4.0)	1.6 (1.0-3.2) / 1.7 (1.0-3.3)	2.4 (1.8-4.2)
Aβ40/Aβ42 ratio	12.7 (6.0-20.6)	8.1 (5.8-11.9)	12.4 (10.4-15.5) / 11.7 (10.1-16.1)	9.4 (6.9-12.3)

[a] Aβ40, Aβ42, Aβ40/Aβ42 ratios and SLAAC were transformed to log10

[b] Serum levels of Alb were significantly lower in MDD ($p<0.001$) (Student's *t*-Test, df=65 in younger group, df=81 in elderly group)

[c] LOMDD were significantly older (df=60, $p=0.047$) and serum levels of Alb in LOMDD were significantly lower (df=60, $p<0.001$) than elderly comparison (Student's t-Test)

LOMDD: Late-onset major depressive disorder, ApoE4: apolipoprotein ε4 carrier, Alb: albumin, Aβ: amyloid β protein, MMSE: Mini-Mental State Examination

Table 3. Results of 2 x 2 ANOVA

	2 (age-group; younger vs. elderly) x 2 (diagnosis; MDD vs. comparison) analysis of variance (ANOVA)[a]					
	Main effect of age-group		Main effect of diagnosis		Interaction: age-group x diagnosis	
	F Value	*P Value*	*F Value*	*P Value*	*F Value*	*P Value*
Log_{10} Aβ40	0.451	0.503	0.756	0.386	2.082	0.151
Log_{10} Aβ42	0.174	0.677	4.863	0.029	0.488	0.486
Log_{10} Aβ40/Aβ42	0.990	0.321	9.769	0.002	0.142	0.707
Log_{10} SLAAC	0.576	0.449	11.117	0.001	11.507	0.001

Degrees of freedom (1, 147) for 'age-group' and 'diagnosis'

SLAAC: serum levels of albumin-Aβ complex, Alb: alubumin, ApoE4: apolipoprotein ε4 carrier, Alb: alubumin, Aβ: amyloid β protein,

Table 4. Result of Multiple Regression Analysis of SLAAC

	Log $_{10}$ SLAAC [a]	
	β Estimate (SE)	*P Value*
Age	–0.009 (0.006)	0.68
Sex	–0.155 (0.152)	0.49
Ham-D score	–0.286 (0.007)	0.21
Number of Depressive Episodes (No.)	0.200 (0.071)	0.44
Total Dose of Antidepressant (mg) [b]	0.165 (0.001)	0.56
TP	–0.001 (0.241)	0.99
Alb	0.150 (0.426)	0.74

Multiple regression analyses; Log_{10} SLAAC as the dependent variable

P-values are from a t-statistic with 62 df.

HAM-D: Hamilton rating scale of depression, SLAAC: serum levels of albumin-Aβ complex, TP: total protein, Alb: albumin,

[a] SLAAC/Alb values were transformed to log10 (SLAAC/Alb) because of the skewed distributions.

[b] Antidepresants were converted into imipramine doses.