Plasma Amyloid-β Peptides and Homocysteine in Depression in the Homebound Elderly

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Abstract

Objectives: **Both plasma amyloid-β peptide 40 (Aβ40) and homocysteine (tHcy) are linked to vascular disease, which is related to depression in the elderly. We sought to study whether the relationship between tHcy and plasma Aβ40 differs in those with and without depression.**

Study Design and Methods: In a cross-sectional study of 1058 homebound elders, vascular depression was defined as a score ≥ 16 on the Center for Epidemiological Studies Depression scale (CES-D) along with self-reported cardiovascular disease (CVD). Plasma Aβ40 and Aβ42, and serum tHcy and creatinine were measured.

Results: **Elders with high tHcy had higher concentrations of plasma Aβ40 (median: 147.5 vs. 123.1 pg/ml, P < 0.0001) and Aβ42 (median: 20.2 vs. 16.6 pg/ml, P < 0.0001) than those with low tHcy. In elders with depression, the relationship between logarithm of plasma Aβ40 (LogAβ40), but not LogAβ42, and tHcy was significant (β = +0.010, SE = 0.004, P = 0.007); in contrast, this relationship was not observed in those without depression. Subjects with vascular depression had the highest concentration of tHcy (mean ± SD: 12.8 ± 4.6 vs. 11.7 ± 4.5 vs. 11.9 + 5.5, P = 0.008) compared to those without CVD and those without depression. Depressed subjects without CVD had the lowest concentration of plasma Aβ42 (median: 15.5 vs. 19.1 vs. 18.7, P = 0.01) compared to those with CVD and those without depression.**

Conclusions: **Vascular depression, which is associated with tHcy and Aβ40 in blood, appears to be different from depression that is associated with low plasma Aβ42. This suggests that reducing tHcy and Aβ40 may be an adjunct treatment for vascular depression.**

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Introduction

Multiple studies have shown that elevated homocysteine (tHcy) in blood is associated with vascular diseases and Alzheimer's disease (AD)[1]. High tHcy has been shown to be positively associated with amyloid-peptide (Aβ) in clinical patients and in community elderly populations.[2,3] Aβ42 is a major component of amyloid plaques, the AD pathology in the brain[4] (reviewed by Selkoe 2006), and Aβ40 is a component of cerebral amyloid angiopathy (CAA)[5] (reviewed by Zhang-Nuns 2006). Plasma Aβ40 is also linked with white matter hyperintensities (WMHI) in the brain[7]. Although late life depression increases the risk of AD, the relationship between plasma tHcy, Aβ and depression is unknown.

Late life depression is a clinical syndrome with different pathologies and etiologies. Depressed elders without CVD have a lower concentration of plasma Aβ42, but not plasma Aβ40, compared to depressed elders with CVD[15], suggesting a depression subtype for AD, which we have termed "amyloid-associated depression". Another depression subtype, vascular depression was proposed by Alexopoulos et al. based on the finding a group of depressed elderly patients with a higher vascular score than those with a score of 0.[8] If amyloid-associated depression is a separate subtype of depression from vascular depression, then vascular

depression should have a relationship with biomarkers of vascular disease such as tHcy, but not necessarily with low plasma Aβ42. Several published studies have shown that elevated tHcy is associated with depression in elderly with CVD.[16-19]

Since there are high rates of depression as well as vascular disease in the homebound population,[20-22] we examined homebound elders to investigate the relationship between tHcy and plasma Aβ peptides in depression. We sought to observe tHcy and Aβ peptides in different depression subtypes, and to determine whether the relationship between tHcy and plasma Aβ40 is different between elderly with and without depression.

Method

Study Population and Recruitment

We studied a group of 1058 subjects, all of whom had tHcy data from an ongoing, population-based study, the *Nutrition, Aging and Memory in the Elderly (NAME) study*. The sample frame was based on the clients of four homecare agencies between 2003 to 2006 for the Boston area. Anyone receiving homecare services is registered with one of these agencies if he/she lives in the city of Boston, has an annual income < $18,890 and needs homecare service. All homebound elders aged 60 and older at each of the four agencies are invited to participate in the study. To be eligible to be enrolled, the participants must speak English, be physically able to participate in the study home visits, and have sufficient vision and hearing to read and hear the content of the neuropsychological tests. Those with Mini-mental State Exam $\leq$10 or verbal IQ <75 were not eligible to continue in the study. Of these potential subjects, 66% enrolled in the study, and gave informed consent for the study approved by Tufts IRB. They each participated in three home visits administered by a research assistant, who drew fasting blood and collected data on depression and medical conditions.[22]

Measurements

Homocysteine and micronutrients: All measurements were carried out in the Vitamin Metabolism and Aging Laboratory, which is a standard clinical laboratory (USDA-Human Nutrition Research Center, Boston, MA). The tHcy concentration in serum was determined by high-performance liquid chromatography with fluorimetric detection.[23] Plasma folate was determined by a microbial (*Lactobacillus* cases) assay in a 96-well plate. Plasma pyridoxal-5'-phosphate (vitamin B_6) was measured by the tyrosine decarboxylase apoenzyme method, and plasma cyanocobalamin (vitamin B_{12}) was measured by a radioimmunoassay (Quantahase II; Bio-Rad, Hercules, California).[24] High tHcy and micronutrient deficiencies were defined accordingly.

Plasma Aβ40 and Aβ42: The blood samples were centrifuged immediately after the blood draw. The sandwich Aβ ELISA was used. Plates were coated with 2G3 (anti-Aβ40) and 21F12 (anti-Aβ42) antibodies overnight at 4^0C. Samples were then loaded and incubated overnight at 4^0C followed by incubation with a biotinylated monoclonal anti-N terminus Aβ antibody (3D6B) for 2 hrs. Finally, streptavidin-conjugated alkaline phosphatase (Promega, USA) was added and incubated, and the signal was amplified by adding alkaline phosphatase fluorescent substrate (Promega, USA), which was then measured. The lowest detection for both Aβ peptides was 1.6 pg/ml in the standard curves with %CV between 1.1 to 7.2. However, we used 3.1 pg/ml for both Aβ 1-40 (2 samples) and 1-42 (10 samples) as a low cut-point. The samples with higher levels than the standard curve were repeated with dilutions for measurement. The intra-correlations with two other laboratories, which have published the results of the Aβ measurement,[25,26] showed R = 0.63 and 0.84 for Aβ40 and R = 0.90 and 0.96 for Aβ42.

Depression: Depressive symptoms were assessed by using the Center for Epidemiological Studies Depression scale (CES-D);[27] a CES-D score of $\geq$ 16 was used as the cut-off point for clinical depression.[28] This CES-D cut-off point had a sensitivity of 0.90 and a specificity of 0.83 for the DSM-IV diagnosis of major depression by board-certified psychiatrist in our study. Vascular depression was defined by a CES-D score $\geq$ 16 and the presence of CVD.

CVD and other measurements: Subjects were classified as having CVD according to whether they had been previously informed by a doctor that they had congestive heart failure, coronary heart disease, angina pectoris or a heart attack. Stroke history was recorded. Body mass index (BMI) was measured and determined. Current hypertension was defined by the average of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg at two determinations. Renal function, which is associated with plasma Aβ,[29] was assessed by measurements of serum creatinine.

Statistical Analysis

Statistical analysis was performed using SAS (version 9.1). For the variables such as tHcy and creatinine, which were normally distributed, mean $\pm$ SD and T-test were used; for the variables of plasma Aβ40 and Aβ42, which were not normally distributed,[15] median (Q1, Q3) and Wilcoxon rank sum or Mann-Whitney test were used. The Chi-Square test was used for binomial variables. A samples were treated as the cut-points for comparison and regression if their levels were below the cut-point of detection. Both Aβ40 (Log Aβ40) and Aβ42 (Log Aβ42) were transformed to $\log_{10}$ for multivariate regression due to skewed distributions. Linear regression was used to examine associations between tHcy and Log Aβ40 or Log Aβ42 as an outcome after adjusting for other micronutrients, creatinine and other confounders of age, race, gender, BMI, CVD and depression. For all analyses, the level of significance was = 0.05, and P values were two sided.

Results

Study Population

One thousand and fifty eight subjects with tHcy data from the NAME study were used in this analysis (**Table 1**). Since the

Table 1. Demographic status of the homebound elderly population.

	Total Population N = 1058
Age, year, mean ± SD (n = 1058)	75.3 ± 8.4
BMI, kg/m^2, mean ± SD (n = 987)	31.6 ± 8.7
African Americans, n/total (%)	372/1058 (35%)
Female, n/total (%)	805/1058 (76%)
Past Smoker, n/total (%)	475/1023 (46%)
Current Smoker, n/total (%)	175/1023 (17%)
Medical Conditions	
Depression, n/total (%)	329/981 (34%)
Cardiovascular disease, n/total (%)	437/1022 (43%)
Diabetes, n/total (%)	364/1021 (39%)
Blood Data	
High Homocysteine (> 12 umoles/L), n/total %)	418/1058 (40%)
Creatinine, mg/DL, mean ± SD (n =1015)	1.2 ± 1.0
Aβ40, pg/ml, median (Q1, Q3) (n = 955)	132.7 (94.0, 174.1)
Aβ42, pg/ml, median (Q1, Q3) (n = 955)	18.0 (12.4, 29.1)

Mean ± SD, Median (Q1 and Q3) or n/total (%) are presented**.**

subjects were recruited from an ongoing project, the number of subjects thus increased by 531 since the previously published study.[15] The average age of this population was 75.3 (SD = 8.4) years old, and 76% were female. It was multi-ethnic with 61% white, 35% African American and 4% other ethnicities. All the demographic data were similar to the previous published study except that there were fewer Caucasian (54%) and more African American (41%) subjects in the previous dataset.

There were high rates of depression and vascular disease in this study sample. Depression, defined as a CES-D score ≥ 16, was observed in 34% (329/981) of the subjects (**Table 1**). 43% (437/1022) had CVD, 20% (207/1028) had a history of stroke, 36% (364/1021) had diabetes and 39% (383/974) had current hypertension. The average BMI was high, 31.6 ± 8.7 (mean ± SD), and the average creatinine was 1.2 ± 1.0 (mean ± SD) in this population.

Plasma Aβ Peptides and Homocysteine in the Homebound Elderly

Distributions of plasma Aβ40 (median: 132.7 pg/ml; minimum: 1.4 pg/ml and maximum: 1324.9 pg/ml) and Aβ42 (median: 18.0 pg/ml; minimum: 0.1 pg/ml and maximum: 780.8 pg/ml) were skewed. Therefore, median, Q1 and Q3 were used to describe Aβ levels. Two samples of Aβ40 and 10 samples of Aβ42 had levels lower than the detection level of 3.1 pg/ml, and therefore were assigned the value of 3.1

Table 2. Effects of homocysteine vs. the interaction of homocysteine and depression on plasma Aβ40 in the homebound elderly.

Adjusted for Age, Race, Gender, BMI, CVD, Diabetes, Smoking and Micronitrients	Plasma Log Aβ40* N = 812		Plasma Log Aβ40~ N = 812	
	Estimate β (SE)	*P value*	Estimate β (SE)	*P value*
Homocysteine	+ 0.004 (0.002)	0.04	+ 0.002 (0.002)	0.31
Creatinine	+ 0.050 (0.010)	< 0.0001	+ 0.047 (0.010)	< 0.0001
LogAβ42	+ 0.201 (0.022)	< 0.0001	+ 0.199 (0.022)	< 0.0001
Depression	+ 0.013 (0.018)	0.47	- 0.078 (0.048)	0.11
Homocysteine* Depression	-	-	+ 0.007 (0.004)	0.04

Multivariate linear regression analyses were performed. BMI = Body mass index; CVD = Cardiovascular disease; Log Aβ40 = logarithms of Aβ40; Log Aβ42 = logarithms of Aβ42; Micronutrients include vitamin B6, B12 and folate

*DF = 14

˜DF = 15

P values for statistical significance are shown.

pg/ml. There were no differences in plasma Aβ40 or Aβ42 between those with and without micronutrient deficiency of folate, vitamin B12 or vitamin B6 in this homebound population (data not shown).

After controlling for age, race, gender, BMI, smoking, micronutrients and clinical conditions in multivariate linear regression analysis, the logarithm of plasma Aβ40 (LogAβ40) as an outcome remained associated with tHcy (β = +0.004, SE = 0.002, P = 0.04) and creatinine (β = +0.050, SE = 0.010, P < 0.0001) (**Table 2**). The relationship between LogAβ40 and tHcy was greatly attenuated after adjusting for creatinine, indicating that kidney function has a major influence on this relationship. In contrast, the relationship between the logarithm of plasma Aβ42 (LogAβ42) as an outcome and tHcy or creatinine disappeared after adjusting for confounders (data not shown).

The Relationship between Plasma Aβ40 and Homocysteine in those with and without Depression

Using correlation analysis, plasma Aβ40 is correlated with tHcy with r=0.26 and P<0.0001 in those with depression; in contrast, plasma Aβ40 was correlated with tHcy with a smaller slope, r=0.19 and P<0.0001 in those without depression, suggesting that the relationship between Aβ40 and tHcy in blood might be influenced by the depression status. Indeed, it was shown that the interaction between tHcy and depression was associated with higher levels of plasma Aβ40 (β=+0.007, SE=0.004, P =0.04) after adjusting for confounders in multivariate regression analysis (Table 2).

Since we have found that depressed elders without CVD have a significantly lower level of plasma Aβ42 than those with CVD,[15] we assumed that depressed elders with CVD should be a separate subtype, and, therefore, be different in vascular factors such as tHcy. To prove this hypothesis, we divided the study sample into three subgroups: those without depression, and those depressed with and without CVD as shown in **Table 3**. Elders with vascular depression had the highest levels of tHcy (mean±SD: 12.8±4.6 vs. 11.7±4.5 vs. 11.9±5.5; df=2, 962; P =0.008) and creatinine (mean±SD: 1.3 ±1.3 vs.1.1±1.1 vs. 1.1±0.9; df=2,938; P=0.001) in comparison to those without CVD and those without depression. With a larger sample size, we again showed that

Table 3. Homocysteine, plasma Aβ peptides, and kidney function among those with different depression status.

Demographic Information	No Depression N = 640	Vascular Depression N = 162	Depression without CVD N = 152	P value
Age, year, mean ± SD [a]	76.0 ± 8.4	74.8 ± 8.7	73.0 ± 8.4	<0.0001
Female, n/total (%) [b]	436/580 (75%)	117/154 (76%)	108/144 (75%)	0.91
Past or current smoker, n/total (%) [b]	359/569 (63%)	97/154 (63%)	98/144 (68%)	0.71
African Americans, n/total (%) [b]	214/580 (37%)	55/154 (36%)	55/144 (38%)	1.00
Medical Condition				
Diabetes, n/total (%) [b]	192/561 (34%)	69/148 (47%)	45/138 (33%)	0.02
Stroke, n/total (%) [b]	115/567 (20%)	39/149 (26%)	16/142 (11%)	0.002
Blood Data				
tHcy (umoles/L), mean ± SD [a]	11.9 ± 5.5	12.8 ± 4.6	11.7 ± 4.5	0.008
Creatinine, mg/DL, mean ± SD [a]	1.1 ± 0.9	1.3 ± 1.3	1.1 ± 1.1	0.001
Aβ40, pg/ml, median (Q1, Q3) [c]	133.9 (97.2, 172.7)	134.5 (98.4, 185.0)	130.6 (91.7, 131.7)	0.31
Aβ42, pg/ml, median (Q1, Q3) [c]	18.7 (12.4, 27.6)	19.1 (12.6, 29.6)	15.5 (11.4, 23.0)	0.01

[a] Mean + SD, and ANOVA are presented.
[b] Number/total number (%), and Chi-Square test are presented.
[c] Median with 25% (Q1) and 75% (Q3), and Mann-Whitney test are presented.
P values for the statistical significance are shown

depression without CVD had the lowest plasma Aβ42 (median: 15.5 vs. 19.1 vs. 18.7 pg/ml; df = 2,886; P = 0.01) in comparison to those with CVD and those without depression. In the absence of depression, there was no difference in plasma Aβ42 between those with and without CVD (data not shown).

Among these three groups, there were no differences observed in plasma Aβ40, gender, ethnicity, and past or current smoking habit (**Table 3**). As expected, the vascular depression subgroup had higher rates of diabetes (47% vs. 33% vs. 34%, df = 2, P = 0.02) and stroke (26% vs. 11% vs. 20%, df = 2, P = 0.002) compared to those without CVD and those without depression. Additionally, depressed subjects without CVD were youngest (mean $\pm$ SD: 73.0 $\pm$ 8.4 vs. 74.8 $\pm$ 8.7 vs. 76.0 $\pm$ 8.4; df = 2, 962; P < 0.0001) compared to those with CVD and those without depression.

Discussion

Vascular depression,[8] which is related to vascular disease, especially CVD, is a common depression subtype in the elderly. In this study of the homebound elderly, it was found that the elderly with vascular depression had the highest concentration of tHcy compared to those without CVD and those without depression (**Table 3**). By contrast, depressed elders without CVD had the lowest concentrations of plasma Aβ42 compared to those with vascular depression and those without depression. These results suggest that there are at least two separate depression subtypes, 1) vascular depression, associated with tHcy and plasma Aβ40, and 2) amyloid-associated depression, associated with low plasma Aβ42, which we have previously reported.[15] Since both micronutrient deficiency and impaired kidney function due to a vascular disease occur often among the elderly with depression, the combination of these two factors may contribute more to the relationship between tHcy and plasma Aβ40 in late life depression, particularly vascular depression, than those without depression.

Elevated tHcy in blood could be a result of impaired kidney function or dietary B vitamin deficiencies of folate, vitamin B12 or B6. Although Aβ40 and Aβ42 differ by only two amino acids at the C-terminus, in multivariate regression analyses plasma Aβ40 as an outcome, but not plasma Aβ42, was associated with tHcy and kidney function independently (**Table 2**). Since both tHcy and Aβ40 are involved in vascular pathology,[1,5] these two factors are associated with each other. In contrast, Aβ42 is mainly produced in brain and involved in the amyloid plaques in the AD brain. Our study has found that after adjusting for kidney function, plasma Aβ40 was still positively associated with tHcy in elders with depression, but not in those without depression (data now shown). It is shown that many depressed elders have B vitamin deficiencies, particularly in folate, probably due to poor appetite[30-33] that could cause high tHcy in serum in the depressed elderly.[18,19,34,35] Indeed, B vitamin supplements have been shown to improve the outcome of treatment with antidepressants in depressed patients.[36,37] B vitamin deficiencies could also decrease S-adenosylmethionine (SAM) in the one carbon metabolism pathway[38] (reviewed by Coppen A 2005). Decreased SAM reduces methylation of Presenilin1 (PS1) so the γ-secretase complex for APP is activated resulting in increased Aβ production.[39,40]

In this study, kidney function, evaluated by creatinine measurement, accounted for most of the relationship between plasma Aβ40, but not Aβ42, and tHcy in multivariate regression (**Table 2**), which is consistent with other studies.[2,3,29] It is possible that both plasma Aβ40 and tHcy are metabolized or excreted competitively by the kidneys. Kidney function is commonly impaired due to vascular diseases such as CVD, diabetes and hypertension in the elderly. Therefore, elevated plasma Aβ40 might be a result of poor excretion in elders with vascular diseases.

Depressed elders with CVD showed higher concentrations of tHcy than those without CVD and those without depression (**Table 3**), which is in agreement with other studies.[16-19] Although the levels of plasma Aβ40 were similar among the three groups(**Table 3**), the elevated tHcy in vascular depression may interact with plasma Aβ40 to play some synergistic role in causing vascular and neuronal pathology in the brain.[41-43] Several studies have shown that vascular depression in the elderly is associated with executive dysfunction.[8,44-47] WMHI, associated with both elevated plasma Aβ40[7] and higher levels of tHcy in the blood,[32,48,49] is the magnetic resonance imaging (MRI) finding of cerebrovascular pathology in vascular depression.[8-14]

In several large population-based studies, a CES-D score greater than 16 is associated with an increased risk of AD.[50-53] In the homebound elderly, higher CES-D scores are associated with low plasma Aβ42, which we have termed amyloid-associated depression.[54] In this study, with a larger sample we again found that depressed elders without CVD had lower concentrations of plasma Aβ42 than those with CVD and those without depression (**Table 3**). The meaning of the relationship between depression and low plasma Aβ42 is unclear; however, plasma Aβ42 declines significantly at the pre-clinical stage of AD.[55-58] In contrast to amyloid-associated depression, the severity of depressive symptoms in vascular depression with CVD does not change with different concentrations of plasma Aβ42.[54] Depression is a clinical syndrome with multiple pathologies and etiologies.

The clinical implication of this is that there may be different prognoses of the depression subtypes in the elderly, 1) amyloid-associated depression may be a precursor for AD and 2) vascular depression may lead to executive dysfunction. Limitations of this study include the use of the CES-D score, as a basis for classifying depression, rather than the DSM-IV criteria. However, the cut-off CES-D score ($\geq$ 16) had a sensitivity of 0.86 and a specificity of 0.77 when a subset of our subjects were evaluated by a board-certified psychiatrist using DSM-IV criteria (N = 285). An additional limitation is

that we did not collect information with regards to the onset and the course of depression, thus limiting our ability to distinguish early-onset or recurrent depression from late-onset depression. The status of CVD was self-reported, and thus this classification may not be entirely accurate. Lastly, this was a cross-sectional study so we were unable to characterize depression subtypes prospectively.

As a population ages, increasingly more become homebound. Our homebound elderly population showed higher rates of depression and vascular diseases such as CVD than the general elderly population (**Table 1**) as reported by another study.[59] One approach to understanding the differences between the pre-clinical depression of AD and vascular depression would be a comparison of effective interventions and treatments for each. However, such studies are not available. Our study has found that antidepressants, especially Serotonin Specific Reuptake Inhibitors (SSRI), are associated with lower levels of plasma Aβ40, but not Aβ42.[60] Based on this study and others,[19,36,37,60] it is suggested that a well controlled clinical trial to observe the combination of SSRI and folate or other B vitamins in reducing plasma Aβ40 and tHcy as well as vascular depression is probably needed.

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