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Plasminogen Activator Inhibitor-1: Potential Inflammatory Marker in Late-life Depression

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Objective: Although several previous studies have examined the association between late-life depression and blood adipokine levels, a marker of chronic inflammation, no studies have comprehensively considered the effects of metabolic syndrome, which is known to affect blood adipokine levels. This study examined blood adipokine levels in geriatric depression after adjusting for the effects of metabolic syndrome.
Methods: Participants were selected from the Ansan Geriatric Study (depression group [n = 76] and control group [n = 76]). Blood concentrations of four adipokines (adiponectin, resistin, neutrophil-gelatinase-associated lipocalin [NGAL], and plasminogen activator inhibitor-1 [PAI-1]) were measured using immunoassays. The effects of blood adipokine concentration on the diagnosis of depression were analyzed using multivariate logistic regression to adjust for the effects of metabolic syndrome and potential confounding factors.
Results: When the effects of metabolic syndrome and potential confounding factors were adjusted, only PAI-1 could explain the diagnosis of depression among all the adipokines. The depression group showed a lower blood PAI-1 level than the control group. Adiponectin, resistin, and NGAL could not explain the diagnosis of depression when the effects of metabolic syndrome and potential confounding factors were adjusted.
Conclusion: This study suggests the possibility that the blood PAI-1 levels in clinically pathological late-life depression may show contrasting results to those with subclinical depressive symptoms. Additionally, considering that most previous studies have been conducted with pre-geriatric populations, the study suggests the possibility that geriatric depression may show inflammatory changes with patterns that are different from those of depression in the pre-geriatric population.

KEY WORDS: Depression; Plasminogen activator inhibitor 1; Adipokine; Inflammation; Metabolic syndrome.

INTRODUCTION

Neuroinflammation is gaining attention as a major etiology of late-life depression. During aging, the whole body, including the brain and the rest of the central nervous system, becomes pro-inflammatory, causing an imbalance of the immune system [1,2]. The central nervous system is protected from the outside by the blood-brain barrier and has limited lymphatic system involvement. Further, it has an independent immune system. However, the immune system of the central nervous system interacts actively with the peripheral immune system. Important changes in the immune system of the central nervous system can be caused by interactions between the peripheral immune response and the central nervous system. Cytokines and chemokines can activate the immune response by stimulating microglia in the central nervous system by moving through the blood-brain barrier via active transport [3]. If the immune imbalance in the peripheral and central nervous system persists, the immune response triggered by immune proteins and cytokines increases [4], which leads to neurodegeneration and is believed to be involved in the development of various age-related diseases, including late-life depression [2].

Metabolic syndrome is defined as obesity accom-

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panied by a minimum of two conditions among the following: hypertension, hyperlipidemia, or insulin resistance [5]. Previous studies have revealed an association between metabolic syndrome, the prevalence of depressive disorders, and the severity of depressive symptoms [6,7]. Specifically, in the secondary analysis of data from a randomized controlled study conducted in the elderly population, depressive disorder patients with metabolic syndrome showed higher symptom severity and chronic tendency than the control group [8].

Several studies have suggested an association between chronic inflammation and the components of metabolic syndrome diagnostic criteria, such as obesity, insulin resistance, and hyperlipidemia [9-12]. Low levels of chronic inflammation have also been observed in metabolic diseases, including obesity, type 2 diabetes, and metabolic syndrome, along with behavioral changes. Many studies have reported problems such as depressive symptoms, cognitive impairment, fatigue, sleep disturbance, and pain with increased levels of acute-phase proteins and cytokines (C-reactive protein [CRP], interleukin-6 [IL-6], and tumor necrosis factor-α [TNF-α]), the levels of which further increase in metabolic diseases compared to those in the normal state; however, the levels are lower than those in the acute inflammatory state [13].

Various studies have been conducted on cytokines related to an inflammatory response in each depressive disorder, including those for geriatric depression and metabolic syndrome. Specifically, adipokine, a cytokine derived from adipocytes, is gaining attention as a marker of the chronic inflammatory response, and several studies have suggested a relationship between blood adipokine levels, metabolic syndrome, and depression.

Adiponectin is an adipokine secreted exclusively from adipocytes [14], and a positive correlation was found between the blood concentration of CRP, an inflammatory blood marker, and the blood concentration of adiponectin after adjusting for the effects of age and sex [15]. In a series of studies, adiponectin has displayed anti-diabetic and anti-atherogenic activities [14,16,17]. In the pre-diabetes state, a decrease in blood adiponectin precedes a decrease in insulin sensitivity, and a low blood adiponectin concentration predicts the incidence of insulin resistance and type 2 diabetes [18]. The level of blood adiponectin was lower in cases of obesity, coronary artery disease, diabetes, insulin resistance, and hypertension [19-21]. In the study by Diniz *et al.* [22], the serum concentration of adiponectin was found to be significantly decreased in patients with late-life depression ($p < 0.001$). Adiponectin levels were also significantly decreased when the effects of body mass index (BMI), cognitive function, and education level ($p < 0.001$) were adjusted.

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, is a glycoprotein that belongs to the transporter group of small circulating lipophilic molecules. NGAL has recently been characterized as an adipokine [23]. A study by Jang *et al.* [24] provided clinical evidence demonstrating that serum NGAL concentrations are associated with obesity, as well as chronic inflammation and metabolic complications related to obesity. Patients with metabolic syndrome have higher serum NGAL concentrations than those without the syndrome, and serum NGAL has been suggested as a useful biomarker for evaluating outcomes in obesity-related metabolic and cardiovascular diseases [24]. Plasma NGAL concentration was significantly higher in the depressed patient group than in the healthy control group after adjusting for confounding variables such as age, male sex, smoking, and waist circumference [25].

Plasminogen activator inhibitor-1 (PAI-1) is mainly produced in vascular endothelial cells and inhibits the activity of tissue plasminogen activator (tPA) to prevent the conversion of plasminogen to plasmin [26]. PAI-1 is mainly secreted by vascular endothelial cells; however, it is also secreted by some adipocytes and is sometimes classified as an adipokine [26]. Increased blood levels of PAI-1 were associated with a chronic inflammatory state in obesity [9,27]. PAI-1 showed a significant increase in central obesity associated with metabolic syndrome and a positive correlation with metabolic syndrome [28]. In central obesity, depressive symptoms and the blood level of PAI-1 showed a constant association with metabolic syndrome [26,29-31].

Resistin, an adipokine secreted from adipocytes that is involved in the inflammatory response, shows an increase in blood levels in obesity and it is positively correlated with metabolic syndrome [26,32]. In a randomized, double-blind study that examined the relationship between resistin and depression in 37 patients with depression, a 5-week antidepressant treatment using amitriptyline or paroxetine showed a decrease in resistin concentration in patients with remission, while there was no change in the

resistin concentration in patients who did not achieve remission [33].

Many studies suggest that blood adipokine levels related to metabolic syndrome are also associated with depression; however, research on the effects of both metabolic syndrome and depressive disorders on adipokine levels is generally considered together, but not thoroughly. Thus, this study aimed to examine the relationship between blood adipokine levels and geriatric depression after adjusting for the effects of metabolic syndrome on adipokines that have shown a significant correlation with metabolic syndrome and depression. The indicators targeted in this study were adiponectin, PAI-1, NGAL, and resistin. This study aimed to obtain data for a deeper understanding of the biological relationship between adipokines and geriatric depression and the inflammatory mechanism in geriatric depression while evaluating the role of blood adipokine level as a biological marker in geriatric depression.

METHODS

Participants

Participants were recruited from the 2003 Ansan Geriatric (AGE) Cohort Study. The study with AGE cohort study was first conducted in 2002 in Ansan, Gyeonggi-do, Republic of Korea as a prospective, population-based study to examine the prevalence, incidence, and relevant risk factors for geriatric diseases such as late-life depression, dementia, and metabolic syndrome and obtain comprehensive information on the overall health and functional status of the elderly. Detailed protocols and study designs for sampling participants from the AGE cohort are reported in a previous study [34].

After sampling and screening to exclude ineligible recruits, 2,767 participants were selected as the final sample representing the target population. A total of 1,391 participants (595 males and 796 females) were randomly selected from September 2004 to March 2006 in the first wave of the study via probability sampling performed for age and sex from baseline assessment data. The recruits were interviewed and they underwent a comprehensive checkup at the Geriatric Health Clinical Research Institute, Korea University. Participants in the first wave of the study received clinical and neuropsychological assessments. Among these participants, some were lost to follow-up due to reasons such as refusal to participate, relocation of residence, and death.

Follow-up assessments were conducted for data collection with the cohort that was recruited similarly in the second wave of the study from April 2006 to January 2008, the third wave of the study from April 2008 to July 2008, and the cohort for the fourth study conducted in 2009. This study was conducted based on data collected from the first wave of the study conducted with the AGE cohort. Neuropsychological tests, diagnosis of depression, body measurements, and blood collection were performed from September 2004 to March 2006.

Among the 1,391 participants recruited for the first wave of the study, 777 participants were diagnosed using the Mini International Neuropsychiatric Interview (MINI), and the diagnosis of major depressive disorder and psychiatric diagnosis of participants was based on the diagnostic criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) through a discussion of investigators consisting of psychiatrists, neurologists, and clinical psychologists respectively. Based on this information, 124 participants were classified into the depression group and 653 participants were classified as the control group within the cohort. When the standard medium effect size suggested by Cohen [35] was set to 0.5, the significance level (α) was set to 0.05, and the power ($1-\beta$) was set to 0.8, to calculate the required number of samples; a minimum of 51 participants each was required for the depression and control groups. Thus, 76 participants were randomly extracted and assigned to the depression and control groups.

The study was conducted in compliance with the institutional ethics guidelines. All participants provided written consent, and the protocol was approved by the Institutional Review Board of the Korean University Ansan Hospital (IRB No. 2017AS0182).

Assessment

Diagnosis and assessment of depression

The diagnosis of depression was made after screening with MINI, and the final diagnosis was made after an export group discussion. Depressive symptoms were measured using the Korean version of the Center for Epidemiologic Studies Depression Scale (CES-D) and Geriatric Depression Scale (GDS).

MINI is a structured interview for the diagnosis of mental disorders according to DSM-IV and International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and it is a simple and effective interview that takes about 15 minutes. The MINI has shown stable reliability and validity in the structured clinical interview of DSM-IV and also stable inter-rater reliability [36]. This study used the Korean version of the MINI, translated and validated by Yoo *et al.* [37].

The GDS is a self-reported depression scale consisting of 30 questions in total and is designed to be answered easily [38]. In this study, the Short-Form Korean Geriatric Depression Scale (K-GDS) consisting of 15 questions was used [39]. The CES-D is also a self-reported depressive symptom scale with simple questions that are easy to use in epidemiological studies as it measures the severity of the symptoms based on the duration. Although the CES-D is not a diagnostic tool for clinical depression, it reflects the extent of depressive symptoms in the community well and is widely used to compare the prevalence of depressive symptoms between countries, ethnic groups, age groups, and sexes [40]. The CES-D consists of 20 questions with a total score of 60, wherein higher scores indicate a higher severity of depressive symptoms [41].

Diagnosis of metabolic syndrome

Metabolic syndrome was diagnosed based on data on medical history, medication history, waist circumference, fasting plasma glucose (FPG) level, blood pressure, and blood lipid profile collected from the participants and according to the definition proposed by the American Heart Association and the National Heart, Lung, and Blood Institute. For waist circumference, which indicates central obesity in the diagnostic criteria, a stricter criterion was used according to the standards in Korea to take into account the differences between ethnic groups [42]. A diagnosis of metabolic syndrome was made if a minimum of three of the following criteria were met: (1) systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85 mmHg or the use of antihypertensive drugs; (2) FPG $\geq$ 100 mg/dl or the use of drugs for hyperglycemia; (3) high-density lipoprotein (HDL): male $<$ 40 mg/dl, female $<$ 50 mg/dl; (4) triglycerides $\geq$ 150 mg/dl [43,44]; and (5) waist circumference: male $\geq$ 90 cm, female $\geq$ 85 cm [42].

Assessment of cognitive function

Cognitive function was assessed using several neuropsychological assessment tools, and dementia and mild cognitive impairment were diagnosed based on discussions among mental health specialists, neurologists, and clinical psychologists. The neuropsychological assessment tool used was the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) [45], the Mini-Mental State Examination in the CERAD-K battery [45], the Clinical Dementia Rating [46,47], the Korean version of GDS [38], the Barthel Activities of Daily Living [48], and the Korean Instrumental Activities of Daily Living [49]. Dementia was diagnosed according to the DSM-IV diagnostic criteria, and mild cognitive impairment was diagnosed based on the Petersen criteria [50].

Blood Sampling

Blood sampling for this study was conducted from September 2004 to March 2006, when the first wave of the AGE cohort study was being conducted. Blood was sampled intravenously after overnight fasting (12$-$14 hours) for tests including complete blood count, FPG, and lipid profile. Additionally, some of the blood was transferred to ethylenediaminetetraacetic acid tubes for immunoassays. Blood was centrifuged for 4 hours at 3,000 rpm to isolate plasma from cellular components and was stored at $-$70°C until further use.

Once the study was planned, a multiplex kit was purchased from Merck Millipore, and the adipokine index in the blood was analyzed using a multiplex assay using the Milliplex MAP Human Adipokine Magnetic Bead Panel 1 (Human Adipokine Panel, HAP) kit and the Luminex xMAP technique from Luminex Instruments (Luminex Corporation, Austin, TX, USA). HAP includes adiponectin, NGAL, PAI-1, and resistin. The kit was processed according to the manufacturer's guidelines. Reagents were incubated at 4°C for 12 hours to obtain the maximum sensitivity. All samples were processed in a single well plate so that each plate processed one sample.

The precision of the assay reported by the manufacturer was $<$ 15% for adiponectin, NGAL $<$ 15%, PAI-1 $<$ 20%, and resistin $<$ 20% respectively for the intra-assay coefficient of variation, and adiponectin $<$ 10%, NGAL $<$ 10%, PAI-1 $<$ 10%, and resistin $<$ 10% respectively for the inter-assay coefficient of variation.

Statistics

Continuous variables are expressed as mean and standard deviation, and nominal variables are expressed as numbers and percentages. The comparison of the mean of the continuous variables between the depression group and the control group was tested using the independent sample *t* test (Student's *t* test) or the Mann−Whitney *U* test depending on the normality of the sample distribution, while the odds ratio (OR) of the nominal variables was evaluated using the chi-square test. The correlation between GDS and CES-D scores and biomarkers was analyzed by calculating Pearson's correlation coefficient.

To adjust for the effects of the diagnosis of metabolic syndrome in the assessment of blood adipokine index level in depression, logistic regression analysis was conducted using the diagnosis of metabolic syndrome and whether the details for the diagnosis of metabolic syndrome were fulfilled as covariates or not. To adjust for differences due to demographics and clinical characteristics between the depression and control groups, the factors that showed significant differences between the groups, including socio-demographic index, anthropometric index, hematological index, comorbid disease, concomitant drugs, adipokine blood markers, and cognitive impairment, were included in the analysis as covariates. Thus, the effects of these variables were adjusted. As results may vary due to differences in the prevalence of depression according to sex and the presence of obesity, a subgroup analysis was conducted. The primary endpoint of this study was the effect of blood adipokine concentration on the onset of depression after adjusting for metabolic syndrome and contributing factors that could act as confounding variables.

Table 1. Sociodemographic data, depressive symptom measure, metabolic syndrome diagnosis, obesity based on BMI, and cognitive disorders of study groups

Variable		Depression (n = 76)	Control (n = 76)	Test statistics	*p* value
Age		68.05 ± 4.90	66.17 ± 3.75	t = −2.659	0.009
Depressive symptom	CES-D	16.80 ± 7.06	9.82 ± 3.40	t = 7.744	< 0.001
	GDS	18.03 ± 5.72	6.38 ± 4.79	t = 13.577	< 0.001
Sex	Male	16 (21.1)	33 (43.4)	χ^2 = 8.704	0.003*
	Female	60 (78.9)	43 (56.6)		
Alcohol use	≥ 3 times/wk	9 (11.8)	19 (25.0)	χ^2 = 4.378	0.036*
Smoking	Current smoker	55 (72.4)	50 (65.8)	χ^2 = 2.725	0.256
	Ex-smoker	14 (18.4)	12 (15.8)		
	Non-smoker	7 (9.2)	14 (18.4)		
Education	≤ 6 yr	52 (68.4)	28 (36.8)	χ^2 = 17.390	< 0.001*
	7−12 yr	21 (27.6)	34 (44.7)		
	≥ 13 yr	3 (3.9)	14 (18.4)		
Partner	With partner	48 (63.2)	63 (82.9)	χ^2 = 7.515	0.006*
	No partner	28 (36.8)	13 (17.1)		
MetS diagnostic criteria	MetS	36 (48.0)	29 (38.2)	χ^2 = 1.491	0.222
	TG	23 (30.3)	20 (26.3)	χ^2 = 0.292	0.589
	HDL	49 (64.5)	29 (38.2)	χ^2 = 10.534	0.001*
	HTN	50 (65.8)	44 (57.9)	χ^2 = 1.004	0.316
	IR	42 (55.3)	47 (61.8)	χ^2 = 0.678	0.41
	Central obesity	43 (57.3)	39 (51.3)	χ^2 = 0.551	0.458
Obesity (BMI)	≥ 25 kg/m^2	39 (51.3)	34 (44.7)	χ^2 = 0.659	0.417
Cognitive disorder	Normal	32 (42.1)	76 (100)	χ^2 = 61.926	< 0.001*
	MCI	33 (43.4)	0 (0)		
	Dementia	11 (14.5)	0 (0)		

Values are presented as mean ± standard deviation or number (%).
CES-D, Center for Epidemiologic Studies Depression Scale; GDS, Geriatric Depression Scale; MetS, metabolic syndrome; TG, triglycerides > 150 mg/dl; HDL, high density lipoprotein (male < 40 mg/dl; female < 50 mg/dl); IR, insulin resistance; BMI, body mass index; MCI, mild cognitive impairment.
*Statistically significant ($p < 0.05$).

RESULTS

Subject Characteristics

A total of 152 participants were enrolled in this study, with 76 participants each in the depression and control groups. The mean age in the depression group was 68.05 ± 4.90 years, which was significantly higher than 66.17 ± 3.75 years in the control group. The percentage of women in the depression group was 78.90%, which was higher than the 56.60% in the control group. There was a significant difference between the groups in the use of alcohol, presence of a domestic partner, presence of musculoskeletal disorders, and the use of antidepressants (Supplementary Table 1; available online). The mean score for CES-D, a depression symptom scale, showed a significant difference, with 16.09 ± 7.06 in the depression group and 9.82 ± 3.40 in the control group ($p < 0.001$), and the mean GDS score also showed a significant difference, with 18.03 ± 5.72 in the depression group and 6.38 ± 4.79 in the control group ($p < 0.001$) (Table 1).

Regarding the results of body measurements, height was significantly smaller in the depression group than the control group (153.99 ± 7.82 cm in the depression group, 159.11 ± 8.14 cm in the control group), with a lower mean body weight (59.03 ± 8.34 kg in the depression group, 63.23 ± 10.30 kg in the control group); however, there was no significant difference in BMI between the two groups (Supplementary Table 2; available online). In hematological tests, hemoglobin and hematocrit levels were lower in the depression group than in the control group (Supplementary Table 2; available online).

Although the percentage of participants diagnosed with metabolic syndrome did not show a significant difference between the groups, the percentage of participants who fulfilled the diagnostic criteria for HDL abnormality among other detailed diagnostic criteria for metabolic syndrome was significantly higher in the depression group than in the control group (Table 1). Cognitive impairment, including dementia and mild cognitive impairment, was only found in the depression group, and there was a significant difference between the two groups (Table 1).

Comparison of Blood Adipokine Concentration

The concentration of blood adipokines, which is the target of this study, did not show a normal distribution, and the mean levels of blood adipokines between the depression and control groups were compared using the Mann−Whitney *U* test. PAI-1 was the marker that showed a statistically significant difference in the mean between the two groups, and its concentration was lower in the depression group than in the control group (Table 2). Among other endpoints of the study, blood levels of adiponectin, resistin, and NGAL did not show a significant difference between the groups (Table 2, Fig. 1). As the blood markers widely ranged between 10^1 and 10^9 without normal distribution, the value of the markers was transformed to log to ensure normality of the sample distribution. As the empirical cumulative distribution of all blood marker values used in the log-transformed analysis was smooth and symmetric, it was considered that the log-transformed sample values converged to the lognormal distribution. When the means of the log-transformed blood marker levels were

Table 2. Plasma concentration of adipokines

Blood adipokine	Depression	Control	Test variables	*p* value
Adiponectin	15,101,447.37 ± 12,112,324.60	13,772,894.74 ± 10,660,340.06	2,701.00	0.491
Resistin	19,804.34 ± 13,075.04	19,921.97 ± 16,750.71	2,686.50	0.458
PAI-1	32,644.08 ± 16,333.23	46,396.05 ± 25,222.02	1,900.50	< 0.001*
NGAL	77,013.16 ± 42,170.07	65,277.63 ± 26,195.33	2,366.00	0.054
Log adiponectin	7.075 ± 0.301	7.034 ± 0.310	−0.837	0.404
Log resistin	4.224 ± 0.245	4.211 ± 0.257	−0.337	0.736
Log PAI-1	4.461 ± 0.224	4.609 ± 0.226	4.055	< 0.001*
Log NGAL	4.844 ± 0.183	4.783 ± 0.167	−2.147	0.033*

Values are presented as mean ± standard deviation.
PAI-1, plasminogen activator inhibitor-1; NGAL, neutrophil-gelatinase-associated lipocalin.
Values of adipokine concentrations are in pg/ml. The test variable used in the mean comparison of plasma adipokine level is Mann−Whitney's *U*. The test variable used in the mean comparison of log transformed plasma adipokine level is Student's *t*.
*Statistically significant ($p < 0.05$).

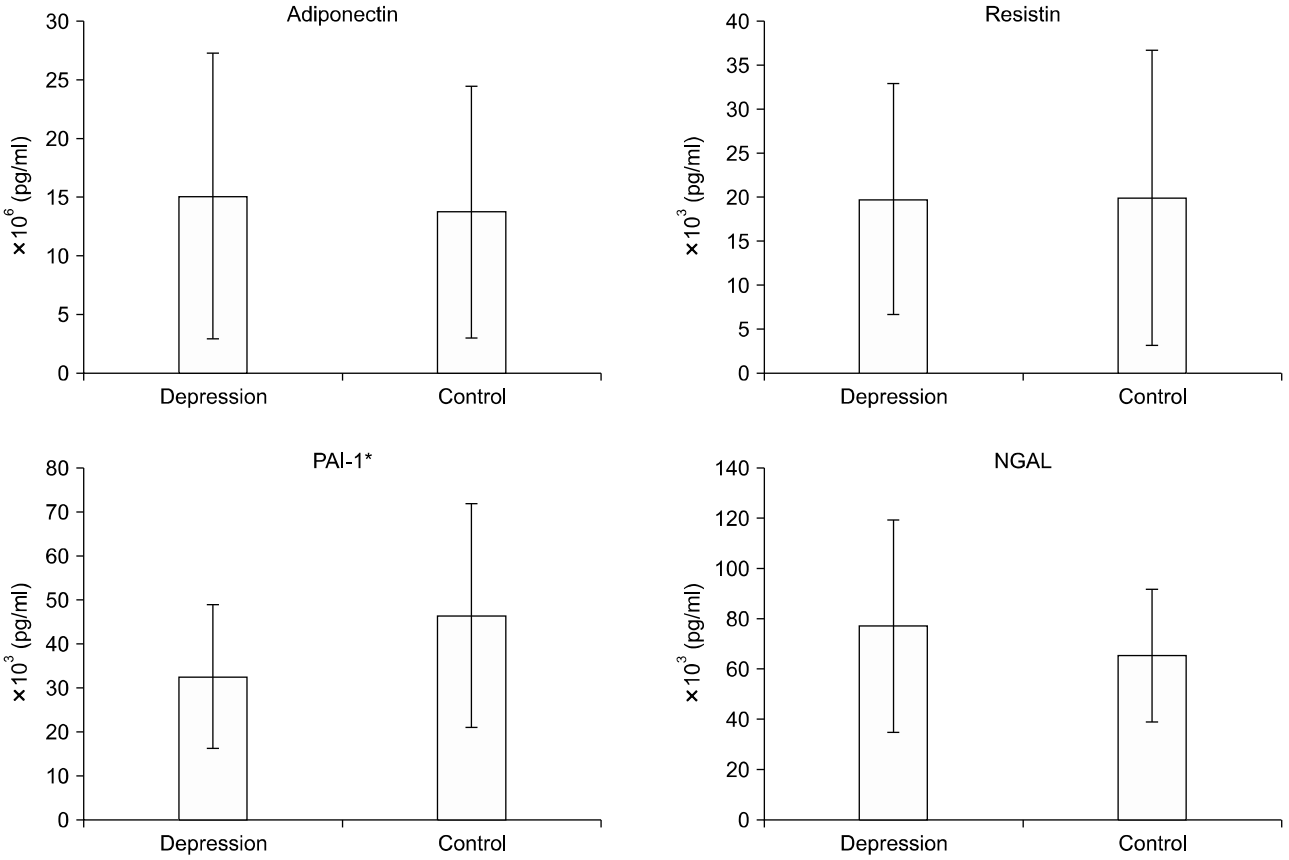

Fig. 1. Distribution of the mean values of plasma adipokine concentration Error bars: ± 1 standard deviation (SD).
PAI-1, plasminogen activator inhibitor-1; NGAL, neutrophil-gelatinase-associated lipocalin.
*Statistically significant result ($p < 0.05$) at Mann−Whitney U test.

compared using the Student's t test, there was a significant difference found in PAI-1 and NGAL between the depression and control groups (Table 2).

Correlation Between Depressive Symptoms and Blood Adipokine Levels

Pearson correlation analysis was performed between the depressive symptoms scales CES-D and GDS and the log-transformed values of each blood marker concentration to observe the correlation between depressive symptoms and blood marker concentration. Among blood markers, the log-transformed value of PAI-1 concentration showed a significant negative correlation with both CES-D and GDS. The detailed results of the Pearson correlation analysis are presented in Table 3.

Table 3. Correlation between depressive symptom measure and plasma adipokine level

Blood adipokine	CES-D		GDS	
	r	p value	r	p value
Log adiponectin	−0.047	0.569	0.149	0.069
Log resistin	0.079	0.338	0.020	0.809
Log PAI-1	−0.169	0.039*	−0.260	0.001*
Log NGAL	−0.010	0.904	0.119	0.146

CES-D, Center for Epidemiologic Studies Depression Scale; GDS, Geriatric Depression Scale; r, Pearson correlation coefficient; PAI-1, plasminogen activator inhibitor-1; NGAL, neutrophil-gelatinase-associated lipocalin.
*Statistically significant ($p < 0.05$).

Logistic Regression

Univariate logistic regression was conducted for the indices that showed a significant difference between the depression and control groups among sociodemographic indices, comorbid diseases, anthropometric indices, hematological indices, and blood markers (Supplementary Table 3; available online). Univariate logistic regression analysis revealed that age, sex, alcohol use, school years, the presence of a domestic partner, height, body weight,

hemoglobin, hematocrit, log-transformed PAI-1 blood concentration, log-transformed NGAL blood concentration, and HDL abnormality among the diagnostic criteria for metabolic syndrome could significantly explain the diagnosis of depression. These variables were included as covariates in the multivariate logistic analysis for the onset of depression. The use of antidepressants and cognitive impairment (dementia or mild cognitive impairment) was not observed in the control group; therefore, they were not suitable for univariate logistic regression analysis. However, the percentages for the use of antidepressants and cognitive impairment were expected to show a significant difference between the control and depression groups and affect the presence of depression; therefore, these were included in the multivariate logistic regression analysis. Additionally, a multivariate binary logistic regression analysis was conducted for the depression and control groups by including the diagnosis of metabolic syndrome and whether or not the details (insulin resistance, HDL abnormality, triglyceride abnormality, central obesity, hypertension) were satisfied. The marker with statistically significant results was log-transformed PAI-1 blood concentration (B = −3.966, $p < 0.001$) with an OR of 0.019 (95% confidence interval [CI] 0.002−0.161) (Table 4).

Results of Subgroup Analysis

Sex

In males, the diagnosis for cognitive impairment (χ^2 = 14.102, $p = 0.001$), endocrine disease (χ^2 = 5.345, p = 0.040), and the presence of neoplasm/tumor (χ^2 = 5.676, $p = 0.017$) showed a significant difference between the depression and the control groups. In a multivariate logistic regression with adjustment for the diagnostic criteria for metabolic syndrome and potential confounding variables, the presence of neoplasm/tumor (OR 0.094, 95% CI 0.009−0.925, $p = 0.43$) explained the diagnosis of depression, while blood markers did not show significant results.

In females, there was a significant difference between the depression and the control groups in age (t = −2.493, p = 0.014), the presence of a domestic partner (χ^2 = 6.383, $p = 0.012$), diagnosis for cognitive impairment (χ^2 = 43.154, $p < 0.001$), HDL abnormality (χ^2 = 11.581, p = 0.001) among the diagnostic criteria for metabolic syndrome, presence of a musculoskeletal disease (χ^2 = 7.949, $p = 0.005$), the use of antidepressants (χ^2 = 4.566, p = 0.033), height (t = 2.388, p = 0.019), and blood HDL level (t = 2.505, p = 0.015); among blood adipokines, log-transformed blood PAI-1 concentration (t = −3.118, p = 0.002) showed a difference. The results of multivariate logistic regression analysis with adjustment for confounding variables showed that HDL abnormality (OR 0.126, 95% CI 0.034−0.474, $p = 0.002$) among the diagnostic criteria for metabolic syndrome and PAI-1 (OR 0.053, 95% CI 0.004−0.750, $p = 0.030$) among the log-transformed values of blood markers explained the diagnosis of depression with statistical significance.

Table 4. Multivariate logistic regression model of the association between PAI-1 and major depressive disorder (n = 152)

Variable	B	p value	Odds ratio (95% confidence interval)
Log PAI-1	−3.966	< 0.001	0.019 (0.002−0.161)

PAI-1, plasminogen activator inhibitor-1.

BMI

Subgroup analysis was conducted by dividing the participants into the normal weight group (n = 79) and the obese group (n = 73) using a BMI of 25 as the cutoff value. In the normal-weight group, height (t = 3.220, p = 0.002), education level in number of years (χ^2 = 11.243, p = 0.004), the presence of a domestic partner (χ^2 = 9.543, p = 0.002), diagnosis of cognitive impairment (χ^2 = 30.399, $p <$ 0.001), presence of a musculoskeletal disease (χ^2 = 9.012, p = 0.003), use of antidepressants (χ^2 = 4.783, p = 0.029), log-transformed blood PAI-1 concentration (t = −2.303, p = 0.024), and log-transformed blood NGAL concentration (t = 2.469, p = 0.015) were significantly different between the depression and control groups. After adjusting for the diagnosis of metabolic syndrome and potential confounding variables, the results of multivariate logistic regression analysis showed that only the presence of musculoskeletal disease (OR 0.181, 95% CI 0.049−0.672, p = 0.011) could significantly explain the diagnosis of depression, and there were no blood markers that showed significant results.

In the obese group, there was a significant difference between the depression and control groups in terms of the number of years (χ^2 = 7.148, p = 0.028), diagnosis of cog-

nitive impairment (χ^2 = 31.171, $p < 0.001$), HDL abnormality among the diagnostic criteria for metabolic syndrome (χ^2 = 7.045, p = 0.008), presence of musculoskeletal disease (χ^2 = 7.343, p = 0.007), body weight (t = 2.683, p = 0.010), hematocrit (t = 2.063, p = 0.043), and PAI-1 (t = 3.509, p = 0.001). After adjusting for the effect of diagnosis for metabolic syndrome and potential confounding variables, the results of multivariate logistic regression analysis showed that the presence of musculoskeletal disease (OR 0.063, 95% CI 0.009－0.418, p = 0.004), HDL abnormality among the diagnostic criteria for metabolic syndrome (OR 0.160, 95% CI 0.026－0.974, p = 0.047), and PAI-1 among log-transformed blood levels of adipokines (OR 0.001, 95% CI <0.001－0.116, p = 0.006) explained the diagnosis of depression with statistical significance.

DISCUSSION

This study was conducted to examine the difference in blood adipokine concentrations between the depression and control groups in the geriatric population and to investigate the relationship between blood adipokine concentration and the diagnosis of depression by adjusting the effects of metabolic syndrome. The blood concentration of PAI-I was significantly lower in the depression group than in the healthy control group, and the log-transformed blood PAI-1 concentration showed a negative correlation with the degree of depressive symptoms. After adjusting for metabolic syndrome and potential confounding variables such as sociodemographic and hematological factors and cognitive impairment, blood PAI-1 concentration explained the diagnosis of depression with statistical significance.

An increase in the T2 signal intensity of the subcortical white matter in patients with depression was observed in a series of brain magnetic resonance imaging (MRI) studies, which was attributed to an increase in the inner diameter and sclerotic change of the arteries, abnormalities in the vascular endothelium, and a decrease in the elasticity of the microvessels. From this, the vascular hypothesis of late-life depression was proposed, which suggests that this causes changes in performance and cognition, leading to late-life depression [51-53].

Plasminogen activation associated with thrombus formation is further regulated by specific plasminogen activator inhibitors that inhibit the effects of tPA. Among plasminogen activator inhibitors, PAI-1 is a major endogenous inhibitor of tPA and it has been associated with various thrombotic disorders [54]. The combination of PAI-1 and tPA terminates the enzymatic activity of tPA in the extracellular space. The components of the tPA-plasmin cascade, such as tPA, plasminogen, and PAI-1, are also widely present in the brain [55]. The possible contribution of PAI-1 to the process of thrombus formation in the cerebrovascular system supports the vascular hypothesis for geriatric depression.

PAI-1 has several other physiological roles in addition to thrombus formation. PAI-1 is produced in the liver, smooth muscle, adipocytes, and platelets under normal physiological conditions [56]. However, in pathological environments such as atherosclerosis, vascular endothelial cells, and other inflammation-activated cells produce a significant quantity of PAI-1 [56]. Thus, it has been suggested that PAI-1 is a marker of inflammation. Additionally, PAI-1 is also found in the cerebrospinal fluid [57] and although it is currently unknown whether PAI-1 itself could cross the blood-brain barrier, Hino *et al.* [58] showed that PAI-1 is immunochemically present in human brain tissues. Therefore, PAI-1 in the blood may reflect the inflammatory state of the central nervous system, including the brain. Based on this evidence, PAI-1 could interact with the inflammatory response of the central nervous system, contributing to the neuropathological mechanism of depression in old age.

However, unlike previous studies that showed a correlation between high blood PAI-1 concentration and depressive symptoms, the depression group showed a lower blood PAI-1 level compared to the control group in this study and, even after adjusting for confounding variables, low blood levels of PAI-1 explained the diagnosis of depression.

These results contradict previous findings that could be explained by the effects of the relationship between the serum PAI-1 concentration and other tPA-plasmin cascade components, such as tPA. Therefore, future studies must examine the components of the tPA-plasmin cascade when investigating the relationship among PAI-1, related factors, and geriatric depression. Furthermore, as PAI-1 is related to low levels of inflammatory response to thrombus formation, other markers for inflammation, including CRP, TNF-α, and IL-6, should also be investigated.

Meanwhile, animal models have shown that PAI-1 gene knockout mice showed a significantly higher tendency of depressive behaviors compared to the wild type [59]. Additionally, the study also showed that PAI-1 depletion affected serotonin and dopamine metabolism regardless of the mechanism of the tPA-brain-derived neurotrophic factor (BDNF). This supports the fact that PAI-1 depletion is associated with depression, along with the fact that PAI-1 was significantly lower in the depression group and that low concentration of PAI-1 in blood explained the diagnosis of depression.

Additionally, previous studies [29-31] that showed a correlation between depressive symptoms and high PAI-1 used the scores from a subjective depressive symptom scale rather than a structured interview when classifying participants into the depression and control groups, which may show a difference from the actual clinical population of patients with depression. In a previous study that investigated long-term adverse mental symptomatology including depressive symptoms in geriatric patients with metabolic syndrome, the increase in PAI-1 was found to be correlated with psychiatric symptoms; however, whether the participants had clinical depression could not be determined [60]. In the study by Jiang *et al.* [26], blood PAI-1 concentration was found to be higher in the group diagnosed with depression than in normal controls; however, the description of the process for the diagnosis of depression was ambiguous and the sample size was relatively small for comparing blood PAI-1 concentration with 17 participants each in the experimental and control groups. Previous studies have shown a correlation between the expression of depressive symptoms and an increase in blood PAI-1 concentration in the general population in which the diagnosis of depression is uncertain; however, this study showed a correlation between low blood PAI-1 levels and depression confirmed through a structured interview. That is, the blood concentration of PAI-1 may increase if depressive symptoms increase in a stressful situation, whereas it may decrease in clinically pathological depression.

Additionally, it should be noted that most of the previous studies that reported high blood levels of PAI-1 in the depression group were conducted with a middle-aged adult population below the age of 60 [29-31]. Cerebrovascular changes and chronic inflammatory changes, which are mechanisms of geriatric depression, may have different patterns from those seen in depression before old age. Pan *et al.* [61] assessed depressive symptoms in 3,289 Chinese community residents aged between 50 and 70 years using inflammation markers and the blood concentration of adipokines, including PAI-1 and CES-D. In this study, after adjusting for age, sex, BMI, blood pressure, smoking history, alcohol use, level of activity, and metabolism, the mean levels of PAI-1 and CRP were found to be lower in the depression group, whereas the mean level of IL-6 was higher in the depression group; however, the difference was not statistically significant. The inflammatory marker TNF-α is also predominantly reported to increase in depression before old age; however, studies conducted with geriatric patients reported mixed results, and the study by Forti *et al.* [62] showed that the risk of the onset of depression had a U-shaped relationship with blood concentration of TNF-α [62-64]. Therefore, based on the results of previous studies and this study, we propose that the expression patterns of some inflammation-related factors, including PAI-1, may have decreased due to the depletion of the inflammatory response in geriatric depression.

In a longitudinal study by Baune *et al.* [65] conducted on a regional geriatric community aged between 70 and 90 years, blood PAI-1 did not show a significant relationship with depressive symptoms measured at baseline and 2 years after the follow-up using a depressive symptom scale, and there was no relationship with the incidence of depressive symptoms. However, the increase in blood PAI-1 significantly explained the case in which there was a previous episode of depression in medical history without the current depressive state at baseline through logistic regression analysis [65]. In the study by Baune *et al.* [65], IL-6 in the blood, which is another factor for inflammation, was associated with depressive symptoms at baseline, while blood IL-8 was associated with the degree of depressive symptoms at baseline and 2 years after follow-up, and significantly explained the onset of depressive symptoms during the follow-up period. Baune *et al.* [65] suggested the possibility that PAI-1 is involved in the recovery mechanism in case of cell damage based on the results of the animal model study, which showed the neuroprotective effect of PAI-1 related to the mechanism of apoptosis, for the significant association demonstrated between blood PAI-1 and complete remission of depression when blood PAI-1 levels increased while showing a dif-

ferent tendency than other factors for inflammation [65-67]. Considering the decrease in PAI-1 in the presence of depression in this study and the fact that it could explain the diagnosis of depression along with the neuroprotective effects of PAI-1 suggested in the study by Baune *et al.* [65], the lack of PAI-1 may interfere with the cell recovery mechanism and contribute to the onset of depression. Additionally, depression was not diagnosed using a structured interview in the study by Baune *et al.* [65], and the percentage of participants without depression was higher at baseline than those showing depressive symptoms, accounting for only 12.9%; thus, there could be differences due to the relationship between baseline depressive symptoms and blood PAI-1.

In the subgroup analysis, there were no blood markers that could significantly explain the diagnosis of depression in males with normal body weight when the effects of confounding factors as well as the effects of metabolic syndrome were adjusted. However, in the female and obese groups, PAI-1 significantly explained the diagnosis of depression. Serum levels of PAI-1 were lower in the depression group than in the control group in both the female and obese groups. The percentage of body fat is generally higher in women than in men of the same body weight, and body fat is likely to be higher in obese women. Considering the relationship between the fact that PAI-1 showed significant results in females and the obese group and the percentage of body fat expected for each group, we suggest that PAI-1 may be associated with a role in adipocytes as an adipokine.

In the study by Kim *et al.* [68] conducted with participants from the Ansan Geriatric Study cohort as in this study, the percentage of body fat, waist-hip ratio, and BMI were significantly higher in the normal control group than in the depression group in females only. Additionally, Kim *et al.* [68] showed that the risk of depression decreased in obese women. Considering the findings by Kim *et al.* [68], the results of previous studies also reported an increase in blood concentration of PAI-1 in obese individuals [28]. The results of this study showed an association between the decrease in blood PAI-1 and depression, a tendency that was pronounced in females and the obese group with a high level of body fat, PAI-1 may lower the risk of depression by showing neuroprotective effects as adipokines secreted from fats, and the risk of depression may increase when PAI-1 level is low for the same percentage of body fat.

In a previous study that showed that the blood concentration of adiponectin was lower in geriatric depression than in the control group, the effects of metabolic syndrome factors (hypertension, insulin resistance, central obesity, and lipoprotein abnormalities) were not adjusted [22]. In a longitudinal study, blood NGAL levels were associated with the onset of late-life depression [25]. However, even in this study, despite adjusting for central obesity among the diagnostic criteria of metabolic syndrome in assessing the effects of blood NGAL concentration on the onset of depression, the effects of insulin resistance, blood lipoprotein abnormalities, and hypertension were not adjusted for in the results [25]. Although resistin has shown potential as a marker for treatment response in depression, no studies have shown an association with the diagnosis of depression [33]. A series of studies have reported that adiponectin, NGAL, and resistin are all associated with metabolic syndrome and chronic inflammation. The effects of metabolic syndrome had to be adjusted when assessing their effects on late-life depression [16,17,24,32]. Adiponectin, NGAL, and resistin did not significantly explain the diagnosis of depression when the effects of metabolic syndrome and potential confounding variables were adjusted.

In current study, the sample size was calculated to be large enough to derive meaningful results by considering the medium standard effect size, significance level, power of anlaysis, and dropout rate as suggested by Cohen [35]. In addition, current study has one of the largest sample size among the studies that reported association with depression and blood PAI-1 measurement [26,29,31,33,61]. Among studies sought for the association between depression and PAI-1, which had a larger sample size than this study, Matthews *et al.* [30] showed that higher blood PAI-1 predicts future onset of depression through a longitudinal study. Pan *et al.* [61] conducted a study on a total sample of more than 3,000 people, but included a significant number of subjects under the age of 65, and did not include the certainty of diagnosis through standardized structured interviews. Also Chan *et al.* [69], in the study of the pre-senile population, confirmed the correlation between serum PAI-1 concentration and antidepressant response. However, the possibility of different results when the number of samples increases cannot be completely excluded, so it is necessary to clarify the rela-

tionship between diagnosis of depression and serum PAI-1 level through studies with a larger number of samples.

The differences in age and sex between the two groups in current study was statistically adjusted through logistic regression analysis, and the effect of sex was again explored through subgroup analysis. Nevertheless, considering the tissue-specific increased expression of PAI-1 along with aging [69], and different impact of serum PAI-1 level according to sex in the studies on other diseases (diabetes, abdominal aortic aneurysm) and PAI-1 [70,71], the age and sex differences between the two groups may have affected the result.

The additional limitations of this study are as follows. First, rheumatoid and immune diseases which can directly affect the body's inflammatory response, and history of steroid use may act as confounding variables; however, their effects have not been sufficiently investigated. Lastly, as this was a cross-sectional study, it is unclear whether the marker presented in the study was a trait marker or a state marker for late-life depression. Additional research with a longitudinal design is, therefore, necessary to explore the role of PAI-1 as a biological marker that reflects the inflammatory state in late-life depression.

In this study, patients with late-life depression had lower blood PAI-1 levels than those in the normal control group. In addition, blood levels of PAI-1 significantly explained the diagnosis of depression, even after adjusting the effects of potential confounding variables and the diagnosis of metabolic syndrome. Although many studies have examined blood levels of PAI-1 in depression, only a few of them were conducted on geriatric depression. This is the first study to examine the effects of adipokines, including PAI-1, on the diagnosis of depression in the geriatric population by adjusting the effects of metabolic syndrome markers. In this study, the blood concentration of PAI-1 were different from those reported in previous studies on depressive symptoms, suggesting that blood PAI-1 in clinically pathological depression shows a contrasting pattern to that seen for depressive symptoms, which are not pathological. Additionally, as previous research on blood PAI-1 and depressive symptoms was conducted in elderly participants, the results of this study suggest that late-life depression may show a different pattern of inflammatory changes than those seen in depression before old age. We anticipate that the results of this study will be replicated with more precision, with subsequent research that could supplement the limitations of this study.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Changsu Han. Data acquisition: Changsu Han, Moon Ho Park, Chi-Un Pae, Cheolmin Shin, Seung-Hoon Lee. Formal analysis: Seung-Hoon Lee, Cheolmin Shin, Chi-Un Pae. Writing−original draft: Seung-Hoon Lee. Writing−review & editing: Cheolmin Shin, Young-Hoon Ko, Moon-Soo Lee, Ho-Kyoung Yoon, Changsu Han. All authors read and approved the final manuscript.

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