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전신홍반루푸스 환자에서 우울증과 삶의 질에 관한 연구

Depression and quality of life in patients with systemic lupus erythematosus

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Depression and quality of life in patients with systemic lupus erythematosus

by

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Contents

ABSTRACT

Introduction: Patients with systemic lupus erythematosus (SLE) are vulnerable to depression because of the chronic nature and neuropsychiatric involvement of the disease. Levels of serum brain-derived neurotrophic factor (BDNF) and vitamin D are reported to be decreased in patients with depression. The aim of the study was to investigate the prevalence of depression and its related factors including quality of life, BDNF and vitamin D in patients with SLE.

Methods: A total of 180 patients were enrolled at the Rheumatology Clinic from January to March 2012. The prevalence of depression was assessed using the center for epidemiologic studies depression (CES-D) scale. We evaluated the physician's global assessment, patient's global assessment (PGA), SLE disease activity index (SLEDAI), and disease-related organ damage. The EuroQol-5 dimensions (EQ-5D), sociodemographic features, and laboratory tests including serum vitamin D level were also surveyed. Serum BDNF was measured using an enzyme-linked immunosorbent assay. Patients with a CES-D score $\geq$ 24 were considered to have depression.

Results: The prevalence of depression in SLE was 22.8% (n = 41). On multivariate analysis, patients with a marital status of single/divorced/ separated/widowed, higher PGA score, and extreme pain/discomfort were significantly associated with depression. The EQ-5D index was negatively

correlated with CES-D score ($r = -0.56$, $p = 1.72 \times 10^{-16}$). Analyzing associated clinical factors in each EQ-5D dimension, depression was significantly associated with moderate to severe problems in self-care ($p = 0.01$) and usual activities ($p = 4.98 \times 10^{-2}$) and extreme pain/discomfort ($p = 0.01$).

Serum BDNF levels were not associated with depression ($p = 0.62$) but they were highly associated with platelet counts ($r = 0.53$, $p = 2.16 \times 10^{-12}$). As platelet is the major storage source of serum BDNF, partial correlation analysis was conducted with adjustment for platelet count. As a result, serum BDNF levels were significantly associated with age ($r = 0.17$, $p = 0.03$), hemoglobin levels ($r = -0.30$, $p = 1.75 \times 10^{-4}$) and SLEDAI ($r = -0.21$, $p = 0.010$). On partial correlation analysis adjusted with use of vitamin D supplement, serum vitamin D levels were not associated with depression ($p = 0.59$) but they were correlated with age ($r = 0.28$, $p = 0.01$), SLEDAI ($r = -0.23$, $p = 0.02$) and mean glucocorticoid dose over the previous 3 months ($r = -0.21$, $p = 0.04$).

Conclusion: Depression is prevalent in patients with SLE, especially those with a marital status of single/divorced/separated/widowed, a higher PGA, and extreme pain/discomfort. Patients with depression had low quality of life. Serum BDNF and vitamin D levels were not associated with depression.

Key Words: systemic lupus erythematosus, depression, prevalence, vitamin D, brain-derived neurotrophic factor, quality of life

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List of Tables

List of Figures

List of abbreviations and symbols

AZP	azathioprine
CES-D	the center for epidemiologic studies depression
EQ-5D	the EuroQol-5 dimensions
GC	glucocorticoid
HRQoL	health related quality of life
MTX	methotrexate
MMF	mycophenolate mofetil
PGA	patient's global assessment
PhyGA	physician's global assessment
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index
SLE	systemic lupus erythematosus
SLEDAI	systemic lupus erythematosus disease activity index

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by alternating periods of active disease and remission. Patients with SLE experience diverse clinical patterns depending on the extent and severity of organ/system involvement, which render them vulnerable to depression. Indeed, the prevalence of depression is reported to be increased in patients with SLE (1-8).

In SLE, several factors are supposed to be associated with the development of depression. First, as in general population, sociodemographic factors such as employment status or age contribute to development of depression in patients with SLE (1-3). Certain sociodemographic factors related to depression are different according to cultural backgrounds. Second, as in other chronic diseases like cancer, depression may be one of coping mechanisms for their disease (1). Third, autoimmune mechanisms may be associated with development of depression in patients with SLE. In neuropsychiatric lupus, inflammation induces increased permeability of blood brain barrier (BBB), and circulating autoantibodies such as anti-N-Methyl-D aspartate (NMDA) receptor antibody penetrate BBB and lead to non-thrombotic and non-vasculitic abnormalities of central nervous system by altering synaptic function or inducing neuronal cell death (9, 10). However, until now, it is inconclusive whether depression in patients with SLE is

associated with certain circulating autoantibodies (1, 11, 12). Lastly, chronic inflammation in patients with SLE may precipitate development of depression. There are many reports that support inflammation is one of pathophysiologic mechanisms of depression; active inflammation is reported to alter monoamines release/reuptake (13-16). Development of depression or suicidal ideation was reported about 30% of chronic hepatitis C patients with interferon (IFN) alpha treatment (14). It is suggested that an altered serotonin metabolism via activation of p38 mitogen activated protein kinase and increased inflammatory cytokines may be associated with depressions during IFN alpha treatment (15). However, type I IFN activity was not associated with depression (17) albeit SLE is type I IFN signature related disease (18-20).

The result of depression is not negligible in patients with SLE. Patients with SLE and depression did not tend to adhere to medication regimens and require more frequent medical attention (8). Furthermore psychological factors are known to affect health related quality of life (HRQoL) in patients with SLE (21-23). Because of diverse clinical manifestations and no standardized blood test to assess disease status, improvement of HRQoL is one of important treatment target in patients with SLE (24). Therefore understanding risk factors for depression and early intervention for depression may improve the treatment results including HRQoL.

Neurotrophic factors (NFs) and vitamin D have been attracted attentions

as molecules untangling neurophysiologic mechanism of depression (25-30). In patients with depression, decreased levels of NFs are supposed to result in volumetric decreases of the hippocampus and other forebrain regions (25-27). Vitamin D insufficiency/deficiency is also reported to be associated with depression (28-30). However, because the most studies about BDNF or vitamin D for depression were conducted among patients with depression irrelevant to comorbid medical conditions, it is unclear whether such molecular pathophysiology of depression is applicable in patients with certain disease subset or not. Considering the inconclusive association between depression and autoantibodies or type I IFN activity (1, 11, 12, 14, 15), pathophysiologic mechanisms of depression may be different in this population.

In the present study, we investigated the prevalence of depression and its related factors including HRQoL and analyzed clinical factors associated with each of the EQ-5D in patients with SLE. In addition, we examined whether BDNF and vitamin D are related to the presence of depression in patients with SLE.

PATIETNS AND METHODS

Study population

A total of 180 patients were enrolled at the Rheumatology Clinic from January to March 2012. All the participants fulfilled the 1997 updated American College of Rheumatology (ACR) criteria for the classification of SLE (31). The study was approved by the ethics committee of Seoul National University Hospital, and all the subjects provided written informed consent.

Data and sample collection

The patients completed questionnaires about sociodemographic factors such as the number of family members, marital status, occupational status, and an annual income. Disrupted marital status included divorce, separation, and spousal death. Disease activity of SLE was evaluated using the patient's global assessment (PGA), physician's global assessment (PhyGA), and SLE disease activity index (SLEDAI) at the time of the interview. Patients with active SLE were defined as those with a SLEDAI ≥ 6. PGA and PhyGA were measured using a 0–100 and 0–3 visual analogue scale, respectively. SLE-related organ damage was assessed using the Systemic Lupus International Collaborating Clinics/ACR damage index (SDI). Laboratory data including complete blood cell count (WBC), hemoglobin (Hb) level, platelet count,

serum creatinine, anti-dsDNA, and complement (C3, C4) levels were measured.

Use of azathioprine (AZP), mycophenolate mofetil (MMF), cyclosporine, tacrolimus, cyclophosphamide, methotrexate (MTX), hydroxychloroquine (HCQ), vitamin D supplement and GC (glucocorticoid) was surveyed retrospectively by reviewing prescribed medications during a year before the study.

Depression was evaluated using the center for epidemiologic studies depression (CES-D) scale. The CES-D is a 20-item scale that is widely used to evaluate current depressive symptoms in adults with physical illness and in the general population (32). The CES-D has been translated into Korean, and its psychometric properties have been validated (33). Patients with a CES-D score $\geq$ 24 were considered to have depression according to a previous study in patients with SLE (34). HR-QOL was assessed by the EuroQol-5 Dimensions (EQ-5D) (35). The EQ-5D questionnaire consists of five domains about patient mobility, hygiene, daily activities, pain, and anxiety/depression. EQ-5D index was obtained through a tariff system developed in South Korea as follows: EQ-5D index = 1 − (0.164 + M2 × 0.003 + M3 × 0.274 + SC2 × 0.058 + SC3 × 0.078 + UA2 × 0.045 + UA3 × 0.134 + PD2 × 0.049 + PD3 × 0.132 + AD2 × 0.044 + AD3 × 0.102 + N3 × 0.345 + I2sq × 0.014) [M, mobility; SC, self-care; UA, usual activity; PD,

pain/discomfort; AD, anxiety/depression; 2, level 2; 3, level 3; N3, 1 in cases of existence of level 3 in any dimension; I2sq, (numbers of level 2 − 1)^2] (36). A higher score on the EQ-5D index indicates that the respondent had fewer problems in each dimension. EQ-5D has been reported to have good validity and sensitivity in assessing HRQoL of patients with SLE (37).

Serum BDNF and vitamin D measurements

Serum samples were obtained from 151 of 180 patients at baseline and stored at –80℃ until analysis. Serum BDNF levels were also analyzed in 50 healthy age- and sex-matched subjects using enzyme-linked immunosorbent assay kits (DuoSet BDNF ELISA; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. All assays were performed in duplicate.

Serum vitamin D [25-hydroxyvitamin D, 25(OH)D] level was measured using liquid chromatography-tandem mass spectrometry (Waters Corp., Milford, MA, USA). Serum vitamin D levels of 10–20 ng/mL and < 10 ng/mL were defined as vitamin D insufficiency and deficiency, respectively.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) or number (percentage of the population) as appropriate. For non-normally distributed

variables, Mann-Whitney U test or Kruskal-Wallis test were used to compare group means as appropriate. Bonferroni correction was applied to multiple comparison procedures. Categorical variables were compared using the chi-square or Fisher's exact tests. Bivariate correlations were analyzed by Spearman's correlation coefficient. The multiple logistic regression analyses were performed to elucidate the associated clinical factors for depression and each dimensions of EQ-5D. Variables of p-value equal or less than 0.10 were included in analysis with adjusting for age and sex. P or corrected p (p_c) values < 0.05 were considered significant. All the analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 180 patients were enrolled (females, 160; 88.9%). The mean age (± SD) was 43.3 ± 13.9 years, and the mean disease duration was 11.1 ± 7.6 years. More than half of the patients were married or at least college graduates. The mean SLEDAI was 3.5 ± 3.9, and the mean SDI was 1.5 ± 1.7. The annual income earned by the bottom 10% of the population was ≤ 18,000,000 Korean Won per year (Table 1).

On laboratory examination, the mean Hb levels and WBC, platelet, lymphocyte count was 12.9 ± 3.1 g/dL, 6213.9 ± 2601.0/mm^3, 214.3 ± 69.6 $\times 10^3/mm^3$, 1247.3 ± 789.1/mm^3, respectively. The mean serum creatinine, anti-dsDNA titer, serum complement C3 and C4 levels were 1.04 ± 1.13 g/dL, 24.6 ± 41.1 IU/mL (reference range: < 10 IU/mL), 81.6 ± 21.5 mg/dL (reference range: 70–150 mg/dL) and 17.3 ± 9.3 mg/dL (reference range: 10–35 mg/dL), respectively.

Depression and sociodemographic and clinical factors in SLE patients

Depression was observed in 22.8% (n = 41) of the patients. Sex, age, and disease duration were not associated with depression. Among the

sociodemographic factors, educational level, marital status, and employment status were significantly associated with depression; patients with less than a college graduates (p = 0.04), a marital status of single/divorced/separated/ widowed ($p = 9.63 \times 10^{-4}$) and unemployment (p = 0.01) were associated with depression in SLE. A lower annual income tended to be associated with depression (p = 0.08). Among the clinical factors, higher scores of PGA and PhyGA were significantly associated with depression in patients with SLE, whereas mean daily glucocorticoid dose over the previous 3 months, SLEDAI or SDI was not. None of the clinical manifestations or laboratory results including Hb levels, WBC count, platelet count, serum creatinine levels, anti-dsDNA titer and complement levels was significantly associated with depression. There was no significant association between depression and medications which were prescribed during a year before the study. The proportion of patients with current use of antidepressant was significantly higher in patient with depression than in those without depression ($p = 1.28 \times 10^{-6}$; Table 1).

HRQoL in patients with SLE

In patients with SLE, EQ-5D index of patients with depression was significantly reduced than those of patients without depression (0.49 ± 0.27 versus 0.73 ± 0.12, $p = 1.23 \times 10^{-6}$). In all dimensions of EQ-5D, patients

with depression had more problems. Of note, in both patients with depression and those without depression, more than half of patients complained of moderate to extreme pain/discomfort (Table 2). There were significant negative correlations between EQ-5D index and CES-D scores ($r = -0.56$, $p = 1.72 \times 10^{-16}$ by the Spearman correlation test), PGA ($r = -0.24$, $p = 1.00 \times 10^{-3}$), PhyGA ($r = -0.33$, $p = 1.43 \times 10^{-5}$), or SDI ($r = -0.17$, $p = 0.02$).

Multiple logistic regression analysis of depression in patients with SLE

Factors with *p*-value equal or less than 0.1 in the univariate analyses were included. Patients with a marital status of single/divorced/separated/ widowed ($p = 0.03$), a higher PGA ($p = 2.13 \times 10^{-3}$), and extreme pain/discomfort ($p = 0.02$) were significantly associated with depression in patients with SLE (Table 3). Patients with lower educational level (less than college graduate; $p = 0.08$) or with moderate to severe problems in usual activity ($p = 0.09$) tended to be associated with depression.

Analysis for associated factors in each dimension of EQ-5D

For analysis, patients were classified as Group 1 and 2; patients with no

problems were classified as Group 1 while those with moderate to severe problems in dimension of mobility, self-care and usual activity were classified as Group 2. Because the most of patients with or without depression had moderate to extreme pain/discomfort, patients with no or moderate pain/discomfort were categorized as Group 1, while those with extreme pain/discomfort were categorized as Group 2 in dimension of pain/discomfort. Because depression, CES-D scores and current use of antidepressant were highly correlated, only depression was involved as a variable in multiple logistic regression analysis.

In dimension of mobility, increased age, a higher score of PhyGA, SDI or CES-D was significantly associated with having moderate to severe difficulties. Mucocutaneous involvement (i.e. malar rash, discoid rash, oral ulcer or photosensitivity), depression, use of MTX during a year before the study were also associated with moderate to severe problems in dimension of mobility (Table 4). In multiple logistic regression analysis, increased age and high SDI was significantly associated with moderate to severe problems in mobility (Table 5).

In dimension of self-care, increased age, a higher score of PhyGA or CES-D was significantly associated with moderate to severe difficulties. Serositis, depression, use of MTX during a year before the study and current use of antidepressant was also associated with moderate to severe problems in

dimension of self-care (Table 4). In multiple logistic regression analysis, increased age, use of AZP or MMF and depression was significantly associated with moderate to severe problems in self-care (Table 5).

In dimension of usual activity, unemployment, a higher score of PhyGA or CES-D was significantly associated with having moderate to severe difficulties. Serositis, depression and current use of antidepressant was also associated with moderate to severe problems in dimension of usual activity. Patients with moderate to severe problems in usual activity showed significantly a higher mean daily GC dose over the previous 3 months of the study (Table 4). In multiple logistic regression analysis, unemployment, serositis, a higher score of PhyGA and depression was significantly associated with moderate to severe problems in usual activity (Table 5).

In dimension of pain/discomfort, unemployment, a lower annual income, a higher score of PhyGA or CES-D and depression was significantly associated with extreme pain/discomfort. Use of AZP or MTX and current use of antidepressant was also associated with extreme pain/discomfort (Table 4). In multiple logistic regression analysis, use of AZP or MTX and depression were significantly associated with extreme pain/discomfort (Table 5).

Serum levels of BDNF and associated factors in SLE

Serum levels of BDNF were measured in 151 patients (females, 136;

90.1%) and 50 healthy age- and sex-matched subjects (females, 45; 90.0%). The mean ages of the patients and healthy subjects were comparable (43.0 ± 14.3 vs. 43.3 ± 12.6 years old, respectively). Serum levels of BDNF in patients with SLE were not significantly different from those in healthy subjects (21.5 ± 7.8 ng/mL vs. 22.0 ± 9.3 ng/mL, p = 0.73). There was no significant difference in serum BDNF levels between the healthy subjects and the patients with SLE with depression (21.0 ± 8.0 ng/mL, p_c = 1.00) or without depression (21.5 ± 7.8 ng/mL, p_c = 1.00; Figure 1A). After subgroup analysis according to disease activity, no difference in BDNF level was seen between active or inactive patients with SLE with or without depression (Figure 1B). However, higher serum BDNF levels were significantly associated with active SLE (p = 0.04) and use of MMF (p = 0.04). There was no significant association between serum BDNF levels and depression. Platelet is the major storage source of BDNF (38-40) and platelet count was highly positively correlated with serum BDNF levels in this study (r = 0.53, p = 2.16×10^{-12}). In addition, platelet count could be decreased in active SLE and 17.4 % (n=31) patients had thrombocytopenia (platelet count < 150,000/mm^3) in the current study. Therefore partial correlation analysis for other continuous variable was done after adjusting platelet count. As a result, serum BDNF levels of patients with SLE were positively correlated with age (r = 0.17, p = 0.03), and negatively correlated with SLEDAI (r = − 0.21, p =

0.01), Hb levels ($r = -0.30$, $p = 1.74 \times 10^{-4}$), a mean daily GC dose over the previous 3 months of the study ($r = -0.22$, $p = 0.01$; Table 7).

Serum 25(OH)D levels and depression in SLE

Serum 25(OH)D levels were measured in 103 patients (females, 94; 91.3%). The mean serum 25(OH)D level was 20.1 ± 10.8 ng/mL. Vitamin D insufficiency was observed in more than half of these patients (57; 53.3%), whereas vitamin D deficiency was observed in only 8 patients (7.5%). Serum 25(OH)D levels were comparable between the patients with SLE with or without depression (20.7 ± 10.8 ng/mL vs. 19.9 ± 10.9 ng/mL, p = 0.60). Serum 25(OH)D levels were not associated with mucocutaneous involvement ($p = 0.54$), renal disorder ($p = 0.59$), and neuropsychiatric disorder ($p = 0.47$). Use of medications except vitamin D supplement was associated with serum 25(OH)D levels ($p = 3.42 \times 10^{-3}$, Table 8). Twenty-three percent (n =24) of patients have taken vitamin D supplement during a year before the study. As serum 25(OH)D levels were highly correlated with use of vitamin D supplement, correlation analysis was conducted with adjustment for use of vitamin D supplement. There was a significant negative correlation between serum 25(OH)D levels and SLEDAI ($r = -0.23$, $p = 0.02$) or a mean daily GC dose over the previous 3 months of the study ($r = -0.21$, $p = 0.04$) while there was a significant positive correlation between age and serum

25(OH)D levels (r = 0.275, p = 0.005; Table 9).

Table 1. Sociodemographic and clinical factors of the patients with systemic lupus erythematosus with or without depression

Variables	All subjects (*n* = 180)	Depression (*n* = 41)	No depression (*n*= 139)	P *
Female, *n* (%)	160 (88.9)	39 (95.1)	121(87.1)	0.15
Age, mean ± SD	43.3 ± 13.9	42.0 ± 18.0	43.5 ± 12.6	0.22
Disease duration, years, mean ± SD	11.0 ± 7.6	10.4 ± 7.34	11.2 ± 7.69	0.54
Educational level, *n* (%)				
Less than college graduate	84 (46.7)	25 (61.0)	59 (42.4)	0.04
At least college graduate	94 (53.3)	16 (39.0)	80 (57.6)	
Marital status, *n* (%)				
Married	110 (60.8)	16 (39.0)	94 (67.6)	9.63×10^{-4}
Single/divorced /separated/widowed	70 (38.9)	25 (61.0)	45 (32.4)	
Living arrangement, *n* (%)				
Alone	8 (4.4)	2 (4.9)	6 (4.3)	1.00
With others	173 (95.6)	39 (95.1)	133 (95.7)	
Unemployed, *n* (%)	111 (61.7)	32 (78.0)	79 (56.8)	0.01

Annual income (n = 161), *n* (%)				
≤ 18,000,000 KRW	36 (21.1)	9 (25.7)	17 (13.5)	0.08
> 18,000,000 KRW	135 (78.9)	26 (74.3)	109 (86.5)	
Clinical manifestation, *n* (%)				
Mucocutaneous †	121 (67.2)	25 (61.0)	96 (69.1)	0.33
Renal	62 (34.4)	12 (29.3)	50(36.0)	0.43
Arthritis	97 (53.9)	23 (56.1)	74 (53.2)	0.75
Serositis	28 (15.6)	7 (17.1)	21 (15.1)	0.76
Neurological	10 (5.6)	3 (7.3)	7 (5.0)	0.70
SLEDAI, mean ± SD	3.5 ± 3.9	4.0 ± 4.2	3.4 ± 3.8	0.37
Active SLE, *n* (%)				
Yes (SLEDAI ≥ 6)	41 (22.8)	12 (29.3)	29 (20.9)	0.26
No (SLEDAI < 6)	139 (77.2)	29 (70.7)	110 (79.1)	
PGA, mean ± SD	17.7 ± 19.7	31.6 ± 23.9	13.6 ± 16.3	3.80×10^{-5}
PhyGA, mean ± SD	0.9 ± 1.8	1.5 ± 3.1	0.8 ± 1.1	0.03
SDI, mean ± SD	1.5 ± 1.7	1.8 ± 1.6	1.8 ± 1.7	0.34

Medications‡, *n* (%)				
AZP	29 (16.4)	10 (25.0)	19 (13.9)	0.09
MMF	15 (8.7)	5 (12.5)	10 (7.6)	0.33
Cyclosporine	1 (0.6)	0 (0)	1 (100.0)	-
Tacrolimus	4 (2.3)	0 (0)	4 (3.0)	-
Cyclophosphamide	30 (17.3)	7 (17.5)	23 (17.3)	0.98
MTX	19 (11.0)	7 (17.5)	12 (9.0)	0.13
HCQ	126 (72.8)	30 (75.0)	96 (72.2)	0.73
GC	157 (90.8)	38 (95.0)	119 (89.5)	0.37
Current use of antidepressant, *n* (%)	15 (8.3)	12 (29.3)	3 (2.2)	1.28×10^{-6}
Mean daily GC dose over the previous 3 months (± SD, mg/day of prednisolone)	6.7 ± 6.7	7.8 ± 6.7	6.3 ± 6.7	0.23

* *P*-value comparing patients with SLE with depression versus those without depression by χ^2- test or student t-test

†Mucocutaneous (malar rash, discoid rash, photosensitivity, and oral ulcers), renal, and neurological involvement is defined as in the 1997 updated American College of Rheumatology (ACR) criteria for the classification of SLE.

‡Medications prescribed during a year before the study.

SLEDAI, SLE disease activity index; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; PGA, patient's global assessment; PhyGA, physician's global assessment; AZP, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; HCQ, hydroxychloroquine; GC, glucocorticoid; SD, standard deviation; KRW, Korean Won; OR, odds ratio; CI, confidence interval

Table 2. Comparison of health related quality of life in the patients with systemic lupus erythematosus with or without depression

Variables	All subjects (n = 180)	Depression (n = 41)	No depression (n= 139)	P *
EQ-5D index	0.68 ± 0.19	0.49 ± 0.27	0.73 ± 0.12	1.23×10^{-6}
Mobility, *n* (%)				
1. I have no problems walking	122 (67.8)	22 (23.7)	100 (71.9)	0.02
2. I have some problems in walking	57 (31.7)	18 (43.9)	39 (28.1)	
3. I am confined to bed	1 (0.6)	1 (2.4)	0 (0.0)	
Self-care, *n* (%)				
1. I have no problems with self-care	161 (89.4)	32 (78.0)	129 (92.8)	0.01
2. I have some problems in washing or dressing myself	16 (8.9)	7 (17.1)	9 (6.5)	
3. I am unable to wash or dress myself	3 (1.7)	2 (4.9)	1 (0.7)	

Usual activities, *n* (%)				
1. I have no problems in performing my usual activities	120 (66.7)	19 (46.3)	101 (72.7)	4.40×10^{-4}
2. I have some problems performing my usual activities	58 (32.2)	20 (48.8)	38 (27.3)	
3. I am unable to perform my usual activities	2 (1.1)	2 (4.9)	0 (0.0)	
Pain/discomfort, *n* (%)				
1. I have no pain or discomfort	65 (36.1)	7 (17.1)	58 (41.7)	1.17×10^{-5}
2. I have moderate pain or discomfort	99 (55.0)	23 (56.1)	76 (54.7)	
3. I have extreme pain or discomfort	16 (8.9)	11 (26.8)	5 (3.6)	
Anxiety/depression, *n* (%)				
1. I am not anxious or depressed	79 (43.9)	5 (12.2)	74 (53.2)	1.87×10^{-10}
2. I am moderately anxious or depressed	90 (50.0)	25 (61.0)	65 (46.8)	
3. I am extremely anxious or depressed	11 (6.1)	11 (26.8)	0 (0.0)	

* *P* -value assessing the trend using linear by linear association comparing the patients with SLE with depression versus those without depression

EQ-5D, the EuroQol-5 dimensions; SLE, systemic lupus erythematosus

Table 3. Multiple logistic regression analysis for depression in the patients with systemic lupus erythematosus

Variables	Coefficient	OR (95% CI)	P
Age	− 0.02	0.98 (0.93, 1.03)	0.42
Sex	− 0.31	0.73 (0.12, 4.55)	0.74
Educational level (less than college graduate)	1.00	2.71 (0.90, 8.15)	0.08
Marital status (single/divorced/separated/widowed)	1.51	4.53 (1.19, 17.25)	0.03
Unemployment	0.47	1.61 (0.51, 5.07)	0.42
PGA	0.05	1.05 (1.02, 1.08)	2.13×10^{-4}
PhyGA	− 0.10	0.91 (0.70, 1.18)	0.48
Use of AZP	− 0.24	0.79 (0.21, 2.96)	0.73
Mobility (moderate to severe problems)	0.19	1.21 (0.37, 3.94)	0.75
Self-care (moderate to severe problems)	0.71	2.04 (0.37, 11.23)	0.41
Usual activity (moderate to severe problems)	1.04	2.83 (0.86, 9.35)	0.09
Pain/discomfort (extreme pain/discomfort)	2.00	7.38 (1.30, 42.06)	0.02

SLE, systemic lupus erythematosus; PGA, Patient's global assessment; PhyGA, Physician's global assessment; AZP, azathioprine; OR, odds ratio; CI, confidence interval

Table 4. Associated factors for each of the EuroQol-5 dimensions (moderate to severe versus no problems) in patients with systemic lupus erythematosus

	Mobility			Self-care			Usual-activity			Pain/discomfort*		
	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P
Female	110 (90.2)	50 (86.2)	0.43	114 (89.4)	16 (84.2)	0.45	105 (87.5)	55 (91.7)	0.40	145 (88.4)	15 (93.8)	1.00
Age	40.9 ± 12.0	48.3 ± 16.4	< 0.05	42.1 ± 12.4	52.6 ± 21.3	< 0.05	41.8 ± 12.1	46.0 ± 16.7	0.13	42.8 ± 14.0	48.1 ± 13.0	0.14
Disease duration, years	10.4 ± 7.7	12.1 ± 7.3	0.27	10.7 ± 7.7	13.4 ± 6.6	0.10	10.8 ± 7.7	11.3 ± 7.5	0.93	10.6 ± 7.6	14.8 ± 6.3	0.13
Educational level												
Less than college graduate	53 (43.4)	31 (53.4)	0.21	75 (46.6)	9 (47.4)	0.95	57 (47.5)	27 (45.0)	0.75	90 (54.9)	6 (37.5)	0.18
At least college graduate	69 (56.6)	27 (46.6)		86 (53.4)	10 (52.6)		63 (52.5)	33 (55.0)		74 (45.1)	10 (62.5)	

Marital status												
Married	79 (64.8)	31 (53.4)	0.15	95 (59.0)	15 (78.9)	0.13	75 (62.5)	35 (58.3)	0.59	100 (61.0)	10 (62.5)	0.91
Single/divorced/ separated/widowed	43 (35.2)	27 (46.6)		66 (41.0)	4 (21.1)		45 (37.5)	25 (41.7)		64 (39.0)	6 (37.5)	
Living arrangement												
alone	5 (4.1)	3 (5.2)	0.71	8 (5.0)	0 (0.0)	-	6 (5.0)	2 (3.3)	0.72	7 (4.3)	1 (6.2)	0.53
not alone	117 (95.9)	55 (94.8)		153 (95.0)	19 (100.0)		114 (95.0)	58 (96.7)		157 (95.7)	15 (93.8)	
Unemployment	51 (41.8)	18 (31.0)	0.17	96 (59.6)	15 (78.9)	0.14	63(52.2)	48(80.0)	< 0.05	97 (59.1)	14 (87.5)	< 0.05
Annual income (KRW)												
≤ 18,000,000	79 (64.8)	31 (53.4)	0.15	23 (16.0)	3 (17.6)	0.42	16 (14.5)	10 (19.6)	0.42	20 (13.6)	6 (42.9)	< 0.05
> 18,000,000	43 (35.2)	27 (46.6)		121 (84.0)	14 (82.4)		94 (85.5)	41 (80.4)		127 (86.4)	8 (57.1)	

Clinical manifestation												
Mucocutaneous[†]	89 (73.0)	32 (55.2)	< 0.05	113 (70.2)	8 (42.1)	0.91	81 (67.5)	40 (66.7)	0.91	112 (68.3)	9 (56.2)	0.40
Arthritis	66 (54.1)	31 (53.4)	0.94	86 (53.4)	11 (57.9)	0.83	64 (53.3)	33 (55.0)	0.83	86 (52.4)	11 (68.8)	0.21
Serositis	17 (13.9)	11 (19.0)	0.38	23 (14.3)	5 (26.3)	0.01	13 (10.8)	15 (25.0)	< 0.05	23 (14.0)	5 (31.2)	0.07
Renal	45 (36.9)	17 (29.3)	0.32	56 (34.8)	6 (31.6)	0.78	45 (37.5)	17 (28.3)	0.22	58 (35.4)	4 (25.0)	0.58
Neurologic	6 (4.9)	4 (6.9)	0.73	9 (5.6)	1 (5.3)	1.00	8 (6.7)	2 (3.3)	0.50	8 (4.9)	2 (12.5)	0.22
SLEDAI	3.57 ± 3.83	3.05 ± 3.90	0.22	3.51 ± 3.95	2.58 ± 2.89	0.33	3.31 ± 3.83	3.58 ± 3.91	0.76	110 (67.1)	10 (62.5)	0.71
Active SLE (SLEDAI ≥ 6)	30 (24.6)	11 (19.0)	0.40	36 (22.4)	5 (26.3)	0.70	24 (20.0)	17 (28.3)	0.21	140 (85.4)	14 (87.5)	1.00
PGA	17.9 ± 21.1	18.4 ± 17.5	0.18	17.7 ± 20.2	20.8 ± 18.7	0.34	17.3 ± 20.5	19.5 ± 19.0	0.11	16.7 ± 17.8	32.5 ± 34.0	0.14
PhyGA	0.80 ± 1.72	1.20 ± 1.49	< 0.05	0.92 ± 1.90	0.97 ± 0.54	< 0.05	0.66 ± 0.67	1.42 ± 2.86	< 0.05	0.79 ± 1.05	2.43 ± 5.12	< 0.05

SDI	1.27 ± 1.64	2.11 ± 1.73	< 0.05	1.49 ± 1.73	2.00 ± 1.49	0.07	1.36 ± 1.60	1.88 ± 1.86	0.06	1.54 ± 1.74	1.64 ± 1.28	0.31
CES-D score	12.4 ± 11.1	17.1 ± 12.0	< 0.05	13.2 ± 11.0	20.3 ± 14.3	< 0.05	11.3 ± 10.4	18.9 ± 12.2	< 0.05	13.0 ± 10.9	25.1 ± 13.1	< 0.05
Depression (CES-D score ≥ 24)	22 (18.0)	19 (32.8)	< 0.05	32 (19.9)	9 (47.4)	< 0.05	19 (15.8)	22 (36.7)	< 0.05	30 (18.3)	11 (68.8)	< 0.05
Medications‡												
AZP	17 (14.2)	12 (21.1)	0.25	23 (14.6)	6 (31.6)	0.06	20 (16.8)	9 (15.5)	0.83	22 (13.6)	7 (46.7)	< 0.05
MMF	10 (8.5)	5 (9.1)	0.91	11 (7.2)	4 (21.1)	0.07	10 (8.7)	5 (8.8)	0.99	14 (9.0)	1 (6.2)	1.00
Cyclosporine	0.00	1 (1.7)	−-	0 (0.0)	1 (5.3)	−	0 (0.0)	1 (1.7)	−	1 (0.6)	0 (0.0)	−
Tacrolimus	2 (1.7)	2 (3.6)	0.60	4 (2.6)	0 (0)	−	3(2.6)	1 (1.8)	1.00	4 (2.5)	0 (0.0)	−
Cyclophosphamide	20 (17.1)	10 (17.9)	0.90	26 (16.9)	4 (21.1)	0.75	17 (14.7)	13 (22.8)	0.18	26 (16.6)	4 (25.0)	0.40
MTX	9 (7.7)	10 (17.9)	0.05	14 (9.1)	5 (26.3)	0.02	10 (8.9)	9 (15.8)	0.16	14 (8.9)	5 (31.2)	< 0.05
HCQ	89 (76.1)	37 (66.1)	0.17	113 (73.4)	13 (68.4)	0.65	88 (75.9)	38 (66.7)	0.20	114 (72.6)	12 (75.0)	1.00
GC	106 (90.6)	51 (91.1)	0.92	139 (90.3)	18 (94.7)	1.00	104 (89.7)	53 (93.0)	0.59	142 (90.4)	15 (93.8)	1.00

Current use of anti-depressant	8 (6.6)	7 (12.1)	0.21	10 (6.2)	5 (26.3)	< 0.05	6 (5.0)	9 (15.0)	< 0.05	10 (6.1)	5 (31.2)	< 0.05
Mean daily GC dose over the previous 3 months (± SD, mg/day of prednisolone)	6.4 ± 6.8	7.1 ± 6.7	0.73	6.55 ± 6.86	7.52 ± 6.36	0.35	5.62 ± 5.04	8.61 ± 8.96	0.05	6.68 ± 6.78	6.51 ± 7.18	0.56

Group 1: patients with no problems in dimensions of motility, self-care and usual activities

Group 2: patients with moderate to severe problems in dimensions of motility, self-care and usual activities

P-value comparing patients with SLE with depression versus those without depression by χ^2- test or Mann-Whitney U test

*In dimension of pain/discomfort, Group 1 represent patients with no or moderate pain/discomfort while Group 2 represent patients with extreme pain/discomfort.

†Mucocutaneous (malar rash, discoid rash, photosensitivity, and oral ulcers), renal, and neurological involvement is defined as in the 1997 updated American College of Rheumatology (ACR) criteria for the classification of SLE.

‡Medications prescribed during a year before the study.

SLEDAI, SLE disease activity index; PGA, patient's global assessment; PhyGA, physician's global assessment SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; CES-D, the center for epidemiologic studies depression; AZP, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; HCQ, hydroxychloroquine; GC, glucocorticoid; CI, confidence interval

Table 5. Multiple logistic regression analysis for each of the EuroQol-5 dimensions and clinical factors in patients with systemic lupus erythematosus

	Coefficient	OR (95% CI)	P
Mobility			
Age	0.04	1.04 (1.01, 1.07)	4.48×10^{-3}
Sex	0.86	2.36 (0.75, 7.40)	0.14
Mucocutaneous involvement	− 0.37	0.69 (0.33, 1.47)	0.34
PhyGA	0.10	1.11 (0.90, 1.67)	0.32
SDI	0.21	1.24 (1.00, 1.52)	4.71×10^{-2}
Use of MTX	0.72	1.93 (0.65, 5.78)	0.24
Depression (CES-D score ≥ 24)	0.72	2.04 (0.87, 4.78)	0.10
Self-care			
Age	0.08	1.08 (1.03, 1.14)	2.45×10^{-3}
Sex	0.35	1.42 (0.26, 7.69)	0.69
Mucocutaneous involvement	− 0.89	0.41 (0.13, 1.27)	0.12
PhyGA	− 0.09	0.91 (0.62, 1.34)	0.64
SDI	0.02	1.02 (0.72, 1.43)	0.93
Use of AZP	1.91	6.72 (1.60, 28.19)	9.24×10^{-3}
Use of MMF	2.06	7.85 (1.46, 42.11)	0.02
Use of MTX	0.63	1.88 (0.47, 7.54)	0.37
Depression (CES-D score ≥ 24)	1.58	4.84 (1.39, 16.80)	0.01

Usual activity			
Age	0.23	1.03 (1.00, 1.06)	0.06
Sex	0.40	0.67 (0.18, 2.49)	0.55
Unemployment	1.06	2.87 (1.27, 6.50)	0.01
Serositis	1.31	3.72 (1.33, 10.35)	0.01
PhyGA	0.37	1.45 (1.01, 2.09)	4.65×10^{-2}
SDI	0.07	1.07 (0.87, 1.32)	0.53
Mean GC dose over the previous 3 months (mg/day of prednisolone)	0.05	1.05 (0.99, 1.12)	0.08
Depression (CES-D score ≥ 24)	0.83	2.30 (1.00, 5.29)	4.98×10^{-2}
Pain/discomfort			
Age	0.06	1.06 (0.99, 1.14)	1.06
Sex	0.72	2.06 (0.12, 35.47)	2.06
Unemployment	1.28	3.58 (0.41, 31.68)	0.25
Serositis	0.89	2.44 (0.37, 16.10)	0.35
PhyGA	0.44	1.56 (0.70, 3.46)	0.28
Annual income (≤ 18,000,000 KRW)	0.94	0.39 (0.04, 3.50)	0.40
Use of AZP	2.54	12.67 (1.73, 92.84)	0.01
Use of MTX	1.83	6.21 (1.05, 36.85)	0.04
Depression	2.45	11.58 (1.82, 73.88)	0.01

EQ-5D, the EuroQol-5 dimensions; SLE, systemic lupus erythematosus; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; PhyGA, physician's global assessment; CES-D, the center for epidemiologic studies depression; AZP, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; GC, glucocorticoid; OR, odds ratio; CI, confidence interval

Table 6. Clinical manifestation in patients with SLE (*n* = 151) and their correlation with serum brain-derived neurotrophic factor levels

Variables	N (%)	P
Female	80 (93.0)	0.03
Clinical manifestation		
Mucocutaneous	102 (67.5)	0.62
Arthritis	80 (53.0)	0.42
Serositis	27 (17.9)	0.29
Renal	53 (35.1)	0.55
Neurologic	10 (6.6)	0.58
Active SLE (SLEDAI ≥ 6)	34 (22.5)	0.01
Depression (CES-D ≥ 24)	36 (33.8)	0.75
Medications		
AZP	24 (16.2)	0.94
MMF	11 (7.6)	0.04
Cyclosporine	–	–
Tacrolimus	3 (2.1)	0.41
Cyclophosphamide	25 (17.2)	0.10
MTX	16 (11.0)	0.06
HCQ	107 (73.8)	0.71
GC	131 (90.3)	0.95

Current use of antidepressant	14 (9.3)	0.34

SLEDAI, SLE disease activity index; CES-D, the center for epidemiologic studies depression; AZP, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; HCQ, hydroxychloroquine; GC, glucocorticoid

Table 7. Partial correlation analysis for serum brain-derived neurotrophic factor levels and associated factors with adjustment for platelet count in patients with systemic lupus erythematosus (*n* = 151)

Variables	Correlation coefficient	P
Age	0.17	0.03
Disease duration	− 0.02	0.85
SLEDAI	− 0.21	0.01
PGA	− 0.00	0.98
PhyGA	− 0.06	0.46
SDI	− 0.01	0.87
CES-D score	− 0.06	0.49
EQ-5D index	0.03	0.71
WBC (/mm^2)	− 0.15	0.06
Hb (g/dL)	− 0.30	1.75×10^{-4}
Anti-dsDNA titer (IU/mL)	− 0.09	0.30
C3 (mg/dL)	0.03	0.69
C4 (mg/dL)	− 0.01	0.96
Serum 25(OH)D levels (ng/dL)	− 0.04	0.73
Mean GC dose over the previous 3 months (mg/day of prednisolone)	− 0.22	0.01

SLEDAI, systemic lupus erythematosus disease activity index; PGA, patient's global assessment; PhyGA, physician's global assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; CES-D, the center for epidemiologic studies depression; EQ-5D, the EuroQol-5 dimensions; WBC, white blood cell count; Hb, hemoblogin; C, complement; GC, glucocorticoid

Table 8. Clinical manifestation in patients with systemic lupus erythematosus (*n* = 103) and their association with serum 25(OH)D level

Variables	N (%)	P
Female	94 (91.3)	0.43
Clinical manifestation		
Mucocutaneous	67 (65.0)	0.28
Arthritis	64 (62.1)	0.42
Serositis	14 (13.6)	0.84
Renal	32 (31.1)	0.35
Neurologic	6 (5.8)	0.99
Active SLE (SLEDAI ≥ 6)	16 (15.5)	0.12
Depression (CES-D score ≥ 24)	22 (21.4)	0.59
Medications		
AZP	15 (14.7)	0.30
MMF	6 (5.8)	0.62
Cyclosporine	1 (1.0)	0.12
Tacrolimus	2 (1.9)	0.76
Cyclophosphamide	18 (17.5)	0.72
MTX	15 (14.6)	0.39
HCQ	77 (74.8)	0.24
Glucocorticoid	96 (93.2)	0.26

Use of vitamin D supplement	24 (23.3)	3.42×10^{-3}
Current use of antidepressant	7 (6.8)	0.97

SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; CES-D, epidemiologic studies depression; AZP, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; HCQ, hydroxychloroquine; GC, glucocorticoid

Table 9. Partial correlation analysis of serum 25(OH)D levels and clinical factors with adjustment for use of vitamin D supplement in patients with SLE (*n* = 103)

Variables	Correlation coefficient	P
Age	0.28	0.01
SLEDAI	− 0.23	0.02
PGA	0.00	0.99
PhyGA	− 0.15	0.15
SDI	− 0.07	0.49
CES-D score	0.02	0.83
EQ-5D index	0.02	0.82
WBC (/mm2)	− 0.14	0.17
Hb (g/dL)	0.12	0.23
Platelet	− 0.05	0.59
C3 (mg/dL)	− 0.07	0.49
C4 (mg/dL)	− 0.04	0.70
Serum BDNF levels (n =86, ng/mL)	− 0.04	0.75
Mean GC dose over the previous 3 months (mg/day of prednisolone)	− 0.21	0.04

BDNF, brain-derived neurotrophic factor; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; PGA, patient's global assessment;

PhyGA, physician's global assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; EQ-5D, the EuroQol-5 dimensions; CES-D, epidemiologic studies depression; WBC, white blood cell count; C, complement; GC, glucocorticoid

Figure 1A.

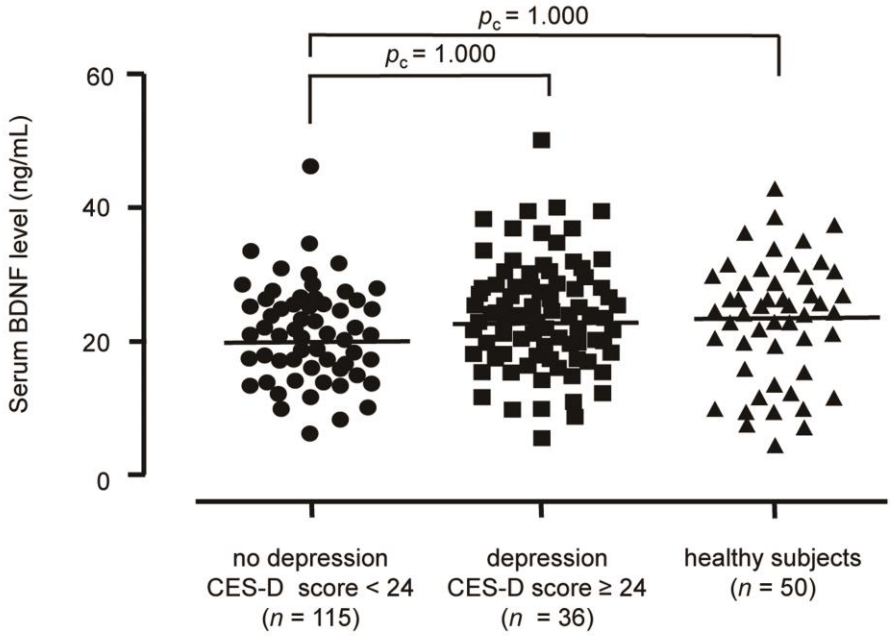

Figure 1B.

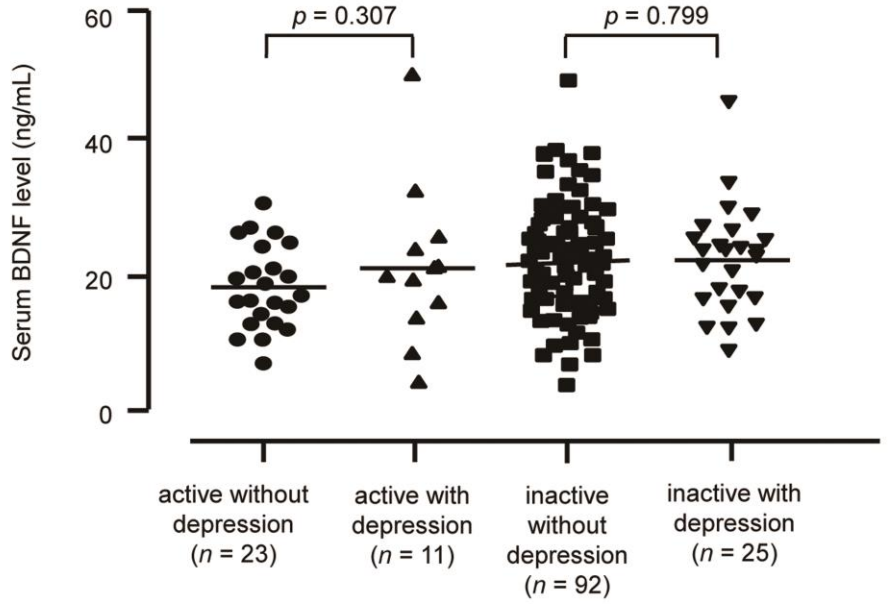

Figure 1. Association between serum levels of brain-derived neurotrophic peptide (BDNF) and depression in the patients with systemic lupus erythematosus (SLE)

The serum levels of BDNF were comparable between the healthy subjects and SLE patients with depression or without depression (Figure 1A). When the patients were divided into active and inactive disease, no difference in serum BDNF levels was found between patients with depression and those without depression (Figure 1B).

DISCUSSION

In the present study, the prevalence of depression was 22.8%, which is higher than that in the general population (3.31–8.68%) as shown by earlier reports (1, 3-8, 23, 41). Among sociodemographic factors, educational level and marital status was significantly associated with depression in patients with SLE. The previous study results are not consistent in terms of the sociodemographic variables related to depression in patients with SLE; Bachen et al reported that none of sociodemographic factors was associated with depression while other studies reported that employment status was related to depression in patients with SLE (2, 3, 5). Those contradictory results may imply that depression can be affected by sociodemographic factors regardless of disease directly in this population. In clinical practice, early intervention of depression for patients with those risk factors may improve treatment results.

In SLE, the evaluation of patient-reported outcomes including HRQoL has been emphasized; for instance, HRQoL was included in Outcome Measures in Rheumatology (OMERACT) SLE core set of outcome domains along with disease activity, damage, and toxicity/adverse events (24). Depression has a substantial impact on the HRQoL of patients with SLE (24, 42, 43). In current study, depression was a significant factor in dimensions of self-care and pain/discomfort in accordance with previous researches that

emphasized psychological factors as one of important and modifiable contributing factors for reduced HRQoL (21, 42, 43). In the current study, use of medications such as AZP or MMF was significantly associated with HRQoL. Considering AZP or MMF prescribed as a steroid sparing agent, patients receiving these drugs may have been exposed to high dose steroid, which resulted in reduced HRQoL by influencing skeletal muscles. Also, the study results may be due to the small sample size; indeed, AZP and MMF were administered in 29 and 15 of 180 patients, respectively.

Of note, depression was highly associated with extreme pain/discomfort in the present study. Considering that pain and depression share norepinephrine or serotonin neurotransmitter pathways, pain may result in depression and vice versa. Indeed, patients with cancer and depression experience more severe pain and have a worse prognosis than those without depression (44, 45). Fibromyalgia, a disease that consists of generalized pain, was observed in 32% of patients with SLE in an earlier study (46). Furthermore, in another study, intensive management of depression has been reported to improve arthritis-related pain and functional outcomes among older adults with arthritis (47). Physicians should be aware of depression in patients complaining of extreme pain/discomfort and keep in mind that the treatment of depression may alleviate pain in patients with SLE.

NFs are a family of polypeptide growth factors that are essential to the

development and maintenance of the nervous system. NFs have emerged as leading candidates of interest as potential neuroprotective treatment target and biomarkers in several neuropsychiatric disorders (39). Decreased BDNF levels have been reported to be related to depression (25, 27). In the present study, serum BDNF levels of patients with SLE were comparable to those of healthy individuals and not associated with depression. Considering that platelets are known to be the major storage source of BDNF (38-40) and that platelet count is often decreased (48) in patients with SLE, altered platelet numbers and functions may override the impact of depression on serum levels of BDNF in patients with SLE. However, it was notable that the serum BDNF levels showed a negative correlation with SLEDAI, Hb levels and GC dose over the previous 3 months of the study even after adjustment of platelet count. The levels of BDNF in supernatant of PBMC were increased in relapse phase while decreased in stable and post-relapse phase of multiple sclerosis (49). Although the study was conducted in small numbers of patients, Ikenouchi et al. speculated their opposite results of serum BDNF among patients with neuropsychiatric lupus might be associated with the presence of active or chronic inflammation (50, 51). In addition, dexamethasone was reported to suppress BDNF-associated synaptic proteins (52), and chronic glucocorticoid treatment resulted in significantly decreased hippocampal BDNF levels (53). Thus, in patients with SLE, chronic inflammation and

glucocorticoid treatment may alter BDNF levels in patients with depression. Taken together, our results suggest that BDNF may play a minor role in the pathophysiological mechanism of depression and is less likely to be a biological marker of depression in patients with SLE. Further studies are needed to evaluate the role of BDNF in patients with SLE.

Vitamin D was shown to regulate NFs and affect the neuronal plasticity process (54). Correction of vitamin D insufficiency was reported to improve the depressive state (29, 55). Vitamin D also exerts marked effects on immune cells: it inhibits Th1 cells, the production of Th1 cytokines (i.e., tumor necrosis factor-α, and interferon-γ [IFN-γ]), and the differentiation/survival of dendritic cells, resulting in impaired alloreactive T-cell activation. In SLE, research into vitamin D levels mainly focused on its correlation with disease activity; lower serum vitamin D levels were related to high disease activity (56-59). Vitamin D deficiency is also associated with antinuclear antibody positivity, increased activity of B cells, and high serum IFN-α activity (60). In the present study, lower serum vitamin D levels were associated with higher SLEDAI, as shown in previous studies (56-59). However, serum vitamin D levels were not associated with depression in contrast to previous studies of vitamin D and depression (28, 30, 55). We hypothesized that use of vitamin D supplement and the impact of inflammatory cytokine exposure in SLE might negate the association between vitamin D and depression in patients with SLE.

The present study has several limitations. First, the sample size was relatively small and the study was performed at a single medical center, so it may not have included patients with various backgrounds. Second, there are some concerns about assessment instruments such as the CES-D and its cutoff value. However, in an earlier study, the CES-D was validated as a tool for assessing mood disorders in patients with SLE (61) and a cutoff point score ≥ 24 was suggested to correctly classify 92% of participants as having a current major depressive disorder (34). Third, we measured only the total BDNF in the sera of patients. The ratio of pro-BNDF and mature BDNF in patients with SLE may differ from that in healthy subjects. Finally, few patients had active neuropsychiatric symptoms at the time of the sampling; therefore, a sub-analysis of patients with active NPSLE could not be conducted.

In conclusion, depression is prevalent in patients with SLE, in particular those with a marital status of single/divorced/separated/widowed, a higher PGA, and extreme pain/discomfort. Patients with depression had a low quality of life, especially in a dimension of self-care and pain/discomfort. Serum levels of BNDF and vitamin D were not associated with depression but were negatively associated with SLEDAI. The treatment of depression may be beneficial in patients with extreme pain/discomfort or high PGA.

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초 록

서론: 전신홍반루푸스는 만성적인 경과 및 신경정신 루푸스로 인해 우울증에 취약할 수 있다. 혈청 brain-derived neurotrophic factor (BDNF) 와 비타민 D 는 우울증에서 감소되어 있다고 보고되었다. 이 연구에서는 전신홍반루푸스 환자에서 우울증의 유병률 및 혈청 BDNF 및 비타민 D 를 포함한 우울증과 연관된 인자를 조사하고자 하였다.

방법: 2012년 2월에서 3월사이에 류마티스 내과에 내원한 전신홍반루푸스 환자 총 180 명을 대상으로 연구를 시행하였다. 우울증은 center for epidemiologic studies depression (CES-D) 척도로 측정하였다. 의사의 전반적인 평가 (physician's global assessment, PhyGA), 환자의 전반적인 평가 (patient's global assessment, PGA), SLE 질병활성도 지수 (SLE disease activity index, SLEDAI) 및 SLE 에 의한 손상지

수 (Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index, SDI) 를 평가하였다. EuroQol-5 dimensions (EQ-5D), 인구사회학적인 특징을 조사하였으며 혈청 비타민 D 농도를 포함한 혈액학적 검사를 시행하였다. CES-D척도 24점 이상을 우울증으로 정의하였다.

결과: 우울증의 유병률은 22.8 % (n= 41) 이었다. 다변량 분석에서 미혼/이혼/별거/사별의 결혼상태, 높은 환자의 전반적인 평가 점수, 극심한 통증/불편이 유의하게 우울증과 연관이 있었다. EQ-5D 지수 점수는 CES-D 점수와 음의 상관관계를 보였다 (r = – 0.56, p = 1.72 × 10^{-16}). EQ-5D 의 각 항목에 관련된 임상적 인자를 분석한 결과, 우울증은 자기 관리 또는 일상 활동에 중등도 이상의 문제가 있는 경우 및 극심한 통증 및 불편감이 있는 경우와 유의하게 연관이 있었다. 혈청 BDNF 농도는 우울증과 연관이 없었으나 (p = 0.62), 혈소판 수 (r = 0.53, p = 2.16 × 10^{-12}) 와 연관이 있었다. 혈소판이 혈

청 BDNF 의 주된 저장소이므로, 혈소판 수를 보정하여 편상관 분석을 시행하였다. 그 결과 혈청 BDNF 의 농도와 나이 (r = 0.17, p = 0.03), 혈색소 (r = 0.30, p = 1.75×10^{-4}) 및 SLEDAI 점수 (r = −0.21, p = 0.010) 정도와 유의하게 상관관계를 보였다. 비타민 D 보충제 복용 여부를 교정한 편상관 분석에서, 혈청 25(OH)D 농도 역시 우울증과는 연관이 없었으나 (p = 0.60), 나이 (r = 0.28, p = 0.01), SLEDAI 점수 (r = − 0.23, p = 0.02) 및 최근 3개월간 복용한 하루 평균 부신 피질호르몬의 용량 (r = − 0.21, p = 0.04) 과 연관이 있었다.

결론: 전신홍반루푸스 환자에서 우울증이 빈번하며, 특히 미혼/이혼/별거/사별의 결혼상태, 높은 환자의 전반적인 평가 점수, 극심한 통증/불편이 연관이 있었다. 우울증은 낮은 삶의 질과 연관이 있었다. 혈청 BDNF 농도 와 비타민 D 농도는 우울증과 연관이 없었다.

주요어: SLE, depression, prevalence, vitamin D, quality of life

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