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Original Article

Depression and Quality of Life in Patients with Systemic Lupus Erythematosus

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Objective. The objective of this study is to examine the prevalence of depression and its related factors including quality of life, brain-derived neurotrophic factor (BDNF), and vitamin D in patients with systemic lupus erythematosus (SLE). **Methods.** Depression was assessed using the center for epidemiologic studies depression (CES-D) scale. Disease activity, disease-related organ damage, the EuroQol-5 dimensions (EQ-5D), sociodemographic features, and laboratory tests including serum vitamin D level were surveyed. Serum BDNF was measured using an enzyme-linked immunosorbent assay. **Results.** Depression was observed in 22.8% of 180 SLE patients (n=41). Patients with marital status of single/divorced/separated/widowed, a higher patient global assessment (PGA) score, and extreme pain/discomfort showed significant association with depression. The EQ-5D index showed negative correlation with CES-D score ($r=-0.56$, $p<0.05$). In each EQ-5D dimension, depression showed significant association with moderate to severe problems in self-care and usual activities, and extreme pain/discomfort. Serum BDNF levels were not associated with depression ($p=0.75$) but associated with SLE disease activity index (SLEDAI; $r=-0.21$, $p<0.05$). Serum vitamin D levels were not associated with depression ($p=0.60$) but showed negative correlation with SLEDAI ($r=-0.23$, $p<0.05$) and mean glucocorticoid dose over the previous 3 months ($r=-0.21$, $p<0.05$) after adjustment for use of vitamin D supplement. **Conclusion.** Depression was prevalent in patients with SLE and was associated with low quality of life, and a higher PGA but not with SLEDAI. Serum BDNF and vitamin D levels were not associated with depression but showed negative correlation with SLEDAI. **(J Rheum Dis 2015;22:346-355)**

Key Words. Systemic lupus erythematosus, Depression, Quality of life, Brain-derived neurotrophic factor, Vitamin D

INTRODUCTION

Depression is one of the most prevalent diseases with substantial disease burden [1]. The prevalence of depression in patients with systemic lupus erythematosus (SLE) is reported to be higher than those in general population [2-6]. In addition to psychological defense to cope with chronic disease, pathological processes of disease such as inflammations contribute the development of depression in patients with SLE. Circulating autoantibodies such as anti-N-methyl-D-aspartate (NMDA) receptor antibody are prone to penetrate blood brain barrier due to increment of its permeability in inflammatory milieu. They may result in non-thrombotic and non-vasculitic abnormalities of central nervous system by modifying synaptic function and inducing neural cell death [7]. Furthermore, inflammatory cytokines lead to decrease neurotrophic support and alter monoamine release/reuptake [8].

The result of depression is also considerable in patients

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with SLE. Patients with SLE and depression do not tend to adhere to medication regimens and require more frequent medical attention [6]. Psychological factors including depression are known to affect health related quality of life (HRQoL) in patients with SLE [9,10]. Considering improvement of HRQoL is one of important treatment target in SLE [11], understanding risk factors for depression and early intervention for depression may improve the treatment results by improving not only compliance to medication but also HRQoL.

Neurotrophic factors (NFs) and vitamin D have attracted attentions as molecules untangling neurophysiologic mechanism of depression [12-15]. In patients with depression, decreased levels of NFs result in volumetric decreases of the hippocampus and other forebrain regions [12,13]. Vitamin D insufficiency/deficiency is observed in patients with depression, and the correction of vitamin D deficiency is reported to improve the depression state [14,15]. However, because the most studies about brain-derived neurotrophic factor (BDNF) or vitamin D for depression were conducted among patients with depression irrelevant to comorbidity, it is unclear whether pathologic mechanisms of such molecules can be applicable in patients with certain disease subset.

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 EuroQol-5 dimensions (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.

MATERIALS 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 [16]. The study was approved by the ethics committee of Seoul National University Hospital, and all the subjects provided written informed consents (IRB: 1308-119-517).

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. 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 to 100 mm and 0 to 30 mm 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 including white cell, hemoglobin (Hb) level, platelet count, serum creatinine, anti-dsDNA, and complement (C3, C4) levels were measured. Use of azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, hydroxychloroquine, vitamin D supplement and 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 [17]. The CES-D has been translated into Korean, and its psychometric properties have been validated [18]. Patients with a CES-D score ≥ 24 were considered to have depression according to a previous study in patients with SLE [19]. HRQoL was assessed by the EQ-5D [20]. 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=$1-(0.164+M2\times0.003+M3\times0.274+SC2\times0.058+SC3\times0.078+UA2\times0.045+UA3\times0.134+PD2\times0.049+PD3\times0.132+AD2\times0.044+AD3\times0.102+N3\times0.345+I2sq\times0.014)$ (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 $2-1]^2$) [21]. A higher score of 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 [22].

Serum BDNF and vitamin D measurements

Serum samples were obtained from 151 of 180 patients at baseline and stored at $-80^{\circ}C$ 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 to 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 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 and factors that are expected to affect depression 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 ver. 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

Patient characteristics

A total of 180 patients were enrolled (160 female patients, 88.9%). The mean age (±SD) was 43.3±13.9 yr, and the mean disease duration was 11.0±7.6 yr (Table 1). The annual income less than 18,000,000 Korean won per year were found in 21.1% of the study patients. 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 (Table 2).

On laboratory examination, the mean Hb levels, white cell, platelet and lymphocyte counts were 12.9±3.1 g/dL, 6,213.9±2,601.0/mm^3, 214.3±69.6×10^3/mm^3, 1,247.3±789.1/mm^3, respectively. The mean of serum creatinine levels, 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 to 150 mg/dL) and 17.3±9.3 mg/dL (reference range: 10 to 35 mg/dL), respectively.

Depression and sociodemographic or clinical factors in SLE patients

Depression was observed in 22.8% of 180 SLE patients (n=41). Sex, age, and disease duration were not associated with depression. Among the sociodemographic factors, educational level, marital status, and employment

Table 1. Sociodemographic factors of the patients with SLE with or without depression

Variable	All subjects (n=180)	Depression (n=41)	No depression (n=139)	p-value*
Female	160 (88.9)	39 (95.1)	121 (87.1)	0.15
Age (yr)	43.3±13.9	42.0±18.0	43.5±12.6	0.22
Disease duration (yr)	11.0±7.6	10.4±7.34	11.2±7.69	0.54
Educational level				
Less than college graduates	84 (46.7)	25 (61.0)	59 (42.4)	0.04
At least college graduates	96 (53.3)	16 (39.0)	80 (57.6)	
Marital status				
Married	110 (61.1)	16 (39.0)	94 (67.6)	9.63×10^{-4}
Single/divorced /separated/widowed	70 (38.9)	25 (61.1)	45 (32.4)	
Living arrangement				
Alone	8 (4.4)	2 (4.9)	6 (4.3)	1.00
With others	172 (95.6)	39 (95.1)	133 (95.7)	
Unemployed	111 (61.7)	32 (78.0)	79 (56.8)	0.01
Annual income (n=161)				
≤18,000,000 KRW	26 (16.1)	9 (25.7)	17 (13.5)	0.08
>18,000,000 KRW	135 (83.9)	26 (74.3)	109 (86.5)	

Values are presented as number (%) or mean±standard deviation. KRW: Korean Won, SLE: systemic lupus erythematosus. *p-value comparing patients with SLE with depression vs. those without depression by χ^2-test or student t-test.

Table 2. Clinical factors of the patients with SLE with or without depression

Variable	All subjects (n=180)	Depression (n=41)	No depression (n=139)	p-value*
Clinical manifestation				
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)	0.7
SLEDAI	3.5±3.9	4.0±4.2	3.4±3.8	0.37
Active SLE (SLEDAI ≥6)	41 (22.8)	12 (29.3)	29 (20.9)	0.26
PGA	18.0±20.0	31.9±23.8	13.9±16.6	3.80×10^{-5}
PhyGA	0.93±1.80	1.46±3.12	0.77±1.11	0.03
SDI	1.5±1.7	1.8±1.6	1.8±1.7	0.34
Medications‡				
Glucocorticoid	157 (87.2)	38 (92.7)	119 (85.6)	0.37
Daily dose§	6.7±6.7	7.8±6.7	6.3±6.7	0.23
Hydroxychloroquine	126 (70.0)	30 (73.2)	96 (69.1)	0.73
Cyclophosphamide	30 (16.7)	7 (17.1)	23 (16.5)	0.98
Azathioprine	29 (16.1)	10 (24.4)	19 (13.7)	0.09
Mycophenolate mofetil	15 (8.3)	5 (12.2)	10 (7.2)	0.33
Methotrexate	19 (10.6)	7 (17.1)	12 (8.6)	0.13
Current use of antidepressant	15 (8.3)	12 (29.3)	3 (2.2)	1.28×10^{-6}

Values are presented as number (%) or mean±standard deviation. 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: SLE disease activity index. *p-value comparing patients with SLE with depression vs. 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 criteria for the classification of SLE. ‡Medications prescribed during a year before the study. §Mean daily prednisolone dose over the previous 3 months (mg/d).

status were significantly associated with depression; patients with less than college graduates (p=0.04), a marital status of single/divorced/separated/widowed ($p=9.63\times10^{-4}$) and unemployment (p=0.01) were associated with depression in SLE. A lower annual income tended to be associated with depression (p=0.08; Table 1).

Among the clinical factors, higher scores of PGA and PhyGA were significantly associated with depression, whereas mean daily glucocorticoid dose over the previous 3 months, SLEDAI or SDI was not. There was no significant association between depression and medications except antidepressant 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 ($p=1.28\times10^{-6}$; Table 2). None of the clinical manifestations or laboratory results including Hb levels, white cell count, platelet count, serum creatinine levels, anti-dsDNA titer or complement levels was significantly associated with depression.

HRQoL and analysis for associated factors in each dimension of EQ-5D 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 vs. 0.73±0.12, $p=1.23\times10^{-6}$). Patients with depression had more problems in all dimensions of EQ-5D (Table 3). There were significant negative correlations between EQ-5D index and CES-D scores ($r=-0.56$, $p=1.72\times10^{-16}$), PGA ($r=-0.24$, $p=1.00\times10^{-3}$), PhyGA ($r=-0.33$, $p=1.43\times10^{-5}$), or SDI ($r=-0.17$, p=0.02 by the Spearman correlation test).

The association between sociodemographic or clinical factors and each dimension of EQ-5D were analyzed (Supplementary Table 1; Supplementary Table in the online version of this article). Of note, in multiple logistic regression analysis, depression was significantly associated with dimensions of self-care, usual activity, and extreme pain/discomfort.

Table 3. Comparison of health related quality of life in the patients with SLE with or without depression

Variable	All subjects (n=180)	Depression (n=41)	No depression (n=139)	p-value*
EQ-5D index	0.68±0.19	0.49±0.27	0.73±0.12	1.23×10^{-6}
Mobility				
I have no problems walking	122 (67.8)	22 (53.7)	100 (71.9)	0.02
I have some problems in walking	57 (31.7)	18 (43.9)	39 (28.1)	
I am confined to bed	1 (0.6)	1 (2.4)	0 (0.0)	
Self-care				
I have no problems with self-care	161 (89.4)	32 (78.0)	129 (92.8)	0.01
I have some problems in washing or dressing myself	16 (8.9)	7 (17.1)	9 (6.5)	
I am unable to wash or dress myself	3 (1.7)	2 (4.9)	1 (0.7)	
Usual activities				
I have no problems in performing my usual activities	120 (66.7)	19 (46.3)	101 (72.7)	4.40×10^{-4}
I have some problems performing my usual activities	58 (32.2)	20 (48.8)	38 (27.3)	
I am unable to perform my usual activities	2 (1.1)	2 (4.9)	0 (0.0)	
Pain/discomfort				
I have no pain or discomfort	65 (36.1)	7 (17.1)	58 (41.7)	1.17×10^{-5}
I have moderate pain or discomfort	99 (55.0)	23 (56.1)	76 (54.7)	
I have extreme pain or discomfort	16 (8.9)	11 (26.8)	5 (3.6)	
Anxiety/depression				
I am not anxious or depressed	79 (43.9)	5 (12.2)	74 (53.2)	1.87×10^{-10}
I am moderately anxious or depressed	90 (50.0)	25 (61.0)	65 (46.8)	
I am extremely anxious or depressed	11 (6.1)	11 (26.8)	0 (0.0)	

Values are presented as mean±standard deviation or number (%). EQ-5D: the EuroQol-5 dimensions, SLE: systemic lupus erythematosus. *p-value assessing the trend using linear by linear association comparing the patients with SLE with depression vs. those without depression.

Multiple logistic regression analysis of depression in patients with SLE

Patients with a marital status of single/divorced/separated/ widowed (p=0.03), a higher PGA ($p=2.13\times10^{-4}$), and extreme pain/discomfort (p=0.02) were significantly associated with depression in patients with SLE. Patients with lower educational level (less than college graduates; p=0.08) or with moderate to severe problems in usual activity (p=0.09) tended to be associated with depression (Table 4).

Serum levels of BDNF and associated factors in SLE

Serum levels of BDNF were measured in 151 patients (136 female patients, 90.1%) and 50 healthy age- and sex-matched subjects (45 female patients, 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±8.2 ng/mL vs. 22.0±9.3 ng/mL, p=0.73). Depression was not associated with serum BDNF levels among patients with SLE (SLE patients with depression vs. those without depression, 21.0±8.0 ng/mL vs. 21.5±7.8 ng/mL, respectively, p=0.75). There was no significant difference in serum BDNF levels between the healthy subjects and the SLE patients with depression ($p_c=1.00$) or without depression ($p_c=1.00$, 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, lower serum BDNF levels were significantly associated with active SLE (active vs. inactive SLE, 18.3±6.7 ng/mL vs. 22.4±7.9 ng/mL, respectively, p=0.04). Because platelet is the major storage source of BDNF [23-25], platelet count was highly positively correlated with serum BDNF levels in this study (r=0.53, $p=2.16\times10^{-12}$). 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. Partial correlation analysis, adjusting platelet count, revealed no correlation between serum BDNF levels and CES-D scores (r=−0.06, p=0.49), but a negative correlation between serum BDNF levels and SLEDAI (r=−0.21, p=0.01),

Table 4. Multiple logistic regression analysis for depression in the patients with SLE

Variable	Coefficient	OR (95% CI)	p-value
Age	−0.02	0.98 (0.93∼1.03)	0.42
Sex (female)	−0.31	0.74 (0.12∼4.56)	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
Annual income (≤18,000,000 KRW)	0.12	1.12 (0.25∼5.11)	0.88
Patient's global assessment	0.05	1.05 (1.02∼1.08)	2.13×10^{-4}
Physician's global assessment	-2.8×10^{-3}	1.00 (1.02∼1.00)	0.48
Use of azathioprine	−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

CI: confidence interval, KRW: Korean Won, OR: odds ratio, SLE: systemic lupus erythematosus.

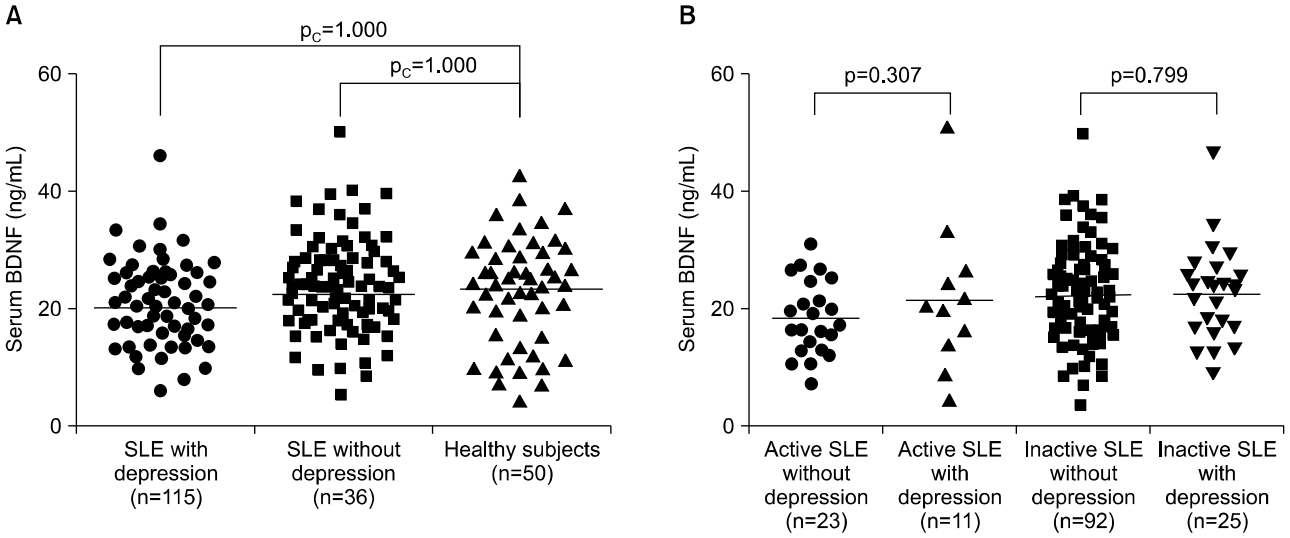

Figure 1. Association between serum levels of brain-derived neurotrophic peptide (BDNF) and depression in the patients with systemic lupus erythematosus (SLE). The serum levels of BDNF were comparable between the healthy subjects and SLE patients with depression or without depression (A). When the patients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

Hb levels ($r=-0.30$, $p=1.74\times10^{-4}$), a mean daily glucocorticoid dose over the previous 3 months of the study ($r=-0.22$, $p=0.01$) (Table 5).

Serum 25(OH)D levels and depression in SLE

Serum 25(OH)D levels were measured in 103 patients (94 female patients, 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 patients, 53.3%), whereas vitamin D deficiency was observed in only 8 patients (7.5%). Serum 25(OH)D levels were comparable between the SLE patients 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 clinical factors such as mucocutaneous involvement (21.0±9.1 vs. 20.0±11.7, p=0.28), renal disorder (p=0.36), or neuropsychiatric disorder (p=0.50). Use of vitamin D supplement was correlated with serum 25(OH)D levels ($p=3.42\times10^{-3}$) while use of other medications was not related to serum 25(OH)D levels. Twenty-three percent (n=24) of patients have taken vitamin D supplement during a year before the study. Partial correlation analysis, ad-

Table 5. Correlation analysis for serum brain-derived neurotrophic factor levels and associated factors with adjustment for platelet count in patients with SLE (n=151)

Variable	Correlation coefficient	p-value
Age	0.17	0.03
Disease duration	−0.02	0.85
SLEDAI	−0.21	0.01
Patient's global assessment	−0.00	0.98
Physician's global assessment	−0.06	0.46
SDI	−0.01	0.87
CES-D score	−0.06	0.49
EQ-5D index	0.03	0.71
White cell	−0.15	0.06
Hemoglobin	−0.30	1.75×10^{-4}
Anti-dsDNA titer	−0.09	0.30
C3	0.03	0.69
C4	−0.01	0.96
Serum 25(OH)D levels	−0.04	0.73
Daily glucocorticoid dose*	−0.22	0.01

C: complement, CES-D: the center for epidemiologic studies depression, EQ-5D: the EuroQol-5 dimensions, SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index, SLE: systemic lupus erythematosus, SLEDAI: SLE disease activity index. *Mean daily prednisolonedose over the previous 3 months (mg/d).

justing use of vitamin D supplement, showed a negative correlation between serum 25(OH)D levels and SLEDAI (r=−0.23, p=0.02) or a mean daily glucocorticoid dose over the previous 3 months of the study (r=−0.21, p=0.04).

DISCUSSION

In the present study, the prevalence of depression was 22.8%, which is higher than that in the general population (3.31% to 8.68%) as shown by earlier reports [2,4-6,18]. Among sociodemographic factors, depression was associated with marital status of single/divorced/separated/widowed in patients with SLE. The previous study results were not consistent in terms of the sociodemographic variables related to depression in patients with SLE [1-4,6,9-10]. Those contradictory results imply that sociodemographic factors rather than disease itself may have more influence on depression in this population. Several previous studies conducted with Koreans showed robust association between disrupted marital status and depression [5,19].

Associations between depression and disease activity are also inconsistent because of methodological difference in measuring disease activity of SLE [2,26-28]. Using the objective disease activity measure such as SLEDAI there was no association between depression and disease activity [2,27-28], whereas using the subjective disease activity measure such as systemic lupus activity questionnaire (SLAQ), disease activity was shown to be associated with depression [2,26,27]. In the current study, PGA, the subjective disease activity measure by patients' perspective was significantly associated with depression while SLEDAI, the objective disease activity measure was not associated with depression in accordance with previous researches. Additionally, PhyGA, the subjective disease activity measure by physician's perspective were not correlated with depression, which suggest the discrepancy in assessment of disease activity according to patient's or physician's perspective in line with preceding study [29].

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 [11]. Depression has been consistently reported to have substantial impact on HRQoL of SLE patients in accordance with the current study [9-11,30,31]. It is noteworthy that 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 [31]. Considering fibromyalgia, characterized by generalized pain, was observed in 32% of patients with SLE in an earlier study [32], although we did not investigate fibromyalgia among the study patients, patients with extreme pain/discomfort might have fibromyalgia, which can influence mood and quality of life. Intensive management of depression has been reported to improve arthritis-related pain and functional outcomes among older adults with arthritis [33]. Therefore, depression should be considered in patients complaining of extreme pain/discomfort. Treatment of depression may alleviate pain and further improve HRQoL in patients with SLE.

BDNF is a NF that has attracted attention as a biomarker and molecular treatment target of depression [24]. The level of serum BDNF has been reported to be reduced in patients with depression [13,24,25]. Several studies reported serum levels of BDNF in patients with SLE, but

they did not evaluate the association of depression and serum levels of BDNF [34,35]. In the current study, however, serum BDNF levels were not associated with depression even after stratified analysis according to degree of inflammation (i.e., disease activity), but they showed a negative correlation with SLEDAI scores. The different results may be due to the net effect of altered platelet count, inflammation status and concurrent medication which may have more influence on serum BDNF levels than those of depression in patients with SLE. Indeed, chronic exposure to dexamethasone reported to result in decrease hippocampal BDNF levels and BDNF-associated synaptic proteins via suppression of ERK-signaling through src homology-2 domain-containing phosphatase 2 (Shp2) and Trk B interaction [36]. Our results suggest that, in patients with SLE, BDNF may not play a major role in the pathophysiological mechanism of depression and is less likely to be a biological marker.

Vitamin D was shown to regulate NFs and affect the neuronal plasticity process [37]. Vitamin D levels are low in patients with depression. Correction of vitamin D insufficiency was reported to improve the depressive state [15]. Vitamin D deficiency is also associated with autoimmunity and inflammation including antinuclear antibody positivity, increased activity of B cells, and high serum interferon-α activity in patients with SLE [38]. In present study, low serum vitamin D levels were associated with high disease activity in line with previous studies SLE [39]. However, in contrast to previous studies of vitamin D and depression [14], serum vitamin D levels were not associated with depression in patients with SLE. We speculate that use of vitamin D supplement and the impact of inflammatory cytokine milieu 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 for depression 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 [40] and a cutoff point score $\geq$24 was suggested to correctly classify 92% of participants as having a current major depressive disorder [19]. 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 neuropsychiatric SLE could not be conducted.

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. The treatment of depression may be beneficial in patients with extreme pain/discomfort or high PGA.

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CONFLICT OF INTEREST

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

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