Original Article

Yonsei Med J 2021 Apr;62(4):359-365
https://doi.org/10.3349/ymj.2021.62.4.359

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Association between *BDNF* Polymorphism and Depressive Symptoms in Patients Newly Diagnosed with Type 2 Diabetes Mellitus

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Purpose: Little is known about the relationship between brain-derived neurotrophic factor (BDNF) gene polymorphisms and psychiatric symptoms in diabetes patients. We investigated the effects of *BDNF* Val/66/Met polymorphism, glucose status, psychological susceptibility, and resilience on anxiety and depression symptoms in patients newly diagnosed with type 2 diabetes mellitus (T2DM).

Materials and Methods: We examined biochemical factors and *BDNF* polymorphism in 89 patients who were newly diagnosed with T2DM. Psychiatric symptoms were investigated with the Hospital Anxiety and Depression Scale (HADS), and the Connor-Davidson Resilience Scale (CD-RISC) and Impact of Event Scale (IES) were used to assess psychological resilience and susceptibility to psychological distress, respectively. Logistic regression analyses were conducted to investigate factors associated with psychiatric symptoms.

Results: We determined that 62 patients (70%) were Met-carriers. No significant differences were found between the Val/Val homozygous and Met-carrier groups regarding age, sex, body mass index, and clinical factors related to glycemic control and lipid profiles. HADS-anxiety and HADS-depression scores and IES factor scores were higher in the Met-carrier than the Val/Val homozygous group. Hemoglobin A1c (HbA1c) level was significantly inversely correlated with the severity of depressive symptoms. Resilience factors showed significant inverse correlations, and IES factors showed positive correlations with depressive symptom severity. In the logistic regression analysis model, depressive symptoms were significantly associated with HbA1c and *BDNF* polymorphism, whereas only the hyperarousal factor of the IES scale was associated with anxiety.

Conclusion: Depressive symptoms are associated with the presence of the Met-carriers and lower HbA1c in patients newly diagnosed with T2DM.

Key Words: Brain-derived neurotrophic factor (BDNF), polymorphism, diabetes mellitus, depression, anxiety

Received: June 9, 2020 **Revised:** January 5, 2021 **Accepted:** January 26, 2021

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•The authors have no potential conflicts of interest to disclose.

INTRODUCTION

The prevalence of depression in diabetic patients is approximately twice that observed in the general population.[1] Type 2 diabetes mellitus (T2DM) and depression are multi-factorial polygenic disorders influenced by both environmental and genetic factors, as well as insulin resistance (IR), and their relationship has been widely investigated.[2] T2DM is a chronic disease that has to be managed with lifestyle modifications and/or medications throughout one's life, and therefore, diabetic patients tend to experience diverse psychological changes, including anxiety, depression, disappointment, and despair, once they are diagnosed. These psychological problems may result in low compliance to treatment, and emotional symptoms can exacerbate T2DM-associated physiological symptoms.[3,4]

Eaton, et al.[5] reported that depressive disorders increase the prevalence of T2DM, whereas others have demonstrated that impaired glucose control can affect mood. Lustman, et al.[6] suggested that hyperglycemia can increase anxiety in type 1 diabetic patients, and Testa and Simonson[7] demonstrated that depressive symptoms in T2DM patients could be ameliorated by improving various metabolic factors. Other studies have also reported that the presence of IR aggravates depressive mood.[2,8,9] Depression is one of the common symptoms that is most likely to occur within 1 year after T2DM diagnosis.[10] Lustman, et al.[11] reported that depressive disorder persisted as long as 5 years in T2DM and that 92% of those who had experienced severe depressive symptoms required medical treatment. Taken together, available evidence suggests that there is an interactive relationship between T2DM and depression and that early diagnosis and treatment are crucial for diabetic patients.

Genetic factors have been reported to be associated with psychological problems, including depression.[12] Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor that plays an important role in neurogenesis and neuroprotection. The *BDNF* gene is located at chromosome 11p14.1 and has some polymorphic markers: a single nucleotide polymorphism (SNP) at nucleotide 196 (G/A) results in the substitution of methionine for valine at codon 66 (val/66/met, rs6265) of the pre-protein. This polymorphism affects BDNF intracellular processing, and the Met-allele is related with reduced activity-dependent BDNF secretion.[13] The *BDNF* Val/66/Met polymorphism is a common genetic variant and is known to be associated with neuropsychiatric disorders, including Parkinson's disease, Alzheimer's disease, depression, obsessive compulsive disorder, eating disorder, and memory impairment.[13-18]

Krabbe, et al.[19] observed a significant relationship between glucose metabolism and *BDNF*, wherein BDNF plasma concentrations in T2DM patients were lower than those in healthy controls. Moreover, BDNF was reported to have a preventive role in the progression to T2DM in a study of pre-diabetic mice.[20] Taken together, this evidence implies that BDNF significantly influences the development of depression and T2DM.[19,20]

Resilience in psychology is defined as an individual's ability to cope with stress and adversity.[21] Resilience is a dynamic process whereby individuals exhibit positive behavioral adaptation when they encounter stressful events. Stress levels in newly diagnosed T2DM patients may vary depending on their resilience capacity.

BDNF polymorphism has been shown to be associated with anxiety and depressive symptoms in neuropsychiatric patients with Parkinson's disease, Alzheimer's disease, obsessive compulsive disorder, and eating disorder.[13-18] However, only a few studies have investigated these relationships among T2DM patients, and it is unclear if this relationship exists in Korean patients. Here, we investigated the effects of the *BDNF* Val/66/Met polymorphism, glucose status, psychological resilience, and susceptibility to emotional distress in newly diagnosed Korean T2DM patients.

MATERIALS AND METHODS

Diabetic patients and clinical evaluation

Patients who were newly diagnosed with T2DM (n=100) were recruited at Gangnam Severance Hospital from 2010 to 2011. Participants were recruited into this study if they met one or more of the following four criteria: 1) fasting plasma glucose (FPG) levels ≥126 mg/dL, 2) 2-hr plasma glucose levels ≥200 mg/dL following a 75-g oral glucose tolerance test, 3) random plasma glucose level ≥ 200 mg/dL with typical diabetes symptoms, and 4) hemoglobin A1c (HbA1c) ≥6.5%.[22] Exclusion criteria were having acute or serious medical illnesses, such as cancer, end-stage renal disease, acute myocardial infarction, and/or liver cirrhosis, which may affect emotional symptoms.

Among 100 subjects, 11 were excluded for the following reasons: three patients refused blood sampling, six provided unreliable answers on the questionnaire, and two had histories of psychiatric medication use. Ultimately, a total of 89 patients were included in the study. Every subject provided written informed consent prior to participation. This study was approved by an Institutional Review Board of Gangnam Severance Hospital at Yonsei University (IRB number: 3-2011-0022).

Blood samples were taken after overnight fasting. Serum glucose levels were measured by a standard glucose oxidase method (747 Automatic Analyzer, Hitachi, Tokyo, Japan). Serum c-peptide and insulin levels were determined by commercially available assay kits (RIA Kit, Daiichi, Japan). IR was estimated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index, calculated from the following formula:

$$\text{HOMA–IR} = \text{fasting insulin } (\mu U/mL) \times \text{FPG } (mmol/L)/22.5$$[23]

Total cholesterol (TC), high-density lipoprotein-cholesterol

https://doi.org/10.3349/ymj.2021.62.4.359

(HDL-C), and triglycerides (TG) were measured with a chemical analyzer (Hitachi 747). Serum low-density lipoprotein-cholesterol (LDL-C) levels were calculated according to the Friedewald formula.[24] HbA1c was measured by immunoturbidimetry (Cobas Integra 800, Roche, Mannheim, Germany). Body mass index (BMI) was calculated with the following formula: weight (kg)/height (m)^2.

Psychological assessment

To examine the effects of psychological resilience and susceptibility on depression and anxiety, psychological status of the subjects was measured with appropriate questionnaires, including the Hospital Anxiety and Depression Scale (HADS), the Connor-Davidson Resilience Scale (CD-RISC), and the Impact of Event Scale (IES).[21,25,26] HADS is a self-reporting questionnaire and consists of seven questions assessing anxiety (HADS-a) and seven questions assessing depression (HADS-d). It is designed to screen for anxiety and depression symptoms in non-psychiatric patients. A score of eight or higher indicates clinically significant emotional distress.[27] Disease-related psychological susceptibility was measured with the IES, which measures the amount of distress that the subjects associate with a specific event or condition, in this case T2DM, for the previous 14 days. The questionnaire consists of 22 questions with five-point Likert scale for four factors: seven items for intrusiveness, eight items for avoidance, two items for sleep problems, and five items for hyperarousal. The CD-RISC measures the amount of resilience, which is defined as an individual's ability to cope with stress.[21] The questionnaire consists of 25 statements that assess five factors: self-efficacy, self-confidence, optimism, self-control, and spirituality/autonomy. The Korean versions of these questionnaires have been validated in medical practice.[26-28] Internal consistency was assessed by calculating Cronbach's alpha values, and the results were found to be satisfactory (HADS-a, 0.89; HADS-d, 0.86; IES, 0.93; CD-RISC, 0.93).[26-28]

Genetic analysis

Blood samples were collected in EDTA tubes and stored at -20°C until the experiments. Genomic DNA (gDNA) was extracted from samples using QIAamp DNA Blood Midi Kits (#51185, Qiagen, Valencia, CA, USA) according to the manufacturer's directions. Amplification of gDNA was carried out using TopTaq™ DNA Polymerase (#200205, Qiagen); the amplification conditions consisted of an initial denaturation at 94°C for 5 min; followed by 35 cycles of denaturing at 94°C for 30 sec, annealing at 60.5°C for 30 sec, extension at 72°C for 30 sec; and post-elongation at 72°C for 10 min. Polymerase chain reaction (PCR) primers were designed with the following sequences of hBDNF: forward 5'-AAACATCCGAGGACAAGGTG-3'and reverse 5'-CCTCATGGACATGTTTGCAG -3'. PCR products were read with an automated ABI Prism 3730 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and were scored using GeneScan, ver. 3.1 (Applied Biosystems). Met/Val *BDNF* polymorphism was determined with Reference SNP ID rs6265. The polymorphism distribution of the polymorphism did not deviate significantly from Hardy-Weinberg equilibrium ($\chi^2(1)$= 0.51, p=0.47).[29]

Statistical analyses

Statistical analyses were performed with SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). Results are expressed as means±standard deviations or proportions. The Kolmogorov-Smirnov test was used to test for normality. Sociodemographic and psychological characteristics of Val/Val homozygous and Met-carrier patient groups were compared using the independent t-test and Mann-Whitney test. The chi-square test was used to assess categorical variables. Since all psychological assessments were conducted using the scores of questionnaires, Spearman's rank correlation analysis was used to assess relationships between two variables. Multivariate logistic regression analysis was employed to identify predictors of clinically significant depressive and anxiety symptoms. The variance inflation factor was calculated in consideration of multicollinearity, and variables with variance inflation factors of 10 or higher were excluded. Among the clinical characteristics, FPG, BMI, C-peptide, TG, TC, HDL-C, LDL-C were excluded, and avoidance factor was excluded among IES. For all analyses, p values<0.05 were considered significant.

RESULTS

As shown in Table 1, no significant differences were found between the Val/Val homozygous (Val/66/Val) and Met-carrier

Table 1. Clinical Characteristics of Newly Diagnosed Type 2 Diabetic Patients

	Met-carriers (n=62)	Val/Val homozygotes (n=27)	*p* value
Age (yr)	49.47±10.51	48.52±10.98	0.689
Sex (M:F)	43:19	21:6	0.416
FPG (mg/dL)	163.27±49.91	174.68±65.72	0.387
HbA1c (%)	8.56±1.96	8.66±2.31	0.837
BMI	25.90±3.98	25.07±2.39	0.420
C-Pep (ng/mL)	2.16±0.86	2.50±1.30	0.179
Ins (mcIU/mL)	8.81±6.56	10.56±5.72	0.116
HOMA-IR	3.43±2.69	4.47±2.58	0.356
TC (mg/dL)	187.18±43.42	192.56±41.59	0.590
TG (mg/dL)	145.25±77.25	136.41±55.68	0.920
HDL-C (mg/dL)	44.57±9.33	41.0±10.11	0.115
LDL-C (mg/dL)	112.78±37.18	115.68±38.61	0.747

M, male; F, female; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; BMI, body mass index; C-pep, C-peptide; Ins, Insulin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; TC, Total cholesterol; TG, Triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol. Data are presented as a mean±standard deviation.

(Val/66/Met) groups with regard to age (mean age: 49.47±10.51 years in Met-carrier group, 48.52±10.98 years in Val/Val group), sex (43:19 in Met-carrier group, 21:6 in Val/Val group), BMI, lipid profiles, or clinical factors related to glycemic control, such as FPG level, HbA1c level, and HOMA-IR. However, we found significant differences in psychological characteristics between groups (Table 2). Depression and anxiety symptoms represented by average HADS-a and HADS-d scores, respectively, were significantly higher in Met-carrier group than the Val/Val homozygous group. Moreover, susceptibility represented by scores for all IES factors (hyperarousal, avoidance, intrusion, and sleep problems) were significantly higher in Met-carriers than Val/Val homozygotes. There were no significant differences between the groups for the five resilience factors (self-efficacy, self-confidence, optimism, self-control, and spirituality/autonomy).

Spearman's rank correlation analysis was performed to assess associations among glucose status at the time of T2DM diagnosis, psychological impact caused by T2DM diagnosis, psychological resilience, depression, and anxiety (Table 3). While there was no significant correlation between glucose status and HADS-a, two resilience factors (self-confidence and self-control) were inversely correlated with HADS-a score, and the IES factors (hyperarousal, avoidance, intrusion, and sleep problems) were positively correlated with HADS-a score. HADS-d score was inversely correlated with serum HbA1c level and four resilience factors (self-efficacy, self-confidence, optimism, and self-control). HADS-d score was positively correlated with all four IES factors.

The subjects were further subdivided according to the presence of clinically significant anxiety or depression symptoms according to HADS cutoff scores. Among the 89 patients, 23.6% exhibited significant anxiety, and 36% appeared to have significant depression when evaluated by HADS-a and HADS-d, respectively. Logistic regression analyses were performed for these subgroups to identify predictors for significant anxiety and depression, and the following variables were included in the analysis as potential predictors: clinical characteristics (sex, age, HbA1c, HOMA-IR, and *BDNF* polymorphism) and psychologi-

Table 2. Psychological Characteristics of Newly Diagnosed Type 2 Diabetic Patients

	Met-carriers (n = 62)	Val/Val homozygotes (n = 27)	*p* value
HADS-a	5.76±3.24	4.22±2.59	0.032
HADS-d	6.73±3.44	4.78 ± 2.59	0.010
Resilience factors			
Self-efficacy	23.79±8.52	23.85±6.18	0.598
Self-confidence	23.27±5.54	23.18±6.53	0.771
Optimism	15.83±2.98	15.88±4.14	0.565
Self-control	9.16±2.23	9.37±2.43	0.629
Spirituality/autonomy	5.46±1.81	5.03±2.36	0.551
IES factors			
Hyperarousal	12.95±10.12	6.51±5.97	0.003
Avoidance	12.66±7.59	7.07±4.64	0.001
Intrusion	6.67±5.60	4.03±3.79	0.027
Sleep problems	6.32±4.86	2.96±3.50	0.001

HADS-a, average scores for anxiety subscales of the Hospital Anxiety and Depression Scale; HADS-d, average scores depression subscales of the Hospital Anxiety and Depression Scale; IES, Impact of Event Scale.
Data are presented as mean±standard deviation.

Table 3. Correlations among HADS Score and Glucose Status, Resilience, and IES Factor Scores

	HADS-a		HADS-d	
	rho	*p* value	rho	*p* value
FPG	-0.080	0.472	-0.125	0.259
HbA1c	-0.179	0.097	-0.232*	0.030
Resilience factors				
Self-efficacy	-0.195	0.067	-0.499**	<0.001
Self-confidence	-0.211*	0.048	-0.458**	<0.001
Optimism	-0.139	0.193	-0.444**	<0.001
Self-control	-0.156*	0.015	-0.432**	<0.001
Spirituality/autonomy	0.041	0.701	-0.176	0.099
IES factors				
Hyperarousal	0.533**	<0.001	0.417**	<0.001
Avoidance	0.320**	0.002	0.208*	0.049
Intrusion	0.339**	0.001	0.335*	0.001
Sleep problems	0.457**	<0.001	0.437**	<0.001

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IES, Impact of Event Scale; HADS-a, anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-d, depression subscale of the Hospital Anxiety and Depression Scale.
*p<0.05, **p<0.001.

Table 4. Logistic Regression Model Odds Ratios for Prediction of Depressive Symptoms

	Odds ratio	95% confidence interval	*p* value
Sex (ref. Male)	2.391	0.600–9.524	0.216
Age	1.072	0.993–1.156	0.076
HbA1c*	0.657	0.456–0.945	0.024
BDNF* (ref. Val/Val homozygote)	4.673	1.040–23.242	0.046
HOMA-IR	1.008	0.799–1.270	0.949
Resilience factors			
Self-efficacy	0.909	0.767–1.077	0.270
Self-confidence	1.131	0.919–1.394	0.246
Optimism	0.844	0.595–1.197	0.341
Self-control	0.837	0.553–1.267	0.400
Spirituality/autonomy	0.773	0.538–1.112	0.165
IES factors			
Hyperarousal	0.992	0.842–1.170	0.077
Intrusion	1.104	0.924–1.319	0.278
Sleep problems	1.164	0.876–1.547	0.295

HbA1c, hemoglobin A1c; BDNF, brain-derived neurotrophic factor polymorphism (Met-carrier vs. Val/Val homozygote); HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IES, Impact of Event Scale; ref, reference.
The Nagelkerke R-square value was 0.56 (p<0.001).
*p<0.05.

https://doi.org/10.3349/ymj.2021.62.4.359

cal characteristics (five resilience factors and three psychological susceptibility factors). These analyses revealed that HbA1c level (β=0.657, *p*=0.024) and *BDNF* polymorphism (β=4.673, *p*=0.046) were associated with depression (Table 4). The only variable associated with anxiety in the final regression model was the hyperarousal factor of the IES scale (β=1.180, *p*=0.044) (Table 5).

DISCUSSION

Our findings demonstrated that depression and anxiety symptoms in patients newly diagnosed with T2DM are related to the presence of the SNP at nucleotide 196 in the *BDNF* gene. Subjects with a valine for methionine substitution (Val/66/Met) showed significantly higher scores for both depression and anxiety symptoms, compared to those carrying Val/66/Val. There are some inconsistent results regarding the role of the Met allele in the development of various psychiatric symptoms. Some studies have reported that the Met allele is protective against psychiatric disorders, including depression, while others have suggested that Met-carriers face an increased risk for anxiety and depression.[17,30-32] Similar results have indicated that the Met substitution for Val is a risk factor for psychiatric symptoms in Korean populations.[33,34] Our findings suggest that the presence of the Met allele in patients with T2DM seems to be a risk factor for depression and anxiety symptoms.

We compared IES and CD-RISC scores and glucose status among Korean patients with T2DM divided into Met-carriers and Val/Val homozygotes. Met-carriers were more susceptible than Val/Val homozygotes when evaluated by IES factors (hyperarousal, avoidance, intrusion, and sleep problems). These results suggest that the Met-carrier group was more susceptible to psychological distress at the diagnosis of T2DM than the Val/Val homozygous group. However, there was no significant difference between these two groups with regard to the five factors of resilience, indicating that resilience capacity may not be significantly associated with *BDNF* polymorphism. Collectively, these findings suggest that *BDNF* polymorphism is associated with emotional distress and psychological susceptibility but not with resilience in patients with T2DM.

Table 5. Logistic Regression Model Odds Ratios for Prediction of Anxiety Symptoms

	Odds ratio	95% confidence interval	*p* value
Sex (ref. Male)	2.064	0.492–8.665	0.322
Age	1.069	0.997–1.147	0.062
HbA1c	0.696	0.462–1.046	0.081
BDNF (ref. Val/Val homozygote)	0.600	0.137–2.623	0.498
HOMA-IR	1.058	0.815–1.373	0.671
Resilience factors			
Self-efficacy	0.951	0.781–1.157	0.613
Self-confidence	1.097	0.865–1.390	0.445
Optimism	0.989	0.652–1.500	0.958
Self-control	0.976	0.627–1.519	0.913
Spirituality/autonomy	0.858	0.610–1.206	0.377
IES factors			
Hyperarousal*	1.180	1.001–1.140	0.044
Intrusion	0.933	0.786–1.107	0.426
Sleep problem	0.987	0.738–1.320	0.931

HbA1c, hemoglobin A1c; BDNF, brain-derived neurotrophic factor (Met-carrier vs. Val/Val homozygote); HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IES, Impact of Event Scale; ref, reference.
The Nagelkerke R-square value was 0.41 (p<0.001).
*p<0.05.

In this study, a logistic regression model including sex, age, HbA1c, *BDNF* polymorphism, HOMA-IR, resilience factors, and susceptibility factors revealed that depression was significantly associated with low HbA1c and the BDNF Met allele. There have been inconsistent reports regarding the relationship between parameters of glycemic control and depression in diabetic patients. One study reported that depressive symptoms are inversely correlated with the parameters of glycemic control, while others found no correlation between the two variables.[6,35,36] However, the mean durations of T2DM in those studies varied from 5 to 10 years. Unlike previous studies, we examined the relationship between depressive symptoms and glycemic control at the time of T2DM diagnosis.

Interestingly, we found that HbA1c levels were lower in subjects with depressive symptoms. Considering that HbA1c represents the average glucose values for the previous 2–3 months, it suggests that patients with depressive symptoms had better glucose control. Patients with more depressive symptoms tend to be concerned about their health and to visit the hospital more frequently with mild illnesses than those without depressive symptoms.[37] That people with depressive symptoms may react more sensitively to changes in their health conditions related to high glucose level and may visit their physicians more frequently may explain the lower HbA1c levels in depressed subjects in the present study. In other words, the interval between T2DM onset and the time to diagnosis may be shorter in patients with depressive symptoms even though we did not exactly assess hospital visit frequency in this study. In another study that conducted 2 years of follow-up after being newly diagnosed with T2DM, depressive symptoms and an increase in HbA1c were not related after 1 year, but were associated after 2 years. Similar findings have been reported in other studies, suggesting that the longer the patient suffers from diabetes, the more diabetes distress, which is characterized as burdens, worries, and fears specific to people living with diabetes, will be associated with an increase in HbA1c.[38] Therefore, in order to accurately understand the association between HbA1c and depressive symptoms, a long-term study over time from the point of diagnosis of diabetes may be meaningful.

Spearman's rank correlation analyses revealed significant

negative correlations between depressive symptoms and resilience scores and significant positive correlations between depressive symptoms and psychological susceptibility. This implies that the susceptibility factor is more important than the protective factor to experience depressive symptoms when patients are newly diagnosed with T2DM.

HADS has been used to assess emotional symptoms in DM patients in previous studies.[1,6] According to HADS-d score, we found that 32 newly diagnosed subjects (36%) appeared to have significant depressive symptoms, and 9 subjects (10%) exhibited severe depressive symptoms. 21 subjects (23.6%) were found to have significant anxiety symptoms, and 7 subjects (7.8%) were found to have severe anxiety symptoms according to HADS-a score. These observations are consistent with previous studies that demonstrated higher prevalence of depression and anxiety in diabetic patients, compared to the general population.[1,39-41] This study provides novel clinical evidence that patients who are newly diagnosed with T2DM show an increased prevalence of depression and anxiety. Adriaanse, et al. reported that pre-diabetic and diabetic females suffered from more depressive symptoms than the general population.[42] They suggested that the prevalence of depressive symptoms might be higher even in pre-diabetes status. However, 72% of the subjects in this study were male, which made it difficult to address the role of sex. In general, depression is more prevalent in females. In this regard, the presence of depressive symptoms in patients newly diagnosed with T2DM may be higher in general than this sample, which needs further investigation.

There are some limitations to this study. First, the sample size was relatively small; however, the genetic distribution of the sample was not significantly deviated from Hardy-Weinberg equilibrium. Second, this study did not include a control group, and thus, we could not directly compare the prevalence of depression and anxiety in patients newly diagnosed with T2DM with those in non-diabetic individuals according to *BDNF* polymorphism. Third, the subjects were not fully evaluated with structured diagnostic interviews or comprehensive psychological tests. Lastly, the male proportion over 2/3 may contribute to equivocal findings about correlation between glucose control (HbA1c) and depressive symptoms in this study. Further large scale study about this issue should be followed.

Despite these limitations, the present study is the first to evaluate relationships between *BDNF* polymorphism and emotional symptoms in Korean patients who were newly diagnosed with T2DM. A larger study is necessary to replicate or confirm these preliminary findings.

In conclusion, our study demonstrated that the *BDNF* Val/66/Met polymorphism is associated with depressive symptoms in patients newly diagnosed with T2DM. This study also showed that depressive patients tended to show better HbA1c levels when they were newly diagnosed, although this may be due to the tendency of depressive patients to frequently seek medical assistance. Additionally, we confirmed that emotional symptoms are associated with psychological characteristics, including resilience and susceptibility to stressful life events.

One study reported that half of diabetic patients suffer from depression; however, only half of clinically depressed diabetic patients are treated for their psychological symptoms.[43] Our findings suggest that when treating patients with diabetes, a biopsychosocial approach to evaluate depression, as well as good glycemic control, may improve treatment outcomes. Physicians and psychiatrists should cooperate to improve early depression diagnosis and facilitate active treatment to improve patient quality of life.

ACKNOWLEDGEMENTS

This project was funded by Sanofi-Aventis.

AUTHOR CONTRIBUTIONS

Conceptualization: Jin Sun Ryu, Young Mi Lee, Ji Sun Nam, and Jeong-Ho Seok. Data curation: Young Mi Lee and Ji Sun Nam. Formal analysis: Jin Sun Ryu and Young Mi Lee. Funding acquisition: Ji Sun Nam. Investigation: Jin Sun Ryu and Young Mi Lee. Methodology: Shinae Kang, Ji Sun Nam, and Jeong-Ho Seok. Project administration: Young Mi Lee. Resources: Yu-Sik Kim, Jong Suk Park, and Ji Sun Nam. Software: Jin Sun Ryu and Young Mi Lee. Supervision: Chul Woo Ahn, Ji Sun Nam, and Jeong-Ho Seok. Validation: all authors. Visualization: Jin Sun Ryu and Young Mi Lee. Writing—original draft: Young Mi Lee. Writing—review & editing: Jin Sun Ryu. Approval of final manuscript: all authors.

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