The BDNF polymorphism is associated with psychiatric symptom among newly diagnosed diabetic patients

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ABSTRACT

The BDNF polymorphism is associated with depressive symptom among newly diagnosed diabetic patients

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Background: The prevalence of depression in diabetic patient is approximately twice than in the general population. The brain-derived neurotrophic factor(BDNF) is one of the neurotrophic factor family and plays an important role in neurogenesis and neuro-protection. Some studies have suggested that BDNF plays an anti-diabetic role as well as its role in the psychiatric symptoms. The BDNF polymorphism is known to contribute to psychiatric illness such as depression and anxiety. However, little is known about the impact of the BDNF gene polymorphism in diabetes. In this study we investigated whether the BDNF Val/66/Met polymorphism, glucose status, psychological susceptibility and resilience contribute to development of anxiety or depression symptom in newly diagnosed Korean diabetic patients.

Methods: We examined biochemical factors and the BDNF polymorphism in 89 newly diagnosed diabetic subjects. Psychiatric symptoms were

investigated by the Hospital Anxiety and Depression Scale (HADS). We intended to analyze stress that the patients might have from perspectives of psychological resilience and susceptibility by using resilience scale(CD-RISC) and impact of event scale(IES). Independent samples t-test and chi-square test were used to assess the differences between groups. Pearson's correlation analysis and logistic regression analysis were conducted to investigate significant factors associated with anxiety and depressive symptom.

Results: Sixty-two out of the eighty-nine were found to be Met-carriers. No significant differences were found between Val/Val homozygotes group and Met-carrier group regarding age, sex, BMI and clinical factors related to glycemic control and lipid profile. HADS-anxiety(Met carrier 5.76 ± 3.24; Val/Val homozygote 4.22± 2.59, p-value=0.03) and HADS-depression(Met carrier 6.73 ± 3.44; Val/Val homozygote 4.78 ± 2.59, p-value=0.01)scale in Met-carrier group were higher than Val/Val homozygotes group. IES factor scores in Met-carrier group were also higher than those in Val/Val homozygotes group(Met-carrier vs. Val/Val homozygote; hyperarousal: 12.95± 10.12vs6.51± 5.97, P<0.01; Avoidance12.66± 7.59 vs. 7.07± 4.64, P<0.01; Intrusion 6.67± 5.60 vs. 4.03± 3.79, P=0.012; Sleep problem6.32± 4.86 vs. 2.96± 3.50, P<0.01).

HbA1c and depressive symptom showed significant inverse correlation (pearson's correlation coefficient R=-0.227; P=0.035), however, anxiety symptom and HbA1c had no significant correlation. Resilience factors

showed significant inverse correlations and IES factors showed positive correlation with depressive symptom severity(self-efficacy R=-0.389, p<0.001; self-confidence R=-0.462, p<0.001; optimism R=-0.448, p<0.001; self-control R=-0.46, p<0.001; hyperarousal R=0.363, p<0.001; avoidance R=0.219, p=0.039; intrusiveness R=0.257, p=0.015; sleep problem R=0.419, p<0.001). Anxiety symptom and psychological factors also showed similar correlation patterns(Self-confidence R=-0.236, p=0.026; Self-control R=-0.253, p=0.017; hyperarousal R=0.5,p<0.001; avoidance R=0.323,p=0.002; intrusion R=0.337,p=0.001; sleep problemR=0.476,p<0.001).

In the final logistic regression analysis model, depressive symptom have significant associations with HbA1c(OR=0.671) and BDNF polymorphism (OR=5.413) whereas hyperarousal was the only variable that proved to be associated with anxiety(OR=1.386).

Conclusion: These results suggest that the depressive symptom is related to presence of the Met-allele and lower HbA1c whereas anxiety symptom is related to hyperarousal in newly diagnosed diabetic patients

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Key words : brain-derived neurotrophic factor(BDNF), polymorphism, diabetes mellitus, depression, anxiety, resilience, impact of event scale(IES)

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I. INTRODUCTION

The prevalence of depression in diabetic patients is approximately twice than in the general population[1]. The relationship between depression and diabetes mellitus (DM) has been widely investigated; and type 2 diabetes mellitus (T2DM) and depression are multi-factorial polygenic disorders that are affected by environmental and genetic factors as well as insulin resistance[2]. DM is a chronic disease that cannot be completely curable, thereby diabetic patients tend to experience diverse psychological changes such as anxiety, depression, disappointment and despair once they are diagnosed. These psychological problems may result in low compliance to treatment for their physiological symptoms; therefore T2DM and emotional symptoms have a bi-directional relationship in cause and effect.

Eaton et al. reported that depressive disorders raise prevalence of T2DM[3], while other demonstrated that impaired glucose control can affect mood. Lustman et al. suggested that hyperglycemia can adversely influence anxiety in type 1 diabetic patients[4]. The study of Testa et al. with T2DM patients demonstrated that depressive symptoms could be ameliorated by improving metabolic factors related T2DM[5]. Other studies also reported that the presence of insulin resistance aggravates depressive mood[2,6,7]. Depression is the symptom that is most likely to occur within one year after the diagnosis with DM[8]. Among DM patients, depressive disorder appeared to persist as long as 5 years; and 92 percent of those who had experienced severe depressive symptoms needed medical treatment[9]. Taken these together, it is suggested that an interactive relationship between DM and depression exists and that early diagnosis and treatment of depression are crucial for diabetic patients.

Some genetic factors were reported to be associated with psychological problems such as depression[10]. The brain-derived neurotrophic factor (BDNF) is one of the neurotrophic factor family and plays an important role in neurogenesis and neuro-protection. 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 (val66met, rs6265) of the pre-protein. This polymorphism results in the changes in intracellular processing of BDNF and the Met-allele is related to reduced activity-dependent BDNF secretion[11].

BDNF Val/66/Met polymorphism is a common genetic variant and is known to be associated with neuropsychiatric disorders, including Parkinson's disease[12], Alzheimer's disease[13], depression[14], obsessive compulsive disorder[15], eating disorder[16] and memory impairment[11]. The relationship between glucose metabolism and BDNF was investigated by Krabbe et al., and they observed lower plasma concentration of BDNF among T2DM patients[17]. Moreover, BDNF was reported to have a preventive role in the progression to diabetes in the study with pre-diabetic mice[18]. Taken together, BDNF seems to have significant influences in the development of depression[19] and DM[17].

Resilience in psychology is defined as an individual's ability to cope with stress and adversity[20]. Resilience is a dynamic process whereby individuals exhibit positive behavioral adaptation when they encounter stressful events; therefore, resilience observed in individuals may vary. For example, when people were diagnosed with DM for the first time, the levels of stress would vary among patients, according to the resilience.

BDNF polymorphism was reported to be associated with anxiety and depressive disorder in some disease groups[11-16], but only a few studies investigated the relationships among T2DM patients, especially among Korean patients. Therefore, we investigated the effects of BDNF Val/66/Met polymorphism, glucose status, psychological resilience and susceptibility on the development of anxiety or depressive symptoms in newly diagnosed Korean diabetic patients.

II. MATERIALS AND METHODS

1. Diabetic patients and clinical evaluation

Newly diagnosed diabetic patients (N=100) were recruited in Gangnam Severance Hospital from 2010 to 2011. The newly diagnosed diabetes patients is limited to those who met more than one of four criteria for T2DM: 1) fasting plasma glucose (FPG) levels ≥ 126mg/dL, 2) 2-hr plasma glucose levels ≥ 200 mg/dL from 75g oral glucose tolerance test, 3) random plasma glucose level ≥ 200 mg/dL with typical diabetes symptom, or 4) HbA1c ≥ 6.5% [21]. Exclusion criteria include acute or severe medical illnesses such as cancer, end stage renal disease, acute myocardial infarction, and/or liver cirrhosis that may deteriorate emotional symptoms.

Among 100 subjects, 11 were excluded for the following reasons: three patients refused sampling; three made untruthful answers during questionnaire survey; two had histories of anti-psychiatric medication; and three dropped out during the study. Therefore, a total of 89 were finally included in the study. Every subject provided written informed consent for his or her participation. This study was approved by an Institutional Review Board (IRB) of Gangnam Severance Hospital, Yonsei University.

Blood samples were taken after an overnight fasting. Serum glucose level was measured by a standard glucose oxidase method (747 Automatic Analyzer, Hitachi, Tokyo, Japan). Serum c-peptide and insulin level was

determined by chemiluminescence (RIA Kit, Daiichi, Japan). The insulin resistance was estimated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index, calculated from the following formula: HOMA –IR =fasting insulin (μU/mL) * fasting plasma glucose (mmol/L)/22.5

Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured by chemical analyzer (Daiichi, Hitachi 747, Japan). Serum LDL-cholesterol level was calculated according to the Friedewald formula. HbA1c was measured by immunoturbidimetry (Cobasintegra 800, Roche, Mannheim, Germany).

2. Mood disorder

To examine the effects of psychological resilience and susceptibility on depression and anxiety, psychological status of the subjects were measured by using survey questionnaires, Hospital Anxiety and Depression Scale (HADS[22]), Connor-Davidson Resilience Scale(CD-RISC[20]) and Impact of Event Scale (IES[23]). HADS is a self-reporting questionnaire and consists of 7 questions assessing anxiety (HADS-a) and 7 questions assessing depression (HADS-d). It is designed for screening of anxiety disorders and depression in non-psychiatric patients. A score of 8 or higher indicates clinical significance of emotional distress[24]. Disease-related psychological susceptibility was measured by using IES which measures the amount of distress that the subjects associate with a specific event, in this case, DM, for the past 14 days.

The questionnaire consists of 22 questions with five(0-4) levels of ratings for four factors: seven-items for intrusiveness, eight-items for avoidance, two-items for sleep problem and five-items for hyperarousal. The CD-RISC measures the amount of resilience which is defined as the individual's ability of coping with stress[20]. The questionnaire consists of 25 statements including 5 factors such as self-efficacy, self-confidence, optimism, self-control and Spirituality/autonomy. The Korean versions of these questionnaires are valid in medical practice[23-25]. Internal consistency was assessed by calculating Cronbach alpha values and the results were found to be satisfactory(HADS-anxiety: 0.89, HADS-depression: 0.86, IES:0.93 CD-RISC:0.93)[23-25].

3. Genetic analysis

Blood samples were collected in EDTA tube and stored at -20℃ until the experiment. Genomic DNA (gDNA) was extracted from the samples using QIAamp DNA Blood Midi Kit (Qiagen, #51185, Valencia, CA, USA) according to manufacturer's description. Amplification of gDNA was carried out using TopTaq™ DNA Polymerase (Qiagen, #200205, Valencia, CA, USA); the amplification conditions were an initial denaturation at 94 ℃ for 5 min, followed by 35 cycles consisting of denaturing at 94℃ for 30 sec, annealing at 60.5℃ for 30 sec, and extension at 72 ℃ for 30 sec, and post-elongation at 72℃ for 10 min. PCR primers were designed with the

following sequences of hBDNF primer: forward 5′-AAACATCCGAGGACAAGGTG-3′ and inverse 5′-CCTCATGGACATGTTTGCAG -3′. PCR products were genotyped by using an automated ABI Prism 3730 Genetic Analyzer (Applied Biosystems, CA, USA), and were scored using GeneScan Ver. 3.1(Applied Biosystems, CA, USA). Met/Val BDNF genotype was determined with Reference SNP ID: rs6265. The genotype distribution of the polymorphism was not significantly deviated from Hardy–Weinberg equilibrium ($\chi^2(1)=0.51$, $p=0.47$).

4. Statistical analyses:

Statistical analyses were performed by 19.0 version of SPSS for Windows. Results expressed as means, standard deviation and proportions were calculated for all study variables. Independent samples t-test and chi-square test were used to assess the differences between groups. Pearson's correlation analysis was used to confirm the relationship between two continuous variables. Logistic regression analysis is used for prediction of significant depressive and anxiety symptom.

III. RESULTS

The characteristics of the subjects are shown in Table 1. Sixty-two subjects were found to be Met-carriers. No significant differences were found between Val/Val homozygote group and Met-allele carrier group regarding age, sex,

BMI, lipid profiles and clinical factors related to glycemic control such as FPG level, HbA1c level and HOMA-IR. The mean HADS-a score of the subjects was 5.29 ± 3.12. HADS-a score in Met-carrier was significantly higher than Val/Val homozygote group (Met carrier 5.76 ± 3.24; Val/Val homozygote 4.22± 2.59, *p=0.03*).The mean HADS-d score in the subjects was 6.13± 3.31. HADS-d score in Met-carrier was significantly higher than Val/Val homozygote group (Met carrier 6.73 ± 3.44; Val/Val homozygote 4.78 ± 2.59, *p=0.01*). Score of Met-carrier group was significantly higher than which in Val/Val homozygote group in all IES factors- hyperarousal, avoidance, intrusion, sleep problem (Met-carrier vs. Val/Val homozygote; *hyperarousal*, 12.95± 10.12 vs. 6.51± 5.97, *p<0.01*; *avoidance*, 12.66± 7.59 vs. 7.07± 4.64, *p<0.01*; *intrusion*, 6.67± 5.60 vs. 4.03± 3.79, *p=0.012*; *sleep problem*, 6.32± 4.86 vs. 2.96± 3.50, *p<0.01*). But there was no significant difference between the groups in five factors representing resilience- self-efficacy, self-confidence, optimism, self-control, spirituality/autonomy (Met-carrier vs. Val/Val homozygote; *self-efficacy* 23.79± 8.52 vs. 23.85± 6.18, p=0.97; *self-confidence*, 23.27± 5.54 vs. 23.18± 6.53, *p=0.94*; *optimism*, 15.83± 2.98 vs. 15.88± 4.14, *p=0.95*; *self-control*, 9.16± 2.23 vs. 9.37± 2.43, *p=0.69*; *spirituality/autonomy*, 5.46± 1.81 vs. 5.03± 2.36, *p=0.35*).

Table 1. Clinical characteristics of the newly diagnosed type 2 diabetic patients.

	Met-carriers	Val/Val homozygotes	p-value
N	62	27	
Age(mean± S.D.)	49.47±10.51	48.52±10.98	0.7
Sex(M:F)			
FPG(mg/dL)	163.27±49.91	174.68±65.72	0.38
HbA1c(%)	8.56±1.96	8.66±2.31	0.83
BMI	25.90±3.98	25.07±2.39	0.42
C-Pep(ng/mL)	2.16±0.86	2.50±1.30	0.17
Ins(mcIU/mL)	8.81±6.56	10.56±5.72	0.32
HOMA-IR	3.43±2.69	4.47±2.58	0.17
TC(mg/dL)	187.18±43.42	192.56±41.59	0.59
TG (mg/dL)	145.25±77.25	136.41±55.68	0.62
HDL-C(mg/dL)	44.57±9.33	41.0±10.11	0.12
LDL-C(mg/dL)	112.78±37.18	115.68±38.61	0.74
HADS-a	5.76±3.24	4.22±2.59	0.03
HADS-d	6.73±3.44	4.78 ±2.59	0.01
Self-efficacy	23.79±8.52	23.85±6.18	0.97
Self-confidence	23.27±5.54	23.18±6.53	0.94
Optimism	15.83±2.98	15.88±4.14	0.95
Self-control	9.16±2.23	9.37±2.43	0.69
Spirituality/autonomy	5.46±1.81	5.03±2.36	0.35
Hyperarousal	12.95±10.12	6.51±5.97	<0.01
Avoidance	12.66±7.59	7.07±4.64	<0.01
Intrusion	6.67±5.60	4.03±3.79	0.012
Sleep problem	6.32±4.86	2.96±3.50	<0.01

S.D., standard deviation; 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, Triglyceride; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; 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;

Pearson's correlation analyses were performed to confirm the association among glucose status at the moment of DM diagnosis, psychological impact caused by diagnosis of DM, psychological resilience, depression, and anxiety (Table 2). While there was no significant correlation among HADS-a and HbA1c (r=-0.196, *p=0.069*), self-confidence (r=-0.236, *p=0.026*), self-control (r=-0.253, *p=0.017*), hyperarousal (r=0.5, *p<0.001*), avoidance (r=0.323, *p=0.002*), intrusion (r=0.337, *p=0.001*), and sleep problem (r=0.476, *p<0.001*) appeared to be significantly correlated with HADS-a.

HADS-d appeared to be significantly associated with HbA1c (r=-0.227, *p=0.035*), self-efficacy (r=-0.389, *p<0.001*), self-confidence (r=-0.462, *p<0.001*), optimism (r=-0.448, *p<0.001*), self-control (r=-0.46, *p<0.001*), hyperarousal (r=0.363, *p<0.001*), avoidance (r=0.219, *p=0.039*), intrusion (r=0.257, *p=0.015*), and sleep problem (r=0.419, *p<0.001*).

Table 2. Correlations between HADS and glucose status, CD-RISC and IES

	HADS-a		HADS-d	
	r	*p*	r	*p*
FPG	0.038	0.727	0.21	0.848
HbA1c	-0.196	0.69	-0.227*	0.035
Self-efficacy	-0.157	0.143	-0.389**	<0.001
Self-confidence	-0.236*	0.026	-0.462**	<0.001
Optimism	-0.19	0.075	-0.448**	<0.001
Self-control	-0.253*	0.017	-0.46**	<0.001
Spirituality/autonomy	0.002	0.983	-0.184	0.084
Hyperarousal	0.5**	<0.001	0.363**	<0.001
Avoidance	0.323**	0.002	0.219*	0.039
Intrusion	0.337**	0.001	0.257*	0.015
Sleep problem	0.476**	<0.001	0.419**	<0.001

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; 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*

The subjects were further divided by the presence of clinically significant anxiety or depression symptom according to HADS scores. Among the 89 patients, 23.6% were classified as HADS-anxiety (HADS-a); and 36% were classified as HADS-depression (HADS-d). Among these sub-divisions, logistic regression analyses were performed in order to figure out interaction between anxiety and depression with sex, age, HbA1c, BDNF polymorphism, HOMA-IR, five factors of resilience, and four factors of psychological susceptibility.

As a result, only hyperarousal ($p=0.024$) appeared to be associated with anxiety symptoms (Table 3); and HbA1c ($p=0.031$) and BDNF polymorphism ($p=0.044$) appeared to be associated with depressive symptoms (Table 4).

Table 3. Logistic regression model odds ratios for prediction of anxiety symptoms

	ß	Odds ratio	95% confidence interval	p
Sex	1.057	2.879	0.582-14.253	0.195
Age	0.063	1.065	0.990-1.145	0.091
HbA1c	-0.384	0.681	0.446-1.040	0.075
BDNF	-0.559	0.572	0.119-2.753	0.486
HOMA-IR	-0.005	0.995	0.751-1.318	0.973
Self-efficacy	-0.066	0.937	0.759-1.155	0.54
Self-confidence	0.1	1.105	0.860-1.421	0.435
Optimism	-0.066	0.936	0.610-1.437	0.763
Self-control	0.039	1.04	0.655-1.651	0.868
Spirituality/autonomy	-0.117	0.89	0.628-1.260	0.511
Hyperarousal*	0.326	1.386	1.044-1.841	0.024
Avoidance	-0.165	0.848	0.699-1.028	0.093
Intrusion	-0.134	0.875	0.716-1.069	0.191
Sleep problem	-0.05	0.951	0.698-1.296	0.752

Logistic regression model adjusted for sex, age, HbA1C, BDNF polymorphism by Met carrier vs. Val/Val homozygote, HOMA-IR, self-efficacy, self-confidence, optimism, self-control, Spirituality/autonomy, hyperarousal, avoidance, intrusion and sleep problem. HbA1c, hemoglobin A1c; BDNF, brain-derived neurotrophic factor; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance. *$p<0.05$

Table 4. Logistic regression model odds ratios for prediction of depressive symptoms

	ß	Odds ratio	95% confidence interval	*p*
Sex	1.05	2.858	0.668-12.219	0.157
Age	0.066	1.068	0.988-1.155	0.098
HbA1c*	-0.394	0.674	0.471-0.965	0.031
BDNF*	1.689	5.413	1.043-28.106	0.044
HOMA-IR	-0.032	0.968	0.759-1.235	0.794
Self-efficacy	-0.103	0.902	0.758-1.072	0.241
Self-confidence	0.119	1.126	0.913-1.390	0.268
Optimism	-0.183	0.833	0.585-1.184	0.308
Self-control	-0.169	0.845	0.557-1.282	0.428
Spirituality/autonomy	-0.243	0.784	0.540-1.139	0.201
Hyperarousal	0.071	1.074	0.861-1.339	0.529
Avoidance	-0.104	0.091	0.748-1.086	0.275
Intrusion	0.072	1.074	0.891-1.295	0.452
Sleep problem	0.145	1.156	0.867-1.542	0.323

Logistic regression model adjusted for sex, age, HbA1C, BDNF polymorphism by Met carrier vs. Val/Val homozygote, HOMA-IR, self-efficacy, self-confidence, optimism, self-control, Spirituality/autonomy, hyperarousal, avoidance, intrusion and sleep problem. HbA1c, hemoglobin A1c; BDNF, brain-derived neurotrophic factor; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance. *$p<0.05$

IV. DISCUSSION

This study showed that depressive symptom is related to presence of the SNP at nucleotide 196 of BDNF. The subjects with the substitution of valine with methionine (Val/66/Met) showed significantly higher scores for depressive symptoms, not anxiety symptoms, compared to those carrying Val/66/Val. This result does not support the role of the Met-allele as a protecting factor for developing various psychiatric diseases, although the results are not consistent. Some studies reported that Met-allele had a protective role against psychiatric disorders such as depression[15,26-28]. Other studies indicated that the Met-carriers represented higher risk for anxiety and depression[29,30]. The same result was reported in studies with Korean populations[31,32], that the existence of Met-allele in diabetic patients seems to be a risk factor of depressive symptom.

In this study, the relationships among HADS, IES, CD-RISC and glucose status were examined in the sub-divisions of Met-carrier T2DM group and Val/Val homozygote T2DM group. Met-carrier group showed significantly higher scores in HADS-a, HADS-d, and four factors of susceptibility such as hyperarousal, avoidance, intrusion and sleep problem than in Val/Val homozygote group. It means that Met-carrier group tends to be more anxious and depressive than Val/Val homozygote group. This can be interpreted that, in clinical practice, Met-carrier group tends to be more arousal with the diagnosis of DM (hyperarousal), deny the situation of being diagnosed with

DM (avoidance), repetitively and ruminatively think about DM (intrusion), and struggle with the situation (sleep problem). However, there was no significant difference between the two groups in five factors representing resilience; this indicates that the ability of coping with the stress does not differ. Conclusively, this study suggests that BDNF polymorphism is associated with emotional distress and psychological susceptibility, but not with resilience in T2DM patients.

Krabbe et al. reported that serum BDNF level had been reported to have a positive effect on DM[17,18]. According to studies on the relationship between serum BDNF level and BDNF polymorphism, it was reported that Met-carrier showed lower serum BDNF concentration than Val/Val group[33]. However, the others didn't show correlation between serum BDNF level and polymorphism in BDNF[17,34]. In this study, we could not confirm relationship between serum BDNF level and glucose control due to the lack of serum BDNF levels of the subjects. However, according to the glucose status and polymorphism in BDNF, it was observed that glucose control was not affected by the polymorphism in BDNF.

In this study, HADS was used to examine depressive and anxiety symptoms for patients with newly diagnosed T2DM. HADS, the questionnaire assessing emotional symptoms while excluding patients' somatic symptom, has been used among DM patients in the previous studies[1,4]. In this study, 32 subjects (36%) appeared to have the score higher than 8 scores in HADS-d, and these

subjects were classified as those who have significant depressive symptoms; and 9 subjects (10%) appeared to have the score higher than 11 scores in HADS-d, and these subjects were classified as those who have severe depressive symptoms. This observation is consistent with previous studies demonstrated higher rate of depressive symptoms in diabetic patients than that in general population[1,35]. In particular, this study showed that prevalence of depressive symptoms is higher even in newly diagnosed diabetic patients. Hoorn et al.[36] reported that females at pre-diabetic status as well as diabetic patients suffered from higher depressive symptoms than general population. They suggested that prevalence of depressive symptoms might be high even in early stage of DM as well as pre-diabetic status. However, in this study, 72% of the subjects were male; therefore a gender bias cannot be ignored. In general, depression is more prevalent in female than in male. In this aspect, the presence of depressive symptoms in newly diagnosed diabetic patients is expected to be higher in general population than the observation of the current study.

Pearson's correlation analysis showed the relationship among psychological susceptibility, resilience, and depression. Significant negative correlations between depressive symptoms and resilience scores and significant positive correlations between depressive symptoms and susceptibility were reported in this study. This can be interpreted that people who have low ability of coping with stress and are sensitive to being diagnosed as DM are subject to suffer

from depressive symptoms.

Furtermore, we sub-divided participants by presence of clinically significant depressive symptoms by HADS-d score and examined the interaction between depression and some clinical and psychological factors. A logistic model adjusted for sex, age, HbA1c, BDNF polymorphism (Met-carrier vs. Val/Val homozygote), HOMA-IR, five resilience factors, and four susceptibility factors showed a significant correlation between depressive symptom and low HbA1c as well as BDNF Met-carrier.

There were inconsistent reports on the relationship between the measures of glycemic control and depression. Some reported depressive symptom could deteriorate glycemic control[4], while others insisted no correlation between depressive symptom and glycemic control[37,38]. However, the mean durations of DM in those studies were from five to ten years. In this study, we examined whether there were differences between patients with or without depressive symptom at the period of diagnosis of DM, and, interestingly, it was shown that HbA1c levels were lower in the subjects with depressive symptoms. Considering that HbA1c represents the average values of glucose in recent 2-3 months, we may expect the better glucose control for last 2-3 months in patient with depressive symptom than in the group of patients without depressive symptom. It is well known that patients with more depressive symptoms tend to be concerned about their health and visit hospital more frequently with mild illness than those without depressive symptoms[39]. The

explanation of lower HbA1c level in the subjects with depressive symptom may be that people with depressive symptom react more sensitively to changes in symptoms as their blood glucose level increase, and therefore they visit the hospital with less hesitation. In other words, the amount of time taken from actually being affected by diabetes to being diagnosed is relatively short in patients with depressive symptom.

There is an consensus that the prevalence of anxiety symptom is higher in DM patients than that in general population[40,41]. This study showed the consistent result- twenty one subjects (23.6%) were to have significant anxiety symptom, and seven patients (7.8%) were to have severe symptom. Pearson's correlation analysis showed the significant relationship among psychological susceptibility, resilience and anxiety. From this result, it is suggested that people with low self-control, self-confidence, and high tendency of being shocked by DM are related to anxiety symptom. A logistic model adjusted by sex, age, HbA1c, BDNF polymorphism(Met-carrier vs. Val/Val homozygote), HOMA-IR, five resilience factors, and four susceptibility factors showed a significant correlation between anxiety symptom and the hyperarousal upon the diagnosis with DM. However, there was no interaction between BDNF polymorphism and anxiety symptom.

There are some limitations in this study. First, the sample size was relatively small. But the genetic distribution of the sample in this study was not significantly deviated from HWE. Second, this study did not include a control

group; therefore, it was not fully evaluated whether diabetic patients were more liable to have mood disorders than the healthy people. Third, the subjects were not fully evaluated for psychiatric illness by structured psychological tests or interviews so we could not confirm any relationship with psychiatric diagnosis. However we reviewed the patients' medical documents and excluded two patients who had a history of psychiatric disorders and who were currently taking anti-psychiatric medications.

In spite of these limitations, this present study is the first to evaluate the relationship between the BDNF polymorphism and mood disorder in newly diagnosed Korean type 2 diabetic patients, and a larger study is necessary for ensuring these preliminary findings in the following years.

V. CONCLUSION

First of all, this present study showed that prevalence of anxiety symptom and depressive symptom in type 2 diabetic patients was higher than that in general population. Additionally, it confirmed that emotional symptoms are associated with psychological characteristics that include resilience and susceptibility to stressful life event. Furthermore, we could find out that BDNF polymorphism had relationship with depressive symptom and susceptibility, while having no relationship with resilience.

It is usually thought that glucose control is impaired in people with depressive symptom, but this study showed that more depression one becomes,

the better glycated hemoglobin level is in the period when patients were diagnosed with diabetes for the first time. These results suggest that the correlation between depressive symptom and HbA1c at the early stage of diabetes could be different from that at the latter stage.

Of people suffering from depression among diabetic patients, only half of them diagnosed with depression, and only half of clinically depressed diabetic patients are being treated[42]. Thereby, in the treatment of patients with diabetes, biopsychosocial approach to evaluate depression as well as glycemic control may be valuable for the better treatment routine. In addition, early diagnosis and active treatment of depression would be needed to improve patients' quality of lives by mutual cooperation of internal medicine and psychiatry.

In conclusion, BDNF Val66Met polymorphism is associated with the depressive symptom in newly diagnosed type 2 diabetic patients.

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ABSTRACT(IN KOREAN)

2형 당뇨병을 처음 진단받은 환자에서 BDNF 유전자 다형성과 우울증상과의 관련성

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서론

당뇨병환자에서 우울증의 유병률은 일반인구에 비해 두 배 정도 높다고 알려져 있다. BDNF(brain-derived neurotrophic factor)는 신경영양 인자 중 하나이며 신경발생과 신경 보호에 중요한 역할을 한다.이전의 연구에서는 BDNF가 정신증상에서의 역할뿐 아니라 항당뇨병의 기능도 있다는 것을 밝히고 있으며, 특히 BDNF 유전자 다형성이 정신질환의 발병에 기여한다는 것이 알려져있다. 그러나 BDNF 유전자 다형성이 당뇨병에 미치는 영향에 대해서는 알려진 바가 많지 않다. 이 논문에서는 당뇨병을 처음 진단받은 환자에서,

BDNFVal66Met의 유전자 다형성과 혈당 수준 및 당뇨 진단으로 인한 심리적 감수성과 유연성이 우울과 불안 등의 정서증상에 어떠한 영향을 미치는지 알아보았다.

방법

2010년부터 2011년까지 강남 세브란스 병원에 내원해 2형 당뇨병을 처음 진단받은 20세 이상의 환자 89명을 대상으로 하여, 공복혈당 및 당화혈색소를 비롯한 생화학적 척도를 확인하였다. 우울증상과, 불안증상은 병원 불안 우울 척도(HADS)를 이용해서 설문 조사 하였으며, 사건 충격 척도(IES)를 과다각성, 침습, 회피, 수면문제의 네 가지 요소로 분석해 당뇨병 진단으로 인한 심리적 감수성 정도를 측정하였고, 심리적 유연성을(CD-RISC) 자기효능감, 자신감, 낙관성, 자기통제성, 영성/자율성의 다섯가지 요소로 분석해 환자의 스트레스에 견디는 능력을 측정하였다.

결과

전체 89명중 62명이 Met-carrier로 나타났다. Val/Val 동형접합체그룹과 Met-carrier 그룹간에 연령, 성별, 신체 비만 지수 및 혈당 조절 및 혈중 지질에 관련된 요인들의 차이는 발견되지 않았다. Val/Val 동형접합체그룹에 비해 Met carrier 그룹에서 불안(P=0.03)과 우울증(P=0.01) 척도가 더 높았으며, 사건 충격 척도인 과다각성(P<0.01), 침습(P<0.01), 회피(P=0.012), 수면문제(P<0.01)점수 역

시 높은 것이 확인되었다.

당뇨병 진단 당시의 당화혈색소와 우울증상 사이에서는 유의미한 역의 상관관계를 보였으나(피어슨 상관계수 R=-0.227, P=0.035), 불안증상과 당화혈색소 사이의 연관성은 유의하지 않았다 (R=-0.196, P=0.069). 심리적 유연성 및 사건 충격 척도의 네 가지 요소와 우울증상 사이에서는 유의한 상관관계가 관찰되었다.(자기효능감 R=-0.389, p<0.001; 자신감 R=-0.462, p<0.001; 낙관성 R=-0.448, p<0.001; 자기통제성 R=-0.46, p<0.001; 과다각성 R=0.363, p<0.001; 회피 R=0.219, p=0.039; 침습 R=0.257, p=0.015; 수면문제 R=0.419, p<0.001). 또한 유연성 및 사건 충격 척도와 불안 증상 사이에서도 유의한 상관관계가 관찰되었다(자신감 R=-0.236, p=0.026; 자기통제성 R=-0.253, p=0.017; 과다각성 R=0.5, p<0.001; 회피R=0.323, p=0.002; 침습 R=0.337, p=0.001; 수면문제 R=0.476, p<0.001). 로지스틱 회귀 분석결과, 우울증상은 BDNF Met-carrier 와 통계적으로 의미 있는 상관관계를 가졌으며 (OR=5.413), 당화혈색소와는 역의 상관관계를 가지는 것으로 (OR=0.671) 나타났고, 불안증상에서는 과다각성만이 영향을 미치는 변수로 확인되었다(OR=1.386).

결론

2형 당뇨병을 처음 진단받은 환자에서 우울증상은 Met-allele의

존재여부와 낮은 당화혈색소 수치와 연관성을 보였고, 불안 증상과는 과다각성만이 연관성을 보였다.

핵심되는 말: 유전자 다형성, BDNF(brain-derived neurotrophic factor), 당뇨병, 우울증, 불안증, 탄력성, 사건 충격 척도