Association between Glycemic Control in Patients with Diabetes and Mental Health Variables Including Depression

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Background: The purpose of this study was to measure several mental health variables according to HbA1c level and examine their relationship among diabetic patients.

Methods: Total 89 outpatients who attended diabetes education program at St. Vincent's Hospital, The Catholic University of Korea College of Medicine, were enrolled in this study. The Beck Depression Inventory (BDI), State-Trait Anxiety Inventory, Stress Response Inventory (SRI), abbreviated version of World Health Organization Quality of Life assessment instrument (WHOQOL-BREF), Insomnia Severity Index, and Epworth Sleepiness Scale (ESS) were administered to all patients. Significant differences between groups were assessed by t-test and chi-squared test. Pearson correlation and multiple linear regression analyses were used to identify the variables that affect HbA1c levels.

Results: The well-controlled group had a significantly lower BDI score than the poorly controlled group. The well-controlled group also showed significantly lower SRI and ESS. HbA1c, BDI, SRI, and ESS were positively correlated. Duration and BDI were the only variables affecting HbA1c levels.

Conclusion: Emphasis should be given to the identification and management of mental health problems, including especially depressive symptoms in patients with diabetes.

Keywords Diabetes mellitus, Depression, Emotional stress, Anxiety

INTRODUCTION

Diabetes mellitus is one of the life-threatening diseases of the 21st century. The prevalence of diabetes worldwide is one in 11 adults [1]. Many diabetic patients may experience depressive and anxiety symptoms due to stress owing to the occurrence of diabetes, lifestyle changes to normalize blood sugar, use of drugs or insulin injections and diabetes-related complications [2].

The prevalence of depression among diabetic patients is known to be about twice as high as that of general population, reaching about 28.5% [3]. The prevalence of

anxiety disorders increased in patients diagnosed with diabetes. Moreover, about 40% of diabetic patients present with clinically significant anxiety symptoms [4]. The depression and anxiety in diabetic patients may worsen the prognosis of diabetes by making the patients neglect selfcare, reducing treatment compliance [5] and quality of life [6], and increasing their mortality [7].

There have been studies on the correlation between diabetes and depression, but no common genetic factors have been found to affect the occurrence of both diseases [8,9]. It was suggested that diabetes and depression have a bidirectional relationship and share common risk

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factors [10,11]. In particular, the need for in-depth study of the common risk factors that can affect the development of type 2 diabetes and depression such as the low socioeconomic status [12,13], poor sleep quality [14,15], decreased physical activity [16,17] and chronic stress [18] has been emphasized. Partial remission of depressive symptom has been reported after improvement of high blood sugar levels in diabetic patients [19].

Although glycemic control and depression are expected to be correlated with each other, previous studies have shown contradictory results regarding the association between depression and glycemic control [20,21]. It is also reported that diabetic patients have a higher prevalence of depression than the general population. However, fewer number of diabetic patients have been diagnosed with depression and have started treatment compared to the general population [22]. Therefore, it is thought that identification and evaluation of the psychopathology associated with HbA1c will have a major influence on mental health as well as glycemic control of diabetic patients. The aim of this study was to confirm the association between HbA1c and various psychopathologies including depression.

MATERIALS AND METHODS

1. Study population

This study is conducted based on face-to-face medical examinations and surveys of patients who participated in diabetes classes from July 2012 to January 2014 at St. Vincent's Hospital, The Catholic University of Korea. Patients with organic mental disorders, epilepsy, eating disorders, alcohol and other substance-related disorders, obsessive compulsive disorder and other severe acute physical illnesses were excluded. Eighty-nine subjects who were willing to participate in this study with written consent and did not meet the exclusion criteria were enrolled (n=89).

This study was approved by the Institutional Review Board (IRB No. VC12QISI0154) for Human Research of the St. Vincent's Hospital, The Catholic University of Korea.

2. Evaluation

All subjects were surveyed for age, sex, marital status,

education, occupation, duration of diabetes, economic status and family history of diabetes with face-to-face medical examination and questionnaires. Education was classified as lower school graduate, middle school graduate, high school graduate, university graduate and postgraduate school graduate. Economic status was divided into upper, middle and lower class. Alcohol consumption status, smoking status, body mass index, current treatment status for diabetes, treatment method, and history of hospitalization due to diabetes were also investigated. Also, the presence of diabetic retinopathy and hypertension was assessed for complication status of diabetes. All subjects underwent basic blood tests and urine tests including fasting blood sugar, postprandial blood sugar, HbA1c, and total cholesterol level. Subjects with HbA1c level of less than 7% were classified as well-controlled group and subjects with HbA1c level of 7% or higher were classified as poorly controlled group according to the target HbA1c level of 7% recommended by the American Diabetes Association.

Depression in diabetics was assessed with Beck Depression Inventory (BDI). Anxiety was assessed with State-Trait Anxiety Inventory, and stress was assessed with Stress Response Inventory (SRI). The quality of life of the patients was assessed with an abbreviated version of World Health Organization Quality of Life assessment instrument (WHOQOL-BREF) published by the World Health Organization. The WHOQOL-BREF consists of 26 items: overall QOL and general health, each with 4 subdomains of physical health, psychological health, social relationships and environment. Twenty-six items were assessed in five scales, scoring from 1 (not at all) to 5 (completely), where higher score indicates a more positive response to quality of life.

The Korean version of the Insomnia Severity Index (ISI-K) [23] was used to evaluate sleeping disorder. A questionnaire about snoring and uncomfortable leg sensation was added for a detailed assessment of insomnia symptoms. The four following questionnaire items were assessed in 5 scales, scoring 0 (not at all) to 4 (very much) for snoring: 1. Presence of snoring, 2. Snoring bothers other people, 3. Witnessed apnea during sleep, 4. Feeling drowsy, fatigued, or not up to par during wake time. The higher the sum of the scores was, the more severe the snoring was considered. The subjects were also evaluated for disturbance of sleep by uncomfortable leg sensation before entering sleep in 5 scales, scoring from 0 (not at all) to 4 (very much). The severity of daytime

sleepiness symptoms was assessed using the Epworth Sleepiness Scale (ESS).

3. Statistical analysis

Collected data was analyzed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). Any value of $p < 0.05$ was considered statistically significant. The subjects were divided into well-controlled group ($HbA1c < 7\%$) and poorly controlled group ($HbA1c \geq 7\%$) according to their HbA1c level. t-test and chi-square test were used to compare the mental health variables such as demographic characteristics, clinical variables related to diabetes treatment, depression, anxiety, stress, quality of life, and sleep disorder between the two groups. Pearson's correlation coefficient was used to analyze the correlation between the HbA1c level and mental health variables. Also, multiple linear regression analysis was used to identify the variables that affect the HbA1c.

RESULTS

1. Demographic and clinical characteristics

A total of 89 subjects were enrolled. Forty-three subjects were categorized as well-controlled group and the other 46 as poorly controlled group. The HbA1c level was 6.22 ± 0.41 in the well-controlled group and 8.80 ± 1.96 in the poorly controlled group. The difference between the two groups was significant ($p < 0.001$). The duration of disease was 4.88 ± 10.12 months in the well-controlled group and 41.41 ± 66.95 months in the poorly controlled group. The difference between the two groups was significant ($p = 0.010$). In addition, there was no significant difference between the two groups in terms of age, sex, education, occupation, marital status, economic status, family history of diabetes, alcohol consumption and smoking status (Table 1).

As for the treatment of diabetes in the well-controlled group, 24 patients (55.8%) were being untreated. Fourteen patients (32.6%) were being treated with oral hypoglycemic agents, 3 patients (7.0%) with insulin injections, and 2 patients (4.7%) with both oral hypoglycemic agents and insulin injections. In the poorly controlled group, 9 patients (19.6%) were being untreated. Nine patients (19.6%) were being treated with oral hypoglycemic

mic agents, 19 patients (41.3%) with insulin injections, and 9 patients (19.6%) were being treated with both oral hypoglycemic agents and insulin injections. The difference between the two groups was significant ($p = 0.002$). Regarding the patients with hospitalization experience

Table 1. Demographic characteristics of study participants (n=89)

Variable	Well controlled group (n=43)	Poorly controlled group (n=46)	p-value
HbA1c	6.22 ± 0.41	8.80 ± 1.96	$< 0.001^*$
Age (y)	53.09 ± 9.78	51.80 ± 10.42	0.550
Duration (mo)	4.88 ± 10.12	41.41 ± 66.95	0.001^*
Sex			
Male	17 (39.5)	21 (45.7)	0.560
Female	26 (60.5)	25 (54.3)	
BMI	25.80 ± 4.28	24.37 ± 3.57	0.091
Education (y)			
Elementary	4 (9.3)	0 (0.0)	0.162
Middle School	5 (11.6)	7 (15.2)	
High school	25 (58.1)	24 (52.2)	
College	9 (20.9)	14 (30.4)	
Graduate school	0 (0.0)	1 (2.2)	
Occupation			
Yes	21 (48.8)	21 (45.7)	0.764
No	22 (21.2)	25 (54.3)	
Marital status			
Single	0 (0.0)	3 (6.5)	0.242
Married	42 (97.7)	41 (89.1)	
Separate/divorced	1 (2.3)	1 (2.2)	
Bereaved	0 (0.0)	1 (2.2)	
SES			
High	1 (2.3)	1 (2.2)	0.897
Middle	32 (74.4)	36 (78.3)	
Low	10 (23.3)	9 (19.6)	
DM family history			
Yes	22 (51.2)	18 (39.1)	0.254
No	21 (48.8)	28 (67.4)	
Alcohol			
Yes	14 (32.6)	15 (32.6)	0.996
No	29 (67.4)	31 (67.4)	
Smoking			
Yes	4 (9.3)	11 (23.9)	0.066
No	39 (90.7)	35 (76.1)	

Values are presented as mean $\pm$ standard deviation or number (%).

BMI, body mass index; SES, socioeconomic status; DM, diabetes mellitus.

* $p < 0.05$ by independent t-test or chi-square test.

for diabetes, 19 subjects (41.3%) of the poorly controlled group were significantly larger in number compared to 5 subjects (11.6%) of the well-controlled group ($p=0.002$). Fasting blood glucose (134.84 ± 49.72 vs. 176.11 ± 63.22 , $p=0.001$) and 2-hour postprandial blood glucose (223.02 ± 92.47 vs. 306.28 ± 102.55 , $p<0.001$) were significantly higher in the poorly controlled group (Table 2).

2. Mental health variables regarding HbA1c level

The characteristics of mental health variables regarding the HbA1c level are shown in Table 3. The BDI and SRI of the poorly controlled group were significantly higher compared to those of well-controlled group with a p -value of 0.031 and 0.030, respectively. The ESS of the well-controlled group was significantly higher than that of poorly controlled group ($p=0.036$).

3. Correlation between HbA1c level and mental health variables

A correlation analysis was performed between HbA1c and mental health variables (Table 4). It was confirmed that BDI ($\gamma=0.265$, $p=0.012$), SRI ($\gamma=0.214$, $p=0.044$), ESS ($\gamma=0.340$, $p=0.001$) had a significant positive correlation with HbA1c.

The correlation analysis between HbA1c and physical health of WHOQOL-BREF showed a significant negative correlation with a correlation coefficient γ value of -0.229 and a p -value of 0.031. There also was a significant positive correlation between HbA1c and uncomfortable leg sensation ($\gamma=0.223$, $p=0.036$).

4. Association between HbA1c level and mental health variables

Multiple linear regression analysis was performed to identify the correlation between HbA1c and five variables that may affect glycemic control including BMI,

Table 2. Clinical characteristics of study participants (n=89)

Variable	Well controlled group (n=43)	Poorly controlled group (n=46)	p-value
Treatment			
OHA	2 (4.7)	9 (19.6)	0.002*
Insulin	14 (32.6)	19 (41.3)	
OHA+insulin	3 (7.0)	9 (19.6)	
None	24 (55.8)	9 (19.6)	
DM related Admission history	5 (11.6)	19 (41.3)	0.002*
Complication			
Diabetic retinopathy	6 (14.0)	9 (19.6)	0.480
Hypertension	18 (41.9)	12 (26.1)	0.116
FBS	134.84±49.72	176.11±63.22	0.001*
PP2	223.02±92.47	306.28±102.55	<0.001*
Total cholesterol (mg/dL)	190.05±43.41	172.41±45.51	0.065
Triglyceride (mg/dL)	132.95±85.30	125.72±79.91	0.680
HDL-cholesterol (mg/dL)	44.38±10.41	42.59±8.47	0.373
BUN	16.16±4.60	18.40±7.31	0.090
Serum creatinine	0.78±0.18	0.78±0.25	0.904
Proteinuria			
Positive	4 (9.3)	6 (13.0)	0.869
Negative	38 (88.4)	39 (84.8)	
False positive	1 (2.3)	1 (2.2)	

Values are presented as number (%) or mean±standard deviation.

OHA, oral hypoglycemic agent; DM, diabetes mellitus; FBS, fasting blood sugar; PP2, post prandial 2-hour blood sugar; HDL-cholesterol, high density lipoprotein cholesterol; BUN, blood urea nitrogen.

* $p<0.05$ by independent t-test or chi-square test.

Table 3. Comparison of mental health variables between well-controlled group and poorly controlled group

Variable	Well controlled group (n=43)	Poorly controlled group (n=46)	p-value
WHOQOL-BREF			
physical health domain	23.86±4.22	22.52±4.11	0.133
Psychological domain	18.33±3.56	17.02±3.51	0.086
Social relationships domain	9.81±1.87	9.37±1.79	0.255
Environment domain	24.37±4.15	23.96±4.11	0.636
BDI	10.79±8.83	15.22±10.15	0.031*
SA	42.00±5.92	42.15±6.40	0.908
TA	41.16±6.00	42.09±7.72	0.532
SRI	20.05±20.91	36.65±29.29	0.003*
ISI-K	5.86±6.23	8.00±5.77	0.096
Snoring	3.35±3.65	3.24±2.57	0.871
Uncomfortable leg sensation	0.40±0.66	0.70±1.49	0.218
ESS	6.07±2.69	7.78±4.67	0.036*

Values are presented as mean±standard deviation.

WHOQOL-BREF, abbreviated version of World Health Organization Quality of Life assessment instrument; BDI, Beck Depression Inventory; SA, state anxiety; TA, trait anxiety; SRI, stress response inventory; ISI-K, Korean version of the Insomnia Severity Index; ESS, Epworth Sleepiness Scale.

*p<0.05 by independent t-test.

Table 4. Correlation between HbA1c and several mental health variables

Variable	HbA1c	
	γ	p-value
WHOQOL-BREF		
Physical health domain	-0.229	0.031*
Psychological domain	-0.200	0.060
Social relationships domain	-0.105	0.330
Environment domain	-0.112	0.294
BDI	0.265	0.012*
SA	-0.001	0.992
TA	0.058	0.592
SRI	0.214	0.044*
ISI-K	0.106	0.321
Snoring	-0.127	0.234
Uncomfortable leg sensation	0.223	0.036*
ESS	0.340	0.001*

These data represent Pearson's correlation coefficients (γ).

WHOQOL-BREF, abbreviated version of World Health Organization Quality of Life assessment instrument; BDI, Beck Depression Inventory; SA, state anxiety; TA, trait anxiety; SRI, stress response inventory; ISI-K, Korean version of the Insomnia Severity Index; ESS, Epworth Sleepiness Scale.

*p<0.05 by Pearson's correlation test.

duration, BDI, state anxiety, and trait anxiety. In regression analysis, R^2 was 0.210 and F statistic was 4.411 ($p=0.001$), indicating that the regression model is appropriate. Duration ($\beta=0.350$, $T=3.474$, $p=0.001$) and BDI ($\beta=0.266$, $T=2.330$, $p=0.022$) were the only variables affecting the HbA1c (Table 5).

DISCUSSION

Our results showed that depression and stress response were significantly higher in the poorly controlled group with high HbA1c level. Also, the subject of the poorly controlled group had more severe symptoms of daytime sleepiness. The HbA1c level and the quality of life of the physical health domain of WHOQOL-BREF had a negative correlation. The HbA1c level had a positive correlation with depressive symptom, stress response, and daytime sleepiness. Also, disease duration and depression were the variables affecting the HbA1c.

Based on this study, HbA1c level of diabetic patients seems to be associated with depression. There are ongoing studies on the correlation between type 2 diabetes and depression. In many studies, the correlation between the two diseases has been suggested in the following three possible directions.

First, we can consider the common factors associated

Table 5. Association between HbA1c and duration, depressive and anxiety symptoms

Variable	B	HbA1c					
		β	T	p-value	F-value (p)	R	R ²
BMI	-0.046	-0.097	-0.978	0.331	4.411 (0.001*)	0.458	0.210
Duration	0.013	0.350	3.474	0.001*			
BDI	0.053	0.266	2.330	0.022*			
SA	0.026	0.084	0.733	0.465			
TA	-0.031	-0.111	-0.866	0.389			

BMI, body mass index; BDI, Beck Depression Inventory; SA, state anxiety; TA, trait anxiety.

*p<0.05 by multiple linear regression analysis.

with the development of diabetes and depression. Chronic stress activates the hypothalamic-pituitary-adrenal axis (HPA-axis) and stimulates the sympathetic nervous system. This increases the production of cortisol in the adrenal cortex and promotes the release of adrenaline and noradrenaline in the adrenal medulla [24]. The sustained release of these hormones and sympathetic hyperactivity can lead to insulin resistance in the body, which is a characteristic pathogenesis of type 2 diabetes [24]. In addition, chronic stress causes the immune response to increase the production of inflammatory cytokines. These inflammatory cytokines interact with pancreatic β -cells to induce insulin resistance, leading to development of type 2 diabetes [25]. Furthermore, stress can increase the secretion of cortisol in hypothalamus and pituitary gland by promoting synthesis of pre-inflammatory cytokines such as Interleukin-6, Tumor necrosis factor- α , and Interferon- γ from immune tissues and cells through inflammatory reactions [26,27], resulting in increased insulin resistance [28]. Therefore, chronic stress may activate common pathways that may promote type 2 diabetes and depression.

Second, depression itself may increase the risk of developing diabetes. Previous studies have shown significant increase in incidence of type 2 diabetes in depressed patients [29]. A meta-analysis conducted in 2006 reported that depressed adults had 37% increase in risk of developing type 2 diabetes [30]. One study demonstrated a significant improvement in insulin resistance after treatment of depression [31]. Another study showed that noradrenalinergic antidepressants lowered insulin sensitivity in normal controls [32]. In 2013, a meta-analysis published in Korea reported that the selective serotonin reuptake inhibitors and tricyclic antidepressants increased the risk of type 2 diabetes [33]. However, the pathophysiological mechanisms of how depression con-

tributes to the development of diabetes are still unclear. Therefore, further study on the effects of antidepressants on blood sugar control in patients with major depression is needed.

Third, diabetes may increase the chance of depression. A meta-analysis released in 2010 reported that the patients with type 2 diabetes had 24% increase in risk for developing depression compared to the general population [34]. However, an increased prevalence of depression was observed in pre-diabetic patients and undiagnosed diabetic patients compared to the controls with normal blood glucose levels in another study [35]. Thus, there may be other mechanisms by which diabetes increase risk of developing depression. There are many ongoing studies evaluating the association between depression of diabetic patient and biochemical changes of the brain caused by diabetes. A systematic review published in 2006 suggested that diabetes is associated with cerebral atrophy, lacunar infarction, and local changes in cerebral blood flow [36]. Also, in one study, the size of hippocampus was significantly smaller in the diabetics group compared to the control group of similar age, sex, and education level. The study reported that HbA1c has a negative correlation with the size of hippocampus [37]. These structural changes are similar to the neurodegenerative changes that cause hippocampal atrophy in depressed patients [38]. Thus, further study of the relationship between the two diseases is needed.

Type 1 diabetes is characterized by the destruction of pancreatic β -cells by autoimmune mechanisms resulting in deficiency of insulin. There are relatively few studies on the association between type 1 diabetes and depression. A brain magnetic resonance spectroscopy video study showed that glutamate is increased in the prefrontal lobe with the increase of blood glucose in patients with type 1 diabetes, which is positively correlated with

depressive symptoms in patients with type 1 diabetes [39]. Similar to type 2 diabetes, the autoimmune-related cytokines have been reported to not only activate the HPA-axis but also induce inflammatory responses found in depression of type 1 diabetics [40]. In this study, the severity of stress response and depressive symptom regarding the HbA1c level increased with difficulty in controlling blood glucose. This seems to be in agreement with previous studies.

In our study, there was no significant difference in severity of insomnia between the well-controlled group and poorly controlled group. In both groups, ISI-K score was less than 15.5, and they had no clinically significant insomnia [23]. These findings did not support previous studies showing that patients with type 1 and type 2 diabetes have a higher incidence of insomnia than the general population [41,42]. Also, snoring implemented for additional evaluation of sleep disorder and the subjective sleep deterioration due to the uncomfortable leg sensation was not significantly different between the two groups. However, the daytime sleepiness evaluated with ESS was more severe in the poorly controlled group compared to the well-controlled group. The severity of daytime sleepiness was found to be positively correlated with the HbA1c level. This study showed no significant difference in sleep-related symptoms, including insomnia, snoring and uncomfortable leg sensation between the two groups. The more severe daytime sleepiness in the poorly controlled group is thought to be caused by lethargy, fatigue, or hypersomnia that can be accompanied by depressed mood. The daytime sleepiness in poorly controlled group may be associated with fatigue that may occur in diabetic patients. Warren et al. [43] argued that 90% of diabetic patients experience the multiple physical or psychological symptoms with high blood sugar. They also reported that among these symptoms, fatigue is one of the most common symptoms. Some studies have reported that chronic high blood sugar conditions in diabetes can cause fatigue [44]. This is consistent with the results of our study that the higher the HbA1c, the lower the quality of life with regards to physical health. Daytime sleepiness may make it difficult for diabetic patients to perform selfcare, such as exercise or diet therapy [45]. This may cause difficulty in blood sugar management and increased incidence of complications, which requires careful management.

Our study has several limitations. First, it is limited to generalize our results to all diabetic patients because

the study is conducted of a small number of participants from a single institute. Second, because there is no normal control group, the prevalence of depression and anxiety is difficult to be compared with the actual control group represented by the general population. Third, there is limitation for elucidating the causality of temporal relationships between the changes in blood sugar levels and the mental health variables because this study is a cross-sectional study. Fourth, standardized evaluation tools were not used for assessment of uncomfortable leg sensation; also, objective evaluation such as polysomnography was not performed for sleep status assessment. Lastly, a self-reported subjective evaluation scale was used for assessment of depression and anxiety symptoms.

Nevertheless, this study identified the mental health variables related to glycemic control in diabetic patients. In other words, it was concluded that depression, as well as disease duration, can have a negative effect on glycemic control in diabetic patients. Therefore, evaluation and active treatment of depressive symptoms is important in treatment of diabetes.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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