Acta Med. Okayama, 2020
Vol. 74, No. 1, pp. 33-40

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Clinical Relevance of Blood Glucose and Gastroesophageal Reflux Symptoms to Depressive Status in Patients with Type 2 Diabetes Mellitus

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A relationship between diabetes and depression is apparent. To clarify the clinical relevance of diabetic patients' gastroesophageal symptoms to their psychological status, we retrospectively analyzed the data from a Self-rating Depression Scale (SDS) and a Frequency Scale for Symptoms of Gastroesophageal reflux disease (FSSG) among 143 type 2 diabetic patients who visited a general medicine department. Among the 45 Japanese patients enrolled, the group with relatively high SDS scores (≥36) showed higher (FSSG) dysmotility symptom scores versus the low-SDS (<36) group, although the 2 groups' characteristics and laboratory data were not significantly different. Positive correlations of postprandial plasma glucose (PPG) levels with FSSG scores ($R=0.321$, $p<0.05$), particularly with reflux scores ($R=0.455$, $p<0.01$) were revealed. PPG and HbA1c levels were not correlated with SDS scores. The patients' SDS scores were significantly correlated with their FSSG scores ($R=0.41$, $p<0.01$), suggesting that depressive status is linked to GERD-related manifestations. Considering that the patients' PPG levels were correlated with GERD-related symptoms, diabetic patients' blood glucose levels are associated with depressive status. Collectively, key symptoms related to GERD and glucose level values would be helpful for determining the psychological status of diabetic patients complaining of various uncertain symptoms.

Key words: blood glucose, type 2 diabetes mellitus, gastroesophageal reflux, depressive status, postprandial plasma glucose

It is well known that patients with type 2 diabetes are susceptible to various complications and have a poor health status, leading to substantially higher mortality compared to that of people without diabetes. A relatively close association between diabetes and depression is known [1,2], and the complication of depression is recognized to have deleterious consequences in patients with diabetes. In investigations of adult diabetic patients, approx. 40% of the patients had depressive symptoms [2,3], and another study showed that in diabetic patients, the presence of a comorbid disorder can further increase the incidence of depression [4].

Depressive symptoms are also related to the deterioration of diabetic symptoms including poor glycemic control, impaired physical functioning, and lowered quality of life [5,6]. The existence of clinical relationships between depression and diabetic complications (*e.g.*, neuropathy, nephropathy, and retinopathy) has

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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

also been reported [7]. Depression was reported to remain undetected in more than half of all patients with depression in primary care settings, and only about half of those with detected depression receive treatment [8]. Therefore, alternative strategies for detecting comorbid depression in patients with diabetes are important to prevent a progressive diabetic condition and subsequent complications.

The prevalence of gastroesophageal reflux disease (GERD) has been increasing worldwide [9]. GERD is associated with an impairment of the quality of life, esophageal carcinogenesis, and lifestyle-related diseases including metabolic disorders and obesity [10]. The Self-rating Depression Scale (SDS) is widely used for assessing the severity of depression [11, 12], and the Frequency Scale for Symptoms of Gastroesophageal reflux disease (FSSG) is commonly used to assess the symptoms of GERD [13]. We conducted the present study to clarify the potential relationships among physical conditions, laboratory data, and psychological states assessed by using the SDS scores and FSSG scores obtained by patients with type 2 diabetes who visited outpatient general medicine departments.

We analyzed the correlations of SDS and FSSG scores with biochemical markers in patients with type 2 diabetes, and our findings will help predict latent psychological conditions in diabetic patients who visit departments of general medicine with various unidentified complaints.

Patients and Methods

Patients. We retrospectively analyzed the epidemiologic records of 143 patients with type 2 diabetes who had visited the Department of General Medicine in Okayama University Hospital (45 patients) or Okayama City Hospital (98 patients) during the period from Sept. 1, 2016 to Aug. 31, 2018. Eighty patients including 24 patients at Okayama University Hospital (OUH) and 56 patients at Okayama City Hospital (OCH) who had been taking a proton-pump inhibitor (PPI) were excluded since the use of a PPI can affect the FSSG scores. Nine patients (3 at OUH and 6 at OCH) who had been taking an antidepressant were also excluded since antidepressants can affect the SDS score. Three patients at OUH who refused participation in this study were also excluded. Fifty-one patients (15 at OUH and 36 at OCH) were found to be eligible and were included in this study, and their SDS and FSSG scores were obtained twice with a 6-month interval.

After the exclusion of 6 patients with insufficient medical records, the data of a total of 45 Japanese patients with type 2 diabetes (13 patients at OUH and 32 patients at OCH) were included in this study (Fig. 1). Regarding the SDS scores obtained twice from each patient, we selected the higher of the two SDS scores plus the time points corresponding to these higher SDS scores for our further analyses of various other clinical parameters. The protocol of this study (KEN-1608-20) was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

Scoring of the SDS and FSSG. Outpatients who visit our departments have been routinely asked to complete questionnaires including an SDS questionnaire designed to assess the respondent's depressive status [11] and an FSSG questionnaire to assess GERD symptoms [13]. The SDS questionnaire has 20 items with scales rating the 4 common characteristics of depression [12]: pervasive effect, physiological equivalents, other disturbances, and psychomotor activities. There are 10 positively worded and 10 negatively worded questions. The SDS has been recognized as a representative scale for clarifying depression status, with a score of ≥60 indicating a depressive condition [14]. The average SDS score for Japanese patients with

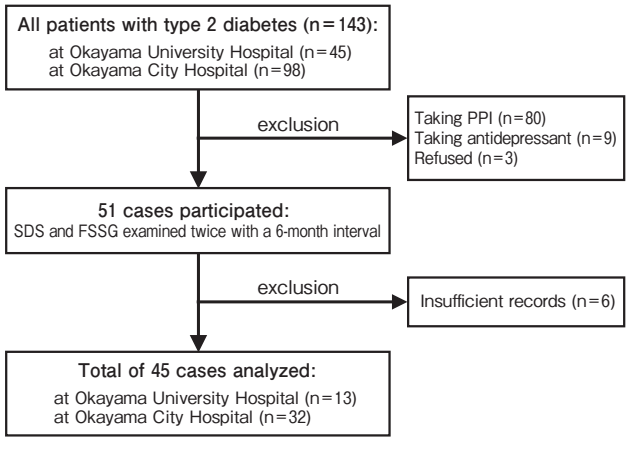

Fig. 1 Selection of study patients. Data for all of the 143 patients from Okayama University Hospital (n = 45) and from Okayama City Hospital (n = 98) were obtained from medical records. Patients who had been taking a PPI (n = 80) or an antidepressant (n = 9), 3 patients who refused participation in the study, and 6 patients whose records were insufficient were excluded. The data of the remaining 45 patients were analyzed.

chronic disease have been reported to be around 36 [15, 16]. The FSSG questionnaire consists of 12 questions: seven assessing acid reflux symptoms and five assessing dysmotility-related symptoms. An FSSG score of ≥ 8 has generally been considered to indicate probable GERD [13].

Statistical analyses. The data were analyzed by the Mann-Whitney *U*-test, chi-squared test, and Fisher's exact test to determine significant differences between groups. We also analyzed the data by performing a linear regression analysis and by obtaining the Spearman's rank correlation coefficients in order to determine relationships between parameters. Probability (p)-values < 0.05 were considered significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, ver. 3.5.2) [17].

Results

Patients' characteristics. Table 1 summarizes the characteristics of the 45 patients divided into those with an SDS score of < 36 (n = 30; the low-SDS group) and those with an SDS score of ≥ 36 (n = 15; the high-SDS group). The higher of the two SDS scores for each patient was used for the analysis. There were no significant differences between the low- and high-SDS groups concerning their characteristics, including age, gender, weight, body mass index, blood pressure, number of diabetic complications (including retinopathy, neuropathy, nephropathy, macro-vascular diseases, hypertension and hyperlipidemia,) number of medications used, or marital status. Of note, the FSSG scores were higher in the high-SDS group, and this group's scores showing dysmotility symptoms rather than reflux symptoms were significantly ($p < 0.05$) increased compared to those of the low-SDS group.

There were also no significant differences between the low- and high-SDS groups in any of the laboratory data, *i.e.*, the hemoglobin concentration, hematocrit, serum levels of electrolytes (sodium and potassium), protein (total protein and albumin), lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride), liver enzymes (aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase), the levels of renal function markers (blood urea nitrogen, creatinine and estimated glomerular filtration rate), and the postprandial plasma glucose (PPG) and hemoglobin A1c (HbA1c) levels.

The relationships between SDS and FSSG scores and diabetic parameters. Figure 2 illustrates the relationships between SDS scores and diabetic parameters, including the correlations between HbA1c levels and SDS scores (Fig. 2A) and between PPG and SDS scores (Fig. 2B). In all 45 of the patients analyzed (Fig. 2A), the SDS score was not significantly correlated with the level of HbA1c (%). As shown in Fig. 2B, the SDS score was also not significantly correlated with the level of PPG (mg/dl). Figure 3 shows the relationships between FSSG scores and diabetic parameters. The FSSG score was significantly correlated with the PPG level ($R = 0.321$, $p < 0.05$) (Fig. 3B) but not significantly correlated with the HbA1c level (Fig. 3A). The FSSG-reflux score ($R = 0.455$, $p < 0.01$) (Fig. 3C) but not the FSSG-dysmotility score (Fig. 3D) was significantly correlated with the PPG level.

Correlations between SDS and FSSG scores. Figure 4 provides the results of the linear regression analysis performed to determine the correlations between the patients' SDS and FSSG scores. A significant correlation was revealed between the FSSG and SDS scores ($R = 0.41$, $p < 0.01$). The SDS scores were also correlated with the FSSG-reflux scores ($R = 0.37$, $p < 0.05$) (Fig. 4B) and with the FSSG-dysmotility scores ($R = 0.444$, $p < 0.01$) (Fig. 4C).

Discussion

Our present analyses revealed for the first time that PPG was a key factor causing GERD-related symptoms in patients with type 2 diabetes mellitus. It is noteworthy that the patients' FSSG scores were significantly correlated with their PPG levels but not significantly correlated with their HbA1c levels. In this regard, Fan *et al.* reported the relationship between esophageal reflex exposure and gastric acidity in patients with GERD, and they demonstrated that their patients' gastric pH levels were transiently increased 1 h after food intake, whereas the patients' postprandial esophageal reflex exposures were thereafter significantly intensified [18]. Horowitz *et al.* reported that the phenomenon of delayed gastric emptying is also related to increased PPG [19]. It is thus possible that the body's PPG level (which is changed by food intake), as opposed to the HbA1c level (which reflects the average blood glucose

Table 1 Comparison of patients' profile and clinical and laboratory parameters

SDS groups	SDS score <36 (n = 30)	SDS score ≥ 36 (n = 15)	*P* value
Patient's profile			
Age [years]	61.6 (2.16)	62.6 (2.48)	0.99
Gender [male % (n)/female % (n)]	70.0 (21)/30.0 (9)	53.3 (8)/46.7 (7)	0.441
Weight [kg]	69.4 (2.89)	65.0 (2.93)	0.571
BMI [kg/m^2]	25.5 (0.68)	25.5 (1.25)	0.709
SBP [mmHg]	134.2 (2.76)	133.3 (3.83)	0.962
DBP [mmHg]	76.7 (2.28)	78.3 (2.42)	0.838
Number of complications	2.4 (0.28)	3.1 (0.43)	0.165
Number of medications	4.4 (0.36)	4.4 (0.49)	0.741
Marital status [married % (n)/unmarried % (n)]	73.3 (22)/26.7 (8)	73.3 (11)/26.7 (4)	1
FSSG score			
Reflux symptoms	1.5 (0.34)	2.9 (0.76)	0.142
Dysmotility symptoms	1.6 (0.30)	3.0 (0.57)	*0.0263
Total	3.1 (0.57)	5.9 (1.29)	0.061
Laboratory data			
Hb [g/dL]	14.4 (0.29)	13.9 (0.36)	0.638
Ht [%]	42.8 (0.73)	41.6 (1.12)	0.523
TP [g/dL]	7.1 (0.07)	6.9 (0.14)	0.205
Alb [g/dL]	4.3 (0.05)	4.0 (0.11)	0.109
Na [mEq/L]	140.5 (0.34)	140.8 (0.54)	0.733
K [mEq/L]	4.4 (0.07)	4.4 (0.09)	0.923
AST [IU/L]	23.9 (1.58)	22.5 (2.12)	0.405
ALT [IU/L]	28.5 (2.86)	22.6 (2.81)	0.311
γGTP [IU/L]	48.1 (8.92)	31.1 (6.02)	0.492
BUN [mg/dL]	14.7 (0.73)	16.6 (1.53)	0.282
Cr [mg/dL]	0.81 (0.03)	0.93 (0.17)	0.47
eGFR [mL/m/1.73m^2]	72.2 (3.11)	66.1 (7.32)	0.639
LDL-C [mg/dL]	103.4 (3.98)	106.1 (8.52)	0.819
HDL-C [mg/dL]	57.5 (3.38)	50.7 (3.43)	0.341
TG [mg/dL]	147.3 (14.51)	144.6 (13.14)	0.656
PPG [mg/dL]	142.1 (6.77)	154.4 (10.64)	0.42
HbA1c [%]	7.0 (0.13)	6.9 (0.28)	0.885

Values are shown as mean (SEM) or % (n) and were statistically analyzed by the Mann-Whitney *U*-test, chi-squared test and Fisher's exact test. Significant level was set at $^*p < 0.05$.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; Ht, hematocrit; TP, total protein; Alb, albumin; Na, sodium; K, potassium; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate $= 194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; PPG, postprandial plasma glucose; and HbA1c, hemoglobin A1c.

level of the past few months [20]) is substantially correlated with gastric emptying and/or gastric pH, leading to GERD symptoms.

The results of our present analyses demonstrated that the patients with diabetes who had relatively high SDS scores (≥36) had a higher frequency of dysmotility-induced symptoms compared to the patients with low SDS scores. Since parameters for depression were significantly correlated with the FSSG scores, it appears that depressive status is closely linked to the manifestation of GERD-related symptoms. In this regard, we recently reported the existence of positive correlations between FSSG and SDS scores regardless of individual chief complaints [21]. In that study, the FSSG-

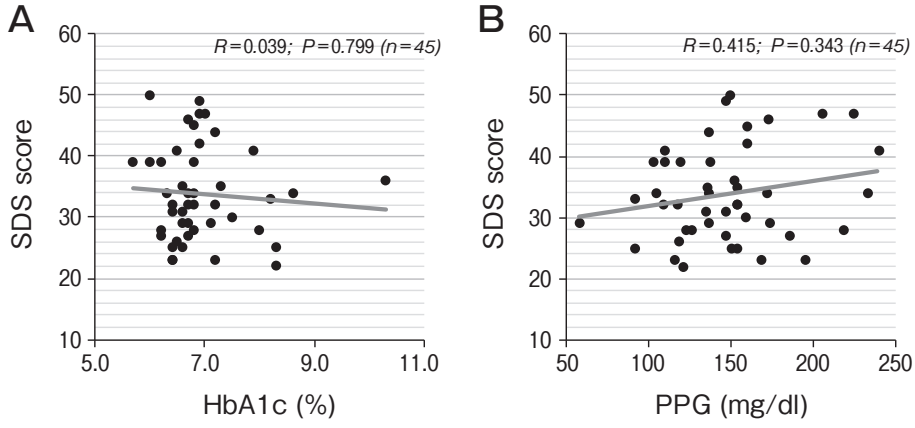

Fig. 2 The relationship between blood glucose levels and the SDS scores. Correlations between the patients' HbA1c levels and SDS scores (**A**) and between their PPG values and SDS scores (**B**) are shown. The data were analyzed by a linear regression analysis.

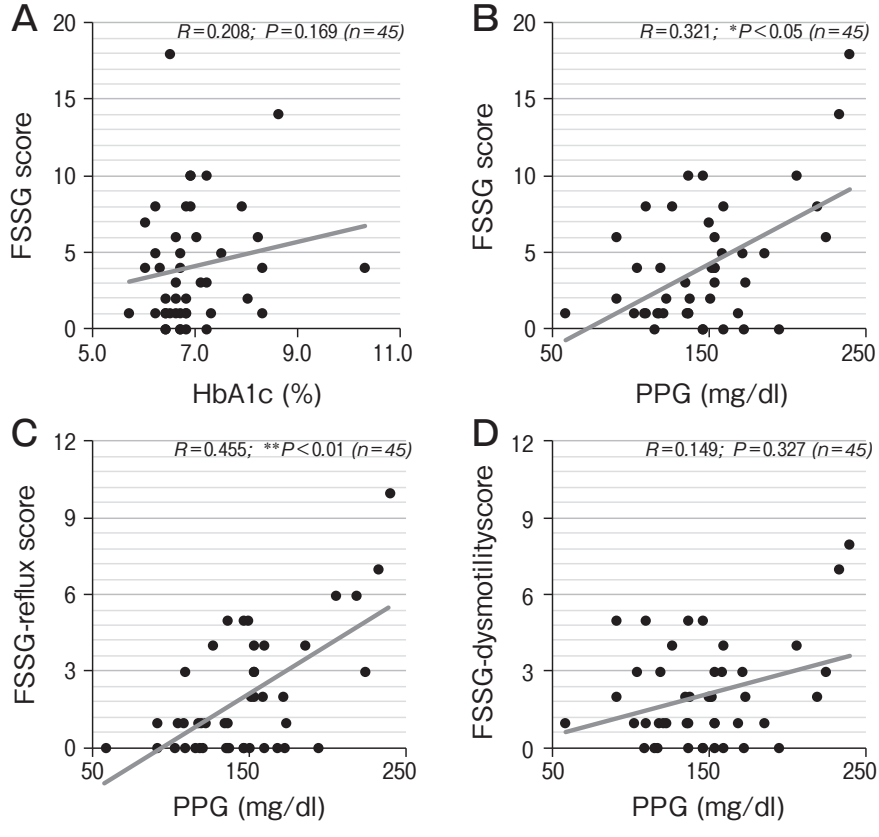

Fig. 3 The relationship between blood glucose levels and FSSG scores. The correlations of the patients' HbA1c values and their FSSG scores (**A**) and the correlations of their PPG values with their FSSG scores (**B**) are shown. The FSSG scores showed a significant positive correlation with the PPG levels ($R = 0.321$, $^{*}p < 0.05$). The correlations of PPG levels with the scores for acid-reflux symptoms (**C**) and dysmotility symptoms (**D**) are shown. The acid-reflux symptom scores showed a significant positive correlation with the PPG levels ($R = 0.455$, $^{**}p < 0.01$). The data were analyzed by a linear regression analysis.

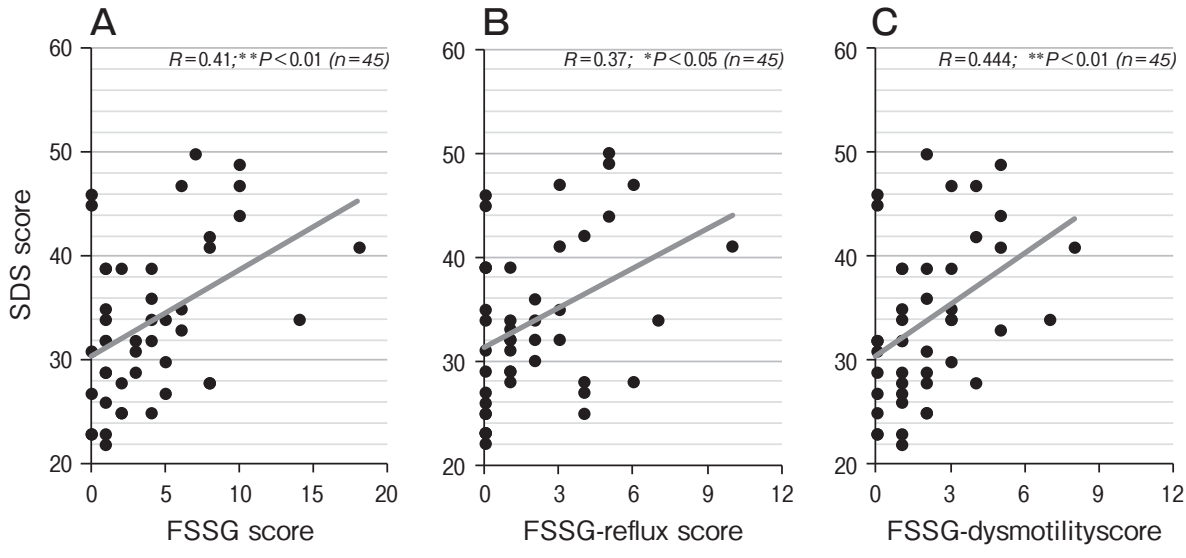

Fig. 4 The relationship between SDS and FSSG scores. The correlations of SDS and FSSG scores including reflux-symptom scores and dysmotility-symptom scores are shown. **A**, The patients' total SDS scores showed a significant positive correlation with the total FSSG scores ($R = 0.41$, $^{**}p < 0.01$); **B**, The patients' SDS scores also showed significant positive correlations with the FSSG acid-reflex symptom scores ($R = 0.37$, $^{*}p < 0.05$) and with (**C**) the FSSG dysmotility symptom scores ($R = 0.444$, $^{**}p < 0.01$). The data were analyzed by a linear regression analysis.

dysmotility score had a stronger positive correlation than the FSSG-reflux score with the SDS score, and this result is in agreement with our present findings for patients with type 2 diabetes.

The FSSG questionnaire has five items regarding gastrointestinal dysmotility symptoms that are related to functional dyspepsia (FD), which is characterized by chronic symptoms of recurrent postprandial fullness, early satiety, and epigastric discomfort despite the absence of any endoscopic abnormality [22]. The possibility of various latent esophageal diseases was not completely excluded by endoscopic examination in the present study; however, the tendency of a high FSSG-dysmotility score may reflect the prevalence of FD. Since mental conditions such as depression and anxiety can be causes of the manifestation of FD [23, 24], it is possible that depressive status is related to high FSSG-dysmotility scores induced by FD-related symptoms. Considering that our patients' PPG levels were correlated with GERD-related symptoms, the levels of blood glucose are indirectly but potentially involved in the depressive status in patients with type 2 diabetes.

Regarding GERD symptoms in diabetic patients, a study of Japanese patients showed that 23% of the patients had an FSSG score of ≥8 and, interestingly, the same study indicated that the coexistence of metabolic syndrome and a low level of serum adiponectin was associated with GERD symptoms [25]. Adiponectin is presumed to be a protective factor against erosive esophagitis, since adiponectin is known to suppress inflammation in various organs [26]. From the clinical point of view, an antidiabetic agent such as thiazolidine derivatives (which are known to increase serum adiponectin) might be effective for patients with type 2 diabetes and GERD symptoms. In order to clarify the involvement of adiponectin in the development of GERD in diabetic patients, we would like to investigate the effects of thiazolidine on serum adiponectin levels in relation to the clinical symptoms of GERD in a future prospective study.

From another viewpoint, the relevance of GERD-related symptoms was shown in patients with male andropause [27] who were suffering from erectile dysfunction (ED), decreased muscle strength, metabolic syndrome with obesity, osteoporosis, and depression due to a decreased level of male testosterone, *i.e.*, the so-called late-onset hypogonadism (LOH) syndrome. In an earlier study by our group, the subjects' FSSG scores were inversely correlated with their serum free testosterone levels, implying that a medical interview regarding GERD symptoms is a critical step for detecting LOH [27]. The relevance of depressive symptoms to

the prevalence of ED has also been reported in Japanese males with type 2 diabetes [28], in whom overweight status seemed to be involved in both ED and lowered testosterone. Thus, a determination of the FSSG scores would be helpful for detecting psychological conditions related to latent complications in male diabetic patients.

Patients with type 2 diabetes have been reported to have a higher prevalence of depressive symptoms compared to the prevalence that in the general population [3,29,30]. It was also reported that the association between depressive symptoms and the occurrence of type 2 diabetes was independent of obesity, habitual and physical activities, chronic medical conditions, and family history [31]. However, moderate to severe levels of depression at baseline seem to be critical for the late occurrence of type 2 diabetes [31].

It has been suggested that depressive disorders are accompanied by increased sympatho-adrenal system activity [32,33] as measured by the level of catecholamine, which is known to facilitate an increase in blood glucose [34]. Depressive disorders have also been shown to be involved in dysregulation of the hypothalamo-pituitary adrenal (HPA) axis [35], leading to impaired glucose tolerance [34]. Underlying endocrine dysregulation related to depressive status might therefore also be involved in the deterioration of diabetic control.

Collectively, the above-described previous findings and our present results show mutual relationships among the blood glucose level, GERD, and depressive state in individuals with diabetes (Fig. 5). We observed that increased blood glucose levels were correlated with GERD-related symptoms, whereas the glucose levels were not directly correlated with depressive status as assessed by the SDS. Since FSSG scores, including both reflux and dysmotility scores, are positively correlated with SDS scores, increased blood glucose may indirectly cause the manifestation and/or progress of the depressive status in patients with type 2 diabetes (Fig. 5).

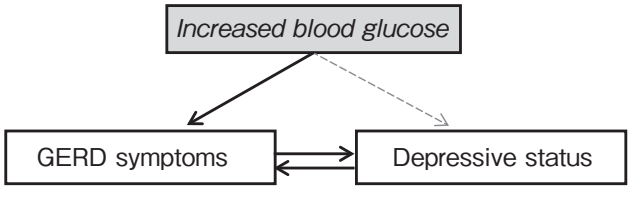

Fig. 5 Mutual relationships among blood glucose levels, GERD, and depressive status. Increased blood glucose levels were correlated with GERD-related symptoms as assessed by the FSSG scoring, whereas the glucose levels were not directly correlated with depressive status as assessed by the SDS. Since the patients' FSSG scores, including both reflux and dysmotility scores, were positively correlated with their SDS scores, increased blood glucose may indirectly affect the depressive status of patients with type 2 diabetes.

A further multicenter study with a large population is necessary to confirm the findings of this study. Our findings indicate that key symptoms related to GERD and the blood glucose value are useful for predicting depressive status in diabetic patients who visit general medicine departments with various uncertain symptoms.

Acknowledgments. We thank all of the physicians and medical staff who contributed to patient care in the Department of General Medicine of Okayama University Hospital and the Department of General Medicine of Okayama City Hospital.

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