Acta Med. Okayama, 2017
Vol. 71, No. 4, pp. 309-314

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

Original Article

Comparison of Psychological Distress between Type 2 Diabetes Patients with and without Proteinuria

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We investigated the link between proteinuria and psychological distress among patients with type 2 diabetes mellitus (T2DM). A total of 130 patients with T2DM aged 69.1 ± 10.3 years were enrolled in this cross-sectional study. Urine and blood parameters, age, height, body weight, and medications were analyzed, and each patient's psychological distress was measured using the six-item Kessler Psychological Distress Scale (K6). We compared the K6 scores between the patients with and without proteinuria. Forty-two patients (32.3%) had proteinuria (≥±) and the level of HbA1c was 7.5 ± 1.3%. The K6 scores of the patients with proteinuria were significantly higher than those of the patients without proteinuria even after adjusting for age and sex. The clinical impact of proteinuria rather than age, sex and HbA1c was demonstrated by a multiple regression analysis. Proteinuria was closely associated with higher psychological distress. Preventing and improving proteinuria may reduce psychological distress in patients with T2DM.

Key words: proteinuria, psychological distress, K6, type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) has become a public health challenge in Japan. The National Health and Nutrition Survey 2012 in Japan estimated that 20 million Japanese have T2DM (http://www.mhlw.go.jp/stf/houdou/0000032074.html, accessed on September 16, 2016). Diabetic nephropathy, which is characterized by proteinuria, is one of the major complications in patients with T2DM [1]. Over 300,000 individuals in Japan are currently undergoing chronic hemodialysis, and the number of patients newly undergoing chronic hemodialysis due to diabetes is also increasing in Japan (http://docs.jsdt.or.jp/overview/pdf2015/p003.pdf, accessed on September 17, 2016). Therefore, a proper strategy for preventing and improving diabetic nephropathy is urgently required in clinical practice.

Higher psychological distress has been reported in patients with T2DM [2-9]. Complications (such as diabetic nephropathy) may be one of the major factors in increased psychological distress. Although there are reports of an association between diabetic complications and physiological distress [10-15], the link between physiological distress and proteinuria in patients with T2DM has not been fully established. In the present cross-sectional study, we compared psychological distress between T2DM patients with and without proteinuria. Our findings demonstrated that among the T2DM patients, proteinuria was closely associated with higher psychological distress.

Patients and Methods

Patients. A total of 130 patients with T2DM aged

Received November 14, 2016; accepted March 14, 2017.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

69.1 ± 10.3 years who met the all of the following criteria were enrolled in this cross-sectional study. (1) They were outpatients of Kagawa Medical Office affiliated with Takamatsu Municipal Hospital in Takamatsu, Japan, between August 4 and October 3, 2015 participating in a previously described study of locomotive syndrome [16]. (2) They underwent psychological distress measurements in addition to common urine and blood examinations. (3) They provided written informed consent. Ethical approval was obtained from the ethical committee of Takamatsu Municipal Hospital (20150727).

Psychological distress. Psychological distress was evaluated using the six-item Kessler Psychological Distress Scale (K6) as described [17]. The 6 questions were as follows [18,19]: "Over the last month, how often did you feel: (1) nervous, (2) hopeless, (3) restless or fidgety, (4) so sad that nothing could cheer you up, (5) that everything was an effort, (6) worthless?" Participants were asked to respond by choosing "all of the time" (4 points), "most of the time" (3 points), "some of the time" (2 points), "a little of the time" (1 point), and "none of the time" (0 points). The total point scores possible thus ranged from 0 to 24.

The K6 was developed using modern psychometric theory and has been demonstrated to be superior to some existing scales in brevity and psychometric properties [20-22]. The Japanese version of the K6 was recently developed, using the standard back-translation method, and has been validated [18]. As suggested by Kessler *et al.* [22], we classified participants with scores of 13 points or more as having psychological distress.

Other clinical parameters. The patients' anthropometric parameters, blood pressure (BP), urine and blood parameters, and medications were evaluated as described [16]. Blood examinations were evaluated using a HITACHI7180 system (Hitachi, Tokyo, Japan). Urine parameters, including proteinuria, were evaluated using Uriflet S test strips (Arkray USA, Edina, MN, USA) (http://www.info.pmda.go.jp/tgo/pack/20800AMZ00109000_A_01_02/, accessed on September 16, 2016). The lowest detection sensitivity was 10 mg/dl, and the correlation coefficient rate between this test and the standard method was reported to be 92% in Japan (http://www.info.pmda.go.jp/tgo/pack/20800AMZ00109000_A_01_02/, accessed on September 16, 2016).

Statistical analysis. Data are expressed as mean ± standard deviation (SD). The comparison of clinical parameters between the T2DM patients with and without proteinuria was performed by the unpaired *t*-test, and multiple groups were compared by performing a one-way analysis of variance (ANOVA). An analysis of covariance (ANCOVA) was also used to adjust for age and sex; *p*-values <0.05 were considered significant. We performed a multiple regression analysis to determine which factor(s) had the greatest impact on physiological distress in patients with T2DM.

Results

The clinical profiles of the patients are summarized in Table 1. The HbA1c values were 7.2 ± 1.2% and the K6 scores were 2.6 ± 4.0. Six of the 130 patients (4.6%) were defined as having psychological distress. Forty-two patients (32.3%) had proteinuria (≥±).

The results of our comparison of clinical parameters between the T2DM patients with and without proteinuria are summarized in Table 2. The K6 scores, creatinine, microalbuminuria and HbA1c of the patients with proteinuria were significantly higher than those of the patients without proteinuria. The HDL cholesterol in the patients with proteinuria was significantly lower than that in patients without proteinuria. The K6 scores of the patients with proteinuria were significantly higher than those of the patients without proteinuria even after adjusting for age and sex.

We compared the K6 scores according to the amount of proteinuria, and no significant difference in K6 scores was revealed (−: 2.0 ± 3.5, ±: 3.7 ± 4.4, +: 2.6 ± 3.4, ≥2+: 5.0 ± 6.0, $p=0.106$). In addition, there was no significant relationship between microalbuminuria and the K6 scores ($r=0.121$, $p=0.169$). There were no significant differences in the other clinical parameters between the patients with and without proteinuria.

The results of the multiple regression analysis conducted to identify factors that are involved in psychological distress in individuals with T2DM are summarized in Table 3. We used the K6 scores as the dependent variable, and proteinuria, age, sex and HbA1c as independent variables. The clinical impact of proteinuria ($\beta=0.165$, $p=0.065$) was the highest on physiological distress compared to age, sex and HbA1c, but not at a significant level.

Table 1 Clinical profile of enrolled patients with type 2 diabetes mellitus

	Total (130)			Men (65)			Women (65)		
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Age	69.1 ± 10.3	38	90	68.9 ± 11.6	38	89	69.3 ± 8.7	45	90
Height (cm)	156.7 ± 9.6	134.4	179.4	163.5 ± 7.3	145.2	179.4	150.0 ± 6.4	134.4	165.0
Body weight (kg)	62.8 ± 13.5	32.2	110.9	67.1 ± 14.2	47.2	110.9	58.5 ± 11.1	32.2	87.8
BMI (kg/m^2)	25.5 ± 4.4	15.4	40.2	25.0 ± 4.4	17.6	38.9	25.9 ± 4.3	15.4	40.2
GOT (IU/l)	23 ± 9	12	56	23 ± 8	12	53	24 ± 9	12	56
GPT (IU/l)	23 ± 14	6	102	23 ± 13	6	92	23 ± 15	7	102
BUN (mg/dl)	17.3 ± 5.6	7.9	38.5	17.6 ± 5.7	7.9	36.0	17.0 ± 5.5	8.1	38.5
Cr (mg/dl)	0.8 ± 0.3	0.4	2.6	0.9 ± 0.3	0.6	2.6	0.7 ± 0.3	0.4	1.8
eGFRcreat (ml/minute/1.73m^2)	67.2 ± 21.5	20.6	128.4	67.1 ± 19.4	20.6	126.3	67.4 ± 23.3	21.0	128.4
Microalbuminuria (mg/gCr)	120.6 ± 367.0	2.7	2,918.0	139.0 ± 345.9	2.7	1,930.9	102.2 ± 383.3	4.6	2,918.0
Triglyceride (mg/dl)	150 ± 94	45	790	148 ± 101	51	790	152 ± 85	45	412
HDL cholesterol (mg/dl)	54 ± 15	31	101	50 ± 14	31	101	58 ± 14	33	98
LDL cholesterol (mg/dl)	118 ± 37	47	241	112 ± 34	60	205	123 ± 38	47	241
Blood sugar (mg/dl)	163 ± 62	62	465	174 ± 67	62	465	152 ± 54	83	358
HbA1c (%)	7.2 ± 1.0	4.9	11.9	7.3 ± 1.1	4.9	10.5	7.2 ± 1.0	5.6	11.9
Systolic blood pressure (mmHg)	128 ± 17	93	188	126 ± 20	93	188	130 ± 14	104	166
Diastolic blood pressure (mmHg)	73 ± 10	46	102	72 ± 11	46	98	74 ± 10	54	102
Number of patients with abnormal urine examination									
Urine sugar (± ≤)	43	−	4+	28	−	4+	15	−	4+
Proteinuria (± ≤)	42	−	3+	22	−	3+	20	−	3+
Hematuria (± ≤)	31	−	3+	10	−	3+	21	−	3+
Number of patients with oral hypoglycemic agents	118			58			60		
Sulfonylureas	44			27			17		
Alpha glucosidase inhibitors	32			19			13		
Meglitinides	10			5			5		
Biganaides	30			15			15		
Thiazolidinediones	25			19			6		
Dipeptidyl Peptidase-4 Inhibitors	73			36			37		
Number of patients with insulin therapy	31			15			16		
Number of patients with injectable glucagon-like peptide analogs	1			1			0		
K6 score	2.6 ± 4.0	0.0	19.0	2.8 ± 4.1	0.0	18.0	2.3 ± 3.8	0.0	19.0

BMI, body mass index; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BUN, blood urea nitrogen; Cr, creatinine.

Table 2 Comparison of clinical parameters between stage of chronic kidney disease in type 2 diabetic patients

	Proteinuria (−)	Proteinuria (±≦)		
	Mean ± SD	Mean ± SD	*p*	*p*[1]
Number of subjects	n = 88 (67.7%)	n = 42 (32.3%)		
Age	68.6 ± 9.8	70.1 ± 11.2	0.448	
Height (cm)	156.7 ± 9.3	156.7 ± 10.4	0.995	
Body weight (kg)	61.6 ± 13.2	65.4 ± 14.0	0.134	
BMI (kg/m^2)	25.0 ± 4.2	26.5 ± 4.7	0.055	
GOT (IU/l)	23 ± 9	24 ± 9	0.972	
GPT (IU/l)	22 ± 13	25 ± 16	0.357	
BUN (mg/dl)	16.9 ± 5.3	18.2 ± 6.3	0.226	
Cr (mg/dl)	0.8 ± 0.2	0.9 ± 0.4	0.016	
eGFRcreat (ml/minute/1.73m^2)	69.0 ± 19.1	63.6 ± 25.8	0.188	
Microalbuminuria (mg/gCr)	24.6 ± 35.3	321.9 ± 599.8	<0.001	
Triglyceride (mg/dl)	147 ± 102	156 ± 73	0.594	
HDL cholesterol (mg/dl)	57 ± 14	49 ± 15	0.004	
LDL cholesterol (mg/dl)	117 ± 39	120 ± 31	0.598	
Blood sugar (mg/dl)	156 ± 62	178 ± 62	0.057	
HbA1c (%)	7.1 ± 0.8	7.5 ± 1.3	0.026	
Systolic blood pressure (mmHg)	127 ± 17	130 ± 18	0.432	
Diastolic blood pressure (mmHg)	74 ± 11	72 ± 8	0.308	
Number of patients with oral hypoglycemic agents	82	36	0.169	
Number of patients with insulin therapy	18	13	0.195	
K6 score	2.0 ± 3.6	3.6 ± 4.6	0.032	0.041

P[1] Adjusting for age and sex. BMI, body mass index; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BUN, blood urea nitrogen; Cr, reatinine.

Table 3 Multiple regression analysis between K6 scores and clinical parameters

	β	*p*
Dependent variables: K6 scores		
Independent variables		
Proteinuria	0.165	0.065
Age	0.091	0.302
Sex	−0.058	0.509
HbA1c	0.078	0.383

Adjusted $R^2 = 0.023$, $p = 0.141$

Discussion

We used K6 scores to evaluate the link between psychological distress and proteinuria in patients with T2DM. A clinical impact of proteinuria on psychological distress was observed.

Chew *et al.* reported that in 700 patients who were ≥30 years of age and had T2DM for >1 year, the prevalence of depression was 41.7% when the Patient Health Questionnaire (PHQ) was used [2]. They also reported that 19.6% of diabetic patients had moderate distress according to their Diabetes Distress Scale (DDS-17) scores [3]. In a cohort study, Hamer *et al.* also reported that psychological distress as measured by the General Health Questionnaire (GHQ-12) was 18.9% in diabetic patients and 13.4% in nondiabetic participants [4]. Domingo *et al.* demonstrated that the prevalence of psychological distress in public school teachers evaluated by the Kessler Psychological Distress Scale (K10) was 15.5%, and a diagnosis of diabetes mellitus was associated with psychological distress (adjusted odds ratio: 3.62) [5].

In the present study, we evaluated psychological distress using K6 scores and found that 4.6% of 130 T2DM patients were defined as having higher psychological distress. The prevalence demonstrated in this study was comparably low and different from previous reports [5]. The methods that we used here were different. However, the prevalence of higher psychological distress defined by the K6 scores was 6.7% in community-dwelling people [23], 6.0% in medical doctors [24], 5.9% in public health nurses [17] and 8.2% in school teachers [25] in Japan. The prevalence of T2DM in the present study was similar to those in previous

reports. The results of this study may be useful reference data for psychological distress in T2DM patients.

Regarding the relationship between diabetic complications and psychological distress, Chew *et al.* demonstrated that depression was more likely in patients with microvascular complications [2]. Using the GHQ-28, Esaki *et al.* also reported that the levels of depression in individuals undergoing chronic hemodialysis were higher than in healthy subjects [26]. In turn, Co *et al.* showed that psychological distress evaluated by the Diabetes Health Profile (DHP-18) Psychological Distress (DHP-PD) subscale and Problem Areas in Diabetes (PAID) were associated with only poorer glycemic control; however, a relationship between K10 scores and glycemic control was not observed [6].

In the present study using K6 scores, psychological distress was significantly higher in the T2DM patients with proteinuria than in those without, even after adjusting for age and sex. In addition, a greater clinical impact of proteinuria rather than age, sex and HbA1c was observed, suggesting that preventing and improving proteinuria may be important for reducing psychological distress in clinical practice. Taken together, a proper strategy for preventing proteinuria including lifestyle modifications and medications is required.

Our study has potential limitations. This was a cross-sectional study, not longitudinal. Second, the 130 outpatients voluntarily enrolled in this study and may thus be more health-conscious than other outpatients. Third, we did not identify the mechanism underlying the relationship between psychological distress and proteinuria. Nevertheless, it is reasonable that preventing and improving proteinuria in patients with type 2 diabetes may be beneficial for reducing their psychological distress. Further prospective investigations are required to clarify the link between proteinuria and psychological distress.

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