


Reproducibility and Validity of a Questionnaire Measuring Treatment Burden on Patients with Type 2 Diabetes: Diabetic Treatment Burden Questionnaire (DTBQ)

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ABSTRACT

Introduction: To measure the burden of pharmacotherapy on patients with type 2 diabetes mellitus (T2DM), we developed the Diabetes

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Treatment Burden Questionnaire (DTBQ), a patient-administered questionnaire composed of 18 questions, and evaluated its reproducibility and validity.

Methods: We enrolled 240 patients with T2DM under pharmacotherapy over 20 years of age at seven institutes in Japan. Their physicians filled out report forms on patient backgrounds, and the patients answered both the DTBQ and the Diabetes Treatment Satisfaction Questionnaire (DTSQ). For evaluation of reproducibility, 48 of the enrolled subjects completed a 2nd DTBQ at home after leaving the medical institutes.

Results: Statistical analyses were performed for two sets of subjects, the validity analysis set ($N = 236$) and the reproducibility analysis set ($N = 47$). Factor analysis found a simple structure in the DTBQ item scores using a three-factor model with varimax rotation; the three subscales were designated as “implementation burden”, “flexibility burden”, and “blood glucose control burden”. All intraclass correlation coefficients for the subscale scores were 0.8 or higher, indicating high reproducibility. Negative correlations were observed between the DTSQ satisfaction score and the DTBQ subscale scores. Moreover, as the dosing frequency of diabetic medicines increased, the DTBQ total score (total burden score) also became higher. Likewise, expected associations were observed between patient backgrounds and DTSQ scores.

Conclusion: The DTBQ has adequate reproducibility and validity as a measurement scale for treatment burden on T2DM patients.

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Keywords: Pharmacotherapy; Questionnaire; Reproducibility; Treatment burden; Type 2 diabetes mellitus; Validity

INTRODUCTION

Pharmacotherapy for type 2 diabetes mellitus (T2DM) has made remarkable progress since the introduction of insulin, the first injectable treatment for diabetes, in the 1920s, and sulfonylureas, the first oral hypoglycemic agent (OHA), in the 1950s [1]. Though the progress of pharmacotherapy has contributed to improving blood glucose (BG) control in T2DM patients, a substantial number of patients are still poorly controlled. In a survey of T2DM adults in the USA, only 52.2% of the subjects achieved a glycemic target of HbA1c < 7.0% in 2007–2010 [2]. Increasing the number of T2DM patients with a sufficient level of BG control is an important medical objective, and one way of achieving this is to improve patient adherence to treatment. This is supported by a report which showed that a considerable portion of patients exhibited poor adherence [3] and some observational studies that also showed a positive correlation between adherence to medication and BG control level in the real world [4, 5].

Multiple factors are considered to affect non-adherence to diabetic treatment [6–9]. Patient factors include demographics (e.g., age, sex), psychological factors (e.g., health belief), physical factors (e.g., concomitant disease), and social and economic status (e.g., education, income). On the other hand, there are specific pharmacotherapy factors: efficacy, safety, cost, complexity (e.g., frequency and interval of dose), and convenience (e.g., ease of swallowing formulation, ease of handling injection device). In addition, T2DM patients, especially older adults, commonly have concomitant diseases, such as hypertension and dyslipidemia, and

therefore have the greater risk associated with polypharmacy [10]. Considering the factors that might be causes of non-adherence, a less complex and more convenient pharmacotherapy would be preferable, and this together with a reduction of treatment burden is a key for improving treatment.

One possible solution for reducing treatment burden is the use of single-tablet fixed-dose combinations of multiple OHAs [11, 12]. Fixed-dose combination therapies require fewer tablets to be taken and lessen treatment complexity, and thereby reduce treatment burden by replacing multiple agents with one fixed-dose combination. Another solution is the use of a long-acting formulation with a hypoglycemic effect sustained for 1 week [13]. Currently, there are two available once-weekly (QW) formulations: an OHA DPP-4 inhibitor and an injectable GLP-1 receptor agonist [14–17]. Some observational studies reported that T2DM patients treated with QW GLP-1 receptor agonist exhibited better adherence than patients treated with a once-daily (QD) agent [18, 19]. QW agents are largely equivalent to the corresponding QD agents in terms of efficacy (i.e., hypoglycemic effect), safety (i.e., adverse events including hypoglycemia), and cost (i.e., drug price). Therefore, if switching from QD to QW agents improved adherence, the reason would be that the treatment burden was reduced by mitigating the complexity of QD treatment. However, there is currently no questionnaire available for measuring quantitatively the difference of treatment burden between QW and QD agents.

To measure burden on patients with diabetes, two scales, PAID (Problem Areas in Diabetes Survey) and DDS (Diabetes Distress Scale) were developed so far [20–22]. However, these scales focus on the generic burden attributable to diabetes, not on the treatment burden caused by pharmacotherapy. Therefore, they are not suitable for differentiating medicines according to their characteristics, such as dosing schedule which dominantly determines the complexity and convenience of implementation of pharmacotherapy. Thus, to measure the treatment burden caused by pharmacotherapy for T2DM, we developed DTBQ

(Diabetes Treatment Burden Questionnaire) focusing on efficacy (i.e., BG control), safety (i.e., hypoglycemia), complexity (i.e., amount, frequency, timing, and interval of dose), and convenience (i.e., ease of taking or injecting medicine), and evaluated its reproducibility and validity. This questionnaire would make it possible to quantify the treatment burden on T2DM patients depending on the characteristics of medicines.

METHODS

Development of DTBQ

We interviewed 16 patients with T2DM treated with pharmacotherapy about treatment burden. Based on the interview, pre-existing questionnaires, and opinions from diabetologists, the first version of questionnaire with 26 questions was drafted. This first version was completed by 20 patients for pilot testing. Based on these results, 18 questions were selected for the final version.

Each question is answered by choosing one of seven ordered categories: (1) strongly disagree, (2) mostly disagree, (3) slightly disagree, (4) neither agree nor disagree, (5) slightly agree, (6) mostly agree, (7) strongly agree. It should be noted that the relations between the category number and level of treatment burden are opposite for questions 1–10 and questions 11–18. In other words, a larger category number means heavier treatment burden in questions 1–10, but a smaller burden in questions 11–18. Therefore, item scores are defined by the category number converted so that 0 means “minimum treatment burden” and 6 means “maximum treatment burden”. Correspondence between the category number and the item score for each question of DTBQ is shown in Table S1 in the electronic supplementary material.

Evaluation of Reproducibility and Validity

All subjects were outpatients with T2DM treated for at least 12 weeks with pharmacotherapy corresponding to one of the following six types of diabetic treatment:

- Injection of GLP-1 receptor agonist, once weekly \pm OHA (Injection/QW)
- Injection of insulin or GLP-1 receptor agonist, once daily \pm OHA (Injection/QD)
- Injection of insulin or GLP-1 receptor agonist, twice a day or more \pm OHA (Injection/BID+)
- Only OHA, once weekly (OHA/QW)
- Only OHA, once daily (OHA/QD)
- Only OHA, twice a day or more (OHA/BID+)

In addition, subjects had to be at least 20 years old and provide written informed consent. Moreover, the following patients were excluded: patients who were diagnosed with or suspected to have dementia, patients with psychiatric disorders, patients without sufficient judgment ability, patients who needed consent from their proxies, and other patients judged to be inappropriate by the attending physicians.

The target numbers of enrolled patients were the following: 210 subjects for validity evaluation who answered DTBQ at least once, and 70 subjects for reproducibility evaluation who answered DTBQ twice. The enrollment was adjusted to balance the number of patients among the different types of diabetic treatment. Patients enrolled as diabetic treatment including injectable medicines had the option to use OHAs together, so they were asked to answer the questions in DTBQ on the injectable medicines only.

The attending physician gave the “Report form for all patients” along with the 1st DTBQ and DTSQ to be filled out to the patient after confirming his/her eligibility; the “Report form for reproducibility evaluation”, which included the 2nd DTBQ, was then delivered only if the patient was a subject for reproducibility evaluation. The patient filled out the “Report form for all patients” without the presence of the attending physician in a room at the medical institute. Then the patient put the form in an envelope and posted it to the data center or gave it to the attending physician. The attending physician filled out the “Report form for physicians” and posted it to the data center with the “Report form for all patients” if he had received it from the patient. Patients who were subjects for reproducibility evaluation filled out the “Report form for reproducibility evaluation”

and posted it to the data center after leaving the medical institute.

DTSQ is the most popular patient-reported questionnaire to evaluate patient satisfaction in diabetic treatment [23]. License and copyright agreement for using DTSQ questionnaire in this study was obtained from Health Psychology Research Limited (University of London, UK). The study was conducted from November 2016 to February 2017 at seven sites in Japan and was registered at University Hospital Medical Information Network (UMIN000026382).

A common protocol was approved at institutional review boards in Nara Medical University and TDE Healthcare Corporation TOSAKI Clinic for Diabetes and Endocrinology. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical Analyses

Enrolled patients who left any unanswered questions in the 1st DTBQ were excluded from the validity analysis set. Of the validity analysis set, patients who completed the 2nd DTBQ collected and without any unanswered questions were included in the reproducibility analysis set. Appropriate descriptive statistics were calculated for background factors, such as type of diabetic treatment, HbA1c, age, and sex, for the validity and reproducibility analysis sets. Mean and standard deviation were calculated for DTBQ item scores, and for the validity and reproducibility analysis sets. In addition, weighted kappa coefficients were calculated for the reproducibility analysis set where the weights (w) were assigned as follows: exact agreement, $w = 1$; one-level disagreement, $w = 5/6$; two-level disagreement, $w = 4/6$; three-level disagreement, $w = 3/6$; four-level disagreement, $w = 2/6$; five-level disagreement, $w = 1/6$; six-level disagreement, $w = 0/6$. Factor analysis of the DTBQ item scores was conducted

for the validity analysis set. Based on the results, subscales were determined and named. Intra-class correlation coefficients (ICC) were calculated for the DTBQ subscale and total scores for the reproducibility analysis set. Correlation coefficients of the DTBQ subscale and total scores and the DTSQ scores were calculated for the validity analysis set. In addition, analysis of variance (ANOVA) or the t test was used to examine associations between DTBQ subscale and total scores and patient background factors.

RESULTS

Patients

Patient disposition is shown in Fig. 1. Out of 240 enrolled patients, 236 were included in the validity analysis set; four were excluded because of unanswered questions in the 1st DTBQ. The numbers of patients by type of diabetic treatment were as follows: (1) Injection/QW, 40; (2) Injection/QD, 41; (3) Injection/BID+, 37; (4) OHA/QW, 38; (5) OHA/QD, 35; and (6) OHA/BID+, 45. Out of 236 patients in the validity analysis set, 48 patients filled out the 2nd DTBQ. One patient was excluded because of unanswered questions, and 47 were included in the reproducibility analysis set.

Patient backgrounds reported by physicians and patients are summarized in Table 1 and Table S2 (in the electronic supplementary material), respectively. All background factors were similarly distributed in the validity and reproducibility analysis sets.

Summary and Reproducibility of DTBQ Item Scores

Descriptive statistics of the DTBQ item scores for the validity and reproducibility analysis sets, and weighted kappa coefficients for the reproducibility analysis set are shown in Table 2. For all questions, item scores of 0 to 2, which indicate a relatively small burden, were reported from more than half of the patients in the validity analysis set. The averages of 14 item scores out of the 18 questions were less than 2.0.

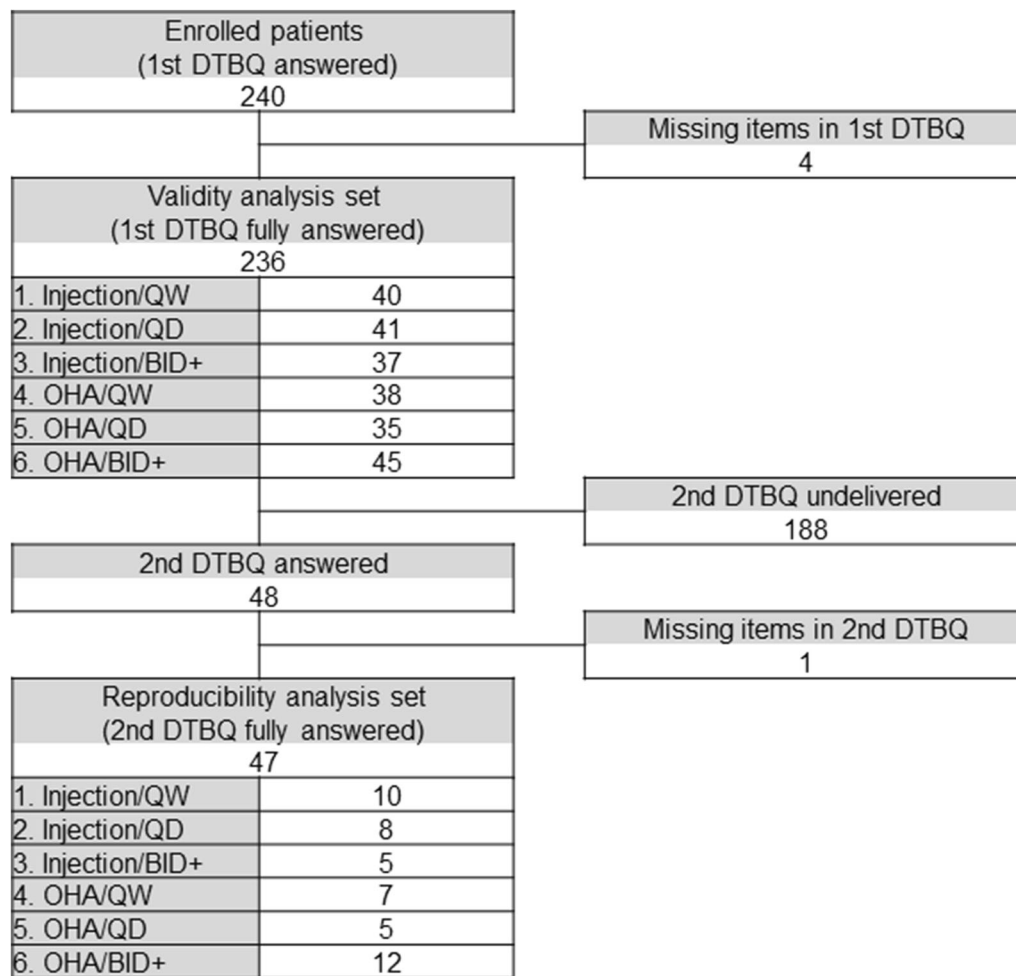


Fig. 1 Patient disposition. Full description of type of diabetic treatment: 1. Injection of GLP-1 agonist, once a week ± oral hypoglycemic agent; 2. Injection of insulin or GLP-1 agonist, once a day ± oral hypoglycemic agent; 3. Injection of insulin or GLP-1 agonist, twice a day or more ± oral hypoglycemic agent; 4. Oral hypoglycemic

agent, once a week; 5. Oral hypoglycemic agent, once a day; 6. Oral hypoglycemic agent, twice a day or more. BID+ twice a day or more, DTBQ Diabetic Treatment Burden Questionnaire, OHA oral hypoglycemic agent, QD once daily, QW once weekly

Four questions whose average scores were greater than 2.0 were as follows: “7. Medication away from home”, “13. Allowing me to take a missed dose”, “16. Feeling less burden to follow diet therapy”, and “18. Satisfaction with my current BG control”.

Means of the 1st and 2nd item scores in the reproducibility analysis set were close to those in the validity analysis set. Weighted kappa coefficients for the reproducibility analysis set were estimated at 0.6 or higher for 14 of the 18 questions. Four questions with point estimates less than 0.6 were “3. Securing time for

medication ($\kappa = 0.550$)”, “8. Concern about hypoglycemia ($\kappa = 0.532$)”, “17. Feeling less burden to continue diabetes treatment ($\kappa = 0.560$)”, and “18. Satisfaction with my current BG control ($\kappa = 0.579$)”, which indicated reproducibility good enough to use in practice.

Factor Analysis of DTBQ Item Scores

Table 3 shows the results of factor analysis of the DTBQ item scores for the validity analysis

Table 1 Patient backgrounds reported by physicians

Background factors	Validity analysis set	Reproducibility analysis set
Number of patients	236 (100.0%)	47 (100.0%)
Type of diabetic treatment		
Injection/QW	40 (16.9%)	10 (21.3%)
Injection/QD	41 (17.4%)	8 (17.0%)
Injection/BID+	37 (15.7%)	5 (10.6%)
OHA/QW	38 (16.1%)	7 (14.9%)
OHA/QD	35 (14.8%)	5 (10.6%)
OHA/BID+	45 (19.1%)	12 (25.5%)
HbA1c (%), mean (SD)	6.98 (0.92)	7.28 (1.14)
Age (years), mean (SD)	63.4 (11.9)	62.8 (12.0)
Sex		
Male	142 (60.2%)	27 (57.4%)
Female	94 (39.8%)	20 (42.6%)
Duration of diabetes (years), mean (SD)	13.1 (9.6)	13.5 (12.4)
Frequency of dose for injection		
None	118 (50.0%)	24 (51.1%)
Once a week	40 (16.9%)	10 (21.3%)
Once a day	41 (17.4%)	8 (17.0%)
Twice a day or more	37 (15.7%)	5 (10.6%)
Type of injection		
Insulin	68 (28.8%)	13 (27.7%)
GLP-1 agonist (QD, BID)	12 (5.1%)	0 (0.0%)
GLP-1 agonist (QW)	40 (16.9%)	10 (21.3%)
Frequency of dose for OHA		
None	21 (8.9%)	3 (6.4%)
Once a week	40 (16.9%)	7 (14.9%)
Once a day	62 (26.3%)	11 (23.4%)
Twice a day	48 (20.3%)	9 (19.1%)
Three times a day or more	65 (27.5%)	17 (36.2%)
Type of OHA		
Sulfonylureas	61 (25.8%)	15 (31.9%)
Glinide	39 (16.5%)	6 (12.8%)
DPP-4 inhibitor	128 (54.2%)	25 (53.2%)

Table 1 continued

Background factors	Validity analysis set	Reproducibility analysis set
Thiazolidine derivative	24 (10.2%)	4 (8.5%)
Biguanide	81 (34.3%)	18 (38.3%)
α -Glucosidase inhibitor	45 (19.1%)	14 (29.8%)
SGLT2 inhibitor	30 (12.7%)	8 (17.0%)
Diabetic neuropathy		
No	147 (62.3%)	27 (57.4%)
Yes	52 (22.0%)	15 (31.9%)
Unknown	37 (15.7%)	5 (10.6%)
Diabetic nephropathy		
No	174 (73.7%)	30 (63.8%)
Yes	62 (26.3%)	17 (36.2%)
Diabetic retinopathy		
No	150 (63.6%)	30 (63.8%)
Yes	61 (25.8%)	16 (34.0%)
Unknown	25 (10.6%)	1 (2.1%)

BID+ twice a day or more, *OHA* oral hypoglycemic agent, *QD* once daily, *QW* once weekly

set. In the factor pattern for a four-factor model without rotation, the first factor loadings were more than 0.4 for all questions, which indicated a unidimensional feature of DTBQ. Therefore, the total score of all 18 questions was designated as the “total burden score”. On the other hand, the variance of three factors was greater than 1.0 in the four-factor model.

In the factor pattern for three-factor model with varimax rotation, focusing on factor loading more than 0.4, a simple structure was obtained, where all questions belonged to one of the three factors. Considering the factor pattern and contents of the questions, three subscales were determined and designated:

- Implementation burden score: sum of item scores 1–10
- Flexibility burden score: sum of item scores 11–13
- Blood control (BG) control burden score: sum of item scores 14–18

Reproducibility of DTBQ Subscale Scores and Total Burden Score

Scatter plots of the DTBQ subscale scores and total burden score (1st vs. 2nd) and the estimates of ICC for the reproducibility analysis set are shown in Fig. 2. The ICC estimates were 0.8 or higher, indicating high reproducibility of all scores.

Correlation Between DTBQ and DTSQ Scores

Table 4 shows the univariate descriptive statistics and correlations of the DTBQ and DTSQ scores for the validity analysis set. Correlations between the DTBQ subscale scores were 0.4 or higher for Spearman’s correlation coefficient (SCC) for every combination. The DTBQ total burden scores correlated positively with all the

Table 2 Reproducibility of DTBQ item scores (reproducibility analysis set)

Questions abbreviated	Reproducibility analysis set ($N = 47$)			
	1st mean (SD)	2nd mean (SD)	Weighted κ coefficient	
			Point estimate	95% confidence interval
1. Medication on time	1.7 (1.6)	1.5 (1.6)	0.785	(0.665, 0.906)
2. Medication during busy hours	1.7 (1.7)	1.6 (1.6)	0.807	(0.710, 0.904)
3. Securing time for medication	0.9 (1.1)	1.1 (1.2)	0.550	(0.355, 0.744)
4. Pain associated with medication	1.3 (1.8)	1.3 (1.7)	0.690	(0.538, 0.841)
5. Feeling that I should not miss a dose	1.8 (1.7)	1.5 (1.5)	0.697	(0.549, 0.846)
6. Feeling guilty when I miss a dose	1.7 (1.9)	1.6 (1.8)	0.839	(0.752, 0.926)
7. Medication away from home	1.9 (1.8)	2.0 (1.9)	0.799	(0.705, 0.892)
8. Concern about hypoglycemia	0.9 (1.2)	1.1 (1.2)	0.532	(0.333, 0.731)
9. Inflexibility to adjust the time for medication	1.0 (1.3)	1.2 (1.3)	0.677	(0.505, 0.848)
10. Worrying about future	1.8 (1.7)	1.9 (1.7)	0.710	(0.579, 0.840)
11. Short time and small effort for medication	1.1 (1.5)	1.1 (1.2)	0.627	(0.434, 0.821)
12. Medication without time pressure	2.0 (1.8)	1.9 (1.9)	0.811	(0.702, 0.920)
13. Allowing me to take a missed dose	1.9 (2.1)	1.9 (1.9)	0.791	(0.693, 0.889)
14. Feeling that my diabetes is getting better	1.9 (1.3)	2.0 (1.3)	0.713	(0.586, 0.839)
15. Allowing me to control BG with small effort	1.8 (1.3)	1.7 (1.3)	0.650	(0.484, 0.816)
16. Feeling less burden to follow diet therapy	2.0 (1.5)	2.1 (1.5)	0.643	(0.481, 0.804)
17. Feeling less burden to continue diabetes treatment	1.5 (1.4)	1.7 (1.3)	0.560	(0.392, 0.728)
18. Satisfaction with my current BG control	2.0 (1.5)	2.1 (1.7)	0.579	(0.414, 0.745)

Range of item scores: 0 (minimum treatment burden)–6 (maximum treatment burden)

DTBQ subscale scores with 0.7 or higher SCC estimates.

The DTSQ hyperglycemic score correlated positively with the DTBQ scores: implementation burden (SCC = 0.31), BG control burden (0.36), and total burden (0.36). Weak correlations were observed between the DTSQ hypoglycemic score and the DTBQ scores within the range of ± 0.2 SCC. The DTSQ satisfaction score correlated negatively with all the DTBQ scores with -0.3 SCC or less. In particular, the BG control burden score (SCC = -0.61) and total burden score (-0.53) were correlated strongly.

Association Between DTBQ Scores and Patient Backgrounds

For the validity analysis set, analysis results of the association between DTBQ scores and patient backgrounds reported by physicians and patients are shown in Table 5 and Table S3 (in the electronic supplementary material), respectively. In addition, the results of pairwise comparisons of the DTBQ/DTSQ scores between types of diabetic treatment are shown in Table S4 in the electronic supplementary material.

Table 3 Factor analysis of DTBQ item scores (validity analysis set)

Questions abbreviated	4-factor model without rotation				3-factor model with varimax rotation			Communality
	Factor loading				Factor loading			
	1	2	3	4	1	2	3	
1. Medication on time	0.743*	− 0.321	− 0.004	− 0.124	0.755*	0.164	0.112	0.609
2. Medication during busy hours	0.734*	− 0.393	0.003	0.006	0.817*	0.105	0.081	0.685
3. Time ensure for medication	0.645*	− 0.329	0.022	0.300	0.694*	0.095	0.097	0.500
4. Pain associated with medication	0.408*	− 0.293	− 0.164	0.449*	0.479*	0.088	− 0.088	0.245
5. To feel that I should not miss a dose	0.705*	− 0.384	− 0.036	− 0.137	0.803*	0.112	0.044	0.659
6. To feel guilty when I miss a dose	0.464*	− 0.276	0.110	− 0.334	0.527*	− 0.004	0.118	0.291
7. Medication away from home	0.711*	− 0.248	0.043	− 0.105	0.720*	0.162	0.169	0.573
8. Concern about hypoglycemia	0.503*	− 0.108	0.023	0.210	0.462*	0.163	0.144	0.261
9. Not to flexibly adjust the time for medication	0.664*	− 0.242	0.086	− 0.092	0.675*	0.122	0.188	0.506
10. To worry about future	0.604*	− 0.190	− 0.093	− 0.048	0.591*	0.219	0.052	0.400
11. Short time and small effort for medication	0.408*	0.331	0.326	0.260	0.124	0.245	0.530*	0.356
12. Medication without time pressure	0.487*	0.426*	0.522*	− 0.033	0.124	0.236	0.796*	0.704
13. To allow me to take a missed dose	0.427*	0.377	0.510*	− 0.058	0.106	0.180	0.741*	0.592
14. To feel that my diabetes is getting better	0.422*	0.520*	− 0.218	0.023	0.025	0.676*	0.189	0.493
15. To allow me to control BG with small effort	0.578*	0.528*	− 0.243	− 0.043	0.144	0.780*	0.222	0.678
16. To feel less burden to follow diet therapy	0.616*	0.454*	− 0.146	− 0.025	0.219	0.694*	0.284	0.611
17. To feel less burden to continue diabetes treatment	0.611*	0.422*	− 0.134	0.117	0.235	0.659*	0.280	0.568
18. Satisfied with my current BG control	0.511*	0.391	− 0.423*	− 0.165	0.180	0.730*	0.001	0.566
Variance of factors	6.061	2.361	1.023	0.619	4.606	2.847	1.846	

Table 3 continued

Questions abbreviated	4-factor model without rotation				3-factor model with varimax rotation			
	Factor loading				Factor loading			Communality
	1	2	3	4	1	2	3	
Cronbach's α	0.885				0.887	0.862	0.775	

$N = 236$. *Factor loading is more than 0.4 or less than -0.4

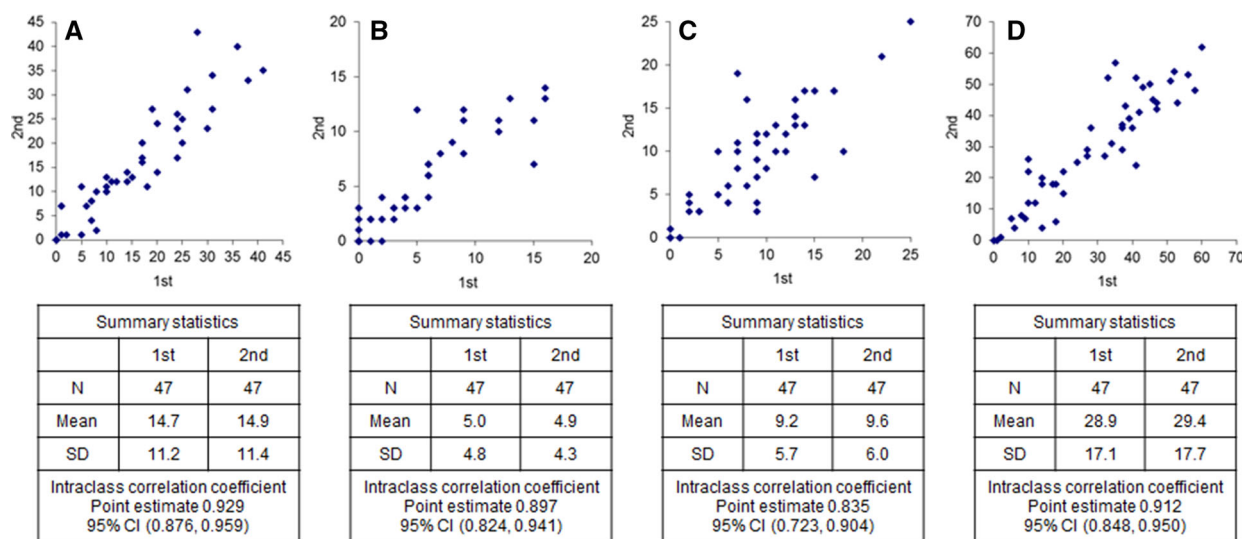


Fig. 2 Reproducibility of DTBQ subscale scores and total burden scores (reproducibility analysis set). **a** Implementation burden score (sum of scores for items 1–10), **b** flexibility burden score (sum of scores for items

11–13), **c** BG control burden score (sum of scores for items 14–18), **d** total burden score (sum of scores for items 1–18). CI confidence interval

DTBQ implementation burden score had significant associations with three items reported by physicians (i.e., type of diabetic treatment, age, frequency of dose: OHA) and five items reported by patients (i.e., BG control, hypoglycemic event, frequency of missed dose: injection, OHA, injection or OHA). DTBQ implementation burden scores were high in the following patients: treated with injection, frequently dosing with injection or OHA, younger age (< 65 years), with BG controlled poorly, with hypoglycemic events, frequently missing dose of injection or OHA.

DTBQ flexibility burden score had significant associations with seven items reported by physicians (i.e., type of diabetic treatment, HbA1c, age, duration of diabetes, frequency of

dose: injection and OHA, diabetic retinopathy) and three items reported by patients (i.e., hypoglycemic event, frequency of missed dose: injection or OHA, time to leave home on weekdays). DTBQ flexibility burden score was high in the following patients: frequently dosing with injection or OHA, higher HbA1c ($\geq 7.0\%$), older age (≥ 65 years), longer duration of diabetes (≥ 10 years), with diabetic retinopathy, with hypoglycemic events, frequently missing dose of injection or OHA, leaving home on weekdays late (8:30 or later).

DTBQ BG control burden score had significant associations with four items reported by physicians (i.e., type of diabetic treatment, HbA1c, diabetic nephropathy and retinopathy) and four items reported by patients (i.e., BG

Table 4 Correlation between DTBQ scores and DTSQ scores (validity analysis set)

Univariate statistics	DTBQ			DTSQ		
	Implementation burden	Flexibility burden	BG control burden	Total burden	Hyperglycemia	Satisfaction
Mean	13.5	5.3	9.3	28.1	2.5	27.4
Standard deviation	11.6	4.9	6.0	17.5	1.8	6.1
<i>N</i>	236	236	236	236	236	236
Minimum	0	0	0	0	0	12
Median	10.0	5.0	9.0	27.0	2.5	28.5
Maximum	51	18	26	76	6	36
Correlation coefficient matrix: Spearman's correlation coefficient						
DTBQ						
Implementation burden	1.00	–	–	–	–	–
Flexibility burden	0.43	1.00	–	–	–	–
BG control burden	0.42	0.46	1.00	–	–	–
Total burden	0.86	0.70	0.73	1.00	–	–
DTSQ						
Hyperglycemia	0.31	0.16	0.36	0.36	1.00	–
Hypoglycemia	0.14	0.10	0.03	0.12	0.25	1.00
Satisfaction	– 0.38	– 0.36	– 0.61	– 0.53	– 0.31	– 0.07

BG blood glucose, *DTBQ* Diabetic Treatment Burden Questionnaire, *DTSQ* Diabetic Treatment Satisfaction Questionnaire

Table 5 Associations between DTBQ scores and patient backgrounds reported by physicians (validity analysis set)

Patients' backgrounds	N	DTBQ scores			
		Implementation burden Mean (SD)	Flexibility burden Mean (SD)	BG control burden Mean (SD)	Total burden Mean (SD)
Validity analysis set	236	13.5 (11.6)	5.3 (4.9)	9.3 (6.0)	28.1 (17.5)
Type of diabetic treatment					
Injection/QW	40	12.3 (11.0)	2.7 (3.5)	9.4 (5.4)	24.3 (14.9)
Injection/QD	41	18.3 (13.9)	6.6 (4.3)	9.3 (6.1)	34.2 (18.3)
Injection/BID+	37	17.5 (13.2)	8.1 (5.4)	11.1 (6.7)	36.6 (20.4)
OHA/QW	38	7.9 (8.3)	2.0 (2.7)	7.0 (4.3)	17.0 (12.0)
OHA/QD	35	8.2 (7.0)	4.6 (4.5)	8.4 (6.8)	21.1 (12.9)
OHA/BID+	45	15.8 (10.1)	7.6 (5.0)	10.6 (6.1)	33.9 (15.8)
ANOVA		$P < 0.001^{***}$	$P < 0.001^{***}$	$P = 0.044^*$	$P < 0.001^{***}$
HbA1c					
< 7.0%	133	12.6 (11.6)	4.7 (4.5)	7.9 (5.3)	25.2 (16.6)
7.0% or higher	103	14.6 (11.5)	6.1 (5.3)	11.1 (6.5)	31.9 (17.9)
<i>t</i> test		$P = 0.186$	$P = 0.022^*$	$P < 0.001^{***}$	$P = 0.004^{**}$
Age					
< 65	115	15.1 (11.5)	4.6 (4.1)	9.6 (5.9)	29.3 (17.1)
65 or older	121	12.0 (11.5)	6.0 (5.5)	9.0 (6.2)	27.0 (17.8)
<i>t</i> test		$P = 0.038^*$	$P = 0.031^*$	$P = 0.486$	$P = 0.310$
Sex					
Male	142	13.1 (11.3)	5.6 (5.1)	9.3 (6.0)	27.9 (17.0)
Female	94	14.2 (12.0)	4.9 (4.6)	9.4 (6.2)	28.4 (18.2)
<i>t</i> test		$P = 0.476$	$P = 0.255$	$P = 0.841$	$P = 0.824$
Duration of diabetes					
< 10 years	93	13.2 (11.9)	4.4 (4.4)	9.1 (5.5)	26.7 (17.7)
10 years or longer	142	13.8 (11.4)	5.8 (5.1)	9.4 (6.3)	29.0 (17.3)
Unknown	1	7.0 (–)	15.0 (–)	25.0 (–)	47.0 (–)
<i>t</i> test (unknown excluded)		$P = 0.698$	$P = 0.030^*$	$P = 0.732$	$P = 0.328$
Frequency of dose: injection					
None	118	11.0 (9.4)	4.9 (4.8)	8.8 (6.0)	24.6 (15.6)
1/week	40	12.3 (11.0)	2.7 (3.5)	9.4 (5.4)	24.3 (14.9)
1/day	41	18.3 (13.9)	6.6 (4.3)	9.3 (6.1)	34.2 (18.3)
2/day	8	10.4 (9.4)	7.1 (5.0)	9.4 (5.7)	26.9 (13.9)

Table 5 continued

Patients' backgrounds	N	DTBQ scores			
		Implementation burden Mean (SD)	Flexibility burden Mean (SD)	BG control burden Mean (SD)	Total burden Mean (SD)
3/day	8	19.5 (13.3)	8.4 (6.1)	14.1 (8.2)	42.0 (25.0)
4/day	21	19.4 (13.9)	8.4 (5.5)	10.5 (6.5)	38.3 (20.3)
ANOVA (none excluded)		$P = 0.082$	$P < 0.001^{***}$	$P = 0.306$	$P = 0.011^*$
Frequency of dose: OHA					
None	21	15.9 (13.4)	8.7 (5.2)	10.8 (5.9)	35.4 (19.3)
1/week	40	9.4 (10.2)	2.2 (2.8)	7.3 (4.4)	18.9 (14.4)
1/day	62	11.9 (11.3)	5.0 (4.8)	9.1 (6.8)	25.9 (16.8)
2/day	48	13.8 (11.0)	5.4 (4.6)	9.2 (6.2)	28.4 (17.7)
3/day or more	65	16.6 (11.6)	6.4 (5.1)	10.4 (5.9)	33.4 (16.5)
ANOVA (none excluded)		$P = 0.009^{**}$	$P < 0.001^{***}$	$P = 0.093$	$P < 0.001^{***}$
Diabetic neuropathy					
No	147	13.0 (11.1)	4.8 (4.7)	9.0 (5.8)	26.8 (16.4)
Yes	52	14.6 (12.8)	5.9 (4.9)	9.4 (6.1)	30.0 (18.9)
Unknown	37	14.0 (11.9)	6.4 (5.6)	10.4 (6.9)	30.7 (19.2)
<i>t</i> test (unknown excluded)		$P = 0.379$	$P = 0.154$	$P = 0.681$	$P = 0.259$
Diabetic nephropathy					
No	174	13.1 (11.4)	5.0 (4.9)	8.8 (6.1)	26.9 (17.2)
Yes	62	14.7 (12.1)	6.2 (5.0)	10.7 (5.8)	31.6 (17.9)
<i>t</i> test		$P = 0.355$	$P = 0.081$	$P = 0.039^*$	$P = 0.069$
Diabetic retinopathy					
No	150	13.0 (11.9)	4.8 (4.7)	8.7 (5.8)	26.4 (17.3)
Yes	61	14.5 (10.0)	6.7 (4.9)	10.7 (6.1)	31.9 (16.4)
Unknown	25	14.2 (13.3)	5.2 (5.4)	9.8 (6.7)	29.2 (20.0)
<i>t</i> test (unknown excluded)		$P = 0.378$	$P = 0.007^{**}$	$P = 0.031^*$	$P = 0.036^*$

ANOVA analysis of variance, BG blood glucose, BID+ twice a day or more, DTBQ Diabetic Treatment Burden Questionnaire, OHA oral hypoglycemic agent, QD once daily, QW once weekly

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

control, hypoglycemic event, frequency of missed dose: injection or OHA, communication with physician on diabetic treatment). DTBQ BG control burden score was high in the following patients: frequently missing dose of

injection or OHA, higher HbA1c ($\geq 7.0\%$), with diabetic nephropathy or retinopathy, with BG controlled poorly, with hypoglycemic events, frequently missing dose of injection or OHA, less communication with their physicians.

DISCUSSION

We developed DTBQ, a patient-administered questionnaire with 18 questions, to measure the treatment burden caused by pharmacotherapy for T2DM. The reproducibility and validity of DTBQ were evaluated through statistical analysis of data collected using the questionnaire from patients with T2DM under pharmacotherapy. This included 236 patients as the validity analysis set and 47 patients as the reproducibility analysis set.

Weighted kappa coefficients were calculated as an index of reproducibility for the DTBQ item scores, with all 18 questions showing reproducibility high enough for practical use. ICCs were also calculated as an index of reproducibility for the DTBQ subscale scores and total burden score. All coefficients were 0.8 or higher, showing high reproducibility of three subscales and total burden score.

Factor analysis of the DTBQ item scores without rotation showed a unidimensional feature of DTBQ, which supported interpreting the total score of all 18 questions as “total burden”. On the basis of the result of the three-factor model with varimax rotation, a simple structure was obtained, and three subscales were determined and designated as follows: “implementation burden”, “flexibility burden”, and “blood control (BG) control burden”.

There were significant associations between type of diabetic treatment and DTBQ total burden score. In terms of administration route (injection vs. OHA), the score was higher for injection than oral administration. For the frequency of dose (QW, QD, BID+), the score increased with order of dosing frequency: QW, QD, and BID+. Comparing the means of total burden score among the type of diabetic treatment (combination of administration route and dose frequency), OHA/BID+ (33.9) was almost the same as Injection/QD (34.2), and Injection/QW (24.3) was smaller than OHA/BID+. These results suggested that the treatment burden of Injection/QW was lighter than that of OHA/BID+.

The DTBQ subscale scores were also significantly associated with type of diabetic

treatment. In particular, the flexibility burden score rose significantly as the frequency of dose increased. Implementation burden score also increased with order of dosing frequency, and was higher for injection than OHA.

HbA1c was significantly associated with total burden score. Total burden score was higher in patients with higher HbA1c ($\geq 7.0\%$). Of the DTBQ subscales, BG control burden score and flexibility burden score also showed significant differences with HbA1c. BG control reported by patients was significantly associated with DTBQ scores as well. These results suggested that patients with worse BG control felt a heavier burden for treatment of diabetes.

Age was not significantly associated with total burden score. However, among the DTBQ subscales, implementation burden score was significantly higher in younger patients (< 65 years). Younger patients might feel heavier implementation burdens because of their greater job demands. On the other hand, flexibility burden score was significantly higher in older patients (≥ 65 years).

Hypoglycemic events were significantly associated with total burden score and DTBQ subscale scores. All scores were significantly higher in patients with hypoglycemic events. Out of the six types of diabetic treatment, the percentage of hypoglycemic events and all DTBQ subscale scores were highest for Injection/BID+, which reflected the association between hypoglycemia and DTBQ scores. This suggests that patients with hypoglycemic events would probably feel a heavier treatment burden for controlling BG.

Daily frequency of dosing non-diabetic agents was not significantly associated with any DTBQ score. This result suggested that DTBQ measured the treatment burden caused by pharmacotherapy for diabetes only, as intended.

Frequency of missed dose of diabetic medication (injection or OHA) was significantly associated with the total burden score and all DTBQ subscale scores. All scores were significantly higher in patients with a missed injection or OHA dose. As the frequency of dosing diabetic medication increased, the frequency of missed dose and all subscale scores also

increased simultaneously, which reflected the association between the frequency of missed dose and the DTBQ scores.

The treatment burden in patients with diabetic retinopathy was higher than that in patients without diabetic retinopathy. In the patients with diabetic retinopathy, 41 out of 61 subjects had injection therapy compared with 63 out of 150 subjects in the patients without diabetic retinopathy. Duration of illness of patients with diabetic retinopathy is relatively longer and insulin therapy is necessary for many patients. Since injection therapy has a higher burden overall, there was a statistically significant difference between the groups.

DTSQ satisfaction score was negatively correlated with all DTBQ scores. The expected results suggested that DTBQ validly measured diabetic treatment burden. Moreover, the results of pairwise comparisons of DTBQ/DTSQ scores among types of diabetic treatment (Table S4 in the electronic supplementary material) showed that the mean DTBQ total burden score and DTBQ satisfaction score were inversely related to the types of diabetic treatment. This indicated that the heavier burden of diabetic treatment might worsen treatment satisfaction.

In the studies comparing QW and BID formulations of GLP-1 receptor agonist, better treatment satisfaction was observed in patients treated with QW medication [24, 25]. Looking at another therapeutic area, some observational/database studies on pharmacotherapy of osteoporosis concluded that QW dosing was associated with better adherence and persistence than QD dosing [26–28]. These results were consistent with the differences among type of diabetic treatment observed in the DTBQ scores.

Recently, patient preference of diabetic treatment has been studied and reported intensively [29–35]. For OHAs, a daily dosing schedule was an important factor in addition to efficacy, safety, and cost. For injections, dosing frequency was the factor which most affected patient preference among all characteristics of GLP-1 receptor agonists, including type of delivery system, nausea, hypoglycemia, BG change, and dosing frequency where QW was

clearly preferred to QD. The questions in DTBQ directly address factors affecting patients' preference, so DTBQ can contribute to a better understanding of patient preference.

This study has some limitations. In the validity analysis set of this study, mean HbA1c was 6.98, which indicated that the study subjects controlled BG better than the general T2DM population. Another study should be conducted to evaluate the validity of DTBQ for poorly controlled T2DM patients. Because the type of diabetic treatment was not randomized, results based on comparisons of DTBQ scores with treatment type should not be interpreted as interventional effects. The treatment burden should be measured from various points of view, and there are some aspects that DTBQ does not cover. For example, side effects other than hypoglycemia (e.g., weight gain, gastrointestinal symptoms) and financial aspects (e.g., cost of drug and device) are not included. Other questionnaires measuring the uncovered aspects should be used together depending on the purpose, such as OHA-Q [36]. The original version of DTBQ was written in Japanese; we translated the questionnaire into English for this publication. If there are plans to use the English version with patients, a validation study will be needed.

It has been already shown that improving treatment satisfaction and quality of life of patients has a positive impact on their adherence and BG control [37, 38]. In this study, DTBQ total burden score correlated negatively with DTSQ satisfaction score. Combining these results, it is expected that increase of the treatment burden leads to worsening BG control. In "Standards of Medical Care in Diabetes—2017" released by the American Diabetes Association [39], the following statements were included:

- Treatment decision should be timely, rely on evidence-based guidelines, and be made collaboratively with patients based on individual preferences, prognosis, and comorbidities.
- Providers should consider the burden of treatment and self-efficacy of patients when recommending treatment.

These statements reflect the importance of patient preference and treatment burden for determining the most appropriate treatment option for diabetes. DTBQ is very much in the same direction indicated by these statements, and it enables quantitative measurement of the treatment burden caused by pharmacotherapy. Measuring the treatment burden on patients with poor adherence would help to better understand their reasons, and some countermeasures might be taken to improve their adherence.

In conclusion, on the basis of the above results and the considerations discussed, DTBQ has adequate reproducibility and validity as a measurement scale for treatment burden on T2DM patients.

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Compliance with Ethics Guidelines. A common protocol was approved at institutional review boards in Nara Medical University and TDE Healthcare Corporation TOSAKI Clinic for Diabetes and Endocrinology. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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