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ORIGINAL ARTICLE

Evaluation of health utility values for diabetic complications, treatment regimens, glycemic control and other subjective symptoms in diabetic patients using the EQ-5D-5L

Mitsuyoshi Takahara[1] · Naoto Katakami[2] · Toshihiko Shiraiwa[3] · Katsushige Abe[4] · Hideo Ayame[5] · Yasuaki Ishimaru[6] · Masahiro Iwamoto[7] · Mitsuo Shimizu[8] · Osamu Tomonaga[9] · Hiroki Yokoyama[10] · Taka-aki Matsuoka[11] · Iichiro Shimomura[11]

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Abstract

Aims This study aimed to reveal health utility values for diabetic complications and treatment regimens with adjustment for glycemic control and other clinical manifestations in a diabetic population.

Methods The EuroQol 5-Dimension 5-Level (EQ-5D-5L) health utility values for 4963 Japanese diabetic patients were analyzed using a multivariate regression model including major complications and treatment regiments (minimally adjusted model), and that additionally included glycemic control and other subjective symptoms (musculoskeletal, dental, respiratory, gastrointestinal, urinary, and cutaneous symptoms, and hearing impairment) (further adjusted model).

Results The mean utility value was 0.901 ± 0.137. In the minimally adjusted model, blindness, overt nephropathy, regular dialysis, cardiac symptom, sequelae of stroke, symptomatic peripheral neuropathy, decreased sensation, claudication, foot ulcer/gangrene, major amputation, and complex treatment regimens were significantly associated with lower utility values, whereas proliferative retinopathy without blindness, coronary artery disease without cardiac symptom, sequela-free cerebrovascular disease, asymptomatic peripheral artery disease, and minor amputation were not. Major complications and treatment regimens that showed significant association in the minimally adjusted model still presented significant impact on the utility decrement in the further adjusted model. However, most of their regression coefficients were lower in absolute value compared to those in the minimally adjusted model.

Conclusions The utility decrement related to each diabetic complication varied with its severity and accompanying symptoms. Complex treatment regimens were independently associated with lower utility values. The utility decrement associated with diabetic complication and complex treatment regimens would be overestimated in the analysis without adjustment for glycemic control or other subjective symptoms.

Keywords Health utility · EQ-5D · Diabetic complications · Treatment regimens · Glycemic control · Other subjective symptoms

Introduction

Health economic evaluation of anti-diabetic interventions is crucial for appropriate allocation of limited medical resources in the struggle against today's diabetes pandemic [1]. In analyses of the cost-effectiveness, health utility values are used to generate quality-adjusted life years (QALYs), a key outcome measure of effectiveness [2, 3]. The values are commonly assessed using the EuroQol 5-Dimension (ED-5D) questionnaire [3, 4], and to date several large-scale studies have provided catalogues of the EQ-5D utility values for major diabetic complications and treatment regimens [5–9].

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✉ Mitsuyoshi Takahara
takahara@endmet.med.osaka-u.ac.jp

Extended author information available on the last page of the article

However, these studies did not adjust for other unhealthy conditions. Moreover, adjustment for glycemic control was not always performed [5–8].

Diabetic patients with major complications and complex treatment regimens often present poor glycemic control, with which other unhealthy conditions, e.g., gastrointestinal symptoms due to autonomic neuropathy [10] and dental problems due to periodontal disease [11], are likely associated. Poor glycemic control and these other clinical manifestations would hence potentially confound the association of major diabetic complications and treatment regimens with utility values.

Furthermore, previous studies used the EQ-5D 3-Level (EQ-5D-3L) questionnaire [5–9]. The EQ-5D-3L is the original version of the EQ-5D, in which five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) are measured at three levels [4]. Although the version was widely used, it was potentially subject to insufficient discriminative power [12–14]. To overcome this shortcoming, a new version of the EQ-5D, the EQ-5D 5-Level (EQ-5D-5L), was recently developed [15]. In the EQ-5D-5L, the level of response for each health dimension is increased from 3 to 5 in number. The EQ-5D-5L is expected to successfully detect minor health difference potentially overlooked in the EQ-5D-3L, while it rates the disutility of major health problems similarly to the EQ-5D-3L, both in a general population [16], and in a diabetic population [17].

Our working hypothesis was that the impact of diabetic complications and treatment regimens on the utility decrement would be confounded by poor glycemic control and other clinical manifestations, and that their impact could be more appropriately evaluated after adjustment for these potential confounders. We also hypothesized that the disutility of various health problems could be successfully detected by use of the EQ-5D-5L questionnaire. The primary objective of the current study was to reveal utility values related to diabetic complications and treatment regimens, with adjustment for glycemic control and other clinical manifestations. The secondary one was to confirm whether the values were different from those without adjustment for these potential confounders.

Materials and methods

The current multicenter cross-sectional study was conducted in 13 centers in Japan between December 2016 and December 2017, and 5000 adult Japanese patients with diabetes participated. Diabetic patients who were treated at the participating centers were asked to participate in the study on their regular visit for their treatment. The patients who consented to the participation were enrolled as study participants. The questionnaires were administered by the attending physicians. No remuneration was involved. Patient recruitment was at the attending physicians' discretion, but they were requested to recruit patients with varying medical backgrounds as much as possible, without biased selection. The participants were asked to respond to the questionnaire during their waiting time at the centers. A paper form of a Japanese version of the EQ-5D-5L questionnaire [15, 18] was used. Of the 5000 study participants, 4963 patients (99.3%) completed the questionnaire, and their responses were analyzed in the current study. Their responses were converted to a single preference-based score (i.e., utility value), in which 0 indicated death and 1 indicated perfect health, based on the Japanese value set [15, 18]. The data on treatment regimens and glycemic control were those on the day when patients responded to the questionnaire. The present status of diabetic complications was similarly collected when the clinical examination was performed on the same day; otherwise the data were collected from medical records. Although the time period for which medical records were retrieved was not prespecified, the data collection and judgment of the clinical validity of the data were on the responsibility of the attending diabetologists. Data on other subjective symptoms were collected using an interview sheet on the same day that the participants responded to the EQ-5D-5L questionnaire. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committees of Osaka University Hospital and other participating centers. In accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, oral consent from the participants was substituted for written informed consent after notification of relevant information on the study and ensured opportunities for refusal, on the grounds of the intervention- and invasiveness-free nature of the study. The current study analyzed the data which were collected for its own purpose, rather than data from some existing databases which were constructed for other purposes.

Definitions

Hemoglobin A1c (HbA_{1c}) levels were divided into categories of $<7\%$ (<53 mmol/mol), 7–8% (53–64 mmol/mol), 8–9% (64–75 mmol/mol), and $\geq 9\%$ (≥ 75 mmol/mol). Body mass index (BMI) was categorized as <25, 25 to 30, 30 to 35, and ≥ 35 kg/m^2, respectively. Medication regimens were classified as no oral or injectable medication, ≤ 2 oral medications without injection, ≥ 3 oral medications without injection, ≤ 2 injections/day, and ≥ 3 injections/day or continuous subcutaneous insulin infusion (CSII). Medications were not limited to anti-diabetic ones, but all medications prescribed to individual patients were considered. Severe or nocturnal hypoglycemia was

determined when patients had either or both of hypoglycemic episodes requiring assistance from another person to treat and those occurring while sleeping. Details of diabetic complications and other subjective symptoms assessed in the current study are summarized in Table 1. Definitions of diabetic complications were in line with the Japanese Diabetes Society guidelines [19]. The number of major complications present was counted without any weight, in accordance with the previous study [6].

Statistical analysis

Data are given as means and standard deviation for continuous variables and as percentages for discrete variables, if not otherwise mentioned. A $p < 0.05$ was considered statistically significant. The EQ-5D utility values were fitted using ordinary least squares (OLS) regression analysis with robust standard errors [20]. We developed two multivariate regression models: a minimally adjusted model and a further adjusted model. The former model included sex, age, type 1 diabetes, duration of diabetes, smoking, BMI, medication regimens, and diabetes-associated complications, whereas

Table 1 Definitions of complication categories and other symptoms

Retinopathy/blindness	
Proliferative retinopathy	Proliferative retinopathy diagnosed by ophthalmologists, or history of photocoagulation for retinopathy or vitreous surgery for vitreous hemorrhage
Blindness	The best-corrected visual acuity of 0.1 or worse
Nephropathy/dialysis	
Overt nephropathy	Persistent proteinuria (or macroalbuminuria) and estimated glomerular filtration rate < 30 ml/min/1.73 m^2
On dialysis	Receiving regular dialysis
Coronary artery disease/cardiac symptom	
Coronary artery disease	Diagnosed coronary artery disease, including history of coronary revascularization
Cardiac symptom	Both or either of angina pectoris and limited physical activity due to heart failure
Stroke/sequelae	
Cerebrovascular disease	Diagnosed cerebrovascular disease
Sequelae of stroke	Currently persisting neurological aftereffects of stroke
Peripheral neuropathy/lower extremity disease	
Symptomatic peripheral neuropathy	Bilateral pedal symptoms considered to be due to diabetic polyneuropathy, including numbness, pain, and paresthesia
Decreased sensation	Bilaterally decreased sensation in the tips of toes and bottom of feet
Asymptomatic peripheral artery disease	Peripheral artery disease diagnosed but not presenting intermittent claudication, foot ulcer/gangrene, or lower extremity amputation
Claudication	Intermittent claudication
Foot ulcer/gangrene	Chronic unhealed pedal tissue loss, either ulcer or gangrene
Minor amputation	Lower extremity amputation performed below the ankle
Major amputation	Lower extremity amputation performed above the ankle
Number of major complications	Accumulated number of the following five major complications (ranging from 0 to 5): (1) retinopathy/blindness, (2) nephropathy/dialysis, (3) coronary artery disease/cardiac symptom, (4) stroke/sequelae, and (5) peripheral neuropathy/lower extremity disease
Other subjective symptoms	
Musculoskeletal symptoms	Musculoskeletal pain and discomfort, including low back pain, knee pain, and other muscle and joint pains
Dental symptoms	Tooth- and denture-related discomfort, including toothaches, sensitive teeth, difficulty in chewing, and having troubles with dentures
Respiratory symptoms	Dyspnea and labored breathing due to respiratory diseases, including lung disease and asthma
Gastrointestinal symptom	Gastrointestinal discomfort, including heartburn, nausea, stomach ache, constipation, and diarrhea
Urinary symptoms	Urinary troubles (dysuria), including difficulty urinating, frequent urination, and urgency to urinate
Cutaneous symptoms	Having troubles with skin, including dermatitis, rashes, and itches
Hearing impairment	Difficulty in hearing

in the latter model, HbA_{1c} levels, severe or nocturnal hypoglycemia, and other subjective symptoms were additionally entered. The regression coefficients are reported with their standard errors. The regression coefficients of medication regimens and diabetes-associated complications were compared between the two models statistically by 2000-time bootstrap resampling.

As sensitivity analysis, the multivariate models were also fitted using the Tobit regression model, in which the dependent variable, i.e., EQ-5D utility values were bounded by one [5]. Similarly to the OLS regression analysis with robust standard errors, two different models, i.e., a minimally adjusted model and a further adjusted model, were developed.

Since some explanatory variables had a few missing values (0.6% of cases on average, and 1.5% ($n=74$) of cases at maximum), we adopted the multiple imputation method ($n=10$) in developing regression models. All statistical analyses were performed using R version 3.1.0 software (R Development Core Team, Vienna, Austria).

Results

Clinical characteristics of the study population are summarized in Table 2. The participants were aged 64 ± 12 years, and 65.4% were male. The proportion of patients registering a severer response level in the EQ-5D-5L increased almost linearly with the accumulation of major complications (Online Resource 1). The mean EQ-5D utility value was 0.901 ± 0.137 (range 0.002–1.000), and 52.0% of the participants had perfect scores of 1.000. Subgroups with more complex treatment regimen, poorer glycemic control, more major complications, and more other subjective symptoms had lower utility values (Table 3). The utility value was not significantly different between patients with type 1 diabetes and patients with type 2 diabetes (0.896 ± 0.123 versus 0.901 ± 0.138, $p=0.46$).

The results of the OLS regression analysis with robust standard error are shown in Table 4. The adjusted R^2 was 0.329 in the minimally adjusted model and 0.400 in the further adjusted model. The minimally adjusted model demonstrated that blindness, overt nephropathy, receiving regular dialysis, cardiac symptom, sequelae of stroke, symptomatic peripheral neuropathy, decreased sensation, claudication, foot ulcer/gangrene, major amputation, and complex treatment regimens (≥ 3 oral medications and injection therapy) were significantly associated with lower utility values, whereas proliferative retinopathy without blindness, coronary artery disease without cardiac symptom, sequela-free cerebrovascular disease, asymptomatic peripheral artery disease, and minor amputation were not. The further adjusted model confirmed that HbA_{1c} levels ≥ 9% (≥ 75 mmol/mol)

Table 2 Clinical characteristics of study population

n	4,963
Male sex	65.4%
Age (years)	64 ± 12
Type 1 diabetes	6.9%
Duration of diabetes (years)	15 ± 10
Current smoking	19.3%
Body mass index	
<25 kg/m^2	54.9%
25–30 kg/m^2	33.9%
30–35 kg/m^2	8.8%
≥35 kg/m^2	2.4%
Medication	
No oral or injectable medication	4.8%
≤2 oral medications without injection	12.4%
≥3 oral medications without injection	49.3%
≤2 injections/day	16.5%
≥3 injections/day or CSII	17.0%
Hemoglobin A1c	
<7% (< 53 mmol/mol)	51.3%
7–8% (53 to 64 mmol/mol)	34.1%
8–9% (64 to 75 mmol/mol)	9.3%
≥9% (≥ 75 mmol/mol)	5.2%
Severe or nocturnal hypoglycemia	3.6%
Retinopathy/blindness	
Proliferative retinopathy without blindness	7.7%
Blindness in one eye	3.8%
Blindness in both eyes	1.0%
Nephropathy/dialysis	
Overt nephropathy	10.5%
On dialysis	1.9%
Coronary artery disease/cardiac symptom	
Coronary artery disease without cardiac symptom	11.8%
Cardiac symptom	3.7%
Stroke/sequelae	
Sequela-free cerebrovascular disease	5.4%
Sequelae of stroke	2.9%
Peripheral neuropathy/lower extremity disease	
Symptomatic peripheral neuropathy	15.7%
Decreased sensation	18.8%
Asymptomatic peripheral artery disease	4.2%
Claudication	15.1%
Foot ulcer/gangrene	1.4%
Minor amputation	0.8%
Major amputation	0.3%
Number of major complications	
No complication	55.8%
1 complication	28.6%
2 complications	10.9%
3 complications	3.3%
≥4 complications	1.4%
Other subjective symptoms	

Table 2 (continued)

Musculoskeletal symptom	45.2%
Dental symptom	20.8%
Respiratory symptom	3.4%
Gastrointestinal symptom	23.8%
Urinary symptom	26.5%
Cutaneous symptom	24.2%
Hearing impairment	19.0%
Number of other subjective symptoms	
No symptom	24.9%
1 symptom	27.8%
2 symptoms	23.2%
≥3 symptoms	24.1%

and severe or nocturnal hypoglycemia were independently associated with lower utility values. Moreover, other subjective symptoms were also independently associated with lower utility values. The diabetes-related complications and treatment regimens that showed significant association in the minimally adjusted model still presented significant association with the utility decrement in this further adjusted model. However, most of the regression coefficients were lower in absolute value compared to those in the minimally adjusted model. The difference was statistically significant in complex treatment regimens, blindness, cardiac symptoms, symptomatic peripheral neuropathy, and claudication (Fig. 1). The most frequent combination of disutility-related diabetic complications was nephropathy/dialysis and peripheral neuropathy/lower extremity disease, which accounted for 5.7% of the study population.

Table 5 shows the results of the Tobit regression analysis. The regression coefficients of most explanatory variables were larger in absolute value than those obtained by the OLS regression analysis. However, the regression coefficients in the Tobit regression analysis were strongly correlated with those in the OLS regression analysis, with the Spearman's correlation coefficient ρ equal to 0.974 in the minimally adjusted model and 0.945 in the further adjusted model (both $p < 0.001$). Furthermore, the findings were the same in regard to statistical significance of the association with utility values.

Discussion

The current study demonstrated the EQ-5D-5L utility values associated with diabetes-related clinical conditions in a diabetic population. The major strength of this study was the regression analysis with further adjustment for glycemic control and other subjective symptoms, as well as the utility evaluation using the EQ-5D-5L instead of the EQ-5D-3L.

Table 3 Utility values of study population

Overall population	0.901 ± 0.137
Sex	
Females	0.878 ± 0.151
Males	0.913 ± 0.128
Age	
< 65 years	0.926 ± 0.112
≥ 65 years	0.883 ± 0.151
Type 1 diabetes	
No	0.901 ± 0.138
Yes	0.896 ± 0.123
Duration of diabetes	
< 15 years	0.916 ± 0.125
≥ 15 years	0.882 ± 0.149
Current smoking	
No	0.898 ± 0.139
Yes	0.913 ± 0.128
Body mass index	
< 25 kg/m^2	0.904 ± 0.137
25–30 kg/m^2	0.902 ± 0.133
30–35 kg/m^2	0.889 ± 0.146
≥ 35 kg/m^2	0.853 ± 0.158
Medication	
No oral or injectable medication	0.952 ± 0.090
≤ 2 oral medications without injection	0.951 ± 0.090
≥ 3 oral medications without injection	0.903 ± 0.133
≤ 2 injections/day	0.877 ± 0.157
≥ 3 injections/day or CSII	0.868 ± 0.154
Hemoglobin A1c	
< 7% (< 53 mmol/mol)	0.909 ± 0.134
7–8% (53 to 64 mmol/mol)	0.899 ± 0.133
8–9% (64 to 75 mmol/mol)	0.882 ± 0.145
≥ 9% (≥ 75 mmol/mol)	0.871 ± 0.166
Severe or nocturnal hypoglycemia	
No	0.905 ± 0.135
Yes	0.831 ± 0.155
Number of major complications	
No complication	0.936 ± 0.099
1 complication	0.889 ± 0.137
2 complications	0.831 ± 0.172
3 complications	0.756 ± 0.204
≥ 4 complications	0.681 ± 0.229
Number of other subjective symptoms	
No symptom	0.969 ± 0.077
1 symptom	0.928 ± 0.107
2 symptoms	0.884 ± 0.136
≥ 3 symptoms	0.815 ± 0.168

A previous EQ-5D-3L-based study [6], analyzing the data of 4641 patients from a multi-national survey of type 2 diabetic patients in Europe, found that the proportion of

Table 4 Results of OLS regression analysis with robust standard errors

	Minimally adjusted model		Further adjusted model	
	Coefficient	(SE)	Coefficient	(SE)
Constant	1.000	(0.012)	1.013	(0.012)
Male sex	0.025**	(0.004)	0.026**	(0.004)
Age (per 10 years)	− 0.001**	(0.002)	− 0.004*	(0.002)
Type 1 diabetes	− 0.009	(0.008)	− 0.002	(0.008)
Duration of diabetes (per 10 years)	0.000	(0.002)	0.002	(0.002)
Smoking	0.001	(0.041)	0.027	(0.039)
Body mass index (vs. <25 kg/m^2)				
25–30 kg/m^2	− 0.001	(0.004)	0.001	(0.003)
30–35 kg/m^2	− 0.014*	(0.006)	− 0.006	(0.006)
≥ 35 kg/m^2	− 0.041**	(0.012)	− 0.030**	(0.011)
Medication (vs. no medication)				
≤ 2 oral medications without injection	− 0.004	(0.006)	− 0.007	(0.006)
≥3 oral medications without injection	− 0.020**	(0.006)	− 0.016**	(0.006)
≤ 2 injections/day	− 0.032**	(0.007)	− 0.022**	(0.007)
≥ 3 injections/day or CSII	− 0.033**	(0.008)	− 0.024**	(0.008)
Hemoglobin A1c (vs. <7%)				
7–8% (53 to 64 mmol/mol)			0.000	(0.003)
8–9% (64 to 75 mmol/mol)			− 0.008	(0.006)
≥ 9% (≥ 75 mmol/mol)			− 0.020*	(0.009)
Severe or nocturnal hypoglycemia			− 0.025*	(0.012)
Proliferative retinopathy without blindness	− 0.003	(0.008)	− 0.003	(0.008)
Blindness in one eye	− 0.034**	(0.012)	− 0.023*	(0.011)
Blindness in both eyes	− 0.111**	(0.026)	− 0.095**	(0.026)
Overt nephropathy	− 0.017*	(0.007)	− 0.017*	(0.007)
On dialysis	− 0.056*	(0.022)	− 0.050*	(0.021)
Coronary artery disease without cardiac symptom	0.001	(0.006)	0.000	(0.006)
Cardiac symptom	− 0.058**	(0.013)	− 0.031*	(0.012)
Sequela-free cerebrovascular disease	− 0.007	(0.009)	− 0.006	(0.009)
Sequelae of stroke	− 0.101**	(0.018)	− 0.098**	(0.018)
Symptomatic peripheral neuropathy	− 0.056**	(0.006)	− 0.044**	(0.006)
Decreased sensation	− 0.014**	(0.005)	− 0.012*	(0.005)
Asymptomatic peripheral artery disease	0.005	(0.009)	0.001	(0.009)
Claudication	− 0.097**	(0.005)	− 0.070**	(0.005)
Foot ulcer/gangrene	− 0.129**	(0.036)	− 0.140**	(0.034)
Minor amputation	0.017	(0.038)	0.002	(0.036)
Major amputation	− 0.178**	(0.063)	− 0.177**	(0.058)
Musculoskeletal symptom			− 0.053**	(0.003)
Dental symptom			− 0.027**	(0.004)
Respiratory symptom			− 0.034**	(0.013)
Gastrointestinal symptom			− 0.016**	(0.004)
Urinary symptom			− 0.019**	(0.004)
Cutaneous symptom			− 0.014**	(0.004)
Hearing impairment			− 0.025**	(0.005)
Adjusted R^2	0.329		0.400	

The variance–covariance matrix of the further adjusted model are provided in Online Resource 2

N/I not included; *SE* standard error

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

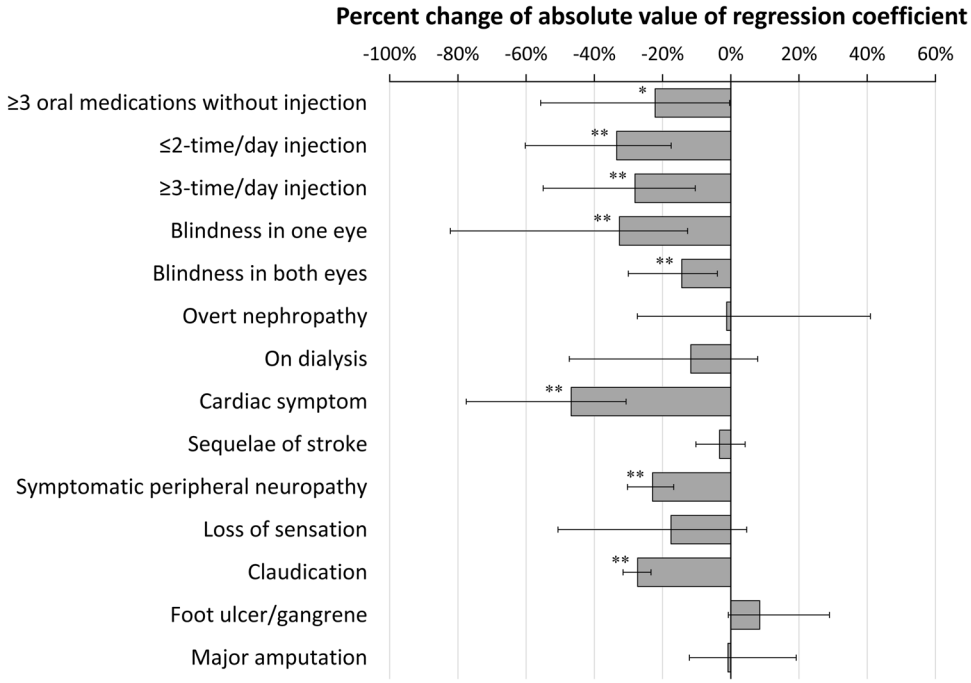

Fig. 1 Attenuated impact of treatment regimens and diabetic complications on the utility decrement after further adjustment for glycemic control and other subjective symptoms. Data are the percent change of the absolute value of the regression coefficient in the further adjusted model compared to the minimally adjusted model (see Table 3). Error bars represent 95% confidence intervals obtained from 2000-time bootstrap resampling. *$p < 0.05$. **$p < 0.01$

patients registering EQ-5D levels 2 and 3 reached a plateau at 3 or more multiple complications, indicating floor effects of the EQ-5D-3L. In contrast, in this EQ-5D-5L-based study, the response levels did not reach a plateau, and utility values demonstrated a linear decrease with the accumulation of major complications, suggesting that floor effects would be lessened in the EQ-5D-5L. The EQ-5D-5L is expected to successfully detect minor health difference potentially overlooked in the EQ-5D-3L. One of the "minor" health problems would be treatment burdens. Although complex treatment regimens likely affect quality of life, previous EQ-5D-3L-based studies did not always demonstrate their significant association with the utility decrement [8]. The disutility of the burdens was hence conventionally regarded as small and negligible in cost-effectiveness analysis [21]. However, it should be noted that patients will receive antidiabetic treatment for years [22]; even if treatment burdens are cross-sectionally light per unit time, the burdens will cumulatively lay heavy on patients over years, and therefore will not be negligible [23]. The current EQ-5D-5L-based study successfully demonstrated that not only injectable medications, but also polypharmacy with ≥ 3 oral medications had a small but significant impact on the decrease of utility values.

Another strength of our study was the analysis with adjustment for glycemic control and other subjective symptoms. Patients with diabetic complications and complex treatment regimens are likely not only to present elevated HbA_{1c} levels [24], but also to have hypoglycemic episodes [25]. We confirmed that both HbA_{1c} levels ≥ 9% (≥ 75 mmol/mol) and severe or nocturnal hypoglycemia were independently associated with utility decrements. Patients with elevated HbA_{1c} levels may have anxiety about future risk of diabetic complications and frustration with the inability to manage the condition [26]. Fear about possible intensification of treatment regimens may also increase anxiety and impair health-related quality of life. Furthermore, patients who have experienced hypoglycemic episodes, especially severe or nocturnal ones, are likely to have an increased fear of hypoglycemia, which diminishes quality of life [27].

Confounding effects of other subjective symptoms are also of note. Periodontal diseases are common in patients with poor glycemic control [11], and their association with cardiovascular disease is also well-recognized [28]. Patients with long-standing diabetes mellitus often have autonomic neuropathy and complain of upper and lower gastrointestinal symptoms [10, 29] and dysuria [10, 30]. Cutaneous symptoms are also common in diabetic patients, and some are linked with poor glycemic control [31]. Some musculoskeletal manifestations such as diabetic hand syndrome are reported to be related to microangiopathy [32]. Low back pain and knee pain are common in obese people [33, 34], and diabetic patients with obesity are likely to have poorer glycemic control [35] and are at high risk of cardiovascular diseases [36]. Furthermore, these musculoskeletal symptoms may be an obstacle to exercise, which would partially cause poor glycemic control and complex treatment regimens. Symptoms of respiratory disease may be another obstacle to exercise, and hence could be associated with deteriorated glycemic control and intensified treatment regimens. Hearing

Table 5 Results of Tobit regression analysis

	Minimally adjusted model		Further adjusted model	
	Coefficient	(SE)	Coefficient	(SE)
Constant	1.185	(0.026)	1.215	(0.025)
Male sex	0.049**	(0.007)	0.049**	(0.006)
Age (per 10 years)	− 0.001**	(0.003)	− 0.006*	(0.003)
Type 1 diabetes	− 0.028	(0.014)	− 0.015	(0.014)
Duration of diabetes (per 10 years)	0.000	(0.004)	0.002	(0.003)
Smoking	0.003	(0.083)	0.067	(0.078)
Body mass index (vs. <25 kg/m^2)				
25 to 30 kg/m^2	− 0.003	(0.007)	0.003	(0.007)
30 to 35 kg/m^2	− 0.024*	(0.012)	− 0.006	(0.011)
≥35 kg/m^2	− 0.073**	(0.020)	− 0.048*	(0.019)
Medication (vs. no medication)				
≤ 2 oral medications without injection	− 0.022	(0.019)	− 0.027	(0.018)
≥ 3 oral medications without injection	− 0.070**	(0.017)	− 0.058**	(0.016)
≤ 2 injections/day	− 0.086**	(0.018)	− 0.062**	(0.017)
≥ 3 injections/day or CSII	− 0.086**	(0.019)	− 0.066**	(0.018)
Hemoglobin A1c (vs. <7%)				
7 to 8% (53 to 64 mmol/mol)	N/I		− 0.003	(0.007)
8 to 9% (64 to 75 mmol/mol)	N/I		− 0.018	(0.011)
≥ 9% (≥ 75 mmol/mol)	N/I		− 0.039**	(0.014)
Severe or nocturnal hypoglycemia	N/I		− 0.039*	(0.016)
Proliferative retinopathy without blindness	− 0.012	(0.012)	− 0.010	(0.011)
Blindness in one eye	− 0.054**	(0.016)	− 0.032*	(0.015)
Blindness in both eyes	− 0.137**	(0.028)	− 0.108**	(0.026)
Overt nephropathy	− 0.024*	(0.010)	− 0.026**	(0.010)
On dialysis	− 0.075**	(0.024)	− 0.065**	(0.022)
Coronary artery disease without cardiac symptom	0.006	(0.010)	0.002	(0.010)
Cardiac symptom	− 0.091**	(0.016)	− 0.042**	(0.015)
Sequela-free cerebrovascular disease	− 0.011	(0.014)	− 0.012	(0.013)
Sequelae of stroke	− 0.130**	(0.017)	− 0.129**	(0.016)
Symptomatic peripheral neuropathy	− 0.093**	(0.009)	-0.066**	(0.008)
Decreased sensation	− 0.024**	(0.008)	− 0.020*	(0.008)
Asymptomatic peripheral artery disease	0.017	(0.016)	0.008	(0.016)
Claudication	− 0.166**	(0.007)	− 0.111**	(0.007)
Foot ulcer/gangrene	− 0.132**	(0.030)	− 0.152**	(0.028)
Minor amputation	0.008	(0.036)	− 0.025	(0.034)
Major amputation	− 0.223**	(0.053)	− 0.216**	(0.049)
Musculoskeletal symptom	N/I		− 0.122**	(0.006)
Dental symptom	N/I		− 0.047**	(0.007)
Respiratory symptom	N/I		− 0.049**	(0.015)
Gastrointestinal symptom	N/I		− 0.034**	(0.007)
Urinary symptom	N/I		− 0.033**	(0.007)
Cutaneous symptom	N/I		− 0.028**	(0.007)
Hearing impairment	N/I		− 0.042**	(0.007)
Pseude R^2	0.456		0.648	

The variance–covariance matrix of the further adjusted model are provided in Online Resource 2

N/I not included; *SE* standard error

*$P < 0.05$. **$P < 0.01$

impairment is frequently observed in older patients [37], who are more likely to have cardiovascular disease. Recent epidemiological studies also suggest the association of diabetes mellitus with hearing impairment [38], possibly related to neuropathy and cardiovascular disease [39]. All of these clinical manifestations lower quality of life by themselves, as demonstrated by the current analysis.

We confirmed that the utility decrement related to some major diabetic complications was significantly attenuated after further adjustment for poor glycemic control and other subjective symptoms. These findings indicate that the negative impact of diabetic complications on the health utility would be overestimated by the analysis without adjustment for these confounders.

Taken together, in previous cost-effectiveness analyses, the merit of anti-diabetic treatments, i.e., the utility increment due to the risk reduction of diabetic complications, might be overestimated, whereas the demerit, i.e., the utility decrement due to the treatments burden, might be underestimated. Consequently, the effectiveness of the treatment of interest would be possibly overestimated. Future re-analyses of their cost-effectiveness might be needed to validate the previous findings.

The current study also demonstrated that the utility decrement related to each diabetic complication varied with its severity and accompanying symptoms, indicating that the utility decrement depends on disease severity and symptoms. Some manifestations of diabetic complications had no significant association with the utility decrement, as suggested by previous reports [40–42]. The finding that major lower extremity amputation but not minor amputation was associated with the utility decrement would be explained by the fact that minor amputation, but not major amputation, leaves a sufficiently functional foot to allow standing and walking without a prosthesis [43]. Previous health utility catalogues and risk prediction models for diabetic complications, especially macroangiopathy and amputation, were conventionally developed without further categorizing them according to their severity or accompanying symptoms. However, the current findings indicate the importance of developing health utility catalogues in which the severity/symptoms of each diabetic complication are taken into account. Furthermore, to simulate QALYs more reliably in cost-effectiveness analysis, not only such severity/symptom-specific utility catalogues, but also severity/symptom-specific risk prediction models will be needed.

Other findings of our study were a positive association of male sex with utility values and a negative association of age and BMI ≥ 35 kg/m^2. Although the true mechanisms remain unknown, the association of sex was consistent with previous studies [5–9]. A small but significant association of aging with utility decrements was also demonstrated previously [6, 9]. Decrease of utility values by morbid obesity would reflect impaired physical functioning and depression in these patients [44, 45].

Compared to the OLS regression model, the Tobit regression model demonstrated an apparently larger impact of diabetes-related conditions on disutility, with a larger constant value, as previous studies demonstrated [5]. This phenomenon would be reasonably explained by the nature of the Tobit model, which was based on the assumption that the true health utility could be larger than one, but was censored at one.

Some limitations of the current study should be mentioned. First, the current study was conducted in a cross-sectional manner. Second, the current study was conducted in only 1 year. A possible change in the disutility of health problems over time remained unrevealed. Third, because the number of type 1 diabetic patients was small, we did not analyze type 1 diabetic patients separately from type 2 diabetic patients. Fourth, we did not collect the data regarding the patients' educational level, cultural level, economic status, employment status, physical activity, or alcohol consumption. It is expected that these aspects could play an important role in responses to questions on quality of life. Furthermore, the current study was conducted in Japan, recruiting Japanese patients. Whether the same effects would be seen in other regions and countries will need to be explored. Fifth, although the current study revealed the disutility of severe or nocturnal hypoglycemia, the influence of its frequency was not evaluated. In addition, detailed information on smoking (e.g., its amount and past history) and subjective symptoms (e.g., severity and subdivision) was not collected. The influence on disutility would vary with their degree and severity. Future studies will be needed to confirm the external validity, and to provide the intra-variable grading in disutility. Finally, data regarding the number of patients in total who were asked to participate in the current study were not collected by the attending physicians and therefore could not be presented.

In conclusion, the current study demonstrated utility values associated with diabetes-related clinical conditions in a diabetic population. Complex treatment regimens, poor glycemic control, and other subjective symptoms were independently associated with lower utility values. The utility decrement related to each diabetic complication varied with its severity and accompanying symptoms. The utility decrement of diabetic complications and complex treatment regimens would be overestimated in the analysis without adjustment for glycemic control or other subjective symptoms. The current findings would facilitate future cost-effectiveness analysis of anti-diabetic treatments.

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Yasuaki Ishimaru (Dr. Yasuyo Ishimaru Memorial Kumagaya Diabetes Clinic, Saitama), Osamu Tomonaga (Diabetes And Lifestyle Center, Tomonaga Clinic, Tokyo), Tetsuyuki Yasuda (Department of Diabetes and Endocrinology, Osaka Police Hospital, Osaka), Yutaka Umayahara (Department of Diabetes and Metabolism, Osaka General Medical Center, Osaka), Hideki Taki and Ken Kato (Department of Diabetes, National Hospital Organization Osaka National Hospital), Mitsuyoshi Takahara (Department of Metabolic Medicine, Osaka University Hospital, Osaka), Toshihiko Shiraiwa (Shiraiwa Medical Clinic, Osaka), Tsunehiko Yamamoto (Department of Diabetes and Endocrinology, Kansai Rosai Hospital, Hyogo), Masahiro Iwamoto (Iwamoto Medical Clinic, Kagawa), Hideo Ayame (Ayame Medical Clinic, Yamaguchi), and Katsushige Abe (Abe Diabetic Clinic, Oita).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval 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 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, written informed consent from the participants was substituted for by their oral consent after notification of relevant information on the study and ensured opportunities for refusal, on the ground of the study's intervention- and invasiveness-free nature.

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Affiliations

Mitsuyoshi Takahara[1] · Naoto Katakami[2] · Toshihiko Shiraiwa[3] · Katsushige Abe[4] · Hideo Ayame[5] · Yasuaki Ishimaru[6] · Masahiro Iwamoto[7] · Mitsuo Shimizu[8] · Osamu Tomonaga[9] · Hiroki Yokoyama[10] · Taka-aki Matsuoka[11] · Iichiro Shimomura[11]

1 Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan

2 Department of Metabolism and Atherosclerosis, Osaka University Graduate School of Medicine, Osaka, Japan

3 Shiraiwa Medical Clinic, Osaka, Japan

4 Abe Diabetic Clinic, Oita, Japan

5 Ayame Medical Clinic, Yamaguchi, Japan

6 Dr. Yasuyo Ishimaru Memorial Kumagaya Diabetes Clinic, Saitama, Japan

7 Iwamoto Medical Clinic, Kagawa, Japan

8 Shimizu Medical Clinic, Gunma, Japan

9 Diabetes and Lifestyle Center, Tomonaga Clinic, Tokyo, Japan

10 Internal Medicine, Jiyugaoka Medical Clinic, Hokkaido, Japan

11 Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan