Improving interpretability of individual Diabetes Symptom Checklist-Revised (DSC-R) scores: the role of patient characteristics

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ABSTRACT

Introduction The Diabetes Symptom Checklist-Revised (DSC-R) is a well-validated patient-reported outcome designed to assess symptom burden in persons with type 2 diabetes mellitus (T2DM) across eight domains. The DSC-R has so far primarily been used in research settings. With the aim to make the DSC-R applicable in clinical practice by improving its interpretability, we sought to identify patient characteristics associated with DSC-R (domain) scores as a first initiative toward reference values.

Research design and methods We used baseline data from two large observational studies to select patient characteristics significantly associated with DSC-R domain and total scores. Multivariable Tobit analyses with the backward procedure per (domain) score were performed. **Results** Data from 1531 participants with T2DM were included. On a 0–100 scale, the median DSC-R total score was 15.88 (7.06–29.41), with domain scores ranging from 5.00 (0.00–22.50) (pain) to 35.00 (10.00–60.00) (fatigue). Low well-being status was most profoundly associated with higher scores across all domains. Persons with one or more complication, as well as one or more symptomatic hypoglycemic episode during the past 3 months, scored higher on (almost) all domains and the total scale.

Conclusions Complications, symptomatic hypoglycemia, and low well-being are important characteristics to take into account when using the DSC-R in individual patients. Further validation of our findings is warranted in diverse patient populations.

BACKGROUND

The Diabetes Symptom Checklist (DSC) was developed by Grootenhuis *et al*¹ almost 25 years ago in the context of the Hoorn study to reliably capture the experience of diabetes-related symptom distress of persons with type 2 diabetes mellitus (T2DM) and changes therein as a result of medical treatment.¹ Based on research data, the DSC was revised in two ways: (1) for the sake of simplicity and to avoid confusion, the frequency scale was replaced by a dichotomous yes/no response for the presence or absence of each symptom; and (2) the scaling was changed from a

Significance of this study

What is already known about this subject?

- ▶ The Diabetes Symptom Checklist-Revised (DSC-R) is a well-validated, widely used patient-reported outcome designed to assess symptom burden in persons with type 2 diabetes mellitus across eight domains.
- ▶ The DSC-R has so far primarily been used in research settings and may have clinical utility.
- ▶ Individual use of DSC-R scores in routine care requires good interpretability, based on reference values.

What are the new findings?

- ▶ Diabetes complications, symptomatic hypoglycemia, and low well-being are characteristics to take into account when using the DSC-R in individual patients.

How might these results change the focus of research or clinical practice?

- ▶ The relevant associations presented and their directions can help improve the interpretability of DSC-R domain and total scores.
- ▶ Especially mood status should be taken into account.
- ▶ The associations found may be a first step for future research to focus on creating reference values or weights for different groups, as well as establishing clinically meaningful differences in diabetes symptom burden.

4-point to a 5-point Likert scale to enhance variability,² resulting in the DSC-Revised (DSC-R).³ The DSC-R consists of 34 items grouped into 8 symptom domains: fatigue, cognitive symptoms, pain, sensitivity symptoms, cardiological symptoms, ophthalmic symptoms, hypoglycemia, and hyperglycemia. It asks about the burden of diabetes symptoms experienced during the past month. The DSC-R has good psychometric properties³ and has been validated in a multitude of languages and used primarily as patient-reported outcome (PRO) in clinical trials.

Table 1 Baseline data of the study population (n=1531)*†

Gender	
Female	750 (49.20%)
Age	61.37 (10.90)
Educational level	
Low	699 (53.60%)
Middle	467 (35.80%)
High	138 (10.60%)
Diabetes duration (years)	7.00 (4.00–12.00)
Complications	
0	881 (62.70%)
≥1	523 (37.30%)
Comorbidities	
0	1367 (89.30%)
≥1	164 (10.70%)
HbA1c	
mmol/mol	69.32 (16.45)
%	8.49 (1.51)
Body mass index	30.53 (6.27)
Treatment	
Oral agents	1021 (66.70%)
Insulin	510 (33.30%)
Symptomatic hypoglycemia during the past 3 months (self-report)	
0 episode	584 (48.90%)
≥1 episode	610 (51.10%)
Severe hypoglycemia during the past 3 months (self-report)	
0 episode	1191 (94.30%)
≥1 episode	72 (5.70%)
WHO-5 score (well-being)	60.00 (40.00–76.00)

*Based on non-imputed data.

†For categorical variables: frequencies (valid percentages); for normally distributed continuous variables: mean (SD); for skewed distributed continuous variables: median (25th–75th percentile). HbA1c, hemoglobin A1c.

When aiming to use the DSC-R as PRO in clinical practice, reference values are an important feature to consider. Interpretability is a key issue for using the DSC-R in clinical practice, that is, in individual patients, and can be defined as ‘the degree to which one can assign qualitative meaning to an instrument’s quantitative scores or change in scores’, or in other words ‘the degree to which it is clear what the scores or change scores mean’.² Interpretability is not a measurement property, like validity and reliability, because it does not refer to the quality of an instrument. Rather, it refers to what the scores on an instrument mean and is a prerequisite for any instrument to be applicable in clinical practice. In this context it is essential to have reference values,² differentiated according to relevant patient characteristics. For example, previous research has shown that symptom report is partly explained by

negative affect.^{4–6} In the Hoorn screening study, negative mood was found to significantly amplify diabetes symptom burden, as measured by the DSC-R.⁵ In other words, when interpreting DSC-R scores on an individual basis, we need to be recognizant of patient-related factors that may influence symptom reporting, such as gender, age, and complication status, and these associations may be generic or domain-specific. For this purpose we need to assess which patient characteristics are associated with DSC-R domain and total scores.

The current study aims to improve the clinical usefulness of the DSC-R through establishing which patient characteristics are associated with DSC-R (domain) scores.

METHODS

Baseline data were used from the SPIRIT (Study of the Psychological Impact in Real care of Initiating insulin glargine Treatment)⁷ and the ESPRIT (Effect Study on Patient-Reported outcomes in Insulin glargine Treatment)⁸ studies and were merged. The SPIRIT data set includes data from 1021 persons with T2DM prior to switching from oral glucose-lowering agents to a long-acting insulin (glargine-100). The ESPRIT data set includes 510 persons with T2DM prior to switching from any long-acting insulin to insulin glargine-100. Details of the SPIRIT and the ESPRIT study are reported elsewhere.^{7,8}

In both SPIRIT and ESPRIT, hemoglobin A1c (HbA1c) was retrieved from the medical chart and demographic and clinical data were self-reported.^{7,8} The DSC-R and the WHO-5 Well-Being Index were completed and used in the current study. The WHO-5 Well-Being Index consists of five positively worded items assessing emotional well-being pertaining to the past 2 weeks.⁹ Scores are transformed to 0–100, with higher scores representing better emotional well-being.^{9,10} Scores were divided into categories: a score ≤28 is indicative of depression,¹¹ a score >28 and ≤50 is indicative of low mood,^{10,12} and a score higher than 50 is indicative of normal well-being.

Analyses

Multiple imputation on the item level was performed, in which imputation models were created per DSC-R domain score. These imputation models contained items of the domain, as well as the original (non-dichotomized) patient characteristics potentially associated with the DSC-R (domain) scores. Multiple imputation using five imputations, which results in five imputed data sets, was performed in SPSS V.22.

Both DSC-R domain and total scores were standardized to 0–100 scores, with higher scores representing higher symptom burden. Because of the large numbers of zero-scores for the DSC-R domains and total scale, Tobit regression analyses were performed using Stata V.15.¹³ All analyses were repeated in five different data sets and consisted of three steps: (1) multivariable Tobit

Table 2 Median and IQR for DSC-R total scores and domain scores (n=1531)*

Total DSC-R	15.88 (7.06–29.41)
Fatigue	35.00 (10.00–60.00)
Cognitive symptoms	15.00 (0.00–40.00)
Pain	5.00 (0.00–22.50)
Sensitivity symptoms	6.67 (0.00–26.67)
Cardiological symptoms	10.00 (0.00–25.00)
Ophthalmic symptoms	8.00 (0.00–24.00)
Hypoglycemia	6.67 (0.00–26.67)
Hyperglycemia	20.00 (5.00–40.00)

*Based on non-imputed (original) data.
DSC-R, Diabetes Symptom Checklist-Revised.

analyses using a backward procedure to select the characteristics significantly associated with the domain scores and total DSC-R score¹⁴; (2) final models were created only for those variables significantly associated with the outcome of interest in at least three imputed data sets; and (3) based on the final models, Rubin's rule was used to obtain pooled regression coefficients and 95% CIs. A *p* value of 0.05 was used as threshold for a statistically significant association.

Patient characteristics potentially associated with DSC-R (domain) scores were dichotomized in order to enhance interpretability and clinical applicability based on medians and guidelines.^{15 16} The following were the variables found to be associated with symptom burden in previous studies and were included as independent variables in the first model for the backward procedure:

- Sociodemographics: gender, age (<70 years vs ≥70 years), and level of education (low, middle, high).
- Clinical characteristics: diabetes duration (<10 years vs ≥10 years), complication status (0 vs ≥1), comorbidity (0 vs ≥1), glycemic control (HbA1c; ≤64.00 mmol/mol (≤8.00%) vs >64.00 mmol/mol (>8.00%)), body mass index (BMI) (non-obese (<30) vs obese (≥30)), treatment (using oral agents vs using insulin), self-reported symptomatic hypoglycemia (0 vs ≥1 episode in the past 3 months), and self-reported severe hypoglycemia (0 vs ≥1 episode in the past 3 months).
- Psychological well-being status (normal well-being, low mood, likely depression).^{3 5 6 17–22}

RESULTS

The total data set included 1531 patients with T2DM, of whom 49.20% were female and with a mean diabetes duration of 7 years (table 1).

The median and IQR (25th–75th percentile) for the DSC-R domain and total scores of the study population are presented in table 2. The median DSC-R total score was 15.88 (7.06–29.41), and the median domain scores ranged from 5.00 (0.00–22.50) (pain) to 35.00 (10.00–60.00) (fatigue).

Tobit analyses

Patient characteristics that were significantly associated with DSC-R scores are presented in table 3. Persons with a diabetes duration of ≥10 years report less burden of fatigue, cognitive symptoms, and hyperglycemia, as well as total burden, compared with those with shorter disease duration. Suffering from one or more complication was associated with a higher total score as well as higher scores on all DSC-R domains, except for the hypoglycemia domain. Reporting one or more symptomatic hypoglycemic episode was found to be significantly associated not only with higher hypoglycemia symptom burden, but also with higher scores on all other domains. Lower well-being status (both low vs normal and likely depression vs normal) showed to be strongly associated with higher scores for all DSC-R domains and the total score.

DISCUSSION

Based on combined data from two large observational studies including insulin-naïve and insulin-treated patients with T2DM, we investigated which patient characteristics are associated with patient-reported diabetes symptom burden. Responses on the DSC-R showed a wide variation in occurrence and degree of troublesomeness, underscoring the need to better understand inter-individual differences, taking patient characteristics into account.

Fatigue is reported as the most common and most burdensome symptom of diabetes. Indeed, fatigue is known to be prevalent in persons with type 1 and type 2 diabetes.^{23–25} Fatigue was most pronounced in patients with lower well-being status. Persons with low mood score around 33 points (on a 0–100 scale) higher compared with persons with normal well-being, while those likely depressed score approximately 46 points as higher relative to normal well-being. Low mood and likely depression do not only impact on fatigue, but amplify scores on all other domains of the DSC-R, in particular cognitive symptoms and hypoglycemic and hyperglycemic symptoms. Our findings are consistent with previous studies that found an association between psychological well-being and subjective symptom report.^{4–6} Several plausible explanations for this association have been suggested, but the causation remains unclear. Painful symptoms may induce or further increase depressed mood,²⁶ while depression can amplify reported symptom burden, possibly due to a focus on symptoms²⁷ and selective recall of negative events.²⁸ Furthermore, negative affect may induce hypervigilance, which leads to an increase in 'scanning' of the body, that is, attention directed to the body, resulting in more somatic symptoms being detected.²⁹ This mechanism may also drive the association between self-reported symptomatic hypoglycemia and DSC-R scores.¹⁹ Future research should aim to clarify this relationship by using continuous glucose monitoring for objective recording of hypoglycemic episodes.

Table 3 Regression coefficients of patient characteristics significantly associated with DSC-R (domain) scores: results from multivariable Tobit analyses*

	Total	Fatigue	Cognitive symptoms	Pain	Sensitivity symptoms	Cardiological symptoms	Ophthalmic symptoms	Hypoglycemia	Hyperglycemia
Gender†		4.96 (1.94 to 7.98)				3.43 (0.45 to 6.41)			
Age				4.88 (0.53 to 9.23)				-10.77 (-15.26 to -6.28)	
Education									
Diabetes duration	-1.49 (-3.00 to 0.02)	-4.10 (-6.96 to -1.24)	-2.95 (-6.09 to 0.19)						-3.73 (-7.12 to -0.34)
Complications	3.52 (1.91 to 5.13)	3.53 (0.75 to 6.31)	4.21 (0.00 to 8.42)	8.75 (5.01 to 12.49)	9.22 (5.87 to 12.57)	5.63 (2.32 to 8.94)	4.92 (1.24 to 8.60)		4.66 (1.27 to 8.05)
Comorbidity	2.29 (0.09 to 4.49)					5.11 (-0.06 to 10.28)			5.66 (0.31 to 11.01)
HbA1c									5.74 (2.60 to 8.88)
BMI	2.57 (1.18 to 3.96)	5.47 (2.63 to 8.31)		5.65 (1.91 to 9.39)		6.67 (3.48 to 9.86)			6.46 (3.30 to 9.62)
Treatment‡					4.61 (0.63 to 8.59)				5.56 (1.70 to 9.42)
Symptomatic hypoglycemia	5.74 (4.25 to 7.23)	11.42 (8.83 to 14.01)	7.43 (4.22 to 10.64)	9.36 (5.54 to 13.18)	8.70 (5.52 to 11.88)	6.32 (2.64 to 10.00)	6.90 (3.51 to 10.29)	12.98 (8.65 to 17.31)	7.94 (4.80 to 11.08)
Severe hypoglycemia	3.92 (0.76 to 7.08)						6.98 (0.20 to 13.76)		
Low mood§	11.09 (9.44 to 12.74)	33.03 (29.85 to 36.21)	20.56 (16.93 to 24.19)	8.38 (3.87 to 12.89)	9.09 (5.39 to 12.79)	10.67 (6.83 to 14.51)	6.29 (2.25 to 10.33)	20.28 (15.42 to 25.14)	16.34 (12.36 to 20.32)
Likely depression¶	19.56 (17.54 to 21.58)	46.44 (42.72 to 50.16)	33.20 (29.12 to 37.28)	14.46 (9.64 to 19.28)	16.42 (11.87 to 20.97)	17.81 (12.89 to 22.73)	17.27 (12.68 to 21.86)	33.67 (27.10 to 40.24)	25.79 (21.67 to 29.91)

*The group with the lowest value(s) is used as reference (see the Methods section for the categories per patient characteristic).

†Male is coded as 0, female as 1.

‡Using oral agents is coded as 0, using insulin as 1.

§Normal well-being is coded as 0, low mood as 1.

¶Normal well-being is coded as 0, likely depression as 1.

BMI, body mass index; DSC-R, Diabetes Symptom Checklist-Revised; HbA1c, hemoglobin A1c.

It is unclear why patients with a diabetes duration of ≥ 10 years report lower fatigue, cognitive, hyperglycemia, and total symptom burden relative to those with shorter disease duration. Response shift or adaptation may play a role in this.² Possibly, people suffering longer from diabetes may be less emotionally burdened compared with those recently diagnosed, resulting in lower negative affectivity in the latter group. Further research into the role of age and diabetes duration as a determinant of symptom distress is warranted.

Besides symptomatic hypoglycemia and diabetes duration, important clinical characteristics to take into account seem to be complication status and BMI. Interestingly, treatment regimen and glycemic control seem to differentiate less in terms of symptom burden. The strength of the association is probably dependent on the level of glycemic control, where one could expect a stronger impact on symptom burden in patients in poorer control versus those in better control.²²

The significant associations and their regression coefficients presented here need further testing, but should help clinicians to interpret DCS-R domain and total scores, taking relevant patient characteristic into account. As to the clinical application of our findings, it is advised to focus on (changes in) DSC-R scores at the domain level.² The total DSC-R score is informative, but we should be aware that no difference in total DSC-R score over time does not exclude the possibility that there actually might have been changes within domains (eg, one domain score worsened while another improved). Further research into the minimal clinically important difference (MCID) for the DSC-R is warranted for interpretation of changes in scores, building on a previous study providing preliminary results.³ The MCID is the smallest benefit of value to persons with T2DM capturing both the magnitude of the improvement and the value persons place on the change.³⁰

Strengths and limitations

The data were derived from a large sample of persons with T2DM from both primary and secondary care settings at different stages of (insulin) therapy across different regions of the Netherlands,^{7 8} which favors the external validity (ie, generalizability) of our findings.

We were unable to study the role of different kinds of complications and comorbidities in symptom burden because of the relatively low prevalence of complications and comorbidities. This is a limitation of the current study as symptoms associated with T2DM may be directly related to complications and comorbidities. In this way, symptom burden domains are likely to be affected differently, depending on the seriousness and impact of complications and comorbidities. Furthermore, the relevant associations were found in a sample of mainly Caucasian patients with T2DM. Future research should replicate our study in diverse patient populations to define and further validate reference values. Here, studying the role of different kinds of complications and comorbidities will

be of value. The relatively large number of missing data is a potential weakness of observational studies and was confirmed in the current study. However, multiple imputation can be viewed as the most robust way of dealing with missing data.³¹

CONCLUSIONS

The relevant associations presented and their directions can help improve the interpretability of the DCS-R domain and total scores. Future research may focus on creating reference values or weights for different patient groups, as well as establishing clinically meaningful differences in diabetes symptom burden.

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Competing interests The data reported here were collected from previous studies conducted with a grant from Sanofi received by the institution (Amsterdam UMC, location VU University Medical Center).

Patient consent for publication Not required.

Ethics approval The current study is based on two existing data sets. Both studies were, in view of their observational and non-invasive nature, not subject to the Dutch Medical Research Involving Human Subjects Act.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The de-identified participant data that underlie the results reported in this article are available from m.dewit@amsterdamumc.nl upon reasonable request to researchers who provide a methodological sound proposal. Other documents that are available are study protocols and analytic codes. Proposals may be submitted up to 24 months following article publication.

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