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## The Confidence in Diabetes Self-Care Scale:

### Psychometric properties of a new measure of diabetes-specific self-efficacy in Dutch and U.S. patients with type 1 diabetes

Nicole C.W. Van der Ven, MsC<sup>1,2</sup>, Herman Adèr, PhD<sup>5</sup>, Katie Weinger, EdD<sup>3,4</sup>, Henk M. Van der Ploeg, PhD<sup>1,5</sup>, Joyce Yi, BA<sup>3</sup>, Frank J. Snoek, PhD<sup>1,2,5</sup>, and Frans Pouwer, PhD<sup>5</sup>

<sup>1</sup>From the Department of Medical Psychology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands

<sup>2</sup>From the Research Institute for Endocrinology, Reproduction and Metabolism, Vrije Universiteit Medical Center, Amsterdam, the Netherlands

<sup>3</sup>From the Behavioral and Mental Health Research Section, Joslin Diabetes Center, Boston, Massachusetts

<sup>4</sup>From the Harvard Medical School, Boston, Massachusetts

<sup>5</sup>From the Institute for Research in Extramural Medicine, Vrije Universiteit Medical Center, Amsterdam, the Netherlands.

#### Abstract

**OBJECTIVE**—To examine psychometric properties of the Confidence in Diabetes Self-Care (CIDS) scale, a newly developed instrument assessing diabetes-specific self-efficacy in Dutch and U.S. patients with type 1 diabetes.

**RESEARCH DESIGN AND METHODS**—Reliability and validity of the CIDS scale were evaluated in Dutch ( $n = 151$ ) and U.S. ( $n = 190$ ) outpatients with type 1 diabetes. In addition to the CIDS scale, assessment included HbA<sub>1c</sub>, emotional distress, fear of hypoglycemia, self-esteem, anxiety, depression, and self-care behavior. The Dutch sample completed additional measures on perceived burden and importance of self-care. Test-retest reliability was established in a second Dutch sample ( $n = 62$ ).

**RESULTS**—Internal consistency (Cronbach's  $\alpha = 0.86$  for Dutch patients and 0.90 U.S. patients) and test-retest reliability (Spearman's  $r = 0.85$ ,  $P < 0.0001$ ) of the CIDS scale were high. Exploratory factor analysis showed one strong general factor. Spearman's correlations between the CIDS scale and other measures were moderate and in the expected directions, and high HbA<sub>1c</sub> levels were associated with low CIDS scores in the U.S. sample only. Low CIDS scores were positively associated with self-care but not with glycemic control in the original samples. CIDS scores in the U.S. and Dutch samples did not show any statistically significant differences. U.S. men had higher CIDS scores than U.S. women.

**CONCLUSIONS**—The CIDS scale is a reliable and valid measure of diabetes-specific self-efficacy for use in patients with type 1 diabetes. High psychometric similarity allows for cross-cultural comparisons.

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Address correspondence and reprint requests to Nicole C.W. van der Ven, Vrije Universiteit Medical Center, Department of Medical Psychology, Van der Boechorststraat 7, 1081 BT Amsterdam, the Netherlands. E-mail: ncw.van\_der\_ven.psychol@med.vu.nl.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Effective self-regulation of diabetes is not just based on simple adherence to a prescribed regimen but requires active behavioral involvement of patients on a day-to-day basis. A key factor in attaining behavioral goals is self-efficacy—the individual's confidence in his or her own ability to perform specific tasks required to reach a desired goal (1). To cope effectively with the complex demands of the diabetes treatment regimen, a sufficient sense of self-efficacy is required.

Self-efficacy beliefs are specific to behaviors and the situations in which they occur, affecting the courses of action people choose to take, the amount of effort invested, how long they will persevere, their resilience to adversity, and what they ultimately accomplish (2). The value of self-efficacy in predicting self-care behaviors and outcomes in patients with diabetes is supported by several studies, in which self-efficacy was associated with self-reported adherence in adults (3-9) and adolescents (10,11), glycemic control (8,12,13), and better perceived general health, mental health, and social functioning (14).

In contrast to more stable personality characteristics, self-efficacy is a dynamic, changeable belief, which may be enhanced by behavioral interventions, resulting in an increased motivation for behavioral efforts (2). In diabetes, such interventions have been successful in enhancing specific aspects (15) or more general self-efficacy beliefs, along with improved HbA<sub>1c</sub> (16) and self-care behavior (17). To assist patients in optimizing their self-care behavior, it may be useful to assess self-efficacy specific to self-care behaviors. When identified, suboptimal levels of self-efficacy can be targeted by tailored behavioral interventions. Several instruments to assess self-efficacy specific to self-care behavior have been used in adult patients with diabetes. In some studies, a single item is used (18); in other studies, data on reliability and validity are lacking (3,8) or not available in English (9). In some cases, the instrument relies heavily on diet-related items (4,15,19) or is concerned with psychosocial issues instead of self-care behavior (20). Measures for use in type 2 diabetic patients (12,21) and children and adolescents (22) are generally well validated and widely used by others (13,11,16). Advancing on these existing scales, we set out to develop a short instrument to assess self-efficacy in adults with type 1 diabetes, in Dutch as well as U.S. patients. The objective of this study was to examine the psychometric properties of this Confidence in Diabetes Self-Care (CIDS) scale.

## RESEARCH DESIGN AND METHODS

### Development of the CIDS scale

The CIDS scale was designed as a short 20-item self-report questionnaire (23) assessing self-efficacy, the perceived ability to perform diabetes self-care tasks, in patients with type 1 diabetes. The CIDS scale was constructed in Dutch and U.S. English simultaneously by two of the authors (K.W. and F.J.S.). After exploring existing measures referred to in the introduction, items were constructed to cover all domains of self-care (e.g., following recommendations about food, exercise, foot care, insulin administration, and self-monitoring of blood glucose [SMBG]; and self-regulation of blood glucose, e.g., adjusting insulin and detecting and treating high and low levels of blood glucose). Social skills (e.g., asking friends/relatives for help) were included because they are considered an essential part of an active problem-solving approach to diabetes. Items were judged on content validity and adapted if necessary by three additional research psychologists working in the field of diabetes. Comprehensibility and ease of use were tested and found to be satisfactory in a small sample of Dutch patients ( $n = 11$ ).

Each item is preceded by, "I believe I can...," with the strength of this belief rated on a 5-point Likert scale ranging from 1 ("No, I am sure I cannot") to 5 ("Yes, I am sure I can"). An example item is, "I believe I can...adjust my insulin for exercise, traveling, or celebrations."

A total CIDS score is calculated by summation of all item scores and then transformed to a 0–100 scale (see STATISTICAL ANALYSIS), with higher scores indicating higher self-efficacy.

## Subjects and procedures

For this study, three distinct samples were used to examine the psychometric properties of the CIDS scale. Inclusion criteria for all samples were 1) age >18 years and 2) having type 1 diabetes, defined as onset of diabetes before age 40 years and treated with insulin from diagnosis.

**Study 1: Evaluation of psychometric properties**—A sample of 200 Dutch type 1 diabetic patients randomly selected from 3,000 patients taking part in a large survey (24) (randomly selected of the 40,000 members of the Dutch Diabetes Association) received a set of self-report questionnaires, including the CIDS scale, by mail. Written consent was obtained to retrieve the most recent HbA<sub>1c</sub> level from the treating physician. A second sample of 192 U.S. type 1 diabetic patients attending a scheduled appointment at the out-patient clinic of the Joslin Diabetes Center completed the self-report questionnaires and gave permission to obtain HbA<sub>1c</sub> results.

**Study 2: Test-retest reliability**—A third sample of 62 type 1 diabetic patients visiting the outpatient diabetes clinic of the Vrije Universiteit Medical Center completed the CIDS scale at the clinic. They received the CIDS scale for a second assessment by mail. Because self-efficacy is considered a dynamic construct, a short time interval (2 weeks) was chosen.

The study was approved by the Joslin Diabetes Center Committee on human subjects and the Medical Ethics Committee of the Vrije Universiteit medical center, and written informed consent was obtained before participation.

## Measures

In addition to the CIDS scale, patients in study 1 filled out several self-report questionnaires:

- Sociodemographical and clinical characteristics, including age, sex, years of education, duration of diabetes, and number of complications.
- Diabetes-related emotional distress was assessed by the Problem Areas in Diabetes (PAID) scale, a 20-item measure assessing a broad range of feelings related to living with diabetes and its treatment, including guilt, anger, frustration, depressed mood, worry, and fear. The PAID scale proved to have high internal consistency in U.S. (Cronbach's  $\alpha = 0.95$ ) (25) as well as Dutch samples (Cronbach's  $\alpha = 0.93$ –0.95) (26).
- Fear of hypoglycemia was assessed by the Hypoglycemia Fear Survey (HFS) worry scale, with good reliability (Cronbach's  $\alpha = 0.89$ –0.96) and validity in U.S. (27) and Dutch samples (Cronbach's  $\alpha = 0.92$ ) (28).
- In the U.S. sample, self-esteem was assessed by the Rosenberg Self-Esteem questionnaire (29) with good reliability (Cronbach's  $\alpha = 0.77$ –0.88) (30). In the Dutch sample, the self-esteem sub-scale of the Dutch Personality Inventory with satisfactory reliability (Cronbach's  $\alpha = 0.74$ ) (31) was used.
- To assess anxiety and depression, the anxiety and depression subscales of the Symptom Check List 90-R (32) were used in the U.S. sample, with good reliability (Cronbach's  $\alpha = 0.90$  for depression and 0.84 for anxiety). The Dutch sample filled out the Hospital Anxiety and Depression Scale (Cronbach's  $\alpha = 0.93$  for anxiety and 0.90 for depression) (33,34).

- Diabetes self-care behaviors were assessed using the Self-Care Inventory (35) in the U.S. sample, with good reliability (Cronbach's  $\alpha = 0.87$ ), and similar items were used in the Dutch sample (questions regarding frequency of taking into account dietary recommendations [1 = "never" and 5 = "always"], SMBG [1 = "never" and 5 = " $\geq 5$  times a day"], performing the prescribed number of daily insulin injections [1 = "never" and 5 = "always"], frequency of exercise [1 = "never" and 5 = ">7 times a week"], adjusting insulin in special situations [1 = "never" and 5 = "always"], and inspection of feet [1 = "never" and 5 = ">20 times a month"]) (36).
- For the Dutch sample, an overall diabetes treatment self-efficacy rating was included, using the question, "I believe I can...manage my diabetes well overall," rated on a scale from 1 ("No, I am sure I cannot") to 5 ("Yes, I am sure I can") preceding the CIDS scale. In addition, the Dutch sample rated the perceived burden and importance to prevent future complications of each behavior on a 5-point scale (1 = "not burdensome/not important" and 5 = "very burdensome/very important").

Glycemic control was assessed by determining the percent of glycosylated hemoglobin. For the U.S. sample, one laboratory in Boston was used (high-performance liquid chromatography ion capture method; Tosoh Medics, San Francisco, CA; reference: 4.0–6.0%). Because multiple laboratories were used for the Dutch sample, correlations with Diabetes Control and Complications Trial target values were calculated and HbA<sub>1c</sub> values were adjusted accordingly. Patients in study 2 (test-retest reliability) filled out the CIDS scale only.

### Statistical analysis

Statistical analyses were performed using SPSS 9.0 for Windows (37). Values are expressed as means  $\pm$  SD. For ease of comparison, all total scores on questionnaires were transformed to a 0–100 scale (using the Medical Outcome Survey scoring techniques, in which the patient raw score minus the lowest possible score is divided by the possible score range and multiplied by 100 [38]). Missing values on the CIDS scale (one missing:  $n = 15$ , four missing:  $n = 1$ ) and PAID scale (maximum of two missing:  $n = 9$ ) were corrected using the same Medical Outcome Survey scoring techniques (38). Cases with missing values on other questionnaires were excluded from the respective analyses. Analyses included Student's  $t$  tests and  $\chi^2$  tests. Because scores on the CIDS are not normally distributed, Spearman's correlation coefficients were estimated to determine associations between variables and for test-retest reliability. The Cronbach's  $\alpha$  coefficient was determined for internal consistency.  $P < 0.05$  was considered to be statistically significant. For comparisons on item level,  $P < 0.01$  was considered statistically significant. Exploratory factor analysis with varimax rotation was performed to examine the factor structure of the CIDS scale in the Dutch and U.S. samples. To reduce skewness and kurtosis caused by nonnormality, CIDS scores were transformed before analysis by squaring variables. Forced four-, three-, two-, and one-factor solutions were considered in the Dutch sample to identify meaningful factors. Missing values in this procedure were substituted by the mean.

## RESULTS

### Study 1: Evaluation of psychometric properties

In the Dutch sample, questionnaires were returned by 152 of 200 patients (76%). The reason for nonresponse was known for only six patients (physical condition did not allow completing the questionnaires [two patients], moved to an unknown address [three patients], questionnaire was sent in too late [one patient]). Of the 152 responders, 140 gave consent to obtain the most recent HbA<sub>1c</sub> level from their physician. A total of 21 physicians did not respond to this request, leaving HbA<sub>1c</sub> values for 119 patients (59.5%). HbA<sub>1c</sub> results were available for 145 patients (76%) in the U.S. sample. Data from three participants (one Dutch, two U.S.) could not be used

because of incomplete data on the CIDS scale. Data were analyzed for 151 Dutch patients and 190 U.S. patients.

Sociodemographic and clinical characteristics of both samples are displayed in Table 1.

The Dutch and U.S. samples had similar characteristics and comparable mean scores on the HFS worry scale (Dutch  $28.0 \pm 16.8$ , U.S.  $30.7 \pm 20.3$ ). The mean PAID score was higher in the U.S. sample ( $36.0 \pm 24.0$  vs.  $21.5 \pm 16.0$ ,  $P < 0.001$ ), confirming earlier findings (26).

**Reliability: internal consistency**—Internal consistency (standardized Cronbach's  $\alpha$ ) of the 20-item CIDS scale was high in both samples (Dutch 0.86, U.S. 0.90). Deletion of any of the items would not result in an increase of Cronbach's  $\alpha > 0.01$ , indicating that the CIDS is a homogeneous scale. Item-total correlations were all positive and ranged from 0.22 to 0.62 (Dutch sample) and 0.32 to 0.67 (U.S. sample).

**Factor structure**—The CIDS was designed to measure the same construct of self-efficacy across a range of self-care behaviors. Exploratory factor analysis was performed on the Dutch sample to assess whether one general underlying factor could be identified. Inspection of the scree plot of the initial unrotated factor solution showed five components with eigenvalues  $> 1$  (6.4, 1.7, 1.4, 1.1, and 1.0), with a sharp elbow between the first two components, accounting for 31.9, 8.4, 6.9, 5.5, and 5.2% of variance, respectively (57.8% in total). Principal components analysis with two to four components showed most items loaded high on the first principal component (0.32–0.72), with only two items loading  $< 0.40$  (“exercise two to three times weekly” and “perform the prescribed number of daily insulin injections”).

To assess whether items clustered into further meaningful underlying factors, forced factor solutions with two, three, and four varimax rotated factors were examined, accounting for 40.3, 47.2, and 52.7% of total variance, respectively. No meaningful interpretable factors could be distinguished. The initial unrotated factor solution in the U.S. sample showed a similar pattern of high loadings on the first component, with “keep daily records of my blood glucose” and “keep my medical appointments” loading  $< 0.40$ . Because analysis of reliability showed that Cronbach's  $\alpha$  was not compromised by any of the items, it was decided to retain all 20 items in one single scale.

The item “performing the prescribed number of insulin injections” did not load substantially on any factor. This is probably because of the very skewed scoring distribution, with 94% (U.S. 86%) indicating, “Yes, I am sure I can do this.”

**Validity**—Mean CIDS scores and scoring distributions were similar in both samples (Dutch  $0.83 \pm 11.5$ , U.S.  $85.0 \pm 12.5$ ), with some small but statistically significant differences between U.S. and Dutch respondents (Table 2). Scoring distributions were very skewed, with 80% scoring above 72.0 (Dutch) and 75.0 (U.S.), respectively, indicating high levels of self-efficacy. Items with highest mean scores were “perform the prescribed number of daily injections” (Dutch sample, mean score 4.88 of 5) and “keep my medical appointments” (U.S. sample, mean score 4.84 of 5). Items with lowest mean scores were similar in both samples: “keep my blood glucose in the normal range when under stress,” with mean item scores of 3.77 (Dutch) and 3.66 (U.S.), respectively. This finding is consistent with former findings (39), in which “maintaining normal blood glucose levels when under stress” was considered a serious problem by a large proportion (44%) of the study participants and “injecting insulin at regular intervals before meals” and “injecting outdoors” was considered no problem by ~80% of the study participants.



When exploring sex differences, mean score of U.S. men appeared higher than that of U.S. women ( $87.6 \pm 11.2$  vs.  $83.4 \pm 13.0$ ,  $P = 0.02$ ). On an item level, there were small differences. Self-efficacy ratings were higher in men on the items “treat a low blood glucose correctly” (4.79 vs. 4.46,  $P < 0.0001$ ) and “keep my blood glucose in the normal range when under stress” (4.00 vs. 3.34,  $P < 0.0001$ ). In the Dutch sample, men also had a higher mean score on this last item (3.99 vs. 3.56,  $P < 0.01$ ) and a lower mean score on “keep my medical appointments” (4.48 vs. 4.86,  $P < 0.0001$ ).

Total CIDS score correlated moderately (0.51,  $P < 0.0001$ ) with the overall rating of diabetes treatment self-efficacy in the Dutch sample.

Spearman correlation coefficients between the CIDS scale and other measures were all in the expected directions. CIDS scores were negatively associated with diabetes-related emotional distress (PAID scale) (Dutch  $-0.44$ , U.S.  $-0.52$ , both  $P < 0.0001$ ), fear of hypoglycemia (HFS worry scale) (Dutch  $-0.16$ ,  $P = 0.05$ ; U.S.  $-0.38$ ,  $P < 0.0001$ ), anxiety (Dutch  $-0.24$ ,  $P = 0.003$ ; U.S.  $-0.26$ ,  $P < 0.0001$ ), and depression (Dutch  $-0.17$ ,  $P = 0.04$ ; U.S.  $-0.26$ ,  $P < 0.0001$ ). CIDS scores were positively associated with self-esteem (Dutch  $0.16$ ,  $P = 0.05$ ; U.S.  $0.35$ ,  $P < 0.0001$ ) and self-care behavior (Dutch  $0.44$ , U.S.  $0.42$ , both  $P < 0.0001$ ). CIDS scores were associated with HbA<sub>1c</sub> in the U.S. sample only (U.S.  $-0.25$ ,  $P = 0.003$ ; Dutch  $-0.09$ , NS).

In the Dutch sample, the positive association between CIDS scores and perceived importance of self-care behavior (0.37,  $P < 0.0001$ ) and the negative association with perceived burden of self-care behavior ( $-0.39$ ,  $P < 0.0001$ ) were also in the expected directions.

### Study 2: test-retest reliability

In the test-retest sample, response to the second assessment after 2 weeks was 69%. Patients in this sample were younger than the first Dutch sample (mean age 36.3 vs. 43.2 years,  $P = 0.001$ ), whereas mean CIDS score and duration of diabetes were comparable. Spearman's correlation coefficient between test and retest was 0.85 ( $P = 0.0001$ ), indicating the CIDS scale is a stable short-term measure.

## CONCLUSIONS

Results of this study support the reliability and validity of the CIDS scale in patients with type 1 diabetes. Moderate correlations in the expected directions support construct validity while indicating that the CIDS scale reflects a unique construct. The CIDS scale demonstrated high psychometric similarity in Dutch and U.S. samples, allowing for cross-cultural comparisons. Examination of the factor structure showed that the CIDS scale is best considered and used as a unidimensional scale.

Because all items relate to different aspects of diabetes self-management and internal consistency is not compromised by any of them, redundancy does not seem to be a major concern. Research has consistently found that diabetes self-care behaviors are relatively independent of one another and that assessing the specific areas is important in determining the need for further support (40). The value of retaining the present items is underlined by the moderate correlation between the full-scale and the single general diabetes treatment self-efficacy item. However, revision of some of the items might further enhance the utility of the CIDS scale. The low discriminating power of the item concerning injection of insulin was recognized earlier by other researchers (6). However, because correct administration of insulin is crucial for good control, we consider this information valuable. Rewording the item in more specific terms, e.g., “I believe I can...always inject my insulin on the correct time/...outdoors/...when at work,” etc., may enhance the variance on this item. The item “...read and hear about diabetes complications without getting discouraged” is referring to mood rather than behavior

and might be better represented on a scale assessing mood and emotional problems, such as the PAID scale. Whereas the topic of stress is relevant to the management of diabetes for most patients, the item “I believe I can...keep my blood glucose in the normal range when under stress” does not clearly state whether stress management or self-management skills are addressed. This item might also be rephrased in future studies.

Data suggest that self-efficacy expectations are not automatically the same for men and women. In addition to the higher mean score of men in the U.S. sample, U.S. as well as Dutch men had a stronger belief in their own capability to keep their blood glucose within the normal range when under stress. These findings may be linked to the specific difficulties women experience with unexpected blood glucose fluctuations due to hormonal changes.

The usefulness of the CIDS scale as a screening tool to identify patients with suboptimal levels of self-efficacy remains open to question. Although glycemic control was associated with self-efficacy in the U.S. sample, self-efficacy was found to be more strongly associated with behavior than with outcome, with moderate correlations between CIDS scores and self-care. This result is in line with our expectations because not all CIDS items have a direct link with blood glucose (e.g., foot inspection), and glycemic control is determined by factors other than behavior (e.g., genetics, treatment prescriptions, etc.). However, discordance still exists between what people feel they are able to do and what they actually do.

The overall high levels of self-efficacy reported reflect that patients believe strongly in their capabilities. It is assumed that self-efficacy beliefs need not be accurate to be adaptive, and they operate partially independent of actual skills (41). High levels of self-efficacy have been considered adaptive because they stimulate people to set higher goals and persevere and surpass their usual level of accomplishment (41,42). In a recent study, patients with type 1 diabetes with more positive efficacy expectancies did use more adaptive coping and reported better mental health than patients holding a less optimistic view (43).

However, beliefs are not the only determinants of behavioral change. High levels of self-efficacy regarding a particular behavior do not automatically mean a person will engage in that behavior: patients do not perform several blood glucose tests per day simply because they feel able to do so (13). Appropriate skills, capabilities, knowledge, and incentives are required as well (44).

Although self-efficacy is not the only explanatory factor, it can add substantially to our understanding of self-care behavior: whereas self-judgements of efficacy may not presume individuals readiness to follow treatment recommendations, they must be present for treatment adherence to occur (13). Enhancing self-efficacy may increase patients' motivation for—and success with—behavioral efforts.

To assess self-efficacy beliefs in adult patients with type 1 diabetes, the CIDS scale proves to be a valuable, reliable, and easy-to-administer instrument, leaving its predictive value and responsiveness to change to be demonstrated in future research.

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## Abbreviations

CIDS, Confidence in Diabetes Self-Care; HFS, Hypoglycemia Fear Survey; PAID, Problem Areas in Diabetes; SMBG, self-monitoring of blood glucose.

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**Table 1**

## Patient characteristics

	Dutch sample	U.S. sample
n	151	190
Age (years)	43.2 ± 13.4	42.6 ± 13.1
Years of education	14.7 ± 3.4	15.3 ± 2.2
Duration of diabetes (years)	21.8 ± 13.0	22.2 ± 13.5
Sex (M/F)	73/78	75/115
% with ≥1 complication	40	38
HbA <sub>1c</sub> (%)	8.1 ± 1.3	8.3 ± 1.5

Data are n, means ± SD, or %. HbA<sub>1c</sub> was available for 118 and 145 patients in the Dutch and U.S. samples, respectively.

**Table 2**

Item content and means of the CIDS scale

	Dutch sample	U.S. sample
n	151	190
I believe I can...		
plan my meals and snacks according to dietary guidelines.	4.24 ± 0.78	4.31 ± 0.93
check my blood glucose at least two times a day.	4.48 ± 0.98	4.67 ± 0.81
perform the prescribed number of daily insulin injections.	4.88 ± 0.55	4.82 ± 0.52
adjust my insulin for exercise, traveling, or celebrations.	4.78 ± 0.53	4.52 ± 0.79 *
adjust my insulin when I am sick.	4.44 ± 0.85	4.34 ± 0.88
detect high levels of blood glucose in time to correct.	4.28 ± 0.90	4.34 ± 0.92
detect low levels of blood glucose in time to correct.	4.17 ± 0.89	4.21 ± 0.94
treat a high blood glucose correctly.	4.50 ± 0.67	4.54 ± 0.73
treat a low blood glucose correctly.	4.45 ± 0.68	4.59 ± 0.71 *
keep daily records of my blood glucose.	4.05 ± 1.25	4.44 ± 0.91 *
decide when it's necessary to contact my doctor or diabetes educator.	4.51 ± 0.62	4.56 ± 0.65
ask my doctor questions about my treatment plan.	4.72 ± 0.54	4.69 ± 0.63
keep my blood glucose in the normal range when under stress.	3.77 ± 0.98	3.66 ± 1.05 *
check my feet for sores or blisters every day.	4.01 ± 1.09	4.54 ± 0.83 *
ask my friends or relatives for help with my diabetes.	3.80 ± 1.17	4.01 ± 1.13
inform colleagues/others of my diabetes, if needed.	4.42 ± 0.79	4.45 ± 0.91
keep my medical appointments.	4.68 ± 0.66	4.84 ± 0.41 †
exercise two to three times weekly.	3.84 ± 1.29	4.19 ± 0.98 †
figure out what foods to eat when dining out.	4.37 ± 0.82	4.32 ± 0.89
read and hear about diabetes complications without getting discouraged.	4.05 ± 1.08	4.02 ± 1.07
Total scale	83.0 ± 11.5	85.0 ± 12.5

Data are *n* or means ± SD. Scoring range: from 1 (“No, I am sure I cannot”) to 5 (“Yes, I am sure I can”).

\* *P* < 0.001,

† *P* < 0.01.