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ORIGINAL ARTICLE

# Validation using item response theory, and assessment of sensitivity to change of the Hypoglycemia Awareness Questionnaire in patients with type 2 diabetes treated with insulin

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**Keywords**
HypoA-Q questionnaire, Type 2 Diabetes, Unawareness hypoglycemia

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## ABSTRACT

**Aims/Introduction:** It is important to develop valid tools to evaluate hypoglycemia perception such as the Hypoglycemia Awareness Questionnaire (HypoA-Q) in patients with Type 2 Diabetes (T2D). The aim of the study is to validate the HypoA-Q in patients with T2D treated with insulin using item response theory.

**Materials and Methods:** Individuals with T2D treated with insulin were included by non-random convenience sampling. A partial credit model was used for validation using item response theory, infit, and outfit statistics were calculated, person-item map and item characteristic curves were plotted, and differential item functioning was assessed.

**Results:** The study included 502 participants, the mean age at diagnosis of diabetes was 47.8 ± 13.9 years, the median time with the diagnosis was 15 years (IQR: 9–22), and the mean HbA1c 71 ± 27.3 mmol/mL (8.6 ± 2.5%), 48.6% had Glomerular Filtration Rate >60 mL/min/min$^2$. Item fit was found with items covering the full range of the construct of the participant population, although response options could be simplified. The person-item map showed that the scale covers a wide range of the construct and that the scale has items to measure these different levels. Item bias was not evident when comparing subgroups by age, sex and treatment.

**Conclusions:** The HypoA-Q is a valid measure for assessing hypoglycemia awareness in insulin-treated T2D patients because it has items that fit the measurement process, measures a wide range of awareness, and is free of biases related to gender, age, treatment, and duration of diabetes.

## INTRODUCTION

Hypoglycemia unawareness (HU) is characterized by plasma glucose levels below 70 mg/dL without the characteristic symptoms of hypoglycemia[1]; however, unlike autonomic neuropathy, HU is dynamic and may be reversible[2]. Long-standing, insulin-treated diabetes patients have a diminished ability to perceive hypoglycemia-related symptoms, a condition known as impaired hypoglycemia perception, and are at increased risk of developing severe hypoglycemia. This condition occurs more frequently in individuals diagnosed with type 1 diabetes (T1D) but can also occur in insulin-treated type 2 diabetes (T2D), with an estimated prevalence of 8–10%[3]. Gold[4] and Clarke[5] have proposed scales to assess impaired awareness of hypoglycemia. The Gold scale consists of only one question, and the response is given on a scale of 1 (no symptoms) to 7 (very severe symptoms)[4]. The Clarke scale has eight questions related

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to patients' awareness of hypoglycemia, frequency of severe or non-severe hypoglycemic episodes, and glucose levels at which hypoglycemic symptoms appear[5], and a Spanish version was validated in 2013[6].

The Hypoglycemia Awareness Questionnaire (HypoA-Q) was developed in the United Kingdom and consists of three subscales (impaired awareness, symptom severity, and symptom frequency) and was validated in 2015 for T1D and in 2023 for T2D using classical test theory (CTT) with the above two scales as reference standards[7, 8]. Receiver operating characteristic curve analysis revealed that the HypoA-Q IA subscale was an excellent predictor of an abnormal symptom response to hypoglycemia[9]. This instrument measures awareness of hypoglycemia while the patient is awake and asleep, as well as the frequency and percentage of recent hypoglycemic episodes and the need for and use of medical assistance. Evidence of criterion validity to assess awareness of hypoglycemia was observed in the correlations between the 'impaired awareness' subscale and measures of awareness on existing scales (correlation with Gold: 0.75 and correlation with Clarke: 0.76)[7]. Moreover, exploratory factor analysis allowed grouping several items of the impaired awareness subscale into a single domain.

Although instrument validation studies conducted using CTT evaluate psychometric properties such as test–retest reliability, internal consistency, criterion validity, construct validity and factor structure[10], which allow the reader to decide whether or not to use an instrument, item response theory (IRT) is a psychometric model that allows analysis of the ability of the instrument or its items to discriminate between different levels of the construct being measured (this is called the information function); to determine whether the items measure the construct for which they were proposed (item fit); to represent simultaneously the levels of the construct from the lowest to the highest, and the items from the one that best measures low levels to the one that best measures high levels, which makes it possible to determine whether the scale lacks items, and at what levels to check whether the response options for each question are appropriate or can be reduced (using item characteristic curves)[8]; and to determine whether responses may be biased by other variables such as age, education level or gender (this is called differential item functioning, which occurs when respondents of comparable ability but from different groups perform differently on an item of the scale).

However, none of the HU scales have been validated using IRT. Considering that a validation study has already been carried out in people with T2D treated with insulin according to the CTT, this study proposes to validate using IRT and analyze differential item functioning of the HypoA-Q scale to assess awareness of hypoglycemia.

## METHODS

### Type of study

A study to validate the HypoA-Q scale using IRT and assess sensitivity to change.

**Table 1** | Characteristics of the study population

| Characteristics of the study population | *n* = 502 |
|---|---|
| Women, *n* (%) | 274 (54.6) |
| Age in years, median (IQR) | 65 (58–73) |
| Diabetes duration in years, median (IQR) | 15 (9–22) |
| Charlson Comorbidity Index, median (IQR) | 4 (2–6) |
| Polypharmacy *n* (%) | 356 (71) |
| Body mass index (kg/m$^2$), median (IQR) | 26.9 (23.8–30.4) |
| Microvascular complications | |
| Nephropathy | 200 (41.6)[1] |
| Retinopathy | 186 (38.5)[2] |
| Neuropathy | 110 (22.8)[3] |
| Diabetic foot | 69 (14.1)[4] |
| Macrovascular complications | |
| Peripheral arterial disease | 162 (33.8)[5] |
| Coronary heart disease | 132 (27.5)[5] |
| Heart failure | 30 (6.2)[6] |
| Cerebrovascular disease | 30 (6.3)[7] |
| HbA1c (mmol/mol), mean (SD) | 71 (27.3) |
| HbA1c (%), mean (SD) | 8.6 (2.5)[8] |
| Glomerular filtration rate (mL/min/1.73 m$^2$) | |
| Stage 1 (GFR >90) | 127 (33.9)[9] |
| Stage 2 (GFR 60–90) | 110 (29.4)[9] |
| Stage 3a (GFR 60–45) | 48 (12.8)[9] |
| Stage 3b (GFR 45–30) | 38 (10.2)[9] |
| Stage 4 (GFR 30–15) | 31 (8.3)[9] |
| Stage 5 (GFR <15) | 20 (5.3)[9] |
| Insulin regimen | |
| Basal-Bolus | 261 (54.6)[10] |
| Basal-plus | 56 (11.7)[10] |
| Basal | 161 (33.7)[10] |
| Basal insulin | |
| Neutral protamine Hagedorn (NPH) insulin | 3 (0.6)[11] |
| Insulin glargine | 323 (67.8)[11] |
| Insulin detemir | 24 (5)[11] |
| Insulin degludec | 126 (26.5)[11] |
| Hypoglycemic agent | |
| Metformin | 221 (46.9)[12] |
| Dipeptidyl peptidase-4 inhibitor | 106 (22.5)[12] |
| Sodium-glucose cotransporters inhibitors | 122 (25.9)[12] |
| Glucagon-like peptide-1 receptor agonist | 106 (22.5)[12] |
| Number of blood glucose readings per day | |
| 1 blood glucose reading per day, *n* (%) | 92 (19.3)[13] |
| 2 blood glucose readings per day, *n* (%) | 133 (28)[13] |
| 3 blood glucose readings per day, *n* (%) | 130 (27.4)[13] |
| ≥4 blood glucose readings per day | 123 (25.9)[13] |
| Use of real-time blood glucose monitoring | 37 (7) |

1. Results of 481 patients 2. Results of 483 patients. 3. Results of 482 patients. 4. Results of 490 patients. 5. Results of 480 patients. 6. Results of 484 patients. 7. Results of 479 patients. 8. Results of 380 patients. 9. Results of 374 patients. 10. Results of 478 patients. 11. Results of 476 patients.12. Results of 471 patients. 13. Results of 475 patients.

### Instrument

The HypoA-Q questionnaire measures the patient's awareness of hypoglycemia while awake or asleep. It consists of 33 items

**Table 2** | Frequency and percentage of responses to the items of the HypoA-Q scale according to the T2D treatment

| Hypoglycemia when awake | | | | | | |
|---|---|---|---|---|---|---|
| Treatment | Never | Once or twice | Three or four times | About once or twice a month | About once a week | More than once a week |
| 3. In the past 6 months how often have you had hypoglycemia when awake? | | | | | | |
| GLP1 | 11 (11.00) | 46 (46.00) | 16 (16.00) | 11 (11.00) | 8 (8.00) | 8 (8.00) |
| Metformin | 44 (19.91) | 87 (39.37) | 39 (17.65) | 17 (7.69) | 14 (6.33) | 20 (9.05) |
| SGLT2 | 14 (11.76) | 53 (44.54) | 19 (15.97) | 11 (9.24) | 8 (6.72) | 14 (11.76) |
| iDDP4 | 8 (7.55) | 44 (41.51) | 28 (26.42) | 13 (12.26) | 7 (6.60) | 6 (5.66) |
| All | 104 (20.7) | 189 (37.6) | 95 (18.9) | 58 (11.5) | 27 (5.4) | 29 (5.8) |
| 4. In the past 6 months how often have you had hypoglycemia while awake in which… | | | | | | |
| (a) …had symptoms and were able to treat yourself? | | | | | | |
| GLP1 | 20 (20.20) | 40 (40.40) | 19 (19.19) | 5 (5.05) | 8 (8.08) | 7 (7.07) |
| Metformin | 65 (29.68) | 78 (35.62) | 36 (16.44) | 14 (6.39) | 12 (5.48) | 14 (6.39) |
| SGLT2 | 29 (24.58) | 46 (38.98) | 15 (12.71) | 6 (5.08) | 8 (6.78) | 14 (11.86) |
| iDDP4 | 27 (25.96) | 41 (39.42) | 19 (18.27) | 7 (6.73) | 7 (6.73) | 3 (2.88) |
| All | 181 (36.35) | 161 (32.33) | 71 (14.26) | 39 (7.83) | 23 (4.62) | 23 (4.62) |
| (b) …had symptoms and were not able to treat yourself? | | | | | | |
| GLP1 | 76 (76.00) | 16 (16.00) | 3 (3.00) | 3 (3.00) | 1 (1.00) | 1 (1.00) |
| Metformin | 170 (77.63) | 34 (15.53) | 9 (4.11) | 2 (0.91) | 1 (0.46) | 3 (1.37) |
| SGLT2 | 92 (77.31) | 18 (15.13) | 4 (3.36) | 4 (3.36) | 0 (0.00) | 1 (0.84) |
| iDDP4 | 74 (70.48) | 21 (20.00) | 3 (2.86) | 3 (2.86) | 1 (0.95) | 3 (2.86) |
| All | 370 (74.15) | 80 (16.03) | 26 (5.21) | 14 (2.81) | 5 (1.00) | 4 (0.80) |
| (c) …someone else had to give you glucose orally? | | | | | | |
| GLP1 | 79 (79.00) | 11 (11.00) | 3 (3.00) | 4 (4.00) | 1 (1.00) | 2 (2.00) |
| Metformin | 176 (80.37) | 29 (13.24) | 7 (3.20) | 4 (1.83) | 1 (0.46) | 2 (0.91) |
| SGLT2 | 94 (78.99) | 17 (14.29) | 2 (1.68) | 4 (3.36) | 0 (0.00) | 2 (1.68) |
| iDDP4 | 76 (72.38) | 20 (19.05) | 2 (1.90) | 3 (2.86) | 2 (1.90) | 2 (1.90) |
| All | 370 (74.15) | 74 (14.83) | 25 (5.01) | 19 (3.81) | 6 (1.20) | 5 (1.00) |

| Treatment | 71 mg/dL or more | 63–70 mg/dL | 54–62 mg/dL | 53–45 mg/dL | Below 45 mg/dL | I don't have any of these symptoms (5) |
|---|---|---|---|---|---|---|
| 6. How low does your blood glucose levels usually have to be before you feel one of the following symptoms? | | | | | | |
| (a) Tremors, racing heart, hot flashes, sweating, hunger | | | | | | |
| GLP1 | 18 (18.00) | 37 (37.00) | 16 (16.00) | 7 (7.00) | 6 (6.00) | 16 (16.00) |
| Metformin | 49 (22.37) | 90 (41.10) | 26 (11.87) | 9 (4.11) | 8 (3.65) | 37 (16.89) |
| SGLT2 | 24 (20.34) | 41 (34.75) | 20 (16.95) | 6 (5.08) | 9 (7.63) | 18 (15.25) |
| iDDP4 | 25 (23.81) | 47 (44.76) | 13 (12.38) | 4 (3.81) | 5 (4.76) | 11 (10.48) |
| All | 118 (23.74) | 184 (37.02) | 60 (12.07) | 24 (4.83) | 25 (5.03) | 86 (17.30) |
| (b) Weakness, lack of coordination, confusion, dizziness, inability to concentrate, slurred speech, blurred vision, sleepiness, tiredness, irritability, odd behavior | | | | | | |
| GLP1 | 14 (14.00) | 34 (34.00) | 15 (15.00) | 4 (4.00) | 8 (8.00) | 25 (25.00) |
| Metformin | 43 (19.72) | 82 (37.61) | 20 (9.17) | 12 (5.50) | 12 (5.50) | 49 (22.48) |
| SGLT2 | 18 (15.25) | 41 (34.75) | 13 (11.02) | 11 (9.32) | 8 (6.78) | 27 (22.88) |
| iDDP4 | 20 (19.05) | 41 (39.05) | 10 (9.52) | 5 (4.76) | 5 (4.76) | 24 (22.86) |
| All | 102 (20.56) | 163 (32.86) | 52 (10.48) | 27 (5.44) | 34 (6.85) | 118 (23.79) |
| (c) Nausea, tingling, headache | | | | | | |
| GLP1 | 9 (9.00) | 7 (7.00) | 5 (5.00) | 0 (0.00) | 1 (1.00) | 78 (78.00) |
| Metformin | 26 (11.87) | 29 (13.24) | 10 (4.57) | 7 (3.20) | 5 (2.28) | 142 (64.84) |
| SGLT2 | 12 (10.17) | 11 (9.32) | 8 (6.78) | 3 (2.54) | 2 (1.69) | 82 (69.49) |
| iDDP4 | 11 (10.38) | 17 (16.04) | 6 (5.66) | 4 (3.77) | 2 (1.89) | 66 (62.26) |
| All | 68 (13.68) | 71 (14.29) | 23 (4.63) | 10 (2.01) | 14 (2.82) | 311 (62.58) |

| | Never | Rarely | Sometimes | Frequently | Always |
|---|---|---|---|---|---|
| 7. I show symptoms when my blood glucose levels are low | | | | | |
| GLP1 | 4 (4.08) | 9 (9.18) | 8 (8.16) | 14 (14.29) | 63 (64.29) |

**Table 2.** (*Continued*)

| | Never | Rarely | Sometimes | Frequently | Always |
|---|---|---|---|---|---|
| Metformin | 21 (9.63) | 31 (14.22) | 30 (13.76) | 31 (14.22) | 105 (48.17) |
| SGLT2 | 9 (7.63) | 14 (11.86) | 13 (11.02) | 16 (13.56) | 66 (55.93) |
| iDDP4 | 7 (6.67) | 14 (13.33) | 16 (15.24) | 15 (14.29) | 53 (50.48) |
| All | 55 (11.07) | 80 (16.10) | 65 (13.08) | 71 (14.29) | 226 (45.47) |
| 8. I just know when I am having hypoglycemia by the way I feel | | | | | |
| GLP1 | 5 (5.05) | 4 (4.04) | 11 (11.11) | 10 (10.10) | 69 (69.70) |
| Metformin | 27 (12.33) | 23 (10.50) | 18 (8.22) | 29 (13.24) | 122 (55.71) |
| SGLT2 | 9 (7.63) | 12 (10.17) | 8 (6.78) | 16 (13.56) | 73 (61.86) |
| iDDP4 | 11 (10.48) | 14 (13.33) | 10 (9.52) | 13 (12.38) | 57 (54.29) |
| All | 81 (16.27) | 60 (12.05) | 57 (11.45) | 61 (12.25) | 239 (47.99) |
| 9. I check my blood glucose levels when I feel unwell | | | | | |
| GLP1 | 4 (4.04) | 7 (7.07) | 13 (13.13) | 9 (9.09) | 66 (66.67) |
| Metformin | 36 (16.44) | 13 (5.94) | 25 (11.42) | 27 (12.33) | 118 (53.88) |
| SGLT2 | 8 (6.78) | 8 (6.78) | 11 (9.32) | 15 (12.71) | 76 (64.41) |
| iDDP4 | 12 (11.43) | 8 (7.62) | 12 (11.43) | 15 (14.29) | 58 (55.24) |
| All | 76 (15.23) | 44 (8.82) | 56 (11.22) | 59 (11.82) | 264 (52.91) |
| 10. Others notice that I am having hypoglycemia before I do | | | | | |
| GLP1 | 62 (62.63) | 4 (4.04) | 5 (5.05) | 3 (3.03) | 25 (25.25) |
| Metformin | 137 (62.56) | 20 (9.13) | 14 (6.39) | 8 (3.65) | 40 (18.26) |
| SGLT2 | 75 (63.56) | 6 (5.08) | 6 (5.08) | 4 (3.39) | 27 (22.88) |
| iDDP4 | 60 (57.14) | 11 (10.48) | 6 (5.71) | 6 (5.71) | 22 (20.95) |
| All | 277 (55.51) | 42 (8.42) | 43 (8.62) | 40 (8.02) | 97 (19.44) |

| Treatment | Strongly disagree | Disagree | Neither agree nor disagree | Agree | Strongly agree |
|---|---|---|---|---|---|
| 11. I am now less aware of when my hypoglycemia starts than I used to be | | | | | |
| GLP1 | 40 (40.40) | 32 (32.32) | 11 (11.11) | 7 (7.07) | 9 (9.09) |
| Metformin | 75 (34.56) | 56 (25.81) | 46 (21.20) | 21 (9.68) | 19 (8.76) |
| SGLT2 | 44 (37.93) | 30 (25.86) | 24 (20.69) | 8 (6.90) | 10 (8.62) |
| iDDP4 | 24 (23.08) | 20 (19.23) | 29 (27.88) | 18 (17.31) | 13 (12.50) |
| All | 145 (29.35) | 138 (27.94) | 122 (24.70) | 47 (9.51) | 42 (8.50) |
| 12. I no longer have symptoms that I used to have when my blood glucose levels were low | | | | | |
| GLP1 | 47 (47.47) | 27 (27.27) | 13 (13.13) | 10 (10.10) | 2 (2.02) |
| Metformin | 77 (35.48) | 72 (33.18) | 44 (20.28) | 17 (7.83) | 7 (3.23) |
| SGLT2 | 48 (41.38) | 33 (28.45) | 21 (18.10) | 9 (7.76) | 5 (4.31) |
| iDDP4 | 32 (30.77) | 28 (26.92) | 28 (26.92) | 7 (6.73) | 9 (8.65) |
| All | 155 (31.31) | 161 (32.53) | 126 (25.45) | 33 (6.67) | 20 (4.04) |
| 13. In the past 6 months I have been more aware of my hypoglycemia than I was before | | | | | |
| GLP1 | 10 (10.10) | 11 (11.11) | 17 (17.17) | 29 (29.29) | 32 (32.32) |
| Metformin | 20 (9.22) | 30 (13.82) | 55 (25.35) | 57 (26.27) | 55 (25.35) |
| SGLT2 | 16 (13.79) | 9 (7.76) | 23 (19.83) | 35 (30.17) | 33 (28.45) |
| iDDP4 | 17 (16.35) | 10 (9.62) | 27 (25.96) | 27 (25.96) | 23 (22.12) |
| All | 50 (10.10) | 72 (14.55) | 155 (31.31) | 115 (23.23) | 103 (20.81) |

Hypoglycemia when asleep

| Treatment | Never | Less than once a month | About once or twice a month | About once per week | About twice per week | Most of the days |
|---|---|---|---|---|---|---|
| 15. In the past 6 months how often have you had hypoglycemia while asleep? | | | | | | |
| GLP1 | 63 (62.38) | 20 (19.80) | 14 (13.86) | 2 (1.98) | 2 (1.98) | 0 (0.00) |
| Metformin | 134 (61.75) | 51 (23.50) | 15 (6.91) | 7 (3.23) | 8 (3.69) | 2 (0.92) |
| SGLT2 | 72 (61.54) | 26 (22.22) | 10 (8.55) | 5 (4.27) | 3 (2.56) | 1 (0.85) |
| iDDP4 | 54 (51.92) | 32 (30.77) | 9 (8.65) | 4 (3.85) | 4 (3.85) | 1 (0.96) |
| All | 316 (63.84) | 100 (20.20) | 44 (8.89) | 17 (3.43) | 14 (2.83) | 4 (0.81) |

| Treatment | Never | Rarely | Sometimes | Frequently | Always | NA |
|---|---|---|---|---|---|---|
| 17. While asleep, do you have symptoms that wake you up when your blood glucose levels are low? | | | | | | |
| GLP1 | 57 (57.58) | 12 (12.12) | 9 (9.09) | 5 (5.05) | 16 (16.16) | 0 (0.00) |
| Metformin | 138 (63.59) | 27 (12.44) | 13 (5.99) | 9 (4.15) | 29 (13.36) | 1 (0.46) |
| SGLT2 | 68 (57.63) | 17 (14.41) | 12 (10.17) | 5 (4.24) | 16 (13.56) | 0 (0.00) |
| iDDP4 | 51 (48.57) | 20 (19.05) | 12 (11.43) | 4 (3.81) | 18 (17.14) | 0 (0.00) |
| All | 314 (63.05) | 62 (12.45) | 38 (7.63) | 17 (3.41) | 66 (13.25) | 1 (0.20) |

**Table 3** | Summary table of the model

| Statistics | Items |
|---|---|
| Mean logit scale location | 0.22 |
| Standard deviation of Logit scale location | 0.78 |
| Mean standard error | 0.11 |
| Standard deviation of standard error | 0.03 |
| Mean Outfit MSE | 0.95 |
| Standard deviation of Outfit MSE | 0.12 |
| Mean Infit MSE | 0.96 |
| Standard deviation of Infit MSE | 0.07 |
| Standardized mean Outfit | −0.85 |
| Standard deviation of standardized mean Outfit | 1.8 |
| Standardized mean Infit | −0.75 |
| Standard deviation of standardized mean Infit | 1.44 |

For the items, infit and outfit statistics were within the range for a good fit: values between 0.5 and 1.9 indicate a good fit in the unstandardized form, as do values between −1.9 and 1.9 in the standardized form.

distributed in 3 subscales: impaired awareness, symptom level, and symptom frequency. The subscales allow the user to decide the aspects to focus on when assessing the patient. The scores for each subscale were obtained instead of providing a single composite score, thus enabling users to choose the aspects or groups of aspects relevant to their objectives. The questionnaire also provides an algorithm to score the subscales. Items 1 and 2 were analyzed to assess the frequency of hypoglycemia events and healthcare services used in the last 6 months, respectively. Items 4c, 4d, 9, 16b, and 16c were scored on a Likert-type scale with 5 or 6 response options. Items 4c and 4d evaluated the frequency of interventions for hypoglycemic events performed by the patient and the caregiver during the day, such as monitoring and correction of oral glucose levels and use of glucagon, whereas items 16b and 16c evaluated these behaviors during the night. Item 9 assessed the capillary blood glucose readings obtained during hypoglycemic events[11]. The English version of the HypoA-Q questionnaire is available in Speight *et al.*[7] and the Spanish version can be found in the study by Carrillo *et al.*[12] This study used the version of the instrument translated and adapted to Colombian Spanish[12].

### Participants

The study population was composed of patients aged 18 years or older, with T2D ≥ 1 year of diagnosis, regardless of HbA1c level, treated with at least one dose of insulin, with a history of hypoglycemia level 1, 2 or 3 in the previous 6 months, without obvious difficulties in reading or understanding the items of the scale, attending three high complexity institutions (Hospital San José, Hospital Universitario San Ignacio, Hospital Clínica San Rafael) and a primary care center (Cafam) in the city of Bogotá, Colombia, between April 2019 and October 2022. All patients signed an informed consent form. The protocol was approved by the institutional ethics committee (code EPR-DEC-I-0276-17, code FM-CIE-0108-19, code CIE-186-2020).

Baseline information on microvascular complications (nephropathy, retinopathy, neuropathy, diabetic foot) and macrovascular complications (peripheral arterial disease, coronary heart disease, heart failure, cerebrovascular disease), HbA1c and creatinine were obtained from clinical records. Glomerular filtration rate was calculated using CKD-EPI.

### Statistical analysis

The qualitative variables were expressed as absolute and relative frequencies, while the quantitative variables were expressed as measures of central tendency and dispersion.

Validation of the scale using IRT involved building a partial credit model. This model was chosen because it allowed for the inclusion of items with different response options between them. For this model, counting questions (1–2d) were excluded; only Likert-type scale items were considered, and given the low frequency of responses in items 4d, 6c, 14, 16 (a–e), 18, and 20, they were not included in the analysis. Considerations for building the model using IRT are listed in the Data S1.

Once the model was fitted, the reliability was calculated (values close to 1 indicate greater reliability), the fit of each item to the measurement objective was assessed (values of the INFIT and OUTFIT statistics are expected between 0.5 and 1.5 without standardization or between 1.9 and 1.9 standardized to conclude that they fit the model; values greater than 1.5 (or 1.9 standardized) indicate misfit and values <0.5 (or −1.9 standardized) indicate that some items are redundant, that is, they measure the same level of the construct), a diagnosis of the measurement scale was made using characteristic curves of the

**Table 4** | Calibration of items

| Item | Outfit | Standardized Outfit | Infit | Standardized Infit |
|---|---|---|---|---|
| 3. In the past 6 months how often have you had hypoglycemia when awake? | 0.94 | −0.9 | 0.96 | −0.7 |
| 4. In the past 6 months how often have you had hypoglycemia while awake in which… | | | | |
| (a) …had symptoms and were able to treat yourself? | 0.94 | −0.8 | 0.99 | −0.01 |
| (b) …had symptoms and were not able to treat yourself? | 0.86 | −1.7 | 0.94 | −0.7 |
| (c) …someone else had to give you glucose orally? | 0.82 | −2.2 | 0.91 | −1.2 |
| 6. How low does your blood glucose levels usually have to be before you feel one of the following symptoms? | | | | |
| (a) Tremors, racing heart, hot flashes, sweating, hunger. | 0.8 | −3.3 | 0.85 | −2.9 |
| (b) Weakness, lack of coordination, confusion, dizziness, inability to concentrate, slurred speech, blurred vision, sleepiness, tiredness, irritability, odd behavior. | 0.84 | −3.1 | 0.86 | −3.2 |
| 7. I show symptoms when my blood glucose levels are low. | 0.94 | −1.04 | 0.97 | −0.69 |
| 8. I just know when I am having hypoglycemia by the way I feel. | 0.93 | −1.3 | 0.95 | −1.1 |
| 9. I check my blood glucose levels when I feel unwell. | 1.2 | 3.04 | 1.14 | 2.7 |
| 10. Others notice that I am having hypoglycemia before I do. | 0.93 | −1.1 | 0.95 | −1.1 |
| 11. I am now less aware of when my hypoglycemia starts than I used to be. | 0.9 | −2.2 | 0.89 | −1.9 |
| 12. I no longer have symptoms that I used to have when my blood glucose levels were low. | 0.9 | −1.7 | 0.92 | −1.4 |
| 13. In the past 6 months I have been more aware of my hypoglycemia than I was before. | 1.02 | 0.53 | 1.01 | 0.26 |
| 15. In the past 6 months how often have you had hypoglycemia while asleep? | 1.2 | 1.8 | 1.02 | 0.3 |
| 17. While asleep, do you have symptoms that wake you up when your blood glucose levels are low? | 1.1 | 1.3 | 1.02 | 0.31 |

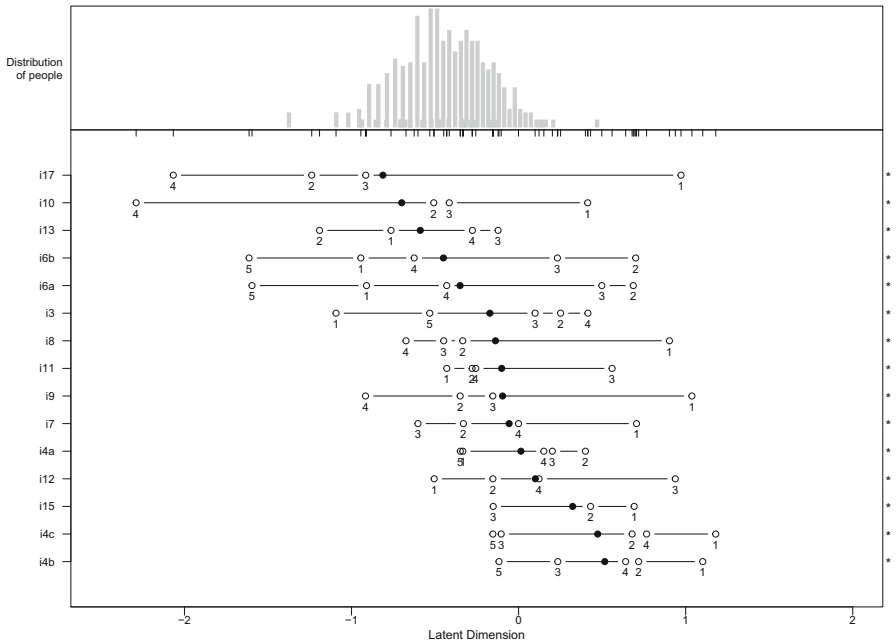


**Figure 1** | Person-item maps. At the top (distribution of people) the distribution of subjects along the latent dimension (hypoglycemia awareness) is observed. At the bottom, you can see the distribution of the items. The black circle (●) corresponds to the item and white circles (○) corresponds to the response options. In this case, all response options cover the entire distribution range of the subjects.

items (each curve represents an option, each curve is expected to measure a range of the underlying construct: if one curve is contained within another, it does not contribute to the measurement), and a map of people and items was made (representation of the distribution of the construct from lowest to highest and of the items along it: Items on the right are appropriate for measuring high levels of the construct, while items on the left are appropriate for measuring low levels)[13].

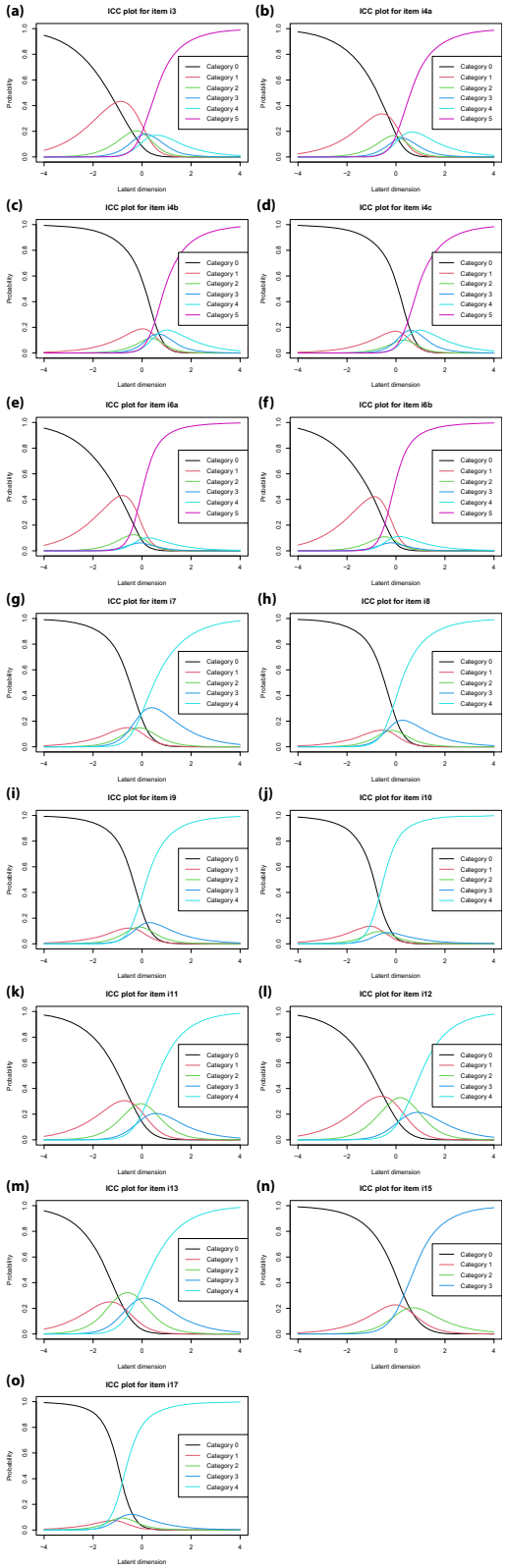


**Figure 2** | Item characteristic curves. The *x* axis represents the range of hypoglycemia awareness from lowest (–4) to highest (+4) according to the TRI. If a subject scores 0, he or she is considered to have average hypoglycemia awareness. The Y axis represents the probability of selecting an option for that item. The colored lines (0–5) correspond to the response options of the items. If a curve is included in other curves, it does not contribute to the measurement, for example, in item 4b, option 5 does not contribute to the measurement because options 0 and 2 are more likely to be selected.

Differential item functioning was assessed by establishing subgroups based on sex, insulin regimen, age, and duration of the disease. This differential functioning refers to a difference in item performance between groups of patients who share the same level of the construct but belong to different groups[14]. It was analyzed using graphs of standardized mean differences: if an item lies outside the limits of the standardized differences, this suggests some degree of differential functioning. The analyses were carried out in the R programming language using the R Studio® integrated development environment and its eRm library[15].

The sample size was determined as reported in the literature for instrument validation by IRT using the partial credit model. Reise and Yu (1990) suggested a minimum of 500 individuals for this model[16]. Additional considerations for building the model are provided in the Data S1.

## RESULTS

### Description of the study population

The study included 502 participants, 54.6% were women, the median age was 65 years (interquartile range (IQR): 58–73), the mean age at diagnosis of diabetes was 47.8 ± 13.9 years, and the median time with diagnosis was 15 years (IQR: 9–22) and mean HbA1c 71 ± 27.3 mmol/mL (8.6 ± 2.5%), 48.6% had TFG >60 mL/min/min$^2$. As for the insulin treatment, the most common long-acting insulin was Glargine (67%), followed by Degludec (26.7%), Detemir (5%), and NPH (0.6%), with median daily doses of 24 (IQR: 16–34), 20 (IQR: 14–32), 28 (IQR: 16–40), and 20 (IQR: 10–30) units, respectively. The basal-bolus regimen was the most common (54.4%). The characteristics of the study population are presented in Table 1. In the year prior to questionnaire administration, the median number of self-reported level 1 or 2 hypoglycemic episodes was 1 (IQR: 0–3). Due to severe hypoglycemia, 1.8% ($n$ = 9) of individuals required paramedic services, 6.9% ($n$ = 34) visited the emergency room, and 8.8% ($n$ = 43) were hospitalized. The threshold for awareness of hypoglycemia as reported by patients on the Gold Score of 1–7 had a median value of 5 (IQR: 3–7).

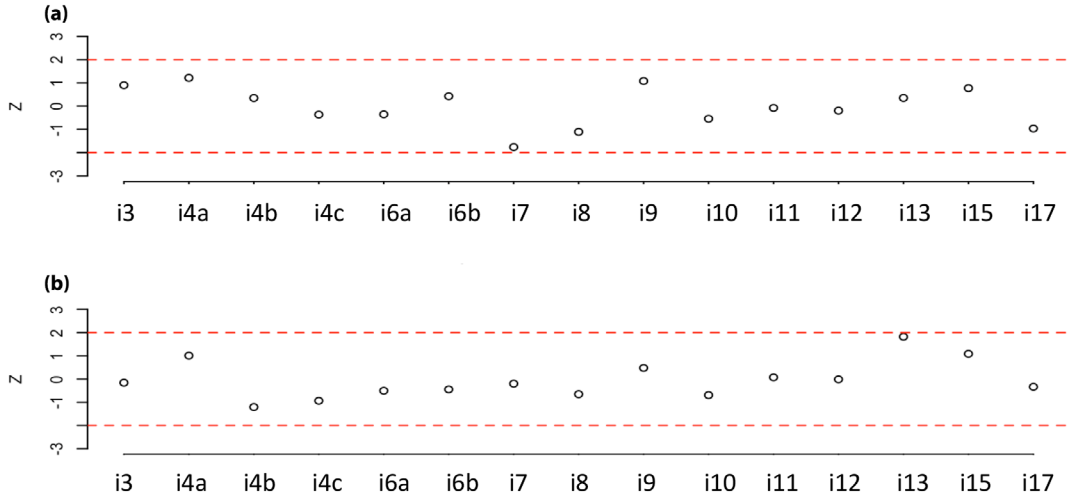


**Figure 3** | Plots of standardized differences for items between subgroups: gender and age. The *x* axis represents each item; the *y* axis represents the standardized mean difference between the groups (*z*-score): If there are no differences between the groups, the score is expected to be 0, and if there is an important difference, the score is expected to be above 2 or below −2. (a) Plot of standardized differences between men and women participants. (b) Plot of standardized differences between participants aged <65 years and ≥65 years.

Table 2 shows the frequency and percentage of responses to the items that were selected for validation using the IRT according to the T2D treatment where it can be observed that the recognition of hypoglycemia varied across the different items. In terms of the HypoA-Q questionnaire variables, less than half (45.8%) of the participants presented with hypoglycemia-related symptoms when hypoglycemia occurred. The Data S1 contains information about symptoms, their frequencies, and percentages.

### Validation using IRT

Compliance with the unidimensionality assumption was verified (likelihood-ratio, chi-squared test (836) = 407.429, $P = 1$). As for the items, infit and outfit statistics yielded results within the range for providing a good fit: no item redundancy or poor item fit was observed, as shown by the values reported in Tables 3 and 4.

Person-item maps were constructed with an approximately normal distribution. The distribution of the participants was observed along the latent dimension (hypoglycemia awareness) and the categories of each item were positioned with respect to the dimension and information of each item. This is shown in Figure 1.

When the item characteristic curves were plotted, the shape of each of the response options became clear, showing that most items had many options, which could be simplified to three or four, as shown in Figure 2.

### Differential item functioning analysis

The differential item functioning analysis did not find any item biased or influenced by subgroups considering the characteristics selected for assessment. Figure 3 shows plots of standardized differences for items between subgroups according to non-modifiable factors such as sex and age. No significant differences were found between the groups. However, subgrouping by type of treatment revealed that item 3 ("In the past six months how often have you had hypoglycemia when awake?") had significant differential functioning as shown in Figure 4 (a)(d) when comparing the basal regimen with the basal-plus and basal-bolus regimens together. Conversely, grouping the basal and basal-plus regimen to compare it with the basal-bolus regimen showed differential functioning for items 3 and 4a ("In the past 6 months how often have you had hypoglycemia when awake in which you had symptoms and were you able to treat yourself?") as shown in Figure 4 (c).

## DISCUSSION

This study found that the scale measures a single latent trait referred to as awareness of hypoglycemia. Secondly, the items fit well with the measurement process, with no mismatch or redundancy. Thirdly, the scale has items to measure different levels of the construct, and the scale provides more information on the mean levels of the construct. Finally, the response options could be simplified. These findings complement those reported in the analyses using classical test theory, in which criterion validity against a reference standard, internal consistency, and a three-factor structure were demonstrated[8]. Taken together, these findings support the use of the scale to assess impaired awareness of hypoglycemia.

The scale validation study is conducted to ensure that a measurement instrument meets certain psychometric characteristics that support its use to measure a given phenomenon[17].

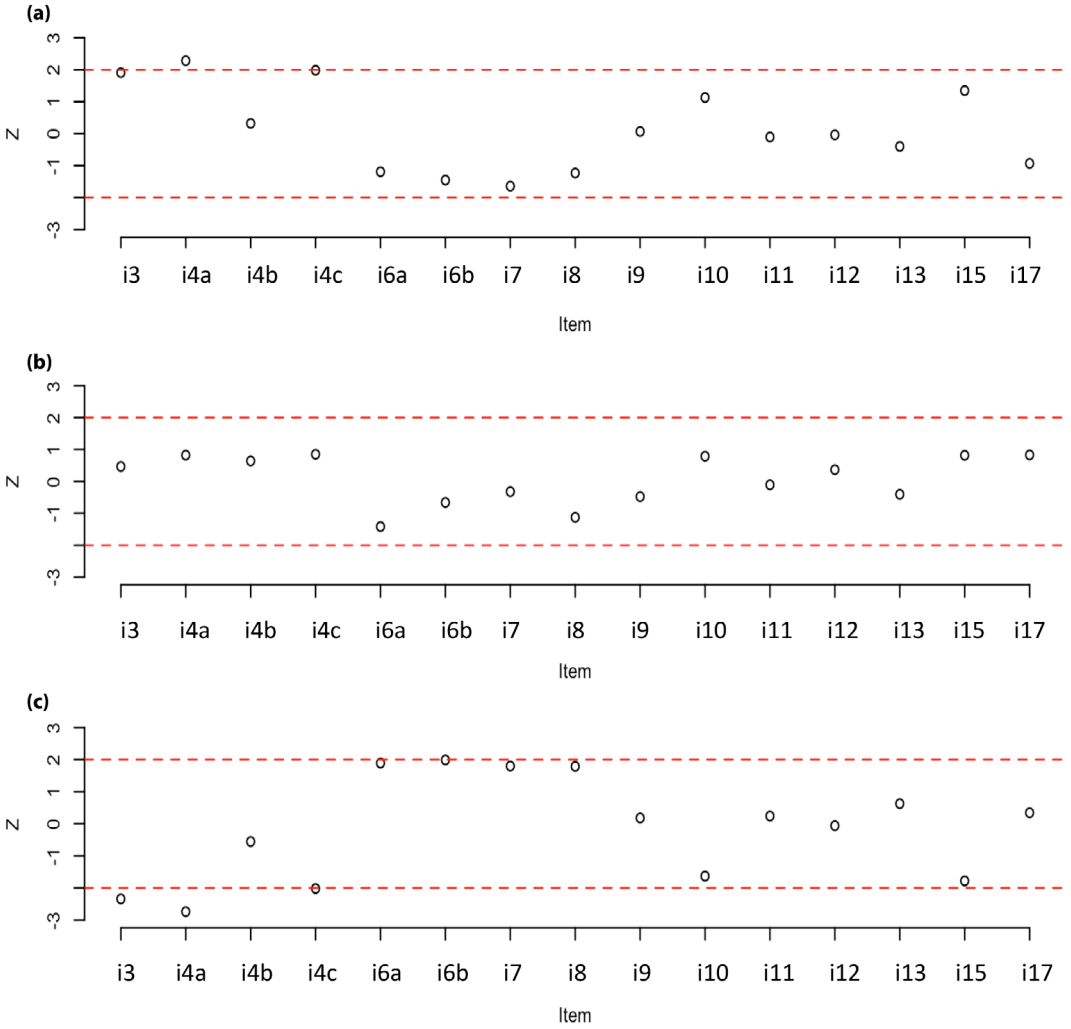


**Figure 4** | Plots of standardized differences for items between subgroups: basal, basal-plus, basal-bolus regimens. The *X* axis represents each item; the *Y* axis represents the standardized mean difference between groups (*Z*-score): if there are no differences between groups, the point is expected to be at the value 0, and if there is a difference in importance, it is expected to be above 2 or below −2. Significant differential functioning is shown in Figure 4a when comparing the basal regimen with the basal-plus and basal-bolus regimens together in item 4a. (a) Plot of standardized differences between basal regimen and subgroup basal-plus and basal-bolus regimens (grouped). (b) Plot of standardized differences between basal-plus regimen and subgroup basal and basal-bolus regimens (grouped). (c) Plot of standardized differences between basal-bolus regimen and subgroup basal and basal-plus regimens (grouped).

Techniques have been developed over the years to conduct this study, usually using classical test theory. However, IRT has become increasingly popular[18] and is used in the present study to demonstrate the validity of the HypoA-Q scale, with favorable results that support its use to assess awareness of hypoglycemia.

Differential item functioning (DIF), the absence of which is understood as the impartiality of the test when applied, that is, no influence of the participants' personal characteristics on the measurement of the construct, indicated that the scale responses are not biased by attributes other than levels of awareness of hypoglycemia. Similar findings have been described in T2D patients with HU using the Gold and Clarke scales since the awareness of hypoglycemia did not depend on age, sex, duration of disease, or duration of insulin therapy, irrespective of the classification method used[19]. The absence of DIF was demonstrated in the present study, except for items 3 and 4a when patients were grouped by treatment.

This is the first validation study of the HypoA-Q scale using IRT and patients with T2D. The strengths of this study include a multicenter study with a large sample size, providing accurate estimates for the partial credit model, and ensuring different levels of awareness of hypoglycemia to assess the behavior of the items across these different levels. In addition, the personnel

in charge of applying the scale were trained to ensure objective and appropriate testing. Finally, the analysis of the properties of the scale was complemented with estimates of the DIF.

The limitations of this study include the low frequency of patients with insulin pumps; therefore, this item could not be investigated. In addition, there were several response options for items with a ceiling or floor effects. Because of the low frequency of responses to some items, they were not included in the analysis. However, the IRT is scored on an item-by-item basis, so excluding some items from the analysis does not affect the fit assessment of the others. An analysis must be carried out to assess the response options for each of the excluded items and their impact on clinical interpretation if there are sufficient responses in all categories. Also, sample selection from a specialist center, in older adults with T2D with long disease duration, may lack generalizability and this extends to subgroup analysis and differential item functioning analysis. Additionally, this study did not include patients taking oral medications such as sulfonylureas, so these results do not reflect the overall picture of people with T2D. However, as the use of this type of medication has fallen to third- and fourth-line therapy, the number of people treated with this medication will decrease over time.

In conclusion, the items of the HypoA-Q scale are valid to assess awareness of hypoglycemia. The items of the scale had a good fit, therefore, they are reliable. No DIF was found, except for two (3 and 4a) in the treatment subgroups (basal and basal-bolus regimens). However, these are different treatments and group homogeneity is lost if they are grouped together. Therefore, this scale can be used to measure awareness of hypoglycemia in individuals diagnosed with T2D treated with insulin.

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## DISCLOSURE

DCH reports speaker fees from Novo Nordisk, Sanofi, and Abbott. The other researchers did not report any conflicts of interest.

Approval of the research protocol: The protocol was approved by the institutional ethics committee (code EPR-DEC-I-0276-17, code FM-CIE-0108-19, code CIE-186-2020).

Informed consent: All patients signed an informed consent form.

Approval date of registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Data S1.** Supplementary Information.