Psychometric Validation of the Hypoparathyroidism Patient Experience Scale (HPES)

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BACKGROUND

- Hypoparathyroidism (HP) is a rare endocrine disorder characterized by absent or inappropriately low levels of circulating parathyroid hormone (PTH)[1,2]
- Many patients have reported experiencing symptoms associated with HP despite being on standard of care (SOC) and/or PTH replacement therapy.[3-6] Research also indicates patients with HP on conventional and/or PTH replacement therapy may have reduced health-related quality of life (HRQOL), experiencing a range of impacts including anxiety, depression, and interference with daily life and work productivity[1,3,4,6-14]
- The Hypoparathyroidism Patient Experience Scales (HPES) were developed as disease-specific, patient-reported outcome (PRO) measures to assess the symptoms and impacts associated with HP in adults: The 17-item HPES-Symptom scale (Physical and Cognitive domains) and the 26-item HPES-Impact scale (Physical Functioning, Daily Life, Psychological Well-being, and Social Life and Relationships domains). Conceptual development of these scales was based on the scientific principles outlined in the FDA PRO guidance[15]
- The purpose of this study was to validate the HPES in order to evaluate the measurement model and psychometric properties of the measure to determine its validity, reliability, sensitivity to change and interpretability

METHODS

STUDY DESIGN

- Data from a non-interventional, observational study and a Phase 2 double-blind, randomized, placebo-controlled parallel group trial (TCP-201 PaTH Forward) were used in the psychometric evaluation of the HPES
- Key inclusion criteria for both studies were age 18 or older with a diagnosis of HP ≥ 6 months (post-surgical, autoimmune, genetic, or idiopathic); in addition, observational study participants had stable HP for at least 3 months (infrequent severe hypo- or hypercalcemia [low or high calcium levels] not more than two or three times a week), and Phase 2 trial subjects were on a stable dose of SOC, had optimization of supplements before randomization, and had thyroid-stimulating hormone within normal lab limits
- A PRO Validation Battery, including all measures needed to conduct the psychometric validation, was administered for both studies

STATISTICAL ANALYSES

- All analyses were conducted following an *a priori* psychometric analysis plan including:
  - Descriptive item measurement characteristics and consideration of item reduction
  - Factor analyses
  - Test-retest reliability
  - Construct validity
  - Known-groups validity
  - Ability to detect change
  - Threshold for meaningful within-patient change (responder definition)

RESULTS

Table 1. Participant Characteristics at Baseline/Screening

Participant Characteristics	Observational Study (n = 300)	Phase 2 Study (n = 59)
Age (years), mean (SD)	44.01 (10.5)	49.82 (12.1)
Sex, n (%)		
Female	196 (65.3)	47 (81.0)
Male	104 (34.7)	11 (19.0)
Race and Ethnicity (check all that apply)		
White	229 (76.3)	48 (81.4)
Hispanic or Latino	72 (24.0)	1 (1.7)
Black or African American	31 (10.3)	0 (0.0)
American Indian/Alaskan Native	27 (9.0)	2 (3.4)
Asian	3 (1.0)	2 (3.4)
Native Hawaiian/Other Pacific Islander	1 (0.3)	0 (0.0)
Other race/ethnicity/Prefer not to answer	4 (1.3)	4 (6.8)
Education		
Grade school or less	1 (0.3)	3 (5.1)
High school or technical school	5 (1.7)	14 (23.7)
Some college	97 (32.3)	10 (16.9)
College Degree	148 (49.3)	21 (35.6)
Masters/professional school or more	49 (16.3)	11 (18.6)

SD = standard deviation.

Table 2. Participant Medical Characteristics

Self-reported Medical Characteristics	Observational Study (n = 300)	Phase 2 Study (n = 59)
Medical history	**Baseline**	**Screening**
Post-surgical	285 (95.0)	48 (81.4)
Idiopathic	10 (3.3)	7 (11.9)
Autoimmune	3 (1.0)	3 (5.1)
Genetic	2 (0.7)	1 (1.7)
Years since diagnosed with HP		
n (%)	300 (100.0)	56 (94.9)
Mean (SD)	6.08 (8.8)	11.88 (9.5)
Median, Minimum-Maximum	2.5, 0.5-54.3	9.2, 0.9-42.8
HP treatment/management		
Natpara (PTH 1-84)	218 (72.7)	0 (0.0)
Calcium supplements	209 (69.7)	58 (98.3)
Prescription vitamin D supplements	206 (68.7)	50 (84.7)
OTC vitamin D supplements	162 (54.0)	29 (49.2)
Magnesium supplements	85 (28.3)	22 (37.3)
Hydrochlorothiazide	35 (11.7)	1 (1.7)

OTC = over-the-counter; SD = standard deviation.

RESULTS

HPES – SYMPTOM MEASURE

DESCRIPTIVE ITEM MEASUREMENT CHARACTERISTICS AND CONSIDERATION OF ITEM REDUCTION

- For both studies, the full 0-4 range (Never to Very often/Always) of item response categories were endorsed by the sample
- For the observational study, an examination of the item-level response distributions of HPES-Symptom items showed no evidence of problematic ceiling effects, and for the Phase 2 study showed a possible ceiling effect for Muscle spasms, Muscle twitching, Being sensitive to heat, and Heart problems
- For both studies, although there was one high inter-item correlation pair for 2b Feeling tired and 2e Low energy, the qualitative and quantitative evidence was not conclusive to support the removal of any items

FACTOR ANALYSES

Table 3. CFA Two-Factor Model-Factor Loadings (SEs) and Fit Indices (Observational Study Data)

	CFA 2-Factor Model With Residual Correlated Standardized Estimates	
HPES-Symptom Domain/Item	**Factor 1**	**Factor 2**
Physical		
1a. Muscle cramping	0.614* (0.037)	-
1b. Muscle spasms	0.578* (0.040)	-
1c. Muscle twitching	0.609* (0.037)	-
1d. Muscle weakness	0.709* (0.031)	-
1e. Tingling WITH numbness	0.691* (0.037)	-
1f. Tingling WITHOUT numbness	0.607* (0.042)	-
1g. Pain	0.760* (0.030)	-
2a. Being sensitive to heat	0.669* (0.035)	-
2b. Feeling tired	0.853* (0.018)	-
2c. Trouble sleeping	0.755* (0.029)	-
2d. Heart problems	0.643* (0.036)	-
2e. Low energy	0.888* (0.016)	-
Cognitive		
3a. Remembering	-	0.893* (0.019)
3b. Finding the right words	-	0.818* (0.023)
3c. Concentrating	-	0.893* (0.018)
3d. Understanding information	-	0.762* (0.028)
3e. Thinking clearly	-	0.883* (0.019)

*P < 0.05 for H0: loading = 0.
CFA = confirmatory factor analysis; SE = standard error; HPES = Hypoparathyroidism Patient Experience Scale.

INTERNAL CONSISTENCY

- For both studies, Cronbach's alpha values for internal consistency reliability were above 0.9 (ranging from 0.91 to 0.96)
  - These values provide further support for the hypothesized structure, indicating high internal consistency among the items and evidence for the computation of total and domain-level scores

CONSTRUCT VALIDITY

- For both studies, all hypotheses per domain and total score were met with moderate to strong correlations

KNOWN-GROUPS VALIDITY

- For both studies, the majority of the hypotheses for the domain and total scores were met

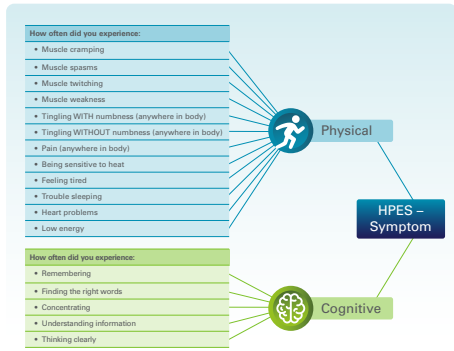
TEST-RETEST RELIABILITY

- For participants without treatment changes, ICCs approached the 0.70 criterion (greater than 0.60 and with 0.70 included within the 95% confidence interval) for all domains in the observational study and exceeded the 0.70 criterion for all domains in the Phase 2 study

ABILITY TO DETECT CHANGE

- Using Phase 2 study data, overall the results were favorable based on *a priori* hypotheses indicating the measure is responsive to change:
  1. Patients who reported improvement on the Patient Global Impression of Severity (PGIS) items (overall, physical, and cognitive) showed greater improvement in HPES-Symptom scores than patients who reported no change or worsening (P < 0.05)
  2. Patients who reported improvement on the HP-Interference items showed greater improvement in HPES-Symptom scores than patients who reported no change or worsening (P < 0.05)
  3. As an exploratory hypothesis, patients who were off SOC (defined as off active vitamin D and taking calcium ≤500 mg/day) and remained on active treatment showed greater improvement in HPES-Symptom scores than patients who are still on SOC (P < 0.05)

Figure 1. HPES-Symptom Conceptual Framework



HPES – IMPACT MEASURE

DESCRIPTIVE ITEM MEASUREMENT CHARACTERISTICS AND CONSIDERATION OF ITEM REDUCTION

- For both studies, the full 0-4 range (Not at all to Extremely) of item response categories was endorsed for majority of responses by the sample
- For the observational study, an examination of the item-level response distributions of HPES-Impact items shows no evidence of problematic ceiling effects. For the Phase 2 study, an examination of the response distributions of HPES-Impact items showed some evidence of ceiling effects providing evidence that the impact of HP on the sample tended to be mild
- Although several high inter-item correlations were found, the qualitative and quantitative evidence was not conclusive to support the removal of any items

FACTOR ANALYSES

Table 4. CFA Four-Factor Model-Factor Loadings (SEs) and Fit Indices (Observational Study Data)

	CFA 4-Factor Model Standardized Estimates			
Impact Domain/Item	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**
Physical Functioning	r_{12} = 0.920	r_{13} = 0.749	r_{14} = 0.799	
1a. Moving your body	0.780* (0.029)	-	-	-
1b. Walking	0.839* (0.023)	-	-	-
1c. Being physically active during the day	0.873* (0.018)	-	-	-
1d. Exercising or doing strenuous activities	0.844* (0.022)	-	-	-
1e. Physically recovering after doing activities	0.877* (0.021)	-	-	-
Daily Life			R_{23} = 0.780	r_{24} = 0.881
2a. Tasks around the home	-	0.895* (0.014)	-	-
2b. Hobbies or leisure activities	-	0.820* (0.020)	-	-
2c. Errands	-	0.823* (0.021)	-	-
2d. Complex tasks	-	0.761* (0.027)	-	-
2e. Work or school	-	0.785* (0.031)	-	-
3a. Plan your day around your symptoms	-	0.823* (0.021)	-	-
3b. Take breaks or pace yourself when doing activities	-	0.821* (0.019)	-	-
3c. Stop what you were doing due to your symptoms	-	0.824* (0.021)	-	-
Psychological Well-Being				R_{34} = 0.794
4a. Anxious	-	-	0.779* (0.031)	-
4b. Frustrated	-	-	0.869* (0.021)	-
4c. Low self-confidence	-	-	0.726* (0.030)	-
4d. Depressed	-	-	0.769* (0.029)	-
4e. Isolated	-	-	0.756* (0.030)	-
4f. Irritable	-	-	0.796* (0.026)	-
4g. Worried	-	-	0.811* (0.023)	-
4h. Angry	-	-	0.767* (0.026)	-
Social Life and Relationships				
5a. Participating in social activities	-	-	-	0.914* (0.014)
5b. The types of activities you do with other people	-	-	-	0.845* (0.019)
5c. Your relationships with friends	-	-	-	0.797* (0.022)
5d. Your relationships with family	-	-	-	0.777* (0.024)
5e. Your relationship with spouse/partner	-	-	-	0.853* (0.027)

* P < 0.05 for H0: loading = 0.
CFA = confirmatory factor analysis; SE = standard error; HPES = Hypoparathyroidism Patient Experience Scale.

INTERNAL CONSISTENCY

- For both studies, Cronbach's alpha values for internal consistency reliability were above 0.70 (ranging from 0.87 to 0.97)
  - These values provide further support for the hypothesized structure, indicating high internal consistency among the items and evidence for the computation of total and domain-level scores

CONSTRUCT VALIDITY

- For both studies, the majority of hypotheses were met with moderate to strong correlations found

KNOWN-GROUPS VALIDITY

- For both studies, results provided strong evidence for known-groups validity, with at least one hypothesis per domain and total score met

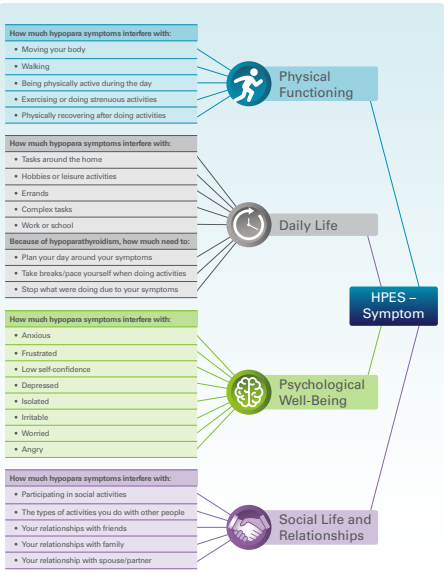
TEST-RETEST RELIABILITY

- For both studies, ICCs were either greater than 0.70 criterion or 0.70 was included within the 95% confidence interval for all domains across all patients without major life events or treatment changes

ABILITY TO DETECT CHANGE

- Using the Phase 2 study data, the responsiveness hypotheses were met:
  1. A greater improvement in HPES-Impact scores was seen in patients who reported improvement on the PGIS items (overall, physical, and cognitive) than those who reported no change or worsening (P < 0.05)
  2. Patients who reported improvement on the HP-Interference items showed greater improvement in HPES-Impact scores than patients who report no change or worsening (P < 0.05)

Figure 2. HPES-Impact Conceptual Framework



CONCLUSIONS

- Overall, for the HPES, the Total and domain scores demonstrated acceptable reliability and validity measurement properties for both the observational and the phase 2 study samples
- Understanding and measuring the impact of treatment, which are important for patients and adequately reflect their experience living with hypoparathyroidism, is critical to assessing treatment benefit as well as improving provider-patient communication
- Both the HPES-Symptom and the HPES-Impact measures, developed according to FDA PRO guidance, have been found to be conceptually sound with adequate evidence to support reliability and validity of the measures
- The incorporation into both clinical and research settings will help to further elucidate and assess the patient experience of living with hypoparathyroidism

REFERENCES:
1. Mannstadt M, Bilezikian JP, Thakker RV, Hannan FM, Clarke BL, Rejnmark L, et al. Hypoparathyroidism (published correction appears in Nat Rev Dis Primers. 2017 Oct 05;3:17080). *Nat Rev Dis Primers.* 2017;3:17055. Published 2017 Aug 31. doi:10.1038/nrdp.2017.55
2. Bilezikian JP, Khan A, Potts JT, Jr., Brandi ML, Clarke BL, Shoback D et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. *J Bone Miner Res.* 2011;26(10):2317-2337. doi:10.1002/jbmr.483
3. Cusano NE, Rubin MR, Irani D, Sliney J Jr, Bilezikian JP. Use of parathyroid hormone in hypoparathyroidism. *J Endocrinol Invest.* 2013;36(11):1121-1127. doi:10.1007/BF03346763.
4. Siljan T, Rolighed L, Nass A, Fuglsang-Frederiksen A, Moeskilde L, Rejnmark L. Effects of PTH(1-84) therapy on muscle function and quality of life in hypoparathyroidism: results from a randomized controlled trial. *Osteoporos Int.* 2014;25(6):1717-1726. doi:10.1007/s00198-014-2677-6.
5. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract.* 2014;20(7):671-679. doi:10.4158/EP13328.OR.
6. Siggelkow H, Clarke BL, Germak J, Marelli C, Chen K, Dahl-Hansen H, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey. *Clin Endocrinol (Oxf).* 2020;92(2):159-168. doi:10.1111/cen.14128.
7. Arlt W, Fremerey C, Callies F, Reincke M, Schneider P, Timmermann W, et al. Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. *Eur J Endocrinol.* 2002;146(2):215-222. doi:10.1530/eje.0.1460215.
8. Büttner M, Mushoff TJ, Singer S. Quality of life in patients with hypoparathyroidism receiving standard treatment: a systematic review. *Endocrine.* 2017;58(1):14-20. doi:10.1007/s12020-017-1377-3.
9. Rejnmark L. Quality of life in hypoparathyroidism. *Endocrine.* 2018;59(2):237-238. doi:10.1007/s12020-017-1479-y.
10. Vokes T. Quality of life in hypoparathyroidism. *Bone.* 2019;120:542-547. doi:10.1016/j.bone.2018.09.017.
11. Astor MC, Løvås K, Debowska A, Eriksen EF, Evang JA, Fossum C, et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. *J Clin Endocrinol Metab.* 2016;101(8):3045-3053. doi:10.1210/jc.2016-1477.
12. Tabacco G, Tay YD, Cusano NE, Williams J, Omeragic B, Majeed R, et al. Quality of Life in Hypoparathyroidism Improves With rhPTH(1-84) Throughout 8 Years of Therapy. *J Clin Endocrinol Metab.* 2019;104(7):2748-2756. doi:10.1210/jc.2018-02405.
13. Winer KK. Does PTH Replacement Therapy Improve Quality of Life in Patients With Chronic Hypoparathyroidism?. *J Clin Endocrinol Metab.* 2018;103(7):2752-2755. doi:10.1210/jc.2017-02593.
14. Arneiro AJ, Duarte BCC, Kulshetskii RM, Cury VBS, Lopes MP, Kliemann BS, et al. Self-report of psychological symptoms in hypoparathyroidism patients on conventional therapy. *Arch Endocrinol Metab.* 2018;62(3):319-324. doi:10.20945/2359-3997000000041.
15. Food and Drug Administration (FDA). Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. Available at: https://www.fda.gov/media/77832/download. Accessed August 13, 2020.

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