



ORIGINAL ARTICLE

Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey

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Abstract

Objective: To address knowledge gaps regarding burdens associated with not adequately controlled chronic hypoparathyroidism.

Design: Global patient and caregiver survey.

Study Populations: Patients with chronic hypoparathyroidism not adequately controlled on conventional therapy and their caregivers.

Measurements: Health-related quality of life (HRQoL) and health status were evaluated using the 36-item Short Form version 2 (SF-36 v2.0) and Five-Level EuroQoL 5 Dimensions (EQ-5D-5L) instruments, respectively. Hypoparathyroidism-associated symptoms were assessed by a disease-specific Hypoparathyroidism Symptom Diary and caregiver burden via the Modified Caregiver Strain Index (MCSI).

Results: Data were obtained from 398 patients and 207 caregivers. Patients' self-rated hypoparathyroidism-related symptom severity was none (3%), mild (32%), moderate (53%) or severe (12%). Per the Hypoparathyroidism Symptom Diary, patients reported moderate, severe or very severe symptoms of physical fatigue (73%), muscle cramps (55%), heaviness in limbs (55%) and tingling (51%) over a 7-day recall period. Impacts (rated 'somewhat' or 'very much') were reported by 84% of patients for ability to exercise, 78% for sleep, 75% for ability to work and 63% for family relationships. Inverse relationships were observed between patient self-rated overall symptom severity and HRQoL and health status assessment scores—the greater the symptom severity, the lower the SF-36 and EQ-5D-5L scores. Caregiver burden increased with patient self-rated symptom severity: none, 1.7 MCSI; mild, 5.4 MCSI; moderate, 9.5 MCSI; and severe, 12.5 MCSI.

Conclusion: Patients with not adequately controlled hypoparathyroidism reported substantial symptoms and impacts. Greater patient symptom severity was associated with decreased patient HRQoL and health status assessments and increased caregiver burden.

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KEYWORDS

caregiver, health status, hypoparathyroidism, parathyroid hormone, patient, quality of life, surveys and questionnaires

1 | INTRODUCTION

Hypoparathyroidism is a rare, complex endocrine disorder resulting from undetectable or inappropriately low levels of parathyroid hormone (PTH).^{1,2} Deficiency of PTH, the principal regulator of calcium and phosphate homeostasis, results in the hallmark biochemical abnormalities of hypocalcaemia and hyperphosphataemia.³

Conventional management of hypoparathyroidism consists of treatment with activated vitamin D analogues and calcium supplements.¹ However, conventional therapy does not replace other functions of PTH to restore physiological mineral homeostasis, resulting in a potential increased risk of physical symptoms, including fatigue, paraesthesia, muscle cramping, tetany, and joint or bone pain,^{4,5} and of long-term complications, such as soft-tissue calcifications and impaired renal function.^{2,4,6,7} For some patients with chronic hypoparathyroidism, a managed transition from a high daily calcium intake to a no calcium (or lower calcium) treatment regimen may reduce adverse events or complications, including kidney stones and hospitalization due to hyper- or hypocalcaemia.⁸ In addition, chronic hypoparathyroidism is associated with cognitive and emotional symptoms such as mental lethargy, inability to concentrate, memory loss or forgetfulness, anxiety and depression.⁵

The negative impact of chronic hypoparathyroidism on health-related quality of life (HRQoL) has been documented^{5,9-12}; however, significant knowledge gaps exist regarding the overall burden of illness associated with chronic hypoparathyroidism, including symptom severity, impact on activities of daily living and caregiver burden, particularly among patients who are not adequately controlled on conventional therapy. In a US-based survey of 374 patients with hypoparathyroidism, 79% of respondents strongly agreed that most physicians do not understand hypoparathyroidism, leading to the perception of an 'empathy gap' between healthcare providers and patients.⁵ In addition, Cho et al¹³ reported that surgeons underestimate potential complications and the negative impact on quality of life (QoL) associated with postsurgical hypoparathyroidism, compared with patients' own perceptions. To address the scarcity of data regarding the specific burdens imposed by not adequately controlled chronic hypoparathyroidism on patients and their caregivers, we conducted a global survey to characterize the burden of not adequately controlled chronic hypoparathyroidism and its impact on HRQoL from the patient and, for the first time, the caregiver perspectives.

2 | MATERIALS AND METHODS

2.1 | Study design

An anonymous, multicountry survey was conducted in patients with chronic hypoparathyroidism not adequately controlled with conventional therapy, and their caregivers, between October 2017 and March 2018. Patients were initially recruited via their treating physician in 10 of the 13 countries (except in Denmark, Norway and Sweden, where local guidelines recommended recruiting via patient associations); additional patients were recruited via patient associations. Of the countries that used recruitment via patient associations, the percentage of patients recruited via this method was 100% for the United Kingdom (UK), Denmark and Norway; 82% for Sweden; 75% for Canada; and 42% for the United States (US). Overall, 35% of the patients were recruited via patient associations, with the remaining recruited through their physicians. All respondents completed the survey either online or by pen and paper. Each survey was completed once and took approximately 25 minutes to complete. When possible, the patient survey was linked to the matching caregiver survey by a corresponding respondent identification number issued by the treating physician. Patients recruited via patient associations generated their own respondent identification numbers and were asked to synchronize identification numbers with their caregivers, so that, when possible, corresponding patients and caregivers were matched during analysis. The study design did not mandate that each patient survey be matched with a corresponding caregiver survey.

The study was performed in compliance with the European Pharmaceutical Market Research Association and in full accordance with the US Health Insurance Portability and Accountability Act of 1996. The study was reviewed and methodology approved by the Freiburg Ethics Commission International.

2.2 | Study populations

2.2.1 | Patients

Patients were eligible to participate if they were aged ≥ 18 years, had a confirmed diagnosis of chronic hypoparathyroidism for ≥ 12 months, were currently receiving conventional therapy for hypoparathyroidism, and their disease was not adequately controlled. Not adequately controlled hypoparathyroidism was determined by patients' report of persistent symptoms and/or poorly controlled

calcium levels as described by their physicians, despite receiving conventional therapy. Patients were excluded if they had prior or current participation in an interventional clinical trial; received non-conventional treatment, including recombinant human parathyroid hormone (1-84) or (1-34); were diagnosed with pseudohypoparathyroidism; or had completed a survey assessing the burden of hypoparathyroidism within the past 3 months.

2.2.2 | Caregivers

Caregivers were eligible to participate if they were aged ≥ 18 years, provided unpaid care for a spouse/partner, son/daughter, parent, sibling, other relative, friend/neighbour or other person completing the patient survey, and were the primary caregiver to a patient with hypoparathyroidism. Professional caregivers providing paid care were excluded.

2.3 | Outcomes

Patients' hypoparathyroidism-associated symptoms were evaluated using the Hypoparathyroidism Symptom Diary, a disease-specific, patient-reported outcome tool that records the severity of symptoms and impacts experienced in the past 7 days.¹⁴ Symptom severity levels were rated on a five-point response scale: none, mild, moderate, severe and very severe. Impacts were rated using a three-point response scale: not at all, somewhat and very much. HRQoL and health status were assessed using two validated instruments, the 36-item Short Form Health Survey version 2.0 (SF-36 v2.0) (www.optum.com/solutions/life-sciences/answer-research/patient-insights/sf-health-surveys/sf-36v2-health-survey.html, accessed on 8 May 2019)¹⁵ and the Five-Level EuroQoL 5 Dimensions (EQ-5D-5L),¹⁶ respectively. The SF-36 is a 36-item questionnaire that assesses generic QoL in eight dimensions of physical and mental health, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Responses are summed and transformed on a 0-100 scale, with lower scores indicating poorer health states. These eight domains are then aggregated into a physical component summary (PCS) score and a mental component summary (MCS) score. The PCS is primarily a function of the physical functioning, role-physical, bodily pain and general health domains, whereas vitality, social functioning, role-emotional and mental health domains contribute most to the scoring of MCS. The EQ-5D-5L measures generic health status using five dimensions of general health including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five response levels. EQ-5D-5L responses are converted to a single index utility value between zero (equivalent to death) and one (full health).^{16,17} The EQ-5D-5L includes the EQ Visual Analogue Scale (EQ VAS), which provides a quantitative measure of health perception by asking patients to rate their overall health on a 20-cm vertical, visual analogue scale, ranging from zero (worst possible health) to 100 (best possible health).¹⁶

Patient employment status and productivity were evaluated using the validated Work Productivity and Activity Impairment (WPAI) questionnaire,¹⁸ a six-item patient-reported quantitative assessment of the extent of absenteeism, presenteeism and daily activity impairment during the past 7 days.

The patient survey also captured demographic information and hypoparathyroidism clinical characteristics. In addition, patients were asked about various comorbidities that occur with an increased prevalence in patients with hypoparathyroidism according to the European Society of Endocrinology guidelines for the management of hypoparathyroidism.¹ Categories of additional data collected from the patient survey included current disease management, satisfaction with current treatment, pill burden and the impact of hypoparathyroidism on relationships.

Categories of data collected from the caregiver survey included demographic information, severity of hypoparathyroidism symptoms as rated by the caregiver, impact of hypoparathyroidism on relationships and level of employment and productivity assessed via the WPAI questionnaire. Caregiver burden was evaluated using the Modified Caregiver Strain Index (MCSI),¹⁹ a validated 13-item tool that measures strain among long-term caregivers in five domains: financial, physical, psychological, social and personal. Total scores range from 0 to 26, with two points conferred for each 'yes' response, one point for each 'sometimes' response and zero points for each 'no' response. Higher MCSI scores correspond to greater caregiver strain.

2.4 | Statistical methods

All analyses were descriptive. No statistical testing was performed. Where missing data occurred in the pen and paper survey, data points were omitted from data entry and the individual survey was assessed for the validity of remaining data points. The total number of patients and caregivers available for analysis differed among variables owing to missing data because some patients and caregivers did not respond to all questions in the survey. There were no missing data from the electronic survey because respondents could have selected 'don't know' or 'other' as a response.

3 | RESULTS

3.1 | Patient and caregiver disposition and demographics, and patient disease characteristics

Data were obtained from 398 patients and 207 caregivers across 13 countries; 160 patient respondents were matched with their caregivers. Patients were recruited from Australia ($n = 20$), Brazil ($n = 35$), Canada ($n = 4$), Denmark ($n = 11$), France ($n = 13$), Germany ($n = 31$), Italy ($n = 35$), Japan ($n = 11$), Norway ($n = 16$), Spain ($n = 35$), Sweden ($n = 17$), UK ($n = 45$) and United States ($n = 125$). The breakdown of caregivers by country was Australia ($n = 10$), Brazil ($n = 18$),

TABLE 1 Demographic characteristics of patients and caregivers and disease characteristics of patients

Characteristics	Patients (N = 398) ^a
Age, ^b y	
Mean (SD)	51.7 (14.0)
Sex, n (%)	
Men	88 (22)
Women	310 (78)
Disease duration, y	
Mean (SD)	8.7 (10.0)
Patient self-rated symptom severity, ^b n (%)	
None	11 (3)
Mild	126 (32)
Moderate	211 (53)
Severe	49 (12)
Primary cause of hypoparathyroidism, ^b n (%)	
Surgery of the thyroid, parathyroid or neck for cancer	166 (42)
Surgery of the thyroid, parathyroid or neck for noncancer reason	152 (38)
Autoimmune disorder ^c	29 (7)
Congenital disorder ^d	7 (2)
Genetic or inherited disorder ^e	23 (6)
Metabolic condition ^f	3 (1)
Other nonsurgical cause	17 (4)
Not adequately controlled hypoparathyroidism, n (%)	
Currently experiencing symptoms despite treatment	364 (91)
Told by a physician that serum calcium levels are poorly controlled/low	267 (67)
Comorbidities, ^b n (%)	
Hypertension	162 (41)
Mental, behavioural or neurodevelopmental disorders	114 (29)
Arrhythmia (irregular heartbeat)	113 (28)
Kidney problems ^g	110 (27)
Hypothyroidism	96 (24)
Infections	70 (18)
Diabetes	69 (17)
Decreased bone mineral density	68 (17)
Cataracts	51 (13)
Soft-tissue calcification	36 (9)
Bone fractures	32 (8)
Coronary heart disease	31 (8)
Seizures, convulsions	31 (8)
Hyperthyroidism	18 (5)
Neurologic conditions	15 (4)
Brain calcification	13 (3)
Increase bone mineral density	10 (3)

(Continues)

TABLE 1 (Continued)

Characteristics	Patients (N = 398) ^a
None	36 (9)
Don't know	13 (3)
Caregivers (N = 207)	
Age of caregiver, y	
Mean (SD)	52.4 (11.9)
Age of patient cared for, y	
Mean (SD)	52.7 (15.0)
Sex of caregiver, n (%)	
Men	103 (50)
Women	104 (50)
Relationship to patient, n (%)	
Spouse/partner	145 (70)
Son/daughter	26 (13)
Parent	19 (9)
Sibling	7 (3)
Friend/neighbour	3 (1)
Other	7 (3)
Length of time providing caregiver support, y	
Mean (SD)	5.7 (6.1)
Number of care hours provided per week	
Mean (SD)	24.1 (33.3)

^aFor some parameters, the total number does not equal 398 and 207 for patients and caregivers, respectively. This is because physician-recruited patients and caregivers in the United States and Japan completed the survey on pen and paper; thus, there are some missing responses.

^bn = 397, except for hypothyroidism and hyperthyroidism (N = 398).

^cA nonsurgical cause, for example autoimmune polyglandular syndrome type 1 (APS-1).

^dCondition existing since birth, for example DiGeorge syndrome.

^eCondition being passed down through the family, for example PTH gene mutation.

^fIncludes conditions related to the digestive system and metabolism (example haemochromatosis, Wilson's disease and thalassaemia).

^gIncludes kidney stones, calcification or impaired function (n = 73; 18%); kidney failure (n = 8; 2%); and chronic kidney disease (n = 29; 7%).

Canada (n = 1), France (n = 13), Germany (n = 22), Italy (n = 34), Japan (n = 10), Norway (n = 6), Spain (n = 28), Sweden (n = 5), UK (n = 10) and United States (n = 50). Demographic and baseline characteristics of patients and their caregivers are provided in Table 1. The majority of patients reported surgery of the thyroid, parathyroid or neck (n = 318/397; 80%) as the primary cause of hypoparathyroidism; 42% developed hypoparathyroidism following cancer surgery, and 38% developed hypoparathyroidism following non-cancer-related surgery. Patients (n = 397) rated their overall hypoparathyroidism-related symptom severity level as no symptoms (3%), mild (32%), moderate (53%), or severe (12%). Among 397 respondents, the most frequently reported comorbidities were hypertension (41%); mental, behavioural or neurodevelopmental disorders (29%); arrhythmia

TABLE 2 Symptom severity and impact assessment from the hypoparathyroidism symptom diary (7-day recall) (N = 397)

Symptoms, n (%)	Symptom severity				
	None	Mild	Moderate	Severe	Very severe
Physical fatigue	12 (3)	96 (24)	153 (39)	99 (25)	37 (9)
Muscle cramps	52 (13)	128 (32)	152 (38)	48 (12)	17 (4)
Tingling	64 (16)	132 (33)	131 (33)	53 (13)	17 (4)
Heaviness in limbs	70 (18)	108 (27)	147 (37)	55 (14)	17 (4)
Numbness	81 (20)	127 (32)	134 (34)	43 (11)	12 (3)
Muscle spasms or twitching	82 (21)	127 (32)	128 (32)	46 (12)	14 (4)
Slow/confused thinking	90 (23)	121 (30)	110 (28)	52 (13)	24 (6)
Anxiety	87 (22)	127 (32)	115 (29)	56 (14)	12 (3)
Sadness or depression	94 (24)	141 (36)	109 (28)	38 (10)	14 (4)

Impacts, n (%)	Impact		
	Not at all	Somewhat	Very much
Ability to exercise	63 (16)	190 (48)	144 (36)
Sleep	89 (22)	202 (51)	106 (27)
Ability to work	101 (25)	193 (49)	103 (26)
Family relationships	147 (37)	182 (46)	68 (17)

(28%); and kidney problems (27%). Demographics and baseline characteristics were generally similar between patients recruited through patient associations and patients recruited via physicians; the greatest differences between these cohorts were observed for sex (92% and 70% women, respectively) and the percentage of patients who had been told by a physician that their serum calcium levels are poorly controlled (45% and 80%, respectively).

3.2 | Hypoparathyroidism-related symptoms and impacts as reported by patients

Findings from the Hypoparathyroidism Diary are shown in Table 2. According to the Hypoparathyroidism Symptom Diary (n = 397), the percentage of patients reporting moderate, severe and very severe symptoms over a 7-day recall period was 73% for physical fatigue (n = 289), 55% for muscle cramps (n = 217), 55% for heaviness in limbs (n = 219), 51% for tingling (n = 201), 48% for numbness (n = 189), 47% for muscle spasms or twitching (n = 188), 47% for slow or confused thinking (n = 186), 46% for anxiety (n = 183) and 41% for sadness or depression (n = 161). Impacts rated as 'somewhat' or 'very much' (n = 397) were reported by 84% of patients for ability to exercise, 78% for sleep, 75% for ability to work and 63% for family relationships.

3.3 | Patient health-related quality of life and health status

There was an inverse relationship between patient self-rated overall hypoparathyroidism symptom severity and both the HRQoL and health status assessment scores: the higher the severity level,

the lower the HRQoL and health status scores. EQ-5D-5L utility scores were 0.9/0.8/0.7/0.4 and EQ-5D-5L EQ VAS scores were 86.9/72.5/57.7/41.1 for patients reporting no/mild/moderate/severe hypoparathyroidism symptoms, respectively (Figure 1A,B). Mean SF-36 PCS/MCS scores were 45.4/53.2 for patients reporting no hypoparathyroidism symptoms, 44.6/44.9 for patients reporting mild symptoms, 37.1/35.2 for patients reporting moderate symptoms and 28.7/31.6 for patients reporting severe symptoms. The most adversely impacted SF-36 individual domains were vitality and general health (Figure 2). There were no notable differences in SF-36 scores between patients recruited through patient associations or via physicians; the mean PCS score for patients recruited through patient associations (n = 141) was 36.0 (range: 14-61) and for physician-recruited patients (n = 257) was 40.2 (range: 16-60). Likewise, the mean MCS score was 37.9 (range: 11-60) for patients recruited through patient associations and 38.7 (range: 10-66) for patients recruited through physicians.

3.4 | Medication and pill burden associated with chronic hypoparathyroidism

Patients reported taking a mean (SD; range) of 8.0 (4.79; 1.0-25.0 [n = 397]) pills/d. The number of pills consumed per day for management of hypoparathyroidism (including calcium supplements, activated vitamin D analogues, vitamin D₃ and any other hypoparathyroidism-related medications) correlated with overall symptom severity; the mean number of pills per day was 4.0, 7.1, 8.1 and 10.0 for patients reporting no hypoparathyroidism symptoms, mild symptoms, moderate symptoms and severe symptoms, respectively. The majority of patients received activated vitamin

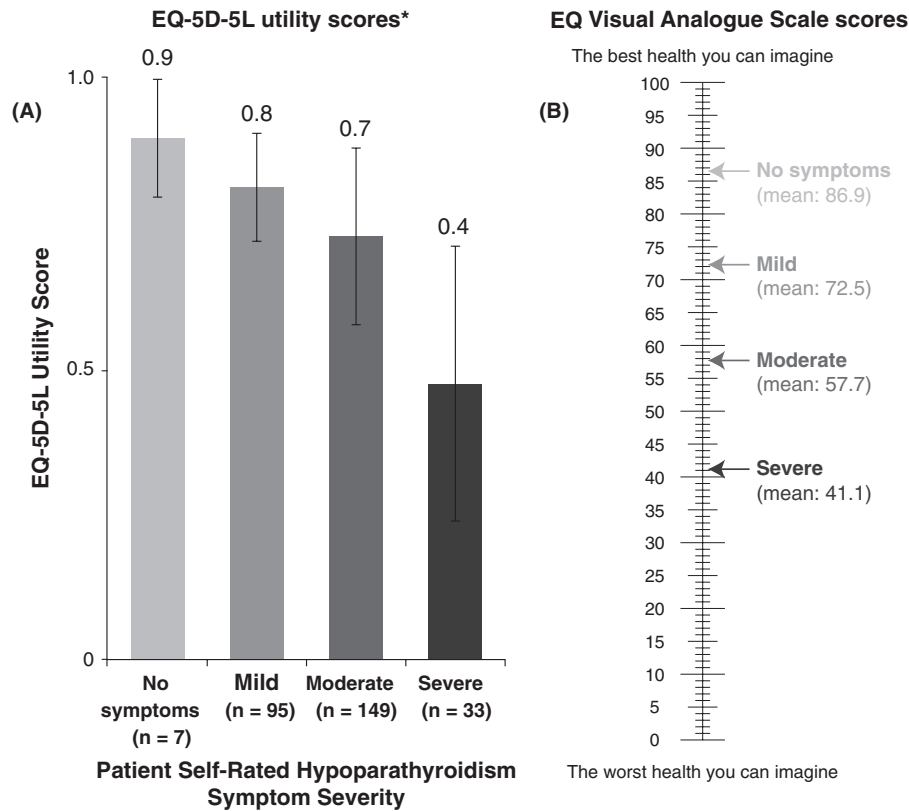


FIGURE 1 (A) EQ-5D-5L utility scores* and (B) EQ Visual Analogue Scale scores stratified by patient self-rated symptom severity. Error bars for (A) represent standard deviation. EQ-5D-5L = Five-Level EuroQoL 5 Dimensions; VAS, visual Analogue scale. *A US scoring algorithm was used for the United States, and an English scoring algorithm was used for Europe and Canada

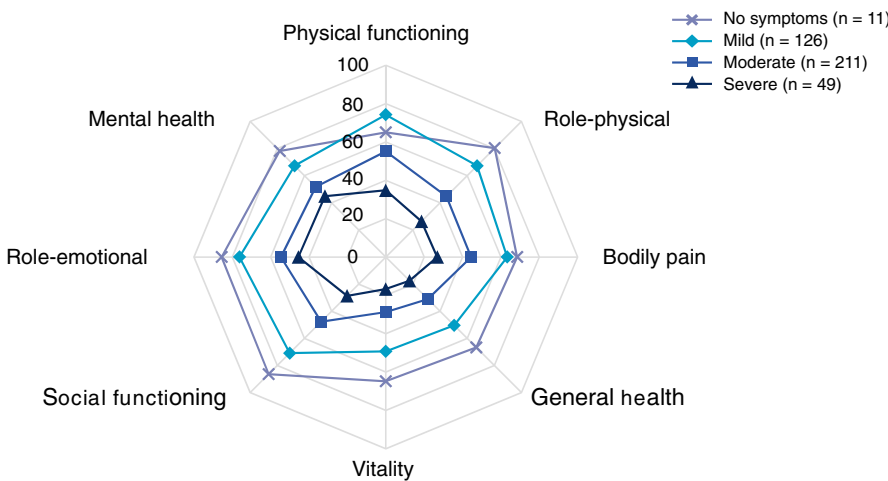


FIGURE 2 SF-36 reported outcomes across domains. SF-36 = 36-item Short Form Health Survey

D capsules or liquid (ie calcitriol, alfacalcidol and dihydrotachysterol [71%; n = 282]); 40% (n = 159) of patients received vitamin D tablets (ie ergocalciferol vitamin D₂ or cholecalciferol vitamin D₃). Most patients reported receiving calcium (92%; n = 366/398), either as oral calcium tablets/chews (ie Caltrate, calcium carbonate and calcium citrate [79%; n = 313]) and/or as oral antacids (13%; n = 53). Other medications patients reported receiving included magnesium supplements (36%, n = 142), diuretics (19%, n = 77) and thyroid treatment (56%, n = 221). Treatment dissatisfaction was reported by 96% (n = 376/393) of patients. Of 394 patients

with data available, 144 (37%) reported disagreement with their physicians' assessments that their disease was well controlled with their current medication.

3.5 | Impact on patient and caregiver employment and productivity

Of 397 patients, the percentage with full-time work decreased from 58% before the diagnosis of hypoparathyroidism to 34% at the time

TABLE 3 Employment status and work productivity in patients and caregivers

	Patients N = 397		Caregivers N = 207	
	Current	Previous ^b	Current	Previous ^b
Employment status, n (%)				
Full-time	135 (34)	232 (58)	84 (41)	106 (51)
Part-time	62 (16)	44 (11)	28 (14)	36 (17)
Homemaker	34 (9)	31 (8)	35 (17)	31 (15)
Retired	88 (22)	43 (11)	41 (20)	21 (10)
Disabled	33 (8)	4 (1)	3 (1)	3 (1)
Full- or part-time student	11 (3)	10 (3)	3 (1)	2 (1)
Unemployed (seeking work)	8 (2)	4 (1)	6 (3)	3 (1)
Unemployed (not seeking work)	7 (2)	5 (1)	3 (1)	2 (1)
Other	19 (5)	8 (2)	4 (2)	3 (1)
NA, I was a child	NA	16 (4)	NA	NA
Work productivity				
Overall activity impairment, %	41.7		32.7	
Employed patients, n ^a	190		115	
Absenteeism, %	9.2		4.6	
Working while sick, %	36.6		19.4	
Overall work impairment, %	40.8		20.8	

Abbreviations: NA, not applicable; WPAI, Work Productivity and Activity Impairment.

^aAccording to the WPAI questionnaire.

^bPrior to hypoparathyroidism diagnosis for patients; prior to caring for a patient with hypoparathyroidism.

of survey (Table 3). Of 161 patients who changed their employment status following a diagnosis of hypoparathyroidism, 59% reported it was due to their illness. The proportion of patients reporting a disease-related change in employment ($n = 95$) correlated with self-rated severity of hypoparathyroid symptoms (no symptoms, 0%; mild, 29% [$n = 12$]; moderate, 67% [$n = 58$]; and severe, 83% [$n = 25$]). WPAI scores reflected patients working and conducting activities at 59% and 58% of their full capacity, respectively. Overall, work impairment and activity impairment were greater with increased patient self-rated symptom severity. Work impairment was reported by 18%, 28%, 49% and 68% of employed patients; likewise activity impairment was reported by 24%, 34%, 57% and 76% of employed patients ($n = 190$) reporting no ($n = 5$), mild ($n = 79$), moderate ($n = 91$) and severe ($n = 15$) symptoms, respectively.

The proportion of caregivers with full-time work decreased from 51% ($n = 106$) before the hypoparathyroidism diagnosis to 41% ($n = 84$) at the time of survey (Table 3). Among caregivers who changed their employment status ($n = 42$), 26% ($n = 11$) attributed the change to caregiving for a patient with hypoparathyroidism. WPAI scores indicated that caregivers were working and conducting activities at 79% and 67% of their full capacity, respectively. The percentage of matched caregivers ($n = 78$) reporting work impairment increased as caregiver-rated severity of the patient's symptoms increased: no symptoms (7%, $n = 6$), mild (20%, $n = 31$), moderate (24%, $n = 33$) and severe (28%, $n = 8$). A similar but steeper trend was observed for matched caregivers' ($n = 159$) activity impairment

(no symptoms, 11% [$n = 9$]; mild symptoms, 26% [$n = 56$]; moderate symptoms, 37% [$n = 75$]; and severe symptoms, 56% [$n = 19$]).

3.6 | Impact on patient and caregiver relationships, and caregiver burden

The percentage of patients reporting a major impact on relationships increased with self-rated symptom severity (Figure 3A). Patients who self-rated as having no symptoms of hypoparathyroidism did not report a major impact on any relationship, whereas a majority of patients who self-rated as having severe symptoms of hypoparathyroidism reported a major impact on relationships with spouses/partners, family and friends. Caregivers also reported that hypoparathyroidism had a major impact on their relationships, with their relationships with their spouse/partner affected the most ($n = 57/206$; 28%) (Figure 3B). Overall, the mean MCSI score for caregivers was 7.8; however, caregiver strain increased with the increasing severity of the patient's symptoms as rated by the caregiver (no symptoms, 1.7; mild, 5.4; moderate, 9.5; and severe, 12.5).

4 | DISCUSSION

This multicountry survey investigated the burden of disease associated with not adequately controlled chronic hypoparathyroidism

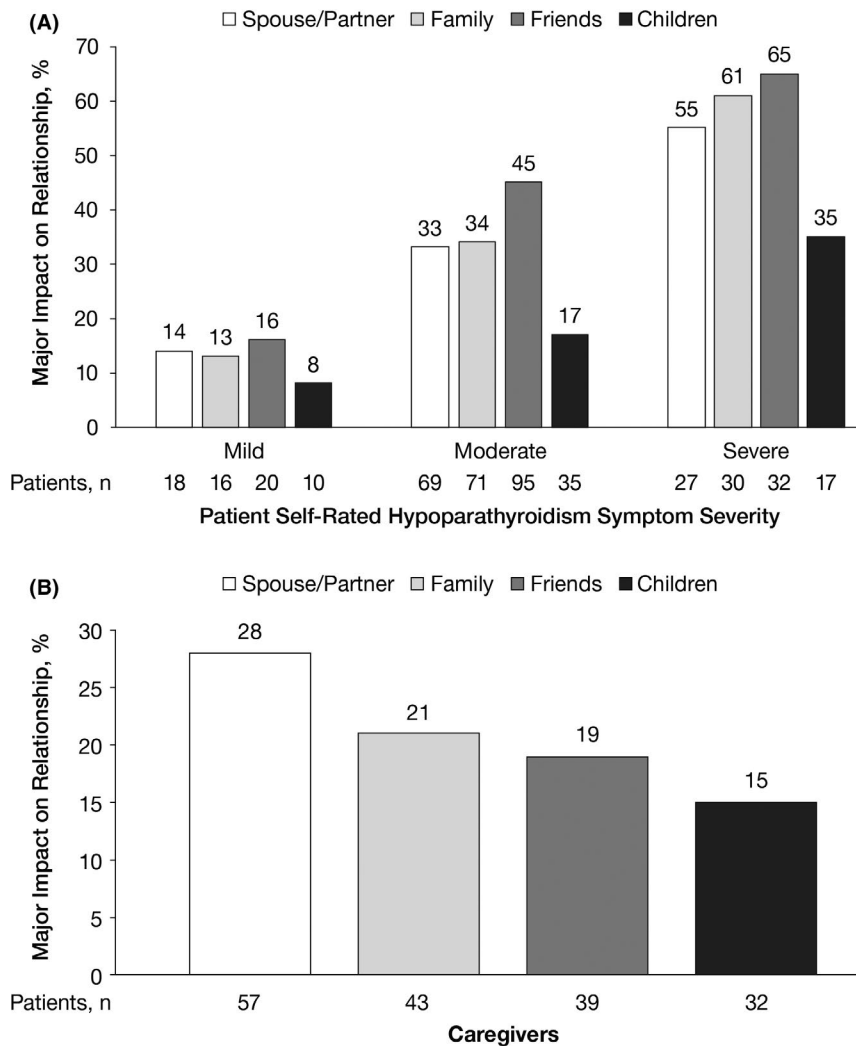


FIGURE 3 Major impact of hypoparathyroidism on (A) patient relationships categorized by self-rated hypoparathyroidism symptom severity* (N = 396[†]) and (B) caregiver relationships (N = 207[‡]). *None of the patients' self-rating as having no symptoms of hypoparathyroidism (n = 11) reported a major impact on any personal relationship. [†]n = 395 for relationships with family, friends and children. [‡]n = 206 for relationship with spouse/partner

from the perspective of patients and their caregivers. The majority of patients reported moderate to severe symptoms while receiving conventional therapy, and most reported treatment dissatisfaction. The magnitude of symptom severity reported by patients with not adequately controlled chronic hypoparathyroidism was inversely related to HRQoL and health status scores. Not adequately controlled chronic hypoparathyroidism negatively affected the ability of patients and caregivers to maintain productive employment and personal relationships; the degree of this burden was associated with increased symptom severity.

Recent studies have examined the consequences of hypoparathyroidism on multiple aspects of a patient's personal and social life while receiving conventional therapy.^{9-13,20} In particular, five studies utilized the SF-36 instrument to evaluate HRQoL in patients with hypoparathyroidism receiving conventional therapy compared with a reference population or control subjects.^{10-13,20} Two of these studies reported significantly reduced scores in most or all SF-36 domains among patients with chronic, postsurgical hypoparathyroidism or nonsurgical hypoparathyroidism, compared with a norm-based US population.^{10,12} Two further studies, one Danish and one Norwegian, showed significantly lower SF-36 domain scores, in

patients with hypoparathyroidism compared with controls.^{11,20} Cho et al¹³ compared the perceived impact of hypoparathyroidism on HRQoL among 340 patients with postsurgical hypoparathyroidism and 102 endocrine surgeons. Patients with postsurgical hypoparathyroidism experienced considerably more adverse impact on QoL than was anticipated by the surgeons, underscoring the existence of an 'empathy gap'. Arguably, comparisons between patients with hypoparathyroidism and healthy controls (those without comparable comorbidities) are likely to overestimate the negative impact of hypoparathyroidism on HRQoL. To overcome this limitation and to assess the impact of hypoparathyroidism on HRQoL more accurately, selected controls should be more comparable to the patients with chronic hypoparathyroidism—ideally, patients who have undergone surgery for thyroid or parathyroid disease.^{9-13,20}

Mean SF-36 PCS and MCS scores reported for patients with hypoparathyroidism in this survey were generally comparable to or lower than scores reported for patients with other long-term disease states, such as heart disease,²¹⁻²³ haematologic disorders,^{24,25} diabetes^{26,27} and cancer.²⁸⁻³¹ Although the HRQoL impact of hypoparathyroidism is on a par with other chronic conditions considered to have a substantial burden of illness, physicians and the general

public can underestimate the consequences of hypoparathyroidism for patients.^{5,13} These findings underscore the debilitating nature of chronic hypoparathyroidism, a disorder that impacts both mental and physical dimensions in the life of a patient, and will contribute towards a better understanding of the burden of illness and improving outcomes for both patient and caregiver.

It is noteworthy that receptors for the parathyroid hormone are expressed in muscle, spinal cord and several brain regions.^{32,33} It is plausible that a deficiency of parathyroid hormone in these tissues contributes to the reduced HRQoL beyond its effects on disrupted mineral homeostasis, particularly in aspects related to mental and emotional health and vitality.³⁴ Notably, the general management goals for chronic hypoparathyroidism outlined in the guidelines from the European Society of Endocrinology emphasize individualized treatment, with a focus on the well-being and QoL of patients, in addition to physiological control of mineral homeostasis.¹

Caregivers for patients with not adequately controlled hypoparathyroidism reported that their ability to carry out daily activities was adversely affected. Caregivers reported a considerable impact on personal relationships, across all 4 relationship categories, with the most impact observed in their relationship with their partner/spouse. Finally, caregivers experienced higher caregiver strain and lower work productivity that was associated with their perception of the patient's symptom severity. These findings are in agreement with previous studies of other chronic diseases, which have also reported higher caregiver strain with increasing functional impairment of the care recipient.³⁵⁻³⁷

4.1 | Limitations

The validity of our survey, like all such surveys, is inherently dependent upon the participants providing accurate data. Patients were asked to rate their hypoparathyroidism-related symptom severity using the scales provided. Patient clinical data were not collected to validate responses, which may have been affected by participants' subjective state of well-being at the time of the survey. Furthermore, perceptions and unmet needs of patients unwilling to participate were not captured. This may have introduced referral and nonrespondent biases in our survey. Finally, the survey did not include a control group; therefore, a direct comparison of the HRQoL between these patients and healthy individuals or individuals with comparable disease cannot be made.

5 | CONCLUSIONS

Findings from this multicountry survey reflected a broad spectrum of symptom severity within a cohort of patients with not adequately controlled hypoparathyroidism. The magnitude of symptom severity as reported by patients was inversely proportional to HRQoL and health status scores. Strikingly, the impact of chronic hypoparathyroidism on HRQoL was similar to or more pronounced than for other

severe chronic diseases. Most patients reported a high pill burden that correlated with their overall symptom severity. In addition to cognitive, emotional and physical symptoms, patients experienced an interference with the activities of daily living, employment and personal relationships. Caregivers also experienced caregiver strain and decreased work productivity that corresponded with caregiver perception of the patient's symptom severity. These findings highlight the substantial impaired HRQoL resulting from burdensome hypoparathyroidism-related symptoms, and impact in daily living and activities in patients with chronic hypoparathyroidism and the attendant burden on their caregivers.

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CONFLICT OF INTEREST

Shire is a member of the Takeda group of companies. HS and JB have served as advisory board members and speakers for Shire. BLC has served as a consultant for Shire. EG is a volunteer with Hypopara UK, which has received donations from Shire. KM is a current employee and DJ and NB-E are former employees of Adelphi Real-World, which was contracted by Shire to conduct this research. KC is an employee of Shire Human Genetic Therapies, Inc, a member of the Takeda group of companies. JG and CM are employees of Shire International GmbH, a member of the Takeda group of companies. HD-H has no conflicts to report.

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DATA AVAILABILITY STATEMENT

Individual participant data behind the results reported in this article (text, tables, figures and appendices) are not planned to be shared but all available aggregated data supporting the results can be shared upon request to the corresponding author.

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