

Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway

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Objective: The epidemiology of hypoparathyroidism (HP) is largely unknown. We aimed to determine prevalence, etiologies, health related quality of life (HRQOL) and treatment pattern of HP.

Methods: Patients with HP and 22q11 deletion syndrome (DiGeorge syndrome) were identified in electronic hospital registries. All identified patients were invited to participate in a survey. Among patients who responded, HRQOL was determined by Short Form 36 and Hospital Anxiety and Depression scale. Autoantibodies were measured and candidate genes (CaSR, AIRE, GATA3, and 22q11-deletion) were sequenced for classification of etiology.

Results: We identified 522 patients (511 alive) and estimated overall prevalence at 102 per million divided among postsurgical HP (64 per million), nonsurgical HP (30 per million), and pseudo-HP (8 per million). Nonsurgical HP comprised autosomal dominant hypocalcemia (21%), autoimmune polyendocrine syndrome type 1 (17%), DiGeorge/22q11 deletion syndrome (15%), idiopathic HP (44%), and others (4%). Among the 283 respondents (median age, 53 years [range, 9–89], 75% females), seven formerly classified as idiopathic were reclassified after genetic and immunological analyses, whereas 26 (37% of nonsurgical HP) remained idiopathic. Most were treated with vitamin D (94%) and calcium (70%), and 10 received PTH. HP patients scored significantly worse than the normative population on Short Form 36 and Hospital Anxiety and Depression scale; patients with postsurgical scored worse than those with nonsurgical HP and pseudo-HP, especially on physical health.

Conclusions: We found higher prevalence of nonsurgical HP in Norway than reported elsewhere. Genetic testing and autoimmunity screening of idiopathic HP identified a specific cause in 21%. Further research is necessary to unravel the causes of idiopathic HP and to improve the reduced HRQOL reported by HP patients. (*J Clin Endocrinol Metab* 101: 3045–3053, 2016)

PPrimary hypoparathyroidism (HP) is caused by a group of heterogeneous diseases in which hypocalcemia and hyperphosphatemia occur as a result of insufficient PTH secretion or receptor dysfunction in target organs. The most common etiologies among adults are surgical damage to the parathyroid glands. Nonsurgical HP can be either autoimmune or genetic (Table 1), but in many cases the cause remains unknown, and is referred to as idiopathic HP.

Epidemiological studies on HP are sparse and mostly cover certain subgroups. In Denmark, the prevalence of postsurgical HP was 220 per million inhabitants, nonsurgical HP 23 per million, and pseudohypoparathyroidism (PTH resistance; pseudo-HP) 11 per million (1–3), totaling 254 per million. An estimate among insured people from the United States revealed that about 77 000 have chronic HP of all causes (4), which translates into an approximate prevalence of 250 per million. In Japan and

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Abbreviations: ADH, autosomal dominant hypocalcemia; APS-1, autoimmune polyendocrine syndrome type 1; CaSR, calcium-sensing receptor; eGFR, estimated glomerular filtration rate; HADS, Hospital Anxiety and Depression scale; HDR, hypoparathyroidism, sensorineural deafness, and renal disease; HP, hypoparathyroidism; HRQOL, health-related quality of life; ICD, International Classification of Diseases; IFN, interferon; PF, physical functioning; QOL, quality of life; RP, role limitations due to physical problems; SF-36, Short Form 36; SSB, social security benefits; VT, vitality; GH, general health.

Table 1. Causes of Hypoparathyroidism

Cause	Gene (When Indicated)	Reference
Postsurgical and/or Following Radioactive Iodine Thyroid Ablation		
Autoimmune		
Isolated		
Component of APS-1	<i>AIRE/21q22.3</i>	(9, 10)
Genetic		
Isolated		
ADH types 1 and 2	<i>CASR/3q21.1, GNA11/19p13.3</i>	(7, 40)
<i>PTH</i> mutations	<i>PTH/11p15</i>	
<i>GCMB</i> mutations	<i>GCMB/6p24.2</i>	(41)
X-linked recessive	<i>SOX3/Xq26-27</i>	
As part of syndromes		
DiGeorge (22q11.2 deletion syndrome)	<i>TBX1/22q11</i>	(14, 42)
HDR syndrome	<i>GATA3/10p13-14</i>	(43)
Hypoparathyroidism-retardation-dysmorphism syndrome (Sanjad-Sakati syndrome) and Kenny-Caffey syndrome	<i>TBCE/1q42.3, FAM111A/11q12.1^a</i>	(44–46)
Mitochondrial associated (Kearns-Sayre and others)		
Stormorken's syndrome	<i>STIM1/11p15.4</i>	(47)
Target organ resistance		
Pseudohypoparathyroidism types 1 and 2	<i>GNAS,STX/20q13.3</i>	(48)
Blomstrand chondrodysplasia	<i>PTHR1/3p22-p21.1</i>	
Hypomagnesemia	<i>TRPM6/9q21.13^b</i>	
Vitamin D-dependent rickets	<i>VDR/12q13.11 (type 2a)</i>	
Idiopathic		
Miscellaneous		
Infiltrative disorders (hemochromatosis, thalassemia, Wilson's disease, metastasis)		

^a Kenny-Caffey syndrome type 2.

^b Hypomagnesemia from *TRPM6* mutations is typically accompanied by secondary hypocalcemia, but severe hypomagnesemia of any cause can give target organ resistance.

Israel, the prevalence numbers of idiopathic HP were 7 and 9 per million, respectively, and of pseudo-HP in Japan 3 per million (5, 6).

Patients with pseudo-HP and vitamin D resistance have elevated PTH, in contrast to classical HP. The clinical picture in pseudo-HP and vitamin D resistance is equal to other forms of HP and is therefore included as a subgroup of HP. Autosomal dominant hypocalcemia (ADH) (7) is probably the most common genetic cause of HP, usually caused by an activating mutation in the calcium-sensing receptor (*CASR*), termed ADH type 1, or rarely in guanine nucleotide binding protein, alpha 11 (*GNA11*), termed ADH type 2 (8). Occasionally, *CASR* mutations induce polyuria and hypokalemic alkalosis, called ADH with mild Bartter syndrome type 5. The severity of ADH is highly variable, and asymptomatic patients and those who exhibit mild symptoms can often go undiagnosed.

Autoimmune HP is mainly seen as part of autoimmune polyendocrine syndrome type 1 (APS-1), in which it is present in about 80% (9, 10). About one-half of the APS-1 patients with HP have autoantibodies against NACHT leucine-rich repeat protein 5 (NALP5), an intracellular

protein with unknown function highly expressed in parathyroid tissue (11). Autoantibodies against interferon omega (IFN- ω) can be detected in nearly all APS-1 patients regardless of organ involvement (12). Autoantibodies that activate CaSR have also been described as an autoimmune cause of HP (13).

HP may occur as part of various syndromes, most commonly the 22q11 deletion syndrome (DiGeorge syndrome). The prevalence of hypocalcemia among patients with this syndrome varies from 17% to 60% in different reports (14), and most have PTH levels below or in the low reference range (15) due to underdeveloped parathyroid glands. Only a minority requires treatment for chronic hypocalcemia, and only 7% of those with DiGeorge syndrome were diagnosed based on hypocalcemia and HP in a Norwegian national survey (16).

The conventional treatment of HP is calcium and active vitamin D supplementation to alleviate symptoms of hypocalcemia. To ensure normal level of 25-hydroxyvitamin D, many patients also need supplementation with calciferol because treatment with calcitriol or alphacalcidol does not affect the 25-hydroxyvitamin D status. Calciferol

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is probably important for several cellular processes because intracellular hydroxylation to active vitamin D occurs in many different cells (eg, bone, gut, prostate). The well-known neuromuscular problems accompanying vitamin D insufficiency, together with proposed association of vitamin D insufficiency to a number of different conditions such as cancer and diabetes mellitus is a reasonable argument to ensure adequate vitamin D status also in HP patients (17). Higher doses of calciferol can also be used instead of active vitamin D, and was the treatment of choice before active vitamin D became available. Calciferol increases the risk of prolonged hypercalcemia, and is now recommended for treatment of HP only if active vitamin D is unavailable.

To minimize the hypercalcuria and hyperphosphatemia following treatment with potent vitamin D analogues, serum calcium should be kept in the low normal range or slightly below. Undertreatment can lead to complications such as convulsions and arrhythmias, and overtreatment to tissue calcification with risk of kidney failure (18). PTH replacement therapy is not approved in Europe, but is advocated as a treatment option for patients who are difficult to manage on conventional therapy (17, 19) and since January 2015 recombinant human PTH (1–84) has been approved in the United States for the treatment of HP.

Given the scarcity of epidemiological data and the unique possibility to obtain nationwide data in Norway, we aimed to establish the epidemiology, etiology, and quality of life (QOL), and to map current treatment modalities in a nation-wide survey of HP.

Materials and Methods

Patients and design

We aimed to identify all living patients with HP in Norway who had been registered in an electronic hospital registry because we assumed that the vast majority of the patients would have been admitted to specialist care at least at the time of diagnosis. The health care system in Norway consists of four regional health authorities that own the health trusts (there are 19 somatic health trusts) that are responsible for the hospitals in each region (varying from one to six hospitals in each trust). Invitations to participate in the study were sent to all but two health trusts comprising five hospitals that were considered too small and lacked endocrinology departments. The research department in two of the health trusts declined participation (seven hospitals), and one health trust (four hospitals) and three single hospitals did not respond to our request. Thus, we searched the inpatient and outpatient registries at departments of medicine, surgery, and pediatrics in 35 of 54 hospitals, including all the tertiary and most of the secondary endocrine centers. Altogether, 80% of the Norwegian population was covered. In addition, the survey was advertised through the Norwegian HP patient association.

The inclusion period was from October 2010 through September 2013. The search criteria were the International Classi-

fication of Diseases, version 10 (ICD10), codes E20.0–9 (HP), E21.4 (other specified disorders of parathyroid gland), E89.2 (postsurgical HP), and D82.1 (DiGeorge syndrome). In two of the university hospitals, the search also included codes E83.5 (disorders of calcium metabolism), R29.0 (tetany), P71.0–9 (transitory neonatal disorders of calcium and magnesium metabolism), and the following ICD9 codes; 252.1, 252.8, 252.9 (disorders of the parathyroid gland); 275.40, 275.41m and 275.49 (disorders of calcium metabolism); 781.7 (tetany); 775.4 (hypocalcemia and hypomagnesemia in the newborn) and 279.11 (DiGeorge syndrome).

Medical records were reviewed and the diagnosis of HP was verified by an endocrinologist in each case. The diagnostic criteria were one of the following: 1) serum calcium below reference range with simultaneously low or inappropriately normal PTH, 2) serum calcium below reference range with simultaneously high PTH and normal renal function (pseudo-HP), or 3) criterion one plus need of permanent treatment for more than 1 year when HP was due to surgery or DiGeorge syndrome. Patients who fulfilled the inclusion criteria were invited to participate in the study and to complete a questionnaire including time of diagnosis and symptoms, treatment, and cause of the disease (if known), the Short Form 36 (SF-36) and Hospital Anxiety and Depression scale (HADS). Blood and urine samples were collected. Nonrespondents received a second invitation and a phone call to ask for willingness to participate. All participants or their guardians gave written informed consent. The regional committee for medical and health research ethics of Western Norway approved the study, and separate approval was given at each participating hospital trust's research department.

Blood and urine analyses

Serum was analyzed for total calcium, albumin, phosphate, magnesium, creatinine, thyroid-stimulating hormone and free thyroxine. Absolute estimated glomerular filtration rate (eGFR) was calculated based on measured creatinine and calculated body surface according to the formula: Calculated eGFR (Modification of Diet in Renal Disease formula) $\times (0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425})/1.73$, where the Modification of Diet in Renal Disease formula is $175 \times (\text{s-Creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if female). Albumin-corrected calcium was calculated from the formula: serum calcium (mmol/liter) $+ 0.02 \times (40 - \text{measured serum-albumin [g/liter]})$. In spot urine, creatinine and calcium per mmol creatinine were assayed. Assays of autoantibodies against NALP5 and interferon omega (IFN- ω) were performed using radioligand binding assay (20). CaSR antibodies were tested using immunoprecipitation (21). All the nonsurgical patients and a random sample of 20 postsurgical patients were tested for CaSR antibodies. All patients with available blood samples ($n = 251$) were analyzed for antibodies against NALP5 and IFN- ω .

Sequencing of genes was carried out by Sanger sequencing. The multiplex ligation-dependent probe amplification technique was used for analysis of large deletions/duplications. DNA was purified from blood using QIASymphony SP Midi Kit. Sequencing of the *CASR* gene and 22q11 were performed in all patients with idiopathic HP. *GATA3* was sequenced to identify one patient with the syndrome of hypoparathyroidism, sensorineural deafness, and renal disease (HDR), and *AIRE* was sequenced in one patient with NALP5 autoantibodies.

Questionnaires

SF-36 is a 36-item QOL questionnaire with response alternative scores 1–6 for each item. A scoring algorithm transforms the raw score to a score from 0 to 100, where a high score indicates better health-related QOL (HRQOL). Eight scales are calculated: perception of physical functioning (PF), role limitations due to physical problems (RP), bodily pain, general health (GH), vitality (VT), social functioning, role limitations due to emotional problems, and mental health. Missing data were replaced by the mean scores of the completed items in the same scale if at least half of the items in the actual scale were answered. HADS is a 14-item questionnaire, seven for anxiety and seven for depression. Scores are 0–3 for each item, and lower scores are favorable. If a single item from a subscale was missing, the data were replaced by using the mean of the remaining six items. If several items were missing, the subscale was discarded. Norwegian normative data are available for both SF-36 (22) and HADS (from the Health Study of Nord-Trøndelag 1995–97, HUNT II) (23).

Statistics

Norway's population in 2012 (4 985 870 inhabitants) was used to calculate prevalence (Statistics Norway) (24). Two sample *t* tests and the Mann-Whitney *U* test were used for continuous data that were normally and not normally distributed, respectively. One-way ANOVA was used to determine differences between the means of three or more independent groups, with post hoc analyses by Fisher's least significance difference test or Games-Howell when appropriate. Data are presented as median, unless specified. A significance level at 0.05 was chosen for all tests. Pearson's ρ was calculated for bivariate correlations.

Results

Patient identification and epidemiology

The initial search in two hospital registries using extended search criteria yielded more than 2000 hits, but only 132 were verified as HP. For subsequent searches, all ICD9 codes and three ICD10 codes (E83.5, R29, and P71.0–9), were omitted. According to the results from

these two centers, using the narrower search criteria we might miss approximately 8% of the HP patients. Even the narrowed search criteria revealed a coding practice that could not alone be trusted to identify patients. The erroneous coding was mostly attributed to hypocalcaemia of other causes, such as critical illness, malignancy, renal failure, and transient HP after surgery.

Altogether 522 patients were identified, of whom 511 were alive at the end of the registration period, yielding an overall prevalence of 102 per million, of whom 94 and 8 per million were genuine and pseudo-HP, respectively. Postsurgical HP comprised 321 individuals (64 per million) and nonsurgical HP 151 individuals (30 per million, pseudo-HP excluded). There were large regional variations in postsurgical HP prevalence (Table 2), which accounts for most of the variation in overall HP prevalence. Among the nonsurgical HP patients, the largest subgroup was idiopathic ($n = 67$, 44%), whereas 85 had genetic or autoimmune HP, of which ADH ($n = 31$, 21%), APS-1 ($n = 25$, 17%), and DiGeorge syndrome ($n = 23$, 15%) were most common. Four patients had HDR, one had vitamin D-dependent rickets type 1, and one had Stormorken's syndrome (Table 3). The patient with vitamin D-dependent rickets is not included in the further analysis, but is included in tables for completeness. Eight percent of the identified patients with DiGeorge syndrome had permanent treatment for HP of more than 1 year duration. Ninety percent of the patients were identified through search of hospital registries, whereas 10% were identified from other sources, in particular the patient organization.

National survey

Two hundred and eighty three (55%) agreed to participate (median age, 53 years [range, 9–89]; 75% females). The sex and age distribution of the identified patients and respondents were similar, but postsurgical HP was slightly

Table 2. Prevalence and Cause of HP in the Health Regions Among Living Patients ($n = 511$)

	All RHA	South-Eastern RHA	Western RHA	Central RHA	Northern RHA
Inhabitants	4 985 870	2 785 259	1 041 886	687 968	470 757
HP and pseudo-HP <i>n</i> (prev/100 000)	511 (10.2)	256 (9.2)	117 (11.2)	72 (10.5)	66 (14.0)
Postsurgical <i>n</i> (prev/100 000)	321 (6.4)	183 (6.6)	47 (4.5)	51 (7.4)	40 (8.5)
Nonsurgical <i>n</i> (prev/100 000)	148 (3.0)	54 (1.9)	59 (5.7)	17 (2.5)	18 (3.8)
Idiopathic	64 (1.3)	31 (1.1)	14 (1.3)	8 (1.2)	11 (2.3)
APS-1	25 (0.5)	9 (0.3)	9 (0.9)	3 (0.4)	4 (0.8)
ADH	31 (0.6)	4 (0.1)	26 (2.5)	1 (0.1)	0
HDR	4 (0.08)	1 (0.04)	3 (0.3)	0	0
DiGeorge	23 (0.5)	8 (0.3)	7 (0.7)	5 (0.7)	3 (0.6)
Other ^a	1	1	0	0	0
PseudoHP (prev/100 000)	41 (0.82)	19 (0.7)	10 (1.0)	4 (0.6)	8 (1.7)
Vitamin D-resistant rickets	1		1		

Abbreviations: prev, prevalence; RHA, regional health authorities.

^a One patient had HP from Stormorken's syndrome.

Table 3. Patients Identified and Survey Respondents, n (%)

	Identified HP (n = 522)	Respondents (n = 283)
Age, y (range)	51 (4–91)	53 (9–89)
Female	381 (73%)	212 (75%)
Postsurgical	329 (63%)	197 (70%)
Nonsurgical	152 (29%)	70 (25%)
Idiopathic	67	26
APS-1	25	15
ADH	31	18
HDR	4	1
DiGeorge	23	8
Other causes	2 ^a	2 ^a
Pseudo-HP	41 (8%)	16 (6%)

^a One patient with vitamin D-dependent rickets (excluded from further analysis) and one with Stormorken's syndrome.

more common among the respondents (Table 3). Patients with postsurgical HP, ADH, and APS-1 had a response rate at about 60%, whereas the response rates for patients with idiopathic HP, pseudo-HP, and DiGeorge syndrome were 35–40%.

Etiology of nonsurgical HP

Positive IFN- ω autoantibodies were found in 16 patients, of whom 15 had APS-1 (100%). One had postsurgical HP and had previously been treated for malignant thymoma and myasthenia gravis. NALP5 autoantibodies were detected in 11 patients, of whom seven had known APS-1 (median titer, 822; range, 787–1555; cutoff, 65). One patient with high titer (1020) was diagnosed with idiopathic HP at age 22; all other tested antibodies were initially negative, including IFN- ω . However, sequencing of *AIRE* confirmed two known disease-causing mutations (c.879+G>A and c.967_979del) consistent with APS-1 (10), and a new serum sample taken 2 years after the first was now clearly positive for IFN- ω . Three patients with positive NALP5 autoantibodies and no evidence of APS-1 had low titers (indices, 66–161). One patient had positive CaSR autoantibodies, although only a slightly elevated index (2.69; cutoff value, 2.26). This patient was later diagnosed with DiGeorge syndrome. Seven patients (21%) formerly classified as idiopathic HP were reclassified after genetic testing. Four had activating mutations in *CASR* (ADH), one had DiGeorge syndrome, one had the HDR syndrome, and one APS-1 (see the previous section).

Treatment and follow-up

Calcium supplementation was used by 198 (70%), vitamin D by 267 (94%) and active vitamin D formulations by 237 (84%) (Table 4). About half (n = 136, 48%) used either ergocalciferol (39%) or cholecalciferol (61%), of which 102 (75%) were used in combination with active

formulations of vitamin D. Eleven used ergocalciferol in high doses as the only vitamin D source. Ten patients were treated with subcutaneous PTH, of whom three received 1–34 injections, five received 1–84 injections, and two received 1–84 continuous infusions by pump. There was no significant difference in types of medication used by postsurgical, nonsurgical, or pseudo-HP patients, except treatment with PTH; nine of these were postsurgical and one nonsurgical. Median albumin corrected serum calcium was below the reference range (2.08 mmol/liter; reference range, 2.20–2.55), whereas the median urine calcium value was slightly above the reference range (0.51 mmol/mmol creatinine; reference range, 0.04–0.50) (Table 4). Postsurgical HP had significantly higher albumin corrected serum calcium and serum magnesium than nonsurgical HP patients ($P = .002$ and $P = .007$, respectively), whereas serum phosphate levels were similar. Eighteen percent had kidney failure (eGFR <60 ml/min), of whom 98% had an eGFR level greater than 30. The median eGFR was 80.8 (14.6–215.7) ml/min. Patients with both postsurgical and nonsurgical HP had significantly higher calcium excretion ($P < .001$ and $P = .003$, respectively) and postsurgical patients also had lower eGFR ($P = .04$) than pseudo-HP patients.

The nonsurgical patients were younger than the postsurgical HP patients both at the time of diagnosis (median 22 vs 40 years) and at the time of the study (median 48 vs 56 years). Pseudo-HP patients were youngest both at time of diagnosis (median, 12 years) and at the time of study (median, 32 years). Overall, the median age at diagnosis was 36 years (range, 0–81). Most (70%) were diagnosed with HP within the first 6 months from presentation of hypocalcemic symptoms, but 17% were diagnosed between 2 and 5 years after the first symptoms. In 9%, the diagnosis was delayed more than 5 years. Many patients with nonsurgical HP were diagnosed late; 14% between 2 and 5 years and 14% more than 5 years after symptom debut, as opposed to postsurgical HP (corresponding numbers were 5% and 6%, respectively). Among patients with pseudo-HP, 19% and 31% were diagnosed between 2 and 5 years and more than 5 years after symptom debut, respectively.

Most of the patients (64%) were diagnosed by an internist, endocrinologist, or pediatrician, but 15% were diagnosed by a general practitioner and 21% by others. A higher percentage of the postsurgical patients were diagnosed by others (24%), primarily a surgeon, but also 16% of nonsurgical patients and 7% of pseudo-HP patients were diagnosed by noninternists, mostly neurologists.

The majority (82%) had their serum calcium levels assessed every 6 months or more frequently. A higher percentage of patients in the surgical group (69%) than the

Table 4. Basal Characteristics, Laboratory Results, and Treatment Among Respondents (Median-Range)

	All (n = 283)	Surgical (n = 197)	Nonsurgical (n = 69)	Pseudo-HP (n = 16)	P Value	
Age (y), median (range)	53 (9–89)	56 (20–89)	48 (10–72)	32 (9–60)	.002 ^a <.001 ^b	
Female, n (%)	212 (75)	161 (82)	40 (58)	10 (63)	<.001 ^a	
BMI (kg/m ²), median (range)	25 (14–60)	25 (15–60)	25 (14–47)	25 (17–34)	NS	
SSB						
Retirement pension, n (%)	51 (18)	46 (23)	5 (7)	0	NS	
Permanent SSB, n (%)	72 (25)	53 (27)	15 (22)	4 (25)	NS	
Temporary SSB, n (%)	42 (15)	33 (17)	9 (13)	0	NS	
Laboratory Results						Ref. Range/Cut off
Corrected s-calcium (mmol/liter)	2.08 (1.47–2.84)	2.09 (1.61–2.69)	2.00 (1.68–2.84)	2.14 (1.47–2.25)	.002 ^a	2.20–2.55
s-Magnesium (mmol/liter)	0.83 (0.64–1.22)	0.83 (0.64–1.22)	0.80 (0.65–1.00)	0.89 (0.69–1.10)	.008 ^a .02 ^c	0.71–0.94
s-Phosphorus (mmol/liter)	1.29 (0.76–2.55)	1.29 (0.77–2.55)	1.32 (0.76–2.27)	1.38 (0.99–2.05)	NS	0.75–1.50 ^a
TSH (mIU/liter)	1.22 (0.01–14.20)	0.69 (0.01–14.20)	1.83 (0.04–5.42)	2.35 (0.01–6.86)	NS	0.40–4.50
FT4 (pmol/liter)	19.3 (9.3–39.6)	20.7 (11.0–39.6)	16.6 (9.3–23.6)	15.1 (10.1–24.2)	<.001 ^a .001 ^b	9.5–22.0
Creatinine (μmol/liter)	75.0 (33–247)	76.0 (34–247)	74.0 (44–168)	60.5 (33–102)	.03 ^c	Male: 60–105 Female: 45–90
eGFR (ml/min)	80.8 (14.6–215.7)	78.6 (14.6–181.5)	86.3 (30.4–152.0)	105.1 (52.6–215.7)	.04 ^b	>90
Urine calcium (mmol/mmol creatinine)	0.51 (0.02–2.29)	0.53 (0.02–1.91)	0.52 (0.03–2.29)	0.17 (0.02–0.74)	<.001 ^b .003 ^c	0.04–0.50
Treatment, Dose Median (Range)						Percentage Receiving Treatment (All)
Calcium (mg/day)	1000 (167–10 000)	1000 (167–10 000)	1000 (250–4000)	1000 (500–2000)	NS	70
Calcitriol (μg/day)	0.75 (0.13–4.00)	0.75 (0.13–4.00)	0.60 (0.25–2.00)	1.00 (0.75–1.40)	NS	40
Alphacalcidol (μg/day)	1.50 (0.25–6.00)	1.50 (0.25–6.00)	1.50 (0.40–5.00)	1.25 (0.50–4.00)	NS	44
Ergocalciferol (D ₂) (U/day)	4286 (1286–210 000)	4286 (1286–150 000)	4286 (2143–210 000)	3214 (2143–4286)	NS	19
Cholecalciferol (D ₃) (U/day)	800 (200–8000)	800 (200–8000)	800 (400–2400)	800 (800–800)	NS	29
Magnesium (mg/day)	300 (120–1200)	300 (120–1200)	300 (120–1200)	300 (120–375)	NS	34
PTH use (n)	10	9	1	0		4

Different reference ranges for different gender and age groups for s-phosphorus and s-creatinine. The results calculated for both sexes and all age groups combined.

Abbreviations: FT4, free thyroxine; NS, not significant.

^a Statistical significant difference between postsurgical and nonsurgical group.

^b Statistical significant difference between postsurgical and pseudo-HP group.

^c Statistical significant difference between nonsurgical and pseudo-HP group.

nonsurgical (44%) and the pseudo-HP group (53%) reported that urine calcium never had been measured.

QOL and working ability

The SF-36 and HADS scores are given in Table 5 as mean ± SD compared with respective Norwegian normative data (22, 23). HP patients had significantly lower SF-36 scores than the normative population in all eight dimensions, but pseudo-HP patients in only three of eight dimensions (RP, VT, social functioning). Overall female patients scored worse than male patients for PF ($P = .03$) and VT ($P = .03$), whereas patients with postsurgical HP scored worse than nonsurgical for RP ($P = .002$), bodily pain ($P = .03$) and VT ($P = .04$) and worse than pseudo-HP for PF and GH (both $P = .03$).

HP patients displayed significantly higher symptom score for anxiety, depression, and total HADS score than normative Norwegian population. The postsurgical group scored worse on depression than nonsurgical ($P = .02$). Thirty-eight percent had anxiety scores of at least 8, and 26% had depression score of at least 8, indicative of clinical significant anxiety and depression. Nine of sixteen

patients (56%) with pseudo-HP had anxiety scores of at least 8. Gender did not affect the HADS scores significantly.

No correlation between SF-36 or HADS scores (overall and subgroups) were found, either with corrected calcium levels or serum magnesium levels. However, there was a weak negative correlation between PF and serum magnesium (Pearson's ρ , -0.2 ; $P = .02$) in postsurgical HP patients.

Working ability

Forty percent received permanent or temporary social security benefits (SSB) (Table 4). Among the general population in Norway aged 18–66 years, the proportion of permanent SSB is about 10% and temporary SSB about 4% (24).

Discussion

We found an overall prevalence of HP in Norway less than half the prevalence recently established in Denmark (1–3)

Table 5. SF-36 and HADS Score, Mean (\pm SD) of the HP Population and Subgroups Compared With Norwegian Normative Data

	SF-36									HADS			Total HADS Score
	n	PF	RP	BP	GH	VT	SF	RE	MH	n	Anxiety	Depression	
Overall													
HP and pseudo-HP	283	74.2 (24.6)	44.9 (43.8)	58.1 (26.9)	50.7 (27.2)	42.2 (22.9)	68.5 (27.3)	65.1 (42.5)	70.5 (19.5)	283	6.5 (4.4)	4.8 (4.1)	11.4 (7.7)
Normative	2311	87.2 (18.7)	77.9 (35.8)	75.1 (26.0)	76.8 (22.0)	60.0 (20.8)	85.5 (22.2)	81.6 (32.4)	78.8 (16.5)	58 784	4.2 (3.3)	3.4 (3.0)	7.5 (5.5)
Females													
HP and pseudo-HP	212	72.4 (25.1)	43.1 (43.6)	56.4 (26.5)	49.3 (27.3)	40.4 (23.0)	67.6 (26.9)	66.3 (42.2)	70.0 (19.1)	212	6.7 (4.3)	4.8 (4.0)	11.5 (7.6)
Normative	1184	84.8 (20.8)	75.4 (37.7)	73.0 (26.6)	76.3 (22.5)	56.9 (21.2)	83.7 (23.1)	79.1 (34.6)	77.6 (17.0)				
Males													
HP and pseudo-HP	71	79.6 (22.0)	50.4 (44.3)	63.0 (27.5)	54.8 (26.6)	47.2 (22.2)	71.2 (28.5)	61.3 (43.4)	72.3 (20.6)	71	5.9 (4.5)	5.0 (4.7)	10.9 (8.2)
Normative	1085	89.8 (15.5)	80.5 (33.6)	77.2 (25.0)	77.4 (21.3)	63.2 (19.9)	87.6 (20.9)	84.5 (29.7)	80.0 (15.8)				
HP subgroups													
Surgical	197	72.2 (24.4)	39.2 (43.1)	55.3 (26.0)	48.7 (27.1)	40.0 (22.6)	67.4 (27.4)	63.9 (42.8)	70.2 (19.0)	197	6.6 (4.3)	5.2 (4.0)	11.8 (7.7)
Nonsurgical	69	73.5 (25.9)	58.6 (43.7)	63.8 (27.7)	52.5 (26.6)	46.4 (23.3)	71.6 (25.5)	68.7 (41.7)	71.8 (20.7)	69	6.3 (4.6)	4.0 (4.3)	10.3 (7.7)
Pseudo-HP	16	86.6 (16.4)	56.3 (39.3)	64.9 (29.5)	64.3 (26.0)	47.5 (20.5)	66.4 (32.5)	62.5 (43.7)	67.5 (22.5)	16	7.0 (4.0)	4.5 (4.6)	11.5 (8.1)

Abbreviations: BP, bodily pain; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health.

Normative data: SF-36: Loge and Kaasa (22) and HADS: HUNT databank (23). The overall SF-36 scores and the scores of postsurgical and nonsurgical patients were significantly different from normative data because the CIs do not overlap. The scores among pseudo-HP were significantly different from the normative scores for three dimensions (RP, VT, SF). Overall HAD scores and postsurgical HAD scores were significantly different from normative data, for nonsurgical HP significantly different for anxiety, and for pseudo-HP significant different for depression.

and the United States (4). This difference mainly reflects fewer with postsurgical HP in our study because the prevalence of nonsurgical HP was higher than in Denmark (2). Nonsurgical HP was most common in Western Norway, where ADH in a few large families (25) and APS-1 accounted for the difference. These differences could be genuine or due to underdiagnosing in other regions. Higher prevalence of idiopathic and pseudo-HP were found in the Norwegian cohort than in studies in Japan (5), but similar to that found in Denmark (3) and in Israel (6).

IFN- ω autoantibodies were detected in all the APS-1 patients, but also in one postsurgical patient, who had thymoma-associated myasthenia gravis, in which IFN- ω autoantibodies are common (26). In concordance with earlier studies (11), NALP5 autoantibodies were detected in 50% of the patients with previously known APS-1. One patient with a high titer of NALP5 autoantibodies, diagnosed as idiopathic HP 39 years previously tested negative for IFN- ω autoantibodies, but sequencing of *AIRE* confirmed APS-1, and a repeat sample 2 years later was clearly positive also for IFN- ω autoantibodies.

Despite testing for underlying causes, about one-third of nonsurgical patients remain idiopathic, which may conceal hitherto unidentified forms of HP. The medical history and clinical vigilance can to some extent guide the clinician to the underlying cause, but in many cases the cause is not obvious. According to our results, it here seems reasonable to test for ADH, APS-1, and DiGeorge syndrome. Antibodies against IFN- ω and NALP5 are excellent markers of APS-1 (11, 27, 28). Testing for anti-

bodies against the CaSR among patients with idiopathic HP does not seem justified based on our results.

We believe that the search for ADH among patients with idiopathic HP is important because these patients should receive treatment with calcium and vitamin D only if the disease is symptomatic. The treatment increases hypercalcuria and risk of kidney failure more than other forms of HP (7). Symptomatic patients should be treated, but only to alleviate symptoms, not to restore normocalcemia, as low dosages of calcitriol results in less frequent renal calcifications (7). Diagnosis of APS-1, DiGeorge, or other syndromes is also of great importance because other components of these disorders need to be identified and treated early to avoid untimely morbidity and mortality. Most of the patients in the Norwegian HP population received conventional calcium and active vitamin D supplementation, which was associated with a high proportion of kidney failure, indicating a need for improvement of the therapy.

Our study corroborates earlier studies showing reduced HRQOL among HP patients (29–31), especially among patients with postsurgical HP who also had significantly lower SF-36 scores than Norwegian patients with Addison's disease in six of eight dimensions and congenital adrenal hyperplasia in five of eight dimensions (32, 33). One plausible explanation could be a higher proportion of absolute PTH depletion or related to the cause of surgery (ie, Graves' disease or thyroid cancer), but there is no correlation to the calcium levels. Receptors for PTH are found in several tissues, including the central nervous sys-

tem and probably the adrenal cortex, and lack of PTH action in tissues not related to calcium homeostasis or bone metabolism may explain the reduced HRQOL. If so, PTH replacement therapy should improve HRQOL; indeed, some PTH intervention studies show convincing improvement (29, 31, 34). Neither the large placebo-controlled study REPLACE nor a Danish study found such improvement (30, 35, 36), but in the Danish study many patients became hypercalcemic because of a high fixed PTH dose. The uncertainty about effectiveness of PTH treatment may be due to dose or delivery, which so far has not restored physiological calcium homeostasis properly. Our study revealed a higher percentage of patients with clinically significant anxiety and depression than other disease groups in Norway, which have been studied using HADS (37, 38). Although not directly comparable, our results are in concordance with the result from one study among 25 postsurgical HP patients (39).

The large sample size and the study design as a national study without major selection bias is the greatest strength of this study. The added inclusion criterion with need of permanent treatment for HP for more than 1 year for patients with postsurgical HP and HP resulting from DiGeorge syndrome ensured that only patients with permanent HP were included. A limitation is that even though the overall sample size is large, it constitutes a very heterogeneous group. The response rate of 55% in the patient survey should ideally have been higher, but the basic characteristics of the respondents and identified patients were not significantly different; we therefore believe that this group is representative. Furthermore, the response among the patients who comprise the largest subgroups of the cohort (postsurgical, APS-1, ADH) were higher than for the patients within the smaller subgroups. The HRQOL data were not adjusted for age and sex because the raw data from the normative were not available for direct comparison. However, the age and sex distributions in the patient populations were comparable to the normative population. For each age and sex stratification, the trends were similar as in the overall data, but not necessarily significantly different because of small numbers in each group.

In conclusion, the prevalence of genetic, autoimmune, and idiopathic HP in Norway is higher than reported elsewhere, whereas the prevalence of postsurgical HP is lower than expected. Systematic assessment of the underlying cause of HP is important to tailor the treatment, especially for patients with ADH, and to identify other syndrome components early in APS-1, DiGeorge syndrome, and HDR. Still, many patients have unknown cause. Despite conventional calcium, magnesium, and vitamin D supplementation, complications such as kidney failure and re-

duced HRQOL are common, indicating a need for improvement of the therapy.

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