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Epidemiology and health related quality of life in hypoparathyroidism in Norway

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Abstract

Objective The epidemiology of hypoparathyroidism (HP) is essentially unknown. We aimed to determine prevalence, etiologies, health related quality of life (HRQoL) and treatment 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. HRQoL was determined by Short Form 36 (SF-36) and Hospital Anxiety and Depression scale (HADS). Assay of autoantibodies and genes were performed for classification of etiology.

Results We identified 522 patients (511 alive) and calculated the overall prevalence to 102 per million divided among post-surgical HP (64 per million) and non-surgical HP (38 per million). The latter comprised pseudo-HP (22%), autosomal dominant hypocalcemia (16%), autoimmune polyendocrine syndrome type 1 (13%), DiGeorge/22q11 deletion syndrome (12%), idiopathic HP (34%), and others, 3%. 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 (30% of non-surgical HP) remained idiopathic. Most were treated with vitamin D (94%) and calcium (70%), and 10 received parathyroid hormone. HP patients scored significantly worse than the normative population on SF-36 and HADS; patients with post-surgical scored worse than those with non-surgical HP, especially on physical health and depression.

Conclusions We found higher prevalence of non-surgical HP in Norway than reported elsewhere. Genetic testing and autoimmunity screening of non-surgical HP seems warranted as HP is often a component of a clinical syndrome. Further research is necessary to unravel the causes of idiopathic HP and to improve the reduced HRQoL reported by HP patients.

Introduction

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

Epidemiological studies on HP are sparse and mostly cover certain subgroups. In Denmark, the prevalence of post-surgical HP was 220 per million inhabitants, non-surgical 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 US revealed that about 77 000 have chronic HP of all causes (4), which translates into an approximate prevalence of 250 per million. In Japan, the prevalence numbers of idiopathic HP and pseudo-HP were 7 and 3 per million, respectively (5). The prevalences in other countries have not been reported.

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. An activating mutation in the *calcium sensing receptor* (*CaSR*) is probably the most common genetic cause of HP, called autosomal dominant hypocalcemia (ADH) (6). Many are asymptomatic or exhibit mild symptoms that can 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% (7, 8). About 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 (9). Autoantibodies against interferon omega (IFN-ω) can be detected in nearly all APS-1 patients regardless of organ involvement (10). Autoantibodies that activate CaSR have also been described as an autoimmune cause of HP (11, 12). HP may occur as part

of various syndromes, most commonly the 22q11 deletion syndrome (DiGeorge syndrome). In this syndrome about 60% have serum calcium levels below the reference range (13, 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 (25(OH)D) many patients also need supplementation with calciferol, as treatment with calcitriol or alphacalcidiol does not affect the 25(OH)D status. Calciferol is probably important for several cellular processes, as hydroxylation to active vitamin D also occurs inside the cell. The well-known neuromuscular problems accompanying vitamin D insufficiency, together with proposed association of vitamin D insufficiency to a number of different conditions like cancer and diabetes mellitus is a reasonable argument to ensure adequate vitamin D status also in HP patients (17).

To minimize the ensuing hypercalcuria and hyperphosphatemia, serum calcium should be kept in the low normal range or slightly below. Undertreatment can lead to complications like 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).

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

Material 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, as 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 (RHA) that own the health trusts, altogether 19 somatic health trusts, responsible for the hospitals in each region (varying from 1 to 6 hospitals in each trust). Invitations to participate in the study were sent to all but two health trusts with altogether 5 hospitals which were considered too small and also 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 in-patient and out-patient registries at departments of medicine, surgery and pediatrics in 35 of altogether 54 hospitals, including all the tertiary and the majority 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 till September 2013. The search criteria were the International Classification of Diseases version 10 (ICD10) codes E20.0-9 (HP), E21.4 (Other specified disorders of parathyroid gland), E89.2 (post-surgical 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) in addition to ICD 9 codes 252.1, -8, -9 (disorders of the parathyroid gland), 275.40, -41 and -49 (disorders of calcium metabolism), 781.7 (tetany), 775.4 (hypocalcemia and hypomagnesemia in the newborn), 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), 3) criterion one plus need of permanent treatment for more than one 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. Non-respondents received a second invitation, and eventually a phone call to ask for willingness to participate. All the participants or their guardians gave written informed consent. The regional committee for medical and health research ethics of Western Norway approved the study, as well as separate approval 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 (TSH) and free thyroxine (FT4). Absolute estimated GFR (eGFR) was calculated based on measured creatinine and calculated body surface according to the formula: Calculated eGFR (Modification of Diet in Renal disease (MDRD) formula) x (0.20247 x height (m) $^{0.725}$ x weight (kg) $^{0.425}$)/1.73, where the MDRD formula is 175 x (s-Creatinine/88.4)$^{-1.154}$ x (age)$^{-0.203}$ x 0.742 (if female). Albumin corrected calcium was calculated from the formula: serum calcium (mmol/L) + 0.02 x (40 – measured serum-albumin (g/L)). In spot urine creatinine and calcium per mmol creatinine was assayed. Assays of autoantibodies against NALP5 and interferon omega (IFN-ω) were performed using radioligand binding assay (20). Calcium-sensing receptor (CaSR) antibodies were tested using immunoprecipitation (21).

Sequencing of genes was carried out by Sanger sequencing. The MLPA (Multiplex Ligation-dependent Probe Amplification) technique was used for analysis of large deletions/duplications. DNA was purified from blood using QIASymphony SP Midi Kit. *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 quality of life questionnaire with response alternative scores 1-6 for each item. A scoring algorithm transforms the raw score to a score from 0-100 were a high score indicates better HRQoL. Eight scales are calculated: perception of physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). 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 items 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 was 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 the prevalence (Statistics Norway) (24). Two sample t-test and the Mann-Whitney U test were used for continuous data that were normally and not normally distributed, respectively. 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 over 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. 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 with HP were identified, of whom 511 were alive at the end of the registration period yielding an overall prevalence of 102 per million. Post-surgical HP comprised 321 individuals (64 per million) and non-surgical 190 individuals (38 per million). There were large regional variations in post-surgical HP prevalence (Table 2), which accounts for most of the variation in overall HP prevalence. Among non-surgical HP patients (n=193) most were idiopathic (n=67, 35%). Forty-one (21%) had pseudo-HP, while 85 had genetic or autoimmune HP, of which ADH (n=31, 16%), APS-1 (n=25, 13%), and DiGeorge syndrome (n=23, 12%) were most common. Four had HDR, one vitamin D-dependent rickets type 1 and one Stormorken's syndrome (Table 3). In our study, 8% of the identified patients with DiGeorge syndrome had permanent treatment for HP of more than one 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 post-surgical HP was slightly more common among the respondents (Table 3). Patients with post-surgical 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

Positive IFN-ω autoantibodies were found in 16 patients, of whom 15 had APS-1 (100%). One had post-surgical HP and had previously been operated on for malignant thymoma and was diagnosed with myasthenia gravis. NALP5 autoantibodies were detected in 11 patients, of whom seven had known APS-1 (median titer 822, range 787-1555, cut-off 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 (8), and a new serum sample taken 2 years after the first was now clearly positive for interferon autoantibodies. 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, cut-off 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 above).

Treatment and follow-up

Calcium supplementation was used by 198 (70%) and active vitamin D formulations by 237 (84%) (Table 4). About half (n=136, 48%) used either ergocalciferol (39%) or cholecalciferol (61%) of whom 102 (75%) in combination with active formulations of vitamin D. Eleven used ergocalciferol as the only vitamin D supplementation. Ten patients were treated with subcutaneous PTH injections or delivery by a pump. There was no significant difference in types of medication used by post-surgical and non-surgical patients, except treatment with PTH; nine of them were post-surgical. Median albumin corrected serum calcium was below the reference range (2.08 mmol/L, 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). Post-surgical HP had significantly higher albumin corrected serum calcium than non-surgical HP patients (P=0.005), whereas serum magnesium and phosphate were similar. Eighteen percent had kidney failure (eGFR <60 ml/min). The median eGFR was 80.8 (14.6-215.7) ml/min. Patients with post-surgical HP had significantly higher calcium excretion (P=0.01) and lower eGFR (P=0.002) than non-surgical HP patients.

The non-surgical were younger than the post-surgical HP patients both at the time of diagnosis (median 18 vs 40 years) and at the time of the study (median 45 vs 56 years). Overall, the median age at diagnosis was 36 years (range 0-81). Most (70%) were diagnosed with HP within the first six months from presentation of hypocalcemic symptoms, but 17% were diagnosed between two and five years after the first symptoms. In 9%, the diagnosis was delayed more than five years. Many patients

with non-surgical HP were diagnosed late; 33% between two and five years and 18% more than five years after symptom debut, as opposed to post-surgical HP (corresponding numbers were 11 and 6%, 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 post-surgical patients were diagnosed by others (23%), primarily a surgeon, but also 14% of non-surgical patients were diagnosed by non-internists, mostly neurologists.

The majority (82%) had their serum calcium levels assessed every six months or more frequently. A higher percentage of patients in the surgical group than the non-surgical group reported that urine calcium never had been measured (66% vs 43% respectively).

Quality of life 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 score than normative population in all eight dimensions, and also lower than Norwegian Addison patients in six of eight dimension (PF, RP, BP, VT, SF, MH) and Norwegian congenital adrenal hyperplasia patients in five of eight dimensions (PF, VT, SF, RE, MH) (25, 26) (data not shown). Female patients scored worse than male patients for PF ($p=0.03$) and VT ($p=0.03$), whereas patients with post-surgical HP scored worse than non-surgical for PF ($p=0.01$), RP ($p=0.001$), BP ($p=0.01$) and VT ($p=0.02$).

HP patients displayed significantly higher symptom score for anxiety, depression and total HADS score than normative Norwegian population. The post-surgical group scored worse on depression than non-surgical ($p=0.04$). Thirty-eight percent had anxiety scores ≥ 8, and 26% had depression score ≥ 8, indicative of clinical significant anxiety and depression. Gender did not affect the scores significantly.

No correlation between SF-36 or HADS scores (overall and subgroups) were found, neither with corrected calcium levels nor serum magnesium levels. However, there was a positive correlation between GH and serum magnesium (Pearson's ρ 0.3; p=0.03) in non-surgical patients.

Working ability

Forty percent had permanent or temporary social security benefits (SSB) (Table 4). Among the general population in Norway aged 18 to 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) and USA (4). This difference mainly reflects fewer with post-surgical HP in our study. Despite the lower overall prevalence in Norway, the prevalence of non-surgical HP was higher than in Denmark (2). Non-surgical HP was most common in Western Norway, where ADH in a few large families (27, 28) and APS-1 accounted for the difference. These differences could be genuine or due to underdiagnosing in other regions. ADH, for instance, can present with only mild hypocalcemia and be easily missed. Higher prevalence of idiopathic and pseudo-HP were found in the Norwegian cohort than in studies in Japan (5), but the prevalence of pseudo-HP in Norway was similar to that recently found in Denmark (3).

Not surprisingly, IFN-ω autoantibodies were detected in all the APS-1 patients, but also one post-surgical patient had a high titer, which was ascribed to thymoma-associated myasthenia gravis, in which IFN-ω autoantibodies have been found in 60% of the patients (29). In concordance with earlier studies (9), NALP5 autoantibodies were detected in 50% of the patients with previously known APS-1. One patient with a high titer of NALP5 autoantibodies, who had been diagnosed with idiopathic HP 39 years ago and in recent years also treated for autoimmune hypothyroidism, initially tested negative for IFN-ω autoantibodies, but sequencing of *AIRE* eventually confirmed APS-1. A new sample taken two years after the initial sample was clearly positive for IFN-ω autoantibodies.

Despite thorough testing for underlying causes of idiopathic HP, about one third of non-surgical patients still have unknown cause. Concealed in this remarkable high fraction of idiopathic HP must be hitherto unidentified forms of HP. The medical history and clinical vigilance can to some extent guide the clinician to the underlying cause of HP, but in many cases the cause is far from obvious. According to our results it seems reasonable to test for ADH, APS-1 and DiGeorge syndrome in cases without findings indicating a specific diagnosis. Antibodies against IFN-ω and NALP5 are excellent markers of APS-1 (9, 30, 31). General testing for antibodies against the CaSR among patients with idiopathic HP does not seem justified based on our results.

We believe that systematic search for ADH among patients with idiopathic HP is important, since these should receive treatment with calcium and vitamin D only if the disease is symptomatic. The treatment itself can increase hypercalcuria and the risk of renal calcifications and renal failure more than other forms of HP (6). 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 (6). Diagnosis of APS-1, DiGeorge or other syndromes is also of great importance, since other components of these disorders needs to be diagnosed 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 need for improvement of the therapy.

Our study corroborates earlier studies showing reduced HRQoL among HP patients (32-34), especially among patients with post-surgical HP. One plausible explanation could be a higher proportion of absolute PTH depletion or related to the cause of surgery (for instance Graves' disease or thyroid cancer). The cause of the overall reduced HRQoL is not obvious, as there is no correlation to low or high calcium levels. Receptors for PTH are found in several tissues, including the central nervous system and probably the adrenal cortex (35), and lack of PTH in tissues not related to calcium homeostasis or bone metabolism is a plausible explanation for the reduced HRQoL. If so, PTH replacement therapy should improve HRQoL, and indeed some studies show convincing improvement

in HRQoL with PTH therapy (32, 34, 36). Another study found no such improvement (33), but many patients became hypercalcemic, which could be an explanation. It is reasonable to assume that the uncertainty about effectiveness of PTH treatment is due to dose or delivery, which so far has not been able to restore physiological calcium homeostasis properly. Our study revealed a higher percentage of patients with clinical significant anxiety and depression compared to 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 post-surgical 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 one year for patients with post-surgical HP and HP due to 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 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 (post-surgical, APS-1, ADH) were higher than for the patients within the smaller subgroups.

In conclusion, the prevalence of genetic, autoimmune and idiopathic HP in Norway is higher than reported elsewhere, whereas the prevalence of post-surgical HP is lower than expected. Systematic assessment of the underlying cause of HP is important to tailor the treatment, especially for patients with ADH, APS-1, DiGeorge syndrome, and HDR. Still, a large proportion of the patients have unknown cause despite systematic investigation. Despite conventional calcium, magnesium, and vitamin D supplementation complications such as kidney failure and reduced HRQoL is common, indicating need for improvement of the therapy.

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Table 1. Causes of hypoparathyroidism

Cause	Gene (when indicated)	Reference
Postsurgical and/or following radioactive iodine thyroid ablation		
Autoimmune		
Isolated		
Component of APS-1	*AIRE*/21q22.3	(7, 8)
Genetic		
Isolated		
Activating *CaSR*-mutations	*CaSR*/3q21.1	(6, 40)
PTH- mutations	*PTH*/11p15	
GCMB-mutations	*GCMB*/6p24.2	(41)
X-linked recessive	*SOX3*/Xq26-27	
As part of syndromes		
DiGeorge (22q11.2-deletion syndrome)	*TBX1*/22q11	(13, 14)
HDR-syndrome	*GATA3*/10p13-14	(42)
Hypoparathyroidism-retardation-dysmorphism syndrom (Sanjad-Sakati syndrome) and Kenny-Caffey syndrome	*TBCE*/1q42.3, *FAM111*A/11q12.1*	(43-45)
Mitochondrial associated (Kearns-Sayre and others)		
Stormorken's syndrome	*STIM1*/11p15.4	(46)
Target organ resistance		
Pseudohypopara type 1 and 2	*GNAS,STX*/20q13.3(type)	(47)
Blomstrand chondrodysplasia	*PTHR1*/3p22-p21.1	
Hypomagnesemia	*TRPM6*/9q21.13**	
Vitamin D dependent rickets	*VDR*/12q13.11 (type 2a)	
Idiopathic		
Miscellaneous		
Infiltrative disorders (Hemochromatosis, Thalassemia, Wilsons disease, metastasis)		

*Kenny-Caffey syndrome type 2.

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

APS-1: Autoimmune polyendocrine syndrome type 1, ADH: Autosomal dominant hypocalcemia, HDR: Hypoparathyroidism, deafness and renal syndrome.

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 n (prev/100000)	511 (10.2)	256 (9.2)	117 (11.2)	72 (10.5)	66 (14.0)
Post-surgical n (prev/100 000)	321 (6.4)	183 (6.6)	47 (4.5)	51 (7.4)	40 (8.5)
Non-surgical n (prev/100 000)	190 (3.8)	73 (2.6)	70 (6.7)	21 (3.1)	26 (5.5)
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)
PseudoHP	41 (0.82)	19 (0.7)	10 (1.0)	4 (0.6)	8 (1.7)
Miscellaneous	2	1	1	0	0

RHA: Regional health authorities, APS-1: Autoimmune polyendocrine syndrome type 1, ADH: Autosomal dominant hypocalcemia, HDR: Hypoparathyroidism, deafness and renal syndrome.

Table 3 Patients identified and survey respondents, n (%)

	Identified HP n=522	**Respondents n=283**
Age, years (range)	51 (4-91)	53 (9-89)
Female	381 (73%)	212 (75%)
Post-surgical	329 (63%)	197 (70%)
Non-surgical	193 (37%)	86 (30%)
Idiopathic	67	26
APS-1	25	15
ADH	31	18
HDR	4	1
DiGeorge	23	8
Pseudo-HP	41	16
Other causes	2*	2*

APS-1: Autoimmune polyendocrine syndrome type 1, ADH: Autosomal dominant hypocalcemia, HDR:Hypoparathyroidism, deafness and renal syndrome.
* One with vitamin D-dependent rickets, one with Stormorken's syndrome

Table 4 Basal characteristics, laboratory results and treatment among respondents (median- range)

	All, n=283	**Surgical, n=197**	**Non-surgical, n=86**		
Age (years), median (range)	53 (9-89)	56 (20-89)	45 (9-72)	P<0.001	
Female n (%)	212 (75)	161 (82)	51 (59)	P<0.001	
BMI (kg/m^2), median (range)	25 (14-60)	25 (15-60)	25 (14-47)	NS	
Social security benefits (SSB)					
Retirement pension, n (%)	51 (18)	46 (23)	5 (6)		
Permanent SSB, n (%)	72 (25)	53 (27)	19 (22)		
Temporary SSB, n (%)	42 (15)	33 (17)	9 (11)		
Laboratory results					**Ref.range/cut off**
Corrected s-calcium (mmol/L)	2.08 (1.47-2.84)	2.09 (1.61-2.69)	2.01 (1.47-2.84)	P=0.005	2.20-2.55
s-Magnesium (mmol/L)	0.83 (0.64-1.22)	0.83 (0.64-1.22)	0.82 (0.65-1.10)	NS	0.71-0.94
s-Phosphorus (mmol/L)	1.29 (0.76-2.55)	1.29 (0.77-2.55)	1.33 (0.76-2.27)	NS	0.75-1.50*
TSH (mIE/L)	1.22 (0.01-14.20)	0.69 (0.01-14.20)	1.87 (0.01-6.86)	P=0.05	0.40-4.50
FT4 (pmol/L)	19.3 (9.3-39.6)	20.7 (11.0-39.6)	16.4 (9.3-24.2)	NS	9.5-22.0
Creatinine (µmol/L)	75.0 (33-247)	76.0 (34-247)	73.0 (33-168)	NS	Male: 60-105 Female: 45-90
Estimated GFR (ml/min)	80.8 (14.6-215.7)	78.6 (14.6-181.5.)	93.8 (30.4-215.7)	P=0.002	> 90
Urine Calcium (mmol/mmol creatinine)	0.51 (0.02-2.29)	0.53 (0.02-1.91)	0.43 (0.02-2.29)	P=0.01	0.04-0.50
Treatment, dose median (range)					**Percentage receiving treatment (all)**
Calcium mg/day	1000 (167-10000)	1000 (167-10000)	1000 (250-4000)	NS	70
Calcitriol µg/day	0.75 (0.13-4.00)	0.75 ((0.13-4.00)	0.61 (0.25-2.00)	NS	40
Alphacalcidiol µg/day	1.50 (0.25-6.00)	1.50 (0.25-6.00)	1.50 (0.40-5.00)	NS	44
Ergocalciferol (D_2) U/day	4286 (1286-210 000)	4286 (1286-150 000)	4286 (2143-210 000)	NS	19
Cholecalciferol (D_3) U/day	800 (200-8000)	800 (200-8000)	800 (400-2400)	NS	29
Magnesium mg/day	300 (120-1200)	300 (120-1200)	300 (120-1200)	NS	34
PTH use, n	10	9	1		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.

Table 5. SF-36 and HADS score, mean (±SD) of the HP population and subgroups compared to Norwegian normative data

	SF-36									HADS			
	n	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**	**n**	**Anxiety**	**Depression**	**Total HADS-score**
Overall													
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)	58784	4.2 (3.3)	3.4 (3.0)	7.5 (5.5)
Females													
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	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)
Non-surgical	86	78.7 (24.5)	58.6 (42.6)	64.5 (27.9)	55.4 (27.0)	47.1 (23.0)	71.0 (26.9)	67.9 (41.8)	71.1 (20.9)	86	6.4 (4.4)	4.1 (4.3)	10.9 (8.2)

Normative data: SF-36: Loge and Kaasa (22) and HADS: HUNT databank (23). All the SF-36 and HADS subscales significantly different from normative data because the confidence intervals do not overlap.