

RESEARCH

Low health-related quality of life in hypoparathyroidism and need for PTH analog

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Abstract

Objective: Hypoparathyroidism (HypoPT) is a rare endocrine disorder in which insufficient levels of parathyroid hormone (PTH) lead to low serum calcium (S-Ca) levels and muscular cramps. The aim was to study the health-related quality of life (HRQoL) and comorbidities in patients with HypoPT compared with the general population and to estimate the need of treatment with PTH analog.

Design: Patients with HypoPT were identified and compared with a population sample. Short Form-36 (SF-36) and EuroQol-5 Dimensions Visual Analogue Scale questionnaires were used. All patients were followed up at the Sahlgrenska University Hospital outpatient clinic.

Methods: From the medical records between 2007 and 2020, 203 patients with HypoPT were identified and compared with a population sample ($n = 414$) from the World Health Organization's (WHO) MONICA project, Gothenburg, Sweden. Of the 203 patients who met the diagnostic criteria, 164 were alive and 65% answered the HRQoL questionnaires.

Results: Patients with HypoPT, 80% postsurgical, and controls had similar age (60 years) and sex distribution (80% women). Patients had lower SF-36 summary component scores for physical (40.0 (interquartile range (IQR): 21) vs 51.2 (IQR: 14.6); $P < 0.001$) and mental (43.1 (IQR:17.4) vs 56.1(IQR:13.3); $P < 0.001$) well-being, irrespective of etiology or calcium levels. Individuals with HypoPT had more medications and lower renal function but not higher mortality than controls. Low HRQoL together with low calcium was present in 23% of individuals with HypoPT.

Conclusion: HRQoL was markedly lower in patients with HypoPT than in controls and independent of S-Ca levels. Treatment with PTH analog could be considered at least among patients with both low HRQoL and low calcium levels.

Key Words

- ▶ hypoparathyroidism
- ▶ parathyroid hormone
- ▶ calcium
- ▶ quality of life
- ▶ comorbidity

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Introduction

Hypoparathyroidism (HypoPT) is a rare endocrine disorder with insufficient levels of parathyroid hormone (PTH), which leads to hypocalcemia and hyperphosphatemia. The phosphate and calcium imbalance increases the risk of ectopic calcifications in the body, for example in the

kidneys, in the basal ganglia of the brain, and in the lenses of the eyes. Patients may also experience various physical and neurocognitive symptoms leading to impaired health-related quality of life (HRQoL) (1, 2, 3). Other chronic manifestations related to both disease and treatments are

impaired skeletal health, renal stones, and increased risk of progressive renal failure (4, 5, 6).

The most common etiology of HypoPT is the accidental removal or devascularization of the parathyroid glands during surgical neck procedures. The number of parathyroid glands preserved *in situ* is also related to the risk for postoperative HypoPT (7). Mutations in several genes can lead to HypoPT, such as *GCM2*, *PTH*, *CASR*, and *GNA11*. The disease can also occur as a part of various syndromes, such as DiGeorge, a.k.a. the 22q11 deletion syndrome.

The prevalence of HypoPT in the United States, Norway, and Denmark was estimated between 10 and 24/100,000 inhabitants (4, 8, 9), of which only 2/100,000 were classified as non-postoperative HypoPT according to a Danish study (10).

The current treatment of HypoPT consists of oral calcium substitution and supplementation with active vitamin D. Possible concomitant vitamin D deficiency is treated with cholecalciferol if necessary. The goal of the treatment is to minimize the symptoms without increasing the risk of soft tissue calcifications, hypercalciuria, and kidney failure. However, in some patient groups, these goals are not achieved (11). In addition, conventional treatment cannot correct the patients' abnormal skeletal metabolism (5).

Since 2015 in the United States and since 2017 in Europe, a new drug for refractory HypoPT has been available as daily subcutaneous injections, a recombinant PTH analog (1–84), which was initially developed for the treatment of osteoporosis. Treatment with a recombinant PTH analog (1–84) is considered safe and has a documented effect on calcium–phosphate balance, reduced urinary calcium excretion, and improved bone metabolism. However, its effects on well-being after up to 8 years follow-up are controversial (2, 3, 12, 13). Recently a new long-acting formula of PTH (1–34) has been investigated with beneficial results on both calcium metabolism and HRQoL based on preliminary results (14).

The aim of our study was to assess the prevalence of patients with HypoPT treated at Sahlgrenska University Hospital, Gothenburg, Sweden, their HRQoL, comorbidity, and mortality. The patients were compared with a population sample from the same city. The hypothesis was that patients with HypoPT have impaired HRQoL, higher morbidity and mortality, compared to the general population. A second aim, based on HRQoL findings, was to estimate the number of patients in need of substitution with PTH analogs.

Materials and methods

Patients

In Sweden, every citizen has a unique identification number, whereby all health records and laboratory analyses are retrievable from regional or national health archives.

We aimed to identify all adult patients with HypoPT, of all causes, in the western region of Sweden, a region of nearly 800,000 inhabitants. Sahlgrenska University Hospital, Gothenburg, is the regional referral center, and all patients with HypoPT are treated and followed up at the Sahlgrenska University Hospital outpatient clinic.

Patients with a potential diagnosis of chronic HypoPT according to the International Classification of Diseases version 10 (ICD 10), codes E20 HypoPT, E83.5 disorders of calcium metabolism, E89.2 postoperative HypoPT, between 2007 and 2020, were identified and their medical records were reviewed (Fig. 1). The diagnosis of HypoPT for each patient was based on the definition of HypoPT described by the European Society of Endocrinology (15) and was verified by an endocrinologist. The etiology of HypoPT was determined as postoperative or non-postoperative (genetic, autoimmune, or idiopathic).

Medical and laboratory records from these individuals, $n = 203$, were compared with a population sample from the same city of Gothenburg, $n = 414$. Of the 203 patients with chronic HypoPT who met the diagnostic criteria above, 164 were alive in 2020 and 106 answered the HRQoL questionnaires, yielding a participation rate of 65%.

Height, weight, x-ray results, medications and drug doses, laboratory analyses, blood pressure, and the occurrence of other comorbidities and complications, such as renal failure and soft tissue calcifications, as well as fracture history were recorded. Patients were divided into two different groups, postoperative HypoPT and non-postoperative HypoPT, based on etiology and the above variables were analyzed. All postoperative HypoPT included were considered permanent; they needed a substitution treatment with calcium and/or active vitamin D exceeding 6 months postsurgery.

Based on blood sample analyses and questionnaire results, the patients were also divided into four groups depending on the recommended/low calcium levels and high/low well-being (i.e. feeling well or unwell) (16), in order to evaluate the need for PTH analog substitution. Patients with both low calcium and low well-being, despite appropriate supplementation with calcium and active form of vitamin D as proposed by the European Society

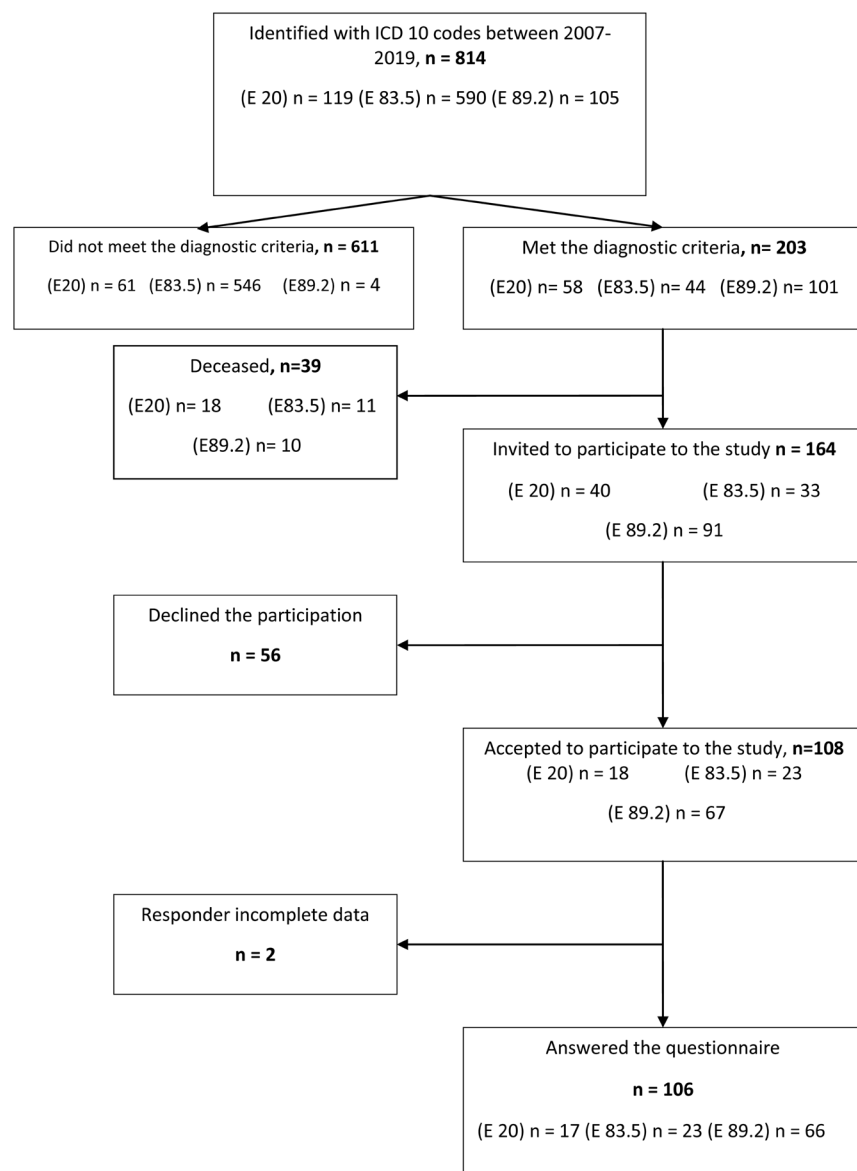


Figure 1 Flow chart depicting the search for the diagnoses of hypoparathyroidism and calcium aberrations according to the ICD 10.

of Endocrinology (15), were considered as candidates for treatment with PTH analogs.

Controls

A population sample of men and women ($n = 414$) of similar age from the World Health Organization’s (WHO) MONItoring of trends and determinants in CArdiovascular disease (MONICA) study, Gothenburg, Sweden, was used as controls (17). This was a part of the third WHO MONICA screening from 1995, in which 1616 men and women aged 25–64 years were randomly selected from the city census of Gothenburg (18). Hormone levels and bone data were studied in every fourth man and woman aged 25–44 and in all women aged 45–64, $n = 662$. Of the 608 subjects who

were alive in 2007–2008, $n = 414$ participated (68%) in a re-examination and answered the HRQoL questionnaires (77% women) (17). This population-based cohort was screened with the objective to serve as a control group for endocrine disease.

Anthropometry

Body weight was measured to the nearest 0.1 kg. Body height was measured to the nearest 1 cm. BMI was calculated as body weight in kilograms (kg) divided by height squared in meters (m) and presented as kg/m^2 . Blood pressure was reported as the mean of three consecutive measurements in the sitting position with a random zero sphygmomanometer (Hawksley & Sons) for the controls.

Medical records were used for information about body weight, body height, and blood pressure for the patients with HypoPT.

Biochemistry

The most recent laboratory findings were used to register patients' serum parathyroid hormone (S-PTH), serum calcium (S-Ca total), serum ionized calcium (S-Ca ion), 25-hydroxy vitamin D (S-25(OH)D), S-free T₄, and serum thyroid-stimulating hormone (S-TSH). S-Ca total was analyzed with photometry, S-Ca ion with ion-selective electrodes, S-PTH with IRMA (Roche Cobas, Rotkreutz, Switzerland), and S-25(OH)D with automated immunoassay (DiaSorin, Stillwater, MN, USA). Reference levels of S-Ca total, 2.15–2.50 mmol/L, S-Ca ion, 1.15–1.31 mmol/L, S-PTH, 1.6–6.9 pmol/L, and for S-25(OH)D ≥ 50 nmol/L was considered as sufficient level of vitamin D. Patients with HypoPT were divided according to their biochemical S-Ca, recommended/low, where low was considered as S-Ca total < 2.10 mmol/L or S-Ca ion < 1.10 mmol/L (16). Similar methods at the accredited laboratory for clinical chemistry were used for both patients and controls.

Medications and comorbidity

Medical records between 2007 and 2020 were reviewed for the patients, and medical history was inquired at the examination for the controls. Identical questionnaires regarding comorbidities, type and date of fracture were used for both patients and controls. The medications were listed according to the Anatomical Therapeutic Chemical classification system. Information about surgeries and x-rays was collected from the medical records regarding the patients. Comorbidities including kidney disease, depression and/or other neuropsychiatric diseases, musculoskeletal diseases (muscle aches and fractures), and cardiovascular disease were specifically searched for.

Questionnaires

Questionnaires were sent to the 164 patients with HypoPT during the spring of 2020. The questionnaires were put in similar order as for the controls. A reminder was sent if no answer was received after 4 weeks. HRQoL assessment was based on two validated questionnaires, Short Form-36 questionnaire (SF-36) and EuroQol-5 Dimensions Visual Analogue Scale (EQ5D-VAS) of the total health status, which yields a score range from 0 to 100 (low to high) (19, 20, 21). Patients were classified as high/low well-being,

depending on their score at the EQ5D-VAS (16). A low total well-being was defined as a score below 80 on the EQ5D-VAS (20).

The SF-36 consists of 36 questions covering 8 domains of physical and mental health: physical functioning (PF), role limitations by physical health problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health problems (RE), and mental health (MH). Scores on all subscales range from 0 to 100, with higher scores indicating better physical functioning and psychological well-being. The eight domains are grouped into two summary measures: the physical component summary (PCS) composed of the PF, RP, BP, and GH and the mental component summary (MCS) composed of the VT, SF, RE, and MH.

Statistical analyses

Means, medians, s.d., interquartile ranges (IQR), and ranges were calculated using IBM SPSS statistics version 26 (IBM) and R-statistics (22). For comparison between groups, two-tailed *t*-test was used, and Fisher's exact test was used for dichotomous variables. The Mann–Whitney test was used for non-parametric variables. A *P*-value < 0.05 was considered statistically significant.

Ethics

The study was approved by the National Ethics Committee (Dnr 2019-05852 date: February 18, 2020, Dnr 088-06 date: May 22, 2006, and Dnr T282-11 date: March 22, 2011). All participants gave their written informed consent. The Declaration of Helsinki was followed.

Results

The calculated prevalence of HypoPT (all-cause) in the studied population was 20.5/100,000 inhabitants. Most of the patients with HypoPT were women (80%) with a median age of 58 years. The main cause of HypoPT was neck surgery in 163 out of 203 (80%) and 77% of performed surgeries had a benign indication, such as Graves' disease or non-toxic goiter. Over 74% of the patients with HypoPT needed daily calcium and active vitamin D supplementation to maintain their calcium balance and avoid symptoms of hypocalcemia (Table 1).

The 163 patients with postoperative HypoPT were older, used higher doses of daily calcium supplementation, and

used levothyroxine more often than those with HypoPT of other causes, $n = 40$. No other significant differences were seen in biochemical analyses, BMI, morbidity, or mortality between postoperative HypoPT vs non-postoperative HypoPT (Table 2).

All patients with HypoPT ($n = 203$) were compared with the population sample ($n = 414$) from the WHO MONICA project. S-creatinine and S-free T4 were higher in HypoPT patients compared with the controls. 25(OH)D as well as anthropometric and demographic characteristics were similar in both groups. Blood pressure was lower in patients with HypoPT than in the population sample despite the similar use of antihypertensive medication in both groups. Total S-Ca, S-TSH, and S-PTH were lower in patients with HypoPT than in the control subjects (Table 3). The total number of medications used was higher in patients with HypoPT; six agents per patient vs two in the controls, including calcium and vitamin D ($P < 0.001$). The difference persisted when calcium and vitamin D supplements were both omitted from the medication list. The use of sedatives and antidepressant agents was 32% among patients and 27% in controls (not significant) and the use of bone-specific agents was rare; <5% in both patients and controls. There was no statistical difference in the use of psychopharmacological treatment between patients with postoperative HypoPT, 30%, or non-postoperative HypoPT, 43%.

Table 1 Descriptive data regarding the patients with hypoparathyroidism (HypoPT) at the Sahlgrenska University Hospital, Gothenburg, Sweden 2007–2020.

All with hypoparathyroidism, n	203
Female, n (%)	162 (80)
Age (median)	58
Postoperative HypoPT, n (%)	163 (80)
Graves' disease	50 (25)
Non-toxic goiter	36 (18)
Primary hyperparathyroidism	28 (14)
Thyroid cancer	35 (17)
Other cancer in neck/head	3 (1)
Other causes	9 (4)
Unknown cause of surgery	2 (1)
Non-postoperative HypoPT, n (%)	40 (20)
Idiopathic	23 (11)
Genetic	16 (8)
Pseudohypoparathyroidism	1 (1)
Medication	
Calcium supplements, n (%)	150 (74)
Average dose calcium/day (mg)	1220
Active vitamin D, n (%)	167 (82)
Alfacalcidol, n (%)	123 (74)
Dihydroxycholesterol, n (%)	40 (24)
Calcitriol, n (%)	4 (2)

There were fewer fractures and no increase in mortality during 2007–2020 in patients with HypoPT compared with the population sample. There were 4 (2%) patients with HypoPT who had renal insufficiency and one with nephrocalcinosis. Five patients (2%) had undergone gastric bypass surgery.

HRQoL was lower in patients with HypoPT vs controls regarding physical (40.0 (IQR: 21) vs 51.2 (IQR: 14.6); $P < 0.001$) and mental (43.1 (IQR: 17.4) vs 56.1 (IQR: 13.3); $P < 0.001$) component scores of the SF-36 as well as the EQ5D-VAS (Fig. 2). There was no difference between patients with postoperative or non-postoperative HypoPT regarding their SF-36 summary component scores for physical (39.0 (IQR: 21) vs 47.8 (IQR: 21.5); $P = 0.332$) and mental (43.1 (IQR: 19.4) vs 43.0 (IQR: 16.2); $P = 0.571$) well-being nor regarding the EQ5D-VAS (68.55 (IQR: 35) vs 70 (IQR: 32); $P = 0.308$).

The division of patients with HypoPT with recommended or low calcium levels in relation to HRQoL is shown in Fig. 3. Among all patients with HypoPT, 70% had an S-Ca within the recommended range (Fig. 3, both left rectangles), but only 22% of these patients scored above the threshold for high well-being using the EQ5D-VAS >80 (Fig. 3, lower left rectangle, recommended S-Ca/high well-being). Low calcium and high well-being were present in 7% (Fig. 3, lower right rectangle). Low calcium together with low well-being was most present in 23% (Fig. 3, upper right rectangle). This final group, approximately 1/5 of all patients included in the study, represents the patients who would probably benefit most from treatment with PTH analog.

Discussion

In this study, HRQoL was lower in patients with HypoPT than in the general population independent of S-Ca levels and cause of the disease. HypoPT is a non-physiological state which results both in acute and chronic manifestations which negatively affect the patients' HRQoL (1, 4, 6, 11, 23, 24). When the patients with HypoPT were categorized on basis of their laboratory findings and their self-estimated HRQoL, 71% had an impaired HRQoL independent of their calcium level and 48% had an impaired HRQoL despite the recommended S-Ca levels. Only 22% of the patients with recommended S-Ca levels reported an unaffected well-being. The combination of biochemical calcium levels and self-related health status was used by the Delphi panel in order to estimate the need for treatment with PTH analog in an earlier study (16). Hence, an estimate in the present study is that one in five patients, that is those with both

Table 2 Comparison between anthropometric data, biochemistry, and medications in patients with and without postoperative hypoparathyroidism (HypoPT).

	Postoperative HypoPT (N = 163)	Non-postoperative HypoPT (N = 40)	P-value
Age (years)			
Mean (s.d.)	61.9 (20.1)	51.8 (18.9)	0.004
Height (m)			
Mean (s.d.)	1.67 (0.09)	1.67 (0.1)	0.913
Body weight (kg)			
Mean (s.d.)	73.5 (17.4)	71.7 (18.3)	0.585
BMI (kg/m ²)			
Mean (s.d.)	26.4 (5.57)	24.6 (4.63)	0.143
Systolic blood pressure (mmHg)			
Mean (s.d.)	128 (18.3)	126 (18.7)	0.402
Diastolic blood pressure (mmHg)			
Mean (s.d.)	75.1 (12.0)	74.1 (11.3)	0.556
S-PTH (pmol/L)			
Median (min, max)	1.66 (0.11, 6.20)	1.60 (0.50, 7.10)	0.556
S-Ca total (mmol/L)			
Median (min, max)	2.21 (0.98, 2.96)	2.19 (1.85, 2.68)	0.664
S-Ca ion (mmol/L)			
Median (min, max)	1.15 (0.81, 1.72)	1.12 (0.95, 1.37)	0.088
S-25(OH)D (nmol/L)			
Median (min, max)	62.0 (32.0, 166)	68.5 (23.4, 98.3)	0.917
S-Creatinine (μmol/L)			
Median (min, max)	82.0 (40.0, 215)	94.0 (55.0, 732)	0.495
S-Free T4 (pmol/L)			
Median min, max)	19.0 (1.50, 30.0)	18.0 (10.0, 27.0)	0.264
S-TSH (mIU/L)			
Median (min, max)	1.30 (0.02, 100)	1.10 (0.73, 2.80)	0.930
Active vitamin D (μg/day)			
Median (min, max)	0.60 (0, 12.75)	0.75 (0, 3)	0.558
Calcium supplements (mg/day)			
Median (min, max)	1000 (0, 12000)	500 (0, 4000)	0.01
Magnesium use, subjects, n (%)	27 (16.6)	9 (22.5)	0.355
Thiazides, subjects, n (%)	14 (8.6)	0 (0)	0.076
Levothyroxine, subjects, n (%)	144 (88.3)	7 (17.5)	<0.001
Deceased, n (%)	32 (19.6)	7 (17.5)	0.759

BMI, body mass index; S-Ca ion, serum ionized calcium; S-Ca total, serum calcium; S-PTH, serum parathyroid hormone; S-TSH, serum thyroid-stimulating hormone; S-25(OH)D, serum 25-hydroxy vitamin D.

low calcium levels and feeling unwell would be candidates for lifelong substitution with PTH analog. No difference in HRQoL could be seen between patients with postoperative or non-postoperative HypoPT which may seem unexpected as individuals who have undergone surgery know the experience of presurgical health with normal calcium levels. The effect of treatment with PTH analog in HRQoL is a controversial issue. One randomized controlled study did not report any improvement in HRQoL after 6 months of treatment (3), while other studies have shown improvement in well-being compared with baseline after up to 8 years of follow-up (2, 12, 13).

Smaller studies in the selected groups have indicated that patients with HypoPT experience impaired HRQoL. In a German study, 25 women with postsurgical HypoPT after thyroidectomy experienced inferior well-being compared

to 25 women after thyroidectomy, but without HypoPT (1). In a study including 54 men and women with both postoperative and autoimmune HypoPT, Cusano *et al.* showed that the patients had lower HRQoL in comparison to the background population (2). The patients in this study were, however, selected to match the criteria for receiving recombinant PTH analog (1–84). In a Danish study, 62 patients, 85% female, were randomized to receive a recombinant PTH analog (1–84) or placebo for 6 months. At baseline, HRQoL was evaluated with SF-36 and the WHO-5 Well-Being Index. This study, also based on selected patients, showed that patients with HypoPT had impaired HRQoL (3). The results on HRQoL from the present study corroborate with the results in HRQoL from a study in Norway which reported SF-36 scores in a group with fewer postsurgical HypoPT and a higher frequency of

Table 3 Comparison between anthropometric data, blood pressure, biochemistry, and medications in patients with hypoparathyroidism (HypoPT) and the WHO MONICA study.

	Hypoparathyroidism (N = 203)	WHO MONICA (N = 414)	P-value
Age (years)			
Mean (s.d.)	59.8 (20.4)	62.8 (9.37)	0.530
Sex			
Women, n (%), Men, n (%)	162 (79.8), 41 (20.2)	318 (76.8), 96 (23.2)	0.402
Height (m)			
Mean (s.d.)	1.67 (0.098)	1.67 (0.087)	0.734
Body weight (kg)			
Mean (s.d.)	73.2 (17.5)	74.5 (14.9)	0.178
BMI (kg/m ²)			
Mean (s.d.)	26.1 (5.44)	26.8 (4.71)	0.071
Systolic blood pressure (mmHg)			
Mean (s.d.)	128 (18.3)	134 (21.0)	<0.001
Diastolic blood pressure (mmHg)			
Mean (s.d.)	75.0 (11.9)	79.6 (10.4)	<0.001
S-Ca total (mmol/L)			
Median (min, max)	2.20 (0.98, 2.96)	2.35 (2.13, 2.66)	<0.001
S-Creatinine (μmol/L)			
Median (min, max)	83.0 (40.0, 732)	69.5 (43.0, 193)	<0.001
S-PTH (pmol/L)			
Median (min, max)	1.63 (0.110, 7.10)	4.77 (0, 22.2)	<0.001
S-25(OH)D (nmol/L)			
Median (min, max)	62.0 (23.4, 166)	58.8 (14.2, 163.0)	0.153
S-Free T4 (pmol/L)			
Median (min, max)	18.0 (1.50, 30.0)	16.0 (10.0, 45.0)	<0.001
S-TSH (mIU/L)			
Median (min, max)	1.30 (0.02, 100)	2.10 (0.005, 16.0)	<0.001
Number of medications per subject, n (%)			
Median (min, max)	6.0 (0, 22.0)	1.0 (0, 10.0)	<0.001
Calcium supplements, subjects, n (%)	150 (73.9)	36 (8.7)	<0.001
Antihypertensive medicine, subjects, n (%)	54 (26.6)	118 (28.5)	0.585
Psychopharmacological agents, subjects, n (%)	66 (32.5)	112 (27.1)	Ns
Fractures, subjects, n (%)	38 (18.7)	191 (46.1)	< 0.001
Deceased, n (%)	39 (19.2)	55 (13.3)	0.057

BMI, body mass index; S-Ca total, serum calcium; S-PTH, serum parathyroid hormone; S-TSH, serum thyroid-stimulating hormone; S-25(OH)D, serum 25-hydroxy vitamin D.

Short Form-36 in subjects with Hypoparathyroidism and Controls, the WHO MONICA Study

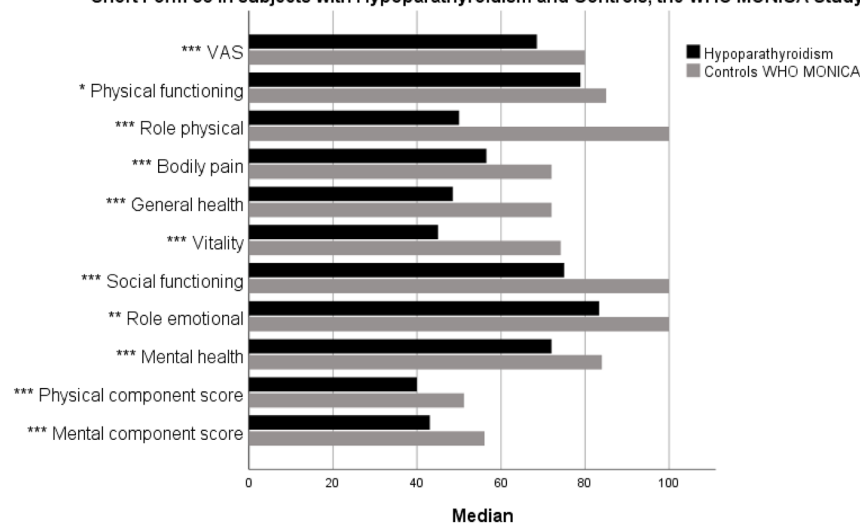
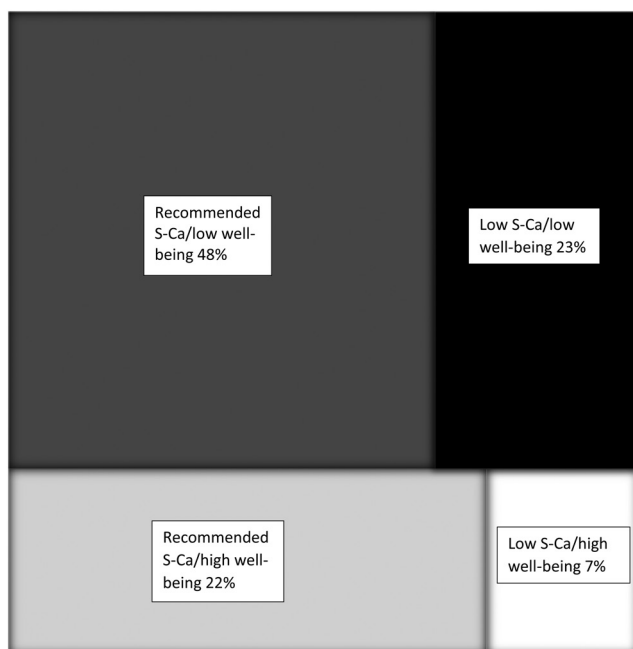


Figure 2

Health-related quality of life according to the Short Form 36 (SF-36) and EuroQol-5 Dimensions Visual Analogue Scale (EQ5D-VAS) 0–100 in 106 patients with hypoparathyroidism and 414 controls from the population, the WHO MONICA study, Gothenburg, Sweden. *P = 0.009, **P = 0.001, and ***P < 0.001.

**Figure 3**

Patients with hypoparathyroidism were categorized according to their biochemical serum calcium levels (S-Ca), recommended/low, where low was considered S-Ca total <2.10 mmol/L, or S-Ca ion <1.10 mmol/L and high/low well-being was defined as <80 using EuroQoL-5 Dimensions Visual Analogue Scale 0–100.

idiopathic, genetic, and autoimmune HypoPT, as well as pseudohypoparathyroidism (9). According to this study, patients with HypoPT had a lower mental and physical score than the general population in Norway.

Of particular interest in our study was that the five patients who had undergone gastric bypass surgery reported the lowest HRQoL scores and that it was difficult for them to sustain stability in their S-Ca levels, possibly because of the malabsorptive effects of the gastric surgery. Other signs of malabsorption were treated with, for example, parental injections of vitamin B12 and despite very high doses per oral of calcium (up to 10 g daily) the patients remained symptomatic. Gastroscopy in those patients did not reveal any signs of celiac disease or malignancy. A recent literature survey highlights the risks of bariatric surgery, which can complicate the treatment of hypocalcemia in postoperative HypoPT (25). The risk for postthyroidectomy hypocalcemia was more pronounced after procedures with the malabsorptive effects than after procedures with only restrictive effects (25).

Comorbidities were similar in patients with HypoPT and the general population with the exception of kidney function. However, nephrolithiasis was rare in the examined patients, 0.5%, as compared with 2% in a Danish

register study with HypoPT (4), and a prevalence as high as 40% has been seen in strongly selected small groups of patients who underwent renal CT scans or ultrasound screening (26, 27).

Of special interest was also the lower fracture prevalence in patients with HypoPT than in the general population. This might be explained by the low prescription of bone-specific agents in the population. However, the treatment frequency was similar in the patient group which was more exposed to fall prevention advice and bone densitometry measurements.

The strength of this study is that we investigated an unselected and fairly large group, which included all patients diagnosed with HypoPT in the region. The sample is therefore representative for all-cause HypoPT, and we report a similar prevalence as previously estimated in Denmark (4, 10). The patients with HypoPT were compared with a population sample, the WHO MONICA study, from the same geographic region, and the same accredited laboratory was used for both patients and controls. Anthropometric variables, age, and sex were nearly identical in patients and controls. All medical and surgical records were available for the present research.

As for the limitations of our study, the laboratory findings in the patients with HypoPT were gathered from the patients' medical records and were not concurrent with when the HRQoL questionnaires were completed. The estimation of renal function was performed with the use of serum creatinine which may be influenced by muscle volume, dehydration, and physical exercise. Only few analyses of 24-h urine calcium excretion had been performed in the patients, and S-Ca ion analyses were not available for the control group. The occurrence of calcifications in the kidneys or other target organs had not been actively screened for.

HypoPT is most often an iatrogenic disease, mainly caused by neck surgery. According to our material, most of the patients who developed a permanent HypoPT underwent surgery for non-cancerous diseases such as Graves' disease, non-toxic goiter, and primary hyperparathyroidism. The high risk of developing postoperative HypoPT was recently confirmed by a national register study in Sweden (28). According to this study, high-volume clinics and high-volume surgeons limit the risk for postsurgical complications, especially HypoPT which developed in 12% after total thyroidectomy (28). In a recent Canadian study, neck surgery was the cause of HypoPT in 75% of the cases (29). Surgeons should be well aware of the potential complication of HypoPT and try to avoid it. A Spanish survey showed that 5% of patients

who underwent thyroidectomy became permanent HypoPT (7). *In situ* preservation of parathyroid glands was critical in the prevention of postoperative HypoPT. Also in patients with the lowest risk with only one parathyroid gland autotransplanted the risk was as high as 3% for HypoPT. Hence, the authors concluded that more glands left *in situ* was the key variable over the predictors for avoiding HypoPT after total thyroidectomy (7). When surgery is indicated, experienced surgeons at high-volume centers should perform the procedure to lower the risk of postoperative HypoPT.

HypoPT is a rare disease where the hormone substitution has been lacking until recently. Standard treatment of calcium and active vitamin D often leads to high calcium concentrations in urine, low calcium concentrations, and high phosphate concentrations in the circulation affecting the calcium-phosphate product. Recombinant PTH analog is a more physiological treatment for these patients but at the moment not yet accessible to everyone. As of date, only PTH (1–84) is approved for treatment of HypoPT but recently published phase 2 trial data reported promising results in treating patients with HypoPT with long-acting prodrug of PTH (1–34) (14).

In conclusion, the present study showed that HRQoL was markedly impaired in HypoPT with a moderate risk for other comorbidities, but no increase in mortality. Algorithms to identify patients who gain the most benefit of treatment with a recombinant PTH analog would be helpful to ensure a cost-effective use of treatment with PTH analog, which today is costly. HRQoL, together with laboratory findings, seems to be an important variable to take into consideration when the treatment approach is to be decided. Based on our data and the findings of low calcium and low HRQoL in approximately 23% of patients, at least every fifth patient with HypoPT may benefit from the treatment with PTH analog in clinical practice.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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