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Epidemiology and Financial Burden of Adult Chronic Hypoparathyroidism

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ABSTRACT

Chronic hypoparathyroidism is characterized by low serum calcium, increased serum phosphorus, and inappropriately low or decreased serum parathyroid hormone. This rare disorder is associated with a variety of complications. The prevalence, incidence, mortality, financial burden, and epidemiology of complications of this disorder are not well understood. This narrative review summarizes current information on the epidemiology and complications of chronic hypoparathyroidism. The reported prevalence of chronic hypoparathyroidism ranges from 6.4–37/100,000, and the incidence is reported to be 0.8–2.3/100,000/year. Mortality is not increased in studies from Denmark or South Korea but was increased in studies from Scotland and Sweden. The financial burden of this disorder is substantial because of increased health care resource utilization in two studies but not well quantitated. Recognized complications include hypercalciuria, nephrocalcinosis, kidney stones, and chronic kidney disease; low bone turnover and possibly upper extremity fractures; cardiac and vascular calcifications; basal ganglia calcifications, cataracts, infections, neuropsychiatric complications, and difficulties with pregnancy. This review concludes that chronic hypoparathyroidism is a rare disorder associated with significant morbidity that may not increase overall mortality but is associated with a substantial financial burden. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: COMPLICATIONS; EPIDEMIOLOGY; FINANCIAL BURDEN; HYPOPARATHYROIDISM; PREVALENCE

Introduction

Chronic hypoparathyroidism (hypoPT) is a rare disorder characterized by decreased serum calcium, increased serum phosphate, and absent or deficient production of parathyroid hormone (PTH).[1-4] The epidemiology and health care burden of this disorder are not well described but are gradually being elucidated in various countries. Many patients develop transient hypoPT after anterior neck surgery, but most of these cases resolve within 6 months to 1 year of surgery.[5-15] This narrative review will focus exclusively on the epidemiology and health care burden of chronic hypoPT (present for more than 6 months after surgery or from birth) and its complications.

Published studies have reported the prevalence of chronic hypoPT to range from 6.4–37/100,000 population in different countries.[16-26] Incidence has been more difficult to estimate, with only two studies reporting this to be between 0.8/100,000/year in hospitalized patients in Denmark and 2.6/100,000/year in India in patients with idiopathic hypoPT.[17,27] Mortality was not reported to be increased in Denmark or South Korea, despite the increased morbidity these patients experience from recognized complications, but was increased in Scotland and Sweden.[18,28]

Patients with chronic hypoPT are at increased risk of complications related to decreased serum calcium, increased phosphorus, and absent or deficient PTH. Lack of circulating PTH leads to increased urinary calcium loss, which may lead to hypercalciuria,

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nephrocalcinosis, kidney stones, or renal insufficiency, as well as decreased skeletal turnover and possibly decreased risk of upper extremity fractures in postsurgical hypoparathyroidism, but increased risk of upper extremity fractures in nonsurgical hypoparathyroidism. Cardiac rhythm, major vessel disease, and cardiac valvular complications, as well as peripheral vascular complications, may be increased. Treatment of this condition with pharmacological doses of calcium and vitamin D may lead to increased serum and urine calcium levels, complicating the renal complications mentioned, as well as increasing the risk of soft tissue calcifications,[4,29] including the calcification of basal ganglia in the brain and the lens of the eye. Chronic hypoPT is associated with immune system dysfunction, not just due to genetic disorders associated with this condition, such as DiGeorge syndrome or autoimmune polyglandular syndrome type 1, but nongenetic forms as well. Immune system dysfunction leads to increased risk of infections and may lead to various benign or malignant tumors. Patients with chronic hypoPT have multiple symptoms related to their mineral abnormalities but frequently have neuropsychiatric manifestations, especially anxiety, depression, or bipolar disorder, as well as a marked decline in their quality of life.

This narrative review will summarize what is currently known about the prevalence, incidence, mortality, health care burden, and complications of chronic hypoPT, and describe a research agenda to guide future research in this area.

Materials and Methods

A literature search was performed of all articles published in the English language on chronic hypoPT from January 1, 1980 to June 30, 2022. The search was performed using the PubMed, MEDLINE, EMBASE, and COCHRANE databases. Articles included original investigations, perspectives, and reviews, but excluded letters, editorials, and abstracts. Search terms used included hypoparathyroidism, parathyroid disorder, epidemiology, financial burden, health care resource utilization, prevalence, incidence, mortality, kidney disease, kidney stones, nephrocalcinosis, hypercalciuria, fractures, bone mineral density, bone turnover markers, cardiac complications, vascular complications, cataract, basal ganglia calcification, infections, depression, anxiety, bipolar disorder, psychiatric disorder, and pregnancy. A total of 861 relevant articles were identified and evaluated for inclusion in this article. Statistical analysis was descriptive when applied.

Results

Prevalence and incidence

Permanent hypoPT is defined in both American[29] and European guidelines[2] as a disease in which the production of PTH is inadequate to maintain normal serum calcium. In patients with postsurgical hypoPT, this needs to persist for more than 6 months to 1 year after surgery, and in those with nonsurgical causes, usually for at least 6 months after birth. The incidence of postsurgical hypoPT varies widely due to variation in the definition of permanent hypoPT used. In the systematic review by Harslof and colleagues,[30] the definition of permanent hypoPT was investigated in 89 articles from January 1, 2010 to January 1, 2017. No less than 20 different definitions were found, and none of them complied with accepted definitions stated in the guidelines above. Mehanna and colleagues[31] also found 10 different definitions of hypocalcemia and permanent hypoPT. They applied all 10 definitions to their cohort of 202 patients and found variation in the incidence of permanent hypoPT ranging from 0.9% to 4.4%, depending on the definition used.

Postsurgical HypoPT

Population-based studies of postsurgical hypoPT have emerged over the last decade (Table 1). The definitions used for permanent hypoPT in these studies are predominantly in alignment with published guidelines. Methods of data collection varied tremendously between studies. Most of the studies used ICD codes to identify patients, but others used national health and prescription registries, insurance databases, or questionnaires. In some cases, diagnosis of chronic hypoPT was confirmed by chart review.

Powers and colleagues[16] identified patients using a large proprietary US health plan claims database and projected estimates of prevalence to the US insured population. The study used data from approximately 7.8 million patients and found 39,008 patients with postsurgical hypoPT, with 38% of those due to total thyroidectomy, 21% to parathyroidectomy, 9% to partial thyroidectomy, and 5% to other types of neck surgery. Projecting to insured patients, they estimated that 77,000 patients had hypoPT in the US in 2007–2008, with the prevalence estimated to be 25/100,000.

A population-based study by Underbjerg and colleagues[17] used ICD-8 and -10 codes covering 100% of the Danish population, and combined results with prescription registries covering 80% of the population. They found 688 hospitalized patients with postsurgical hypoPT due to nonmalignant causes, giving a prevalence estimate of 22/100,000 population. In Tayside, Scotland, Vadiveloo and colleagues[18] found 116 patients with hypoPT, resulting in a prevalence estimate of 23/100,000 population. They used a combination of registries, biochemistries, medications, and hospital admissions. These estimates were higher than the estimate by Astor and colleagues[19] in a Norwegian national database that identified 321 patients, for a prevalence estimate of chronic postsurgical hypoPT of 6.4/100,000 population. This estimate used electronic patient registries covering 80% of the Norwegian population.

Several studies have been conducted in Italy.[20-22] Cianferotti and colleagues[20] and Cipriani and colleagues[21] found the prevalence of all types of chronic hypoPT to be 27/100,000 population, very similar to the Danish and Scottish studies. The hospitalization rate for postsurgical hypoPT was 1.4/100,000 inhabitants per year.[21] Marcucci and colleagues[22] used data from 20 centers homogeneously distributed across Italy, including 363 postsurgical patients, equal to 67.6% of all identified hypoPT patients. Unfortunately, no data are available on the percentage of the Italian population included in this study. The same methods used by Marcucci and colleagues[22] were used in a study in Russia,[23] which identified 165 (82.5%) patients with postsurgical hypoPT. Unfortunately, the overall prevalence was not presented.

Chen and colleagues[24] performed a study of 9316 thyroid surgeries in Taiwan from 1998–2011 and found 234 patients with post-thyroidectomy hypoPT 6 months (2.5%) and 260 patients 12 months (2.8%) after surgery. Ahn and colleagues[25] investigated the changes in incidence rates for postsurgical hypoPT from 2007–2016 in South Korean registries after initiation of a national screening program for thyroid cancer. The incidence increased by 177% from 2.6/100,000 population (95% confidence interval [CI] 2.5–2.8) in 2007 to 7.3/100,000 (95% CI 7.1–7.5) in 2012. The program was later suspended, leading to a decrease in postsurgical hypoPT.

Table 1. Incidence of Transient and Permanent Hypoparathyroidism in Surgical Cohorts With More Than 500 Participants, and Predictors for the Development of Permanent Hypoparathyroidism

Reference no.	*N*	Type of operation	Benign/ malignant	Lymph node resection	Autotrans-plantation	Re-operation	Definition of permanent hypoPT	Time of follow-up	Transient	Chronic	Predictors of permanent hypoPT
[5]	519	TT: 100%	B: 80.7% M: 19.3%	UK	17.3%	UK	Continuing need for vitamin D at 1 year after surgery, regardless of serum PTH value	Up to 10.3 years	At 4 weeks, 8.1%	At 5 mo: 1.5% At 1 year, 1.9%	Very low PTH the 1st day after TT is associated with high risk of hypoPT; autotransplantation protects against hypoPT (OR = 0.95; 95% CI 0.90–0.99)
[6]	7852	TT: 100%	B: 100%	No	21.3%	No	Treatment with calcium and/or activated vitamin D more than 1 year after surgery	Up to 5 years	UK	Activated vitamin D: 5.6%	Autotransplantation (OR = 1.72; 95% CI 1.47–2.01); Center volume <100 thyroidectomies/ yr (OR = 1.22; 95% CI 1.03–1.44); Age >60 years (OR = 1.64; 95% CI 1.36–1.98); Female sex (OR = 1.27; 95% CI 1.05–1.54)
[7]	995	TT: 100%	B: 76.8% M: 23.2%	No	Yes	No	Subnormal (<10 pg/mL serum PTH and requirement for treatment for >1 year	1 year	14.3%	2.7%	Presence of symptoms (OR = 3.08; 95% CI 1.13–8.39); PTH decay 24 hours post-surgery (OR = 1.13; 95% CI 1.09–1.17); Calcium decay 24 hours post-surgical (OR = 1.26;95% CI 1.14–1.39); Parathyroid reimplantation (OR = 22.01; 95% CI 1.58–306.81)
[8]	1792	TT: 86.5% ComT: 13.5%	B: 18.9% M: 81.1%	41.2%	8.1%	13.6%	Treatment with calcium or calcitriol at the last follow-up visit	1 year	22.9%	1 year: 16.7%	Presence of parathyroid at histology (OR = 1.84; 95% CI 1.24–2.74); Lymph node dissection (OR = 2.07; 95% CI 1.29–3.32); 2-stage thyroidectomy (OR = 2.16; 95% CI 1.20–3.88); Specialized surgical team (OR = 0.53; 95% CI 0.30–0.94); Thyroid cancer (OR = 0.42; 95% CI 0.25–0.71); Postoperative corrected Ca mg/dL (OR = 0.22; 95% CI 0.17–0.28)
[9]	3250	TT: 36.7% Near TT: 51.1% SubTT: 9.7% ComT: 2.5%	B: 84% M: 16%	9.2%	No	6.3%	Serum PTH level <10 pg/mL	UK	6.3%	0.3%	Extended thyroidectomy (OR = 12.6; 95% CI 1.7–92); Repeated surgery (OR = 3.1; 95% CI 2.1–4.7)

(Continues)

Table 1. Continued

Reference no.	*N*	Type of operation	Benign/ malignant	Lymph node resection	Autotrans-plantation	Re-operation	Definition of permanent hypoPT	Time of follow-up	Transient	Chronic	Predictors of permanent hypoPT
[10]	933	TT: 100%	B: 90% M: 10%	TT: 12.0% LLND: 2.9% BLND: 5.5%	No	No	Low serum PTH <13 pg/mL requiring therapy with calcium and/or vitamin D replacement 1 year after TT requiring treatment for >3 months to maintain	1 year	20.6%	2.1%	Surgery due to malignancy (OR = 10.57; 95% CI 2.90–38.58); Tumor multifocality (OR = 3.84; 95% CI 1.02–14.44); Preoperative 25(OH)D level (OR = 0.77; 95% CI 0.65–0.91)
[11]	531	TT: 100%	M: 100%	86.2%	45%	No	Requiring medication >12 months after surgery	>1 year	21.8%	3.6%	Presence of parathyroids at histology (OR = 3.06; 95% CI 1.16–8.03)
[12]	1071	TT: UK SubTT: UK	B: UK% M: UK%	UK	Yes: UK%	UK	Requirement for vitamin D or calcium (or both) to maintain	≥1 year	5.4%	0.5%	Fewer than 3 parathyroid glands preserved in situ (OR UK); Early serum PTH <12 pg/mL, delayed serum calcium <8 mg/dL, or delayed serum phosphorus >4 mg/dL under calcium therapy (OR UK)
[13]	2631	TT: 96.1% NearTT: 0.7% ComT: 3.2%	B: 84.9% M: 15.1%	CND: 9.0% LLND: 3.6%	No	3.2%	Ionized calcium <1.12 mmol/L 6 months after surgery	≥6 months	27.9%	0.9%	Identified parathyroid glands intraoperatively (OR/RR UK, $p < 0.0003$); Thyroid cancer (OR/RR UK, $p < 0.004$); Symptomatic hypocalcemia (RR = 4.97; 95% CI 2.20–10.56)
[14]	1054	TT: 95.7% ComT: 4.3%	B: 67.2% M: 32.8%	CND: 9.1% MRND: 6.6%	17%	4.3%	No recovery of parathyroid gland function: PTH ≥10 pg/mL and need for therapeutic calcium (>2000 mg/d) or activated vitamin D	1 year	18%	1.9%	Parathyroid tissue on pathology report (OR = 3.6; 95% CI 1.1–11.5)
[15]	546	TT: 42% TT+ CND: 58%	B: 38% M: 62%	58%	Yes: UK%	No	Need for calcium and/or vitamin D supplementation at 6 months postop to maintain normal blood calcium	1 year	UK	4.03%	PTH concentration 1st day after surgery (OR = 2.93; 95% CI 1.13–7.62); Calcium concentration 1st day after surgery (OR = 2.58; 95% CI 1.02–6.57); PTH ≤5.51 pg/mL 1st day after surgery

B = benign; BLND = bilateral lymph node dissection; CI = confidence interval; CND = central lymph node dissection; ComT = complementary thyroidectomy; hypoPT = hypoparathyroidism; LIT = lobectomy with isthmectomy; LND = lateral lymph node dissection; M = malignant; MRND = modified radical neck dissection; *N* = number of included patients; NearT = near-total thyroidectomy; OR = odds ratio; SubTT = subtotal thyroidectomy; TT = total thyroidectomy; UK = unknown.

Vadiveloo and colleagues[18] reported an incidence of 1–4/100,000/year in the general population, with significant yearly variation. This incidence was higher than reported in the Underbjerg Danish study[17] with an incidence of 0.8/100,000/year.

Villaroya-Marquina and colleagues[26] evaluated 811 patients undergoing total thyroidectomy for benign goiter and reported that premenopausal women developed a higher prevalence of chronic hypoparathyroidism than men despite similar number of parathyroid glands remaining in situ at the end of surgery.

Most studies of the incidence of transient and chronic hypoPT following neck surgery were single or small center studies (Table 1). The definitions of postsurgical hypoPT, the applied methods, and selection of patients varied tremendously.

Transient hypoPT is common, and the accepted definition requires recovery within 6 months. However, many studies used a definition of transient hypoPT that included patients up to 1 year postoperatively. In this review, analysis was limited to studies with more than 500 participants.[5-15] These studies are shown in detail in Table 1. Transient hypoPT varied in definition regarding length, presence or absence of symptoms, and/or availability of PTH measurements. Some studies may have underestimated mild, transient hypoPT by treating prophylactically with calcium supplements before or after surgery. In the included studies, incidence of transient hypoPT varied from 5.4% to 27.9%. The incidence of permanent hypoPT was difficult to establish even when only including studies with large numbers of patients. As shown in Table 1, none of the studies are directly comparable. There is great variation in the types of surgeries performed, reasons for surgery, and extent of surgery. Moreover, as listed in Table 1, only a few of the definitions of permanent hypoPT are similar. The incidence of permanent hypoPT varied from 0.3% to 16.7%. Most of the studies found an increased risk of permanent hypoPT when PTH levels were low on the first postsurgical day,[32] or with malignancy, inexperienced surgeons, extensive surgery, or parathyroid glands identified in the histological specimen. There were diverging results concerning the risk or benefit of identifying all parathyroid glands during surgery, autotransplantation, and lymph node dissection.

Nonsurgical hypoPT

Population-based studies of nonsurgical hypoPT (NS-hypoPT) cover many different etiologies, including genetic disorders with known etiology, autoimmune diseases, and idiopathic hypoPT.

The prevalence in the Danish[33] and Norwegian[19] studies is quite similar at 2.3/100,000 population and 3.0/100,000 population, respectively. The South Korean study by Kim and colleagues[34] found, using a claims database covering the entire South Korean population, a slightly lower prevalence of NS-hypoPT. In 2005, the prevalence was estimated at 0.2/100,000 population, with an increase to 1.1/100,000 by 2015.

Nakamura and colleagues[35] used a questionnaire distributed to different medical departments across Japan to investigate NS-hypoPT. In total, 900 patients were identified, with a prevalence of 0.72/100,000 population. In 1981, Zlotgora and Cohen[36] studied idiopathic hypoPT in Israel and found a prevalence of 0.9/100,000 population. A higher prevalence was reported by Vadiveloo and colleagues[18] using the registry described previously, with 106 patients identified with NS-hypoPT in Tayside, Scotland, giving a prevalence of 17/100,000 population. The study by Gronskaia and colleagues[23] in Russia found 20 (10%) patients with NS-hypoPT and 4.5% with hypoPT due to genetic syndromes.

Infiltrative deposition diseases such as thalassemia major (iron) and Wilson's disease (copper), which deposit these elements within the parathyroid glands, or hypoPT due to radiation therapy have been described. The literature covering these rare conditions is sparse.

Mortality

Data regarding mortality due to hypoPT are sparse and inconsistent. Five registry studies have investigated mortality among patients with hypoPT.[17,18,28,33,34] A Swedish study by Almquist and colleagues[28] investigated 246 patients with postsurgical hypoPT and matched them with 4653 controls who had undergone surgery without resultant hypoPT. Vadiveloo and colleagues[18] investigated 116 patients with postsurgical hypoPT and 106 patients with NS-hypoPT and matched them with 5 controls per case from the background population. Kim and colleagues[34] found 210 patients with NS-hypoPT and matched them with 2075 controls. Finally, two Danish studies[17,33] investigated mortality among 688 patients with postsurgical hypoPT from nonmalignant causes and 180 patients with NS-hypoPT. Both groups where matched with three randomly selected patients from the background population.

No differences were found in mortality when comparing NS-hypoPT with controls in the studies by Underbjerg and colleagues[33] (hazard ratio [HR] $= 1.25$, 95% CI 0.90–1.73, $p = 0.06$) and Kim and colleagues[34] (HR $= 1.56$, 95% CI 0.86–2.84, $p = 0.15$]. These findings contrast with those in Vadiveloo and colleagues,[18] who reported a 2.18-fold (HR $= 2.18$, 95% CI 1.55–3.05) increased risk of mortality.

Only the study by Almquist and colleagues[28] reported increased mortality among patients with postsurgical hypoPT. Risk of mortality was increased by 2.1-fold (HR $= 2.1$, 95% CI 1.4–4.2). The Danish and Scottish studies found a comparable mortality risk among patients compared with matched controls.

Health care burden

Only two studies have addressed the financial burden and health care resource utilization of patients with chronic hypoPT. Chen and colleagues[37] evaluated the clinical burden and health care resource utilization of this disorder in a retrospective review of patients in the US, Canada, and five countries in Europe during a 1-year observation period. A total of 614 patients were included, with 442 felt to be adequately controlled, defined as meeting clinical management targets recommended by clinical guidelines, and 172 not adequately controlled. Mean age of the entire cohort was 43.6 years, with 61.6% female, 78.8% White, and 74.4% with postsurgical hypoPT. Patients had hypoPT for a mean duration of 46.0 months. HypoPT-related symptoms and comorbidities were reported by 59.4% of adequately controlled patients, and by 46.7% of not adequately controlled patients, with 90.7% reporting at least one hypoPT-related health resource utilization event. Among not adequately controlled patients, 57.6% experienced at least one comorbidity, including calcium or phosphate abnormalities, or brain, cardiovascular and metabolic, or renal disorders (all $p < 0.01$) compared with 42.5% of adequately controlled patients. Among not adequately controlled patients, 27.9% had at least one hypoPT-related hospitalization compared with 16.3% of adequately controlled patients, and 47.7% of not adequately controlled patients had emergency room visits compared with 38.5% of adequately controlled patients. Patients not adequately controlled had 3.6 outpatient visits compared with 2.6 outpatient visits for adequately controlled patients (all $p < 0.05$). Limitations of the

Table 2. Renal Complications

			Proportion with renal complication			
	Location	*N*	CKD	Nephrolithiasis	Nephrocalcinosis	Hypercalciuria
Single-center studies	Boston, USA[39]	120	41% (44/107)[a]	31% (17/54) by imaging		26% (14/53)
	Leuven, Belgium[40]	170	NA	21.8% (19/87) by imaging 14.7% (25/170) clinical kidney stones		38% (49/129)[b]
	Delhi, India[41]	165	14.4% (23/160)[c]	4.8% (8/165) by imaging	6.7% (11/165) by imaging	18%[d]
	Medellin, Colombia[42]	108	NA	36.4% (4/11) by imaging	27.3% (3/108) by imaging	39.1% (9/23)
	Curitiba, Brazil[43]	55	16.4% (9/55)[a]	25% (10/40) by imaging	27.3% (15/55)[b]	
	Mexico City, Mexico[44]	39	10.3% (4/39)[a]	NA	NA	NA
			CKD risk (95% CI)	Nephrolithiasis risk (95% CI)	Nephrocalcinosis risk (95% CI)	Hypercalciuria risk (95% CI)
Population studies	Denmark[17]	688	HR = 3.10[e] (1.73–5.55)	HR = 4.02 (1.64–9.90)	NA	NA
	Denmark[33]	180	HR = 6.01[e] (2.45–14.75)	HR = 0.80 (0.17–3.85)	Not increased	NA
	Korea[34]	897	HR = 3.44[e] (1.63–7.23)	HR = 2.13 (1.10–4.13)	NA	NA
	Scandinavia[45]	239	HR = 4.88[e] (2.00–11.95)	HR = 1.71 (0.22–13.11)	NA	NA
	Russia[23]	200	22.2% (34/151)[a]	51% (49/96)		21% (21/100)[f]
	Canada[46]	130	23%[a]	23.7% (18/76)		35.8% (24/67)[g]

CI = confidence interval; CKD = chronic kidney disease; HR = hazard ratio; NA = not applicable.
[a]eGFR >60 mL/min/1.73m^2 using Modification of Diet in Renal Disease equation.
[b]Hypercalciuria defined as >8 mmol/24 hours.
[c]<50 mL/min/1.73 m^2 using plasma clearance of ^{99m}Tc-DTPA.
[d]Hypercalciuria defined as >7.5 mmol/24 hours.
[e]Based on ICD coding.
[f]Hypercalciuria defined as >8 mmol/24 hours.
[g]Hypercalciuria defined as >7.5 mmol/24 hours.

study included possible underestimation of disease burden, limited sample size, and inability to rule out selection bias. These findings suggested that patients with chronic hypoPT have significant symptom and comorbidity burdens that lead to increased health care resource utilization.

The study by Hadker and colleagues[38] performed a web-based survey of 374 adult US patients with chronic hypoPT. Mean age was 49 ± 12 years, with 85% female, with mean duration of hypoPT 13 ± 12 years. A total of 30.5% of the cohort self-rated their condition as severe. Participants visited a mean of 6 ± 8 physicians for chronic hypoPT before and after their diagnosis. More than half (56%) reported that they felt unprepared to manage their condition when they were diagnosed, and 60% indicated that it was more difficult to control their hypoPT than they anticipated. A total of 75% of participants indicated they were concerned about long-term complications of their current medications. A total of >10 symptoms were experienced by 72% of participants in the year before the survey, despite receiving conventional medical therapy for hypoPT. Patients reported experiencing symptoms for a mean of 13 ± 9 hours each day. A total of 79% of the patients required hospitalization or emergency department visits during the year. Significant interference with daily life was experienced by 45% of patients, and 85% indicated they could not perform household activities. A total of 20% had a disease-associated change in their employment. The study concluded that patients with hypoPT had a significant burden of illness and a wide range of symptoms, with a major detrimental impact on their lives.

Complications

Hypercalciuria, nephrocalcinosis, kidney stones, renal insufficiency

A summary of single-center retrospective chart review studies and population studies of prevalence of renal complications is given in Table 2. Additional coverage of renal complications is also addressed in the accompanying narrative review, Etiology and Pathophysiology of Hypoparathyroidism.

Risk factors for renal complications

Underbjerg and colleagues[47] assessed predictors of renal complications in 431 cases of hypoPT, with 88.2% postsurgical, median age 41 years, 81.4% female, and median disease duration 12.7 years. Chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <60 mL/min) occurred in 21%. Predictors of CKD included longer duration of disease (>median of 12.7 years; adjusted odds ratio [OR] = 2.19, 95% CI 1.24–3.87) and higher calcium × phosphate product (>median of

2.80 mmol/L; adjusted OR = 2.21, 95% CI 1.24–3.87). Occurrence of 4 or more hypercalcemia episodes increased the risk of CKD threefold. Vadiveloo and colleagues[48] evaluated 116 cases of postsurgical hypoPT and 106 with nonsurgical hypoPT and compared these to matched controls. Risk of renal failure defined as eGFR <30 mL/min was twofold greater in postsurgical hypoPT (HR = 2.18, 95% CI 1.11–4.25), with 10-fold increased risk in nonsurgical hypoPT (HR = 9.94, 95% CI 5.53–17.85). However, in the latter group, increased risk was only found within the first 5.5 years of follow-up. Coudenys and colleagues[49] reported on 101 postsurgical hypoPT patients with median age 50 years, range 18 to 75 years, 79.2% female, 56% with benign thyroid disease, and mean follow-up duration 6.6 years. Calcium × phosphate product and cumulative duration of calcitriol therapy correlated with decline in renal function (1.06 mL/min/yr of calcitriol). In a study of 54 patients with hypoPT, Garcia-Pascual reported higher serum 1.25-dihydroxyvitamin concentration was associated with hypercalciuria in 21 patients but not in patients with normal urinary calcium excretion (<300 mg/24 hours), with 45.8 ± 9.5 versus 33.5 ± 11.9 pg/mL, respectively.[50] A cut-point of 33.5 pg/mL predicted absence of hypercalciuria with 100% sensitivity and 63.6% specificity. Gosmanova and colleagues[51] evaluated data from a large managed care claims database in the US from 2007–2017 and identified 8097 patients with and 40,485 patients without hypoPT (5:1 ratio) followed for 5 years. Compared with controls, patients with hypoPT showed increased adjusted risk of developing incident CKD (HR = 2.91, 95% CI 2.61–3.25), progression to worse CKD stage (HR = 2.14, 95% CI 1.23–2.01), progression to end-stage renal disease (ESRD; HR = 2.56, 95% CI 1.62–4.03) and decline in eGFR ≥30% (HR = 2.56, 95% CI 1.62–4.03). Khan and colleagues[46] found that hypercalciuria was found most commonly in those with nephrocalcinosis, nephrolithiasis, and those with CKD.

Skeletal complications

Most of our knowledge of the potential clinical consequences of these changes is based on observational data from either small patient series or larger referral- or population-based cohorts with significant variability in testing and monitoring. This is further complicated by the heterogeneity of hypoPT patients in terms of baseline characteristics and completeness of follow-up across studies.

Bone mineral density

Initial observations of children and adults with hypoPT showed higher bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). Shukla and colleagues showed that BMD was significantly higher in 7 adult women with hypoPT with mean disease duration of 22 years compared with controls, with *Z*-scores ranging from 1.4 to 6.2 (median, 2.8).[52] Similar results were noted on imaging with quantitative CT (QCT). The use of more advanced imaging with dual-energy QCT by Fujiyama and colleagues similarly showed higher bone mass at the lumbar spine (LS) in 13 postmenopausal women with postsurgical hypoPT.[53] Subsequently, these results were validated in other cohorts showing that BMD by DXA can be 8% to 28% higher compared with controls.[54,55] Most of this difference persisted after adjustment for age, sex, and body mass index (BMI).

Although not consistent among all studies, determinants of increased BMD include duration of hypoPT, increased age, and decreased PTH levels.[54,56,57] In addition, BMD changes did not seem to differ based on whether chronic hypoPT was postsurgical or nonsurgical.[58]

Using lateral LS imaging, Duan and colleagues[56] showed that bone mineral content (BMC) was increased in both the vertebral body, which is almost exclusively trabecular bone, and the posterior spinous process, which is mostly cortical bone, indicating that the overall increase in BMD at the LS reflects increased mass of both trabecular and cortical compartments.

Longitudinal studies support that hypoPT impacts bone remodeling rate. In a study of postmenopausal women with postsurgical hypoPT, those within 5 years of menopause during the phase of rapid bone loss had a slower rate of BMD loss of 0.51 (±3.05)%/yr, as opposed to a rate of loss of 2.49 (±1.86)%/yr in age-matched controls ($p < 0.05$).[52] The lower turnover was independent of thyroid-stimulating hormone (TSH), duration of thyroid replacement, or dose of levothyroxine. Other studies also suggested that subjects with hypoPT have either stable or increased BMD over time compared with age-related bone loss seen in controls.[54,56]

Markers of bone turnover

In hypoPT, the skeleton has low turnover, as evidenced by multiple studies showing a significant decrease in bone turnover markers. Most studies have shown significant decreases in makers of bone resorption (C-terminal telopeptide of type I collagen, pyridinoline, and deoxypyridinoline),[53,57] as well as decreased markers of bone formation (bone-specific alkaline phosphatase, osteocalcin, N-terminal propeptide of type I procollagen).[53,57,59]

Trabecular bone score

The recent addition of the trabecular bone score (TBS) to the DXA-generated LS image allows for additional insights into the trabecular changes in hypoPT. A retrospective cohort of 62 adults[60] with postsurgical hypoPT with median age 59 years showed maintained trabecular bone with a mean TBS of 1.386 ± 0.140. TBS did not correlate with time after surgery. However, a third of these patients had a low TBS (<1.31). The low TBS group were mostly postmenopausal women, older, and had a higher rate of obesity and diabetes compared with the remainder of the cohort.

Bone material strength index

A more direct assessment of bone quality, albeit more invasive, is use of a microindentation technique to measure the bone material strength index (BMSi). In a study of 17 women[61] with hypoPT (14 postsurgical) with mean disease duration of 8.2 years, BMSi was 11% lower compared with controls ($p = 0.01$) and correlated with PTH levels. BMSi also improved after treatment with rhPTH 1–84.

Fractures

Despite the strong evidence showing reduced bone remodeling and increased bone mass in patients with hypoPT, the clinical complications are far less clear. Risk factors for fragility fractures include older age, increased BMI, hyperglycemia, and low BMD.[60] Although the overall risk of fracture does not seem to be significantly increased,[62] there are site-specific differences among published reports.

A lower incidence of upper extremity fractures was reported in patients with postsurgical hypoPT,[48,63] in contrast to a higher incidence in patients with nonsurgical hypoPT,[33] with a propensity toward forearm and proximal humerus fractures.

Several reports highlighted the increased risk of morphometric vertebral fractures in hypoPT.[34,54,57] In one of the studies,[54] however, the results were confounded by a higher rate of seizures and a longer duration of use of anti-epileptics in hypoPT subjects who sustained fractures. In addition, a higher proportion of those who fractured in other studies were postmenopausal women.[53,56] A recent meta-analysis reported twofold increased risk of vertebral fractures in nonsurgical hypoPT.[64]

Other skeletal complications

The impact of hypoPT on the skeleton is not limited to bone remodeling and fractures. Case reports of ossification of paravertebral and/or parapelvic ligaments and spinal deformities have been published. In comparative studies, however, there has been no increase in the rate of overall spinal deformities or spinal stenosis in patients with hypoPT compared with controls.[53,63]

In a survey study[38] of US patients with confirmed hypoPT, with 85% women, mean age 49.4 years, and mean disease duration of 12.6 months, most of whom had postsurgical disease, two-thirds reported having had joint or bone pain within the preceding 12 months, and 53% indicated pain, heaviness, or weakness in the extremities, with 29% reporting dental problems. The incidence of these self-reported symptoms was higher in those with moderate or severe disease compared with those with mild disease.

Cardiovascular complications

Chronic hypoPT has been associated with cardiac and vascular complications in several registry studies and retrospective case–control studies. Studies have shown different results in patients with nonsurgical and postsurgical hypoPT.

Underbjerg and colleagues[33] reported that 180 patients with nonsurgical hypoPT, with mean age 50 years and followed for nearly 50 years, had increased risk of cardiovascular disease (HR = 1.91, 95% CI 1.29–2.81, $p = 0.01$) and increased ischemic heart disease (HR = 2.01, 95% CI 1.31–3.09, $p = 0.01$), cardiac arrhythmia (HR = 1.78, 95% CI 0.96–3.30, $p = 0.03$), and stroke (HR = 1.84, 95% CI 0.95–3.54, $p = 0.03$), but mortality was not increased. Evaluation of 56 patients with nonsurgical hypoPT with mean age 47 years by Underbjerg and colleagues[63] showed increased pulse wave velocity, arterial stiffness, and heart rate. Kim and colleagues[34] reported an increased risk of cardiovascular disease during a mean follow-up period of 9.5 years in 210 patients with nonsurgical hypoPT, specifically arrhythmia (HR = 2.03, 95% CI 1.11–3.70) and heart failure (HR = 2.43, 95% CI 1.22–4.83).

In contrast, Underbjerg and colleagues[17] did not find increased risk of cardiovascular disease or cardiac arrhythmia in 688 hospitalized patients with postsurgical hypoPT, with mean age at diagnosis of 49 years, and mean follow-up of a mean of 8.4 years, after adjusting for prevalent cardiovascular disease before hospitalization. Whether these postsurgical patients will eventually develop cardiovascular disease with longer follow-up remains unclear.

Underbjerg and colleagues[47] also showed that long-term follow-up of 431 patients with chronic hypoPT of any type, with median disease duration 12.7 years, and mean age at diagnosis 41 years had increased risk of cardiovascular disease with lower time-weighted serum ionized calcium, increased episodes of hypercalcemia, or longer duration of disease.

Cataracts

Cataracts are a long-recognized complication of hypoPT, although their etiology remains incompletely understood. Although one early case series described predominantly posterior subcapsular disease,[65] cortical opacities predominated in other series.[66,67] In a modern cohort in which 20 women with postsurgical hypoPT systematically underwent slit lamp examination, cataracts were found in 11 (55%), of which 8 (73%) were cortical, 2 (18%) were nuclear, and 1 (9%) was subcapsular.[68] In the Nuf ("nuclear fleck") mouse, identified in a screen for eye mutations and found to carry an activating mutation of the calcium-sensing receptor, pathologic exam of the predominantly nuclear lesions revealed swelling and degeneration of lens fibers without significant mineralization.[69] These and other data suggest that altered electrolyte composition of the aqueous humor may precede cataract development in hypoPT.[69,70]

Prevalence of cataract

Estimates of the prevalence of cataracts among patients with hypoPT vary significantly based on methodology but are generally substantially higher among patients with nonsurgical compared with postsurgical hypoPT. Among nonsurgical patients, prevalence based on diagnostic codes in regional and national databases was consistently approximately 11% in Scotland, Denmark, and South Korea.[18,33,34] In two case series from South Africa and India, prevalence based on chart reviews was 51% and 33%, respectively.[71,72] Subsequent systematic ophthalmologic examination of 165 patients from the same center in India[41] revealed a 66% prevalence of cataracts.

Among patients with postsurgical hypoPT, examination of regional and national databases revealed cataract prevalence of 9.5% in Scotland and 2.3% in Denmark.[18,33] Direct ophthalmoscopy of a cohort of 32 patients in 1968 showed 50% with macroscopic and 41% with microscopic cataract.[67] Of the 55% of patients with cataracts described by Arlt and colleagues,[68] 15% had macroscopic and 40% had microscopic disease.

Relative risk of cataract

The relative risk of cataracts in patients with hypoPT compared with unaffected controls has been evaluated in the Danish, Korean, and Scottish registry studies.[18,33,34] Among nonsurgical patients, the HR for cataract in the different registries was 4.21, 1.81, and 1.90, respectively. In addition, in the Danish study,[33] among the patients with cataracts, the average age of those with hypoPT was 53 years, whereas controls averaged 60 years. Among patients with surgical hypoPT, the HR among Danish patients[62] was 1.17, not significantly different from controls, whereas in the Scottish cohort,[18] the HR was increased to 1.87.

Predictors of cataract

Among risk factors for cataract, beyond having nonsurgical hypoPT, longer duration of disease has been associated with cataracts in both surgical and nonsurgical patients.[67,68,73] The presence of basal ganglia calcifications has also been associated with cataract,[73,74] but renal calcifications were not associated with

cataracts in one study.[41] Mean serum calcium has not been associated with cataract prevalence.[48,73]

Basal ganglia calcification

Basal ganglia calcification (BGC) has been associated with chronic hypoPT for many years. Determination of BGC prevalence depends in part on imaging technique and in part on diagnostic criteria. In the 1980s, BGC was detected incidentally in 0.24% to 0.75% of head CT scans of patients in the general population,[74] whereas two decades later it was reported to be 12.5%.[75] A very large study[76] recently showed that BGC were present in 1.3% of 11,941 patients undergoing non-contrast head CT imaging in the general population.

Goswami and colleagues[72] reported finding BGC by head CT imaging in 73.8% of 93 patients with idiopathic hypoPT. Illum and Dupont[77] reported a prevalence of 69% in an early small series of 16 patients with idiopathic hypoPT. Sachs and colleagues[78] reported that 11 of 12 (91.7%) patients with idiopathic hypoPT had BGC. Mean age of onset of idiopathic BGC, and whether prevalence may differ by sex, is currently unknown.[79]

Rubin and colleagues[80] reported that 4 of 33 (12.1%) patients with chronic hypoPT had BGC, but brain imaging was carried out only in symptomatic patients. Mitchell and colleagues[39] showed that 52% of 31 patients with head CT scans available in a large cohort of 120 patients with chronic hypoPT had BGC. Zavatta and colleagues[81] reported that 25.4% of 142 patients followed clinically for a median of 17 years after diagnosis of chronic hypoPT had BGC. Khan and colleagues[46] found BGC in 15% of patients with postsurgical hypoPT and in 37% of those with nonsurgical hypoPT.

Prevalence of BGC in chronic hypoPT may vary with the etiology of the hypoPT. Series of postsurgical hypoPT cases are usually small and have shorter disease duration and follow-up, and therefore may miss BGC development and, consequently, give lower prevalence estimates. Raue and colleagues[82] reported a case series of 25 patients with autosomal dominant hypocalcemia type 1 caused by activating mutations of the calcium-sensing receptor (CaSR) with BGC prevalence of 36%. Forman and colleagues[74] reported one of the first series of postsurgical hypoPT that evaluated brain morphology by CT imaging, and found that 5 of 9 (55.6%) patients had BGC. Patients in this series had hypoPT for a minimum of 8 years before detection of BGC. Lorente-Poch and colleagues[83] recently demonstrated a four-fold increase in BGC in a small cohort of 29 patients with postsurgical chronic hypoPT.

Infections

Chronic hypoPT is associated with increased risk of infections, likely due to impaired immune function.[84] Infections are increased in certain genetically inherited forms of nonsurgical hypoPT, such as DiGeorge syndrome or autoimmune polyglandular syndrome type 1 (APS-1), but are also increased in nongenetic forms of hypoPT. Calcium signaling is an important regulator of immune function and affects mast cell cytokine production and degranulation, target cell lysis by cytotoxic T cells, cytokine production by T cells, most responses initiated by T cells, B cells, and Fc receptors, cytokine production by natural killer cells, and lymphocyte differentiation.[84]

Underbjerg and colleagues[62] first reported that patients with postsurgical hypoPT were at increased risk of hospitalization due to infections (HR = 1.42, 95% CI 1.20–1.67). Further evaluation showed a borderline increased risk of urinary tract infections (UTI) (HR = 1.36, 95% CI 0.97–1.91), with an increased risk of respiratory tract infections and any infections. Exclusion of UTIs did not eliminate risk of other infections, however (HR = 1.38, 95% CI 1.14–1.67), and exclusion of infections occurring within 90 days of hospitalization did not change the risk of infection (HR = 1.36, 95% CI 0.97–1.91). Patients with hypoPT had increased risk of recurrent infections causing hospitalization. Underbjerg and colleagues[47] subsequently showed that infections, including upper respiratory infections, were associated with hyperphosphatemia, increased episodes of hypercalcemia, and increased disease duration, and that treatment with high-dose activated vitamin D reduced the risk of infections.

Nonsurgical hypoPT was also reported to be associated with risk of infection by Underbjerg and colleagues[33] (HR = 1.94, 95% CI 1.55–2.44, $p < 0.01$). Upper respiratory infections (HR = 2.90, 95% CI 2.12–3.99), UTIs (HR = 3.84, 95% CI 2.24–6.60), and other infections excluding UTIs (HR = 1.51, 95% CI 1.18–1.95) were increased. Exclusion of patients with DiGeorge syndrome or APS-1 did not change these results.

Valdiveloo and colleagues[18] showed that only patients with nonsurgical hypoPT were at increased risk of infection (HR = 1.87, 95% CI 1.20–2.92) and that postsurgical patients did not have increased risk of infection.

Malignancy

Underbjerg and colleagues[62] reported that risk of malignant diseases did not differ between hospitalized patients with postsurgical hypoPT and age- and sex-matched controls from the general population. However, the risk of gastrointestinal malignancy was significantly lower in patients (HR = 0.63; 95% CI 0.44–0.93). Stratification by type of cancer showed a borderline significant reduced risk of colorectal cancer ($p = 0.06$) but no effect on only colon cancer ($p = 0.18$). Nine controls had melanoma, but no patients were identified with this cancer ($p = 0.08$).

Underbjerg and colleagues[33] showed that hospitalized patients with nonsurgical hypoPT also had reduced risk of any malignancy compared with age- and sex-matched controls from the general population (HR = 0.44; 95% CI 0.24–0.82). However, risks of specific malignancies were not reduced in patients with nonsurgical hypoPT.

Neuropsychiatric complications

Patients with chronic hypoPT are at increased risk of depression/bipolar affective disorder and possibly anxiety. Underbjerg and colleagues[62] first showed that patients with postsurgical hypoPT have increased risk of depression, bipolar disorder, and other types of neuropsychiatric illness (HR = 1.99, 95% CI 1.14–3.46). After adjusting for previous diagnosis of depression or bipolar affective disorders, risk of depression or bipolar disorders was increased twofold (HR = 2.01, 95% CI 1.16–3.50). Risk of diagnosis of other neuropsychiatric disease was also increased (HR = 1.26, 95% CI 1.01–1.56), but risk of anxiety was not.

Underbjerg and colleagues[33] subsequently showed that patients with nonsurgical hypoPT also have increased risk of neuropsychiatric disease (HR = 2.45, 95% CI 1.78–3.35, $p = 0.01$). Risk of depression (HR = 2.76, 95% CI 0.97–7.90, $p = 0.05$) and other types of neuropsychiatric disease (HR = 2.53, 95% CI 1.84–3.48) was increased, but anxiety was not increased. Kim and colleagues[34] also found that depression and bipolar disease were increased in patients with nonsurgical hypoPT (HR = 1.82, 95% CI 1.30–2.56, $p = 0.0006$). Vadiveloo

and colleagues[48] found an increased risk of mental illness in patients with chronic hypoPT (HR = 1.59, 95% CI 1.21–2.11).

Psychosis is a rare feature of hypoPT and case reports indicate that it may coexist with other neuropsychiatric complications such as ataxia and cognitive impairment and be partly reversible with calcium and active vitamin D supplementation.[85,86] Depression,[87] anxiety,[88] and mania[89] have all been reported in this context.

Underbjerg and colleagues[90] assessed health-related quality of life in 57 patients with nonsurgical hypoPT using the SF-36v.2 and WHO-6 Well-Being Indices and found that 12% of patients had depression, and 33% had poor emotional well-being. Patients had significant reductions in all physical and mental domains of the SF-36v.2 when compared with the general population. The cohort contained patients with genetic causes of hypoPT, including 22q11 deletions, which are known to be associated with psychiatric disorders, so that the effects found may not be attributable to hypoPT alone.

Astor and colleagues[19] also found lower SF-36 scores in all dimensions and higher symptom scores for anxiety and depression in Norway, with higher rates of depression in the postsurgical group.

Arlt and colleagues[68] evaluated well-being and mood in 25 patients with postsurgical hypoPT and compared results in 25 controls with previous thyroid surgery and intact parathyroid function. Assessment with the revised version Symptom Checklist 90 (SCL-90-R), Giessen Complaint List (GBB-24), and von Zerssen Symptom List (B-L Zerssen) showed that patients with hypoPT had increased global complaint scores, with increased subscale scores for anxiety and phobic anxiety, and their physical equivalents. Conventional therapy with calcium and vitamin D supplementation did not restore well-being.

Sikjaer and colleagues[91] found that patients with postsurgical hypoPT and hypothyroidism had greater impairment of quality of life than those with postsurgical hypoPT alone. Buttner and colleagues[92] also reported lower quality of life in patients with hypoPT after treatment for thyroid cancer.

Future Research and Recommendations

The data presented in this review clarify certain aspects of the epidemiology and financial burden of hypoPT but leave many unanswered questions for future research:

1. Most of the studies of the epidemiology of hypoPT published to date are from Europe and North America. Further studies from outside Europe and North America are needed.
2. Most studies published have addressed the prevalence of hypoPT, but only a few studies have evaluated mortality related to hypoPT. Future studies should address these aspects of epidemiology also.
3. Future studies should clarify the complications of hypoPT in nonsurgical patients with autoimmune or infiltrative disease and those with isolated or genetic disorders.
4. Studies of the epidemiology of hypoPT published to date show that patients with postsurgical hypoPT appear to have lower risks of complications than patients with nonsurgical hypoPT. Future studies should assess whether the differences observed are attributable to longer duration of disease in those with nonsurgical disease or other factors that differ between these types of patients.
5. The effect of pre-existing disease, such as hyperthyroidism or hyperparathyroidism, on BMD is not well understood. This should be clarified in future studies.
6. Future studies of less common complications of hypoPT, including cardiovascular disease, cataracts, basal ganglia calcifications, infections, malignancy, neuropsychiatric disorders, and pregnancy are needed.
7. Further studies are needed to establish the financial burden of hypoPT, given that health care resource utilization appears to be increased in these patients.

Summary and Conclusions

Understanding of the epidemiology and financial burden of chronic hypoPT is gradually increasing, but investigation has thus far been restricted mostly to national or regional registries, insurance claims databases, and retrospective case–control studies. Multiple studies of the national or regional prevalence, incidence, and mortality of this disorder have been published from various countries in North America, Europe, and Asia in recent years. Investigations of the complications of chronic hypoPT have demonstrated that risks of postsurgical and nonsurgical hypoPT appear to differ in certain respects, perhaps due to longer follow-up of cohorts with nonsurgical hypoPT. Further research is needed to clarify the epidemiology and financial burden of chronic hypoPT.

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Data Availability Statement

The data that support the findings in this study are openly available in PubMed, MEDLINE, EMBASE, and the Cochrane databases.

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