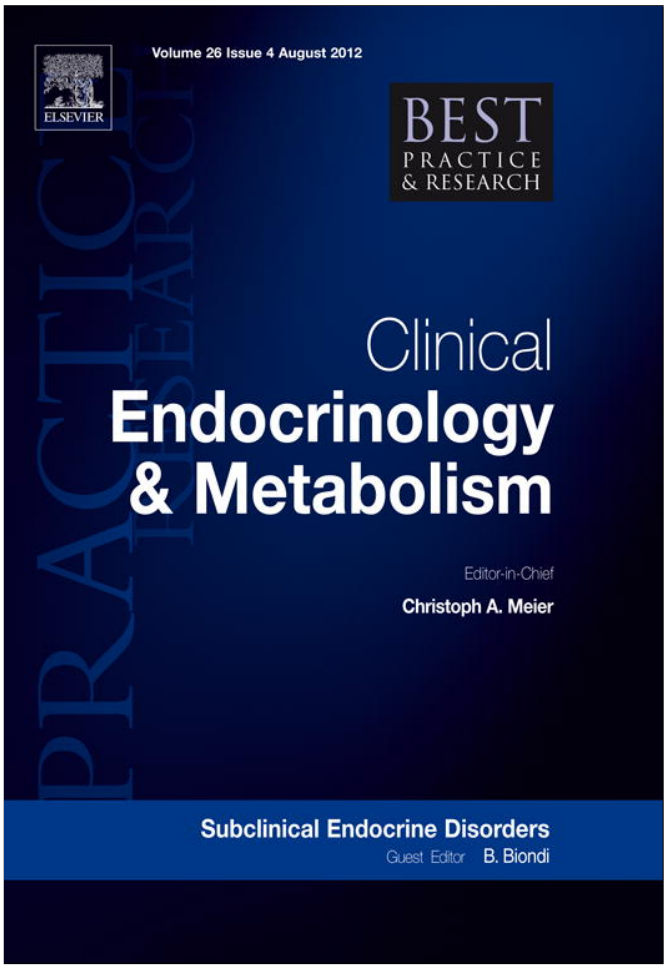

Best Practice & Research Clinical Endocrinology & Metabolism 26 (2012) 517–522

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

11

Hypoparathyroidism

Hafsah Al-Azem, MD, Internal Medicine [a,c], Aliya A. Khan, MD, FRCPC, Professor of Clinical Medicine [b,*]

[a] McMaster University, 1101-75 Bold St, Hamilton, Ontario L8P 1T7, Canada
[b] McMaster University, 331#209 Sheddon Avenue, Oakville, Ontario L6J 5T4, Canada

Keywords:
hypocalcemia
hypoparathyroidism
parathyroid hormone
PTH
vitamin D
calcium

Hypoparathyroidism is characterized by hypocalcemia, hyperphosphatemia and low or inappropriately normal levels of parathyroid hormone (PTH). Pseudohypoparathyroidism is characterized by similar findings however PTH is elevated due to PTH resistance. PTH is a key calcium regulating hormone essential for calcium homeostasis, vitamin D-dependant calcium absorption, renal calcium reabsorption and renal phosphate clearance. The most common cause of hypoparathyroidism is iatrogenic in the setting of anterior neck surgery. Hypoparathyroidism may be due to congenital or acquired disorders. Causes include autoimmune diseases, genetic abnormalities, destruction or infiltrative disorders of the parathyroids. Impaired secretion of PTH may be seen with hypomagnesemia or hypermagnesemia Work-up includes a comprehensive history, physical examination, and a relevant biochemical investigation. Treatment of symptomatic or profound asymptomatic hypocalcemia (Corrected Calcium (Ca) $<$ 1.9 mmol/L) is aimed at rapid intravenous administration of calcium and oral supplementation of vitamin D metabolites. Oral calcium and vitamin D analogs are critical in the treatment of hypocalcemia. In the long-term management of hypoparathyroidism thiazide diuretics are of value as they enhance renal calcium reabsorption and increase serum calcium and are of particular benefit in those with activating mutations of the calcium-sensing receptor. Parathyroid hormone replacement is of great value in improving serum calcium and lowering serum phosphate as well as the doses of calcium and calcitriol supplementation required. It has been shown to lower urinary calcium losses. Careful monitoring of vitamin D, phosphorous, and calcium is necessary during acute and long-term therapy.

* Corresponding author. Tel.: +1 905 844 5677; Fax: +1 905 844 8966.
E-mail addresses: halazem@sympatico.ca (H. Al-Azem), Aliya@mcmaster.ca, draliyakhan@gmail.com (A.A. Khan).
[c] Tel.: +1 905 746 4145.

1521-690X/$ – see front matter
doi:10.1016/j.beem.2012.01.004

Although hypocalcemic patients commonly present with symptoms of neuromuscular irritability with perioral numbers paresthesias, tingling, seizures and, bronchospasm; hypocalcemia may be identified on the biochemical profile of an asymptomatic patient.

Background

Hypoparathyroidism is characterized by a parathyroid hormone-deficient or resistant state leading to hypocalcemia, hyperphosphatemia and hypercalciuria.[1] The parathyroid glands function to maintain calcium homeostasis and increase the synthesis and secretion of PTH in response to hypocalcemia as detected by the calcium-sensing receptor (CaSR) on the chief cells.[2] PTH mediates its effects at the level of the kidneys, bone, and indirectly at the gastrointestinal tract through its effects on vitamin D hydroxylation. In the kidney PTH stimulates the conversion of 25-hydroxyvitamin D (25[OH]D) to 1,25-dihydroxyvitamin D3 (1,25 $[OH]_2D3$), its active metabolite, thereby enhancing calcium absorption in the gut. PTH enhances renal calcium reabsorption and promotes renal phosphate excretion. The clinical presentation of hypoparathyroidism may be variable. The hypocalcemic patient may present with fatigue, confusion, paresthesias, muscle cramps, twitching, laryngospasm, bronchospasm, seizures and congestive heart failure.[2] Subclinical hypoparathyroidism may be an incidental finding on routine blood work. Basal ganglia calcification can occur in the presence of hyperphosphatemia. Hypocalcemia and low serum phosphate levels are associated with mineralization abnormalities and the development of osteomalacia in adults and rickets in children.

The prevalence of hypoparathyroidism is difficult to quantify. Its variable presentation and the potential for subclinical cases to be missed render this challenging.

Etiology

Hypoparathyroidism can be caused by an inability to synthesize or secrete PTH, by destruction of parathyroid tissue, or by peripheral resistance to PTH.

The most common cause of hypoparathyroidism is iatrogenic in the setting of surgical procedures to the neck, and commonly, the thyroid gland.[3] Direct damage to or removal of the parathyroid glands, as well as disruption of the blood supply can lead to transient, and uncommonly permanent hypoparathyroidism. Transient hypoparathyroidism has been reported to occur significantly more often than permanent hypothyroidism following thyroid surgery, with an incidence ranging anywhere from 6.9% to 46% for the former, and from 0.9% to 1.6% for the latter.[1] Persistent hypocalcemia beyond 6 months of surgery confirms the presence of permanent post-operative hypoparathyroidism. The incidence of post-operative hypoparathyroidism appears to be reduced with intra-operative PTH monitoring.[4] It is more commonly seen following repeat neck surgeries and in the hands of inexperienced surgeons.

Less frequently, radiation (external or rarely following radioactive iodine thyroid ablation), metastatic infiltration, or deposition of iron in hemochromatosis or copper in Wilson's disease can be the cause of hypoparathyroidism.[1]

A number of genetic causes of hypoparathyroidism have been identified.

DiGeorge syndrome, or velocardiofacial syndrome, is due to an embryologic defect in the development of the 3rd, 4th and 5th branchial pouches and results in hypoparathyroidism. It is also characterized by cardiac defects, cleft palate, dysmorphic facial features, renal and ocular defects, and hypoplasia or agenesis of the thymus in addition to the parathyroid glands.[5] Hypocalcemia occurs in up to 60% of these patients, and may first appear in adulthood. The mutation isolated in DiGeorge syndrome, a de novo heterozygous deletion of chromosome 22q11, includes the gene TBX1, which

encodes a transcription factor necessary for thymic and parathyroid gland development. DiGeorge syndrome is usually sporadic however autosomal dominant transmission has also been reported.

Hypoparathyroidism has also been described in the hypoparathyroidism–deafness–renal dysplasia syndrome. In this syndrome, an autosomal dominant mutation leading to reductions in GATA3, a transcription factor essential for parathyroid, renal, and otic vesicle development, has been identified.

Two other syndromes, Kenny–Caffey syndrome and Sanjad–Sakati syndrome, have been described, which include hypoparathyroidism. The former is associated with short stature, ocular and bony abnormalities, while the latter is associated with facial abnormalities, short stature, and retardation.[6,7] Both have been linked to autosomal recessive loss of function mutations of TBCE, a gene involved in microtubule assembly in target tissues. Both syndromes are referred to generally as hypoparathyroidism–retardation–dysmorphism syndromes.[2]

Maternally inherited mitochondrial DNA defects have been associated with hypoparathyroidism in addition to other features as seen in the MELAS syndrome as well as other disorders including the, mitochondrial trifunctional protein deficiency syndrome (MTPDS), and the Kearns–Sayre syndrome.[1]

Other forms of inherited hypoparathyroidism include familial hypercalciuric hypocalcemia, in which an autosomal dominant gain of function mutation in the calcium sensing receptor causes an oversensitivity of the CaSR to calcium.[8] This, in turn, causes a left shift in the set point for PTH secretion. The set point is the calcium level required for half-maximal suppression of PTH release. PTH levels are inappropriately suppressed in the presense of lower serum calcium.

Familial hypoparathyroidism can also occur as a result of mutations in the auto-immune regulator (AIRE) gene.[9–11] This is usually inherited in an autosomal recessive manner however; autosomal dominant inheritance has also been described. The condition can be isolated, or part of an autoimmune polyglandular syndrome (APS).[10,11] APS type 1 also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome, usually appears in childhood as persistent mucocutaneous candidiasis. It is characterized by hypoparathyroidism (usually present in approximately 80% of cases), Addison's disease, and candidiasis. In addition other features of autoimmunity may be present such as: type 1 diabetes, hypothyroidism, pernicious anemia, hepatitis, ovarian atrophy, keratitis, vitiligo, and alopecia.[10,11] Acquired autoimmune hypoparathyroidism with antibodies to the CaSR, has also been described in isolation or in association with other autoimmune diseases such as Grave's disease or adrenal insufficiency.[1,12]

Isolated hypoparathyroidism has been described due to mutations in the PTH, glial cells missing homolog B (GCMB), and the CaSR genes. The GCMB gene regulates the development of the parathyroid glands.[1,11] The majority of idiopathic cases of hypoparathyroidism are due to an unknown defect.

Reversible hypoparathyroidism

Hypoparathyroidism may be transient or reversible in the setting of hypomagnesemia (alcohol intake, malnutrition, malabsorption, renal wasting, etc) or hypermagesemia (i.e. tocolysis). Magnesium plays an important role in the secretion of PTH and in the activation of PTH receptors.[2]

Pseudohypoparathyroidism

Like hypoparathyroidism, pseudohypoparathyroidism (PHP) is characterized by hypocalcemia and hyperphosphatemia. Unlike hypoparathyroidism, however, PHP is not a defect in PTH production, but rather, peripheral resistance to the hormone. Elevated PTH levels are seen in PHP. In PHP, an inherited mutation in the GNAS gene leads to a deficiency in the level of the α subunit of the Gs protein in several tissues including the proximal tubule renal. Gsα plays an important role in the coupling of PTH to the adenylate cyclase enzyme for the formation of cyclic adenosine monophosphate (cAMP).[13,14] The Ellsworth–Howard test helps to distinguish between PHP and hypoparathyroidism. In both disorders, urinary excretion of cAMP is reduced. Stimulation with exogenous PTH causes an increased excretion of cAMP in hypoparathyroid patients, whereas those with PHP will continue to demonstrate resistance to the hormone itself and will continue to have low urinary cAMP levels.[1]

Various types of PHP have been identified.[1,3]

1. Pseudohypoparathyroidism type 1a
   - Maternal inheritance of GNAS mutation.
   - Resistance to other hormones may also occur (i.e. TSH, GHRH, FSH, LH) in the maternally inherited form;
   - Albright's hereditary osteodystrophy (AHO) (short stature, round face, short 4th metatarsals, obesity, mental retardation seen in approximately 50%).
2. Pseudohypoparathyroidism type 1b
   - PTH resistance only;
   - May have some features of osteodystrophy.
3. Pseudohypoparathyroidism type 1c
   - A variant of type 1a with resistance to other hormones;
   - Current assays used to detect Gsα deficiency do not detect the decreased Gsα activity.
4. Blomstrand lethal chondrodysplasia
   - Due to mutations in the PTH/PTHrP receptor leading to impaired function;
   - Autosomal recessive, lethal.
5. Pseudopseudohypoparathyroidism
   - Paternal inheritance of GNAS mutation;
   - The mutant allele is imprinted, AHO present, laboratory values are normal.

In practice

A thorough history is very important in the work-up of a hypocalcemic patient. This includes surgical history, history of radiation or systemic illness and family history. Symptoms such as cramping, tetany, twitching, and seizure history should be elicited. On physical examination, assess for the presence of Trousseau's and Chvostek's signs which can be indicative of neuromuscular irritability. Careful examination of the skin for vitiligo and mucocutaneous candidiasis (as in APS) or, for craniofacial or skeletal abnormalities or other features of genetic diseases should be done.

Laboratory findings in keeping with hypoparathyroidism include low serum ionized calcium and elevated or high-normal phosphate levels. Total calcium should be adjusted appropriately to correct for calcium binding to albumin [corrected calcium (mmol/L) = calcium measured (mmol/L) + {40 − albumin (g/L) × 0.02}]. Intact PTH levels are inappropriately low or normal in patients with hypoparathyroidism.[1]

Serum levels of magnesium and 25(OH) vitamin D should be measured to rule out a deficiency that could contribute to reduced serum calcium levels.[1,2] Renal function should also be assessed, as well as a 24-h urine collection to identify hypercalciuric hypocalcemia.

Treatment

The treatment of acutely symptomatic hypocalcemia or corrected calcium <1.9 mmol/L is intravenous infusion of 10ml (1 ampoule) of 10% of calcium gluconate over 10 min. Each ampoule provides 93 mg of elemental calcium, with an effect lasting 2–3 h. This should be followed by a continuous infusion of 15 mg/kg of elemental calcium diluted in 1 L of D5W, infused at a rate of 1 mg/kg/h.[1,2] Treatment should be guided by frequent serum calcium measurements and be performed with cardiac monitoring. A central venous catheter is recommended to avoid sclerosing of veins by calcium.[2]

Oral replacement of calcium, in addition to vitamin D supplementation should be initiated. Calcium citrate is the agent of choice in achlorhydric patients or those taking proton pump inhibitors. Calcium dosing can range from 1 to 9 g/d and is usually given every 6 hours.[1,2]

Calcitriol, $1,25(OH)_2D3$ the active metabolite of vitamin D, can increase serum calcium levels within a few days.[1,3] Concurrent treatment with parent vitamin D (ergocalciferol or cholecalciferol) should be initiated to maintain normal vitamin D levels. Vitamin D toxicity is an important consideration when administering high doses of supplements and monitoring is essential.

Careful monitoring of calcium, phosphate, 24-h urine calcium excretion and the calcium phosphate product is warranted. Total calcium should be raised into the low–normal range, as high doses of calcitriol supplementation can promote calcium-phosphate precipitation into soft tissues. Reduced dietary phosphate intake and the use of phosphate binders are of benefit.[2] Calcium-phosphate product should remain <4.4 mmol^2/L^2. Avoid hypercalcemia and hypercalciuria as this can increase the risk of nephrolithiasis and nephrocalcinosis and impair renal function. Thiazide diuretics are used to enhance calcium reabsorption in the distal renal tubules and to reduce calciuria.[1,2] Thiazide diuretics allow reductions in the dose of calcium and calcitriol supplementation.

The prospect of PTH replacement therapy has been explored in several small, randomized controlled trials in adults and children. Winer et al. have evaluated the effects of long-term treatment of twice-daily synthetic PTH 1–34 compared to calcitriol and calcium in 27 patients.[15] Both treatments had similar effects on serum calcium, phosphorous and magnesium concentrations, as well as 24-h urine calcium excretion. An increase in markers of bone turnover was seen in the PTH-treated group, but overall bone mineral density (BMD) remained stable over the 3-year study period. A non-significant downward trend was appreciated in the BMD and bone mineral content (BMC) of the distal one-third radius in the PTH-treated patients. A recent study by Rubin and colleagues evaluated intact parathyroid hormone (1–84) in 30 hypoparathyroid subjects over a 24-month period and demonstrated that fewer patients required high-dose calcitriol supplementation in conjunction with PTH replacement therapy in order to maintain normocalcemia.[16] An increase in lumbar spine BMD and a decrease in the one-third distal radius BMD was observed with PTH treatment. These findings suggest the possibility of a hormone-mediated increase in trabecular bone density and possible endosteal resorption. Similar changes have been observed in the treatment of osteoporosis with PTH (1–34).[17] Decreases noted in BMD may not necessarily represent a decrease in overall bone strength but could reflect changes in bone volume and microarchitecture which may confer a biomechanical advantage. 3D micro-computed tomography (μCT) study of hypoparathyroid of bone showed increased cancellous bone volume and increased trabecular number and thickness in addition to reduced trabecular separation compared to cadaver controls.[18] The effect of these changes on bone strength remains unknown. Further studies evaluating the effects of PTH on bone strength in those with hypoparathyroid will be of great interest.

Clinical practice points

- Hypocalcemic patients can present with a wide range of symptoms, including fatigue, cramping, tetany, seizures and congestive heart failure. Mild chronic hypocalcemia can be asymptomatic.
- Identification of the etiology of hypocalcemia is essential for appropriate diagnosis and management.
- In hypoparathyroidism, hypocalcemia is associated with hyperphosphatemia, and low or inappropriately normal levels of parathyroid hormone.
- Hypocalcemic patients who are acutely symptomatic, or those with a corrected calcium of <1.9 mmol/L should receive intravenous replacement in a monitored setting.
- For asymptomatic or mildly symptomatic patients with hypocalcemia, oral calcitriol and calcium supplements are indicated. Calcium citrate is recommended for achlorhydric patients (i.e. on proton pump inhibitors). Magnesium deficiency should be corrected.
- Caution should be exercised when replacing calcium in hypoparathyroid patients with gain of function calcium-sensing receptor mutations, as higher urinary excretion of calcium can lead to nephrocalcinosis and renal impairment. Target calcium levels should be in the low normal range. Thiazide diuretics may be used to enhance calcium reabsorption in the distal renal tubule and reduce calciuria.
- Use of PTH replacement therapy for hypoparathyroidism has shown benefit in recent studies, allowing reductions in the dose of calcitriol and calcium supplements, and is a promising therapeutic option.

Research agenda

- PTH replacement therapy will be further explored. Current studies on small patient populations have shown short-term benefit with reductions in calcium and calcitriol requirements. Long-term effects of PTH therapy need to be evaluated.
- Further research is needed to investigate the effect of PTH on other organ systems, as well as their effects on bone remodeling bone, mineral density and bone strengths.

References

*1. Bilezikian JP, Khan A, Potts Jr JT et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, targetorgan involvement, treatment, and challenges for future research. *Journal of Bone & Mineral Research* 2011; **26:** 2317–2337.
*2. Shoback D. Clinical practice: hypoparathyroidism. *New England Journal of Medicine* 2008; **359:** 391–403.
*3. Marx SJ. Hyperparathyroid and hypoparathyroid disorders. *New England Journal of Medicine* 2000; **343:** 1863–1875.
*4. Richards ML, Thompson GB, Farley DR et al. Reoperative parathyroidectomy in 228 patients during the era of minimal-access surgery and intraoperative parathyroid hormone monitoring. *American Journal of Surgery* 2008; **196:** 937–943.
5. Kobrynski LJ & Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. *Lancet* 2007; **370:** 1443–1452.
6. Parvari R, Diaz GA & Hershkovitsz E. Parathyroid development and the role of tubulin chaperone E. *Hormone Research* 2007; **358:** 12–21.
7. Sanjad SA, Sakati NA, Abu-Osba YK et al. A new syndrome of congenital hypoparathyroidism, severe growth failure, and dysmorphic features. *Archives of Disease in Childhood* 1991; **66:** 193–196.
*8. Pollak MR, Brown EM, Estep HL et al. Autosomal dominant hypocalcemia caused by a calcium-sensing receptor gene mutation. *Nature Genetics* 1994; **8:** 303–307.
*9. Kifor O, McElduff A, LeBoff MS et al. Activating antibodies to the calcium-sensing receptor in two patients with autoimmune hypoparathyroidism. *Journal of Clinical Endocrinology & Metabolism* 2004; **89:** 548–556.
10. Eisenbarth GS & Gottlieb PA. Autoimmune polyendocrine syndromes. *New England Journal of Medicine* 2004; **350:** 2068–2079.
*11. Thakkar RV. Genetic developments in hypoparathyroidism. *Lancet* 2001; **357:** 974–976.
*12. Brown EM. Anti-Parathyroid and Anti-Calcium Sensing Receptor Antibodies in Autoimmune Hypoparathyroidism. *Endocrinology & Metabolism Clinics of North America* 2009; **38:** 437–445.
13. Weistein LS, ShuHua Y, Warner DR et al. Endocrine manifestations of stimulatory G protein alpha-subunit mutations and the role of genomic imprinting. *Endocrine Reviews* 2001; **22:** 675–705.
14. Bastepe M. The GNAS locus and pseudohypoparathyroidism. *Advances in Experimental Medicine & Biology* 2008; **626:** 27–40.
*15. Winer KK, Ko CW, Reynolds JC et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *Journal of Clinical Endocrinology & Metabolism* 2003; **88:** 4214–4220.
*16. Rubin MR, Sliney Jr. J, McMahon DJ et al. Therapy of hypoparathyroidism with intact parathyroid hormone. *Osteoporosis International* 2010; **21:** 1927–1934.
17. Neer RM, Arnaud CD, Zanchetta JR et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *The New England Journal of Medicine* 2001; **344:** 1434–1441.
18. Rubin MR, Dempster DW, Kohler T et al. Three dimensional cancellous bone structure in hypoparathyroidism. *Bone* 2010; **46:** 190–195.