HYPOCALCEMIA AND HYPOPARATHYROIDISM

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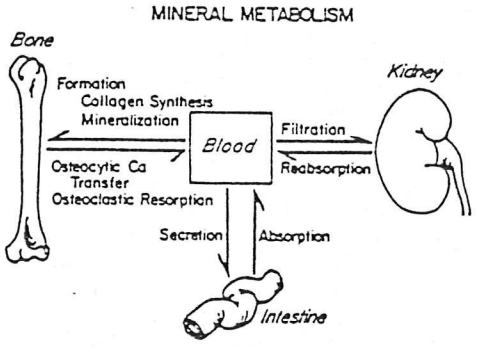
Internal Medicine Grand Rounds

October 18, 1990

Introduction

Precise regulation of serum Ca is essential because of the important role of Ca as a second messenger in the secretion and action of a number of hormones and enzymes, and because of the influence of serum Ca concentration on neuromuscular transmission. Under normal circumstances, the circulating concentration of ionized Ca is maintained within a narrow range by various homeostatic mechanisms. This integrated control is so precise that, in a normal individual, serum ionized Ca fluctuates by no more than 0.1 mg/dl in either direction from its normal set point throughout the day(1). The major regulatory system involves the control by the PTH-vitamin D axis of the flux of Ca across three target organs (Fig. 1).

Figure 1



Normal Hormonal Regulation

The parathyroid glands are exquisitely sensitive to minor changes in serum ionized calcium. A decline in serum calcium stimulates secretion of PTH. The integrated actions of PTH on bone resorption, distal renal tubular calcium reabsorption, and 1,25-$(OH)_2D$-mediated intestinal calcium absorption are chiefly responsible for the precise regulation of serum ionized calcium in humans. The rapid mobilization of calcium from bone, requiring both PTH and 1,25-$(OH)_2D$, and the stimulation of distal tubular calcium reabsorption are the major control points in minute-to-minute serum calcium homeostasis. Adjustments in the rate of intestinal calcium absorption via the calcium-PTH-1,25-$(OH)_2D$ axis require about 24-48 hours to be maximal. Another role of the increased PTH secretion in response to hypocalcemia is to decrease tubular phosphate reabsorption so that the increased amount of phosphate mobilized from bone and absorbed from the intestine along

with calcium will be excreted into the urine. A decline in serum calcium also inhibits secretion of calcitonin and 24,25-$(OH)_2D$, which conceivably could help to restore serum calcium, although the physiological importance of the latter two metabolites in humans remains unclear. It is of interest that during a prolonged hypocalcemic challenge, the initial requirement for calcium mobilization from the skeleton is largely replaced by a more efficient absorption of calcium from the intestine. However, when severe intestinal malabsorption of calcium and vitamin D (e.g., steatorrhea) precludes intestinal adaptation, a marked secondary hyperparathyroidism develops to defend the serum Ca level at the expense of the skeleton.

Failure of Ca Homeostatic System - Hypocalcemia

Since PTH is responsible for minute-to-minute regulation of the blood Ca concentration within narrow limits, the occurrence of hypocalcemia must mean a failure of the homeostatic action of PTH. This can occur if PTH is simply absent due to hereditary or acquired parathyroid gland failure. It can occur if the hormone is rendered ineffective by any of several mechanisms that interfere with its action at target organs. For example, in states of reduced vitamin D effect (as in chronic renal failure, vitamin D deficiency or abnormal vitamin D metabolism), calcium flux from intestine to blood is decreased; in addition, PTH mobilization of calcium from bone to blood is impaired. PTH may also be rendered ineffective if there are abnormalities of the hormone receptor-adenylate cyclase complex (PsHP) or if there is resistance to 1,25-$(OH)_2D$ owing to deficiency in 1,25-$(OH)_2D$ receptors. Hypocalcemia could also occur if the action of PTH to raise blood calcium is simply overwhelmed by the loss of Ca from the extracellular fluid at a rate faster than it can be replaced. Examples of the latter mechanism would include the acute hyperphosphatemia of tumor lysis or rhabdomyolysis with accompanying soft tissue deposition of Ca salts, and bone hunger following parathyroidectomy. This pathophysiologic approach provides a functional classification of the hypocalcemias (Table 1)(2).

TABLE 1 Functionally based classification of hypocalcemia (excluding neonatal conditions)

I PTH absent
- *A* Hereditary hypoparathyroidism
- *B* Acquired hypoparathyroidism
- *C* Hypomagnesemia

II PTH ineffective
- *A* Chronic renal failure
- *B* Active vitamin D lacking
  - *1* ↓ dietary intake or sunlight
  - 2 Defective metabolism:
    - Anticonvulsant therapy
    - Vitamin D dependent rickets—type I
- *C* Active vitamin D ineffective
  - *1* Intestinal malabsorption
  - 2 Vitamin D–dependent rickets—type II
- *D* Pseudohypoparathyroidism

III PTH overwhelmed
- *A* Severe, acute hyperphosphatemia
  - *1* Tumor lysis
  - 2 Acute renal failure
  - *3* Rhabdomyolysis
- *B* Osteitis fibrosa after parathyroidectomy

Criteria for Diagnosis of Hypocalcemia

Typically, the hypocalcemic patient will present with numbness and tingling of the lips and extremities or with muscle cramps associated with carpo-pedal spasm. A similar picture could result from hypokalemia, hypomagnesemia or respiratory alkalosis, so serum Ca, Mg, K and blood gases should be checked. The normal total serum Ca concentration in most laboratories is 8.5 to 10.5 mg/dl. Therefore, a serum Ca concentration less than 8.5 mg/dl indicates hypocalcemia. However, it is the ionized (unbound) fraction of total serum Ca that participates directly in most biological reactions, including prevention of neuromuscular irritability. Decreased total serum Ca concentration, with a normal ionized fraction, can exist with hypoproteinemia or acidosis(3). Hypoalbuminemia is commonly found in chronic illness, nephrotic syndrome and liver disease(4). Therefore, it is useful to correct serum Ca for the serum albumin as follows: Corrected Ca = measured total Ca + 0.8 (4.0 - serum albumin). To assess changes in ionized Ca due to alterations in blood pH, the serum ionized Ca may be measured directly. The normal serum ionized Ca level is 3.8 to 4.6 mg/dl. Binding of Ca to its carrier proteins increases with a rise in pH. A rise in blood pH from 7.4 to 7.6 may decrease ionized Ca by 1.0 mg/dl and may precipitate tetany(5).

Clinical Manifestations of Hypocalcemia(1-3,5,6)

Subjective

Hypocalcemia may vary in its clinical presentation from an asymptomatic biochemical abnormality to a life-threatening condition. Although the presence of symptoms primarily reflects the severity of the hypocalcemia, a rapid rate of fall of the serum Ca and the presence of alkalosis will also adversely affect the patient's response. The symptoms of hypocalcemia are due to enhanced neuromuscular irritability. Sensations of numbness and tingling commonly are noted in the digits and perioral region. In severe or acute hypocalcemia, a syndrome manifested by sharp flexion of the wrist and ankle joints (carpo-pedal spasm), muscle twitching, cramps, convulsions, and sometimes laryngeal stridor may develop. This frightening syndrome is known as tetany. The associated muscle cramping may be quite painful.

Hypocalcemia may also result in mental changes including irritability, paranoia, depression and frank psychosis. Hypocalcemic seizures are usually not associated with loss of consciousness or incontinence and are not preceded by an aura. They may consist of a "glassy-eyed" fixed gaze and prolonged twitching of a limb. Increased intracranial pressure occurs in some patients with long-standing hypocalcemia, accompanied by headache, blurred vision and papilledema (pseudotumor cerebri)(7,8). The condition usually improves with normalization of serum Ca and phosphate. In untreated hypoparathyroidism where there is a combination of chronic hypocalcemia and hyperphosphatemia, basal ganglia calcification often occurs and

sometimes leads to extrapyramidal disorders (classic Parkinsonism, choreoathetosis). Parkinsonism of hypoparathyroidism is resistant to L-dopa therapy, but may be responsive to restoration of normal serum Ca and phosphate(9). Other features that may be associated with chronic hypoparathyroidism include reduced vision from cataracts(10), greasy stools with weight loss (intestinal malabsorption), and congestive heart failure(CHF).

Several clinical reports have provided convincing evidence of a relation between hypocalcemia and CHF(11,12). In one report, a 76 yr-old BF with limited cardiac reserve developed severe cardiac failure on three occasions after the development of hypoparathyroidism, each time associated with marked hypocalcemia, and with recovery only after serum Ca was restored to 8.0 to 9.0 mg/dl(11). Her CHF had not responded to bed rest, digoxin and furosemide. In another report, a 39 yr-old BF with hypocalcemia due to untreated hypoparathyroidism presented with CHF(12). The serum Ca level was restored to normal within one week by administration of Ca carbonate and calcitriol, associated with complete clearing of the signs and symptoms of CHF. Improvement in cardiac function was documented by an increase from 25 to 50 percent in the left ventricular ejection fraction. The patient had no evidence of underlying cardiac disease. Contraction of cardiac muscle requires availability of Ca from extracellular fluid, as well as release from the sarcoplasmic reticulum. The inotropic action of digitalis is also dependent on extracellular calcium, and this drug may become ineffective during hypocalcemic phases. In addition to its effects on myocardial contractility, calcium can also influence the renal tubular reabsorption of sodium. Hypocalcemia reduces sodium excretion, whereas an increase of intracellular Ca promotes natriuresis.

Objective

Overt tetany will be obvious to the physician. Latent tetany may be recognized by eliciting certain signs which are suggestive of lesser degrees of neural excitability. Chvostek's sign entails tapping the facial nerve as it exits the parotid gland just anterior to the ear and watching for twitching of the circumoral muscles. Although Chvostek's sign is a classic manifestation of hypocalcemia, it is also present in 25 percent of normal adults. Trousseau's sign, or carpal spasm elicited by inflation of the blood pressure cuff to just above systolic blood pressure for 2 minutes, also reflects the heightened irritability of the neuromuscular system. The physical examination may also be helpful in detecting the underlying cause of the hypocalcemia. Evidence of previous neck surgery would suggest the diagnosis of post-surgical hypoparathyroidism. Vitiligo, alopecia and moniliasis would be consistent with immunological abnormalities seen in idiopathic hypoparathyroidism. A short stocky build with brachydactyly, and in particular, shortening of the 4th metacarpals and metatarsals, would indicate Albright's hereditary osteodystrophy (AHO), a common feature of pseudohypoparathyroidism.

The presence of rachitic deformities would suggest vitamin D deficiency or abnormal vitamin D metabolism.

Routine laboratory tests such as complete blood count, electrolytes, chest x-ray and urinalysis are usually normal, whereas the chemistry screen (SMA-12) may help in the differential diagnosis of hypocalcemia (see below). It should be noted that patients with hypoparathyroidism may have sustained elevations of muscle enzymes (CPK and LDH) in serum without overt muscle dysfunction or histologic evidence of myopathy(13). These elevated muscle enzymes will decrease as the serum Ca level is raised. It is believed that hypocalcemia impairs muscle membrane integrity, leading to leakage of muscle enzymes. Electrocardiographic manifestations of hypocalcemia include prolongation of the QT interval and T-wave changes such as peaking and inversion.

Differential Diagnosis of Hypocalcemia

Although chronic hypocalcemia is less common than hypercalcemia, because of the serious neuromuscular symptoms associated with untreated hypocalcemia, its pathogenesis must be carefully sought and proper treatment initiated. A variety of disorders may cause hypocalcemia. In narrowing down the possibilities, a useful initial step is to consider whether the serum phosphate is increased or decreased (Table 2).

Table 2. Differential Diagnosis of Hypocalcemia Based on Serum Phosphate Level

Low calcium high phosphate	Low calcium, low phosphate
Renal insufficiency	Vitamin D deficiency
Hypomagnesemia	Abnormal vitamin D metabolism
Excessive phosphate intake	Vitamin D resistance
Massive cell destruction (e.g. chemotherapy, rhabdomyolysis)	Acute pancreatitis
Hypoparathyroidism	"Hungry bone" syndrome
	Osteoblastic metastases to bone

Specific Causes of Hypocalcemia

Selected causes of hypocalcemia will now be discussed representing each of the major pathogenetic mechanisms, i.e. PTH deficiency, PTH ineffective and PTH overwhelmed.

PTH Deficiency - Example: Hypomagnesemia

Magnesium (Mg) deficiency is fairly common. Ten percent of patients admitted to city hospitals are hypomagnesemic and as many as 65% of patients in an intensive care unit may be hypomagnesemic(14). Hypomagnesemia is usually due to losses of Mg from either the gastro-intestinal tract or the kidney (Table 3)(15). In addition to the drugs listed in the table, there was

Table 3 . Common causes of magnesium deficiency

GASTROINTESTINAL DISORDERS	RENAL LOSS (continued)
Prolonged nasogastric suction	Metabolic acidosis
Malabsorption syndromes	Chronic renal disease
Extensive bowel resection	ENDOCRINE AND METABOLIC
Acute and chronic diarrhea	Diabetes mellitus
Intestinal and biliary fistulas	Phosphate depletion
RENAL LOSS	Primary hyperparathyroidism
Chronic parenteral fluid therapy	Hypoparathyroidism
Osmotic diuresis (glucose, urea)	Primary aldosteronism
Hypercalcemia	Hungry bone syndrome
Alcohol	
Drugs	
Diuretics (furosemide, ethacrynic acid)	
Aminoglycosides	
Cisplatin	
Cyclosporin	
Amphotericin B	

a recent report of a patient with AIDS who developed profound and symptomatic hypocalcemia and hypomagnesemia due to renal Mg wasting after receiving a course of parenteral pentamidine therapy for Pneumocystis carinii pneumonia(16).

Hypocalcemia generally occurs when serum Mg is substantially below normal. Normal serum Mg is 2-3 mg/dl or 1.5 to 2.5 meq/L. In the majority of cases in which hypomagnesemia is associated with hypocalcemia, serum Mg has been below 1.0 mg/dl or 0.8 meq/L. There are at least two separate causes for hypocalcemia, impaired secretion of PTH and reduced peripheral responsiveness to hormone action, both of which involve function of adenyl cyclase. Magnesium is necessary for cAMP formation as substrate (Mg ATP) as well as being an allosteric activator of adenylate cyclase.

PTH levels are usually undetectable or inappropriately low despite the extreme stimulus of severe hypocalcemia. Even when PTH levels are elevated, acute repletion of Mg leads to a further increase in PTH concentration. The overall data are interpreted to mean that PTH secretion is blunted in virtually all patients

with severe hypomagnesemia (Fig. 2)(14). The brisk response in hormone excretion following Mg repletion, sometimes demonstrable

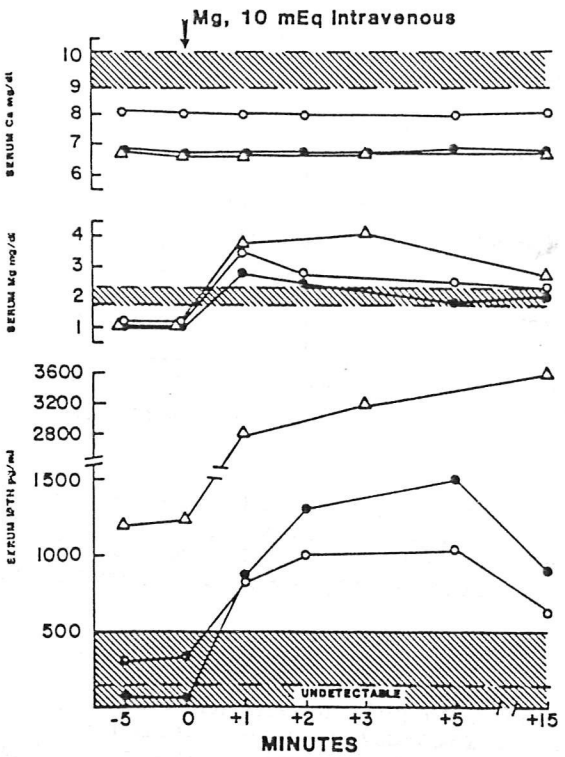


Fig. 2 The effect of an intravenous injection of 10 mEq magnesium on the serum concentration of calcium, magnesium, and iPTH in hypocalcemic magnesium deficient patients with undetectable ●——●, normal ○——○, or elevated △——△, levels of iPTH. Shaded area represents the range of normal for assay. The broken line for the iPTH assay represents the level of detectability. The magnesium injection resulted in a marked rise in PTH secretion within one minute in all three patients.

within minutes of giving a large parenteral dose of Mg, indicates that hormone biosynthesis is not impaired, only secretion.

Diminished peripheral responsiveness to administered PTH can be shown in some patients with severe hypomagnesemia in addition to defects in hormone secretion. This would account for the presence of normal or elevated PTH levels in some hypomagnesemic, hypocalcemic patients. Patients with hypocalcemia due to Mg deficiency have both renal and skeletal resistance to exogenously administered PTH as manifested by subnormal urinary cyclic AMP and phosphate excretion and diminished calcemic response (Fig 3)(17).

This renal and skeletal resistance to PTH is reversed following several days of magnesium therapy.

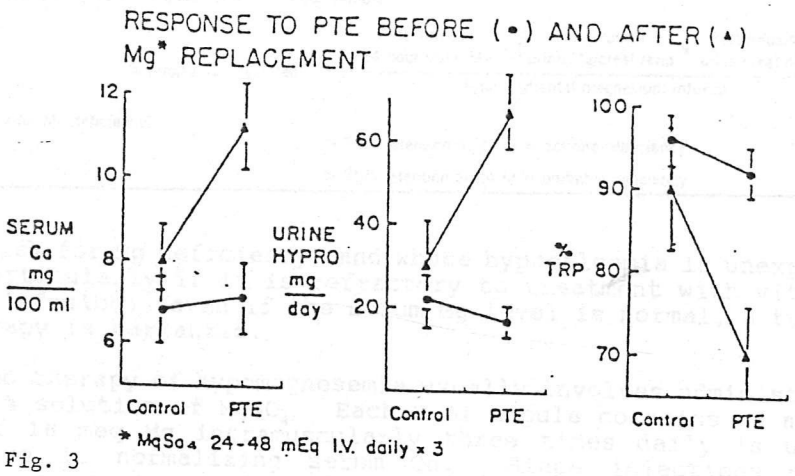


Fig. 3

Clinically, patients with hypocalcemia due to Mg deficiency are resistant not only to PTH, but also to parenteral Ca and to vitamin D therapy. The vitamin D resistance may be due to impaired metabolism of vitamin D, as serum concentrations of 1,25-$(OH)_2D$ are low(18).

Despite the functional hypoparathyroidism induced by hypomagnesemia, serum phosphate is not always elevated because Mg deficiency often occurs in the setting of nutritional deficiency, steatorrhea or alcoholism. When an appropriate background disorder is present and a patient is hypocalcemic, there should be a high index of suspicion for Mg deficiency. Generally, if Mg deficiency is the cause of hypocalcemia, the serum Mg will be quite low. However, occasional patients may have normal serum Mg concentrations(14). This reflects the fact that Mg is principally an intracellular cation with less than 1% of the body's Mg in the extracellular fluid. Mg deficiency in the presence of normal serum Mg may be demonstrated by whole body retention of infused Mg (Table 4)(15), as assessed by the amount of Mg appearing in the urine following infusion. Magnesium retention by the kidney is usually seen until Mg deficiency is repleted. Therefore, in a patient who

Table 4 Suggested protocol for clinical use of magnesium tolerance test

1) Collect baseline urine (spot or timed) for magnesium/creatinine ratio.
2) Infuse 0.2 mEq (2.4 mg) elemental magnesium per kg lean body weight in 50 ml 5% D/W over 4 hours.
3) Collect urine (starting with infusion) for magnesium and creatinine for 24 hours.
4) Calculate % magnesium retained using following formula:

$$\% \text{ Magnesium retained} = 1 - \frac{\text{Post-infusion 24 hour urine Mg} - \left(\text{Pre-infusion urine Mg/creat ratio} \times \text{Post-infusion urine creatinine}\right)}{\text{Total elemental magnesium infused}} \times 100$$

5) Criteria for Mg deficiency:

> 50% retention at 24 hr = definite deficiency

> 25% retention at 24 hr = probable deficiency

is at risk for Mg deficiency, and whose hypocalcemia is unexplained (and particularly if it is refractory to treatment with vitamin D and Ca infusion), even if the serum Mg level is normal, a trial of Mg therapy is warranted.

The therapy of hypomagnesemia usually involves administration of a 50% solution of $MgSO_4$. Each 2 ml ampule contains 8 meq. A dose of 16 meq Mg intramuscularly three times daily is usually effective in normalizing serum Ca. Since injections may be painful, a continuous iv infusion of 48 meq per 24 hours may be preferable. Therapy is usually continued for several days. Despite the fact that PTH secretion increases within minutes after beginning Mg administration, the serum Ca may not return to normal for 3-7 days.

PTH-Ineffectiveness - Example: Vitamin D Disturbances

PTH can be considered ineffective when the hormone's action to promote Ca absorption from the diet is interfered with because of a primary deficiency of vitamin D or because of an abnormality in vitamin D metabolism. Not only does vitamin D deficiency impair intestinal Ca absorption, but it also reduces the ability of PTH to mobilize Ca from bone. Typically, hypophosphatemia is more severe than hypocalcemia due to the increased secretion of PTH which while ineffective to elevate blood Ca, still promotes renal phosphate excretion. Varying degrees of bone disease featuring impaired mineralization and/or frank osteomalacia may be the consequences of inadequate vitamin D action.

Causes of osteomalacia include the following(19):

a) Reduced availability of vitamin D(20): low UV exposure, dietary deficiency, malabsorption.

b) Reduced availability of 25-(OH)D: liver disease(21,22), anticonvulsants(23-24), nephrotic syndrome.

c) Reduced availability of $1,25\text{-}(OH)_2D$: vitamin D dependency rickets type I(25), oncogenic osteomalacia(26).

d) Resistance to 1,25-$(OH)_2D$: vitamin D dependency rickets type II(27).

Measurement of PTH would confirm the presence of secondary hyperparathyroidism. Assays for 25-(OH)D and 1,25-$(OH)_2D$ would also be quite helpful. A low level of 25-(OH)D indicates vitamin D deficiency due to lack of sunlight, inadequate vitamin D intake, or intestinal malabsorption. It also may indicate deranged hepatic metabolism of vitamin D as occurs in primary biliary cirrhosis or with anticonvulsant therapy. A low level of 1,25-$(OH)_2D$ might be seen in severe vitamin D deficiency, in vitamin D-dependent rickets type I (hereditary absence of renal 25-(OH)D 1α-hydroxylase) or in oncogenic osteomalacia (tumor production of a substance impairing proximal tubule phosphate reabsorption and 1,25-$(OH)_2D$ synthesis). It should be noted that secondary hyperparathyroidism and a low level of 1,25-$(OH)_2D$ would also be encountered in chronic renal failure and PsHP, but these conditions are associated with hyperphosphatemia. Rarely, a hypocalcemic hypophosphatemic individual with secondary hyperparathyroidism will have increased 1,25-$(OH)_2D$ levels signifying tissue resistance to 1,25-$(OH)_2D$ (vitamin D dependent rickets type II).

Therapy depends on the underlying disorder. In patients who are merely vitamin D deficient, the cheapest therapy would be parent vitamin D. Patients with advanced liver disease or who are receiving anticonvulsants would do better with 25-(OH)D. For individuals with impaired renal 1α-hydroxylase function (chronic renal insufficiency, hypoparathyroidism, vitamin D dependent rickets type I or oncogenic osteomalacia), the fully activated metabolite 1,25-$(OH)_2D$ would make physiologic sense. For patients with vitamin D dependent rickets type II, who have a deficiency or abnormality in the 1,25-$(OH)_2D$ receptor, even high doses of 1,25-$(OH)_2D$ (30 to 60 mcg/day) have been largely unsuccessful . It has recently been reported that prolonged intravenous infusions of Ca may cure the rickets and correct the secondary hyperparathyroidism in these patients(28).

PTH-Overwhelmed - Example: "Bone Hunger"

Hypocalcemia following parathyroidectomy in patients with primary hyperparathyroidism is fairly common. In one recent series of nearly 200 consecutive patients with primary hyperparathyroidism operated on at the MGH, about 50 patients (25%) developed at least transient hypocalcemia (serum Ca <8.5 mg/dl)(29). In some instances, hypocalcemia may be due to functional or anatomic hypoparathyroidism, in which case serum phosphate should be high. In other cases, however, hypocalcemia may be due to mineralization of osteoid which was formed pre-operatively. This syndrome has been called "remineralization tetany" or the "hungry bones" syndrome by Albright(30). It has also been described following thyroid surgery for hyperthyroidism(31), which, like primary hyperparathyroidism also leads to accelerated bone turnover. Hypocalcemia is accompanied by hypophosphatemia and contrasts

therefore to the hypocalcemia of surgical hypoparathyroidism which is associated with hyperphosphatemia. In the recent MGH series, of the 25% of patients that developed hypocalcemic post-parathyroidectomy, half had serum P <3.0 mg/dl by post-op day 3 and were believed to have bone hunger, whereas the other half had serum P >4.5 mg/dl consistent with hypoparathyroidism (Fig.4)(29). Compared to patients with uncomplicated metabolic responses to parathyroid surgery, the patients with bone hunger were older by a mean of 10 years; they had higher preoperative serum levels of Ca, alkaline phosphatase, N-terminal PTH and BUN; and their resected parathyroid adenomata were larger(29). The mean duration of hospitalization averaged three days longer in the group with hungry bone disease.

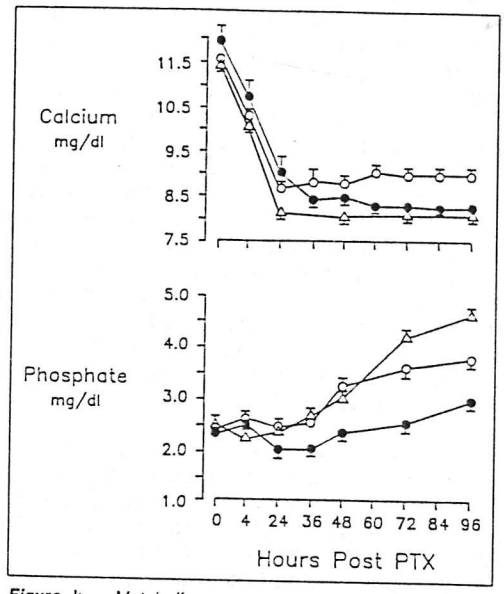


Figure 4 Metabolic response to parathyroidectomy (PTX). Calcium and phosphate levels after parathyroidectomy for 151 patients with uncomplicated courses (O-O), 25 patients in whom hungry bone syndrome developed (●-●), and 22 patients with hypoparathyroidism (Δ-Δ). For the patients with hungry bone disease, all calcium and phosphate values after 48 hours are significantly less than the corresponding value for the group with an uncomplicated course ($p < 0.05$). For the patients with hypoparathyroidism, all calcium values after 48 hours are significantly less ($p < 0.05$), and all phosphate values after 72 hours are significantly greater ($p < 0.05$) than the corresponding value for the group with an uncomplicated course.

Severe hypocalcemia after parathyroid surgery is less common now that osteitis fibrosa cystica is an infrequent manifestation of hyperparathyroidism. When osteitis fibrosa cystia is severe, however, bone mineral deficits can be large. After

parathyroidectomy, blood Ca levels can fall to the hypocalcemic range and remain depressed for days, weeks or even months, despite the best attempts at Ca replacement. As the following case report will illustrate, even with the addition of calcitriol and oral Ca supplementation, parenteral administration of huge amounts of elemental Ca (100 mg/hr) may be required for weeks. Initially, despite the tremendous infusion of Ca, urinary Ca excretion may remain near zero, attesting to the sponge-like action of the demineralized bone. Interestingly, it has been noted that the period of active bone remineralization may last for 2-6 months, corresponding to the life span of the activated osteoblasts(29).

"Bone Hunger" Case Study

An 80 year old BF had complaints of nausea and vomiting, poor appetite, weight loss and generalized bone pain, requiring her to use a walking stick. Thirty years earlier, she had total hysterectomy and bilateral oophorectomy for uterine fibroids, and was never given estrogen replacement. Eight years earlier, symptoms of dyspepsia lead to a diagnosis of hyperparathyroidism, but even though two enlarged parathyroid glands (600 mg) were identified and removed, the patient continued to have hypercalcemia in the 12 mg/dl range. Hand x-rays showed subperiosteal resorption and bone cysts and radial bone density was very low at .328 g/cm^2 (normal for age .500 g/cm^2). As shown in Table 5 re-evaluation at baseline confirmed persistent, severe primary hyperparathyroidism with biochemical evidence of significant bone involvement. Renal function was only modestly impaired with serum Cr 1.2, C_{Cr} 57 ml/min. Serum 25-(OH)D was reduced at 2 ng/ml (normal 7 to 42 ng/ml) and 1,25-$(OH)_2$D was increased at 58 pg/ml (normal 20-50 pg/ml). On 3/17/88, a large parathyroid carcinoma eroding into the right lobe of the thyroid, the recurrent laryngeal nerve and the esophagus was nearly totally resected. Within a few days of the resection serum PTH mid-region decreased from >10,000 pg/ml to 465 pg/ml (normal 100-400 pg/ml). Serum Ca declined to 6.7 mg/dl, phosphate was 1.3 mg/dl and the patient developed progressive paresthesias and carpo-pedal spasms. Despite institution of oral calcitriol 2 mcg/day and Ca citrate 400 mg·tid, for the first month, the patient required 20 amps of iv Ca gluconate daily to maintain serum Ca in the 7.0 mg/dl range. During this time, urinary Ca excretion was <10 mg/day. It took nearly 12 months of treatment with calderol 50 mg daily and effervescent Ca citrate 500 mg tid, for the bone hunger to finally resolve. By that time, the patient no longer had skeletal complaints and did not require the use of a cane, hand films showed healing of bone cysts and subperiosteal resorption, and bone density of the radius had increased from .328 to .403 g/cm (a gain of 23%).

Table 5. Resolution of Bone Hunger in Patient NG

Time (mos)	Serum Ca	Serum P	Serum PTH	Serum Alk Phos	24-hr Urine OHP	24-hr Urine Ca
Baseline	13.1	2.5	>10,000	2975	193	296
0.5	6.7	1.3	465	3000	---	<10
1	7.4	3.2	621	983	25	10
2	8.0	2.3	411	914	22	15
6	8.4	4.1	359	266	20	57
12	8.9	4.6	237	117	10	159
(Normal Values:	8.5-10.5	2.5-4.5	100-400	<130	<30	100-200)

PTH-Overwhelmed - Example: Rhabdomyolysis-induced Acute Renal Failure

The blood calcium phosphorus molar product, when exceeded, leads to spontaneous precipitation of calcium phosphate salts in soft tissues. The [Ca] x [P] product, when estimated from total serum Ca and phosphate concentrations (as mg/dl) normally is less than 60(32). Hyperphosphatemia sufficient to cause hypocalcemia usually has an abrupt onset, is severe in magnitude, and usually occurs in the setting of impaired renal function. A good example of this syndrome is rhabdomyolysis-induced acute renal failure, which may occur with trauma, or drug or alcohol abuse. The combination of an increased release of phosphate from muscle and an impaired ability to excrete phosphorus secondary to the renal failure causes moderate to severe hyperphosphatemia (serum P usually in excess of 6 mg/dl, typically in the 8-15 mg/dl range)(33). Calcium loss from the blood results in hypocalcemia of mild to moderate severity during the early oliguric phase. Of interest, moderate to severe hypercalcemia often occurs in the subsequent polyuric phase(32,33). There is debate as to the cause of this hypercalcemic phase. Some attribute the appearance of hypercalcemia during the diuretic phase to the rapid development of secondary hyperparathyroidism during the initial hypocalcemia(32,33). Others ascribe the hypercalcemia to redistribution of the widespread Ca deposits in the tissues back into the ECF after return of renal function and restoration of phosphate levels to normal(2). Our ward team recently debated these alternative pathogenetic mechanisms when we were presented with a patient who presented with severe rhabdomyolysis and acute renal failure, who was initially hypocalcemic, but predictably became hypercalcemic during the recovery phase. To settle the issue, we measured serum intact PTH with new IRMA assay during the hypercalcemic phase. The intact PTH was suppressed favoring the scenario of a rapid mobilization of Ca salts from the soft tissues as the cause of hypercalcemia.

During the hypocalcemic phase, treatment is directed toward lowering of blood phosphate by the administration of phosphate-binding antacids or dialysis, often needed for the management of renal failure. Although Ca replacement may be necessary if hypocalcemia is severe and symptomatic, calcium administration during the hyperphosphatemic period may increase extra-osseous cellular Ca deposition thereby aggravating ultimate tissue damage. Although the levels of $1,25\text{-}(OH)_2D$ may be low during the hyperphosphatemic phase(33) and may return to normal during the polyuric phase of recovery, mineral ion imbalance per se seems to be the principal pathophysiologic mechanism(2). During the hypercalcemic phase, specific treatment is often unnecessary beyond maintaining adequate hydration.

Hypoparathyroidism - Current Concepts

The diagnosis of hypoparathyroidism must be considered when hypocalcemia and hyperphosphatemia occur in the presence of normal serum creatinine and magnesium concentrations, and in the absence of a source of massive phosphate leakage into the circulation. Hypoparathyroidism is a bihormonal disease in which the abnormalities in serum chemistry are the sequelae of reduced PTH action and $1,25\text{-}(OH)_2D$ deficiency. Hypocalcemia is invariably found in hypoparathyroidism; it is the result of (1) reduced PTH-dependent osteoclastic resorption, (2) decreased osteocytic calcium transfer (rapid bone calcium mobilization) consequent to $1,25\text{-}(OH)_2D$ deficiency and reduced PTH action, (3) low renal tubular reabsorption of calcium from reduced PTH action, and (4) impaired intestinal calcium absorption from $1,25\text{-}(OH)_2D$ deficiency. Hyperphosphatemia results primarily from the impaired renal phosphate clearance consequent to reduced PTH action. The retained build-up of phosphate in the serum lowers the serum calcium by physiocochemical means and by further reducing synthesis of $1,25\text{-}(OH)_2D$.

Within recent years, the development of assays for PTH, $1,25\text{-}(OH)_2D$, urinary cyclic AMP, and components of the adenylate cyclase enzyme system has permitted the separation of hypoparathyroidism into several distinct types. The specific sites at which a defect could potentially lead to deficient PTH action is shown in Fig. 5 (modified from ref.5) and the resulting classification scheme for various forms of hypoparathyroidism is outlined in Table 6. A discussion of each of these forms of hypoparathyroidism will follow.

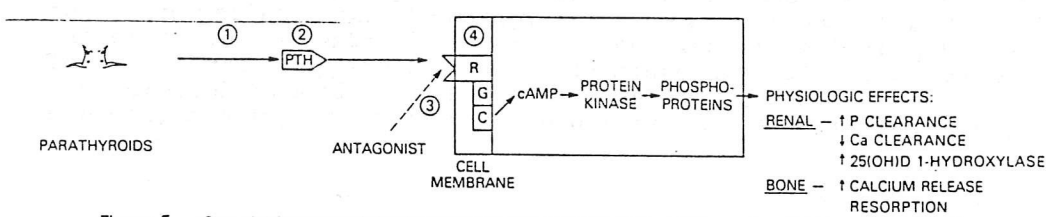


Figure 5 -Sites of defect potentially leading to deficient PTH action: (1) deficient PTH secretion; (2) biologically inactive PTH; (3) PTH antagonist; (4) target cell defects—these could involve the PTH receptor (R), the guanine nucleotide coupling protein (G), the catalytic unit (C) of adenylate cyclase, cAMP-dependent protein kinase, or the protein substrate(s) of the kinase.

Table 6. Classification of Hypoparathyroidism

PTH-deficient hypoparathyroidism
- Post-operative
- Idiopathic

PTH-ineffective hypoparathyroidism
- Biologically inactive PTH
- PTH antagonist

PTH-resistant (pseudo) hypoparathyroidism
- Type IA
- Type IB
- Type IC
- Type II

Pseudopseudohypoparathyroidism

PTH-Deficient Hypoparathyroidism (1,6,34)

This condition is characterized by a reduced or absent synthesis of PTH; the target tissues are responsive to the action of PTH. Thus, the serum concentration of PTH is low or undetectable and the basal urinary cyclic AMP level is low. When challenged by exogenous PTH, PTH-dependent adenylate cyclase in bone and kidney is stimulated, as shown by a marked increase in the renal excretion of cyclic AMP and phosphate. The circulating concentration of $1,25\text{-}(OH)_2D$ is low, accounting for the subnormal intestinal calcium absorption. During exogenous PTH challenge, there is a rapid rise in serum calcium ("calcemic response") attributed to the combined action of PTH and newly synthesized $1,25\text{-}(OH)_2D$.

Postoperative hypoparathyroidism

The most common cause of PTH-deficient hypoparathyroidism is the inadvertent removal of excessive parathyroid tissue during thyroid or parathyroid surgery. Although in the recent MGH series(29), about 12 percent of patients operated on for primary hyperparathyroidism developed transient hypoparathyroidism, the incidence of permanent hypoparathyroidism is actually less than 5 percent (and often only 1-2 percent). It is much more likely to occur in patients who have had total thyroidectomy for thyroid cancer or in patients who have had recurrent parathyroid surgery for parathyroid hyperplasia or a persistent parathyroid adenoma. The surgical procedure and disease, as well as the skill of the surgeon, are important factors in determining the potential risk.

Idiopathic hypoparathyroidism

This is a rare disorder characterized by absent or decreased secretion of PTH from hypoplastic parathyroid glands. An onset at infancy would suggest DiGeorge syndrome. The DiGeorge syndrome is due to developmental abnormalities in the third and fourth branchial pouches resulting in congenital absence of the parathyroids and thymus. In addition to hypoparathyroidism and cellular immune deficiency, infants with this syndrome may have facial and cardiac anomalies. It is more common for idiopathic hypoparathyroidism to occur in later childhood between 5 and 10 years of age or even much later in life. This more common form of the disease may be associated with other endocrine deficiency states such as hypoadrenalism, gonadal failure and diabetes as well as with moniliasis. In this setting, the hypoparathyroidism is presumed to be autoimmune in origin because of the autoimmune nature of the endocrinopathies. Isolated hypoparathyroidism may also occur at any stage of life and may also have an autoimmune basis, since antiparathyroid antibodies are occasionally found(35) and histologic examination of the affected glands may reveal infiltration with lymphocytes and plasma cells as well as atrophic and fibrotic changes(36). In patients with multiple endocrine deficiencies, there is frequently a sequence in the appearance of the disorders(34). The first clinical manifestation is often moniliasis, followed years later by hypoparathyroidism, and then at a later age, adrenal insufficiency. While the sequence may vary, moniliasis almost always precedes other manifestations. Moniliasis may affect the skin, mucosal surfaces of the mouth and vagina, as well as the nails. Previously, moniliasis was intractable, but more recently it has been controllable with ketoconazole. The combination of hypoparathyroidism, adrenal insufficiency and moniliasis is known as the HAM syndrome. Additional autoimmune features may include alopecia and vitiligo.

Miscellaneous causes of PTH deficiency

As noted earlier, hypomagnesemia may cause a functional hypoparathyroidism by impairing PTH secretion, but this is readily reversible by Mg replacement. Partial hypoparathyroidism has been observed in a small number of patients who have received extensive radiation to the neck and mediastinum. Infiltrative destruction of the parathyroid glands has been reported with hemochromatosis, thalassemia (from repeated transfusions), Wilson's disease and metastatic carcinoma.

PTH-Ineffective Hypoparathyroidism

PTH may be ineffective because of an alteration in PTH synthesis such that a biologically inactive hormone is produced, or because there is a circulating antagonist to the action of PTH. When the antagonist is removed then PTH regains its effectiveness.

Biologically inactive PTH

This very rare condition is characterized by synthesis of PTH that is biologically inactive; the target tissues are responsive to the action of exogenous PTH(37). Typically, a patient presents with hypocalcemia, hyperphosphatemia, and normal renal function, but increased serum PTH. Even though the PTH is biologically inactive, it is immunologically detectable. Infusion of exogenous PTH elicits normal cyclic AMP and phosphaturic responses.

Circulating antagonist to PTH

Several studies have reported an apparent dissociation between plasma levels of endogenous immunoreactive and bioactive PTH in patients with pseudohypoparathyroidism. Despite high circulating levels of immunoreactive PTH, the levels of bioactive PTH in many patients with pseudohypoparathyroidism type I have been found to be within the normal range when measured with the highly sensitive renal cytochemical bioassay(38). Furthermore, plasma from some of these patients has been shown to diminish the biological activity of exogenous PTH in the renal cytochemical bioassay system(39). Currently, the nature of this putative inhibitor or antagonist remains unknown. It may be an aberrant form of PTH (or another agent such as an antibody) capable of binding to the PTH receptor but incapable of activating adenylate cyclase. The infrequent observation that parathyroidectomy or prolonged hypercalcemia can remove or reduce significantly the level of inhibitory activity in the plasma of patients with pseudohypoparathyroidism has suggested that the parathyroid gland may be the source of the inhibitor(40). Moreover, analysis of circulating PTH immunoreactivity after fractionation of patient plasma by reversed-phase HPLC has disclosed the presence of aberrant forms of immunoreactive PTH in some of these patients(41). Whereas, it is conceivable that a PTH inhibitor may provide the pathophysiologic basis for PTH resistance for some patients with pseudohypoparathyroidism, it remains equally possible that a circulating antagonist of PTH action arises as a consequence of protracted secondary hyperparathyroidism that results from the primary biochemical defect(40). I have classified this type of hypoparathyroidism in the PTH-ineffective category because resistance to exogenous PTH may be reversible in these patients, and because the mechanism for PTH-ineffectiveness is different from the target organ cell membrane defects in classic pseudohypoparathyroidism.

PTH-Resistant Hypoparathyroidism (Pseudohypoparathyroidism)

The term pseudohypoparathyroidism (PsHP) describes a heterogeneous syndrome characterized by biochemical hypoparathyroidism (i.e., hypocalcemia and hyperphosphatemia), increased plasma levels of PTH, and peripheral unresponsiveness to the biological actions of PTH. In the initial description of PsHP, Fuller Albright and his associates focused on the failure of patients with this syndrome to show either a calcemic or a phosphaturic response to administered parathyroid extract(42).

These observations provided the basis for the hypothesis that biochemical hypoparathyroidism in PsHP was due not to a deficiency of PTH, but rather to resistance of the target organs, bone and kidney, to the biological actions of PTH. Accordingly, PsHP is today acknowledged as the first human disorder characterized by diminished responsiveness to a hormone by otherwise normal target organs.

Pathogenesis of PsHP

Characterization of the molecular basis for PsHP began with the observation that cyclic AMP mediates many of the actions of PTH on kidney and bone, and that administration of biologically active PTH to normal subjects leads to a significant increase in the urinary excretion of nephrogenous cyclic AMP(43). The PTH infusion test remains the most reliable test available for the diagnosis of PsHP, and enables distinction between several variants of the syndrome. Thus, patients with PsHP type I fail to show an appropriate increase in urinary excretion of both cyclic AMP and phosphate(44), while subjects with the less common type II show a normal increase in urinary cyclic AMP excretion but have an impaired phosphaturic response(45,46).

Adenylyl cyclase system(47-49)

Recent studies have shown that the adenylyl cyclase system consists of at least three types of proteins embedded in the plasma membrane (Fig. 6)(40).

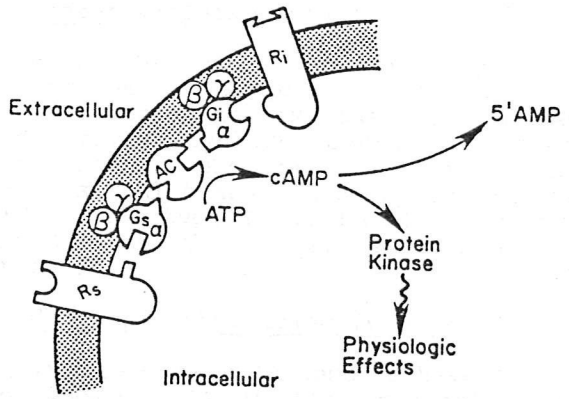


Fig. 6 . Schematic outline of the adenylyl cyclase system. R_s and R_i, stimulatory and inhibitory receptors; and G_s and G_i, the stimulatory and inhibitory guanine nucleotide-binding regulatory proteins. AC denotes the catalytic unit of adenylyl cyclase. The subunit structure of the G proteins and their interactions with the catalytic unit are described in the text.

Receptors for a large number of hormones and neurotransmitters face the extracellular space and interact with appropriate ligands and drugs. The interaction of such ligands with many types of

receptors results in stimulation of adenylyl cyclase activity. Stimulatory receptors (R_s) include those for β-adrenergic agonists, PTH, TSH, gonadotropins, glucagon and many others. Adenylyl cyclase activity is also under inhibitory control by such agents as somatostatin, α_2-adrenergic and muscarinic agonists and opioids. These ligands bind to specific inhibitory receptors (R_i). Receptors communicate with the actual catalyst of adenyl cyclase through their interaction with a pair of homologous guanine nucleotide-binding regulatory proteins (G), one of which (G_s) mediates stimulation of adenyl cyclase activity, while the other (Gi) is responsible for inhibition.

The G proteins that regulate activity of adenylyl cyclase are members of a family of guanine nucleotide-binding proteins that are composed of three subunits, α, β, and γ. The molecular mechanisms involved in the G protein-coupled regulation of adenylyl cyclase have been recently reviewed in detail by Dr. Gilman at the University Lecture Series(47). Binding of stimulatory hormones to R_s promotes interaction between R_s and G_s such that G_s exchanges GDP for GTP and dissociates, releasing an active $G_s\alpha$-GTP unit and a Gβγ dimer. $G_s\alpha$-GTP stimulates adenylyl cyclase activity and thereby increases synthesis of cyclic AMP. The intracellular accumulation of cyclic AMP produces a biochemical chain reaction that begins with activation of protein kinase A and phosphorylation of specific protein substrates, ultimately concluding with the appropriate physiologic response. Adenylyl cyclase is under "dual control". Hormonal inhibition of adenylyl cyclase activity is mediated through activation of Gi by inhibitory receptors (Ri).

Pseudohypoparathyroidism Type I

Patients with PsHP type I have markedly blunted nephrogenous cyclic AMP responses to exogenous PTH. This observation has suggested that PTH resistance is caused by a defect in the plasma membrane-bound adenylyl cyclase complex that produces cyclic AMP in renal tubule cells. By measuring various components of the hormone receptor-signal transduction system in the cell membranes of patients with PsHP type I, it has been possible to elucidate several distinct forms of PTH resistance: PsHP type IA, PsHP type IB and PsHP type IC.

Pseudohypoparathyroidism Type IA

Patients with PsHP type IA tend to have Albright's hereditary osteodystrophy (AHO). As in the original classic patients of Albright, this constellation of somatic characteristics includes round face, short stature, brachydactyly and ectopic calcification. They have reduced activity of the stimulatory G protein (G_s) (Figure 7)(50).

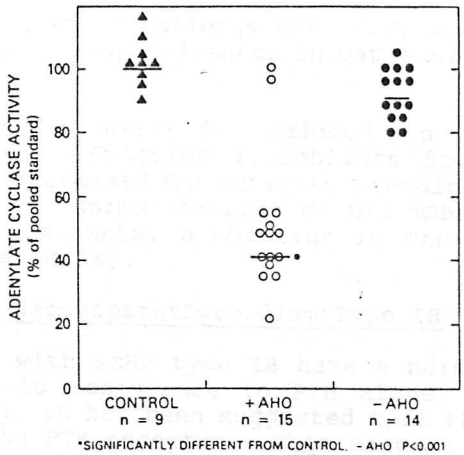


Figure 7. Erythrocyte membrane G-unit activity in control, positive AHO, and negative AHO subjects. G-unit activity was measured by adding solubilized human erythrocyte membranes containing G units to solubilized turkey erythrocyte membranes containing catalytic units; resultant adenylate cyclase activity is expressed as percentage of a pooled standard of normal human erythrocyte membranes. AHO = Albright's hereditary osteodystrophy.

As a consequence of this generalized G_s deficiency, patients are resistant not only to PTH, but also to other peptide hormones including thyroid-stimulating hormone (TSH), glucagon, and gonadotropins(51). Clinical hypothyroidism and gonadal dysfunction are quite common in these patients. Deficient G_s activity is presumed to limit cyclic AMP production and thereby cause resistance to multiple hormones in PsHP type IA.

In contrast to the well-documented resistance of patients with G_s-deficient PsHP type IA to the actions of PTH, TSH, glucagon, and gonadotropins, they are not resistant to vasopressin(52). Apparently, there is considerable variability in the extent to which G_s deficiency impairs hormonal responsiveness of different target tissues. One possible explanation for this variability is that the amount of cyclic AMP required to activate a given protein kinase and, in turn, generate a physiologic response may vary from tissue to tissue.

Since an abnormality in the activity of the adenylate cyclase inhibitory coupling protein (G_i) could influence hormone responsiveness, Downs et al(53) measured pertussis toxin-catalyzed(32) P-ADP ribosylation of the 40,000-dalton α-subunit of Gi (Giα) in erythrocyte membranes from patients with PsHP and normal subjects. There were no significant differences in the amounts of Giα in membranes from normal subjects, patients with PsHP who had low G_s associated with AHO and multiple hormone resistance, and patients with PsHP who had normal G_s. Abnormal Gi is not likely to cause

hormone resistance in patients with PsHP who have normal G_s or to influence hormone responsiveness in patients with PsHP who have low G_s.

The molecular basis for reduced $G_s\alpha$ activity has not been clearly defined. Cultured fibroblasts from most (but not all) patients with decreased $G_s\alpha$ activity contain reduced quantities of $G_s\alpha$ mRNA(54,55). Normal amounts of $Gi\alpha$ mRNA are present(54). At least in some patients, a mutation in the gene encoding $G_s\alpha$ has been demonstrated(56).

Pseudohypoparathyroidism Type IB

Patients with PsHP type IB have a normal appearance, normal G_s activity, and resistance to PTH alone. Since resistance is limited to PTH, it has been suggested that these patients may have a defect in the PTH receptor. This concept has been supported by the observation that skin fibroblasts from most subjects with PsHP type IB have selective resistance to PTH with respect to cyclic AMP response (Table 7)(57). Since the defect persisted in culture (after five passages), it was felt to be more consistent with an intrinsic defect in the PTH receptor than with a substance blocking the PTH receptor (such as abnormal PTH or receptor antibody).

Table 7 Selective PTH Resistance in PsHP Type IB

Subject No.	Age (yr)	Sex	Fibroblast cAMP (pmol/100 μg protein) Basal	PTH	PGE (10 μM)	Forskolin (1 μM)
PHP 1B						
1	37	F	1.54	4.99	140	40.1
2	26	F	0.43	2.26	113	43.8
3	14	M	1.17	3.71	86.2	48.7
4	23	F	1.49	4.51	196	180
5	25	F	0.54	4.54	93.2	78.5
6	48	M	0.63	4.03	55.3	32.4
7	58	F	1.40	3.98	203	72.4
Normal						
1	19	F	0.62	22.9	77.6	33.1
2	22	F	2.44	11.8	191	114
3	20	M	0.53	15.9	89.3	55.5
4	22	M	0.62	14.7	88.5	45.0

Pseudohypoparathyroidism Type IC

A 21-year-old man presented with classic AHO and resistance to multiple hormones including PTH, TSH, gonadotropins, and glucagon(58). In addition to PsHP, he had clinically significant hypothyroidism and hypogonadism. In order to account for his multiple hormone resistance, it was anticipated that his erythrocyte membranes would reveal a deficiency of G_s. Surprisingly, his erythrocyte membrane G_s activity was 120% of a pooled normal control (normal range, 80%-120%). The G_s activity in the patient's

skin fibroblast membranes was also normal. The G_i was measured by pertussis toxin-induced ADP-ribosylation and was also found to be normal(53). Despite the normal G_s level, the patient's fibroblasts showed a deficient cyclic AMP accumulation following stimulation by a variety of agonists including isoproterenol, prostaglandin E, and PTH. Receptor-G_s interaction was assessed in the fibroblast membranes and was found to be normal. Although G_s activity in the patient's fibroblasts was normal when extracted and reconstituted into other cell membranes (which lacked G_s but had normal catalytic units), fluoride-stimulated adenylate cyclase activity was reduced in the patient's own fibroblast membranes. These data suggested that if G_s was normal, as shown by the complementation experiments, then a lesion might exist within the patient's own adenylate cyclase catalytic subunit.

Catalytic unit activity was assayed by stimulating fibroblast membranes with Mn^{-2}, which has been shown to stimulate the catalytic unit directly via a metal ion binding site and to uncouple the catalytic unit from tonic inhibition by Gi. Compared to normal fibroblast lines, there was a marked reduction (49% of normal) in Mn-stimulated adenylate cyclase catalytic unit activity in the patient's fibroblast membranes. Treatment with both Mn^{-2} and forskolin provoke maximal activity of the catalytic unit, which is not dependent on G^s. The stimulation of adenylate cyclase activity in the patient's membranes by forskolin plus Mn^{-2} was only 54% that found in normal fibroblast membranes. Therefore, this patient appears to represent a new form of PsHP with normal G_s but multiple hormone resistance explainable by a defect in the catalytic enzyme(58).

Pseudohypoparathyroidism Type II

There is evidence that in some forms of PsHP, PTH-resistance may ensue from biochemical derangements distal to the generation of cyclic AMP (e.g., abnormal protein kinase or phosphate transport protein). In 1973, Drezner et al reported studies performed on a 22-month-old male with symptomatic hypocalcemia and an elevated PTH level. The infant had no phosphaturic response to a single intravenous infusion of PTH, nor did he demonstrate a calcemic or hypophosphatemic response to parathyroid extract administered intramuscularly for 4 days. Since he was small and mentally retarded, the diagnosis of PsHP seemed likely. However, an elevated basal urinary cyclic AMP excretion and a normal increase in urinary cyclic AMP after intravenous administration of PTH appeared to exclude the diagnosis of PsHP type I in spite of the undeniable evidence of end-organ resistance to the phosphaturic action of PTH. The dilemma was resolved by postulating normal PTH-receptor-adenylate cyclase activity in the renal cell membrane and attributing the defect to an inability of intracellular cyclic AMP to initiate the hormone-specific chain of events at the kidney that would normally result in phosphaturia. Drezner termed the disorder "PsHP type II."

Since the initial description, at least 19 additiional patients with PsHP type II have been recognized. When measured, G_s has been found to be normal. AHO is absent, age of onset has varied from 22 months to 70 years, and there is no evidence of familial transmission. PsHP type II may be an acquired defect.

Pseudopseudohypoparathyroidism

There remains a fair amount of confusion in the literature regarding the use of this unfortunate term. The term was coined by Fuller Albright to describe a patient who had all the features of AHO and yet had normal serum Ca and P, and presumably lacked any resistance to PTH(59). The confusion results partly from the fact that several clinical syndromes, such as familial brachydactyly, multiple epiphyseal dysplasia, Turner's syndrome, and even idiopathic hypoparathyroidism, may have the skeletal abnormalities of AHO without any evidence of resistance to PTH. It would be clearer to refer to such patients as just having AHO.

However, there are many reports in the literature of patients with the skeletal abnormalities of PsHP who are frequently relatives of patients with PsHP, and who may undergo transitions from hypocalcemia to normocalcemia or vice versa(60). These patients also have been classified as having pseudopseudohypoparathyroidism, but they should probably be considered as having an incompletely expressed form of the disease entity, PsHP, the hallmark of which is some degree of renal resistance to PTH. For example, when the renal responses to 250 U PTH were studied in eight normocalcemic first-order relatives of patients with PsHP, these people had significantly impaired cAMP, potassium, and bicarbonaturic responses to PTH (Fig.8)(6). These patients, who also often have elevated serum PTH levels, should more properly be considered to be in a normocalcemic phase of the PTH-resistant condition PsHP(61). Recently, they have even been shown to have deficient G_s (Fig.9)(62).

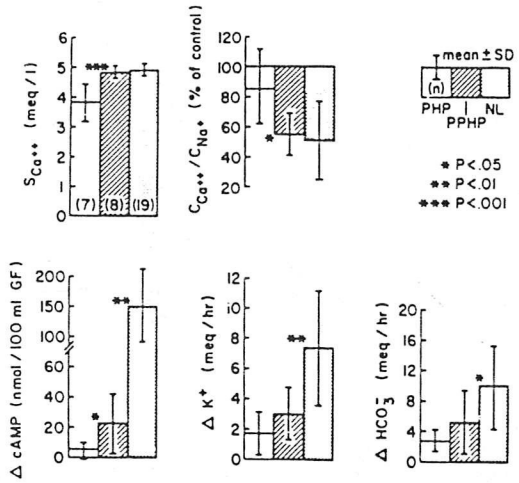


Figure 8. Serum calcium levels and responses to 250-U PTH in patients with pseudohypoparathyroidism (PHP), pseudopseudohypoparathyroidism (PPHP), and normal subjects (NL). The percent decreases in $C_{Ca^{++}}/C_{Na^+}$ in patients with PHP is based on data from four patients who had measurable urinary calcium.

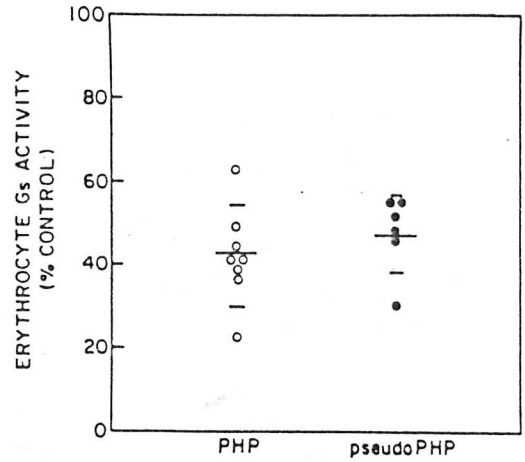


Figure 9. Erythrocyte membrane G_s activity in family members with PHP or pseudoPHP. G_s activity was measured by adding solubilized patient erythrocyte membranes containing G_s to G_s-deficient membranes prepared from cyc-S49 cells; the resultant adenylate cyclase activity is expressed as a percentage of pooled normal human erythrocyte membranes.

Summary

The pathogenetic mechanisms of the various forms of hypoparathyroidism are summarized in Table 8(61).

Table 8. Pathogenetic Mechanisms of Hypoparathyroidism

Type	Appearance	S_{Ca}	S_{PO_4}	PTH	Response to PTH: UcAMP	Response to PTH: U_{PO_4}	Defect
PTH-deficient	N	↓	↑	↓	↑	↑	↓PTH
PTH-ineffective	N	↓	↑	↑	↑	↑	Biologically inactive PTH.
PTH-resistant:							
PsHP IA	AHO	↓ or N	↑	↑	—	—	↓ G_s; multiple hormone resistance.
PsHP IB	N	↓ or N	↑	↑	—	—	Abnormal PTH receptor; selective PTH resistance.
PsHP IC	AHO	↓ or N	↑	↑	—	—	Defective adenylate cyclase catalytic subunit; multiple hormone resistance.
PsPH II	N	↓	↑	↑	↑	—	Defective protein kinase or phosphate transport protein.
Pseudo-PsHP	AHO	N	N	N	↑	↑	Skeletal abnormality. No PTH resistance.

N = normal; AHO = Albright's hereditary osteodystrophy; — = no change; G_s = stimulatory guanine nucleotide-binding protein; ↑ = increase; ↓ = decrease.

Therapeutic Approach to Hypocalcemia(2,3,5,34,40)

Acute

The treatment for acute symptomatic hypocalcemia (tetany) of any cause is intravenous calcium infusion. Generally, 1-2 ampules of 10% calcium gluconate containing approximately 90 mg of elemental Ca/ampule is infused over 5 to 10 minutes. If additional intravenous Ca is needed, continuous administration of 10% calcium gluconate (one to two 10 ml ampules in 500 ml of fluid) every 6 hours is preferable to more rapid iv push. The hypomagnesemic patient who is also hypocalcemic will require treatment of the hypomagnesemia before the hypocalcemia can be expected to resolve.

Chronic

With respect to long-term management, resolution of hypocalcemia depends on treating the underlying cause. When this is not possible, chronic therapy with vitamin D and calcium may be required. The management of hypoparathyroidism or PsHP, chronic renal failure and hereditary defects in vitamin D metabolism all feature the use of vitamin D or vitamin D metabolites and Ca supplementation. A typical regimen might entail the use of 1,25-$(OH)_2D$ (calcitriol; Rocaltrol) in doses of 0.5 to 1.5 mcg daily plus 0.8 to 1.5 g of elemental Ca daily. Calcitriol is a rational form of vitamin D because it overcomes the block in renal 1,25-$(OH)_2D$ production in the aforementioned disorders. Moreover, calcitriol has a rapid onset of action (1-2 days) and a short biologic half-life (1-2 days). The vitamin D parent compound, although considerably less expensive, has to be given in very high doses to overcome the block in renal 1α-hydroxylation (50,000 to 150,000 U/day). Vitamin D may take 4-8 weeks to produce normocalcemia and may be stored in body tissues for months. Since with high dose vitamin D therapy, intoxication is likely to occur at some point, the prolonged half-life is a distinct disadvantage.

Popular calcium salts include calcium carbonate (250 mg or 500 mg elemental Ca) and calcium citrate (200 mg elemental Ca). Numerous studies have shown superior absorption of Ca from the citrate salt, particularly if there is reduced stomach acid. In equivalent doses, calcium citrate results in greater urinary citrate than calcium carbonate, which reduces stone risk. The risk of kidney stones is an important concern in patients with PTH-deficient hypoparathyroidism and may be further minimized by raising serum Ca only to low normal levels, encouraging adequate hydration, and adding a thiazide diuretic if urinary Ca is consistnetly greater than 300 mg/day(63).

The doses of vitamin D and calcium required for the management of PsHP are usually lower than those required for hypoparathyroidism(64), reflecting incomplete resistance to the action of PTH in PsHP(65,66). Indeed, because of enhanced PTH-mediated renal Ca reabsorption(65), patients with PsHP are not at risk for kidney

stones and do not require addition of thiazides. However, because they depend partly on PTH-mediated bone resorption to maintain blood calcium levels, they are subject to low bone density or even osteitis fibrosa, and may become hypocalcemic if anti-resorptive agents such as estrogens (birth control pills) are taken(66,67).

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