

A Multidisciplinary Perspective on the Management of Hypoparathyroidism

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Program Goals

- Evaluate current and emerging treatment options for patients with hypoparathyroidism
- Apply the latest advances in the treatment of hypoparathyroidism to clinical practice
- Outline a multidisciplinary treatment plan for patients with hypoparathyroidism

Hypoparathyroidism: Introduction

- Disorder characterized by hypocalcemia and low or absent parathyroid hormone and abnormal bone remodeling
- Etiology
 - 75% postsurgical
 - 25% medical
 - Autoimmune disease
 - Genetic diseases
 - Infiltration of the parathyroid glands
 - Radiation
 - Hypomagnesemia (the only reversible cause)
- Classified as an orphan disease

Hypoparathyroidism: Complications

Long-term complications of hypoparathyroidism include^a

- Extraskeletal calcifications
 - Cataracts
 - Calcification of the basal ganglia
- Renal complications
 - Hypercalciuria
 - Nephrocalcinosis or kidney stones
 - Renal failure
- Brain fog and neurocognitive complaints
- Reduced quality of life
- Low skeletal metabolism
- Increased incidence of psychiatric disorders and infections^b

Patient Case Presentation

A 47-year-old woman with papillary thyroid carcinoma with nodal metastases undergoes a total thyroidectomy with central neck dissection

Patient Case: Post-Op Care

Postoperative management (can vary at different institutions)

- Check (normal levels: 10-55 pg/mL)
- Suggested algorithm depending on PTH level:
 - >20 pg/mL: no further action needed
 - >10 pg/mL and <20 pg/mL: check ionized calcium level in the PM and repeat in AM
 - If calcium low or patient exhibits symptoms begin calcium treatment
 - <10 pg/mL: treat more aggressively with calcium and check ionized calcium level in PM and AM

Patient Case: Follow-Up

- Patient goes home after surgery on calcium replacement treatment
- At follow-up appointment
 - Laboratory assessment: PTH, Ca, Mg, phosphate
- If patient's parathyroid function has not recovered patient continues calcium treatment and returns in 12 weeks
- If parathyroid function is not recovered refer to endocrinologist

Postsurgical Hypoparathyroidism

- 20%-30% of patients experience transient hypoparathyroidism after total thyroidectomy (<3-6 months)
- Only 1%-3% have persistent or permanent hypoparathyroidism
- These numbers increase substantially with re-operative surgery

Hypoparathyroidism: Symptoms

Due to hypocalcemia and neuromuscular irritability

- Muscle cramps
- Paresthesias
- Chvostek's or Trousseau's sign
- Heart arrhythmias
- Laryngospasm
- Seizures

Goals of Treatment

Ameliorate symptoms of hypoparathyroidism

Maintain serum calcium within the low-normal range

Maintain serum phosphorus within the high normal range

Avoid hypercalciuria

Avoid an elevated calcium-phosphate product ($55 \text{ mg}^2/\text{dL}^2$ or $4.4 \text{ mmol}^2/\text{L}^2$)

Conventional Therapy for Hypoparathyroidism

Calcium supplementation

- Calcium carbonate
- Calcium citrate

Active vitamin D analogues

- Calcitriol
- Alphacalcidol

Parent vitamin D

- Longer half-life than calcitriol

Thiazide diuretics

- Can reduce urinary calcium excretion

Potential Advantages of Parathyroid Hormone

- A reduction in the amount of calcium and vitamin D requirements
- Reduction in urinary calcium
- Improvement in quality of life
- Reduction in ectopic soft tissue calcification
- Improvement in abnormal bone dynamics

REPLACE Trial Findings

- Randomized, double-blind study assessed safety and efficacy of daily PTH (1-84) vs placebo
- Results:
 - Changes in supplementation requirements
 - 52% decrease in calcium
 - 78% decrease in vitamin D
 - Serum calcium levels were maintained even with these decreased requirements
 - Results for PTH (1-84) group at week 24
 - Serum phosphate levels decreased by 0.05 mmol/L ($P = .00098$)
 - Mean calcium-phosphate product decreased from 3.2 to 2.8 mmol²/L² ($P < .0001$)
 - Urinary calcium findings: no difference between drug and placebo groups

Safety of Parathyroid Hormone

Hypercalcemia

- No episodes in patients taking PTH (1-34) for 3 years^a
- 11 episodes occurred in 8 patients over 4 years of PTH (1-84) treatment^b

Osteosarcoma

- Increased incidence in rats given high doses for long periods of time^c
- No increased incidence in PTH (1-34) and PTH (1-84) in humans^{d,e}
- Black box warning for PTH (1-84)

a. Winer KK, et al. *J Clin Endocrinol Metab.* 2008;93:3389-3395^[16]; b. Cusano NE, et al. *J Clin Endocrinol Metab.* 2013;98:137-144^[7]; c. Watanabe A, et al. *J Toxicol Sci.* 2012;37:617-629^[12]; d. Andrews EB, et al. *J Bone Miner Res.* 2012;27:2429-2437^[13]; e. Capriani C, et al. *J Bone Miner Res.* 2012;27:2419-2428.^[14]

PTH (1-84)

- PTH (1-84) has been approved for the treatment of patients with hypoparathyroidism whose disease cannot be controlled with calcium and vitamin D
- Close monitoring and readjustment of calcium and active vitamin D supplementation is necessary

PTH (1-34) Teriparatide*

- Lowers calcium and active vitamin D requirements^a
- Improvement in bone remodeling^b
- Pump study of PTH (1-34) in adults showed a 59% reduction in urinary calcium^c

	PTH (1-34)	PTH (1-84)
Structure	First 34 amino acids of intact PTH	Same as intact PTH
Half-life	Short	Longer
Dosing	Multiple doses per day	Once daily
Method of administration	Subcutaneous injection	Subcutaneous injection

*This agent is currently not approved by the US FDA for use in hypoparathyroidism

a. Winer KK, et al. *J Clin Endocrinol Metab.* 2003;88:4214-4220^[16]; b. Gafni RI, et al. *J Bone Miner Res.* 2012;27:1811-1820^[17]; c. Winer KK, et al. *J Clin Endocrinol Metab.* 2012;97:391-399.^[18]

Role of Primary Care Physicians

- PCPs play an important role in managing and following up patients
- Specific treatment choices are important to understand
- Appreciate difficulty of compliance with numerous medications and ensure treatment adherence
- Hypoparathyroidism is a lifelong disease that will require continuous collaboration between endocrinologist and PCP

PARADOX Study

The Patients' Attitudes and Responses About Hypoparathyroidism Toleration Explored (PARADOX) study

- Key findings (no control group):
 - 56% felt "unprepared" to manage disease at diagnosis
 - 75% concerned about long-term complications of treatment
 - 72% experienced more than 10 symptoms in the previous year
 - Symptoms experienced for mean 13 hours per day
 - 79% of patients had hospital stays or ED visits in the last year

Patient Care Road Map

- Importance of monitoring serum calcium, serum phosphorus, urinary calcium levels
- Subspecialists and primary care clinicians should communicate and guide each other regarding patient care to optimize results
 - Example: choosing calcium supplementation based on patient preference, GI issues, and medication history

Parathyroid Transplants

- Parathyroid autotransplantation can preserve parathyroid function in patients who have hyperparathyroidism
- Parathyroid allograft is rare
- Procedure
 - Involves taking parathyroid tissue and placing it into the brachioradialis in the forearm
 - Parathyroid tissue can grow their blood supply centripetally and sustain itself without a vascular pedicle

Closing Comments

Coordination of care, timely diagnosis, referral, and continuous management are important to:

- Optimize the results of treatment
- Reduce disease morbidities
- Improve patients' quality of life

Recently approved parathyroid hormone formulation PTH (1-84) can offer the possibility of reducing the need for large doses of calcium and vitamin D supplementation^a

Abbreviations

ARB = angiotensin receptor blocker

Ca = calcium

ED = emergency department

FDA = US Food and Drug Administration

Mg = magnesium

PCP = primary care physician

PARADOX = Patients' Attitudes and Responses About Hypoparathyroidism Toleration
Explored study

PTH = parathyroid hormone

REPLACE = Efficacy and safety of recombinant human parathyroid hormone (1-84) in
hypoparathyroidism trial

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