Parathyroid and Rare Skeletal Disorders: Their Pathogenesis and Clinical Presentations

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Objectives

• Describe the characteristics and differential diagnosis of parathyroid and rare skeletal disorders
• Recognize laboratory and imaging techniques useful in the diagnosis of these conditions
• Summarize medical and surgical management options for these disorders

Primary Hyperparathyroidism

Mechanism of Hypercalcemia in Primary Hyperparathyroidism

Pathophysiology of Primary Hyperparathyroidism

• Hypercalcemia due primarily to increased skeletal resorption, increased 1,25-dihydroxyvitamin D and intestinal absorption, and decreased renal excretion of calcium
• Skeletal resorption increases primarily due to increased PTH, but comorbidities may contribute to hypercalcemia by other mechanisms
• Intestinal absorption increases due to increased 1,25-dihydroxyvitamin D
• Hypercalcemia occurs because renal clearance fails to keep up with filtered calcium load
Pathophysiology of Primary Hyperparathyroidism

- **Adenomas:**
  - Loss of normal sensitivity to circulating calcium
  - Change in “set point” for calcium
- **Hyperplasia:**
  - Normal set point for calcium
  - Increased number of secreting parathyroid cells

Differential Diagnosis of Primary Hyperparathyroidism

- Parathyroid adenoma or lipoadenoma
- Parathyroid hyperplasia
- Parathyroid carcinoma
- Neck or mediastinal parathyroid cyst
- Ectopic PTH secretion
  - Small cell lung or ovarian cancer
  - Squamous cell lung cancer
  - Ovarian adenocarcinoma
  - Thymoma
  - Papillary thyroid carcinoma
  - Hepatocellular carcinoma
  - Undifferentiated neuroendocrine tumor

Spectrum of Primary Hyperparathyroidism

- Sporadic Primary Hyperparathyroidism
  - Symptomatic
  - Asymptomatic
  - Acute
  - Neonatal
  - Normocalcemic
- Familial Primary Hyperparathyroidism
  - MEN I Syndrome (Wermer Syndrome)
  - MEN IIA Syndrome (Sipple Syndrome)
  - Hyperparathyroidism-Jaw Tumor Syndrome
  - Familial Isolated Primary Hyperparathyroidism

Diagnosis of Primary Hyperparathyroidism

- Biochemical Parameters:
  - High-normal to increased serum calcium
  - Low-normal to decreased serum phosphate
  - Inappropriately normal or increased intact parathyroid hormone
  - Increased total alkaline phosphatase
  - Increased markers of bone turnover
  - Serum bone specific alkaline phosphatase
  - Serum CTx-telopeptide
  - Increased urinary calcium and calcium to creatinine clearance ratio (>0.01)
  - Increased serum 1,25-dihydroxyvitamin D
  - Increased serum chloride and decreased serum bicarbonate

Primary Hyperparathyroidism

- Most common cause of outpatient hypercalcemia
- Third most common endocrine disorder
- Incidence in US, UK, and Sweden currently estimated at 27-30/100,000 person-years
- Prevalence is 2-3:1,000 women and 1:1,000 men
- Detection significantly increased by introduction of autoanalyzer in July 1974
- Diagnosed at all ages: most frequently in 6th decade
  - Female: male ratio of 3:1
  - Most frequently found in postmenopausal women

Incidence of PHPT by Racial Group

- Kaiser-Permanente Southern California insurance database has 3.5 million enrollees
- All patients with at least one SCa >10.5 mg/dL between 1995-2010 included, with 2° and 3° HPT excluded
- 15,234 identified with high serum calcium, and 13,277 (87%) with PHPT
- Highest incidence in blacks and whites
Incidence of Classic PHPT in Women by Racial Group

Incidence of Classic PHPT in Men by Racial Group

Etiology of Primary Hyperparathyroidism

- Precipitating Cause: unknown in most cases
  - External neck radiation in occasional cases
  - Genetic abnormalities in adenomas, hyperplasia, and carcinomas
    - CCND1/PRAD-1 translocation and oncogene action in 8% of adenomas, CCND1 overexpression in 20-40% of adenomas and 31% of hyperplastic glands
    - Somatic loss of one allele of chromosome 11 MEN I tumor suppressor gene in 25-40% of adenomas, with 50% having inactivating mutation of other allele
    - SDHAF2 (SDH5) mutations
    - Rare inactivating mutations in CASR gene
    - Promoter methylation of APC and RASSF1A tumor suppressor genes
    - Aberrant Wnt/β-catenin signaling
    - Loss of heterozygosity on 1p, 3p, 6q, 11p, 13q, 15q
    - HRPT2 mutations in parathyroid carcinoma

Complications of Primary Hyperparathyroidism

- Skeletal: <5% of cases in 1970-2000
  - Osteitis fibrosa cystica
  - Brown tumors and bone cysts
  - Salt-and-pepper skull
  - Subperiosteal resorption of phalanges
  - Distal resorption of clavicles
  - Loss of lamina densa around teeth

Primary Hyperparathyroidism: Increased Skeletal Uptake on Bone Scan

Complications of Primary Hyperparathyroidism

- Renal: 15-20% of cases
  - Nephrolithiasis
  - Nephrocalcinosis
  - Renal insufficiency or failure
  - Hypercalcemia in up to 30% of patients
- Neuropsychiatric: Common
  - Fatigue, muscle weakness, myalgias, arthralgias
- Cardiovascular: Mild
  - Hypertension, valvular calcification, diastolic dysfunction
- Gastrointestinal: Rare
  - Peptic ulcer disease
  - Pancreatitis
Medical Management of Primary Hyperparathyroidism

• Oral hydration, and avoid thiazide diuretics
• Calcium intake of 800-1,000 mg/day
• ERT or raloxifene in postmenopausal women
• Bisphosphonates
• Calcimimetics: Cinacalcet (Sensipar)
• Non-calcemic vitamin D analogues: Paricalcitol (Zemplar)
• Calcitomin, plicamycin, or gallium nitrate
• Hemodialysis with low- or zero-calcium dialysate rarely used, except for parathyroid crisis

Cinacalcet Reduces Hypercalcemia Across Spectrum of Primary Hyperparathyroidism

• Study to evaluate the efficacy of cinacalcet in reducing serum Ca in patients with PHPT across a wide spectrum of disease severity
• Study was pooled analysis of 3 multicenter clinical trials of cinacalcet in PHPT
• Patients grouped into three disease categories for analysis based on the following: 1) history of failed parathyroidectomy (n = 29), 2) meeting one or more criteria for parathyroidectomy but without prior surgery (n = 37), and 3) mild asymptomatic PHPT without meeting criteria for either above category (n = 15)
• Patients were treated with cinacalcet for up to 4.5 years
• Extent of cinacalcet-induced serum Ca reduction, proportion of patients achieving normal serum Ca (≤10.3 mg/dl), reduction in serum PTH, and increase in serum phosphate similar across all three categories
• Except for decreased aBMD at the total femur in group 2 at 1 yr, no significant changes in aBMD occurred
• Efficacy of cinacalcet maintained for up to 4.5 yr follow-up
• AEs mild and similar across the 3 categories
• Concluded that cinacalcet is equally effective in the medical management of PHPT patients across a broad spectrum of disease severity, and that cinacalcet is well tolerated

Surgical Management of Primary Hyperparathyroidism

• 2013 Fourth International Workshop Indications for Surgery:
  – Symptomatic patients
  – Patients less than age 50 yrs
  – Serum calcium >1.0 mg/dL (0.25 mmol/L) above upper limit of normal range, acutely or chronically
  – Complications:
    • Osteitis fibrosa cystica or osteoporosis (T-score <-2.5)
    • Calcium-containing kidney stones, or creatinine clearance >30% less than age- and gender-matched controls
    • Neuropsychiatric imbalances

Surgical Management of Primary Hyperparathyroidism

• 492 elective parathyroidectomies for primary hyperparathyroidism at single center from 2005-2007
• 96% were cured
• Sestamibi scans: 91% positive, and 82% true positive
• Neck ultrasounds: 51% positive with negative Sestamibi scan, 43% true positive
• Those with positive Sestamibi scans had higher rate of single gland disease and cure, no difference in rate of ectopic glands, and lower rates of double adenoma and asymmetric hyperplasia, compared to those with negative scans
• Concluded that neck ultrasound is indicated for localization in patients with negative Sestamibi scans
4D-CT Scan as Initial Imaging for Primary Hyperparathyroidism

- 87 consecutive patients underwent initial parathyroidectomy after imaging by 4D-CT scans, Sestamibi scans, and ultrasound.
- 84% had neck ultrasound, 60% Sestamibi scan, and 38% 4D-CT scan.
- 4D-CT scan had localization sensitivity for correct neck quadrant of 82.7%, Sestamibi scan of 40%, and neck ultrasound of 40%.
- 4D-CT scan had localization sensitivity for neck lateralization of 94%, Sestamibi scan of 71%, and neck ultrasound of 62%.
- 4D-CT scan recognized multi-gland disease in 86% of 7 patients where this was present, whereas Sestamibi scan and neck ultrasound failed to detect this in all cases.
- Concluded that 4D-CT scan provided greater sensitivity for localization of tumor in primary hyperparathyroidism with first operation than either Sestamibi scan or neck ultrasound.

BMD Improves After Surgery in Postmenopausal Women with Primary Hyperparathyroidism

- BMD response to parathyroidectomy is heterogeneous and difficult to predict.
- Longitudinal prospective cohort study of 103 postmenopausal women with osteopenia or osteoporosis at the femoral neck site successfully operated on for PHPT.
- BMD and metabolic variables recorded before and 1 year after surgery.
- After surgery, 1.3% increase in median BMD at femoral neck (0.615 versus 0.623 g/cm²; P = 0.001), with 0.4% increase at total hip, and 2.3% increase at lumbar spine.
- Analysis of individual responses showed that 45 of 97 patients (46%) showed a significant BMD increase of at least 3.7% at the femoral neck compared to baseline surgery, and that 52 had a decreased (n = 15) or unchanged (n = 37) femoral neck BMD.
- Concluded that almost half the postmenopausal women with PHPT and low BMD had significant BMD response one year after parathyroidectomy, and that BMD response after surgery is related to severity of PHPT, age, and renal function.

Neurocognitive Symptoms Improve After Surgery for Primary Hyperparathyroidism

- 212 subjects with primary hyperparathyroidism of mean age 50 years evaluated for neurocognitive symptoms before and after parathyroidectomy for primary hyperparathyroidism.
- 78% underwent minimally invasive parathyroidectomy, with 99% cured.
- Neurocognitive assessment before and after surgery with multiple instruments.
- Greatest improvement after surgery was seen in depressive and anxiety symptoms, and visuospatial and verbal memory.
- Decrease in PTH level correlated best with improvement in state anxiety and visuospatial working memory.

PHPT: Summary and Conclusions

- Remains most common cause of outpatient hypercalcemia.
- PHPT in U.S. and Europe is most commonly asymptomatic, but may be symptomatic.
- PHPT may develop while taking thiazides or lithium, but cannot be distinguished biochemically from effect of these medications.
- Parathyroid Sestamibi scan detects about 90% of primary tumors, and parathyroid ultrasound about 70%, but 4D-CT scan may be helpful if other imaging is negative.
- Surgical criteria for primary hyperparathyroidism refined by 2013 Fourth International Workshop.
- Medical management options for PHPT increasing, but still relatively limited.
Trousseau’s Sign

Cardiac Manifestations: Long QT

Abnormal Bone Microarchitecture in Hypoparathyroidism

Bone Turnover Decreased and BMD Increased


Other Manifestations of Hypoparathyroidism

Dental enamel hypoplasia
Short, blunted roots (premolars)
Delayed eruption of eruption
Hypoplastic → prone to caries

Cataract

Basal ganglia calcifications

Differential Diagnosis of Hypoparathyroidism

- Post-surgical hypoparathyroidism
- Autoimmune hypoparathyroidism
- Iron overload due to thalassemia or hemochromatosis
- Copper overload due to Wilson’s Disease
- Metastatic disease to parathyroid glands
- Radioactive iodine therapy
- Magnesium deficiency or excess
- Genetic causes

Calcium 7.3 mg/dL
Calcium 9.2 mg/dL
• Anterior neck surgery is most common acquired cause of acute or chronic hypoparathyroidism
  - Post-surgical hypoparathyroidism usually due to inadvertent removal of, or damage to, parathyroid glands or their blood supply
  - May occur with surgery on thyroid or parathyroid glands, or during neck dissection surgery
  - Permanent hypoparathyroidism present for longer than 6 months after surgery

• Post-surgical hypoparathyroidism:
  - Estimates of post-thyroid surgical permanent hypoparathyroidism range from 0.5-6.6%, with centers doing endocrine surgery reporting 0.9-1.6%
  - Estimates of post-thyroid surgical transient hypoparathyroidism range from 6.9-46%
  - Higher risk of hypoparathyroidism if reoperation, more extensive thyroid resection, substernal goiter, cancer, or Graves’ disease

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• Estimates of post-thyroid surgical transient hypoparathyroidism range from 6.9-46%
• Higher risk of hypoparathyroidism if reoperation, more extensive thyroid resection, substernal goiter, cancer, or Graves’ disease

• Acquired Disorders:
  - Autoimmune hypoparathyroidism
    - Autoimmune polyglandular syndrome type I
    - Isolated
  - Accumulation of iron (thalassemia or hemochromatosis): 13% of 44 cases of hemochromatosis
  - Accumulation of copper (Wilson’s disease): prevalence of 1-4/100,000
  - Very rarely may occur after I-131 therapy for thyroid disease
  - Rarely occurs with metastatic infiltration of glands
  - Magnesium deficiency (e.g., PPI therapy) or excess (e.g., tocolytic therapy during pregnancy)

• APS-1: Due to autosomal recessive mutations in AIRE on 21q22.3
  - Characterized by mucocutaneous candidiasis, hypoparathyroidism, and Addison’s disease, as well as chronic active hepatitis, alopecia, and primary hypogonadism
  - Prevalence estimates vary:
    - Northern Italy: 1:200,000
    - Norway: 1:90,000
    - Finland: 1:25,000
    - Sardegna, Italy: 1:14,400
    - Iranian Jews: 1:6,000 to 1:9,000
Frequency of Major and Minor Clinical Features in Finnish APS-1 Patients


- Frequency (%):
  - Candi
diasis: 100
  - Hy
poparathyroidism: 80
  - Addison’s Disease: 70
  - Alope
cia: 60
  - Hy
pogonadism: 50
  - Int
estinal Dysfxn: 40
  - Vitiligo: 30
  - Pe
rnici
ous An
eaemia: 20
  - Hepatitis: 10
  - Diabetes Mellitus: 0
  - Thyroidop
athy: 0

Genetic Causes of Hypoparathyroidism

- Genetic Disorders:
  - Autosomal dominant familial hypocalcemia: activating mutations in CaSR on 3q13 may be among most common causes of isolated hypoparathyroidism
  - DiGeorge (velocardiofacial) syndrome: 1:2,000-3,000 live births, with TBX1 and other mutations on 22q11.2
  - Familial isolated hypoparathyroidism due to autosomal recessive or dominant mutation in pre-proPTH on 11p15, or parathyroid gland dysgenesis due to mutations in transcription factors and other regulators of parathyroid gland development such as GCMB (glial cells missing B) or GCM2 (glial cells missing 2)

Diagnosis of Hypoparathyroidism


- Biochemical Parameters:
  - Low-normal to decreased serum calcium
  - High-normal to increased serum phosphate
  - Inappropriately low-normal or decreased intact parathyroid hormone
  - Low-normal to decreased total alkaline phosphatase
  - Low-normal to decreased markers of bone turnover
    - Serum bone specific alkaline phosphatase
    - Serum beta-CTx-telopeptide
  - Low-normal to decreased urinary calcium and calcium to creatinine clearance ratio (<0.01)
  - Low-normal to decreased serum 1,25-dihydroxyvitamin D
  - Decreased serum chloride and increased serum bicarbonate
  - Normal serum magnesium

Prevalence, Incidence, and Mortality of Hypoparathyroidism


<table>
<thead>
<tr>
<th></th>
<th>Hypoparathyroidism</th>
<th>Postsurgical Hypoparathyroidism</th>
<th>Nonsurgical Hypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>37/100,000 person-years</td>
<td>29/100,000 person-years</td>
<td>8/100,000 person-years</td>
</tr>
<tr>
<td>Incidence</td>
<td>0.8/100,000 person-years</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mortality</td>
<td>-</td>
<td>HR 0.98; 95% CI, 0.76-1.26</td>
<td>HR 1.25; 95% CI, 0.90-1.73</td>
</tr>
</tbody>
</table>

Prevalence of Hypoparathyroidism


Data from a large health plan claims database: 77 million unique patients, combining 75 health plans from across the U.S.

1. Estimated number of diagnoses of hypoparathyroidism over 12 months and projected to the U.S. population
2. Proportion of neck surgeries resulting in hypoparathyroidism: entered into an epidemiologic model to derive an estimate of prevalence
3. ~60,000 patients in the US: 75% postsurgical, 75% female, and 75% 45 years or older
### Risk of Complications of Hypoparathyroidism

<table>
<thead>
<tr>
<th>Risk of hospitalization for Complications</th>
<th>Postsurgical Hypoparathyroidism</th>
<th>Nonsurgical Hypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Insufficiency</td>
<td>HR 3.10; 95% CI, 1.73-5.55</td>
<td>HR 6.01; 95% CI, 2.45-14.75</td>
</tr>
<tr>
<td>Renal stones</td>
<td>HR 4.02; 95% CI, 1.64-9.90</td>
<td></td>
</tr>
<tr>
<td>Ischemic CV disease</td>
<td>HR 1.05; 95% CI, 0.83-1.45</td>
<td>HR 2.01; 95% CI, 1.31-3.09</td>
</tr>
<tr>
<td>Neuropsychiatric Disease</td>
<td>HR 1.26; 95% CI, 1.01-1.56</td>
<td>HR 2.45; 95% CI, 1.78-3.35</td>
</tr>
<tr>
<td>Seizures</td>
<td>HR 3.82; 95% CI, 2.15-6.79</td>
<td>HR 10.05; 95% CI, 5.39-18.72</td>
</tr>
<tr>
<td>Cataracts</td>
<td>HR 1.17; 95% CI, 0.66-2.09</td>
<td>HR 4.21; 95% CI, 2.13-8.34</td>
</tr>
<tr>
<td>Upper Extremity Fractures</td>
<td>HR 0.69; 95% CI, 0.49-0.97</td>
<td>HR 1.93; 95% CI, 1.31-2.85</td>
</tr>
<tr>
<td>Intracranial Calcifications</td>
<td>59%</td>
<td>69-74%</td>
</tr>
</tbody>
</table>

### Higher Anxiety Scores in Patients with Postsurgical Hypoparathyroidism

- 25 women with postsurgical hypoparathyroidism
- 25 age- and sex-matched controls status-post thyroidectomy but with intact parathyroid glands

### Quality of Life is Reduced by SF-36 Assessment

- Cusano et al (Columbia) (n=54)  
  - Significantly worse in all 8 domains compared to normative data
- Cho et al (Harvard) (n=340) and controls (n=200)  
  - Scores lower in all 8 domains
- Sikjaer et al (Denmark) (n=62)  
  - QOL significantly reduced

### Diagnosis of Chronic Hypoparathyroidism

- Low-normal to decreased albumin-adjusted serum calcium on at least 2 occasions, separated by at least 2 weeks
- Inappropriately low-normal or decreased parathyroid hormone by 2nd or 3rd generation assay in presence of hypocalcemia on at least 2 occasions
- High-normal to increased serum phosphate
- Chronic hypoparathyroidism after neck surgery is diagnosed only if present for more than 6 months

### Treatment of Acute Symptomatic Hypoparathyroidism

- Dilute 10 mL of 10% calcium gluconate solution in 100 mL D5W and infuse over 5-10 minutes to give 90 mg elemental calcium immediately
- Longer infusion of 10 ampules of calcium gluconate (900 mg) diluted in 1 L D5W at 50 mL/hour to give 15 mg elemental calcium/kg
- Infusion will raise serum calcium by 2 mg/dL over 8 hours
- Avoid calcium chloride due to venous irritation
- Magnesium supplementation if deficient
- Begin oral calcium and vitamin D supplementation as appropriate

### Conventional Management of Chronic Hypoparathyroidism

- Guidelines published by:
  - European Society of Endocrinology
  - First International Conference on the Management of Hypoparathyroidism
  - AACE/ACE Disease State Clinical Review on Postoperative Hypoparathyroidism
- Treatment targets:
  - Low-normal serum calcium
  - High-normal serum phosphorus
  - 24-hr urine calcium <7.5 mmol
  - Calcium-phosphate product <55 mg2/dL2
Conventional Management of Chronic Hypoparathyroidism

- Calcium citrate or carbonate, 1-9 g/day in divided doses
- Calcitriol 0.25-2.00 mcg/day, often in divided doses
- Vitamin D2 or D3 800-2,000 IU/day
- Thiazide diuretics and low-salt diet when necessary to manage hypercalciuria
- Phosphate binders and low phosphate diet if necessary to control hyperphosphatemia

European Society of Endocrinology Guidelines for Management of Chronic Hypoparathyroidism

- Serum calcium in lower half of reference range without hypocalcemia
- Serum phosphate within reference range
- Calcium x phosphate product within reference range
- Serum magnesium within reference range
- Urinary calcium within reference range for gender
- Adequate vitamin D
- Focus on long-term well-being and QOL

Indications for Considering Use of rhPTH(1-84) in Hypoparathyroidism

- Inadequate control of serum calcium
- Oral calcium/vitamin D medications required to control serum calcium or symptoms that exceed 2.5 g calcium or >1.5 μg active vitamin D
- Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (< 60 ml/min)
- Hyperphosphatemia and/or calcium x phosphate product that exceeds 55 mg²dl² (4.4 mmol²L²)
- GI tract disorder associated with malabsorption
- Reduced Quality of Life

Monitoring Guidelines on Conventional Therapy of Hypoparathyroidism

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monitoring Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>During initial treatment phase or with change in therapy weekly to monthly</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>After treatment stabilization: Twice yearly to yearly</td>
</tr>
<tr>
<td>Serum magnesium</td>
<td></td>
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<tr>
<td>Serum creatinine/BUN</td>
<td></td>
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<tr>
<td>Serum eGFR</td>
<td></td>
</tr>
<tr>
<td>24-Hour urinary calcium/creatinine</td>
<td>Yearly or as clinically indicated</td>
</tr>
<tr>
<td>Renal imaging for nephrolithiasis and nephrocalcinosis</td>
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<tr>
<td>Ophthalmology exam for cataracts</td>
<td></td>
</tr>
<tr>
<td>CNS imaging for basal ganglia and other intracerebral calcification</td>
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<tr>
<td>Bone Mineral Density</td>
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</tbody>
</table>

Treatment of Hypoparathyroidism

- Possible adjunctive options for treatment of chronic hypoparathyroidism:
  - PTH 1-34 (Teriparatide)
  - PTH 1-84 (Natpara)
  - Other PTH analogues
  - PTH by pump therapy
  - PTH by implantable microchip
  - Stem cell therapy
  - Parathyroid gland transplantation

PTH 1-84 Reduces Need for Calcium and Vitamin D Supplementation

- Double-blind, placebo-controlled, randomized phase 3 trial in 134 patients with hypoparathyroidism
- 90 received SQ PTH 1-84 and 44 SQ placebo for 6 months
- Primary outcome was % patients at week 24 achieving ≥50% reduction in calcium and active vitamin D while maintaining serum calcium at or above baseline and below ULN
- 53% of patients on PTH 1-84 achieved primary outcome, vs. 2% of patients on placebo
- AEs similar between groups, with hypocalcemia, muscle spasms, paresthesias, headache, and nausea most common
- Concluded that PTH 1-84 is efficacious and well-tolerated
PTH 1-84 Reduces Need for Calcium and Vitamin D Supplementation

FDA Approval of PTH 1-84 (Natpara)
• FDA Advisory Board approved PTH 1-84 on September 12, 2014
• FDA announced delay in final decision on October 24, 2014 to allow time for an amendment to the New Drug Application to be processed
• Final approval given on January 24, 2015

Hypoparathyroidism: Summary and Conclusions
• Hypoparathyroidism is a rare disorder caused by surgery in 75% of cases
• Other acquired causes are due to autoimmunity, iron or copper overload, metastatic disease, radioactive iodine therapy, or magnesium deficiency or excess
• Genetic causes occur rarely, and are often associated with syndromes
• Treatment includes calcium and calcitriol supplementation, magnesium and thiazide-type diuretic as needed, and PTH 1-84 adjunctive treatment

Osteogenesis Imperfecta (OI)
• Genetic disorder of connective tissue characterized by fragile bones and low-trauma fractures: “brittle bone disease”
• Broad range of clinical expression, ranging from lethality in perinatal period to mild or early osteoporosis: incidence of 1:20,000 births
• Short stature, defective tooth formation (dentinogenesis imperfecta), hearing loss, macrocephaly, blue sclerae, scoliosis, barrel chest, and lax joints

Osteogenesis Imperfecta
• Classical OI is due to autosomal dominant type I collagen mutations
• Sillence classification first proposed in 1979, based on clinical and x-ray features
• Mild Sillence type I OI is most common, and due to quantitative defects in type I collagen
• Moderate and severe Sillence type I OI due to structural defects in either A1 or A2 chains forming type I collagen heterotrimer
• Rare recessive forms of OI types V-XVI overlap with lethal and severe Sillence types
COL1 Mutations Cause OI

Osteogenesis Imperfecta

- Mutations causing recessive OI alter:
  - Prolyl-3-hydroxylation complex (cartilage-associated protein, prolyl-3-hydroxylase I, cyclophilin B, or transmembrane protein 38B) which modify the α1(I) collagen chain
  - Chaperones involved in collagen folding and intracellular transport: HSP47, FK506BP65, or 2-oxoglutarate 5 dioxygenase 2
  - Interferon-induced transmembrane protein 5 (Bril) or multifunctional pigment epithelium-derived factor
  - Transcription factor 7/Osterix, wingless-type MMTV integration site family member 1, or cAMP responsive element binding protein 3 like 1

Types of Osteogenesis Imperfecta

<table>
<thead>
<tr>
<th>Category</th>
<th>Silence Type</th>
<th>Inheritance</th>
<th>Bone Deformity</th>
<th>Gene Defect</th>
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</thead>
<tbody>
<tr>
<td>Collagen</td>
<td>I</td>
<td>AD</td>
<td>Mild to very severe</td>
<td>COL1A1/COL1A2</td>
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<tr>
<td>Synthesis</td>
<td>II</td>
<td>AD</td>
<td>Mild to very severe</td>
<td>COL1A1/COL1A2</td>
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<tr>
<td>Structure</td>
<td>III</td>
<td>AD</td>
<td>Mild to very severe</td>
<td>COL1A1/COL1A2</td>
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<tr>
<td>or Processing</td>
<td>IV</td>
<td>AD</td>
<td>Mild to very severe</td>
<td>COL1A1/COL1A2</td>
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<td>Collagen Modification</td>
<td>V</td>
<td>AR</td>
<td>Milder to severe</td>
<td>MMP</td>
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<td>Inactivation of Collagen</td>
<td>VI</td>
<td>AR</td>
<td>Severe disorganization</td>
<td>CR3AP</td>
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<tr>
<td>Modification</td>
<td>VII</td>
<td>AR</td>
<td>Severe disorganization</td>
<td>CPPEP1 (P3H1)</td>
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<tr>
<td></td>
<td>VIII</td>
<td>AR</td>
<td>Severe disorganization</td>
<td>PPIB (CypB)</td>
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<td></td>
<td>IX</td>
<td>AR</td>
<td>Severe</td>
<td>SP7</td>
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<tr>
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Osteosclerosis

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Types of Osteogenesis Imperfecta

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### Osteosclerosis
- Osteosclerosis: thickening of trabecular bone
- Hyperostosis: thickening of cortical bone
- Differential diagnosis of osteosclerosis:
  - Many rare (often hereditary) osteochondrodysplasias
  - Variety of dietary, metabolic, endocrine, hematologic, infectious, or neoplastic disorders

### Causes of Osteosclerosis
- Dietary Disorders: Hypervitaminosis A or D, milk-alkali syndrome
- Metabolic Disorders: Carbonic anhydrase deficiency, fluorosis, heavy metal poisoning, LRP5 and -6 activation, hypophosphatemic osteomalacia, renal osteodystrophy, X-linked hypophosphatemia, axial osteomalacia, diffuse idiopathic skeletal hyperostosis (DISH), fibrogenesis imperfecta ossium, hypertrophic osteoarthropathy, ionizing radiation, osteomyelitis, osteonecrosis, Paget’s disease of bone, sarcoidosis, tuberous sclerosis
- Endocrine Disorders: Hyperparathyroidism, hypoparathyroidism, pseudohypoparathyroidism

### Other Causes of Osteosclerosis
- Hematologic Disorders: Erdheim-Chester disease, leukemias, lymphomas, mastocytosis, multiple myeloma, myelofibrosis, sickle cell disease
- Infectious Disorders: Hepatitis C-associated osteosclerosis
- Neoplastic Disorders: Skeletal metastases

### Skeletal Dysplasias Causing Osteosclerosis
- Autosomal dominant osteosclerosis
- Cranial osteosclerosis with ectodermal dysplasia
- Craniodiaphyseal dysplasia
- Cranio- and metaphyseal dysplasia
- Endosteal hyperostosis: van Buchem disease and sclerosteosis
- Frontometaphyseal dysplasia
- Infantile cortical hyperostosis (Caffey disease)
- Juvenile Paget’s disease: osteoectasia with hyperphosphatasia
- Melorheostosis
- Metaphyseal dysplasia (Pyle disease)
- Mixed sclerosing bone dystrophy
- Oculodento-osseous dysplasia
- Osteodysplasia of Melnick and Needles
- Osteopathia striata
- Osteopetrosis
- Osteopoikilosis
- Progressive diaphyseal dysplasia (Camurati-Engelmann disease)
- Pycnodysostosis
- Trichodento-osseous dysplasia
- Tubular stenosis (Kenny-Caffey syndrome)
Hypophosphatasia


- Rare heritable form of rickets or osteomalacia
- Characterized by subnormal activity of tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP), due to mutations on chromosome 1p
- TNSALP present in all tissues, but decreased activity leads primarily to skeletal and dental abnormalities
- Muscle weakness may be present

About 350 cases reported

4 overlapping clinical forms:
  - Perinatal
  - Infantile
  - Childhood
  - Adult

Odonto-hypophosphatasia affects teeth only

Severity of clinical course correlates with age of diagnosis

Adult Hypophosphatasia


- Usually presents in middle age
- Characterized by poorly-healing, recurrent, metatarsal stress fractures
- Thigh or hip pain may be due to femoral pseudofractures
- Some patients have rickets or premature loss of deciduous teeth in childhood

Chondrocalcinosis, pseudogout, and pyrophosphate arthropathy may occur due to calcium pyrophosphate dihydrate crystal deposition

X-rays show osteopenia, metatarsal stress fractures, chondrocalcinosis, and subtrochanteric femoral pseudofractures

Biochemistries:
  - Low serum alkaline phosphatase
  - Normal serum calcium and phosphorus
  - 50% have hyperphosphatemia due to increased TmP/GFR
  - Suppressed PTH and 1,25-D if hypercalcemia
  - Bone biopsy: osteomalacia without secondary hyperparathyroidism
  - Increased phosphoethanolamine, inorganic pyrophosphate, and pyridoxal-5-phosphate
Adult Hypophosphatasia

- Commercial TNSALP mutation analysis is available: 280 mutations identified to date
- Treatment: no established treatment
  - Marrow cell transplantation in infants
  - Teriparatide
  - Bone-targeted enzyme replacement therapy with recombinant TNSALP: Asfotase alpha
  - Phosphorus dietary restriction and phosphate binders

Lab Findings

Other Causes of Hypophosphatasemia

- Pernicious anemia
- Severe Hypothyroidism
- Vitamin C deficiency
- Wilson's disease
- Vitamin D intoxication
- Inappropriate reference range
- Adynamic renal osteodystrophy
- Bisphosphonate therapy
- Major trauma/surgery

- Starvation
- Mg or Zn deficiency
- Cushing syndrome
- Milk-Alkali syndrome
- Celiac disease
- Analytic error or inappropriate specimen
- Radioactive heavy metal contamination
- Cardiac bypass surgery
- Multiple myeloma/other cancers/chemo

Parathyroid and Rare Skeletal Disorders: Summary and Conclusions

- Endocrinologists need to understand and be conversant with parathyroid and rare skeletal disorders
- Parathyroid disorders are fairly common and generally treatable
- Osteogenesis imperfecta is rare but treatable with antiresorptive therapy
- Osteosclerosis is occasional cause of high BMD that may lead to fractures
- Hypophosphatasia is rare cause of osteomalacia