The Hyperparathyroidisms

With A Look at Calcium, Phosphate and Vitamin-D Physiology

Ronald J. Innerfield, MD, FACE
Endocrinology Section
Department of Medicine
Marshall University School of Medicine
Filling in the (Many) Gaps Left from Evidence Based Data

Favoring One’s Own Hypotheses
- Good sugar/triglyceride control can decrease macrovascular death
- A1c is a better surrogate marker for Type 2 Diabetes than weight
- Everyone should die with normal lab data
- Low testosterone in men is bad and should be rectified
- Hypogonadotropic Hypogonadism is endemic in males
- In the 1970’s, the ADA Dietary recommendation for all diabetics was to consume >70% of calories as carbohydrates

Occam’s Razor
Murphy’s Law (Murphy is the “Grand Dean” of all medical schools)
What is the best index of Vitamin D metabolism?

- A) 25-OH D3
- B) 1,25 OH D3
- C) Both
- D) Neither
Low levels of Vitamin D3 should be repleted until they are above 30ng/ml.

A) True
B) False
• Normocalcemic Hyperparathyroidism should be treated with Parathyroidectomy.
  • A) True
  • B) False
Question of the Day for Me:-

IS WHAT WE CALL “PRIMARY HYPERPARATHYROIDISM” REALLY NOT MOSTLY “TERTIARY HYPERPARATHYROIDISM”

AND, THEREFORE, PREVENTABLE?
Interrelationship of Intestinal, Skeletal, and Renal Systems to the Overall Maintenance of Normal Calcium Homeostasis

Dietary Ca (800 mg/d)

Absorption (500 mg)
Resorption (500 mg)
Formation (500 mg)

Blood Calcium

Filtration (8000 mg/d)
Reabsorption (7800 mg/d)

600 mg lost in stool
800 mg output
200 mg lost in urine
Loss of Calcium from Its Major Pool

Osteoporosis

Patient at age 50...

and 25 years later

Changing Perspectives in Hyperparathyroidism over Time

Figure 2: Changing proportion of asymptomatic patients with clinical manifestations of HPT at 6 year intervals.
Model for the Proposed Changes in Calcium Homeostasis and Bone Turnover with Age

Aging

- Decreased 25OHD
- Decreased 1a-hydroxylase
- Intestinal resistance to 1,25(OH)₂D
- Decreased bone formation

Decreased production of 1,25(OH)₂D

- Decreased calcium absorption
- Secondary hyperparathyroidism

Bone loss

Remember This
Vitamin D Metabolism
Biochemistry of Calcitriol Synthesis
Are Osteoporosis and Atherosclerosis Correlated?

Serum sclerostin level and its relation to subclinical atherosclerosis in subjects with type 2 diabetes

Magui Abdel Moneim Shalash, Kamel Hemida Rohorna, Noha Said Kandil, Mohsen Ahmed, Abdel Mohsen, Aya Abdul Fattah Taha
RANKL, *Atherosclerosis*, and *Osteopetrosis*

- A large number of studies have demonstrated a relationship between bone pathology and vascular disease. The coexistence of osteoporosis and features of atherosclerosis, particularly vascular calcification, has been consistently demonstrated and is most prevalent in postmenopausal women and elderly people. These observations suggest that there are common pathways which negatively affect bone metabolism and the vasculature. New insights in this field are emerging since the discovery of osteoprotegerin (OPG) in 1997 as a key regulator in bone turnover.

- In a mouse model, deficiency of OPG (OPG $^{-/-}$) resulted in severe osteoporosis but also the unexpected phenotype of vascular calcification. Since this combination of osteoporotic bone loss and arterial mineral accumulation mirrors similar associations seen in patients, OPG was suggested as a key link between bone and vascular disease.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729052/
Nice Schematic of Calcium Metabolism

Vitamin D from skin and diet

25-hydroxylase

25(OH)-D — inactive (?)

1α-hydroxylation

Stimulated by PTH
Inhibited by 1,25(OH)₂-D
Low PO₄, High PO₄

PTH effects on the kidney
1. Stimulates activation of vit D.
2. Promotes phosphate excretion.
3. Reduces calcium resorption.

1,25(OH)₂-D effects on kidney
Increases Ca resorption

1,25(OH)₂-D effects on gut
Increases Ca²⁺ and PO₄ absorption

PTH production
Main stimulus is low Ca²⁺, inhibited by 1,25(OH)₂-D. Mg required.

Calcitonin production
Main stimulus high Ca²⁺ (ionized >1.15) — also glucagon, gastrin, β-adrenergic agonists (?reason for low Ca in acute illness)

Parathyroid hormone

Vit D direct effect on bone?
Unclear

PTH effect on bone
Calcium export

Calcitonin

Calcitonin effects on bone
- inhibits osteoclast resorption
- thereby lowers Ca and PO₄
- no effect on Mg
Figure 1: Vitamin D metabolism.
Vitamin D Receptor
Calcium Sensing Receptor-1

Available structures
- PDB: Ortholog search: PDBe RCSB
- List of PDB id codes [show]

Identifiers
- Aliases: CASR, CAR, EIG8, FHH, FIH, GPRC2A, HHC, HHC1, HYPOC1, NSHPT, PCAR1, calcium sensing receptor, hCasR, Calcium-sensing receptor+CaSR
- External IDs: OMIM: 601199 MGI: 1351351 HomoloGene: 332 GeneCards: CASR

Gene location (Human) [hide]
- Chr. 21 Chromosome 3 (human) [1]
- Band: 3q13.33-q21.1
- Start: 122,183,683 bp [1]
- End: 122,291,629 bp [1]
Calcium Sensing Receptor-2
Overview

- PTH
  - Major physiological regulation of calcium level
  - Secreted by the parathyroid glands in response to hypocalcemia, hyperphosphatemia, and/or ↓ calcitriol
  - Changes in serum calcium are the primary stimulus (sensed by the Calcium Sensing Receptor)
  - Expression in parathyroid glands tightly regulated at the translation and transcription levels
  - It increases serum calcium by three different mechanisms:
    1. Stimulates bone resorption
    2. Enhances GI absorption of calcium and phosphorus by stimulating renal production of calcitriol
    3. Augments renal calcium reabsorption
Overview - 2

- Low Serum Calcium Increases PTH Secretion
- PTH Increases Kidney Calcitriol Production
- Calcitriol Down Regulates PTH Secretion
- Serum Calcium and Phosphate Down Regulate Calcitriol Production
- Calcitriol Down Regulates Itself and Down Regulates Renal Calcium Excretion
- PTH and Calcitriol Increase Serum Calcium and Filtered Load
- PTH and Calcitriol Decrease Calcium Excretion, PTH Increases and Calcitriol decreases Renal PO₄ Excretion
- The Kidney Cell Surface Calcium Receptor (CaSR) Regulates Renal Calcium Retention
- PTH and FGF23 Signal Bone Mineral Release
PTH Receptor-1
Renal Calcium Metabolism

Mechanisms of calcium absorption per segment (summary)

- **A** Proximal
  - Ca/Na/H₂O
  - Na
  - NHE3
  - K/Na-ATPase

- **B** Thick Ascending Limb
  - Ca
  - Na
  - NKCC2
  - K/Na-ATPase
  - Calciuric hormone (CaSR)

- **C** DCT-CNT
  - NCC:ENaC
  - Na
  - TRPV5
  - Ca
  - CB28
  - NCX1
  - Ca
  - PMCA4

- **D** Collecting Duct
  - Na
  - H₂O
  - ENaC
  - AQP2
  - Ca
  - K/Na-ATPase
  - H⁺

*J Physiol Renal Physiol 2016;310:F1337-F1350*
Segment Specific Mechanisms of Calcium Re-absorption: PT

- **Proximal tubule:**
  - Passive diffusion (80% paracellular)
  - Active transport (10-15%)

- Claudin2 controls permeability of the tight junctions in the PT
- Sodium and Ca directly compete to enter via these channels
- Molecular mechanisms of active transport are not known but may involve L-type calcium channels and TRV1
- Genetic mutations of NH3 lead to metabolic acidosis, hypercalciuria and osteopenia
- **NH3 is regulated (inhibited) by PTH**

J Physiol Renal Physiol 2016;310:F1337-F1350
Pfugers Arch – Eur J 2017; 469:105-113
Genetic Disorders of the TAH are associated with hypercalciuria

- Mutations of the ROMK or the NKCC2 lead to Bartter’s syndrome:
  - Manifestations similar to giving furosemide (salt-wasting, hypokalemic alkalosis and hypercalciuria)

<table>
<thead>
<tr>
<th>Transporter or molecule</th>
<th>Disease name</th>
<th>Effect on calciuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKCC2 or SLC12A1</td>
<td>Bartter’s syndrome I</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>ROMK or KCNJ1</td>
<td>Bartter’s syndrome II</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>Claudin 16</td>
<td>Familial hypomagnesemia with hypercalciuria and nephrocakinosis</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>Claudin 19</td>
<td>Familial hypomagnesemia with hypercalciuria and nephrocakinosis</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>Calcium-sensing receptor</td>
<td>Familial hypocalciuric hypercalciemia (heterozygous) or neonatal severe hyperparathyroidism (homozygous)</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td></td>
<td>Autosomal dominant hypocalcemia with hypercalciuria</td>
<td>Hypercalciuria</td>
</tr>
</tbody>
</table>
ROMK
Inwardly Rectifying K⁺ Channel
Collecting Duct

Segment Specific Mechanisms of Calcium Re-absorption: CD

• Collecting Duct:
  - A transcellular mechanism accounts for the transport of calcium in this segment
  • Three step active process:
    1. Entry of calcium into the epithelial cells from the apical transient receptor vanilloid 5 (TRPV5): controlled via calcitriol and PTH
    2. Diffusion of calcium into the cytoplasm bound to calbindin-D28k (same complex as in enterocytes)
    3. Active transport of Ca out of epithelial cells through the sodium – calcium exchanger and the plasma membrane calcium-ATPase

Mutations of NCC (Gitelman syndrome) or thiazides diuretics (act on NCC) lead to hypocalciuria and hypercalcemia (also low potassium, metabolic alkalosis)

J Physiol Renal Physiol 2016;310:F1337-F1350
Pflugers Arch – Eur J 2017; 469:105-113
Renal PO₄ Metabolism

Regulation of Renal P Excretion

When Ca and P both high FGF-23 action predominates
In low calcium, high P states PTH action predominates

American Journal of Kidney Diseases 2011; 58:1022-1039
Regulatory Schematic
The main function of FGF23 seems to be regulation of phosphate concentration in plasma. FGF23 is secreted by osteocytes in response to elevated calcitriol. FGF23 acts on the kidneys, where it decreases the expression of NPT2, a sodium-phosphate cotransporter in the proximal tubule. Thus, FGF23 decreases the reabsorption and increases excretion of phosphate.
- FGF23 promotes phosphate excretion in the urine by suppressing the expression of sodium-phosphate co-transporters, NaPi-2a and NaPi-2c, in the proximal tubule.
- FGF23 acts as a counter-regulatory hormone for vitamin D through inhibition of the renal 1α-hydroxylase, and stimulation of the 24-hydroxylase.
- FGF23 also regulates PTH production by the parathyroid gland.
• Compound heterozygous and homozygous (comp/hom) mutations in solute carrier family 34, member 3 (SLC34A3), the gene encoding the sodium (Na(+))-dependent phosphate cotransporter 2c (NPT2c), cause hereditary hypophosphatemic rickets with hypercalciuria (HHRH), a disorder characterized by renal phosphate wasting resulting in hypophosphatemia, correspondingly elevated 1,25(OH)2 vitamin D levels, hypercalciuria, and rickets/osteomalacia.
## Renal Targets

<table>
<thead>
<tr>
<th>Region</th>
<th>Cellular Target</th>
<th>Biological Effects</th>
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</thead>
<tbody>
<tr>
<td>PCT/PST</td>
<td>↓PTH1R</td>
<td>↓(P_i) transport</td>
</tr>
<tr>
<td></td>
<td>↑1-Hydroxylase activity</td>
<td>↑1,25(OH)_2D_3 synthesis</td>
</tr>
<tr>
<td></td>
<td>↑p38 MAPK</td>
<td>↑VDR expression</td>
</tr>
<tr>
<td>MTAL</td>
<td>↑H^+-K^+-ATPase</td>
<td>↑Urine acidification</td>
</tr>
<tr>
<td></td>
<td>↓Calcitonin- and AVP-induced cAMP production</td>
<td>↓NaCl/Ca^{2+}/Mg^{2+} transport</td>
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<tr>
<td>TAHL</td>
<td>↓CLDN-16</td>
<td>↓Ca^{2+}/Mg^{2+} transport</td>
</tr>
<tr>
<td></td>
<td>↓NKCC2</td>
<td>↓NaCl/Ca^{2+}/Mg^{2+} transport</td>
</tr>
<tr>
<td></td>
<td>↓ROMK</td>
<td>↓NaCl/Ca^{2+}/Mg^{2+} transport by inhibiting K channel</td>
</tr>
<tr>
<td></td>
<td>↓PTH-induced second messenger production</td>
<td>↓Transcellular Ca^{2+} transport</td>
</tr>
<tr>
<td>DCT/CNT</td>
<td>↑TRPV5</td>
<td>↑Ca^{2+} reabsorption</td>
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<tr>
<td>CCD/OMCD</td>
<td>↑H^+-ATPase</td>
<td>↑Urine acidification</td>
</tr>
<tr>
<td>OMCD/IMCD</td>
<td>↓AVP-dependent AQP2 apical insertion</td>
<td>↓Urine concentration</td>
</tr>
<tr>
<td>JG cells</td>
<td>↓AC-V, renin gene expression</td>
<td>↓Renin secretion</td>
</tr>
</tbody>
</table>
Any Active Protection from Hypercalcemia?

Thyrocalcitonin

Elevated calcium

Parafollicular cells thyroid release

Calcitonin

Bone

Inhibits osteoclast

Osteoblast – build new bone using calcium from blood
Osteoclast – breakdown bone, release calcium into blood
Increased Ca++ causes CaSR to stimulate calcitonin release

Parafollicular cells
- Located between follicles
- Secrete calcitonin
- ↓ blood Ca++ levels
  - Inhibits osteoclasts
  - ↑ Ca++ secretion in kidney

25.7bc
Serum calcitonin (CT) levels in C⁺P⁺, C⁺P⁻, and C⁻P⁻ mice as a function in serum Ca²⁺ concentration. Mice were maintained on standard chow and 0% Ca²⁺ water for 1 wk, 1% Ca²⁺ water for 1 wk and finally, 2% Ca²⁺ water for a 3rd wk. Serum samples were obtained at the end of each of the 3 wk, and levels of Ca²⁺ and CT were determined as described in materials and methods. Data are plotted as serum Ca²⁺ concentration in any given serum sample vs. the CT concentration in that sample. Trend lines represent C⁺P⁻ and C⁺P⁺ (solid) and C⁻P⁻ (dotted).
FHH and CaSR Defect

Familial Hypocalciuric Hypercalcemia: Calcium sensing receptor
Familial primary hyperparathyroidism

- Hereditary hyperparathyroidism-jaw tumor syndrome
- Familial hypocalciuric hypercalcemia
- Multiple endocrine neoplasia, type 1
- Multiple endocrine neoplasia, type 2a
- Hereditary isolated primary hyperparathyroidism
Hereditary hyperparathyroidism-jaw tumor syndrome

- Parathyroid adenomas, can be cystic and sometimes multiple, serial
- Fibrous tumors of jaw, not caused by hyperparathyroidism
- Autosomal dominant, two hits for tumor
- Wilm’s tumor, adult nephroblastomas, parathyroid cancer
- Gene mutated in most parathyroid cancers
- Can present as isolated, not obviously familial, parathyroid cancer
Jaw tumor in Hyperpara-Jaw Tumor syndrome

Moon, S.-D. et al. J Clin Endocrinol Metab 90:878-883(05)
Genetic Hyperparathyroidisms-4 (FHH)
MEN-1

The patient presented at age 17 with kidney stones, calcium 10.7 mg/dl (2.68 mmol/L), PO4 2.3 mg/dl (0.74 mmol/L), and PTH 3 times normal. She had a mother, aunt and uncle, each with primary hyperparathyroidism and a cousin who subsequently developed a prolactinoma. She had a three + gland parathyroidectomy and she remained normocalcemic for 10 years, but then first her ionized calcium and then both ionized and total calcium became modestly elevated again. She had a kidney stone during the second of her three pregnancies but none at any other times. Her calcium has been less than 11 mg/dl (2.75 mmol/L), with PTH 2-4 times normal.

She has never had any evidence of a pituitary tumor, but she developed diarrhea that responded to prilosec at age 29, with elevation of gastrin. She has not had a secretin test or gastrin measurement, but has multiple small tumors noted in her pancreas and a probable small tumor in the wall of the second portion of her duodenum.
Changes in The Biochemical Signature of PHPT in the Modern Era

<table>
<thead>
<tr>
<th>Index</th>
<th>1984-1991 N=103</th>
<th>2000-2014 N=100</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>10.6 ± 0.6</td>
<td>10.7 ± 0.6</td>
<td>0.14</td>
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<tr>
<td>PTH (pg/mL)</td>
<td>127 ± 69</td>
<td>85 ± 48</td>
<td>&lt;0.0001</td>
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<tr>
<td>25-hydroxyvitamin D (ng/mL)</td>
<td>23 ± 10</td>
<td>29 ± 10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (pg/mL)</td>
<td>57 ± 20</td>
<td>69 ± 24</td>
<td>0.002</td>
</tr>
<tr>
<td>Urinary calcium excretion (mg)</td>
<td>229 ± 119</td>
<td>250 ± 144</td>
<td>0.28</td>
</tr>
</tbody>
</table>

None of the patients in the prior cohort were taking vitamin D supplements compared to 64% in the new cohort (median 800 IU daily)

Walker MD et al. Osteoporos Int 2015
Persistently Elevated PTH After Parathyroidectomy at One Year: Experience in a Tertiary Referral Center

Marie Caldwell, Jeff Leux, Marshall Clark, Lawrence Kim, Janet Rubin

*The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 10, October 2019, Pages 4473-4480, [https://doi.org/10.1210/jc.2019-00705](https://doi.org/10.1210/jc.2019-00705)*

Published: 12 June 2019  Article history
Figure 1.

Patients with CPT 60500 (parathyroidectomy) AND ICD9 252.0 OR ICD10 E21 (hyperparathyroidism)  
N = 570

Patients with Cr ≤ 2  
N = 499

PTH measured day 1+ post PTx  
N = 407

Patients without PTH measured 3-18 mo post PTx  
N = 263

Patients with PTH measured 3-18 mo post PTx  
N = 144

Patients with PTH <72 mo post PTx  
N = 101

Patients with PTH >72 mo post PTx  
N = 43

Patient cohort.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>No</th>
<th>Yes</th>
<th>P</th>
<th>Reference Range</th>
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<tr>
<td><strong>N</strong></td>
<td>144</td>
<td>101</td>
<td>43</td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>121 (84)</td>
<td>87</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (16)</td>
<td>14</td>
<td>9</td>
<td>0.417</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>57.90 ± 14.24</td>
<td>56.82 ± 14.54</td>
<td>59.22 ± 14.75</td>
<td>0.374</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>29.53 ± 7.6</td>
<td>28.96 ± 7.90</td>
<td>30.49 ± 6.73</td>
<td>0.301</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium</strong></td>
<td>11.1 [10.6–11.4]</td>
<td>11.1 [10.6–11.5]</td>
<td>11 [10.5–11.3]</td>
<td>0.305</td>
<td>8.5–10.2 mg/dL</td>
</tr>
<tr>
<td><strong>24-h urine calcium</strong></td>
<td>296 [176–385]</td>
<td>267 [185–393]</td>
<td>311 [137–357]</td>
<td>0.683</td>
<td>100–300 mg/24 h</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>0.84 [0.74–1]</td>
<td>0.81 [0.74–1]</td>
<td>0.91 [0.8–1.09]</td>
<td>0.03*</td>
<td>0.6–1 mg/dL</td>
</tr>
<tr>
<td><strong>Phosphorus</strong></td>
<td>3.13 ± 0.54</td>
<td>3.17 ± 0.52</td>
<td>3.05 ± 0.6</td>
<td>0.279</td>
<td>2.9–4.7 mg/dL</td>
</tr>
<tr>
<td><strong>PTH</strong></td>
<td>122.8 [85–168.9]</td>
<td>102.5 [75.6–145]</td>
<td>156.5 [122.8–240.5]</td>
<td>&lt;0.001*</td>
<td>12–72 pg/mL</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td>32.61 ± 13.51</td>
<td>35.57 ± 11.64</td>
<td>26.12 ± 15.38</td>
<td>0.019</td>
<td>20–80 ng/mL</td>
</tr>
<tr>
<td><strong>Gland weight</strong></td>
<td>0.80 [0.40–1.70]</td>
<td>0.80 [0.40–1.50]</td>
<td>1.00 [0.60–1.70]</td>
<td>0.139</td>
<td>grams</td>
</tr>
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</table>
**Biochemical Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SE</th>
<th>Range</th>
<th>NI Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium (mg/dL)*</td>
<td>9.4 ± 0.1</td>
<td>8.5-10.2</td>
<td>8.5-10.4</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>93 ± 5</td>
<td>65-182</td>
<td>10-65</td>
</tr>
<tr>
<td>Serum Phosphorus (mg/dL)</td>
<td>3.3 ± 0.1</td>
<td>2.4-4.8</td>
<td>2.1-4.3</td>
</tr>
<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>72 ± 5</td>
<td>39-134</td>
<td>20-125</td>
</tr>
<tr>
<td>Urinary Calcium (mg/24h)</td>
<td>193 ± 12</td>
<td>71-350</td>
<td>50-300</td>
</tr>
<tr>
<td>Urinary NTX (nM BCE/mM Cr)</td>
<td>38 ± 5</td>
<td>7-69</td>
<td>10-110</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/mL)**</td>
<td>33 ± 1</td>
<td>20-54</td>
<td>30-100</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (pg/mL)</td>
<td>62 ± 4</td>
<td>31-109</td>
<td>19-67</td>
</tr>
</tbody>
</table>

*Corrected for serum albumin
**By definition, 25-hydroxyvitamin D was >20 pg/mL

Lowe, McMahon, Rubin, Bilezikian
Silverberg, J Clin Endocrinol Metab, 2007
When "Experts" Get Together

Normocalcemic PHPT is a clinical presentation of PHPT; management approach is recommended.
Guidelines from the Experts

Management of Asymptomatic NPHPT: A Proposal for Discussion

- Calcium and PTH annually
- DXA every 1-2 years

Progression to hypercalcemic PHPT
- Follow guidelines

Progression of disease
- Worsening BMD or fracture
- Kidney stone or nephrocalcinosis
- Surgery

Do you agree?

• Is there any other data you might like to see?
Hyperparathyroidism and 25-OH Vitamin D

![Hyperparathyroidism Table](image)

**Primary Hyperparathyroidism:**

<table>
<thead>
<tr>
<th></th>
<th>New York</th>
<th>Beijing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dl)</td>
<td>10.7 ± 0.1</td>
<td>12.4 ± 1.1</td>
</tr>
<tr>
<td>Alk Phos (% &gt; nl)</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>PTH (x nl)</td>
<td>1.86</td>
<td>21.4</td>
</tr>
<tr>
<td>Uca (% &gt; nl)</td>
<td>38%</td>
<td>51%</td>
</tr>
<tr>
<td>Phos (% &lt; nl)</td>
<td>25%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>25-OH D (ng/ml)</strong></td>
<td><strong>21.1 ± 1</strong></td>
<td><strong>8.8 ± 7.2</strong></td>
</tr>
</tbody>
</table>

*Bilezikian, Meng, Shi, Silverberg. 2000*
Hyperparathyroidism and 25-OH Vitamin D

PTH Levels as function of Vitamin D status
(Stein et al. JCEM, 2011)

Mean ± SD

P<0.01
Vitamin D Resistance [Rickets]

A 49-year-old white female presented to the bone clinic at Mayo Rochester with a history of intermittent joint pains affecting her hands, feet and elbows since her 20s, periarticular growths, and bilateral conductive hearing loss. There was no history of fractures, renal dysfunction, nephrolithiasis or hypercalcemia.
Figure 1. Plain radiograph demonstrating bowing of right femur.

Vitamin D Resistance [Rickets]

<table>
<thead>
<tr>
<th>LabTest</th>
<th>Patient</th>
<th>1st Degree</th>
<th>Normals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>1.9*; 2.1**</td>
<td>2.5**</td>
<td>2.5-4.5</td>
</tr>
<tr>
<td>Serum PTH (pg/mL)</td>
<td>156*; 47**</td>
<td>83**</td>
<td>15-65</td>
</tr>
<tr>
<td>eGFR (mL/minute)</td>
<td>&gt; 90</td>
<td>87</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Renal TRP (%)</td>
<td>76.6*; 75.8**</td>
<td>86.4**</td>
<td>&gt; 80</td>
</tr>
<tr>
<td>Intact FGF23 (mg/mL)</td>
<td>94.7</td>
<td>93.77</td>
<td>10-50</td>
</tr>
<tr>
<td>C-terminal FGF23 (RU/mL)</td>
<td>103</td>
<td>190</td>
<td>&lt; 180</td>
</tr>
<tr>
<td>25 (OH)D (ng/mL)</td>
<td>24</td>
<td>27</td>
<td>20-80</td>
</tr>
<tr>
<td>1,25(OH)_2D (pg/mL)</td>
<td>94*; 32**</td>
<td>54**</td>
<td>18-64</td>
</tr>
</tbody>
</table>
Figure 2. Plain radiograph demonstrating periarticular calcifications in the right shoulder (A) and both feet (B).
<table>
<thead>
<tr>
<th>Disease</th>
<th>Abbreviation</th>
<th>Gene</th>
<th>FGF23 levels</th>
<th>Hypophosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Linked Hypophosphatemia</td>
<td>XLH</td>
<td>PHEX</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Autosomal dominant hypophosphatemic rickets</td>
<td>ADHR</td>
<td>FGF23</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Autosomal recessive hypophosphatemic rickets 1</td>
<td>ARHR1</td>
<td>DMP1</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Autosomal recessive hypophosphatemic rickets 2</td>
<td>ARHR2</td>
<td>ENPP1</td>
<td>↑</td>
<td>Y</td>
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<tr>
<td>Autosomal recessive hypophosphatemic rickets 3 (Raine Syndrome)</td>
<td>ARHR3</td>
<td>FAM20C</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Hypophosphatemic rickets with hypercalciuria</td>
<td>HHRH</td>
<td>SLC34A3 (NPT2C)</td>
<td>-</td>
<td>Y</td>
</tr>
</tbody>
</table>

Vitamin D Resistant Rickets
Vitamin D Resistance [Rickets]

- Hereditary hypophosphatemia is a form of FGF23-mediated hypophosphatemia categorized as X-linked hypophosphatemia, autosomal dominant hypophosphatemic rickets or the much rarer autosomal recessive hypophosphatemic rickets (ARHR) types 1 and 2. ARHR2 is associated with deficiency of the ENPP1 enzyme, which generates pyrophosphate (PPi) from adenosine triphosphate, but its association with FGF23 is unclear. The clinical features of ARHR2 in adults include:
  - Periarticular calcifications with a waxing and waning clinical course over years
  - History of rickets
  - Conductive hearing loss

Rickets and hypophosphatemia are mediated by FGF23 produced by bones, which decreases renal phosphate reabsorption and decreases 1-alpha hydroxylase activity. Hence a patient with hypophosphatemia, high PTH, and high 1,25(OH)2D for the level of hypophosphatemia should raise concern for FGF23-mediated hypophosphatemia.
Vascular health screening demonstrated increased carotid intima-media thickness but no vascular calcification. This patient was treated with calcium and calcitriol, which led to improvement in serum calcium and phosphorus.
May 1, 1997  Age  76.18

• Problem  Left pelvis and leg pains in the presence of osteoporosis

• HPI  Mrs. E. has no family history of osteoporosis. She has not consumed much in the way of milk and dairy products especially for the last 20 years. In 1963 she was found to have some ileitis. In 1966 she had bowel obstruction and 12" of small bowel removed + right tube + right hysterectomy of the remaining organs. In 1968 she had an abscess in the right pelvis and the ascending colon and ileocecal valve were removed. In 1978 she was given steroids for asthmatic symptoms. In 1978 pernicious anemia was diagnosed requiring B12 injections every 2 weeks. She was told of malabsorption [of B vitamins].
<table>
<thead>
<tr>
<th>Date</th>
<th>Ca++</th>
<th>PTH</th>
</tr>
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<tbody>
<tr>
<td>1997/05/01</td>
<td>8.5</td>
<td>344.0</td>
</tr>
<tr>
<td>1997/05/28</td>
<td>8.5</td>
<td>388.0</td>
</tr>
<tr>
<td>1997/07/21</td>
<td>9.3</td>
<td>102.0</td>
</tr>
<tr>
<td>1997/08/21</td>
<td>9.3</td>
<td>167.0</td>
</tr>
<tr>
<td>1997/11/14</td>
<td>10.4</td>
<td>11.4</td>
</tr>
<tr>
<td>1998/01/26</td>
<td>11.2</td>
<td>0 (!)</td>
</tr>
<tr>
<td>1998/04/28</td>
<td>9.7</td>
<td>8.6</td>
</tr>
<tr>
<td>1998/06/26</td>
<td>9.5</td>
<td>11.4</td>
</tr>
<tr>
<td>1999/04/28</td>
<td>9.4</td>
<td>15.2</td>
</tr>
<tr>
<td>2000/02/04</td>
<td>8.7</td>
<td>16.0</td>
</tr>
<tr>
<td>2000/05/01</td>
<td>9.3</td>
<td>15.1</td>
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</table>
## Pre-Treatment Values

<table>
<thead>
<tr>
<th></th>
<th>Ca++</th>
<th>PTH</th>
</tr>
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<tbody>
<tr>
<td><strong>Total</strong></td>
<td>516.42</td>
<td>7015</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>9.06</td>
<td>123.07</td>
</tr>
<tr>
<td><strong>Count</strong></td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td><strong>Maximum</strong></td>
<td>10.10</td>
<td>388.00</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>8.5</td>
<td>71.00</td>
</tr>
<tr>
<td><strong>Variance</strong></td>
<td>6.08</td>
<td>3520.98</td>
</tr>
<tr>
<td><strong>Standard Deviation</strong></td>
<td>2.47</td>
<td>59.34</td>
</tr>
<tr>
<td></td>
<td>Ca++</td>
<td>PTH</td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Total:</td>
<td>910.70</td>
<td>4170.00</td>
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<tr>
<td>Average:</td>
<td>9.49</td>
<td>73.16</td>
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<tr>
<td>Count:</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Maximum:</td>
<td>11.70</td>
<td>211.00</td>
</tr>
<tr>
<td>Minimum:</td>
<td>4.90</td>
<td>12.00</td>
</tr>
<tr>
<td>Variance:</td>
<td>1.38</td>
<td>1923.70</td>
</tr>
<tr>
<td>SD:</td>
<td>1.18</td>
<td>43.86</td>
</tr>
</tbody>
</table>
99% Confidence Intervals of the PTH Difference

Difference between sample means = -49.9

% confidence required: 99

Standard error of difference = 9.77  d.f. = 112  t = 2.62

99% confidence interval for the difference between means is:

-75.5  to  -24.3
Does Anyone Remember this Slide?

Model for the Proposed Changes in Calcium Homeostasis and Bone Turnover with Age

- Aging
  - Decreased 25OHD
  - Decreased 1a-hydroxylase
  - Intestinal resistance to 1,25(OH)₂D
  - Decreased bone formation

- Decreased production of 1,25(OH)₂D
- Decreased calcium absorption
- Secondary hyperparathyroidism
- Bone loss
Normocalcemic Hyperparathyroidism should be treated with Parathyroidectomy.
  - A) True
  - B) False
- Low levels of Vitamin D3 should be repleted until they are above 30ng/ml.
  - A) True
  - B) False
• What is the best index of Vitamin D metabolism?
  • A) 25-OH D3
  • B) 1,25 OH D3
  • C) Both
  • D) Neither
Is PTH the best surrogate marker for Vitamin D Metabolism?

Is calcitriol the best and safest treatment for normocalcemic [secondary] hyperparathyroidism? Is there any enhanced risk of stone formation?

Is what we have been calling “Primary” Hyperparathyroidism really “Tertiary” Hyperparathyroidism and, therefore, preventable [with calcitriol Rx?]
Calcitriol to Prevent Hyperparathyroidism (CaPH) Trial
[to be presented at EndoSociety March 2020]

• Double-blind, randomized, parallel-controlled clinical trial stratified by history of nephrolithiasis with follow-up for 5-year duration
• Calcitriol Rx to keep PTH < 70 vs Ergocalcitriol to keep 25-OH D3 > 30
• N=100 patients/arm
• Visits q90 days
• Bone densitometry [including lateral spine] qyear
• Telopeptides, Crosslinks, Alkaline Phosphatase, UV/P_{calcium/creatinine ratio} vs UV/P_{creatinine}, Flat Plates
• Exclusion: P_{creatinine} > 2.0 mg/dl, Ca^{++} > 10.0 mg/dl
• Inclusion: PTH > 70 pg/ml
• Primary Efficacy Variable: Number of documented cases of Hypercalcemic Hyperparathyroidism
• Secondary Variables: Mortality, Kidney stones, Bone density, Fractures
Go Herd!

Questions

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