A New Clinical Presentation of Primary Hyperparathyroidism

Normocalcemic Primary Hyperparathyroidism ("Form Fruste" of an old disease)

Silverberg & Bilezikian et al. J Clin Endocrinol Metab 2003
“Normocalcemic PHPT”

- First coined by Wills et al. (1969)
  
  Wills MR, Pak CY, Hammond WG, Bartter FC.
  
  Normocalcemic primary hyperparathyroidism.

- Cited multiple series from 1950’s
- Mainly in patients with severe & recurrent renal stones disease
- Series obtained from “stone” clinics
- Patients were often intermittently hypercalcemic (which is typical of modern PHPT)
Normocalcemic PHPT
Definition

- The **total serum calcium** is normal, virtually “all the time”
- The **ionized serum calcium** is also normal

Silverberg & Bilezikian et al. J Clin Endocrinol Metab 2003
Patients with osteoporosis who had PTx 15/64 had “normocalcemic hyperparathyroidism”

- Only six had persistent normal serum calcium
- Ionized calcium elevated in 95% of values in these patients
Patients who had PTx

39/60 had “normocalcemic hyperparathyroidism”
- Only 16 had normal ionized serum calcium
- Ionized calcium elevated in 41% of values in these patients
Normocalcemic PHPT

sharpening the definition further exclude the following:

Any secondary causes for elevated PTH

✓ Vitamin D insufficiency  (25-hydroxyvitamin D < 30 ng/ml)
✓ Renal insufficiency (GFR <60 ml/min)
✓ Medications that could alter calcium homeostasis
✓ Hypercalciuria
✓ Any other known metabolic bone disease
Prevalence of Vitamin D Insufficiency in an Adult Normal Population

M.-C. Chapuy¹, P. Preziosi², M. Maamer³, S. Arnaud¹, P. Galan², S. Hercberg² and P. J. Meunier¹

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Fig. 1. Relationship between serum intact parathyroid hormone (iPTH) and 25-hydroxyvitamin D (25(OH)D) values in the whole population studied. For a 25(OH)D concentration higher than 78 nmol/l (31 ng/ml), there is a plateau level at 36 pg/ml for iPTH. When 25(OH)D values are lower than 78 nmol/l (31 ng/ml), the serum iPTH values begin to increase.
These studies are confounded by the lack of any prospective data that would track an individual’s PTH level as the 25-hydroxyvitamin D levels is increased from 20 to 30 ng/mL.

Example:
Individual with a “normal” PTH level of 40 pg/mL when the 25-hydroxyvitamin D level is 20 ng/mL might show reduction to a PTH level 25 pg/mL when the 25-hydroxyvitamin D level is raised to 30 ng/mL.
**Normocalcemic Primary Hyperparathyroidism**

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To be confident in the diagnosis of normocalcemic primary hyperparathyroidism, it would seem advisable to:

Ensure that the 25-hydroxyvitamin D level is greater than 30 ng/ml

Normocalcemic pts with high PTH levels will become hypercalcemic when 25- hydroxyvitamin D levels are raised to higher than 30 ng/ml

The correct diagnosis is **traditional hypercalcemic primary hyperparathyroidism** that is masked by the vitamin D deficiency
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Relationship between PTH and creatinine clearance

PTH rises out of the normal range until the creatinine clearance fell to less than 60 ml/min

Fajtova et al. Calcif Tissue Int 1995
GFR <60 ml is associated with increased parameters of bone resorption


<table>
<thead>
<tr>
<th>Structural indices</th>
<th>GFR &lt;60 (n = 5)</th>
<th>GFR ≥60 (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical width (µm)</td>
<td>695 ± 184</td>
<td>626 ± 209</td>
<td>0.51</td>
</tr>
<tr>
<td>Cancellous bone volume (%; BV/TV)</td>
<td>22.1 ± 6.2</td>
<td>23.2 ± 7.0</td>
<td>0.75</td>
</tr>
<tr>
<td>Trabecular number (1/mm)</td>
<td>1.82 ± 0.23</td>
<td>1.93 ± 0.42</td>
<td>0.61</td>
</tr>
<tr>
<td>Trabecular separation (µm)</td>
<td>435 ± 92</td>
<td>424 ± 134</td>
<td>0.88</td>
</tr>
<tr>
<td>Trabecular width (µm)</td>
<td>121 ± 35</td>
<td>119 ± 25</td>
<td>0.89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remodeling indices</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoid surface (%)</td>
<td>25.2 ± 12.7</td>
<td>29.3 ± 12.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Osteoid width (no. lamellae)</td>
<td>13.3 ± 1.3</td>
<td>13.5 ± 3.1</td>
<td>0.88</td>
</tr>
<tr>
<td>Mineralization lag time (d)</td>
<td>34 ± 14</td>
<td>50 ± 34</td>
<td>0.59</td>
</tr>
<tr>
<td>Mineralizing surface (%)</td>
<td>19.0 ± 11.3</td>
<td>19.3 ± 10.3</td>
<td>0.95</td>
</tr>
<tr>
<td>Mineral apposition rate (µm/d)</td>
<td>0.65 ± 0.09</td>
<td>0.63 ± 0.12</td>
<td>0.69</td>
</tr>
<tr>
<td>Bone formation rate (µm³/µm² · d)</td>
<td>0.13 ± 0.09</td>
<td>0.11 ± 0.06</td>
<td>0.63</td>
</tr>
<tr>
<td>Eroded surface (%)</td>
<td>12.0 ± 4.2</td>
<td>8.3 ± 2.7</td>
<td>0.02a</td>
</tr>
<tr>
<td>Activation frequency (cycles/yr)</td>
<td>0.62 ± 0.15</td>
<td>1.07 ± 0.62</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Values represent mean ± sd. BV/TV, Bone volume/tissue volume.

a Statistically significant when controlling for multiple comparisons.
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Thiazide-induced Parathyroid Stimulation

By Jack R. Pickleman, Francis H. Straus II, Marvin Forland and Edward Paloyan

Mitabolism. Vol. 18, No. 10 (October) 1969

Serum Ca and P in dogs on increasing doses of HCT

Parathyroid from thiazide-fed dog
Note area of less dense cells at the top

Bulging, granular cytoplasm and vacuolar change
Lithium Treatment Increases Intact and Midregion Parathyroid Hormone and Parathyroid Volume*

LAWRENCE E. MALLETTE, KHALIL KHOURI, HIRAM ZENGOTITA, BRUCE W. HOLLIS, AND SRINI MALINI

*J Clin Endocrinol Metab 68: 654, 1989

Long term lithium treatment increases circulating PTH and causes parathyroid enlargement
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Evidence for Secondary Hyperparathyroidism in Idiopathic Hypercalciuria

Fredric L. Coe, Janet M. Canterbury, John J. Firpo, and Eric Reiss

The Journal of Clinical Investigation Volume 52 January 1973
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Gastrointestinal disorders associated with calcium malabsorption

Role of calcium malabsorption in the development of secondary hyperparathyroidism after biliopancreatic diversion

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Bone Loss in Celiac Disease Is Related to Secondary Hyperparathyroidism*

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