Primary Hyperparathyroidism: Applying New Guidelines to Patient Management

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UCSF CME - Diabetes Update and Advances in Endocrinology and Metabolism
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NOTHING to DISCLOSE

NO CONFLICTS of INTEREST
Objectives

• How presentation of primary HPT has changed over time
  – Symptomatic vs asymptomatic HPT
• Vitamin D and primary HPT
• New etiologies of FHH
• New management guidelines – 2014
• 3 case presentations

Clinical Features - Changed With Time!

• “Classic”
  Renal stones (40%)
  Bone pain, pathologic fractures, cystic bone lesions
  Gastrointestinal complaints
  Myopathy
  Mental status, memory, concentration deficits

• Contemporary
  Stones (10-15%)
  Discovered in workup for osteopenia or osteoporosis
  Fatigue and depression
**Clinical Features – Continue to Change With Time!**

- Newest forms of disease presentation
  - Biochemical parameters – even milder
  - Patients with normal (even low) PTH levels
  - “Normocalcemic” variant of primary HPT

- Imaging much more sensitive
  - Parathyroid “incidentaloma” by U/S (without biochemical abnl)

**Contemporary HPT Cohorts: US and Europe**

- ~ 80% asymptomatic
- ~ 20% symptomatic
- ? % “normocalcemic variant”

- Most patients identified by screening lab tests for something else, general health
Who Is Truly “Asymptomatic” with Primary HPT? (Cipriani et al, JCEM, 2015)

- Confounded by how we define symptomatic vs asymptomatic – clinically based
- Contemporary cohort of 140 pts (referred 2009-2013; Univ of Rome)
- 127 women (86% postmenopausal), 13 men
- Clinical assessment + prevalence of kidney stones (U/S) and vertebral fractures (xray)

→ Not the classic approach

140 Patients Consecutively Evaluated with PHPT

Queried for polyuria, dehydration, N, V, constipation, anorexia, fatigue, N-M symptoms, h/o fragility fracture; h/o stones (1 episode renal colic/5 yrs), nephrocalcinosis and/or +renal imaging - - NOT attributable to other conditions

64 “SYMPTOMATIC”  
76 “ASYMPTOMATIC”

Cipriani C et al, J Clin Endo Metab, 2015
Findings in Cohort of Primary HPT
(Cipriani et al, JCEM, 2015)

• **55%** of patients had evidence of kidney stones by imaging
  – 16% had bilateral stones
• **35%** had vertebral fractures (xray)
  – 5% gave h/o vertebral frx
  – 7.8% h/o distal radius frx

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic (N=64)</th>
<th>Asymptomatic (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62</td>
<td>64</td>
</tr>
<tr>
<td>Serum Ca (mg/dl)</td>
<td>11.3 ± 0.9</td>
<td>11 ± 0.8</td>
</tr>
<tr>
<td>Serum PTH (pg/ml)</td>
<td>115</td>
<td>106</td>
</tr>
<tr>
<td>Urine Ca (mg)</td>
<td>294</td>
<td>288</td>
</tr>
<tr>
<td>% Osteoporosis</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>% Stones</td>
<td>**78 ***</td>
<td>36 *</td>
</tr>
<tr>
<td>% Vertebral Fractures</td>
<td>34 **</td>
<td>35 **</td>
</tr>
</tbody>
</table>

* p < 0.0001
** many more than those with + history
Although stones & fractures by imaging MUCH MORE common, still disease has 2 main presentations (age, BMD) *

<table>
<thead>
<tr>
<th></th>
<th>Only kidney stones (N=22)</th>
<th>Only osteoporosis and or fracture (N=45)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.9 ± 14.2</td>
<td>65.7 ± 9.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LS T Score</td>
<td>-0.8 ± 0.8</td>
<td>-2.6 ± 1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FN T Score</td>
<td>-1.1 ± 0.6</td>
<td>-2.3 ± 0.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TH T Score</td>
<td>-0.7 ± 0.9</td>
<td>-1.8 ± 0.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Radius T Score</td>
<td>-0.7 ± 0.8</td>
<td>-2.7 ± 1.1</td>
<td>&lt; 0.0001</td>
</tr>
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</table>

Vitamin D and Primary HPT

- 25(OH) vit D levels tend to be low
  - Insufficiency (20-30 ng/ml) and deficiency (<20 ng/ml) – frequent in primary HPT
  - Low 25 OH D assoc with higher rates of bone turnover, lower BMD, & potential for post-op hypocalcemia and persistently high PTH levels

- 1,25 (OH)2 D levels – maintained or elevated

- Why is 25 OH D low ?
  - 24 hydroxylase induced (by high 1,25 D, maybe PTH) → metabolism of 25 (OH) D → 24,25-(OH)2 D

- Concern for safety of vit D “repletion” in pts with primary HPT
Vitamin D Treatment in Primary HPT  
(Rolighed et al, JCEM, 2014)

• DB, placebo-controlled RCT  
• 46 pts with hypercalcemic primary HPT planned for surgery  
• Placebo vs 2800 IU vit D3/day X 1 yr  
• PTX performed at week 26  
• Pts followed on treatment for additional 26 weeks  
• **End-points:** pre-op PTH (1°) and safety measures (2°) – S-Ca, creat, U-Ca

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Ref Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>59 yrs</td>
<td></td>
</tr>
<tr>
<td>S-Calcium</td>
<td>1.41 mM</td>
<td>1.18-1.32</td>
</tr>
<tr>
<td>S-PTH</td>
<td>13.0 pM</td>
<td>1.6-6.9</td>
</tr>
<tr>
<td>S-25 OH vit D</td>
<td>54 nM (48-60)</td>
<td>75-80</td>
</tr>
<tr>
<td>S-Creatinine</td>
<td>69 mM</td>
<td>45-90</td>
</tr>
<tr>
<td>S-Phosphate</td>
<td>0.77 mM</td>
<td>0.76-1.41</td>
</tr>
<tr>
<td>Alk phosph</td>
<td>84.6</td>
<td>35-105</td>
</tr>
<tr>
<td>Urine Ca</td>
<td>9.4 mmol/d</td>
<td>2-9</td>
</tr>
</tbody>
</table>

~21 ng/ml
• 25 OH Vitamin D levels rose expectantly
(solid symbols = vitamin D3 treated)

• PTH levels came down to greater extent in vitamin D treated – pre- and post-op (met primary end-point)
• **Bone resorption marker** (serum C-telopeptide) – fell pre-op in vitamin D treated group but fell at same rate in both groups post-operatively

**PTH is the driver!**

• **Urinary Ca levels did not differ in both groups** – pre- and post-op, came down after surgery

**IONIZED Ca++ DID NOT DIFFER ACROSS GROUPS NO INCREASE – WITH SUPPLEMENTATION**
SUMMARY

• BMD/DXA rose to greater extent in 1 year in D-treated vs PBO pts
  – Total hip 2.8% vs 1.5% (p=0.09)
  – Fem neck 2.2% vs 0.1% (p=0.08)

• Serious AE’s and AE’s: “no signal” and no imbalances across study groups

• Biochemical criteria for study withdrawal –
  – Never close to being met (serum creat >170 mM, Ca > 1.70 mM)

Vit D repletion can be done safely in pts with MILD HPT → lower pre- and post-op PTH levels

Familial Hypocalciuric Hypercalcemia - An Important Mimicker of Primary HPT
FHH Is Genetically Heterogeneous

- **FHH1**: ~65% patients with phenotype
  - Heterozygous inactivating *CASR* mutations
  - >100 identified
- **FHH2**
  - Heterozygous loss of function mutations in G alpha 11
- **FHH3**
  - Loss of function of protein involved in CaSR trafficking


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**FHH type 2**

**FHH3** — mutations in adapter protein involved in CaSR trafficking, determining surface CaSR #
Exclude FHH

- **Will now require more than CASR sequencing**
- **Consider other forms – FHH2 and 3** (testing not commercially available)

RENAL CALCIUM: CREATININE CLEARANCE RATIO

\[
\frac{U-Ca \times S-creat}{S-Ca \times U-creat}
\]

**Evaluate all patients with possible PHPT (esp if asymptomatic)**
**Greatest overlap in CCCR between PHPT and FHH (0.01-0.02 range)**
**Ratio < 0.01** – suggests FHH (genetic testing to confirm)
**Ratio > 0.02** - more likely primary HPT

No cut-point perfect

Christensen et al, Clin Endo, 2008; Eastell et al, JCEM 2014

- More extensive evaluation of skeletal and renal systems
- Skeletal/renal evaluation is part of future recommendations for surgery
- More specific monitoring guidelines for those who do NOT meet criteria for surgery (more proscriptive)

Bilezikian JP et al, J Clin Endo Metab, 8/2014
### 2013 - Guidelines for Recommending Surgery (*new*)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca</td>
<td>1.0 mg/dl (0.25 mM) above ULN</td>
</tr>
</tbody>
</table>
| Skeletal  | (a) BMD T score < -2.5 (LS, TH, FN, 1/3 radius) or by Z score if < age 50  
(b) Vert frx by xray, CT, MRI, VFA  
(c) Fragility frx at any site |
| Renal     | (a) Creat clear < 60 ml/min  
(b) 24 h U-Ca > 400 mg (10 mmol) and increased stone risk by biochem stone risk analysis  
(c) Presence of stones by xray, CT, US |
| Age       | < 50 years |

*Bilezikian JP et al, J Clin Endo Metab, 8/2014*

### 2013 – Medical Monitoring Guidelines - Those Who Do Not Undergo Surgery (*new*)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca</td>
<td>Annually</td>
</tr>
</tbody>
</table>
| Skeletal  | Every 1-2 years with DXA (3 sites)  
Xray or VFA if clinically indicated |
| Renal     | Serum creatinine and eGFR annually  
If stones suspected, obtain 24 h urine biochemical stone profile and or renal imaging (xray, US or CT) |
| Clinical  | Annually – checking for symptom/complication development over time |

*Bilezikian JP et al, J Clin Endo Metab, 8/2014*
~NEW~ 2013 – Changes in Specific Endpoints During Monitoring → Recommend Surgery

### Parameter | CHANGE
---|---
Serum Ca | An INCREASE to > 1 mg/dl (0.25 mM) above ULN
Skeletal | (a) T score falls to -2.5  
(b) Progressive fall in BMD exceeding LSC* at any site and T score between -2.0 and -2.5 (may opt for surgery)  
(c) Fragility frx occurs
Renal | Creat clearance → < 60 ml/min  
Kidney stone occurs

* 2.77 X precision error  
Bilezikian JP et al, J Clin Endo Metab, 8/2014

~New~ Algorithm for Monitoring Patients with Normocalcemic PHPT

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

- Progression to hypercalcemic primary HPT  
- Progression of disease  
  - Worsening BMD or fracture  
  - Kidney stone or nephrocalcinosis

- Follow guidelines  
- Surgery

Bilezikian JP et al, J Clin Endo Metab, 8/2014
Case 1

50 yo female referred by primary care MD for hypercalcemia

- + HTN, low energy, muscle aching, remote h/o kidney stone (in her 40’s); NO fractures; is perimenopausal with symptoms
- Meds: atenolol, ACE-I; NO Ca, MVI, vit D, HCTZ
- FH: neg
- PE: wnl BP 140/85
- S-Ca 10.3, 10.5 mg/dL (8.5-10.5)
- PTH 105, 117 pg/ml (12-65) 25-OH D 24 ng/ml
- Creat 0.8 mg/dL
- 24 hr urine: creat 1200 mg Ca 317 mg
- DXA: LS - 2.5 Fem neck - 2.1
### WATCH or OPERATE?

<table>
<thead>
<tr>
<th>Recommend Surgery If -</th>
<th>YES or NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of hypercalcemia</td>
<td>Maybe (old stone)</td>
</tr>
<tr>
<td>Age &lt; 50</td>
<td><strong>YES (close enough)</strong></td>
</tr>
<tr>
<td>Serum total Ca 1.0 mg/dl above ULN</td>
<td>No</td>
</tr>
<tr>
<td>Creat clearance &lt; 60 ml/min</td>
<td>No</td>
</tr>
<tr>
<td>BMD DXA &lt; -2.5</td>
<td><strong>YES</strong></td>
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> 25 OH vit D low (would replete to 30 ng/ml)
> Urine Ca - high/317 mg (CCCR = **0.025**)

### NEW GUIDELINES
- do abd U/S
- 24 hr urine stone risk analysis
- vertebral xrays
- Agreed to surgery, MIP after 2 concordant localizing studies → single adenoma, normocalcemic since; BMD/DXA being followed for response post-PTX
CASE 2

70 yo African American female referred from Endo Surgeon

• Recurrent hypercalcemia
• Left inferior PTX in 2001
• Path: 1.5 x 1.5 x 0.5 cm hypercellular PT tumor
• S-Ca normalized X 2 yrs; recurrent hypercalcemia in 2004 (was ignored) → seen 8 years later
• NO stones, fractures, ulcers; + depressed
• PMH: +HTN, +hyperlipidemia
• Meds: beta blocker, ACE-I, CaCB, HCTZ (12.5 mg), atorvastatin
• FH – negative

CASE 2 – cont’d

• Exam: elderly woman, healed cervical scar; depressed affect
  P 60  BP  140/90
• LABS and STUDIES:
  • Serum Ca 11.4, 11.1 mg/dL (8.9-10.3), Alb 3.5 G/dL
  • Plasma PTH 269, 330 pg/mL (10-65)
  • Creat 1.5 (0.5-1.30); eGFR 42
  • 25 OH vitamin D 15 ng/mL
  • 24 hr U-Ca 152 mg (nl U-creat)
  • DXA T scores: LS -1.6  TH -2.2  FN -2.4
## WATCH or OPERATE?

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<td>Age &lt; 50</td>
<td>No</td>
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<tr>
<td>Serum total Ca 1.0 mg/dl above ULN</td>
<td>Intermittently YES</td>
</tr>
<tr>
<td>Creat clearance &lt; 60 ml/min</td>
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</tr>
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<td>BMD DXA &lt; -2.5</td>
<td>Almost</td>
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→ 25 OH vit D low (would replete to 20 - 30 ng/ml)
→ Urine Ca - not high, African American

## WATCH or OPERATE?

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**NEW GUIDELINES**

→ do abd U/S
→ if neg – NO stone risk analysis
→ vertebral xrays

**Refused surgery**
Given cinacalcet, ALN
2 yrs later (not feeling better) → agreed to surgery, 2nd large adenoma found, CURED
CASE 3

30 yo male met by an endocrine fellow at a medical informatics and computer science conference

- Reported that he had been feeling very fatigued
- Found to have a Ca in the mid-11’s, PTH elevated
- No FH, stones, fractures, complaints referable to other endocrine tumors
- U Ca ~400 mg/24 hrs

WATCH or OPERATE?

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**NEW GUIDELINES**

⇒ do abd U/S
⇒ if neg – NO stone risk analysis
⇒ no xrays

Recommend surgery
Consider genetic testing
Should Genetic Testing Be Done?
(Starker et al, Horm Cancer, 2012)

- Sequenced MEN1, CASR, HRPT2/CDC73 in all 86 pts (< age 45)
- NONE had h/o familial HPT or tumors - - suggestive of MEN1, HPT-jaw tumor syndrome
- 8/86 or 9.3% of these patients - germ-line mutations in these genes (4 MEN1, 3 CASR, 1 HRPT2)
- TOTAL (age < 45): 23.5% had genetic explanation for HPT (add those w/familial dis @ outset)
  - 15 MEN1, 4 RET, 3 CASR, 2 HRPT2 (mutations)

Concluded
- Germ-line inactivating mutations – COMMON
- "Enhanced use of genetic analysis may be warranted"
CONCLUSIONS

- Range of complications in patients with mild PHPT – enlarged
  - More renal and skeletal involvement
- “Normocalcemic variant” – better appreciated
- Genetic heterogeneity in FHH – 3 types
- RCT → safe to replete vit D in mild PHPT
- NEW 2013 Management Guidelines –
  - Surgery is only curative modality
  - Monitoring of asymptomatic PHPT - more extensive – skeletal/renal parameters
  - Specific monitoring for “normocalcemic” PHPT proposed and considerations for surgical intervention
FHH 3

- Confirmed in subset (11 of 50) pts with “FHH phenotype” and neg for CASR mutations (~20%)
  - Heterozygous loss of function mutations in AP2S1 (adapter protein-2 → 4 subunits α, β, μ, σ)


*All mutations in Arg15 (11 probands) - - affect signaling, endocytosis – explain FHH3

Nesbit MA et al, Nat Gen, 2013
Other Diagnoses Must Be Considered: Elevated/Normal PTH

- Vitamin D deficiency → 25 OH vitamin D checked and repleted if low (common in population & pts with HPT)
- Familial hypocalciuric hypercalcemia: check urinary Ca clearance – all pts (uncommon; ~1/70,000)
- “Normocalcemic” primary HPT
  - 2º HPT – renal leak, malabsorption, CKD