"Asymptomatic" Hyperparathyroidism: Reasons for Parathyroidectomy

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## Primary Hyperparathyroidism

### Clinical Presentation

“Bones, stones, abdominal groans, and psychic moans”

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<th>Renal</th>
<th>Gastrointestinal</th>
<th>Neuropsychiatric</th>
<th>Neuromuscular</th>
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<td>• Nephrocalcinosis&lt;br&gt;• nephrolithiasis&lt;br&gt;• calciuria&lt;br&gt;• polyuria&lt;br&gt;• overflow incontinence</td>
<td>• Nausea/vomiting&lt;br&gt;• Anorexia&lt;br&gt;• Constipation&lt;br&gt;• abdominal pain&lt;br&gt;• Pancreatitis&lt;br&gt;• Reflux&lt;br&gt;• peptic ulcers</td>
<td>• Depression&lt;br&gt;• Anxiety&lt;br&gt;• psychosis&lt;br&gt;• memory loss&lt;br&gt;• concentration problems</td>
<td>• Fatigue&lt;br&gt;• Myalgias&lt;br&gt;• muscle weakness</td>
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<td><strong>Bone</strong></td>
<td><strong>Cardiovascular</strong></td>
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<td>• Osteitis fibrosa cystica&lt;br&gt;• osteopenia/osteoporosis&lt;br&gt;• bone pain&lt;br&gt;• pathological fractures</td>
<td>• Hypertension</td>
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Primary Hyperparathyroidism

*Diagnosis*

- Elevated serum calcium (>10.5 mg/dl)

- Intact PTH level (>65 pg/ml)
  - Inappropriately normal value with ↑ Calcium
  - If Calcium is normal – check Vit D

- High or high normal urinary calcium levels
  - low urinary calcium with high serum calcium suggestive of Familial Hypocalcuric Hypercalcemia (FHH) -- no intervention needed
NIH Consensus Guidelines 2002:  
Indications for Parathyroidectomy

1. Serum calcium >1 mg/dl above upper limit of normal (>11.2-11.5 mg/dL)
2. 24 hours urinary calcium > 400 mg/24 hr
3. Presence of Kidney Stones
4. Creatine clearance reduced by more than 30% compared with age-matched controls
5. Bone density > 2.5 SDs below peak bone mass (T score) at any site
6. Age under 50
7. Adequate follow-up not possible or desired

*Ignored patients with more subjective symptoms, elderly patients, and those with milder disease*
Asymptomatic Hyperparathyroidism

Reasons to consider parathyroidectomy

- Symptomatic Improvement
- Improved Quality of Life
- Improvements in Bone Mineral Density/Fracture Rates
- Cardiac Benefits
- Decreased Mortality
Symptomatic Improvement after Parathyroidectomy
Symptomatic Improvement

Are they really symptomatic?

- No subjective symptoms are included in NIH Guidelines
- Symptoms are common in all patients with 1º HPTH (whether or not they meet the NIH Guidelines)

Symptomatic Improvement

Do they improve?

Symptomatic improvement in patients that do not meet the NIH Guidelines is just as great.

Symptomatic Improvement

*Are the changes real?*

Could it just be a placebo effect of surgery?

Quality of Life Improvements after Parathyroidectomy
Quality of Life Improvement

*SF-36 Scores Improve*

Fig. 3. Radar plot shows SF-36 scores for patients with HPT at baseline \((n = 56)\) and 6 months \((n = 23)\).
Quality of Life Improvement

Symptomatic vs. Asymptomatic

- 82 pts 1 to 2 or more years after parathyroidectomy
  - 47 were asymptomatic and 35 symptomatic
  - Both groups demonstrated improvement of general health, muscle strength and improvement of emotional or physical problems on daily activity, anxiety, mood and energy level.

"Improvement in the health-related quality-of-life and symptoms of hyperparathyroidism is durable on long term follow-up."

Quality of Life Improvement

Mild Asymptomatic Hyperparathyroidism

Randomized Control Trials:
Parathyroidectomy vs. Observation

1. “Even in patients with mild asymptomatic disease (Ca 10.3 mg/dL, normal PTH in 36%) modest benefits occurred in bone density, quality of life and psychological function after parathyroidectomy”
   J Clin Endocrinol Metab. 2004 Nov;89(11)

2. After 1 year, the surgery patients showed significant differences in four quality of life measures: bodily pain (P = 0.001), general health (P = 0.008), vitality (P = 0.003), and mental health (P = 0.017).
   J Clin Endocrinol Metab. 2007 Aug;92(8)
Bone Improvements after Parathyroidectomy
Bone Effects after Parathyroidectomy

**Bone Mineral Density Changes**

121 pts. with primary hyperparathyroidism

**Surgery vs. Observation**

- **Increase in lumbar-spine bone mineral density**
  - 8 ±2 percent after 1 year (P=0.005)
  - 12 ±3 percent after 10 years (P=0.03)

- **Increase in femoral neck BMD**
  - 6 ±1 percent after 1 year (P=0.002)
  - 14 ±4 percent after 10 years (P=0.002)

- **BMD of the radius did not change significantly**

Bone Effects after Parathyroidectomy

*Bone Mineral Density Changes*

Elderly Patients with HPTH

- Lumbar Spine improves the most
  - Baseline: $T = -3.1$
  - 12% at 1 yr: $T = -2.6$
  - 19% at 3 yr: $T = -2.0$
  - 29% at 5 yr: $T = -1.2$

- Some improvement in Femoral head
- Minimal improvements in radial head

*JBMR 2007. 25:226-231*
Bone Effects after Parathyroidectomy

Decrease in Fracture Risk

674 pts with Primary HPTH treated with parathyroidectomy vs. 2020 controls

Bone Effects after Parathyroidectomy

Decrease in Fracture Risk

• Risk of fracture is increased up to 10 years before surgery in patients with primary hyperparathyroidism.

• The risk of fracture was not related to the degree of hypercalcemia.

• The fracture risk returns to normal 1 year after surgery.

Vestergaard BMJ 321: 598-602, 2000
Bone Effects after Parathyroidectomy

Decrease in Fracture Risk

Fracture-free survival of 1569 patients with primary hyperparathyroidism: parathyroidectomy vs. observation

10-yr fracture rate

27% - parathyroidectomy

41% - observation

P<0.001

Bone Effects after Parathyroidectomy

Decrease in Fracture Risk

What about medical therapy – why not just use bisphosphonates?

22 elderly patients with primary hyperparathyroidism

- Surgery
- Bisphosphonate Therapy

20% increase in Lumbar BMD

10% increase in Lumbar BMD

Cardiac Benefits of Parathyroidectomy
Cardiac Benefits of Parathyroidectomy

**Decrease in LVH**

- Left Ventricular Hypertrophy is a frequent finding in asymptomatic hyperparathyroidism (65% of patients)
  - It is independent of hypertension
  - It correlates with blood PTH level

- Parathyroidectomy decreases LV hypertrophy by 6 months

Clinical Endocrinology 50:321-8, 1999
Cardiac Benefits of Parathyroidectomy

*Decrease in MI*

- Risk of MI is increased up to 10 years prior to parathyroidectomy
- The risk of MI returns to normal after surgery

Improved Mortality after Parathyroidectomy
Increased Mortality with Hyperparathyroidism

*Increase in Heart Disease, Stroke, and Cancer*

Cohort of 1578 pts. with 1º Hyperparathyroidism

- 20% died during the 15 year f/u period

- The standard mortality ratio
  - women  1.7  (95% CI 1.5–1.9)
  - men  1.6  (95% CI: 1.3–2.0)

- Increased mortality from:
  - ischemic heart disease
  - cerebrovascular disease
  - cancer

Increased Mortality with Hyperparathyroidism

*Increase in Cardiovascular Death*

All patients (4461) operated on for primary hyperparathyroidism in Sweden 1987-1994 versus normal Swedish Controls matched for age, sex, and calendar year

- Increased risk ratio for death from cardiovascular disease
  - 1.71 for male
  - 1.85 for female patients

Increased Mortality with Hyperparathyroidism

*Elderly at Highest Risk*

- 13.2% Excess death due to all causes (p<0.001)
  - cardiovascular disease (p<0.001)
  - cancer (p<0.001)

- Death rate increased for all age groups with greatest increase from 50 to 70 years of age

**Why then do the NIH consensus suggest that patients over 50 years of age can be "followed"?**

Increased Mortality with Hyperparathyroidism

Improved with Parathyroidectomy

Mortality Rate

• 32% in 172 hyperparathyroid patients
• 23% in 344 eucalcemic controls

The greater risk of death appeared to decrease after the initial 5 to 8 postoperative years
Conclusion:

Virtually all patients with HPT benefit from parathyroidectomy (symptomatically, metabolically, and improved survival)