Asymptomatic Hyperparathyroidism: Operative Cure vs. Observation

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Primary Hyperparathyroidism

• Inappropiate or excessive secretion of PTH by one or more parathyroid glands, leading to hypercalcemia.

• Etiology
  – 85% from single adenoma
  – 15% from multiple gland hyperplasia
  – <1% from CA

Current Surgical Therapy. John Cameron, ed. 9th Ed. 2007
Primary Hyperparathyroidism

Historical Perspective

• 1852  Sir Richard Owen discovers parathyroid glands in an Indian rhinoceros

• 1887  Ivar Sandström, a 25-year-old medical student, publishes, “On a New Gland in Man and Fellow Animals.”

• 1903  William J MacCallum (Johns Hopkins) suggests parathyroids have a role in calcium metabolism

• 1925  First parathyroidectomy (Felix Mandl, Vienna).

• 1928  First successful parathyroidectomy in the U.S. (Issac Y. Olch, Barnes Hospital)

1  Organ CH  JACS 2000(3); 191:284-299
Historical Perspective

• 1963  Berson and Yalow win nobel prize for the development of an immunoassay for the measurement of parathyroid hormone and other peptides.

• 1969 Introduction of the serum chemical autoanalyzer with routine calcium determinations

• 1970’s: Four to fivefold increase in incidence of primary hyperparathyroidism

1  Organ CH  JACS 2000(3); 191:284-299

NIH Guidelines for Operation

- Overt clinical manifestations of disease
  - Kidney stones or nephrocalcinosis
  - Fractures or classic radiographic findings of osteitis fibrosa
  - Classic neuromuscular disease
  - Symptomatic or life-threatening hypercalcemia

- Serum calcium >1 mg/dL above the upper limit of normal
- Urinary calcium excretion >400 mg/day
- Creatinine clearance <70% of predicted
- Bone mineral density low (T score <2.5) at any site
- Young age (<50 years)

Uncertain prospects for adequate medical monitoring

‘Asymptomatic Hyperparathyroidism’

• The Hypercalcemic Incidentaloma
  – Most pts present asymptomatic disease (~80%) ¹
  – Many have nonspecific complaints: primarily neuropsychological and quality of life²
  – Some have no complaints but family members notice nonspecific changes. ²

• 80% do not meet current NIH recommendations for PTX

The Debate

• How to manage asymptomatic patients
  (i.e. those that meet the guidelines)

• How to manage ‘asignomatic’ patients (i.e. those who do NOT meet the guidelines)
Practice Patterns

- 75% of endocrinologist would not refer a patient who met criteria by hypercalcemia\(^1\) (cf. Keith J)
- Estimated incidence of 1.5% in pts 65 yrs or older, but approximately 12,000 parathyroidectomies per year \(^2\)
- 80% of endocrine surgeons would operate on patients who do not meet guidelines \(^3\)
- Almost 75% of patients undergoing PTX are asymptomatic \(^4\)

Medical Therapy

• Bisphosphonates:
  – No study has included more than 45 patients
  – None have shown decreased Ca or PTH at 2 years
    • Decreased calcium at 2-6 months
    • Return to baseline at one year
    • Increased PTH during first year
    • 10% increase BMD with etidronate
    • 20% increase BMD with PTX

Medical Therapy

• Calcimimetics:
  – Peacock, et al (2005) RCT of Cinacalcet (Sensipar) for one year
    • Rapid and sustained normalization of PTH and Ca
    • No clinically significant change in BMD

  – No trials to evaluate long-term PTH suppression, evaluation of influence on QOL and cardiovascular risk
  – Cost for one year of treatment (wholesale): $7000.00
  – Common short-term side effects include: diarrhea, muscle pain, dizziness, HTN, weakness and fatigue, loss of appetite. i.e. Abdominal groans and psychiatric overtones. (Bones and stones yet to be determined.)

Medical Therapy

• **Estrogen:**
  
  – Women with mild asymptomatic hyperparathyroidism on ERT have greater mean bone mass values greater than controls \(^1,2\)
  
  – Does not decrease parathyroid hormone levels; Presumably acts at level of the bone
  
  – Must be weighed against risks of estrogen therapy and likely should not be used outside the setting of post-menopausal women


• “No convincing data support the long-term efficacy of medical therapy or simply observation in the management of PHPT”

Surgery for Hyperparathyroidism

• “It seems hardly credible that the loss of bodies so tiny as the parathyroids should be followed by a result so disastrous.”

-- W. Halsted
Standard Parathyroidectomy

- Bilateral Neck Exploration
  - No pre-op localization
  - Intraoperative frozen section
  - 95-98% cure rate at initial exploration
  - 1-2% complication rate
  - General anaesthesia
  - 1-2 day hospital stay
Minimally Invasive Parathyroidectomy

• **MIP**
  – Preoperative localization with intraoperative PTH
  – Vast majority are discharged on the day of surgery.
  – 96-100% cure rate.
  – Theoretical lower complication rate

• Has lowered the threshold for surgical referral
Parathyroidectomy

• Complications
  – Recurrent laryngeal nerve injury
    • Reported 1-10%
  – Persistent Hyperparathyroidism
    • Lowest in high volume centers
    • Remedial parathyroidectomy 85-95% cure rate
  – Hypocalcemia
    • Seldom requires long term replacement

Townsend: Sabiston Textbook of Surgery, 18th ed.
Benefits of Parathyroidectomy

- **Osteoporosis:**
  - Normalized bone remodeling at 6 months\(^1\)
  - Increased BMD at sites rich in cancellous bone\(^2\)
  - Up to 6% increase in lumbar spine, hip, and whole body BMD at 12 months and sustained for more than 6 yrs.\(^3\)

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Benefits of Parathyroidectomy

– Risk of fracture:
  • 9-14% of pts have fx at time of diagnosis
  • Risk of further fracture decreased with PTX
  • 10 yr fx free survival increased with PTX: 73% v. 59%
  • Decreased fracture risk at 10 yrs: 8% hip, 3% extremity

– Hip fracture:
  • One-year mortality 20%
  • 40% of survivors can perform all routine activities of daily living
  • 54% of survivors can walk without an aid.

Benefits of Parathyroidectomy

- Neuropsychological abnormalities:
  - Increased cognitive skills, concentration, memory, and ability to perform tests accurately increased with PTX \(^1,2\)
  - Improved psychopathological symptoms with PTX\(^3\)
    - Improved attention, memory, and reasoning.\(^2\)

Benefits of Parathyroidectomy

• Quality of Life:
  – Studies consistently show decreased QOL ¹
  – PTX significantly improves patient-reported QOL²,³
  – Greatest improvement in first 3 months. ²,³
  – Improvement regardless of calcium levels. ¹

Benefits of Parathyroidectomy

• Quality of Life:
  – Eigelberger, et al. (2004) Prospective trial compared pts who do and do not meet
  guidelines v. Controls
  • Equivalent pre-operative somatic and
  neuropsychological symptoms and increased
  compared to controls (thyroidectomy)
  • Improvement of symptoms was dramatic and equal
  in the two groups

Quality of Life

Changes in the frequency of symptoms after surgery in the combined hyperparathyroid group versus the thyroid group.
Postoperative symptomatic improvement in the NIH HPT group versus the non-NIH HPT group.
Benefits of Parathyroidectomy

• Lipid metabolism:
  – Increased dyslipidemia and body mass index with PHPT\(^1\)

• Cardiac Morbidity:
  – Improved LV hypertrophy\(^2\) and dysfunction\(^4\), decreased HTN and PVC’s (during exercise)\(^3\), and decreased cardiac death with PTX.\(^2\)

• Glucose Tolerance:
  – Improved in 37% of patients with PHPT and DM after PTX\(^5\)

• Overall Mortality:
  – 33,000 men <50yrs old followed 10 yrs.: Pts with serum Ca>2.6 had doubled mortality compared to pts with Ca<2.45

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Benefits of Parathyroidectomy

• Cost Effectiveness: 1

  – Operation remained cost-effective until the average cost of parathyroidectomy increased from the estimated value of US$4778 to US$14,650.

  – Pharmacological therapy was not cost-effective unless the annual cost of therapy decreased from an estimated US$7,406 (for cinacalcet) to US$221.


Parathyroidectomy

- Elderly patients (>80 yrs)
  - Sx: fatigue, weight loss, nocturia, bone pain, constipation, and major depression.
  - Improvement in all categories noted after PTX
  - 25% had 5 yr delay in referral.

High Risk PHPT Patients

- 14 pts refused operation: continued bisphosphonates
- 19 pts underwent miPTX under local anaesthesia
- Bisphosphonates:
  - Significantly increased incidence of episodes of hypercalcaemic crisis, deteriorating renal function and weight-bearing bone fractures
- miPTX:
  - No operative complications, mortality or recurrent hypercalcaemia (mean follow-up of 35.5 months)
  - Higher incidence of improved ASA and NYHA class
  - Better 3-year overall survival rate (83.1% vs. 60.8%, P = 0.032)
  - Lower medical costs

Asymptomatic?

• Prospective long-term study of 360 patients undergoing PTX: ¹
  – Only 6% truly asymptomatic as evaluated by pre- and post-operative studies.
  – Many were unaware of symptoms (e.g. fatigue) prior to surgery.

• Epidemiological cohort-study of 582 consecutive PTX patients: ²
  – 116 patients (21%) considered asymptomatic before operation
  – 4% of the entire cohort confirmed asymptomatic post-op
  – Postoperative improvement reported in over 80% of patients considered ‘asymptomatic’.

Benefits of Parathyroidectomy

- BMD
- Risk of fracture
- Neuropsychological function
- Quality of life
- Overall mortality and health

- Asymptomatic
- Minimal biochemical derangements
- Advanced age
- Higher operative risk
Conclusions and Recommendations:

“PHPT remains a relatively common disorder of calcium metabolism that is readily cured by a low-risk operation in 95 to 98% of patients when performed by a qualified surgeon. Operative management is the treatment of choice for all symptomatic patients and all asymptomatic patients younger than age 50 years or for patients who cannot participate in adequate medical follow-up. Operative management should also be considered for all other asymptomatic patients with suitable risk and a reasonable life expectancy.”

American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons position statement on the diagnosis and management of primary hyperparathyroidism.
More Problems

• Adherence to monitoring guidelines ranged widely
  – 6% obtained creatinine clearance
  – 78% of physicians ordered serum calcium measurements every 6 months. ¹

• Progression of disease on medical therapy:
  – 27% of asymptomatic pts who initially do not meet criteria for operation develop at least one criteria for operation by 10 years ²
  – Most common sequelae include ongoing bone loss, nephrolithiasis, and renal colic ³

³ AACE/AAES Task Force on Primary Hyperparathyroidism, American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons position statement on the diagnosis and management of primary hyperparathyroidism, Endocr Pract 11 (2005), pp. 49–54
Practice Patterns

• Survey of 146 Endocrinologists (2004)
• Awareness of guidelines: High-volume 75%; Low-volume 50%

• Surgical referral:
  – 39% of all patients were referred for surgical management
  – 25% of all physicians referring a 40-year-old patient with PHPT when hypercalcemia was mild (< or = 1 mg/dL above normal),
  – 39% when hypercalcemia was moderate *
  – 31% when hypercalcemia was severe (>1.5 mg/dL above normal)
  – 4% reported that hypercalcemia alone was not sufficient justification to refer a patient for surgical intervention.

* Moderate hypercalcemia now an NIH criteria

Practice Patterns

• Survey of Endocrine Surgeons (Surgery 2006)
  – 89% aware of NIH guidelines
  – 71% would operate on pts who did not meet criteria
    • If elevated Ca, decreased BMD, or decreased crt clearance
  – 85% would operate for nonspecific complaints
    • Especially with neurophysiologic or GI symptoms
  – Most favored operation in pts with adenoma localization
  – Age and MEN status did not affect decision

Indications for operative intervention in patients with asymptomatic primary hyperparathyroidism: Practice patterns of endocrine surgery

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Table II. Indications for parathyroidectomy in patients with asymptomatic PHPT who do not fulfill the NIH Consensus Guidelines for operative intervention

<table>
<thead>
<tr>
<th>Indication for operation</th>
<th>Respondents, N</th>
<th>Respondents who would operate, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Almost always</td>
</tr>
<tr>
<td>Test abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum calcium concentration above normal, but &lt;1 mg/dl above upper normal limits</td>
<td>85</td>
<td>48 (57)</td>
</tr>
<tr>
<td>BMD below peak bone mass, but t-score &gt; −2.5</td>
<td>85</td>
<td>51 (60)</td>
</tr>
<tr>
<td>Nonspecific symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychologic abnormalities*</td>
<td>84</td>
<td>67 (80)</td>
</tr>
<tr>
<td>Depression</td>
<td>82</td>
<td>52 (63)</td>
</tr>
<tr>
<td>Onset of menopause before age 40 years</td>
<td>82</td>
<td>31 (38)</td>
</tr>
<tr>
<td>Cardiovascular abnormalities†</td>
<td>83</td>
<td>46 (55)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms and no MEN1†</td>
<td>83</td>
<td>61 (74)</td>
</tr>
<tr>
<td>Patient age older than 50 years</td>
<td>84</td>
<td>51 (61)</td>
</tr>
</tbody>
</table>

*Eg, Weakness, easy fatigability, intellectual weariness, increased sleep requirements.
†Eg, Hypertension.
‡Eg, Peptic ulcer, pancreatitis.
Table III. Effects of sestamibi scan findings on decision-making for parathyroidectomy in patients with PHPT and unspecified symptoms who do not fulfill the NIH Consensus Guidelines for Operative Intervention

<table>
<thead>
<tr>
<th>Nonspecific symptoms</th>
<th>Respondents, N</th>
<th>Respondents who would almost always operate, n (%)</th>
<th>Respondents who would observe, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sestamibi scan positive</td>
<td>Sestamibi scan negative</td>
</tr>
<tr>
<td>Neuropsychologic abnormalities</td>
<td>85</td>
<td>77 (91)</td>
<td>45 (53)</td>
</tr>
<tr>
<td>Depression</td>
<td>84</td>
<td>77 (92)</td>
<td>55 (66)</td>
</tr>
<tr>
<td>Early onset of menopause</td>
<td>84 or 83*</td>
<td>74 (88)</td>
<td>47 (57)</td>
</tr>
<tr>
<td>Late onset of menopause</td>
<td>85 or 84†</td>
<td>68 (80)</td>
<td>39 (46)</td>
</tr>
<tr>
<td>Cardiovascular abnormalities</td>
<td>85</td>
<td>73 (86)</td>
<td>44 (52)</td>
</tr>
</tbody>
</table>

*Total number of respondents to the scenario with early menopause and positive (84) or negative (83) sestamibi scan.
†Total number of respondents to the scenario with late menopause and positive (85) or negative (84) sestamibi scan.
Parathyroidectomy

• Benefits v. Observation: RCT’s
    • 121 patients, 83% asymptomatic. 50% underwent PTX
    • PTX
      – Normalization of serum calcium concentrations
      – Lumbar-spine BMD increased $8 \pm 2\%$ at 1 y ($P=0.005$), $12 \pm 3\%$ at 10 yrs ($P=0.03$).
      – Femoral neck $6 \pm 1\%$ at 1 year ($P=0.002$) and $14 \pm 4\%$ at 10 years ($P=0.002$).
      – Radius did not change significantly.
    • No PTX
      – No change in serum calcium, urinary calcium excretion, or bone mineral density.
      – 14 of 52 (27%) developed at least one new indication for parathyroidectomy.
      – All 20 patients with symptoms had kidney stones. None of the 12 PTX pts
Parathyroidectomy

• Benefits v. Observation: RCT’s
    • PTX-
      – increase in BMD of the spine (1.2%/yr, $P < 0.001$), femoral neck (0.4%/yr, $P = 0.031$), total hip (0.3%/yr, $P = 0.07$), and forearm (0.4%/yr, $P < 0.001$)
    • Observation-
      – Decreased BMD at the femoral neck (−0.4%/yr, $P = 0.117$) and total hip (−0.6%/yr, $P = 0.007$) but gained at the spine (0.5%/yr; $P = \text{ns}$) and forearm (0.2%/yr, $P = 0.047$).
Parathyroidectomy

• Benefits v. Observation: RCT’s
    • At baseline, pts had lower QoL and more psychological symptoms than controls
    • Calcium and PTH normalized after surgery.
    • The areal bone mineral density increased in the group randomized to operation.
    • Bone mineral density remained stable in the medical observation group.
    • No change in kidney function (creatinine) or blood pressure was observed longitudinally or between the groups.
Parathyroidectomy

• Benefits v. Observation: RCT’s
    • Change in BMD:
      – at lumbar spine (+4.16 ± 1.13 for PTx vs. −1.12 ± 0.71 for no PTx; \(P = 0.0002\)).
      – Total hip (+2.61 ± 0.71 for PTx vs. −1.88 ± 0.60 for no PTx; \(P = 0.0001\)).
      – No difference in BMD at the one-third radius site.
  • Improved QOL v. observation group in four areas:
    – Bodily pain \((P = 0.001)\), general health \((P = 0.008)\), vitality \((P = 0.003)\), and mental health \((P = 0.017)\)
Primary Hyperparathyroidism

- Parathyroid Adenoma
  - Increased number of cells $\rightarrow$ Increased PTH
  - Inappropriate response to serum calcium

Kronenberg: Williams Textbook of Endocrinology, 11th ed
Primary Hyperparathyroidism

• Epidemiology
  – 1-5 patients per 1000
  – 13 patients per 1000 over age 65
  – 4:1 Female

• Classical Symptoms
  – “Stones, Bones, etc.”

Current Surgical Therapy. John Cameron, ed. 9th Ed. 2007