Primary Hyperparathyroidism Guidelines

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What is asymptomatic HPT?

- Lacks specific symptoms or signs traditionally associated with hypercalcemia or PTH excess.

Guidelines for Management of Asymptomatic Primary HPT

Parameter	Value
Serum calcium	>1.0 mg/dL above ULN
DXA BMD, T-score	< -2.5 any one site: lumbar spine, total hip, femoral neck, distal 1/3 radius
Vertebral fracture	Present by X-ray, CT, MRI or VFA
Creatinine clearance	< 60 cc/min
24 hour urine calcium	>400 mg/dL
Kidney imaging	Nephrolithiasis/Nephrocalcinosis by X-ray, CT, or Ultrasound
Age, yrs	<50

Fourth International Workshop, 2013

Surgery is the only definitive therapy for PHPT and is always an option, even among those not meeting guidelines.

Serum calcium >1.0 mg/dL ULN

- 1990: Recommended >1.0-1.6 mg/dL ULN
- 2002: Recommended >1.0 mg/dL ULN

Panel of experts believed patients above this limit may be at greater risk for symptomatic hyperparathyroidism and for complications of the disease.

- No change in recommendation in 2008 or 2013.

“There is no new information on the natural history of PHPT that clarifies when surgical therapy is appropriate in either hypercalcemic or normocalcemic variants of the disease.”

DXA BMD T-score < -2.5

- 1990: DXA BMD z-score-2.0
- 2002: DXA BMD T-score <-2.5

Experts felt advances in DXA and improvement reported in BMD after surgery warranted a standardization with definition of osteoporosis.

- 2008 and 2013: essentially no change.

Newer techniques suggest both trabecular and cortical bone is affected.

No clear role for FRAX yet.

Vertebral Fracture Assessment

- New in 2013
- “Data from mixed case populations suggest an increased risk of fractures in PHPT…Limited data available on patients with mild PHPT suggest that risk of vertebral fracture is increased.”

Creatinine clearance <60 cc/min

- One study suggested biochemical effects in PHPT when the GFR falls below 60 mL/min.
- No data about PHPT and surgery to improve or slow decline of renal function.

Kidney Stone assessment: imaging and 24 hr urine

- Most common clinical manifestation of PHPT, 15-20%.
- 400 mg /24 hr: This was expert opinion, taking into account that increased urinary calcium is risk for stones.
- Imaging: Recommended by variety of methods, superiority of one over others not proven.

Age, < 50 yrs

- Unchanged from initial guidelines in 1990.
- Evidence that younger patients are at risk for reduced bone density.

Not enough evidence or consensus

- Cardiovascular disease
- Neuropsychiatric symptoms
- Cognitive dysfunction

Monitoring in absence of surgery

- Serum calcium annually
- DXA BMD every 1-2 yr
- eGFR annually

Triggers for surgery during monitoring

- Calcium > 1mg/dL ULN
- Development of osteoporosis on BMD or significant decline in BMD
- Vertebral fracture
- CrCl, 60
- Clinical or imaging evidence of kidney stone

Efficacy of Parathyroidectomy vs Active Surveillance

- Meta analysis, but small number of RCT studies and observational studies: 8
- No significant differences
  - Bone health
  - QOL
  - Neuropsychiatric symptoms
- Limited numbers of events
- Short-term follow-up

Singh Ospina et al. Osteoporosis Int 2016(27) p3395

AAES Guidelines 2016

- Not limited to asymptomatic PHPT
- Differences from workshop exist but weakness of evidence is acknowledged.

Diagnosis and evaluation

- Blood tests: calcium, PTH, creatinine, and 25 hydroxyvitamin D level
- 24 hour urine
- BMD hip spine radius
- In asymptomatic, renal imaging for stones (weak recommendation, low quality evidence)
- Obtain family history

Surgical intervention

- Symptomatic disease
- Calcium >1mg/dL ULN
- Osteoporosis or vertebral fracture
- Age <50 yrs
- Unwilling or unable to comply with observation
- Neurocognitive symptoms, heart disease, muscle weakness, functional capacity, sleep abnormality.
- Maybe: fibromyalgia, GERD

Definition of cure

- Reestablishment of normal calcium homeostasis lasting a minimum of 6 months.
- Normocalcemic PHPT: normal calcium and PTH levels more than 6 months after surgery. (insufficient evidence)

Conclusions

- Current guidelines about asymptomatic PHPT have not changed much over the years 1990-2013.
- Evidence from large RCT and observational studies is minimal about about superiority of surgery or surveillance.
- Treatment decisions remain a collaborative discussion between provider and patient.

Non-surgical Management of Primary Hyperparathyroidism

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Disclosure

- Off label use of cinacalcet, bisphosphonates, denosumab

Goals of Managing PHPT

- Relieve contribution to existing co-morbidities
  - Kidney stones
  - Osteoporosis/fractures
- Relieve symptoms
- Prevent complications
  - Bone, renal, ?cancer, ?CVD etc.

Surgery

- Definitive treatment
- Low risk
  - Esp. initial neck surgery
  - Experienced surgeon
- Studies of mixed disease severity generally support improvement

Ethanol Ablation

- Requires identification of abnormal gland by US in a location amenable to percutaneous injection.
- Most often used for recurrent/persistent disease in remnant gland after initial surgery
- Less long lasting “cure” than with surgery
- May be less risk of permanent hypoparathyroidism

Observation

- Suitable for older individuals with uncomplicated, mild disease
- Monitor calcium annually
  - Cohort studies of mixed disease severity do not suggest rapid progression of biochemical disease.
- Ensure adequate calcium and vitamin D intake
  - Lowers bone turnover
- Periodic assessment of BMD, renal stone risk.

Ideal Medical Therapy

- Normalize calcium and PTH
- Prevent disease progression
- Prevent co-morbidity development or progression
- Relieve symptoms

Cinacalcet

- Positive allosteric modulator of CaSR
- Increases sensitivity of CaSR to calcium
- Lowers PTH and calcium
- Approved to treat secondary HPT in renal disease
  - Use in PHPT is off label.
- Most common side effects: Nausea/vomiting

Cinacalcet in PHPT: Calcium and PTH

- Meta analysis of 28 studies
- Patient mix:
  - refusal of surgery/contraindication,
  - bridging to surgery,
  - refractory disease after surgery.
- Calcium normalization 90%, durable effect
- Reduction in PTH, normalization in only 10%
- Increase in Phos

Han Ng et al. Endocrine Connections, 2020, 9(7):724-735

Cinacalcet and PHPT: Calcium and PTH

- Caveats:
  - Included studies with combination therapy with vitamin D and/or bisphosphonates
  - Some studies included MEN1 patients
  - Variable study designs: RCT, retrospective, prospective.
  - Most studies are relatively short term.

Cinacalcet and PHPT: Bone

- No major effects on BMD and bone turnover

Leere et al, Frontiers in Endocrinology, 2017, 8:79

Cinacalcet and PHPT: Renal

- No consistent lowering of urinary calcium
- Not much assessment of renal stone disease progression

Leere et al, Frontiers in Endocrinology, 2017, 8:79
Manaka et al, Endocrin J, 2019, 66(8):683-689

Bisphosphonates

- Most commonly used was alendronate
- Initial lowering of calcium, but not durable
- Reduction in bone turnover
- Stabilizing to improvement in BMD
- Similar improvement in BMD as compared to parathyroidectomy

Leere et al, Frontiers in Endocrinology, 2017, 8:79
Sankaran et al, JCEM, 2010, 95:1653

Combinations: Cinacalcet and Bisphosphonate

- Small non-randomized studies
- Relatively short duration
- Support the effects of the individual agents:
  - Increase BMD
  - Decrease calcium

Combinations: Cinacalcet and Denosumab

- Randomized, controlled, double blind study
- 3 arms
  - Placebo (n=15)
  - Denosumab 60 mg Q6 mos (n= 16)
  - Denosumab + cinacalcet 30 mg daily (n = 14)
- 1 year duration
- Primary outcome: change in BMD by DXA

Leere et al, Lancet Diabetes Endocrinol 2020, 8:407-417

Combinations: Cinacalcet and Denosumab

- BMD significantly improved in denosumab and combinations arms
  - Spine, total hip, femoral neck
- BMD in radius did not improve significantly
- Calcium normalized in 64% of combination group.
  - Calcium transiently lowered in denosumab group.
- PTH increased in denosumab and combo groups, then declined.
- Renal Calcium excretion not changed among groups.
- No change in Major Depression Inventory scores.

Summary

- The ideal medical therapy for PHPT does not exist.
- Available agents affect one but not all aspects of disease.
- Studies are generally small, non randomized and include a range of disease severity, so generalization is challenging.
- An individualized approach based on specific patient concerns and complications