

## Parathyroid Hormone: Approach to Asymptomatic Hypercalcemia/ Indications for Parathyroidectomy Who needs an MEN work-up

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### Case 1: 35yo woman with hypertension and diarrhea

- PMHx unremarkable
- Medications – Losec for GERD
- Non smoker
- BP 160/90 BMI 25 – exam unremarkable
- Calcium 2.89 mmol/L (2.1-2.55)
- Phosphate 0.79 mmol/L (0.8-1.4)
- Alk phos 72 U/L(40-120)
- TSH 1.7 mU/L (0.38-5.5)

## Common Causes of Hypercalcemia

### Increased Calcium production

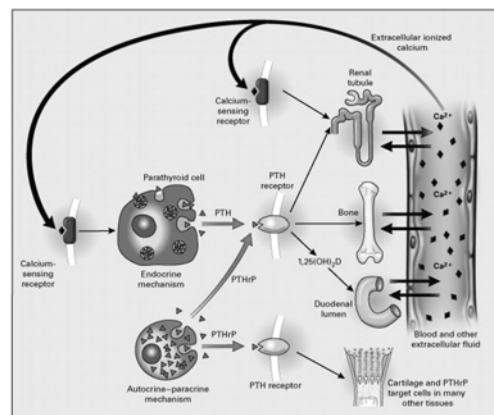
- Hyperparathyroidism
- Malignancy (due to PTHrP effect or metastases)
- Hyperthyroidism
- Hypervitaminosis A
- Paget's disease

### Increased Calcium absorption

- Hypervitaminosis D
  - Granulomatous disease / lymphoma
  - Increased vitamin D intake
- Milk-alkali syndrome

### Others

- Familial Hypercalcemic Hypocalciuria
- Acromegaly/ Pheochromocytoma/ Adrenal insufficiency
- Rhabdomyolysis
- Immobilization
- Drugs (e.g. lithium, theophylline, thiazide diuretics)



## Diagnostic Approach

- Serum Calcium (corrected or ionized)
- Phosphate
- Creatinine
- PTH
- 24hr urine calcium and creatinine – for fractionated calcium/creatinine clearance
- 25-OH-vitamin D or 1,25-(OH)<sub>2</sub>-vitamin D
- Imaging

## Case 1: Results

- Calcium 2.89 mmol/L (2.1-2.55)
- Creatinine 64 umol/L (GFR 113 mL/min)
- Urine calcium 12.7 mmol/d (2.5-7.5)
- Urine creatinine 10.1 mmol/d (7.1-17)
- Calculated fractionated calcium/creatinine clearance: 0.03
- 25OH vitamin D 78 nmol/L
- PTH 7.8 pmol/l (<6.4)

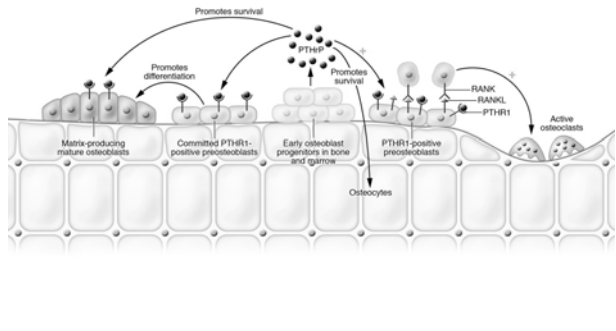
## How to distinguish between the causes?

	PHPT	FHH	SHPT	THPT	Other
Ca	N/ ↑	↑	N/ ↓	N/ ↑	↑
PO <sub>4</sub>	↓	N/ ↓	↑	N/ ↑	N
PTH	N/ ↑	N/ ↑	↑↑	↑↑	↓
Ca/Cr ratio	>0.02	<0.01	NA	NA	>0.02

## Primary Hyperparathyroidism

- Prevalence 1 in 1000; female predominance of 1:3
- Elevated calcium, low phosphate, hypercalciuria, PTH 1-2x normal
- 80% - autonomous solitary adenoma
- 20% hyperplasia of parathyroid gland (familial, MEN, etc) – 2-5% may be multiple adenomas

### Paracrine actions of PTHrP in bone



Martin, T. J. J. Clin. Invest. 2005;115:2322-2324  
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### Skeletal Complications of PHPT

- Classic rarely seen (e.g. osteitis fibrosa cystica)
- Loss of cortical bone (relative sparing of cancellous bone) which improves by 8-12% at spine and hip with surgical cure
- However, minimal progression of fracture without intervention

### Renal & Cardiac Complications

- 15-20% incidence of renal stones
- 40% hypercalciuria in normocalcemic PHPT
- Cardiac complications – based on epidemiological data
  - Valvular disease, CAD and LVH with severe PHPT – LVH regresses with cure
  - Vascular stiffness and carotid-intimal thickness increases
  - Prothrombogenic dyslipidemia
  - Regression with therapy unknown?

### Neuropsychiatric symptoms

- Contradictory data
- Social and emotional functioning and self-perception of improvement with surgical therapy (Talpos et al Surgery, 2000; Quiros et al, Surgery 2003 ) – not consistent and lack of objective data (Chiang, et al, Clin Endo 2005)

## Changes in Presentation of PHPT

- Disease of “bones, stones & psychic groans”

	Nephrolithiasis	Overt skeletal disease	Hypercalciuria
Cope et al (1930-65)	57%	23%	NR
Heath et al (1965-74)	51%	10%	36%
Mallette et al (1965-74)	37%	14%	40%
Silverberg, Bilezikian, et al (1984-2000)	17%	1.4%	39%

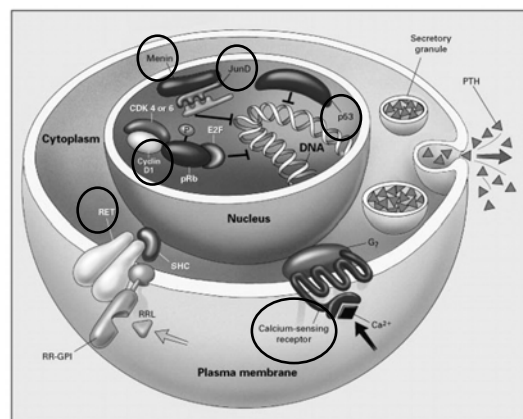
*Silverberg, et al NCPENDMET 2006*

## Guidelines for Parathyroidectomy

- Serum total calcium >2.9 mmol/L
- 24h urine >400 mg/d (>9.98 mmol/d)
- Overt manifestation of hyperPTH (nephrolithiasis, osteitis fibrosa cystica, neuromuscular disease)
- Reduced creatinine clearance >30% compared with age-matched controls
- Osteoporosis of lumbar spine, hip or distal radius – T-score <-2.5
- Age < 50 years
- Medical surveillance not possible or desirable

## Case 1

- Tx: Due for Parathyroidectomy
- Family history: mother – “died of hypercalcemia-related complications”
- Brother – Pancreatic tumor – on therapy
- Do I need to do any genetic testing?



## Genetic syndromes with HPT

Syndrome	Clinical Features	Gene	Gene Product
MEN 1	PHPT, Pituitary, Enteropancreatic (carcinoid/adrenal/lipoma)	11q13	Menin
MEN 2A	MTC, PHPT Pheochromocytoma	10q11	RET
<i>MEN 2B</i>	<i>MTC, pheochromocytoma, intestinal/mucosal ganglioneuromas, Marfanoid</i>	<i>10q11</i>	<i>RET</i>
HPT-JT	PHPT, fibro-osseous tumors, renal tumor	1q21-q32	CDC73 (HRPT2)
FHH	Hypercalcemia, hypocalciuria	3q21-q24	CaSR

## Who to test?

- Young patients (<35yo)
- Family history
- Multifocal or recurrent disease
- Other associated endocrinopathies or malignancies

## Case 1

- Elevated Gastrin levels (>1000)
- 2 cm adrenal mass
- Diagnosis: MEN-1
- Daughter – positive testing
- 1<sup>st</sup> cousin – longstanding history of diarrhea and hypercalcemia

## Case 2: 68yo PMW with fatigue, leg cramps, osteopenia

- Ionized calcium 1.32 mmol/L (1.1-1.3)
- Phosphate 0.88 mmol/L (0.6-1.45)
- Alk phos 86 U/L (43-133)
- Creatinine 83 umol/L (GFR 62 mL/min)
- PTH 8.5 pmol/L (1.5-7.6)
- 24hr urine Calcium 6.8 mmol/d (<7.5); creatinine 13 mmol/d; Ca/cr ratio 0.03
- Dx: Mild Primary Hyperparathyroidism

### Normocalcemic Hyperparathyroidism or Mild, Asymptomatic primary Hyperparathyroidism

- Not candidates for surgery based on current guidelines
- Any risks of progression or monitoring?

### Any benefit of Parathyroidectomy in Asymptomatic patients?

- Nephrolithiasis (14%), fragility fractures (11%), osteoporosis (57%) in NC PHPT (*Lowe, et al JCEM 2005*)
- Increased metabolic abnormalities with slight improvement in lipids and BMD (*Hagstrom, et al EJ Endo 2006*)
- Increased femur BMD post surgery compared to surveillance group
- Significant benefit at lumbar spine; Impact on fracture unknown
- Some benefit on QOL with surgery in some but not all studies

Rao, DS et al JCEM 2004; Bollerslev J et al JCEM 2007; Ambrogini E et al JCEM 2007

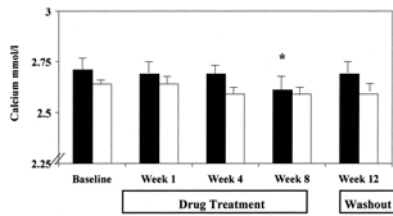
Are there any alternative options to surgery?

### Non-surgical Management Guidelines for Hyperparathyroidism

- Adequate Calcium (1000-1200mg/d) + vitamin D (400-800 IU/d)
- Biannual serum calcium
- Annual serum creatinine to estimate CrCl
- BMD (3 sites) every 1-2 years, dependent on baseline values
- Baseline abdominal U/S to assess for silent nephrolithiasis and 24hr urine Calcium clearance only
- Alternative therapeutic options...

## Raloxifene lowers Calcium in PHPT

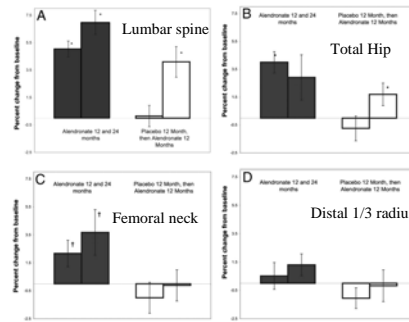
- RCT Raloxifene 60mg/day vs Placebo x 8 weeks (N=19 PMW)
- No change in PTH or other parameters
- Decline in bone markers



Rubin MR, et al JCEM 2003

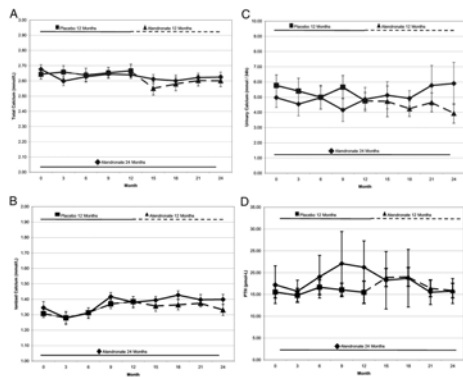
## Alendronate for PHPT

- RCT Alendronate 10mg/d vs Placebo (N=44) x 2yr



Khan A, et al, JCEM 2004

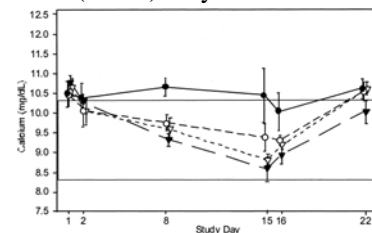
## No changes in Ca/PTH with Alendronate



Khan A, et al, JCEM 2004

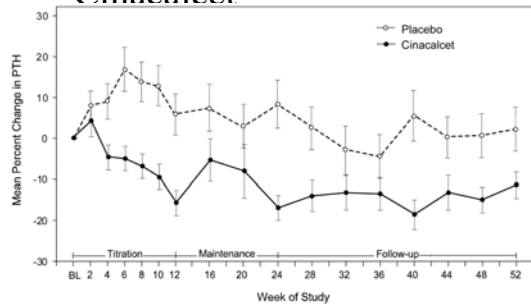
## Calcimimetics in PHPT

- Modulate CaR and enhance its sensitivity
- RCT: Cinacalcet 30mg, 40mg, 50mg BID vs placebo (N=78) x 1y



Shoback DM et al, JCEM 2003

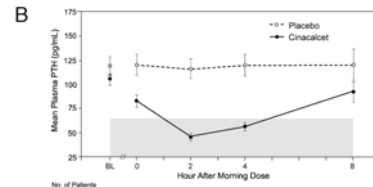
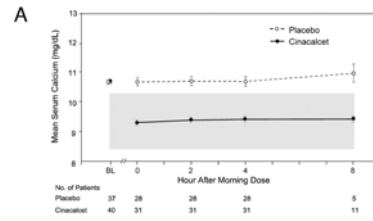
## Reduction in PTH with Cinacalcet



No. of patients  
 Titration: Weeks 2-16, Maintenance: Weeks 16-36, Follow-up: Weeks 36-52  

Placebo	37	31	28	28
Cinacalcet	40	33	31	

*Peacock, M et al, JCEM 2005*



No. of Patients  

Placebo	37	28	28	27	5
Cinacalcet	40	31	31	31	11

*Peacock, M et al, JCEM 2005*

- 20% reduction in PTH per 24hr cycle
- Calcium levels maintained
- No change in BMD or bone markers

## Summary

- Distinguish hyperparathyroidism from FHH
- Genetic testing warrants consideration in young patients or those with family history or other disease
- Increased risk of complications in NCHPT but without significant impact of parathyroidectomy
- Close monitoring and possible medical treatment options may be considered



