ANZGMU

AUSTRALIA & NEW ZEALAND GENERAL MEDICINE UPDATE

ANZGMU 2021

My patient has a calcium of 2.7! Should I worry?

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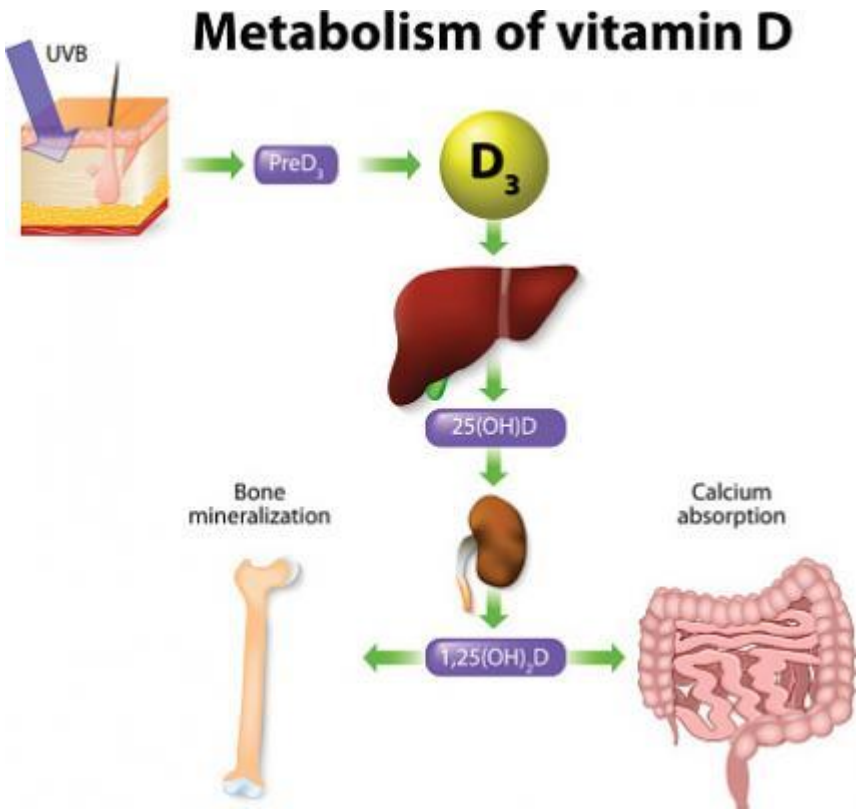
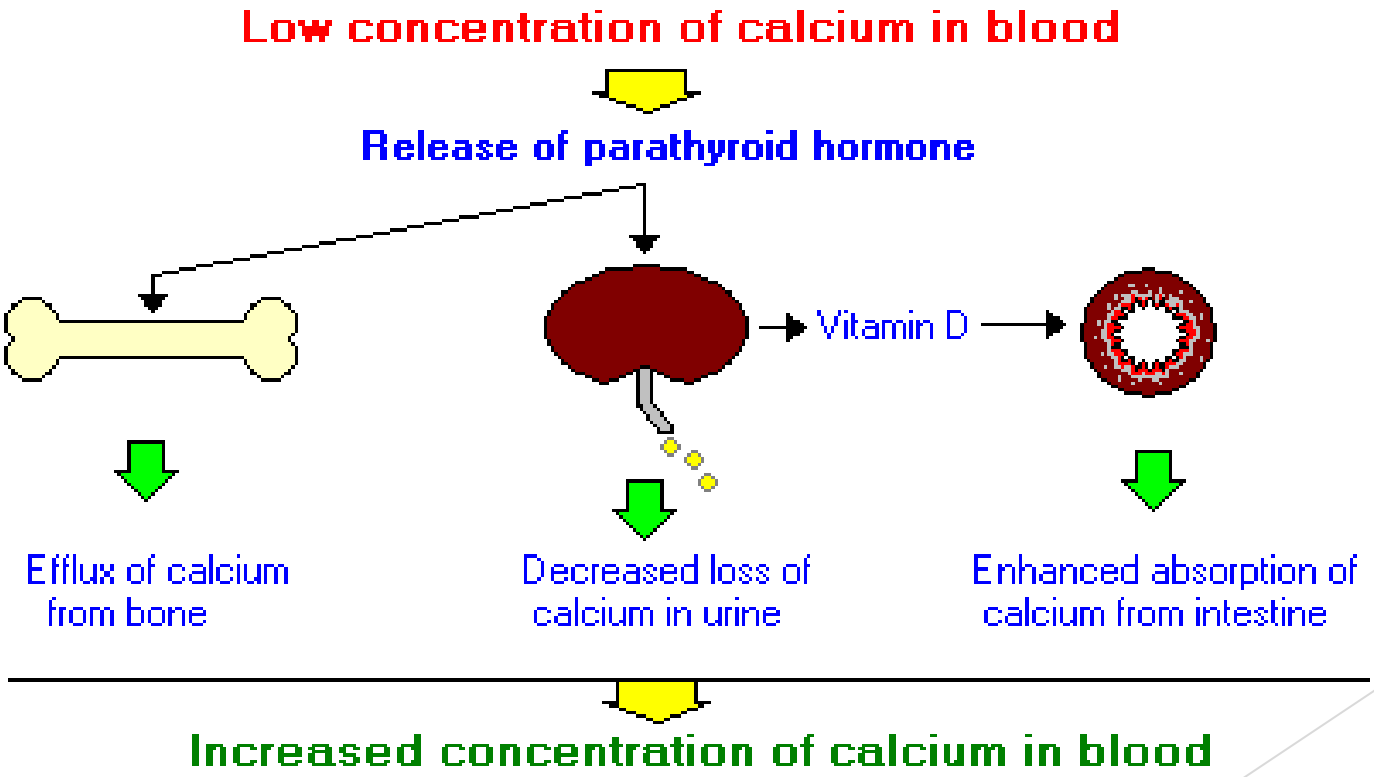
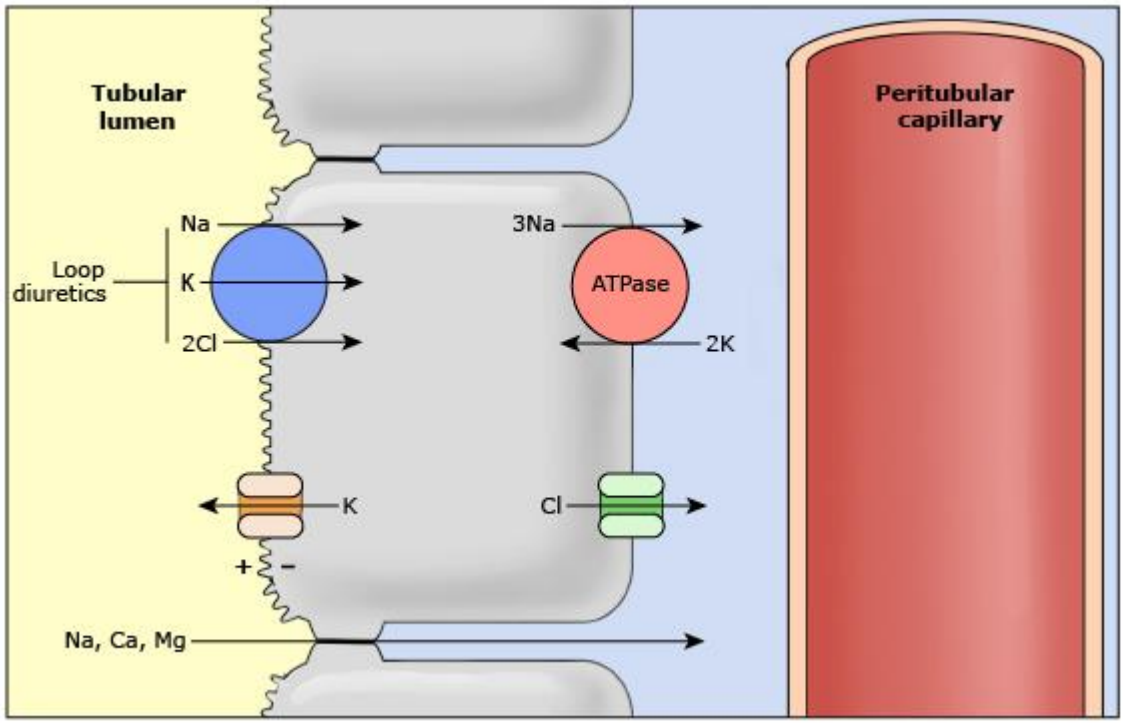
Vitamin D and Calcium



Parathyroid hormone and calcium



Calcium reabsorption in the ascending limb of loop of Henle



Hypercalcemia mechanisms

- Accelerated bone resorption
- Excessive gastrointestinal absorption
- Decreased renal excretion of calcium
- Often more than one mechanism involved

- Primary hyperparathyroidism increases bone resorption, tubular calcium reabsorption, renal synthesis of calcitriol (1,25-dihydroxyvitamin D), and intestinal calcium absorption

Causes of Hypercalcemia

- PTH-mediated
  - **Primary hyperPTH**
  - **Familial hypocalciuric hypercalcemia (FHH)**
  - Tertiary HyperPTH (usually in the setting of CKD)
  - MEN syndromes
  - Lithium
- Non-PTH mediated
  - Hypercalcemia of malignancy
    - PTHrp
    - Osteolytic bone mets
    - Lymphoma (excess 1-alpha OH)
  - Chronic granulomatous disorders- sarcoidosis, TB (excess 1-alpha OH)
  - Thiazide, Teriparatide
  - Vitamin D intoxication
  - Milk Alkali syndrome
  - Miscellaneous: Immobilization, Addison disease, Hyperthyroidism

The patient

- 64 years old gentleman admitted for analgesia
  - Left undisplaced distal radius fracture following a mechanical fall
  - Conservative management with splint & NWB for 6 weeks as per Ortho

- Background
  - Paraplegic (work related spinal injury in 2007)
  - Wheelchair bound but can do independent bed transfers
  - IHD Stents: LAD (1999), LCx (2012)
  - Hypercholesterolemia
  - Depression
  - Hypothyroidism
  - Renal calculi

Medications

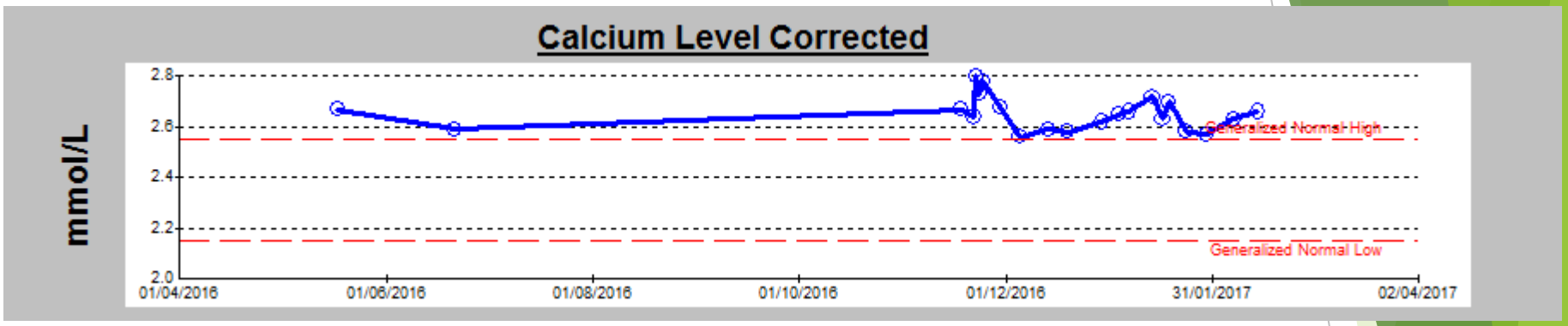
- Bisoprolol 2.5 mg nocte
- Clopidogrel 75 mg nocte
- Thyroxine 250 mcg daily
- Venlafaxine 187.5 mg nocte
- Atorvastatin 80 mg nocte
- Fenofibrate 145 mg nocte

Examination

- Hemodynamically stable
- No edema
- Normal cardiovascular exam
- Good air entry with few left basal crackles
- Soft abdomen and no organomegaly

- A- Clinically euvolemic

Review of bloods



- Corrected Ca 2.5 – 2.8 mmol/L
- Albumin 30 – 35 g/L
- Creatinine 70 – 80 umol/L (eGFR >90 ml/min)

Hypercalcemia - Immediate questions ?

1. Is the patient on ……..drugs
2. Any known cancer?
3. Do we know the PTH?

Answers and investigations

- Not on lithium, thiazide or Vit.D/Calcium
- No known cancer
- PTH level 9.1 pmol/L (NV 1.6-7.5)
- Corrected Ca 2.80 mmol/L
- 25-hydroxy Vitamin D 58 nmol/L (normal)

My patient- Primary Hyperparathyroidism? or FHH?

To call the surgeon or not to?

Investigations

24H Urine output	Value (mmol/24H)	Normal range (mmol/24H)
Calcium	11.82	2.50 – 7.50
Creatinine	17.60	7.00 – 18.00

Primary Hyperparathyroidism

- MOST COMMON cause of mild/moderate hypercalcemia
  - Incidental finding in routine tests and mostly asymptomatic
  - Affects 1 in 1000 persons (>with increasing age)
- Incidence peaks in the 7th decade
  - Most cases in women (74%)
  - Incidence similar between M=F before 45 years

NEJM, 365;25, 2011

Primary Hyperparathyroidism

- Usually sporadic
  - SINGLE ADENOMA (80-85%)
  - Four-gland hyperplasia (10-15%)
  - Carcinoma (1-2%)
- Rare associations

- Familial (MEN1 and 2 syndromes)

- Head & neck XRT in childhood

NEJM, 365;25, 2011

Mutiple Endocrine Neoplasia

- MEN1

  -Parathyroid (95%)

  -Pituitary(70%)

  -Pancreas (50%)

  -Adrenal (40%)-usually non-functional adenoma

- MEN 2a

  - Pheochromocytoma

  - Medullary thyroid carcinoma

  - Parathyroid (70%)

- MEN 2b

  - Above with marfanoid features and visceral gangliomas

Clinical Presentation

- **Most commonly asymptomatic (>80%)**
- Constitutional : weakness, easy fatigability, anxiety, cognitive impairment
- Hypercalcemia: bones..stones..groans..moans..
- Renal disease: Decreased GFR (17%), nephrolithiasis (15-20%), nephrocalcinosis, hypercalciuria
- Osteitis Fibrosa Cystica: rare now

NEJM, 365;25, 2011

Clinical Presentation

- Metabolic: Increased incidence of hypertension, LVH, type 2 diabetes, gout
- Low BMDs
  - Particularly at sites enriched in cortical bone is common (distal 3rd radius)
  - Increased rates of fractures

Imaging

- Renal ultrasound – r/o nephrolithiasis
- Bone mineral density scan
  - Measured at lumbar spine, hip, distal 3rd forearm

    -PTH has a catabolic effect on cortical bone → sites enriched in cortical bone are preferentially reduced
- Neck imaging (Sestamibi) used for localization ONLY if for surgery

When to operate?

Guideline for Surgery in asymptomatic primary hyperparathyroidism	
Serum Calcium	>0.25 mmol/L of upper limit of normal
Skeletal	1. BMD: T- score <-2.5 at LS, total hip, femoral neck or distal third of radius 2. Vertebral fracture by XR, CT, MRI
Renal	1. Creatinine clearance <60 ml/min 2. 24H urine for Calcium >10 mmol/day and increased stone risk by biochemical stone risk analysis 3. Presence of nephrolithiasis or nephrocalcinosis by XR, US or CT
Age	<50 years

Patients need to meet only one of these criteria to be advised to have parathyroid surgery.

Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014; 99:3561

My patient

- With high PTH and high urine 24 hours calcium (>10 mmol/L over 24 hours) along with h/o renal calculi…..
- Primary hyperparathyroidism diagnosed and ended with parathyroidectomy

Patient no.2

- 67 years old woman admitted with exacerbation of gout
- Background of HTN, COPD, ex-IVDU and hepatitis C (awaiting to see hepatologist)
- No h/o weight loss, altered bowel habit, decreased appetite bone pain or malignancy
- Denies taking Vitamin D or calcium supplements
- Denies taking any natural medicines

Medications

-Allopurinol 100 mg or

-Amlodipine 5 mg

-Prazosin 1 mg TDS

-Pantoprazole 40 mg

-Fluticasone-salmeterol (Seretide MDI 250 mcg-25 mcg/inh pressurised inhalation) 1 puff BD

-Salbutamol 2.5 mL, Nebulisor QID

-Spiriva 18 mcg inhalation 1 puff OD

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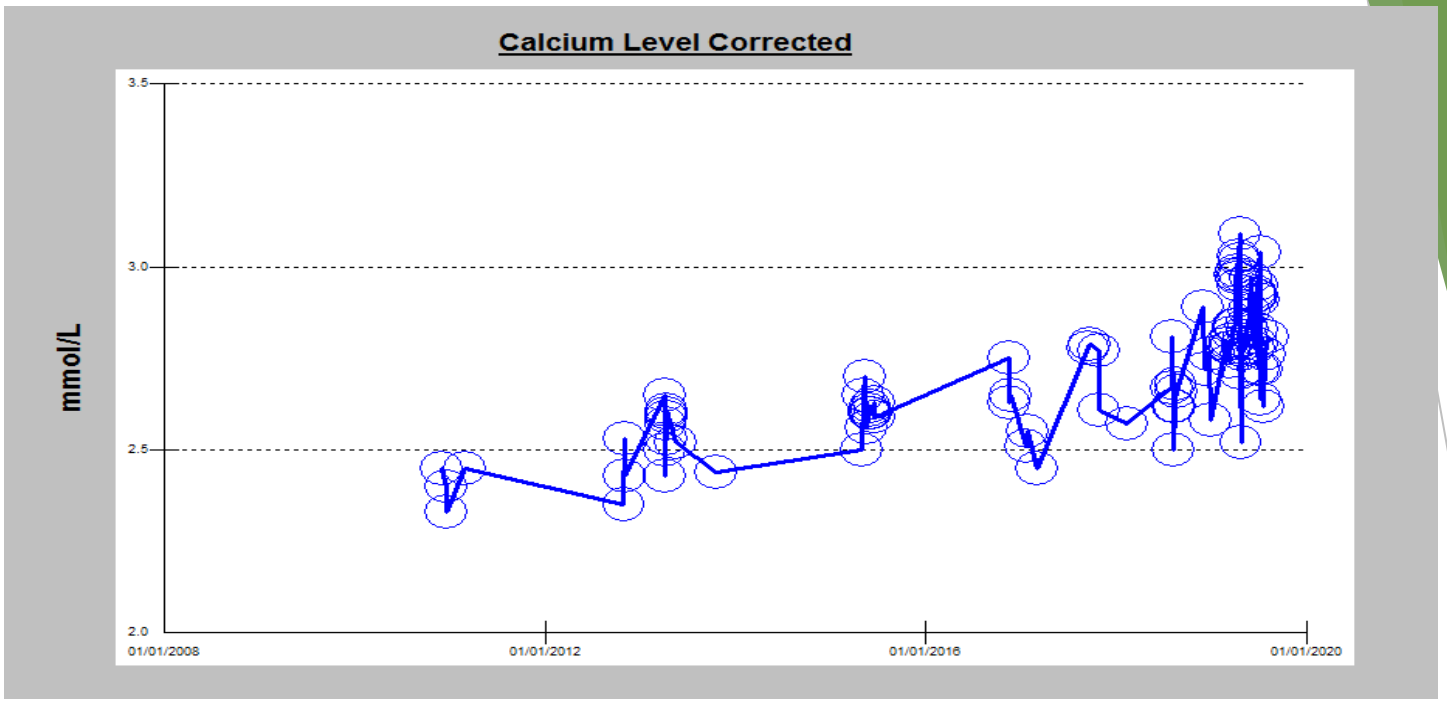


- Corrected Ca 2.5 – 2.8 mmol/L (Ref range 2.15 to 2.55)
- PTH – 7.6 pmol/L (Ref range 1.5 to 7.5)
- Albumin 26-29g/L (Ref range 35 to 50)
- Phosphate 0.6 – 0.9mmol/L (Ref range 0.75 to 1.5)
- Creatinine 90-100 umol/L (eGFR 48 to 50 ml/min)

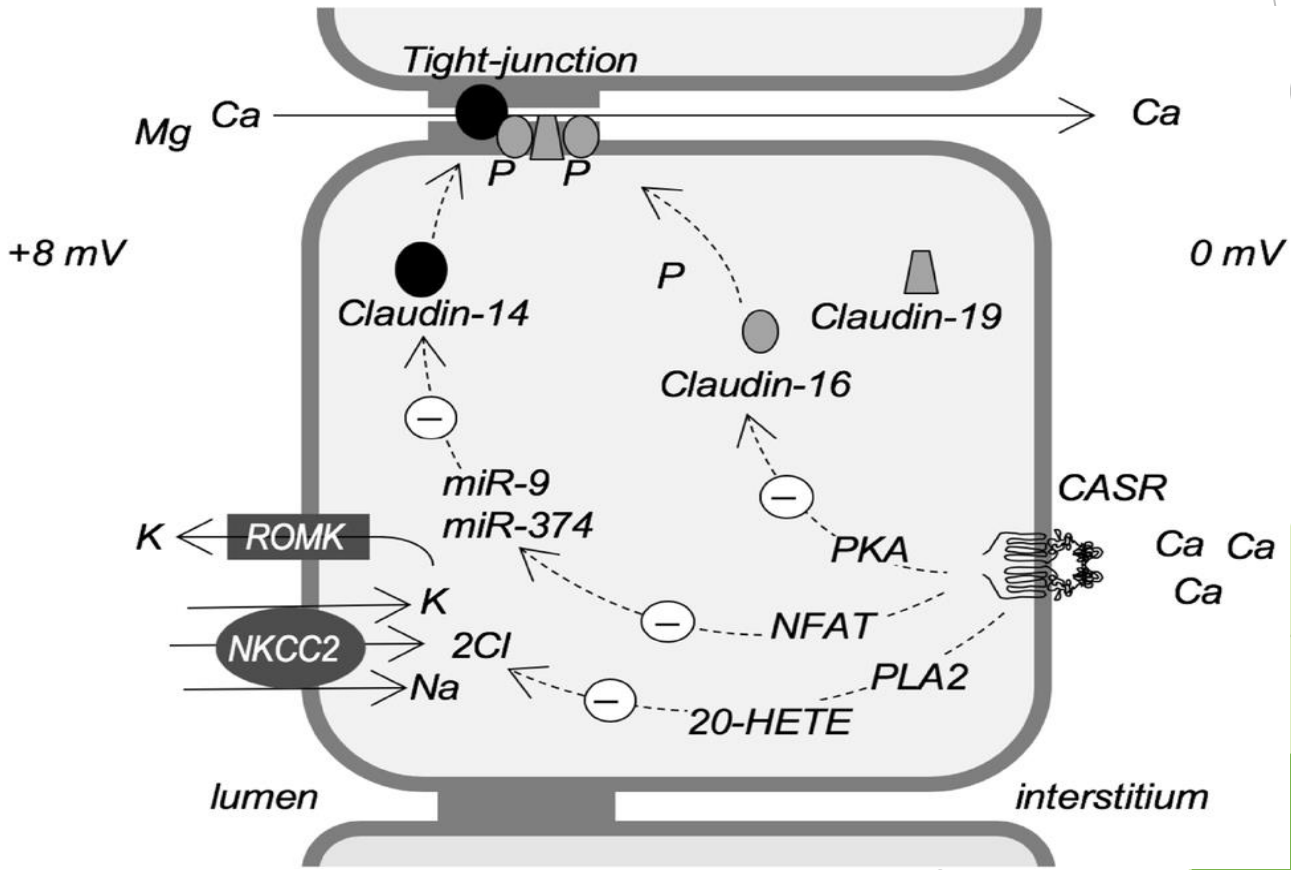
Urinary Ca

- Spot Urine Ca: Undetectable Ca
- After 1 month of vitamin D replacement: 24 hours urinary Ca **STILL** undetectable

- So what do we have?

- *Hypercalcemia*
- *High PTH*
- *Undetectable urinary Ca (hypocalciuria)*

Calcium sensing receptor (CaSR) inhibits claudrin 14, 16 and 19 (Ca carrier proteins)



Familial Hypocalciuric Hypercalcemia(FHH)

- Autosomal dominant disorder characterized by longstanding, mild hypercalcemia; normal/highish PTH levels and low urinary calcium excretion
- Mutations in the calcium-sensing receptor (CaSR) gene result in

- Altered calcium sensing by the renal tubules (thick ascending limb) and therefore increased reabsorption causing hypocalciuria

- Altered calcium sensing by CaSR on parathyroid cause inappropriate PTH release with respect to the serum calcium concentration

- Urinary Ca/Cr clearance ratio < 0.01 and 24-hour urinary calcium excretion typically < 5 mmol/day
- Benign condition and often many family members effected

Looks like my patient has an acquired FHH like disease….

- Reports of patients who have antibodies to CaSR causing hypercalcemia with hypocalciuria and raised PTH
- Patients often have evidence of other autoimmune disorders e.g. tropical sprue or hashimoto thyroiditis
- Possible role of glucocorticoids or calcimimetic drugs like cinacalcet to sensitise the parathyroid glands to Ca

1. *The Journal of Clinical Endocrinology & Metabolism*, Volume 88, Issue 1, 1 January 2003, Pages 60–72, https://doi.org/10.1210/jc.2002-020249

A Syndrome of Hypocalciuric Hypercalcemia Caused by Autoantibodies Directed at the Calcium-Sensing Receptor

Olga Kifor et al

2. N Engl J Med. 2004 Jul 22;351(4):362-9.

Acquired hypocalciuric hypercalcemia due to autoantibodies against the calcium-sensing receptor

Pallais JC[1], Kifor O, Chen YB, Slovik D, Brown EM

Management of hypercalcemia

- Avoid/cease lithium, thiazide and calcium/vit D
- Ca >3.5 mmol/L or acute increase/symptomatic:

-Volume expansion with normal saline with/without frusemide

- Calcitonin (4 IU/kg) and repeat 6-12 hourly upto 48 hours after which not effective
- Bisphosphonate: zoledronic acid (4 mg IV over 15 minutes) or pamidronate (60 to 90 mg over two hours) with the former more effective in malignancy related hypercalcemia
- Denosumab in refractory cases or renal failure
- Hemodialysis: last resort

Always treat the cause e.g. steroids in sarcoidosis

Beware of your surgeon saying this during the surgery…

- Damn! Page 47 of the manual is missing.
- Better save that. We'll need it for the autopsy.
- Wait a minute, if this is his spleen, then what's that?
- Oh no! I just lost my Rolex.
- Anyone see where I left that scalpel?

- THANK YOU