Ca n PO4 metab dr.

Hypercalcemia (>11mg%)

- Clinical symptoms:

- Fatigue, Anorexia, Vomiting, Constipation
- Freq of micturition, nephrolithiasis
- Seizures, Mental confusion, Depression

Hypercalcemia: Causes

1. PTH-related
2. Malignancy-related
3. Vit.D-related
4. High bone turnover ds
5. CKD-related

PTH-related hypercalcemia

I. Pr. HyperPTH
- Solitary adenoma
- MEN

II. Lithium therapy

III. Familial hypocalciuric hypercalcemia

Pr. Hyperparathyroidism: Etio

1. Solitary adenoma (80%); Rarely Carcinoma
2. MEN 1 (Wermer's synd: Pitutary n Pancreas)
3. MEN 2A (Medullary Ca thyroid + Pheochromo)
4. MEN 2B (Multiple Neuromas + MCT + PC

Pr. Hyperparathyroidism: S/S

- Clinical features:

i. Asymptomatic

ii. Bone, Stone, Groan, Mone

➢ Bone→ high turnover bone ds

→ Osteitis fibrosa cystica

→ X-ray: subperiosteal resorption

→ Histo: multinucleated osteocasts at bone surface pits

→ Formation/Resorption markers: ALP, Procollagen/Collagen telopeptide

Pr. Hyperparathyroidism: S/S

- Stone → Nephrocalcinosis
  → Nephrolithiasis

- Groan → Refractory gastritis
  → Zollinger-Ellison syndrome
  → Pancreatitis

- Mone → Neuropsychiatric manifestations
  → Neuropathy, Parathyroid myopathy

Pr. Hyperparathyroidism: Mx

- Diagnosis: Hypercalcemia with î S. PTH
- Treatment: Medical or Surgical ?

➢ Medical Mx:

i. > 50 yrs of age

ii. Unfit or unwilling for surgery

Annual S. Creat, DEXA scan n Biannual S. Ca

➢ Drugs:

i. SERMs (Raloxifene)

ii. Calcimimetics (CaSR +)

Pr. Hyperparathyroidism: Mx

- Surgery: single resection Vs 3+1/2 resection

I. Severe hyperCa (>15 mg%)
   or hypercalciuria (>400 mg/d)
II. Asymp hyperPTH with age < 50 yrs
III. T-score < -2.5 at any site
IV. CCL reduced by 30% or more

- Pre-op Radiolabelled Tec SPECT & intra-operative S. PTH sampling (before n 5 min after removal.....>50% decline

Pr. Hyperparathyroidism: Mx

- Post-surgical monitoring

i. S. Ca decline within 24 hrs n it persists for 3-5 days…thereafter lower normal levels

ii. Ca suppl if post-surgical hypoPTH; if no adequate response or continued req for parenteral Ca…..start Vit.D suppl also

iii. Mg suppl (1-2 g of MgSO4) if concurrent hypomagnesemia

Familial hypocalciuric hypercalcemia

- Mutation in CaSR in PTH gland n Kidney
- Excess PTH secretion in the absence of negative feed-back from raised S. Ca through CaSR
- Usually asymptomatic
- Must be differentiated from Pr. hyperPTH as medical therapy or surgery not useful (*Hypocalciuria)

Malignancy-related hypercalcemia

1. Tumors with bone mets (Ca Breast)
2. Humoral-mediated hypercalcemia of malig. Or PTHrP-related hypercalcemia (Ca lung)
3. Hematologic malignancies (Multiple myeloma, lymphoma, leukemia)

- Although S. Ca high n PO4 low in PTHrP and Pr. HyperPTH but….S. PTH low in PTHrP
- Treat malignancy + Std therapy for hyperCa

Vit.D-related hypercalcemia

1. Dietary Vit.D intoxication

- Chronc ingestion of Vit.D > 50,000 U/d (upper limit of normal dietary intake =2000)
- Δ: 25(OH)D > 100 ng/mL
- Treatment:

i. Stop Vit.D suppl n restrict dietary Ca

ii. Hydrocrtisone < 100mg/d if î S. Ca > 4 wks (* substantial fat stores of Vit D)

Vit.D-related hypercalcemia

2. Chr granulomatous dr

- Sarcoidosis, TB, Fungal infxns
- Excess Vit.D synthesized by Macrophages (25(OH)D --→ 1,25(OH)2D)
- No negative feed-back from S. Ca or PTH
- Treatment:

➢ Treat underlying condition

➢ Avoid sunlight exposure, limit dietary Ca n Vit.D; may use steroids

HyperCa with high bone turnover diseases

- Hyperthyroidism
- Secondary hyperPTH (e.g. CKD)
- Vit. A intoxication
- Prolonged immoboilisation
- Thiazide diuretics (↑PCT reabs of Na n Ca) usually in asso with Vit.D therapy or hyperPTH

HyperCa with CKD

- Severe Sec. HyperPTH
- Adynamic bone ds (Aluminium toxicity)…in asso with Vit.D n Ca suppl…Al minimizes osteblast activity
- Milk-alkali syndrome….results from excessive consumption of absorbable CaCO3 antacids…. hyperCa + Alkalosis + Renal Failure

Clinical n Lab approach to HyperCa

- Chronicity, Severity n Symptoms:
  - Chronic hyperCa (>1yr)→ malignancy unlikely
  - Severe hyperCa (>15mg%)→ malignancy likely
  - Asymptomatic hyperCa → hyperPTH likely

- S. PTH….. High = Hyper PTH
- S. PTH….. Low = all other except hyperPTH (malig-related, Vit.D-related)

Treatment of hyperCa

- Mild hyperCa: hydration + diuresis (Loop) (11-13 mg%)
- Mod (13-15) to Severe (>15) hyperCa:
  - Biphosphonates …Zolandronate 3mg iv over 3 min SD
  - Clacitonin
  - Glucocorticoids (Hydrocortisone 100 mg/d)
  - Dialysis…severe or refractory cases or CKD

Hypocalcemia (< 8 mg%)

- Clinical Manifestation: (Neuromuscular)

  - Muscle cramps, carpopedal spasm
  - Laryngeal spasm (dysphonia/stridor)
  - QT prolongation, Torsade-de-pointes
  - Seizures, Psychosis, Depression

Hypocalcemia: Causes

- Acute hypoCa:

1. Redistributive (critically ill patients)
2. Drugs/Medications…ethanol, heparin

- Chronic hypoCa:

1. HypoPTH n PHP
2. Vit.D deficiency
3. CKD

Clinical approach to hypocalcemia

- Acute hypocalcemia…drugs/acute severe ds

- Chronic hypocalcemia….

Alcoholics….dietary def of Ca n hypoMg

Elderly…….dietary def of Ca n Vit.D

Adolescents……HypoPTH n PHP, CKD, Malabsorption syndrome

Siezure disorder……Anticonvulsants

Lab clues for hypoCa Etiology

- Low Ca n Low PO4:

1. Vit.D deficiency
2. Malabsorption synd
3. Anticonvulsants

- Low Ca n High PO4:

1. CKD
2. HypoPTH n PHP
3. Massive tissue destruction

Lab aproach to hypoCa

Hypocalcemia

↓

S. PTH

Low to Normal

HypoPTH

HypoMg

Raised

Severe tissue injury

Sec. HyperPTH

-Vit.D dr or Malabs

- CKD

Hypocalcemia: Causes

- HypoPTH: hereditary or acquired

A. Hereditary…Isolated or Asso disorders

- Asso developmental defects, basal ganglia calcification & extrapyramidal symptoms, alopecia, candida infxns

1. PTH + Thymus = DiGeorge synd
2. PTH + Thyroid/Adrenal = Polyglandular Auto immune Defect
3. PTH + Mitochondria dysfunc (MELAS synd)

Hypocalcemia: Causes

- HypoPTH: hereditary or acquired

B. Acquired HypoPTH

1. Post-surgical (thyroidectomy, PTHectomy)
2. Post-radiotherapy
3. Hemchromatosis, hemosiderosis

HypoCa: Cuases & Treatment

- Treatment of HypoPTH→

  - Oral Ca n Vit.D suppl
  - Avoid overzealous treatment…may ppt renal calculi
  - Use thiazide diuretics if hypercalciuria

HypoCa: Causes & Treatment

- Hypomagnesemia: (< 0.4 mmol/L)

- Causes reduced PTH secretion n end-organ resistance
- Common in Alcoholics n Malnutrition
- Δ clue → Low Ca + Low PO4 + Low PTH…..
  (and low Mg)
- Treatment → Mg suppl (parenteral)

HypoCa: Causes & Treatment

- Chronic Kidney Disease (CKD):
  - Reduced Vit.D; PTH resistance for bone resorption n Extra-osseous calcification (high Ca-PO4 product).....all lead to hypoCa
  - Treatment ....

Ca (1-2 g/d) & Vit.D (0.25-1.0 µg/d Calcitriol)

Avoid Al containing antacids n phosphate binders....adynamic bone disease

HypoCa: Causes & Treatment

- Vit.D disorders:

1. Deficiency from poor dietary intake, reduced sunlight exposure or low absorption i.e. small bowel ds, Liver ds
2. Defective/altered metabolism from Liver ds, CKD, Anticonulsants, INH, HypoPTH, Vit.D dependent Rickets type I (genetic defect for encoding 1-hydroxylase) & II (end-organ resistance)

Hypocalcemia: Acute Management

- 180 mg of elemental Ca/ 2 g of Cagluconate iv over 10 min f/b 6 g in 500 mL NS iv over 6 hrs
- Treat HypoMg if present
- Pts on Digoxin highly predisposed to cardiac arrhythmias
- Ca and $NaHCO_3$ not compatible iv admixture

PO4 metabolic dr.

Hypophosphatemia: Causes

I. A) Dietary inadequacy….Rare

B) Impaired absorption….Al-based antacids

II. Renal loss

A) PTH/PTHrP-related

- HyperPTH…Pr. Or Sec. (CKD, Vit.D def)
- PTHrP

B) PTH/PTHrP-independent

- XLHR (PHEX) & ADHR (FGF)
- Wilson ds
- Fanconi's synd
- HypoMg
- DM
- Steroids
- Diuretics
- Estrogen

Hypophosphatemia: Causes

III. Redistributive

i. IV Dextrose
ii. Insuline therapy
iii. Catecholamine
iv. Ac. Resp. alkalosis
v. Severe sepsis
vi. Refeeding syndrome
vii. Rapid cellular growth…leukemic blast crisis
EPO or CSF therapy
viii. Vit.D suppl or osteoblastic mets

pophosphatemia: S/S & Lab Ix

inical manifestations reflect generalised efect in cellular energy metab

ox. Myopathy, Bone pain, Pseudofractures, ckets n Short-stature (children)

thargy, Confusion, Enceph, Seizures

nisocoria, Nystagmus, Oculomotor palsy

taxia, Cerebellar tremors

ripheral neuropathy, GBS-like ds

pophosphatemia: Treatment

Acute or Severe HypoPO4:

Cumulative deficit not predictable

Therapy is empiric with frequent monitoring
of S. PO4 n Ca (Ca-PO4 product < 50)

Na3PO4 or K3PO4

0.2-0.8 mmol/Kg of elemental phosphorus iv
6 hr.

Oral phosphate

pophosphatemia: Treatment

Chronic HypoPO4:

If Vit.D def with Sec HyperPTH…Vit.D

Genetic dr (XLHR, ADHR)…Oral PO4 with Ca n Vit.D

perphosphatemia: Causes

HypoPTH

HypoPTH →

) Hereditary/Developemental

) Acquired….Autoimmune, Post-Sx or Rx

gain-in-function mutation in CaSR

. HypoPTH → (Sec to HyperCa)

) Vit.D or Vit.A intoxication

) Chr. Granulomatous ds

) Milk-Alkali Synd

perphosphatemia: Causes

- CKD
- Redistributive
  - Severe tissue injury…burns, crush injuries, fulminant hepatic failure, cytotoxic agents
  - severe hemolytic anemia
- Resp/Metab acidosis
- Iatrogenic (rapid IV admin of PO4)

perPhosphatemia

inical manifestations:

ue to hypoCa from heterotropic calcification

aised Ca-PO4 prdct→ ppt of Ca3(PO4)2

etany, seizures, cardiac arrhythmias,
ephrocalcinosis

reatment:

olume expansion

/Ca-based phosphate binders, Sevelamer

Osteomalacia

teomalacia: Causes

- a deficiency
- O4 deficiency
- Misc. … Hereditary hypophosphatasia,
  CKD, RTA
  Biphosphonate therapy

Ca deficiency:

- Vit.D def…Dietary def
  Increased GI loss
  Abn metabolism
  End-organ resis.

- HypoPTH….Pr./Developmental or Acquired
  PHP

PO4 deficiency:

- Dietary def
- Impaired absorption
- Renal loss….PTH or PTHrP-dependent
  PTH or PTHrP-independent

Diagnosis:

1. Vit.D levels (<15 ng/mL)
2. S.Ca, PO4, ALP
3. S. PTH
4. X-ray…reduced radio-opacity of cortical bone in the long bones, Looser's zone or Pseudo-fractures, widened and expanded growth plate (in children)

Treatment:

- Calciferol 50,000 IU wkly X 3-12 wks
  f/b 800 IU/d
  OR
  Calcitriol 0.25-0.5 µg/d (esp. CKD)
  OR
  Inj. Vit.D 2.5 M IU i/m Biannually
- Ca supplements (1-2 g/d of elemental Ca)

Monitoring of therapy:

- Normocalcemia within a week
- PTH n ALP take 3-6 months
- 24-hr urinary Ca excretion
  - …. 100-250 mg/d→ Desirable
  - …. < 100 mg/d → Defect in Vit.D or Ca abs
  - …. > 250 mg/d → Nephrolithiasis