Refeeding syndrome (RFS)

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Jan/9/08

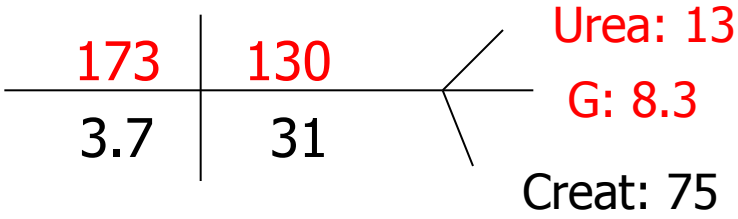
The case -Hx

- YC is a 15 yrs old girl.
- Dx: AN- Restrictive type with bulemic traits (December/06)
- Admitted with Hx of being not eating for 2 wks, Wt loss (5 Ib/3 days)
- Found to have hypernatremic dehydration (N= 173)
- Hx of neck pain for 2 wks → found to have subcutaneous emphysema (No chest pain, abdominal pain or RD)
- GIT consulted for possibility of Esophageal rupture
- FHx

The case - Exam

- O/E: looked apathic but fully conscious & alert, moderately dehydrated, not toxic, not in pain
- V/S: HR 137- RR: 25- BP:119/76- Temp: 37.5→ 40, Saturating well on RA
- Neck: evidence of Subcutaneous emphysema
- Chest, CVS, Abdomen → Normal
- Normal CNS exam
- MSK: leg ulcers

The case- Lab

- CBC- WBC:13.8 (Neut: 11.7) - Hb:157 - Plt: 127
- Lytes:
- 

- Ph: 0.38 (0.87-1.52)- Mg:1.14 (0.74-0.99)- Ca: 2.52
- pH: 7.47-44-65-31-6.7
- Normal Liver enzymes – Albumin: 45- INR: 1.31
- PTT: 29.6- Fibrinogen: 5.77 (4.44)- D dimer:4.49 (<0.2)

He case—Mx—Day 1

- NS bolus 20 cc/kg over 4 hrs (Na did not change but Urea 11.3)
- Started initially on D5 NS @ 55cc/hr (2/3 M)+ 20 mEq/l OF KCL
- Started on Triple Abx (after the cultures taken) → ? Sepsis, Mediastinitis
- Po Ph → iv Ph bolus
- Thiamine 100 mg IV OD
- Normal ECG
- IV vitamin K 5 mg OD
- Esophageogram: Normal

The case - Day 2

- Na: 170- K: 3.1 – Ph: 0.66- Mg: 0.9
- Gl: 7.2-8.9
- IVF increased to 100cc/hr → Na drop to 165
- Po Ph & increase IV potassium supplementation to 40 mEq/L
- Nasal bleed→ Normal ENT exam

The case -

- Increment of NG feed was held on Day 4 till Ph corrected to 0.88
- Then increased gradually on Day 5 to 40 % of the total calories
- Na came to normal
- By day 8, full NG feed with IVF TKVO
- The patient looked more interactive & chatty
- Transferred to ED service

History of RFS

- Initial reports of refeeding syndrome were made following the refeeding of adult survivors of concentration camps in 1945 following the Second World War .
- Oral feeding of starved victims resulted in cardiac insufficiency and neurological complications such as coma and convulsions.
- The syndrome was also seen in refeeding of healthy volunteers who had undergone starvation for 6 months

  (Keys A,Brozek J,Henshel A et al. The Biology of Human Starvation. Minneapolis: University of Minnesota Press,2001).
- In the 1970s, the refeeding syndrome was reported following the introduction of TPN .

Definition of RFS

- Refeeding syndrome is defined as the occurrence of severe fluid and electrolyte shifts (especially, but not exclusively, of phosphate) and their associated complications in malnourished patients undergoing enteral/parenteral refeeding
  (Solomon S M,Kirby D F. J Parenter Enteral Nutr 1990; 14: 90–97)
- Marik et al. defined refeeding syndrome as a fall in phosphate levels by more than 0.16 mmol/l to below 0.65 mmol/l.
  (Marik P E,Bedigian M K. Surg 1996; 131: 1043–1047)
- It usually occur within 4 days of starting the feed.
- Refeedingsyndrome is not uncommon and severe hypophosphataemia (<0.35 mmol/l) has been reported in 0.8% of all hospitalized adult patients (Halevy J,Bulvik S.Arch Intern Med 1988; 148: 153–155

Definition of RFS

- Hypophosphatemia is said to be the hallmark clinical manifestation of RFS and the primary cause for morbidity and mortality.

- Hypokalaemia, hypomagnesaemia and hypocalcaemia, hyperglycemia, and thiamine deficiency also occur; they are often inter-related and may or may not be associated with hypophosphataemia (Connan et al, 2000; Stroud et al, 2003).

- Spectrum: Potential or biochemical refeeding syndrome→ symptomatic refeeding syndrome

RF for RFS

- Anorexia nervosa
- Chronic alcoholism
- Radiation therapy
- Major stressors without food for >7 days
- Oncology patients
- Postoperative patients
- Chronic malnutrition
  - Marasmus
  - Kwashiorkor
  - Profound weight loss (< 75 % of IBW)
  - Hunger strikes
  - Prolonged fasting
  - Malabsorption diseases

Lauts, Journal of infusion nursing, 2005

Epidemiology

- The exact incidence of RFS is not known.
- However, studies of patients receiving TPN have shown that the occurrence of hypophosphatemia is 30% - 38% when phosphorous is added to the TPN solution & can reach up to 100 % if Ph was not added to TPN.
- Hypophosphatemia among cancer patients receiving TPN is reportedly as high as 25%.

(McCray S, Walker S, Parrish CR. Pract Gastroenterol. 2005;29(1):26–44.)

Epidemiology

- In a prospective study of 62 adult ICU patients who were refed after at least 48 hours without nutrition, it was observed that refeeding hypophosphatemia occurred in 34% of patients.
- The only risk factor determined to predict hypophosphatemia was a low serum prealbumin (average 7.9 ± 4.0 g/L compared to 12.7 ± 3.4 g/L, *P*<.001).
- In fact, 81% (17/21) of the patients developing hypophosphatemia had a prealbumin of <11 g/dL, while only 30% of patients who did not develop hypophosphatemia had levels <11 g/dL.

(Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. *Arch Surg.* 1996;131:1043-1047.)

- **Hernández-Aranda JC, et al. [Malnutrition and total parenteral nutrition: a cohort study to determine the incidence of refeeding syndrome]** [Article in Spanish]

Objectives

- Starvation pathophysiology
- Phosphate physiology
- RFS pathophysiology
- Discuss some clinical manifestation of RFS
- Prevention & Mx Guidelines
- Others ,,,

Pathophysiology of starvation

- Starvation → shift from carbohydrate metabolism to fat and protein catabolism for energy → an intracellular loss of electrolytes, magnesium, potassium, and most significantly, phosphate.

- During starvation, the body compensates for the loss of these essential electrolytes with the movement of ions out of the cells and into plasma → maintain either normal or near normal serum levels (though the stores are depleted).

- The secretion of insulin is also decreased in response to the lack of carbohydrates.

Pathophysiology of starvation

- This shift to protein catabolism causes a gradual loss of cellular/muscle mass.
- Major organs (Muscles, heart, lungs, liver, and intestines) are the most severely affected.

Phosphate physiology

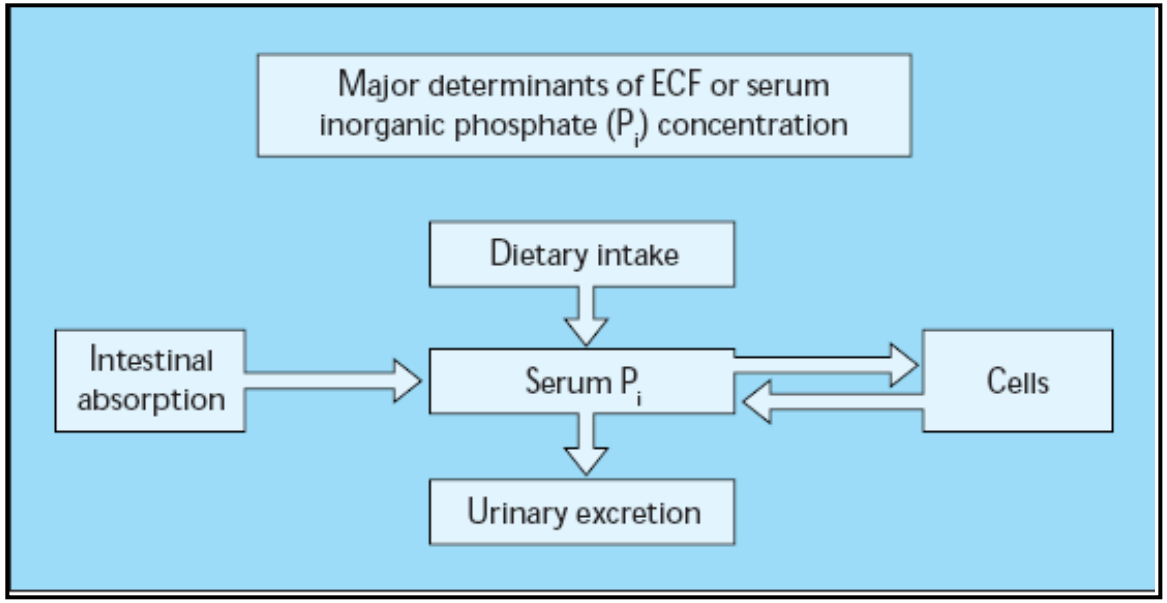
- Phosphate (PO4-2) is the most abundant intracellular anion available for transcellular shift between the intracellular and extracellular milieus

- Transcellular shifts may result in acute depletion of serum phosphorus (systemic alkalosis , hyperglycemia or hyperinsulinemia)

- Dietary phosphorus is absorbed via the jejunal mucosa by passive transport mechanisms and is subsequently filtered at the glomerulus (75% of it reabsorbed by proximal tubules)

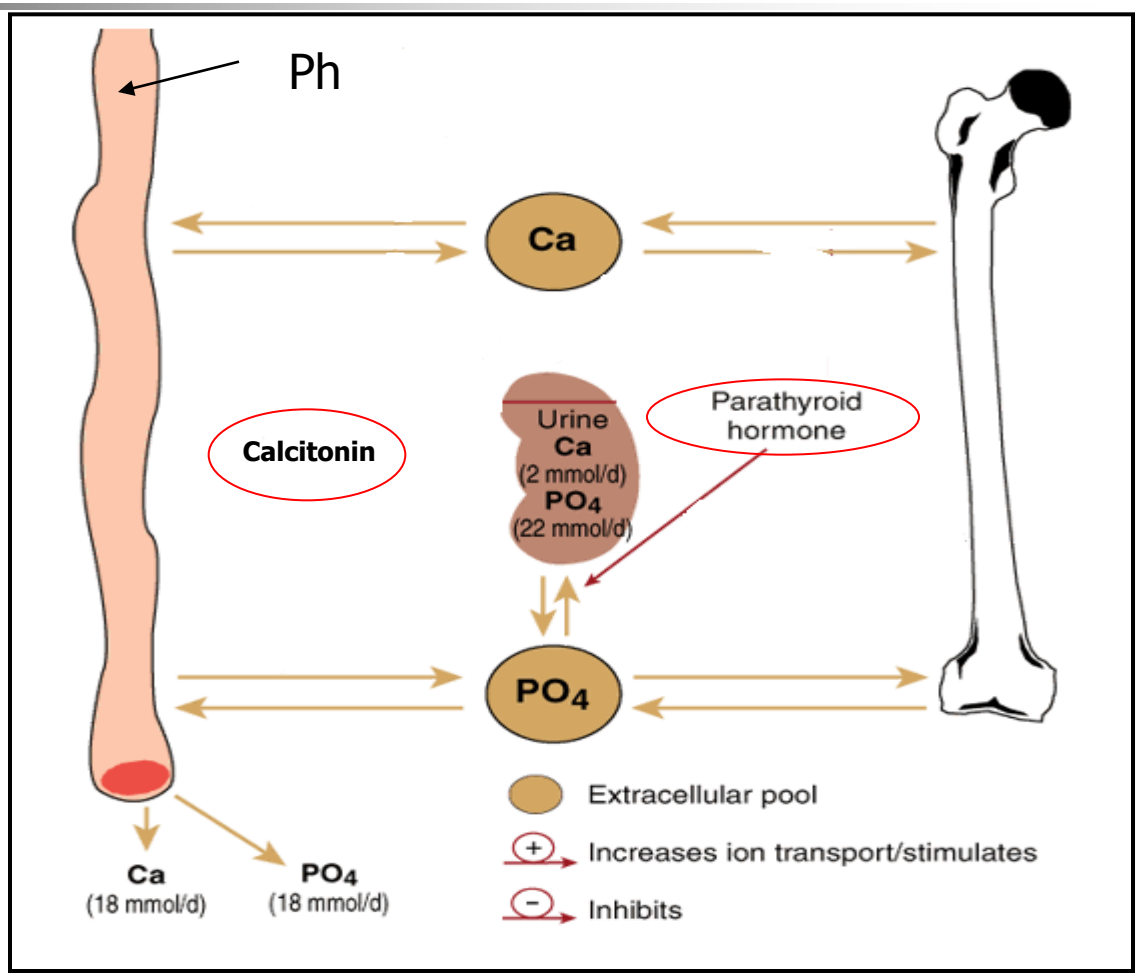
Phosphate physiology

- Of the 500 to 800 g of phosphate stored in the body, 80% can be found in the bones, while 20% is present in soft tissues and muscle.



Phosphate physiology

- Hypophosphatemia → inhibition of PTH secretion
  → stimulation of calcitonin release
- <u>Reduction in Ph renal excretion</u>
- Increase Ph intestinal absorption
- Bone resorption



Phosphate physiology

- Phosphorus is a vital component of cellular membranes, enzyme systems, nucleic acids, and various nucleoproteins.
- The most important role of phosphorus is the formation of ATP , an enzyme vital to cellular energy production.
- Phosphorus is essential for formation of 2,3 diphosphoglycerate (DPG) → depletion of 2,3-DPG results in decreased oxygen unloading in tissues → hypoxia.
- The muscle enzyme creatine phosphokinase (CPK) relies on phosphorus for normal myocyte function.

MAJOR CAUSES OF HYPOPHOSPHATEMIA

Internal redistribution	Decreased intestinal absorption	Increased urinary excretion
Increased insulin, particularly during refeeding	Inadequate intake	Primary and secondary hyperparathyroidism
Acute respiratory alkalosis	Antacids containing aluminum or magnesium	Vitamin D deficiency or resistance
Hungry bone syndrome	Steatorrhea and chronic diarrhea	Fanconi's syndrome
		Miscellaneous: osmotic diuresis, proximally acting diuretics, acute volume expansion

Phosphate physiology..

- There are several mechanisms that maintain the serum phosphate during starvation.

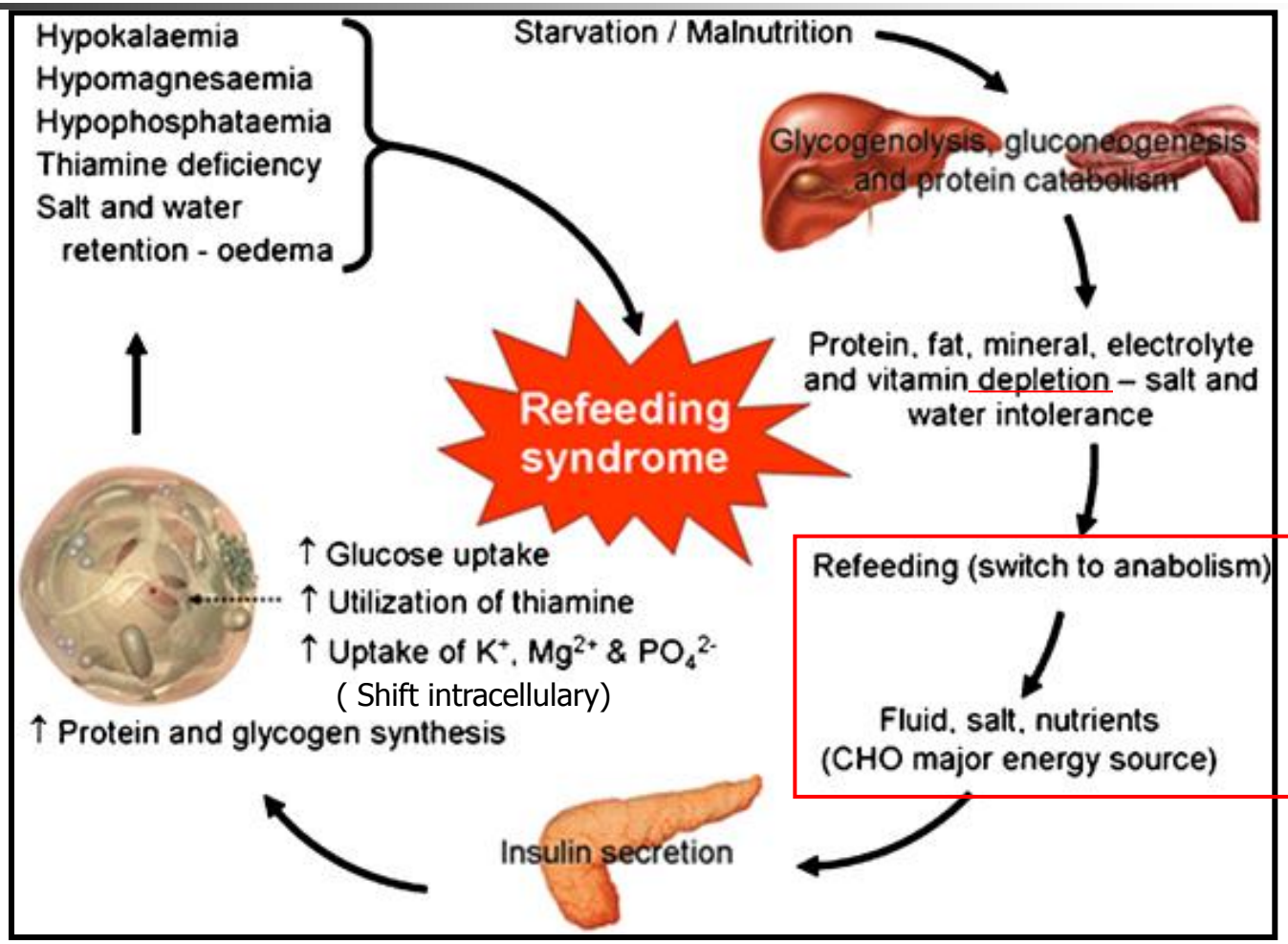
1- Overall phosphate requirements are decreased during starvation

2- serum levels are initially maintained by mobilizing bone reserves.

2- A poor phosphate intake suppresses secretion of parathyroid hormone (PTH), which increases tubular phosphate re-absorption to more than 80%.

(Weisinger J R et al. Magnesium and phosphorus. Lancet 1998; 352: 391–396)

Pathophysiology of RFS



Complications of Refeeding Hypophosphatemia

Table 3. Complications of Refeeding Hypophosphatemia

Cardiac	Pulmonary	Musculoskeletal
Sudden death Arrhythmia Heart failure Hypotension Shock	Diaphragm weakness Dyspnea Respiratory failure	Rhabdomyolysis Myalgia Muscle weakness
Hematologic	**Neurologic**	**Miscellaneous**
Hemolysis Thrombocytopenia Decreased 2,3-DPG Leukocyte dysfunction	Delirium Parasthesia Paralysis Seizures Hallucinations Tetany	Metabolic acidosis Insulin resistance Acute tubular necrosis

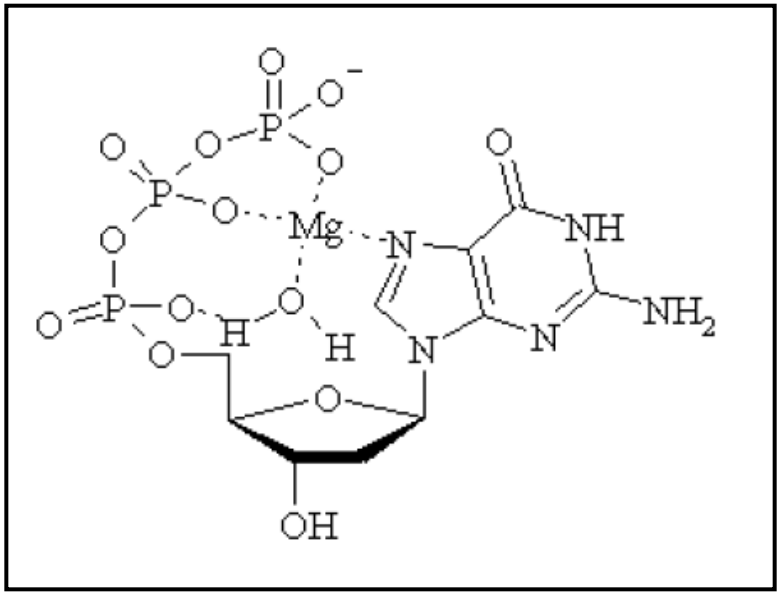
Marinella. J intensive care Med. 2005;20:155-159

Hypophosphatemia

- Serum phosphate concentrations of < 0.5mmol/l (normal range 0.85-1.40 mmol/l) can produce the clinical features of refeeding syndrome
- Severe hypophosphatemia (< 0.3 mEq/L) can happen within hours of refeed.
- A majority of the clinical manifestations of refeeding syndrome are the result of reduced phosphorylated compounds (ATP, 2,3 DPG in erythrocytes.

Hypomagnesemia

- Magnesium is an essential intracellular cationic metal that is a cofactor for many enzymes found mainly in bone and muscle (reactions involving ATP and those of oxidative phosphorylation)



Mg2+ stabilization of the ATP molecule by interaction with negative phosphate groups

Hypomagnesemia

- Up to 70% of dietary magnesium is eliminated and not absorbed (kidneys are the main route of excretion)
- The mechanism by which this occurs has not been elucidated.
- In severe hypomagnesemia (< 0.5 mmol/l) :
  cardiac arrhythmias, abdominal discomfort, anorexia, and neurological findings (tremor, paresthesias, tetany, irritability, confusion, weakness, and ataxia)

Hypokalemia

- Potassium is a predominant intracellular cation essential for maintaining cell membrane action potentials.
- The kidney regulates total body potassium (distal nephron) secretes potassium into the urine
- Clinical manifestations of hypokalemia occur at level < 3.0 mEq/L (cardiac arrhythmias, hypotension, cardiac arrest, and gastrointestinal upset secondary to ileus and constipation)
- Neuromuscular symptoms such as weakness, paralysis, paresthesias, confusion, rhabdomyolysis, and respiratory depression may be seen.

Thiamine deficiency

- Thiamine is a cofactor for many enzymatic activities
- Thiamine deficiency can result in Wernicke's encephalopathy (delirium, oculomotor paresis, nystagmus, and ataxia) or Korsakoff's syndrome (anterograde and retrograde memory loss).
- When malnourished patients are refed carbohydrates, an increase in cellular thiamine utilization occurs→ post-refeeding thiamine deficiency.

- Some authors have cited that the result in neurological conditions, including delirium and hallucinations, sometimes present in Refeeding Syndrome could be related to the concept of tissue hypoxia.

Why Peripheral edema in RFS?

- The development of peripheral edema without evidence of cardiac failure ("refeeding edema") is common during refeeding in anorexia nervosa.
- This is due to the reintroduction of fluids and solutes to a patient who was previously malnourished and dehydrated, as well as hypoalbuminemia
- This increase of insulin has a direct effect on the renal tubules.
  → increase sodium and fluid reabsorption.

Kalambokis GN, et al. The edematogenic properties of insulin. Am J Kidney Dis 2004; 44:575-90.

- ? RAA system

Why cardiac dysfunction?

- The cardiac dysfunction associated with refeeding caused by:

  1- directly related to the plasma loss of phosphate, magnesium, and potassium, and

  2- it is compounded by the loss of cardiac muscle mass during starvation.

  3- The quick administration of nutrients and fluids, which increase circulatory volume so that it cannot be handled by the cardiovascular system.

Crohn disease & RFS ?

- Most of the report cases of RFS with enteral feed in pediatrics were reported in patients with AN, Patients with prolonged hospital admission esp. in ICU & patients with Kwashiorkor.

- RFS is well documented post TPN

- Only one case reported in CD who had RFS with polymeric enteral feed (14 yrs old girl newly Dx CD with Wt loss of 7 kg in 8 wks).
  (Afzal et al. Clinical Nutrition (2002) + my search as of Jan/15/08

No internationally validated guidelines for the treatment of the refeeding syndrome…!!!

Guidelines for the prevention of refeeding syndrome

- In patients at high risk for RFS, or less that 75% of ideal body weight, refeeding should be gradual.
- The greatest caution is required during the first week after commencing nutritional support

******Monitoring***

- Before initiating refeeding by any route, and during the first 3–5 days of feeding, careful assessment of the following is required:

1. Hydration and nutritional state (Early weight gain may be secondary to fluid retention)

2. Serum electrolytes , Initial glucose and albumin (pre-albumin), Daily sodium, potassium , urea, creatinine , phosphate, Mg and calcium

3. Cardiac status: Pulse (compensatory tachycardia), ECG +/- Echo

Guidelines for the prevention of refeeding syndrome using enteral feed: Afzal et al. Clinical Nutrition (2002).

Guidelines for the prevention of refeeding syndrome

- It is advisable that patients at high risk for RFS receive enteral or parenteral nutrition at a reduced caloric rate (initially at 1,000 calories per day, or 20 Kcal/kg OR 20-25 % of the total calories , and 1 to1.2 g of protein/kg).

  (Ladage E. Refeeding syndrome. *ORL–Head and Neck Nursing.* 2003;21(3):18-20.

- Attempt to increase daily caloric intake slowly by 100-200 kcal/day

- Aim for sustained weight gain of 1-2 pounds per week is achieved.

Guidelines for the prevention of refeeding syndrome

2. Protein:

- Clinical significant milk intolerance is rare in patients with RFS

- If a milk-based feed induces diarrhea, a hydrolysate may be used.

- An initial regimen for malnourished children suggests 0.6–1 g/kg/day

- The feed should be rich in essential amino acids and gradually increased as an intake of 1.2–1.5 g/kg/ day is needed for anabolism to occur

Guidelines for the prevention of refeeding syndrome using enteral feed: Afzal et al. Clinical Nutrition (2002).

3. Supplements

- Na:1 mmol/kg/day - K: 4 mmol/kg/day - Mg: 0.6 mmol/kg/day, Phosphate up to 1 mmol/ kg/ day intravenously and oral supplements up to 100 mmol/ day for children over 5 years of age.
- Hypocalcaemia may occur during phosphate supplementation
- Thiamine ,folic acid, riboflavin ,ascorbic acid, pyridoxine
- fat-soluble vitamins A,D,E and K should be supplemented.
- Trace elements, including Selenium, may also be deficient

In Summary

- Before refeeding is instituted, 3 things need to be corrected:
  1- Electrolyte imbalances
  2- Vitamin and trace-element deficiencies (thiamine & other water soluble vitamins)
  3- Volume restored (generally takes 12 to 24 hours)

- Feeds should provide minimum of 1 kcal/ ml to minimize volume overload.
- Minimize salt intake, unless the patient is salt depleted.
- Monitor patient carefully for development of tachycardia or edema.

(Mehler PS, Gray MC, Schulte M: Medical complications of anorexia nervosa. J Womens Health 1997 Oct; 6(5): 533-41)

IV or PO phosphate supplementation ?

- The most effective treatment used to prevent RFS is IV phosphate boluses with monitoring of it's level.
- Recent research has documented that oral phosphate replacement is inadequate.
- Aim to reach to a ph level of 0.65 mmol/l

  (Rosen GH et al. *Crit Care Med.* 1995;23:1204-1210)
- Overcorrecting Ph may lead to hypocalcaemia, tetany, hypotension

Thiamine .. Thiamine. Thiamine

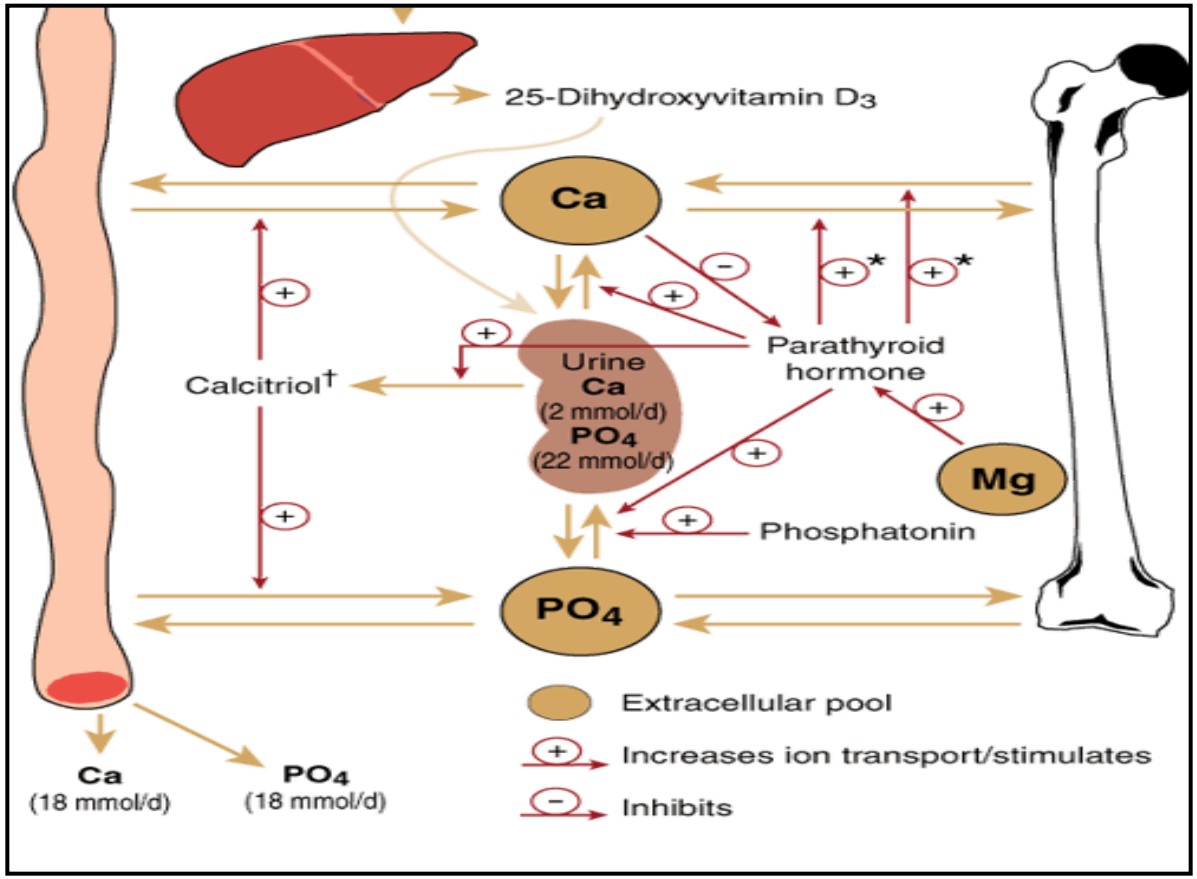
- Thiamine deficiency is of particular importance, as refeeding before correction of the deficiency may precipitate acute neurological deterioration and cardiac failure.

- Winston et al, Prevalence of thiamin deficiency in anorexia nervosa : 38% had results in the deficient range; 19% met the most stringent published criterion for deficiency.

- Deficiency was not related to duration of eating restraint, frequency of vomiting, or alcohol consumption.
  (International Journal of Eating Disorders. 2000: 28(4) 451-454

- Thiamine should be given a minimum of 30 minutes before refeeding, and additional amounts might be needed until the patient is stabilized.

Do not underestimate Refeeding syndrome


25-Dihydroxyvitamin D3
Ca
Parathyroid hormone
Urine
Ca
(2 mmol/d)
PO4
(22 mmol/d)
Calcitriol†
Mg
Phosphatonin
PO4
Ca
(18 mmol/d)
PO4
(18 mmol/d)
Extracellular pool
Increases ion transport/stimulates
Inhibits