Micronutrient and Calcium Disorders in the Preterm Infant

Jatinder Bhatia

Calcium, Phosphorus and Magnesium

- 98% Ca, 80% P and 65% Mg are in the skeleton
- Homeostasis
  - Adequate supply
  - Intestinal absorption
  - Parathormone, vitamin D, calcitonin
  - Daily accretion of 120 mg Ca, 70 mg P, 3 mg Mg per kg in last trimester
  - After birth, relative osteopenia in preterm infants and to a lesser degree, term infants as well

Calcium

- 1-2% of adult weight
- 1% of calcium present in skeleton is freely transferable with extracellular fluid
- 55% is present as free ionized calcium, 40% non diffusible complexed with protein, 5% with citrate, bicarbonate and phosphate
- Ionized fraction is the physiologically important fraction

Calcium

- Ionized calcium is regulated by fluxes at the level of the bones, kidney and intestine
- Controlled by calciotropic hormones > calcium sensing receptor protein
- Any change in extracellular calcium triggers a response with parathyroid hormone [PTH], 1,25-dihydroxycholecalciferol [1,25$[OH]_2D_3$] and calcitonin

PTH

Decrease in ionized calcium > Ca sensing receptor [CaR] > PTH secretion

Catecholamines, aluminium, histamine, active vitamin D metabolites, glucagon, cortisol, calcitonin > influence PTH

Acute decrease in magnesium stimulates PTH

Placental Transport

- Materno-fetal calcium transfer during third trimester of pregnancy; 1:1.4
- Active transport
- Maternal hypocalcemia can be associated with congenital rickets and neonatal hypocalcemia; bone mass of infant may be related to maternal Vit D status.
- Adequate supply of phosphorus [P] is important for skeletal mineralization
- Active transport, third trimester

Placental Transport

- Towards the end of pregnancy, plasma concentrations of total and ultrafiltrable magnesium are higher in fetus than mother
- Active transport; mechanisms not clear
- Fetal growth alteration , IDM
  - Bone mineral content decreased
  - Increased incidence of hypo calcemia and magnesemia
  - Bone mineral content in SGA decreased

Neonatal Hypocalcemia

- Variously defined as calcium less than 2 mmol/l [<8 mg/dL], <1.75 to 1.87 mmol/L
- Variable definition secondary to lack of clinical signs in many neonates
- Serum total and ionized Ca decrease sharply during first 24h of life
- Phosphate, bicarbonate, citrate decrease ionized calcium and increase bound calcium
- A better definition would be to use ionized calcium
- Under normal acid-base balance and normal albumin, calcium and ionized calcium levels are linearly correlated

Calcium Absorption

- Active and passive processes in the small intestine
- 60% of intake is absorbed
- Human milk Ca and fortifiers added is similar
- Glucocorticoids inhibit intestinal transfer; phenytoin directly inhibits absorption or indirectly by interfering with vit D metabolism [phenytoin and phenobarbital]

Causes of Neonatal Hypocalcemia

- Early [1-4d]
  - Prematurity
  - Maternal diabetes
  - Perinatal stress/asphyxia
  - Intrauterine growth restriction
  - Anticonvulsants
  - Alkalosis
- Late [5-10d]
  - Hyperphosphatemia
  - Hypomagnesemia
  - Transient neonatal pseudo-hypoparathyroidism
  - Hypoparathyroidism
    - 22q11 deletion
    - Maternal hyperparathyroidism
    - Hypocalcemic hypercalciuria
    - Other

Preterm Infants

- Inversely proportional to birthweight and gestational age
- Postnatal decline occurs more rapidly than in term infants
- Ca++ is not proportional to total calcium perhaps due to lower pH and lower albumin

Early hypocalcemia

- Abrupt disruption of active transport when cord is cut
- Low intake by parenteral or enteral route
- Insufficient release of PTH
- Inadequate response to PTH
- Rise in calcitonin
- End organ resistance to $1,25(OH)_2D_3$

Hypocalcemia

- Temporary
- Increased calcium intake from feedings
- Increased renal P excretion
- Improved PTH function
- Calcium supplementation may facilitate recovery

Other Conditions

- IDM
  - Exaggerated postnatal drop in Ca
  - Prematurity and asphyxia may further contribute
  - Related to hypomagnesemia [fetal Mg deficiency and secondary functional hypoparathyroidism]
  - Also seen in gestational diabetic offspring
  - Correlated with severity of diabetes

Perinatal Asphyxia

- Delayed feeding
- Increased P load due to decreased GFR
- Increased serum calcitonin
- Hyperphosphatemia > induce PTH resistance

Late Hypocalcemia

- More common in term infants
- Elevated P supply
- Relative resistance of the kidney to PTH
- Renal retention of P
- Cow's milk, evaporated milk; high P; human milk has low P
- Ameliorated with current day formulas but still seen
- "transient hypoparathyroidism"

Hypomagnesemia

- Mg deficiency inhibits PTH secretion and its responsiveness
- Neonatal hypocalcemia
- Rare autosomal recessive disorder
  - Primary defect in intestinal transport
  - Chromosome 9
  - PTH low
  - Treat with magnesium

Transient Hypomagnesemia

- Diuretics
- Aminoglycosides
- Amphotericin B
- Urinary tract obstruction
  - Renal wasting of Mg
  - Mistaken for hypoparathyroidism
  - Barter's syndrome- hypokalemic alkalosis and hypercalciuria

Clinical Manifestations

- Asymptomatic
- Jitteriness
- Generalized seizures
- Lethargy, emesis, abdominal distention
- Thorough history, examination, CXR [presence of thymus, DiGeorge Syndrome]
- Calcium gluconate

Treatment

- Complicated by coexisting conditions – asphyxia, hypoglycemia
- Seizures which may a different etiology
- May remain asymptomatic
- Time of onset also needs to be considered
- Calcium salts
- Extravasation, cutaneous necrosis, bradycardia
- Avoid arterial infusions
- Late onset is usually symptomatic and treatment may include change of formula, Mg, Vit D etc

Hypercalcemia

- Iatrogenic
- Disorders of Parathyroid function
- Idiopathic infantile hypercalcemia
- Infantile hypophosphatemia
- Other – William syndrome, sub Q fat necrosis

- History
- PE
- Total and iCa
- pH, Total protein, creatinine
- Urinary studies
- Renal ultrasound
- PTH, Vit D
- Molecular genetic studies

Osteopenia of Prematurity

- Daily accretion of 120 mg calcium and 70 mg P per Kg in last trimester
- Not Vit D related
- Prolonged parenteral nutrition
- Unfortified human milk
- Diuretics
- Prolonged sedation, immobilization
- Significant bone demineralization by DEXA: 50% <1500g and 100% <1000g

Zinc

- Approximately 2g in human adults, second to Fe among trace elements
- Increase in maternal hepatic metallothionein in pregnancy
- May enhance maternal store of Zn which is available to the fetus
- Fetus at risk only if excessive maternal decline in Zn such as zinc deprivation or alcohol abuse

Zinc

- Maternal Zn restriction associated with IUGR in rodents
- Conflicting data in humans
- LBW infants at risk
- Exclusive breastfed infants may require Zn after 4-6 months
- 2 mg/kg/d
- Little is known about molecular regulation of Zn in face of excess; current intakes appear appropriate

Zinc Deficiency

- Genetic disorder: Acrodermatitis enteropathica
- Autosomal recessive
- Chromosome 8q24.3
- Encodes for a member of Zn transporter protein
- Defect in absorption or transport
- Low plasma Zn
- Acute vesicobullous, eczematous eruption around eyes, mouth and genitals
- Secondary infection common

Iron Deficiency Anemia

- Leading cause of anemia in infancy and childhood
- Iron storage proportional to birth weight
- Term infants: 4-6 months
- Preterm infants
  - Weigh less at birth
  - Faster growth rate
  - Blood loss

Iron

Term: 1 mg/kg/d from 4 months

Preterm: 2 mg/kg/d from 2 months; may be higher in VLBW infants

Breast milk iron more bioavailable, but may be insufficient after 6 months

Formulas with Fe should always be used

Prolonged parenteral nutrition without iron supplementation will lead to deficiency

Iron

- Bone marrow stores reduced
- RDW increases
- Lower serum iron, ferritin, transferrin
- Hypochromic microcytic anemia
- Free erythrocyte protoporphyrin elevated
- Irreversible cognitive effects demonstrated

Anemia of Prematurity

- Low reticulocyte count
- Inadequate response to erythropoietin
- EPO data controversial

Summary

- Neonates are susceptible to a wide variety of micro and macronutrient deficiencies as well as alterations in homeostasis
- Adverse effects can be minimized by careful attention to progression of illness or wellness
- Nutritional strategies of paramount importance

Summary

- Exclusive human milk feeding in preterm infants
  - Metabolic bone disease
  - Growth faltering
  - Zinc deficiency
  - Hyponatremia

Summary

- Errors of omission or commission
  - Hypo-hypercalcemia
  - Hypo-hypermagnesemia
  - Hypophosphatemia and resultant hypercalcemia
  - Anemia
  - Prolonged parenteral nutrition
    - Metabolic bone disease
    - Hepatic dysfunction
    - Iron and zinc issues