Dietitians' Session (2004)

Metabolic bone disease

Geila Rozen, Israel
Metabolic Bone Disease

Long term TPN

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„Critical illness“

- Trauma/Infection
- Acute Stress Response
- Iatrogenic Factors
- Immunological Response
- Metabolic Response
- Neuroendocrine Response
Causes of low BMD

Low peak bone mass
- Genetic
- Poor diet (calcium)
- Inactive
- Disease
- Drugs

Early menopause
- Surgery
- Pituitary tumor

Rapid bone loser at the menopause

Accelerated bone loss
- Disease
- Drugs

Bone Mass

Years
0 10 20 30 40 50 60 70

Fracture Zone

RICHARD EASTELL, Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 2004
Basic definitions

Bone is a specialized connective tissue with a unique ability to become calcified.

Bone functions: mechanical, protective, metabolic

Long bone types: Cortical, Trabecular

Microscopic organization: Collagen with plate-shaped crystals of hydroxyapatite \([\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\)

Bone is a specialized connective tissue with a unique ability to become calcified.
Bone cell types

**Osteoblasts** – responsible for bone formation
100-400 per bone forming site
Plasma membrane reach in Alk-p
Receptors for PTH, Vitamin D, local factors (IGF-1, Intraleukines)
Ability to express cytokines (CSF-1, OPG/RANK/OCIF, TNFs/RANKL)

**Osteoclasts** - responsible for bone resorption
Giant multinuclear cell, usually 1-2 per bone resorption site
Receptors for Calcitonin (Estrogen & vitamin D controversial)
Endocrine & Auto/Paracrine influences on bone

**Endocrine:**
- PTH
- Vitamin D
- Calcitonin
- Growth hormone
- Insulin
- Gonadal hormones

**Local factors:**
- IGF-1
- CSFs
- TNFs
- OPG
- Intraleukines
- Prostaglandines
Bone remodeling

Activation → Resorption

Resting Phase → Resorption

Reversal Phase → Formation

Formation → Resting Phase
Duration of phases of normal remodeling sequence

Eriksen EF, Axelrod DW, Melsen F 1994 Bone Histomorphometry.
Coupling of osteoblast (OBL) differentiation and bone formation is caused by growth factors being released from bone in active form as a consequence of osteoclastic (Ocl) resorption.

Mundy GR, Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 2004
Rapid vs. Low Turnover Bone disease

Calcium, Vitamin D

Low turnover

PTH

High turnover

Adynamic

Normal bone formation

Osteomalacia

Osteitis fibrosa

Al^{+3}

Based on - Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 2004
Bone disease under TPN

Hypocalcemia / Hyperphosphatemia

PTH Secretion

Bone

Resorption

Demineralization

Kidney

Urinary Phosphate

Urinary Calcium

25(OH) D → 1,25(OH)2D

Intestine

Calcium Absorption

Phosphate Absorption

↑ Serum Calcium

Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 2004
Vitamin D

• Vit. D + PTH increase bone resorption when calcium levels are low

- Fatty fish
- Fish liver oils
- Fortified milk & dairy products
- Egg
- Butter

Nutrient Sources:
- Fatty fish
- Fish liver oils
- Fortified milk & dairy products
- Egg
- Butter

Vitamin D Metabolism:

1. **Food (Dietary Vitamin D)**
   - Plasma Vitamin D₂, D₃

2. **Skin**
   - 7-OH-Cholesterol

3. **Liver**
   - 25 OH D₃

4. **Kidney**
   - 1αD₃

   - 24,25 (OH)₂D₃
   - 1,25 (OH)₂D₃ (Active Compound)

   - Decreased PTH
   - Increased P, Ca

   - Increased PTH
   - Decreased P, Ca
25(OH)D3 Serum Level in Hip Fracture Pt’s

60.4% (58) patients 25(OH)D3 serum level below 25 ng/ml

Segal E, Tamir A, Zinman C, Raz B, Ish-Shalom S. not published
Vitamin D – are current ref. ranges correct?

Malabanan A, Veronikis IE, Holick MF 1998 Lancet
Vitamin D serum levels
New considerations

• Current normal values (15-80 ng/ml) are based on modern life style
• Below 30 ng/ml calcium absorption significantly reduced, rise in PTH levels and bone absorption
• Hypovitaminosis D is associated with insulin resistance

• Vitamin preparations high in vitamin A are problematic for bone health
• calcium and phosphate solutions, contain aluminum

Heaney 2003, Chiu KC 2004, Genaro 2004
Adynamic Bone Disease

Etiology

- **Aluminum toxicity - TPN**
- Aluminum toxicity - Renal dialysis pt’s
- Corticoid therapy
- Hypothyroidism : surgical, medical
- **Diabetes**
- Immobilization
- Malnutrition
Aluminum toxicity

- Aluminum has no known physiologic function
- Shown to be toxic both to plants & animals
- Sources: food, water, antiperspirants, medication (drugs, dialysis, TPN)
- Transported in blood bound to transferrin
- Enters cells via transferrin receptor
- Capable of crossing BBB
- In experiment animals was found in Bone, Kidney, Liver, Heart & Brain
Aluminum toxicity – human Pt’s

- Osteomalacia / Adynamic Bone Disease
- Microcytic anemia (without iron deficiency)
- Neurologic deficits:
  - dialysis encephalopathy
  - Dementia
  - Alzheimer’s disease (?)

In TPN 100% amount given. Main sources
mineral & vitamin preparations; and AA solutions
Aluminum Bone Disease

- Suppresses PTH secretion
- Inhibits OB differentiation & proliferation
- Reduces collagen synthesis
- Interferes with bone mineralization

- In children – reduced linear growth
- In preterm – no bone reserve, and undeveloped kidney complicate matters
WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.
Hypercalcemia has been reported in patients receiving total parenteral nutrition…. involves inadvertent aluminum toxicity derived from amino acid hydrolysates added to the hyperalimentation fluid. These patients presented after having been on TPN for months to years and were found to have hypercalcemia and low turnover osteomalacia, characteristic of aluminum bone disease. Now that aluminum has been removed from the TPN formulations, this syndrome has disappeared.
some more thoughts on this issue...

A very small % of the population receives long term Home TPN

On the other hand...

most of us use aluminum containing antiperspirants, and drink out of cans

It is controversial if Aluminum causes Dementia
Is it debatable that we are already demented?
Rules to apply back at home TPN...

- maintain normal Calcium and P levels
- Vitamin D levels > 32 nanog/ml
- Monitor PTH levels
- Monitor Alk-P levels
- Monitor Aluminum levels:
  - in TPN solution < 25 microg/L
  - in serum < 100 microg/L
  - in urine < 0.3 microg Al/mg creatinine
Thank you

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