Metabolic Bone Disease in Parenteral Nutrition Dependent Patient. Challenges and Management

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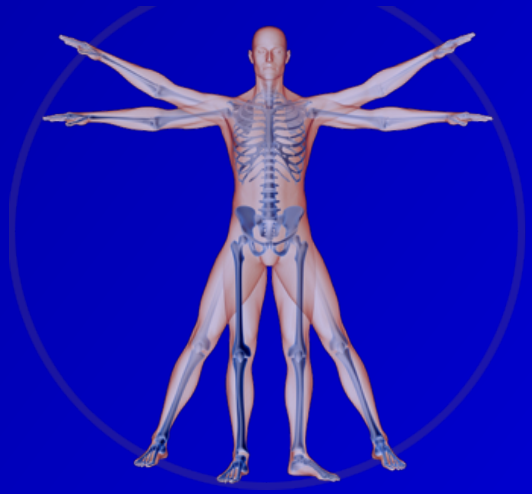
Weston



Objectives

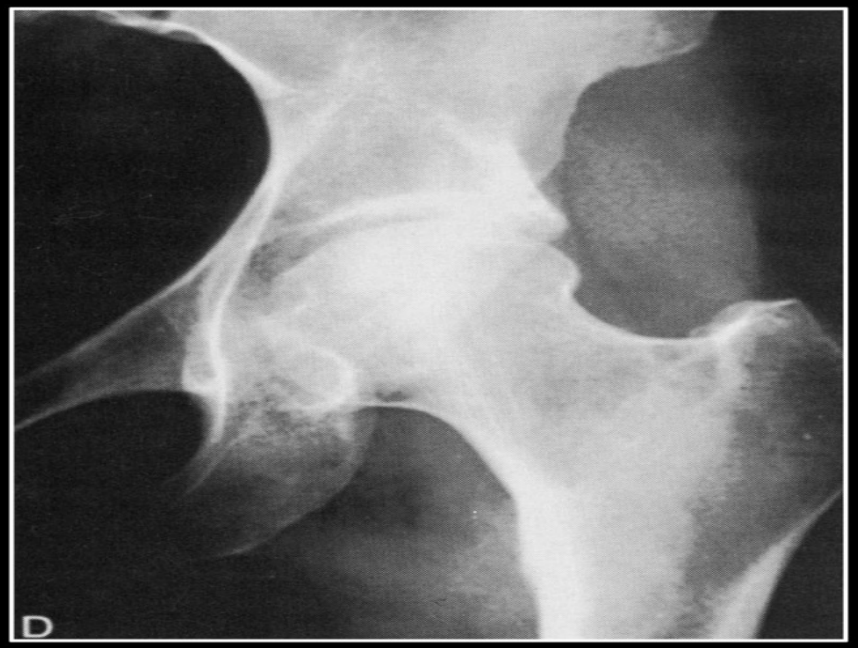
- What is metabolic bone disease (MBD)?
- Importance of MBD
- How to diagnose MBD?
- Causes of MBD in PN patients
- Effects of PN on bone metabolism
- Prevention and therapy for MBD

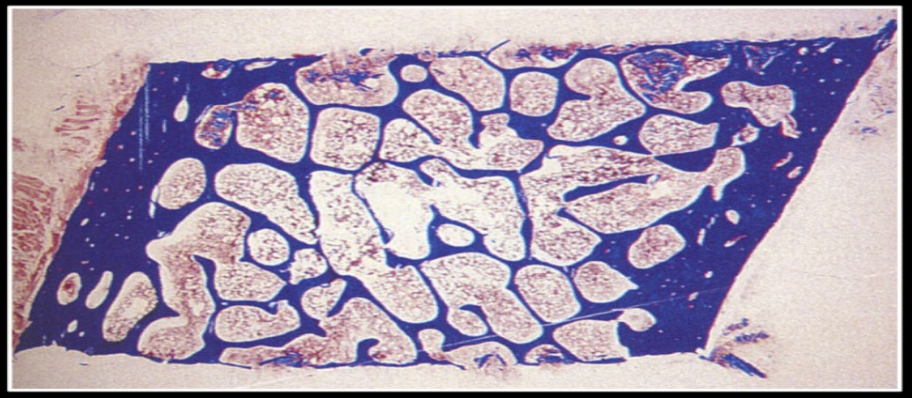
Introduction
Significance of MBD/Osteoporosis

- Hallmark of OP- fractures spine and hip
- Fractures due to OP occur every 3 sec. around the world
- 1 in 3 women after age 50 - fragility fracture
- Substantial morbidity and mortality due to OP related fractures
- Bisphosphonates reduce risk of fractures: vertebral 40-70%, hip 20-50%

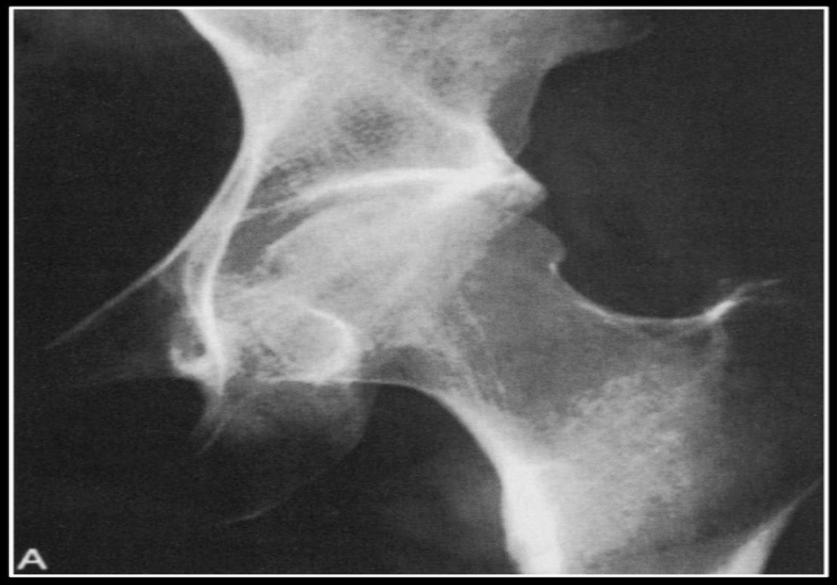
Adler R. et al. J Bone and Mineral Research 2015:31:16

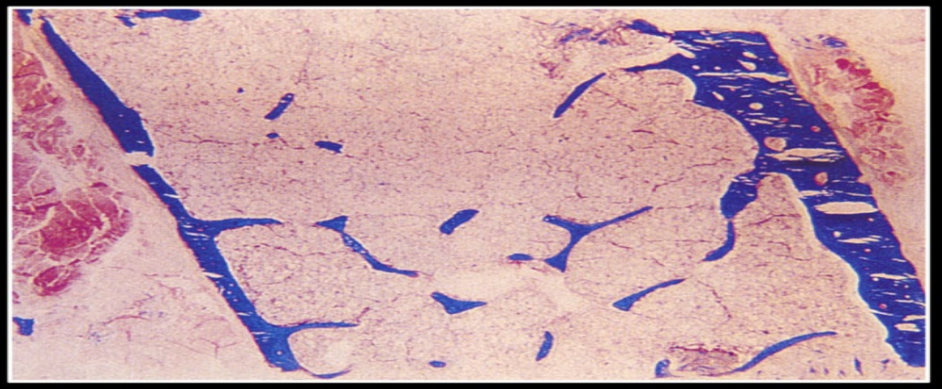
Normal Trabecular Bone



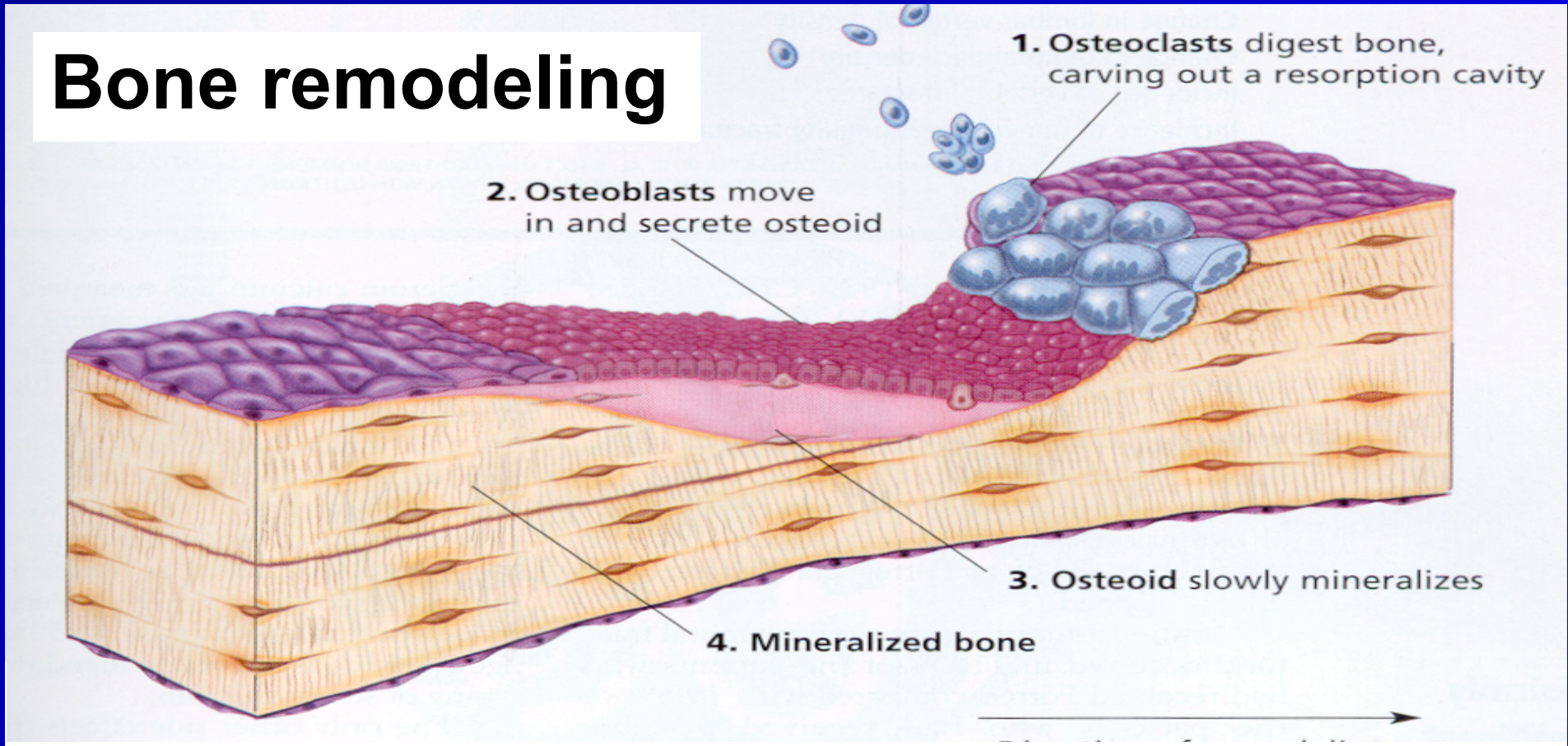


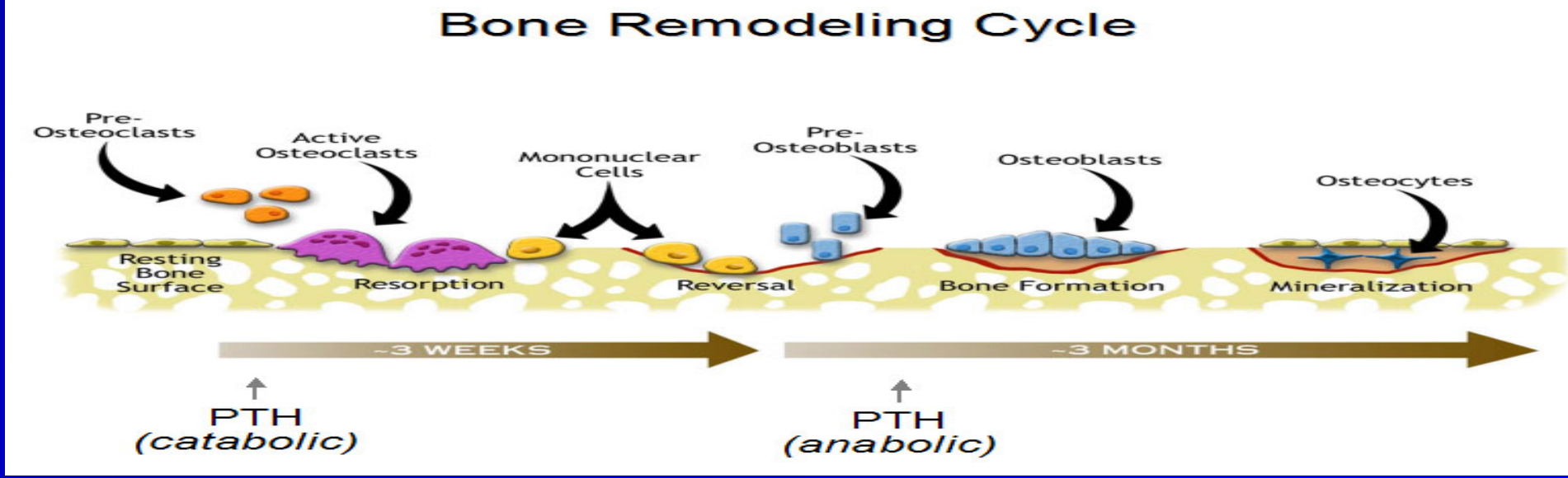
Osteoporosis

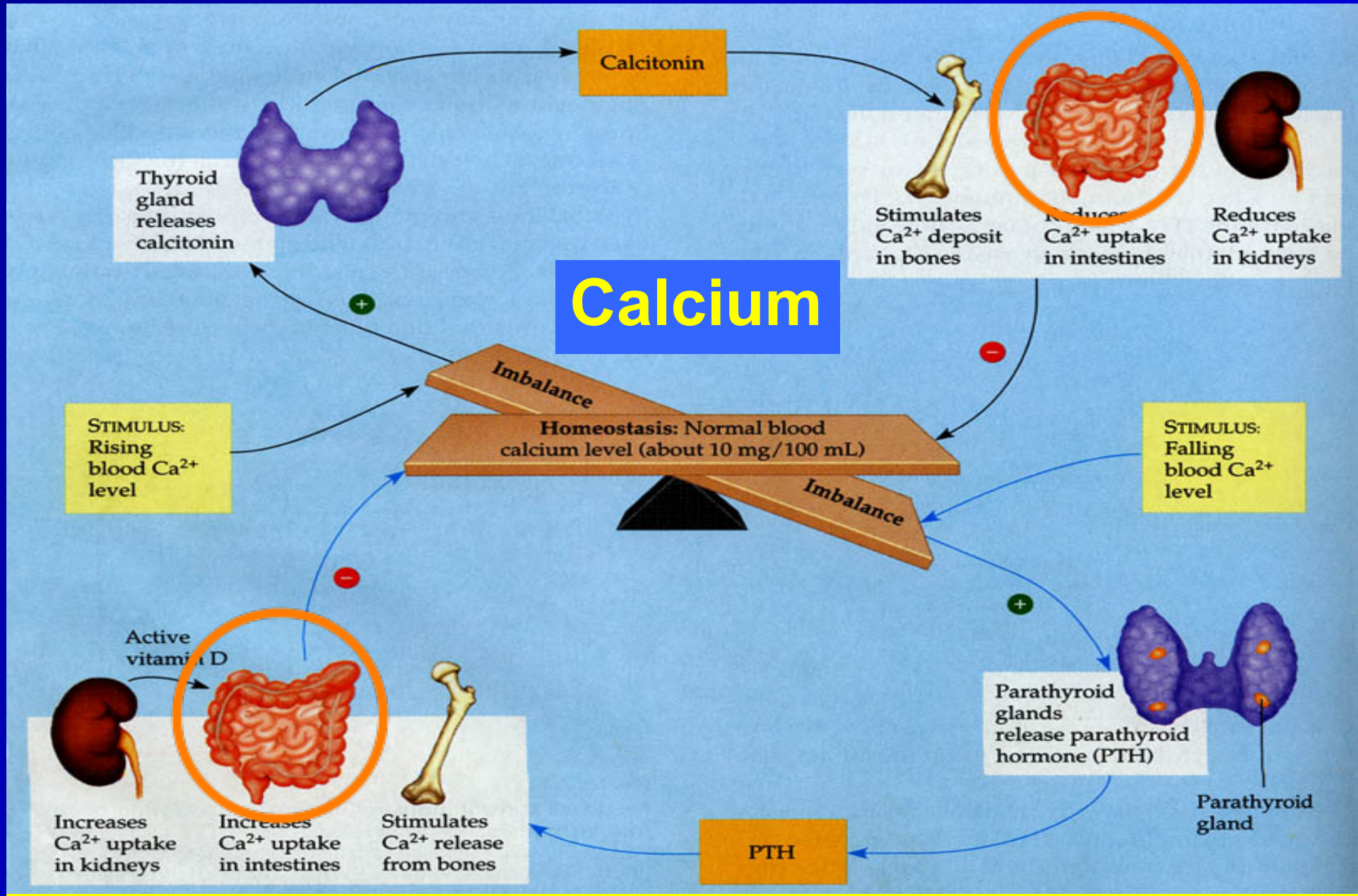




Bone remodeling

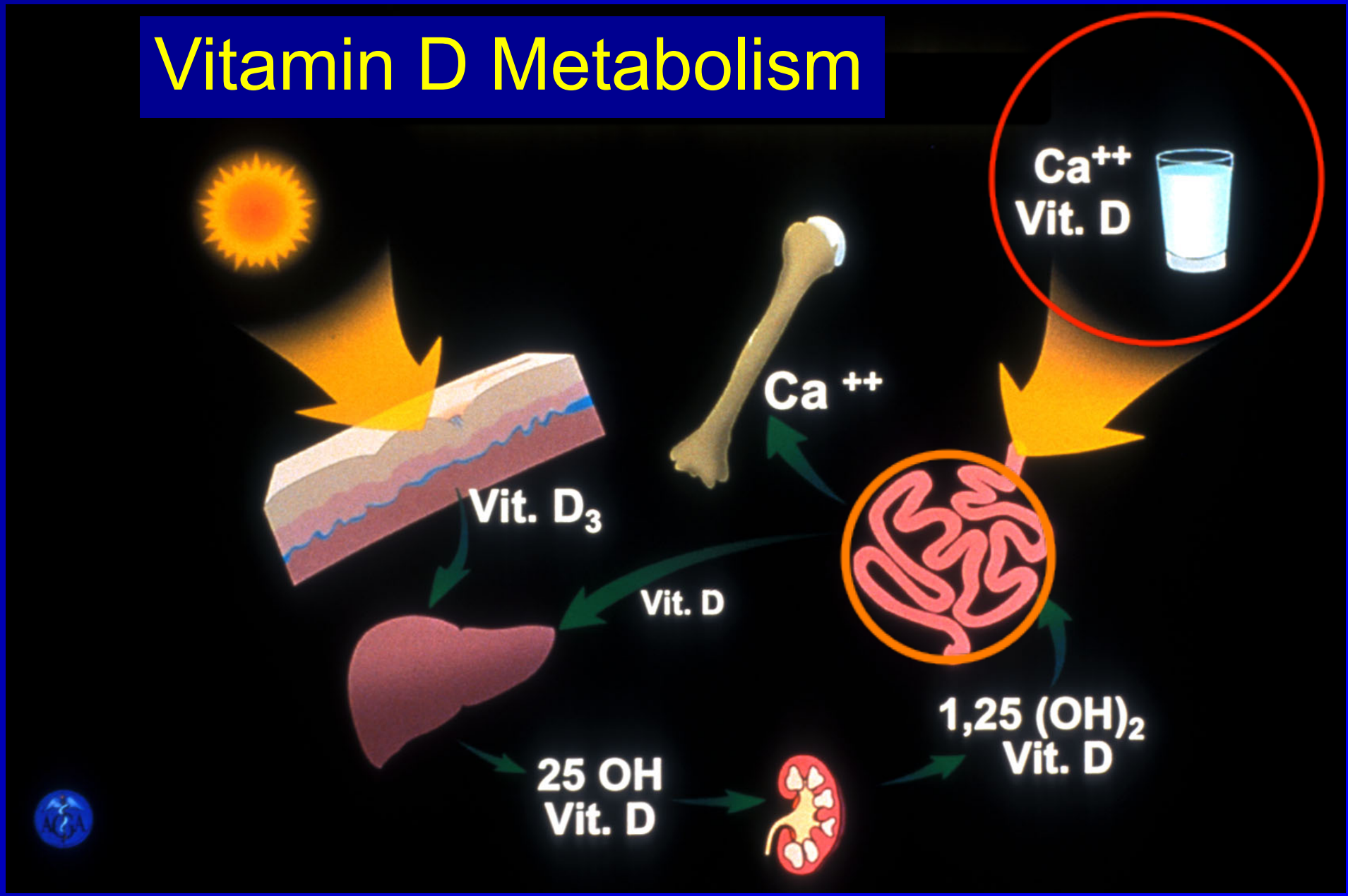






Hormonal Control of Calcium Homeostasis

Vitamin D


Vitamin D Metabolism
Ca++
Vit. D
Ca ++
Vit. D3
Vit. D
1,25 (OH)2
Vit. D
25 OH
Vit. D

Diagnosis of Osteoporosis

Measurement of BMD

- **DEXA (dual energy x-ray absorptiometry)**

- Quantitative ultrasonography o the os calcis
- Quantitative CT
- Bone biopsy

Biochemical markers

Reabsorption:

-Type 1 collagen

- Osteocalcin, AP

Formation:

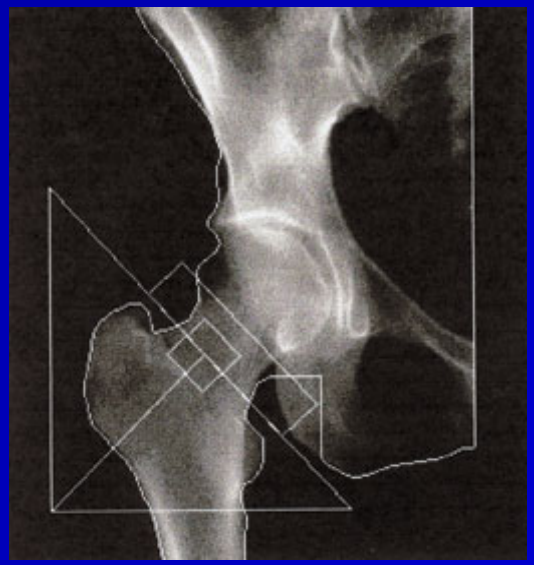
Urinary excretion of deoxypyridinoline collagen cross linked N-telopeptide

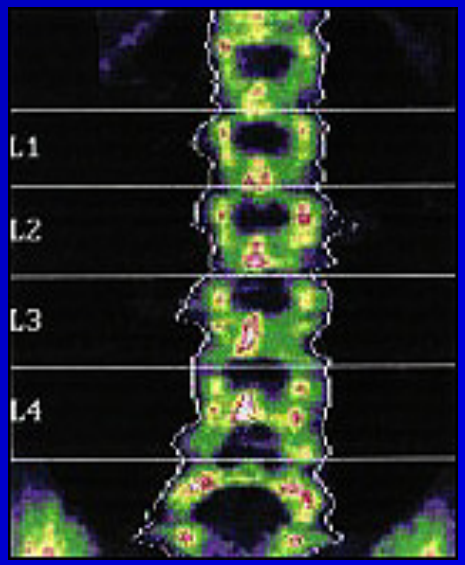
Serum markers:

PTH, 1,25(OH) Vit. D, Calcium

Dual Energy X-ray Absorptiometry DEXA Scan

- Quantifies bone mass: lumbar spine, femoral neck, radius
- Precise, accurate, quick, low radiation exposure, low cost

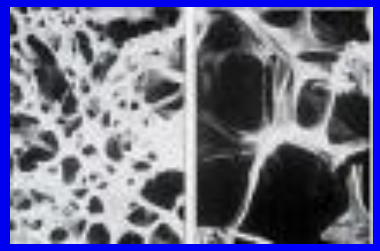


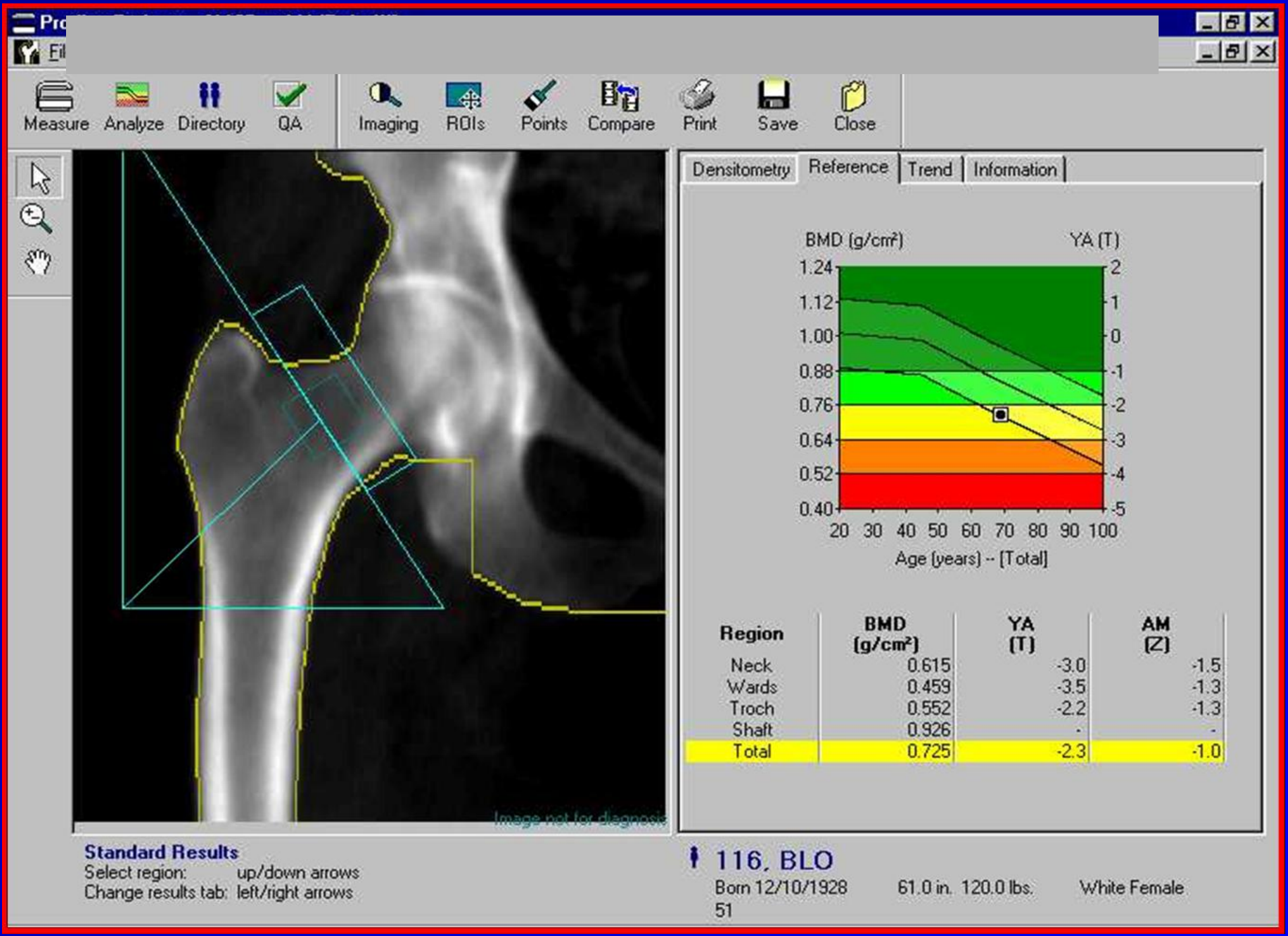


Interpreting DEXA
Definitions

- **T score** = SD from average young adult bone mass
- **<u>Osteoporosis:</u> T-score <u>≤</u> -2.5**
- Osteopenia: T-score from -1.0 to -2.49

- **Results parallel fracture risk!!!!**



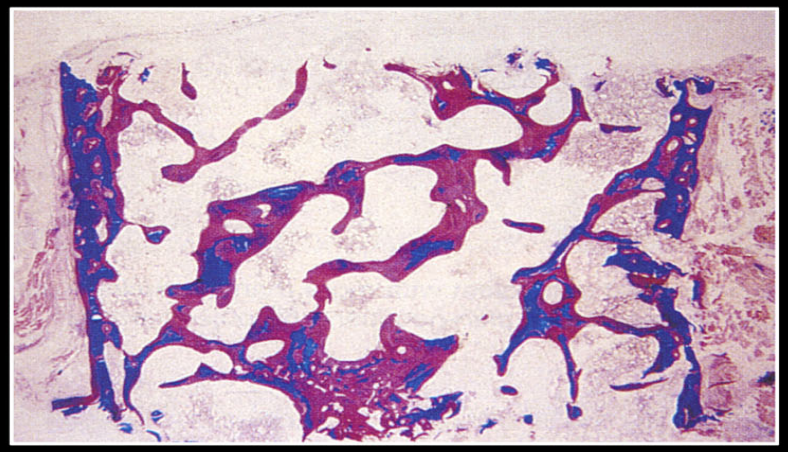

Measure
Analyze
Directory
QA
Imaging
ROIs
Points
Compare
Print
Save
Close
Densitometry
Reference
Trend
Information
BMD (g/cm²)
YA (T)
1.24
1.12
1.00
0.88
0.76
0.64
0.52
0.40
2
1
0
-1
-2
-3
-4
-5
20 30 40 50 60 70 80 90 100
Age (years) -- [Total]
Region
BMD (g/cm²)
YA (T)
AM (Z)
Neck 0.615 -3.0 -1.5
Wards 0.459 -3.5 -1.3
Troch 0.552 -2.2 -1.3
Shaft 0.926 - -
Total 0.725 -2.3 -1.0
Standard Results
Select region: up/down arrows
Change results tab: left/right arrows
116, BLO
Born 12/10/1928
61.0 in. 120.0 lbs.
White Female
51

MBD and Parenteral Nutrition

- MBD associated with long-term TPN use first described in 1980
  - Patient suffered from bone pain
  - Labs:
    - Hypocalciuria and AP
    - Normal levels of serum calcium, phosphorus and 25-hydroxyvitamin D
  - Bone biopsy: osteomalacia, increased osteoid, and bone turnover

Klein GL, et al. Lancet 1980;2:1041

Osteomalacia



- Defective bone mineralization
- Abnormal calcification at the bone-osteoid interface
- bone volume but increased fracture risk

MBD in TPN Patients

- Incidence of MBD in PN patients is unknown
  - 40-100% long-term PN patients have some degree of bone demineralization

- Symptoms: bone pain, back pain, non-traumatic fractures (vertebra, rib)
- Many patients are asymptomatic!!!

- Normal serum Ca, P, Vitamin D, PTH
- Hypercalciuria

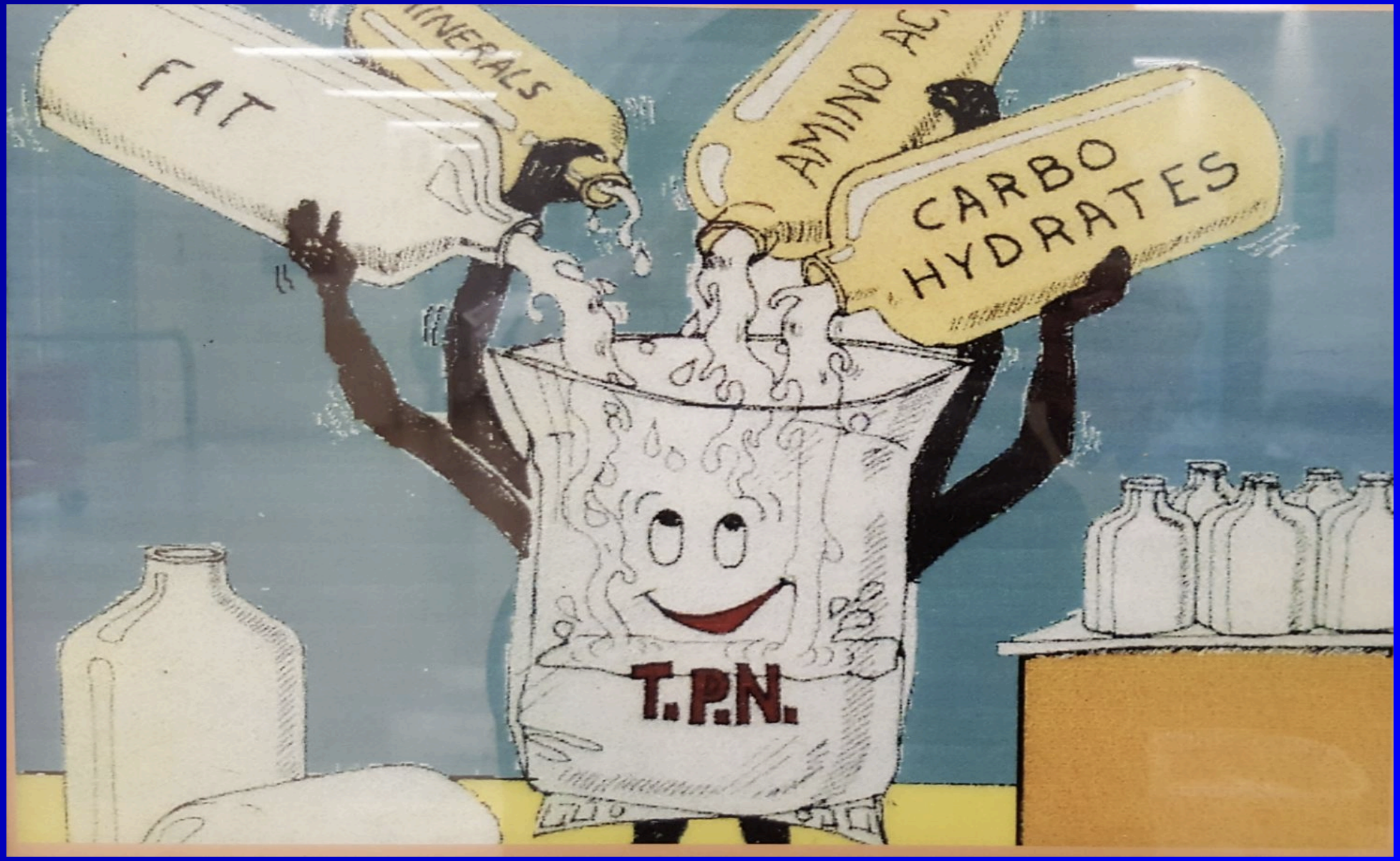
Risk Factors for MBD in PN Dependent SBS Patients

- MalNutrition
- Low body weight
- Low intake of dietary vitamin D and calcium
- Malabsorption (vit. K)
- Low absorption of vitamin D & calcium
- Corticosteroids use (IBD)
- Smoking
- Alcohol

PN Related Factors Promoting MBD

- Deficiency of
  - Calcium
  - Phosphorus
  - Vitamin D
- Aluminum toxicity
- Vitamin D toxicity
- Excess of
  - Amino acid infusion
  - Dextrose infusion

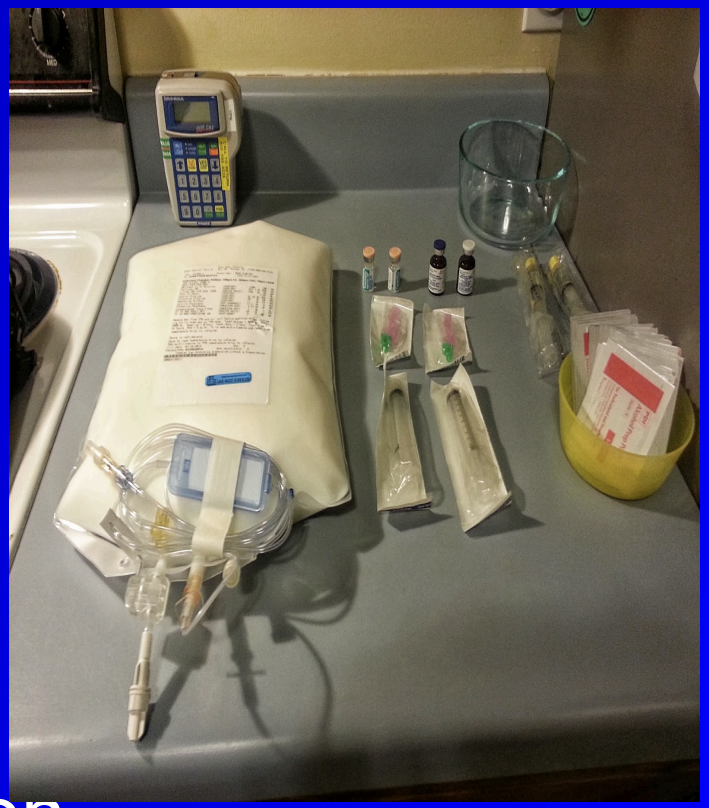
PN Factors



PN Factors
Calcium Losses and Hypocalcemia

urinary calcium excretion

- Amino acid (titratable acid)
- Dextrose (insulin)
- Calcium in PN
- Sodium (increase GFR)
- Cyclic PN infusion
- Metabolic acidosis
- Phosphorus supplementation



PN Factors Promoting MBD

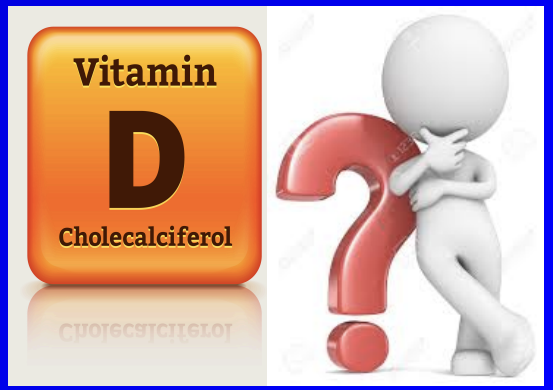
- Altered bone metabolism
  - Magnesium
    - PTH secretion and action
  - Metabolic acidosis
    - Amino acids produce weak organic acids
    - Chronic diarrhea, D-lactic acidosis
  - Heparin
  - Vitamin D
  - Aluminum

Aluminum Toxicity and MBD

- Aluminum toxicity causes osteomalacia
  - Impaired calcium bone fixation
  - PTH secretion, Inhibited conversion vit. D to 1,25-OH vit.D
- Casein hydrolysate [2300 mcg Al/L] – not used in TPN since 1981
- Contaminant in PN - MVI, trace elements, calcium, phosphate salts
- PN Package insert Al < 25mcg/L
  - FDA safe upper permit < 4-5 mcg/kg/d

Vitamin D Toxicity and MBD

- Vitamin D supplement in PN: 200 IU/d
- Vit. D in PN may be potentially toxic to bones
- Removal of Vit. D from PN - improvement in bone mineralization in HPN patients
  - Calcuria and phosphaturia
  - Positive calcium balance
  - Bone pain
  - Normalization of PTH level



Evaluation for MBD

History
- Indication for PN
- FH of osteoporosis
- Tobacco/alcohol use
- Menopausal status
- Thyroid disease
- Bone pain

Medications
- Estrogens
- Glucocorticoids
- Loop diuretics

- Physical exam
  - Atraumatic fractures
  - Skeletal deformity

- Bone density measurement
  - DEXA

Evaluation of MBD in PN Patients

Evaluation	Comment
Serum	
CMP	Initial followed q wk for 3 months
PTH	Malabsorption or hyperparathyroidism suspect
25-Hydroxyvitamin D	Malabsorption suspect
TSH	Hyperthyroidism suspect
N-Teliopeptide collagen	MBD detected
Urine	
N-Teliopeptide collagen	MBD detected
24-hour Ca, Mg	Monitor every 6 to 12 months
Radiographic	
DEXA	Baseline, every 1 to 3 years

Therapy for MBD

Prevention. Lifestyle Measures Eliminate Secondary Causes of MBD

- Manage underlying disease
- Discontinue smoking
- Minimize alcohol intake
- Treat hyperthyroidism, hypogonadism, hyperparathyroidism
- Taper or stop glucocorticoids
- Encourage weight bearing exercise

* Vit. D and calcium supplementation

Weight Bearing Exercises

Regular exercise - 30 min. 3x /week!!!

Prevention of MBD Adjustments in PN

- Sufficient calcium & phosphorus concentration in PN
- ? Removal of vitamin D in PN
- Monitor/limit aluminum in PN solution
- Monitor Vit. D, Ca & Phosphorus
- Amino acids - 1.5 g/kg/d, reduce when visceral proteins normalize
- Add Acetate – keep serum bicarb mid-range

Guidelines for Pharmacologic Interventions

- History of hip or vertebral fracture
- T-score ≤-2.5 femoral neck or spine
- T-score -1 to -2.5 femoral neck or spine and 10 yr. probability of hip fracture ≥3% or 10 yr. probability of major OP-related fracture > 20% based on the WHO algorithm (FRAX)

FRAX - fracture risk assessment

Clinical Risk Factors for Fracture

- Advanced age
- Previous fracture
- Low body mass index (19 kg/m2)
- Maternal hip fracture (<60 years)
- Premature menopause (age <45 years)
- Physical inactivity/lack of exercise
- Excessive alcohol consumption
- Smoking
- Corticosteroid therapy
  (prednisolone >5mg/d x 3 months)
- Hypogonadism
- Malabsorption
- IBD/Chronic liver disease

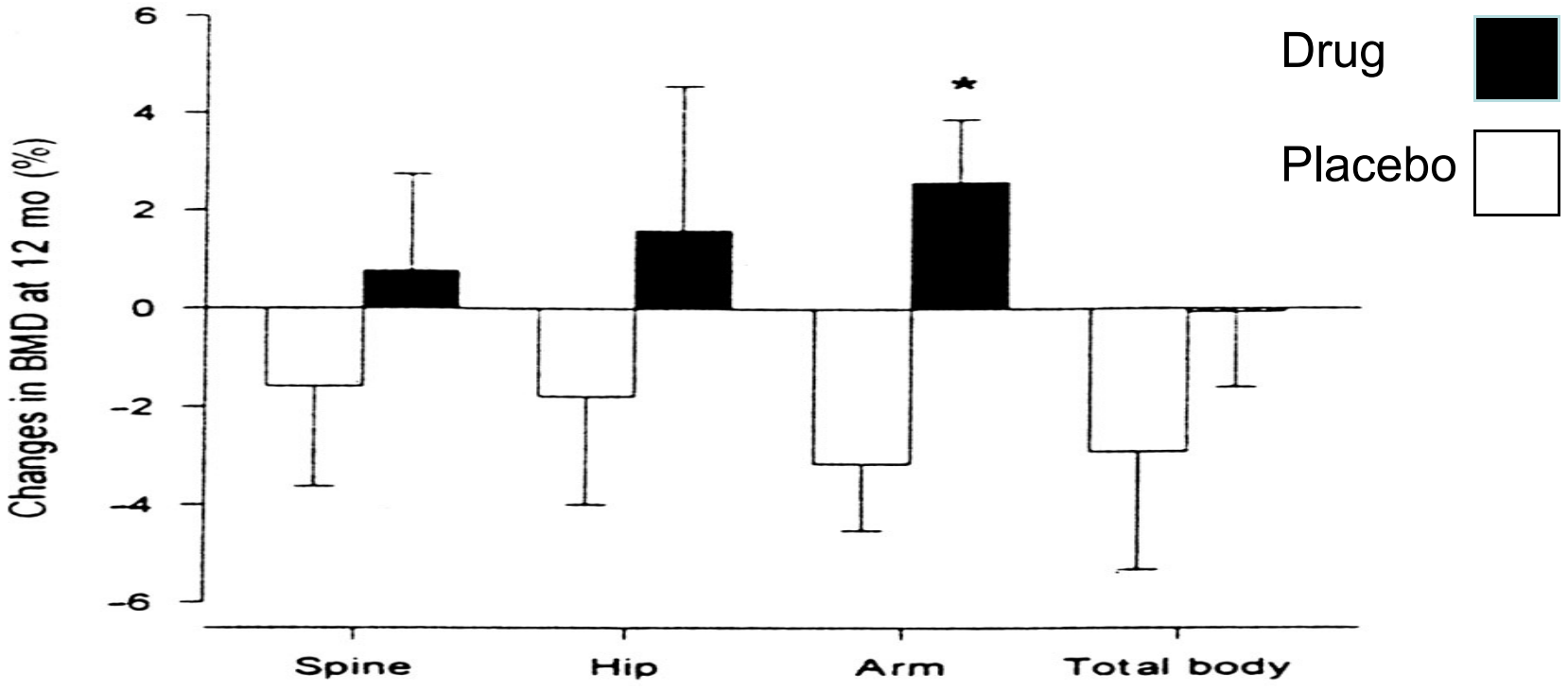
Drug Therapy

- Inhibition of osteoclasts
  - Conjugated estrogens
  - Selective estrogen receptor modulators
  - Calcitonin
  - Bisphosphonates
  - Denosumab (Prolia)
- Stimulation of osteoblasts
  - PTH (Forteo)

Drug Therapy

Bisphosphonate IV in HPN Patients

RCT; N=18 HPN pts. (>1yr); DEXA: T-Score <-1
IV Clodronate (x 1 year) vs. Placebo



Change in BMD (%)

Haderslev, et al. AJCN 76:482, 2002

Bisphosphonates IV (BPs)

- Treat or prevent OP
- Bone resorption inhibitors

- Ibandronate (Boniva) 3 mg IV q 3 months
- Pamidronate (Aredia) 60 mg IV over 4 hr. q 3 months (off label)
- **Zoledronic acid (Reclast) IV infusion 5 mg over 15 min. q 1 year**

- Concerns: Osteonecrosis of the jaw, atypical femur fracture
- Contraindicated - renal failure GFR <30 ml/min

Mottaghi P. Official Journal of Isfahan University of Medical Sciences. 2010;15(3):175-184.

New Guidelines on Long-Term Bisphosphonate (BPs) Use

- Fracture risk should be reassessed after 5 yrs. of oral BPs vs. 3 years with IV BPs

- High risk pts. (low T-score; prior OP Fx)
- Oral BPs for up to a decade
- IV BPs should not be continued longer > 6 yrs.
- Fracture risk reassessment q 2-3 yrs.
- Low risk pts. - Stop treatment after 3 yrs. IV BPs therapy – monitor Fx risk

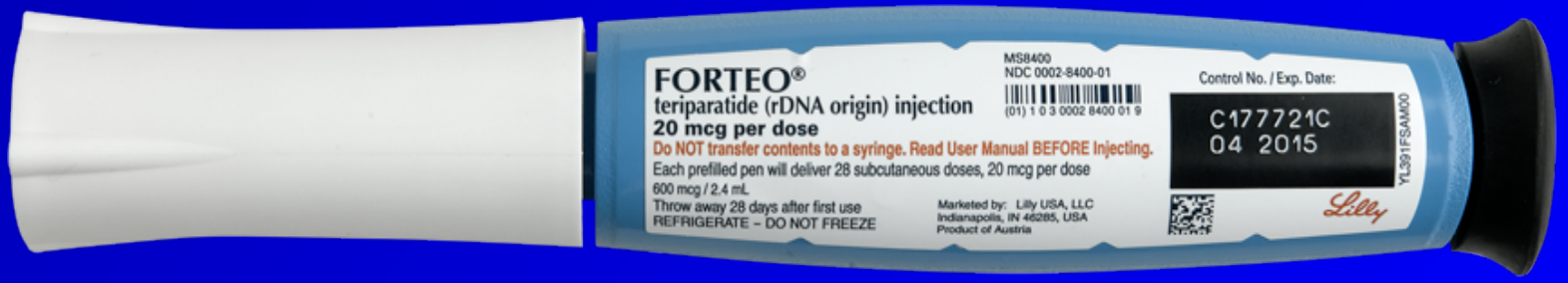
American Society for Bone and Mineral Research
Adler R. et al. J Bone and Mineral Research 2015:31:16

Denosumab (Prolia)

- Bone resorption inhibitor; human monoclonal antibody specific for receptor activator of nuclear factor kappa-B ligand (RANKL)
- OP pts. at high risk of fracture (history of OP Fx; multiple risk factors for Fx); and pts. who failed or intolerant to other therapy
- Prolia [60 mg] single SC injection every 6 months
- All pts. give calcium 1000 mg/d + at least 400 IU vit. D daily

Teriparatide (Forteo)

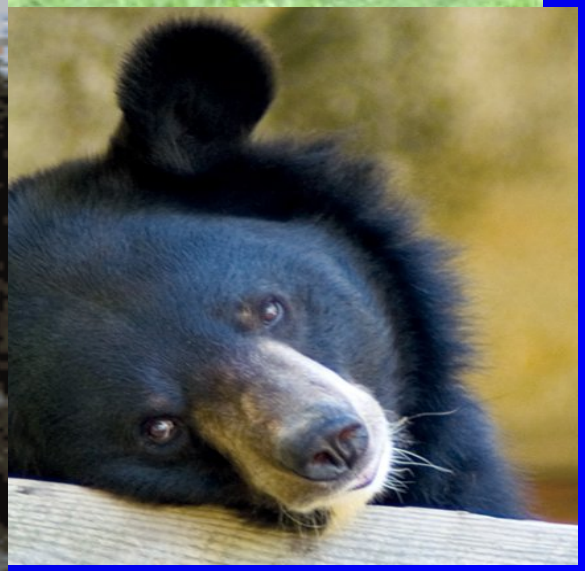
- Based on PTH
- Given as SC injections daily (20mcg)
- Safety and efficacy of Forteo have not been evaluated beyond 2 yrs. of treatment
- Use of Forteo for > 2 years during a patient's lifetime is not recommended!!!
- Concerns: osteosarcoma



Conclusions

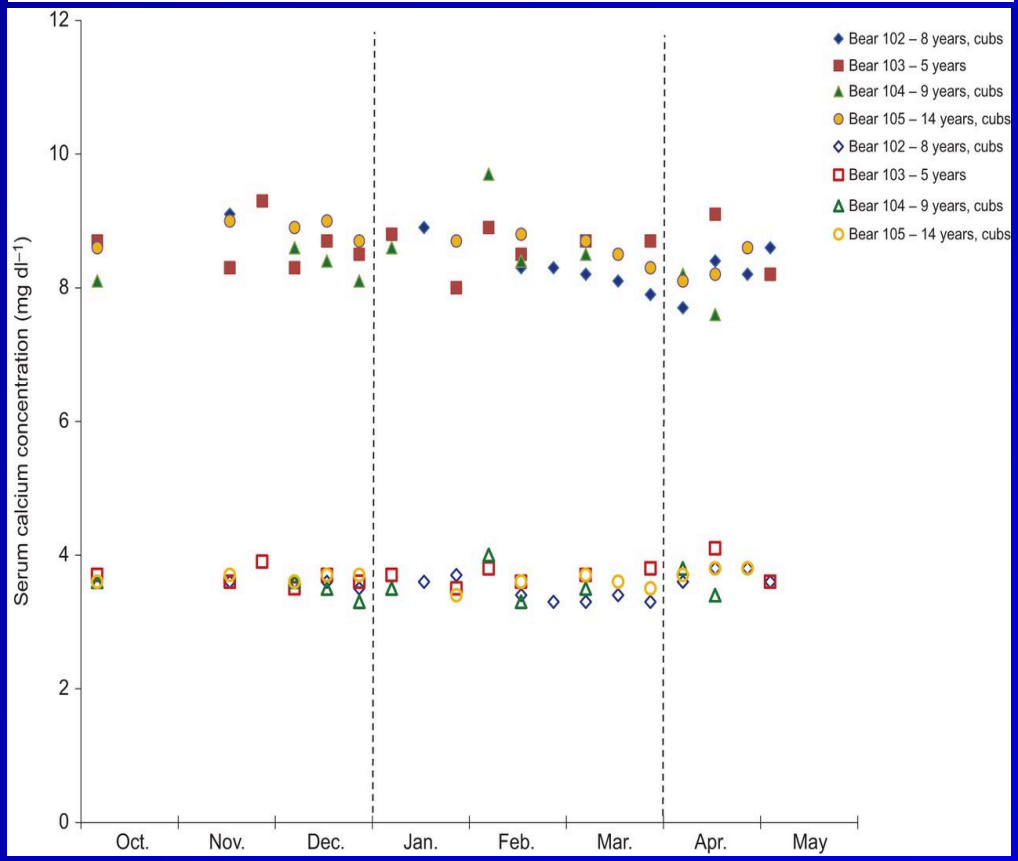
- MBD is a debilitating complication
- MBD is very common in PN patients
- PN adversely effects calcium metabolism
- All patients receiving long-term PN should be monitored for MBD
- Prevention of MBD is important
- Therapy for MBD is effective and should be implemented early

Bone Issue in Black Bear

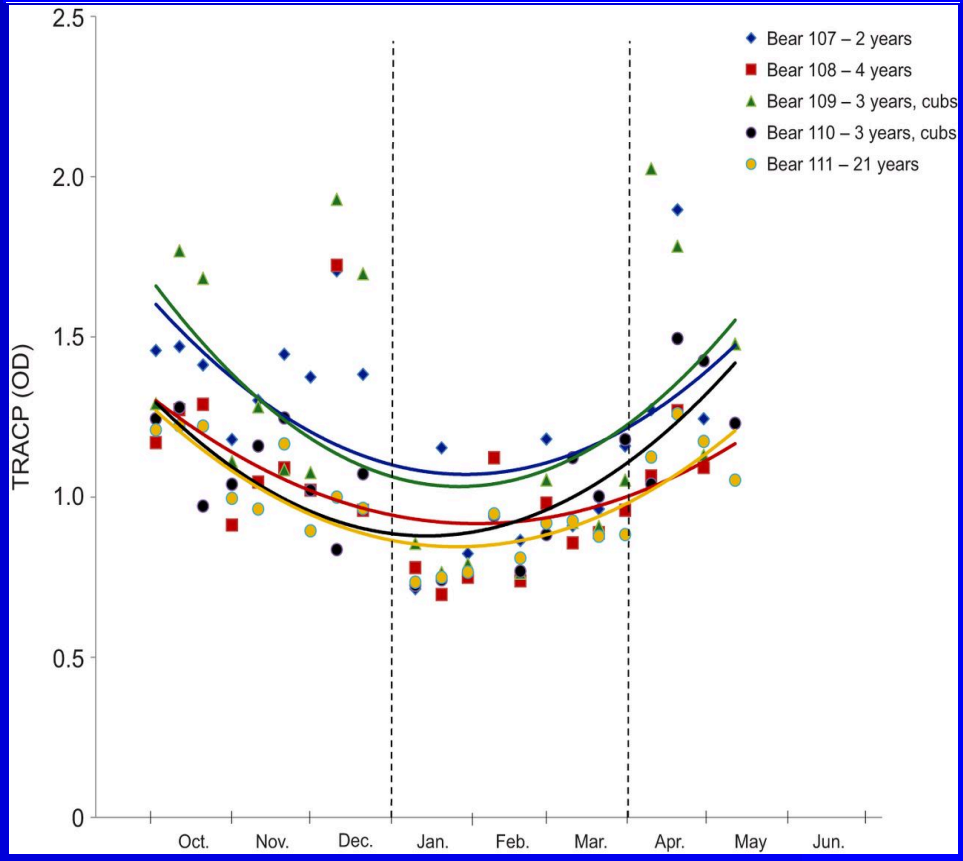


Suppressed bone remodeling in black bears conserves energy and bone mass during hibernation

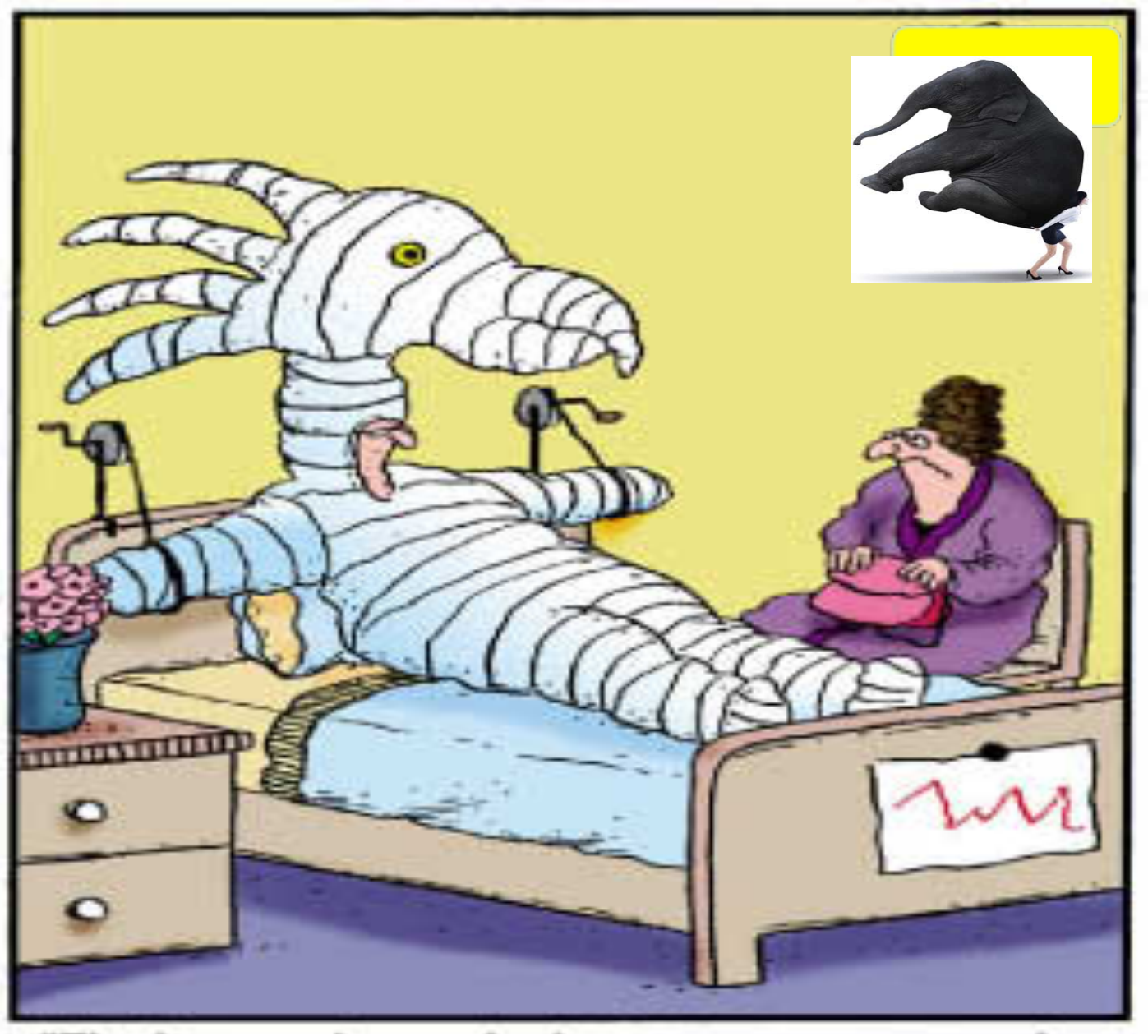
Total and ionized calcium concentration in serum from 4 black bears



Optical density for the serum marker of osteoclast number from 5 black bears



The Journal of Experimental Biology (2015) 218, 2067-2074 doi:10.1242/jeb.120725



The intern who worked on me was an
art major before going to medical school