Nutrition and Primary Sclerosing Cholangitis (PSC)

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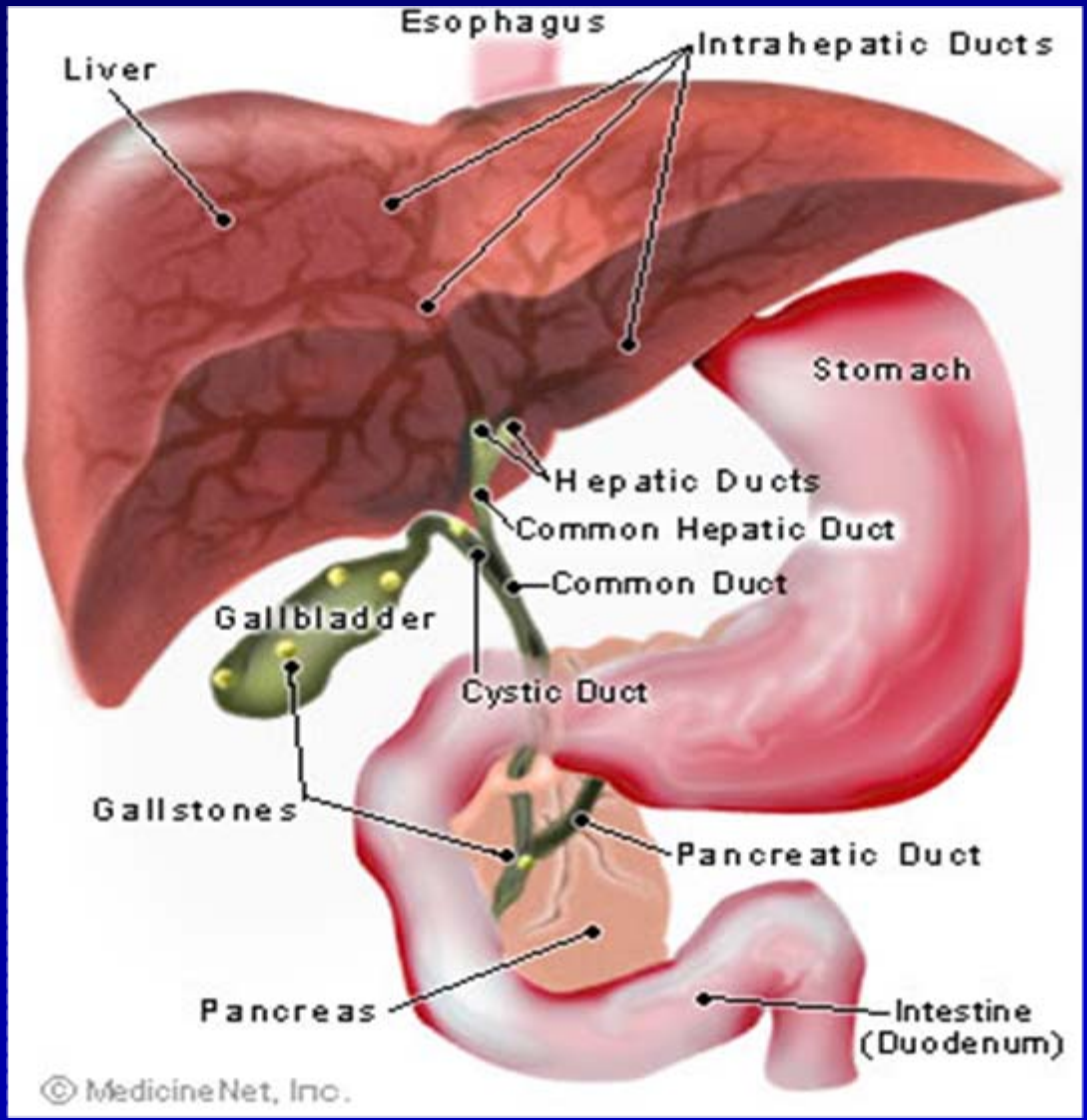
Esophagus
Intrahepatic Ducts
Liver
Stomach
Hepatic Ducts
Common Hepatic Duct
Common Duct
Gallbladder
Cystic Duct
Gallstones
Pancreatic Duct
Pancreas
Intestine
(Duodenum)
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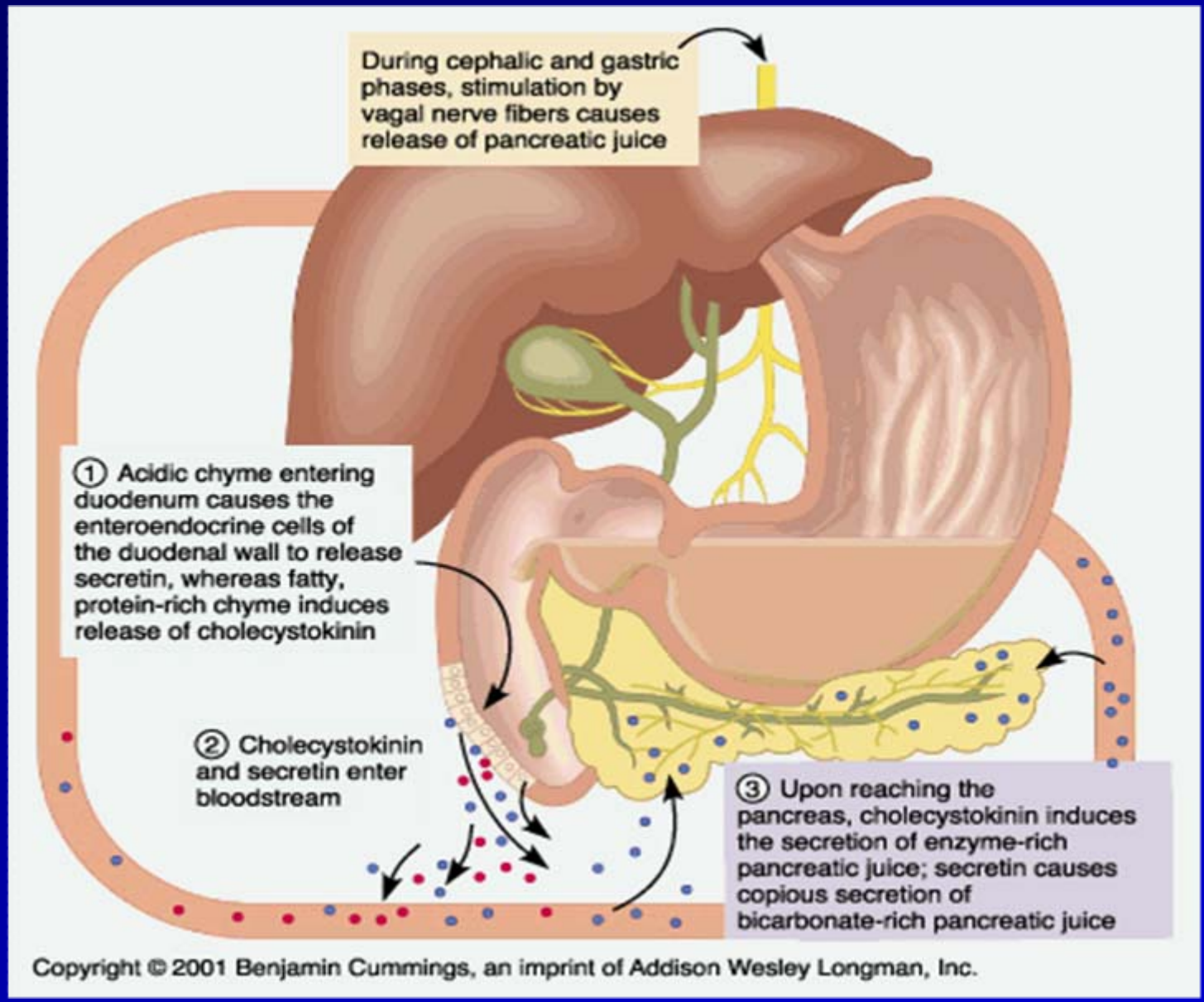

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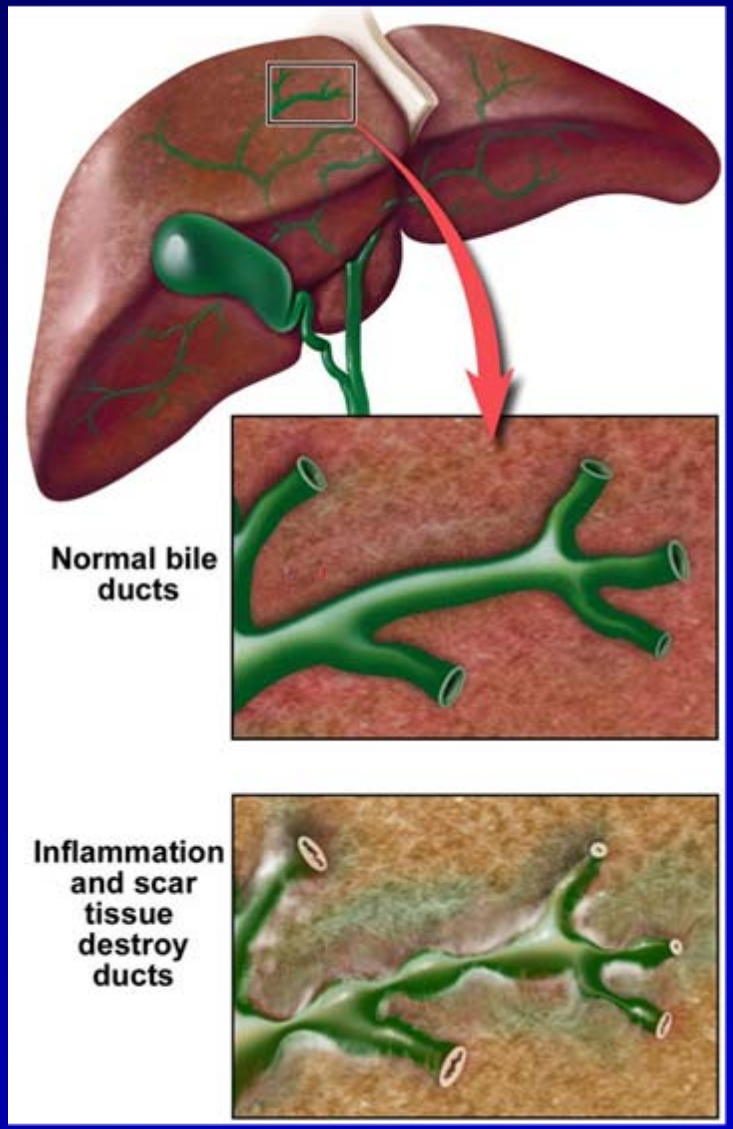
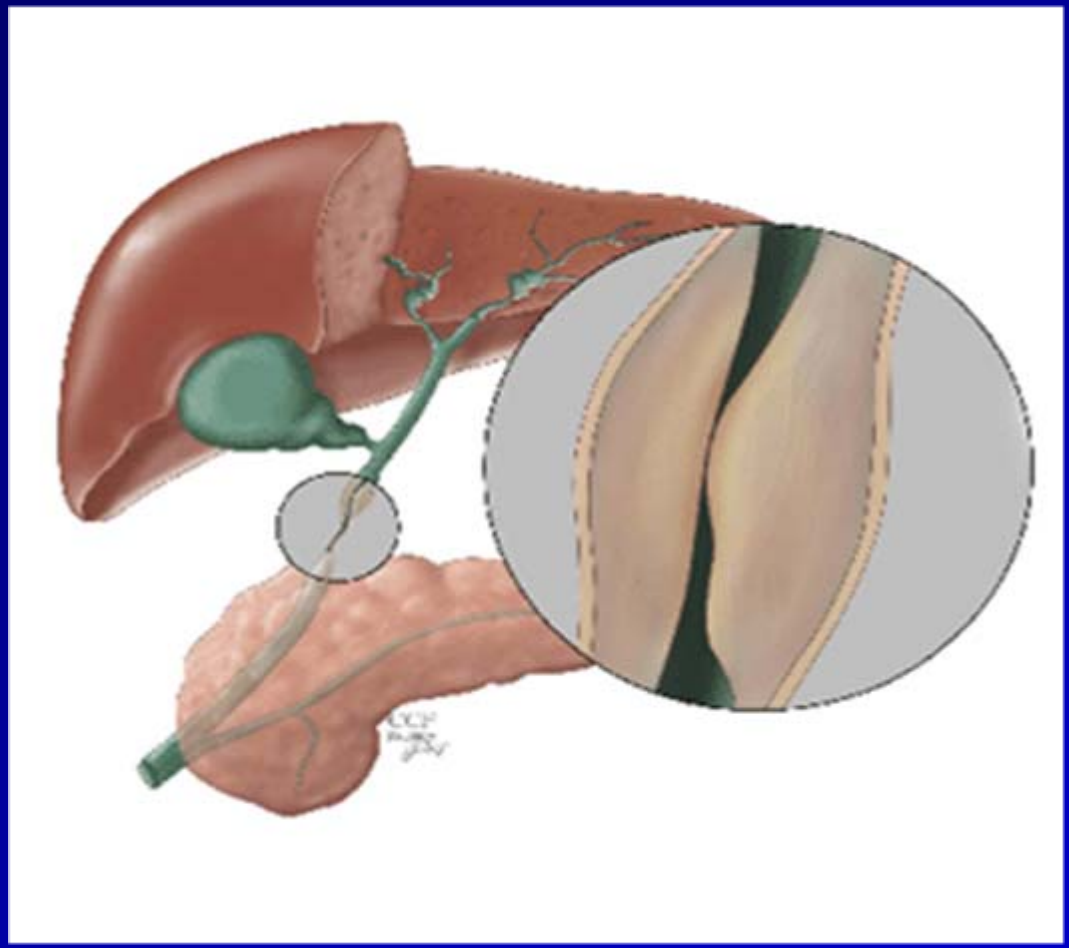
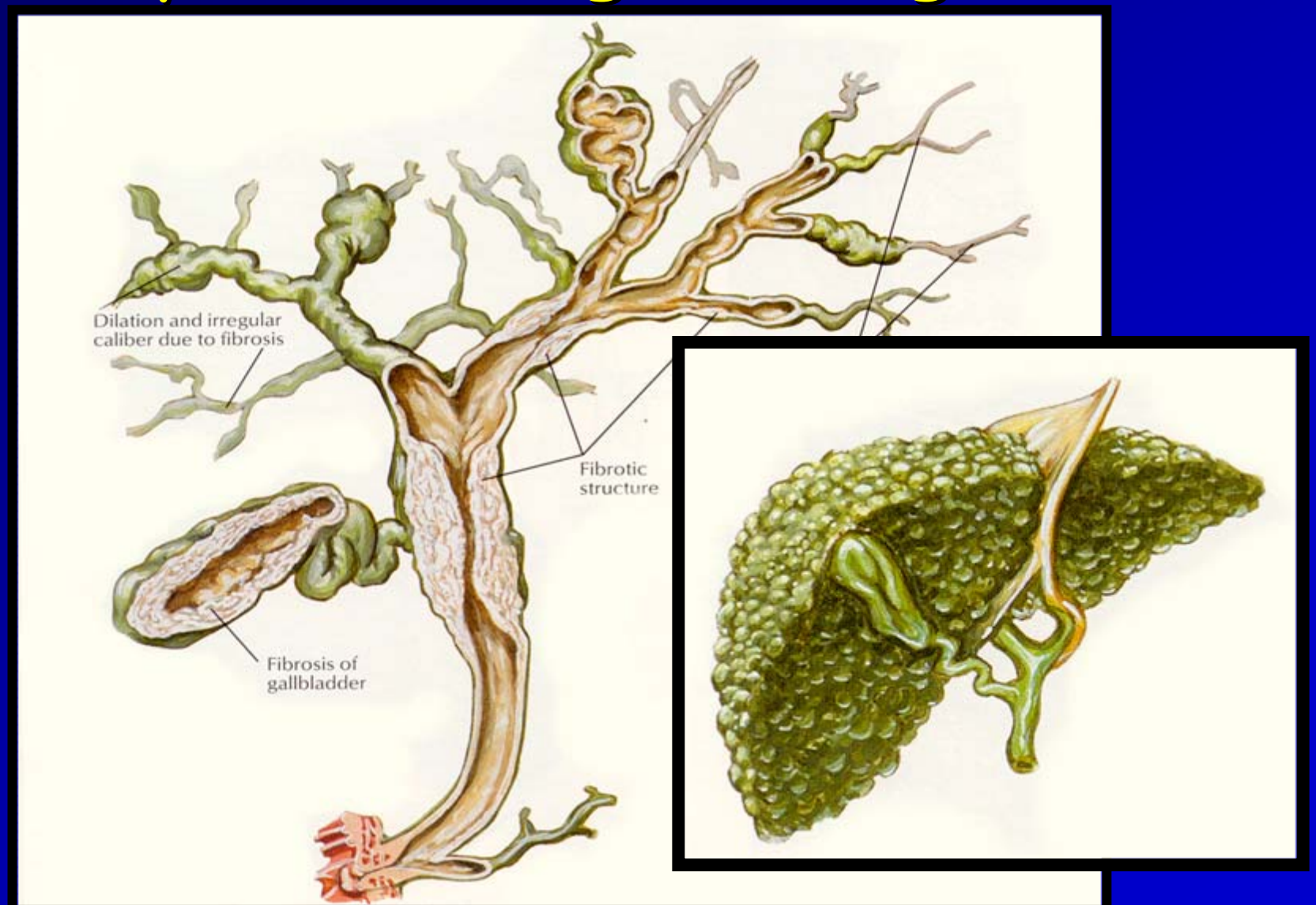

Normal bile ducts
Inflammation and scar tissue destroy ducts



Primary Sclerosing Cholangitis



Chronic Liver Disease

Complications

- Fluid retention – ascites and peripheral edema
- Encephalopathy - confusion
- Gastrointestinal bleeding – varices
- Cholangiocarcinoma and Hepatocellular carcinoma
- Malnutrition

Malnutrition is common in cirrhosis

Deficiencies of vitamins and minerals may develop in chronic liver disease without cirrhosis – Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

Other deficiencies can be present if Inflammatory Bowel Disease is present – Crohn's Disease

Malnutrition

- ✓ General risks for malnutrition in chronic liver disease
- ✓ Specific risks for malnutrition in primary sclerosing cholangitis
  - Lipids – fat metabolism
  - Vitamins -A,D,E,K
  - Bone disease in chronic liver disease

Nutrition in Liver Disease "Facts"

- Malnutrition is common but frequently "underdiagnosed"
- Malnutrition is multifactorial
- Degree of malnutrition correlates to the severity of liver disease
- Malnutrition is universal in patients with end-stage liver disease waiting for liver transplantation regardless of the etiology

- Malnutrition can be diagnosed in 25% in patients with cirrhosis.
- Malnutrition is present in > 60 % in patients with complications of cirrhosis.
- Moderate to severe malnutrition is found in > 80% of liver transplant patients.

Campillo B Nutrition 2003
*Alvares-da-Silva MR Nutrition 2005

"Multifactorial"

Poor dietary intake

- Anorexia, hospitalization
- Dietary restrictions (Na and protein)
- Ascites / encephalopathy
- Increased in inflammation

"Multifactorial" continue..

Nutrient malabsorption

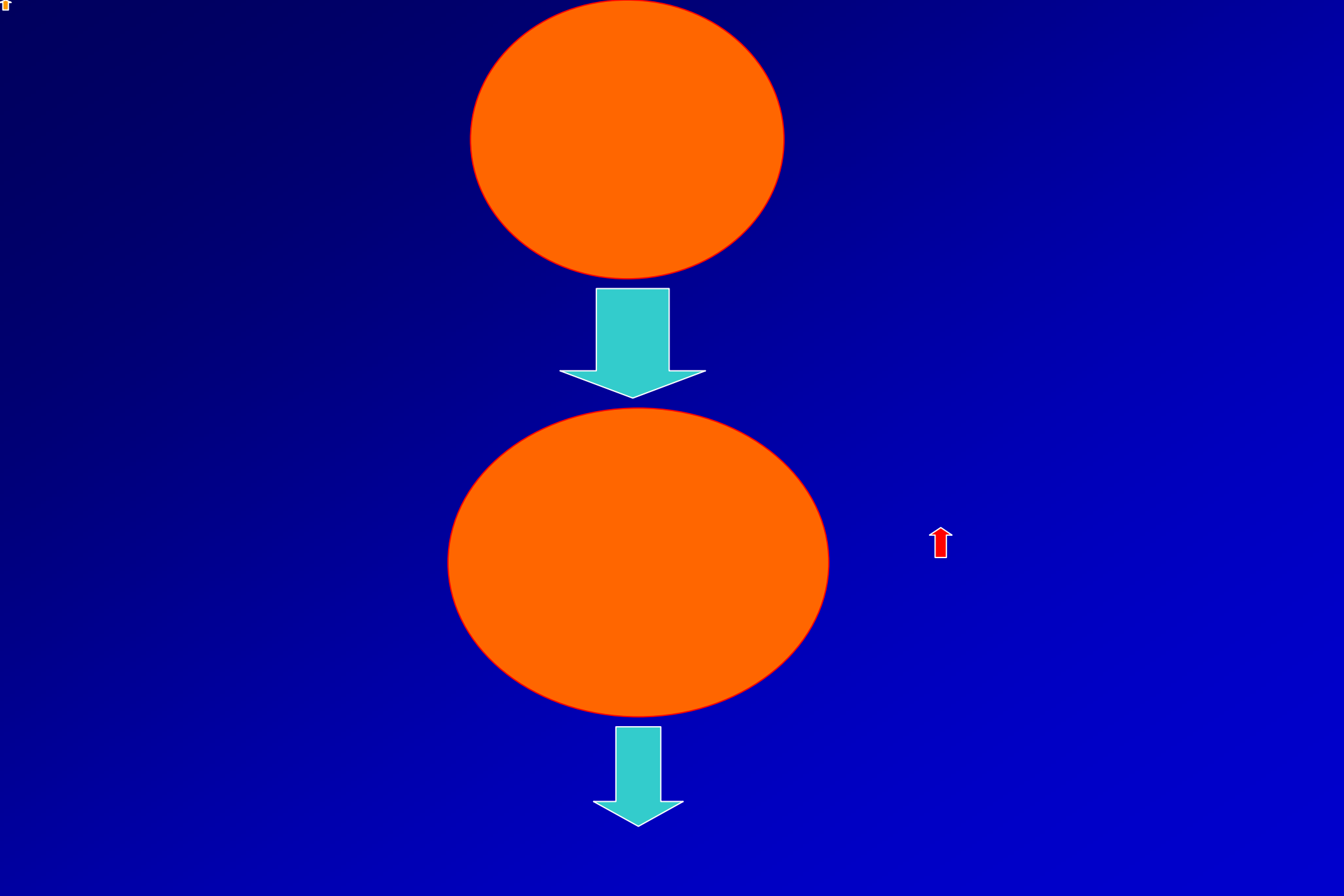
- Cholestatic liver disease
- Excessive protein losses

Medications

- Neomycin, lactulose, cholestyramine, prednisone

Iatrogenic

- Large volume paracentesis
- Sodium and protein restriction



PSC - Cholestasis

"lack of bile flow"

- Fatigue
- Pruritus – itching
- Diarrhea - loose fatty stools (Steatorrhea)
  - ✓Foul smelling, flatulence
- Fat-soluble vitamin deficiencies (A,D,E,K)
- Hyperlipidemia
- Metabolic bone disease
  - ✓Bone pain
  - ✓Bone fractures

Hyperlipidemia in PSC

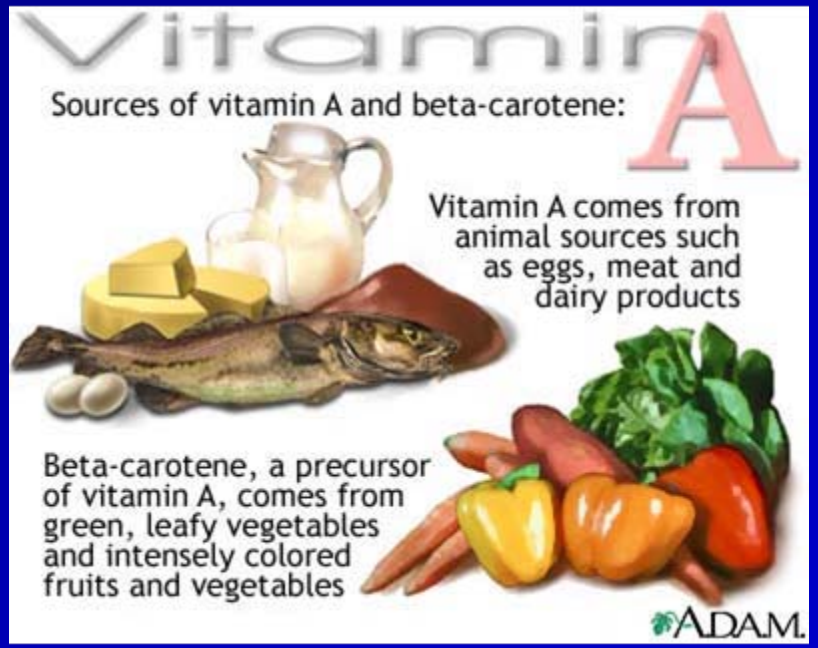
- ↑ Triglyceride levels
- ↑ Cholesterol levels
- May develop xanthomas and xanthelasma
- Not associated with Cardiovascular mortality

Vitamins

Vitamin A

Vitamin A

- Absorption requires fat and bile acids
- Serum levels are frequently low - 82%
- Antioxidant
- Occasionally symptomatic
  - ✓ Eye
  - ✓ Skin
  - ✓ Bone
  - ✓ Immune system



Vitamin A

- Eye – xerophthalmia

- Skin - hyperkeratosis

Vitamin E

- Absorption requires fat and bile acids
- Prevalence is 17%
- Antioxidant
- Significance in PSC is unknown
- Symptoms are rare
  - ✓ Neurological
  - ✓ Eye muscles
  - ✓ Muscle

Vitamin E is widespread in foods. About 20 percent of vitamin E in the diet comes from vegetable oils and vegetable oil-products, like margarine, salad dressing, and shortening. Another 20 percent comes from fruits and vegetables. Smaller percentages come from a variety of other foods.

Vitamin K

- Absorption requires fat and bile acids
- Required for clotting factors
  - ✓ Prothrombin time (INR)
- Bone metabolism - osteocalcin

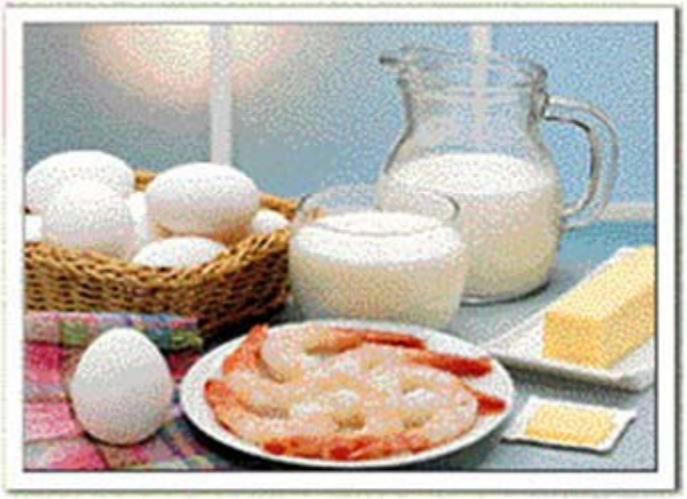
Vitamin K is made by intestinal bacteria, but the total need for vitamin K cannot be met by bacterial synthesis alone. Many foods contain an ple amounts of the vitamin, especially liver, green leafy vegetables, and cabbage. Milk, meats, eggs, and cereals provide smaller, but significant amounts.

Vitamin K

- Easy bruising

- Mucosal bleeding

Vitamin D



Only a few foods, egg yolks, liver, and fortified milk products, supply significant amounts of vitamin D. Exposure to sunshine for a few minutes each day stimulates the formation of vitamin D in the skin.

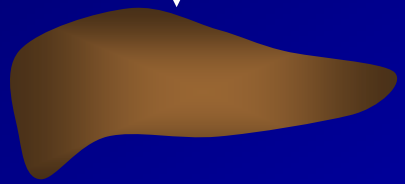
Vitamin D Metabolism

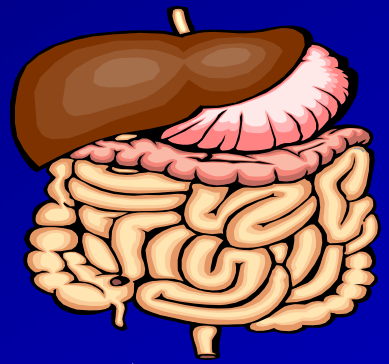
Diet

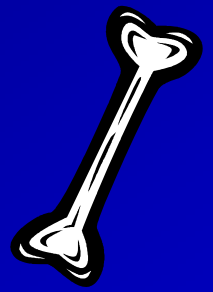
Skin/UVB

↑ Ca, PO4

Vitamin D3



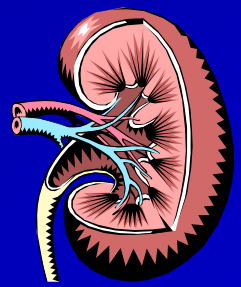




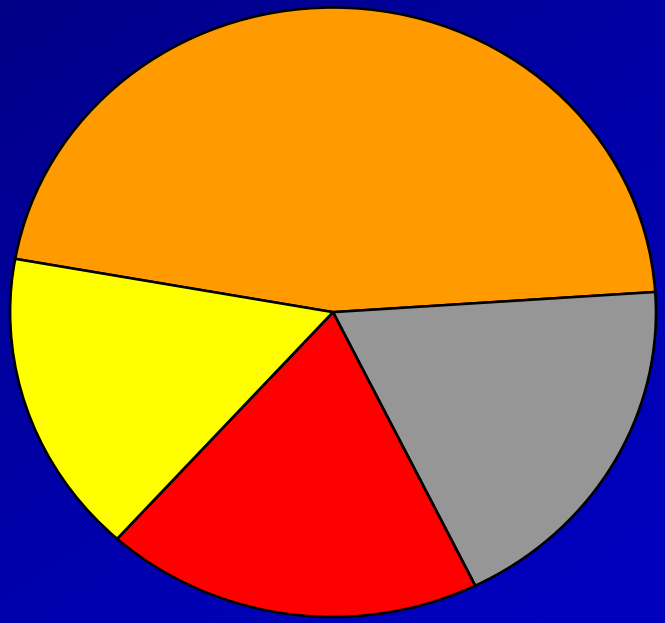
Resorption & Mineralization

25-OH-Vit-D

1,25(OH)2Vit-D3



More Than 1.5 Million Fractures Yearly



NIH/ORBD National Resource Center, October 2000

Common Causes of Vit.D Deficiency

- Decreased intake
  - ✓Poor oral intake
  - ✓↓ uV light
- Impaired gut absorption
  - ✓Malabsorption (short bowel, pancreatitis, IBD, celiac sprue, cholestais)
- Defect in liver
  - ✓Liver disease
- Defective activation in Kidney
  - ✓ Aging
  - ✓Renal failure (GFR < 60 ml/min)

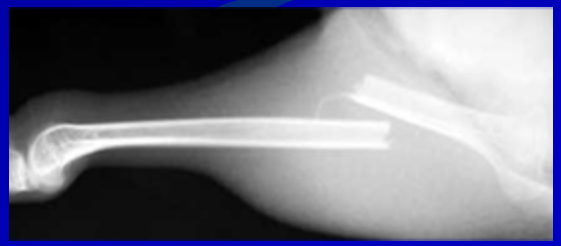
DHC: dihydro-cholesterol. VDB: vitamin D binding. GFR: glomerular filtration rate.

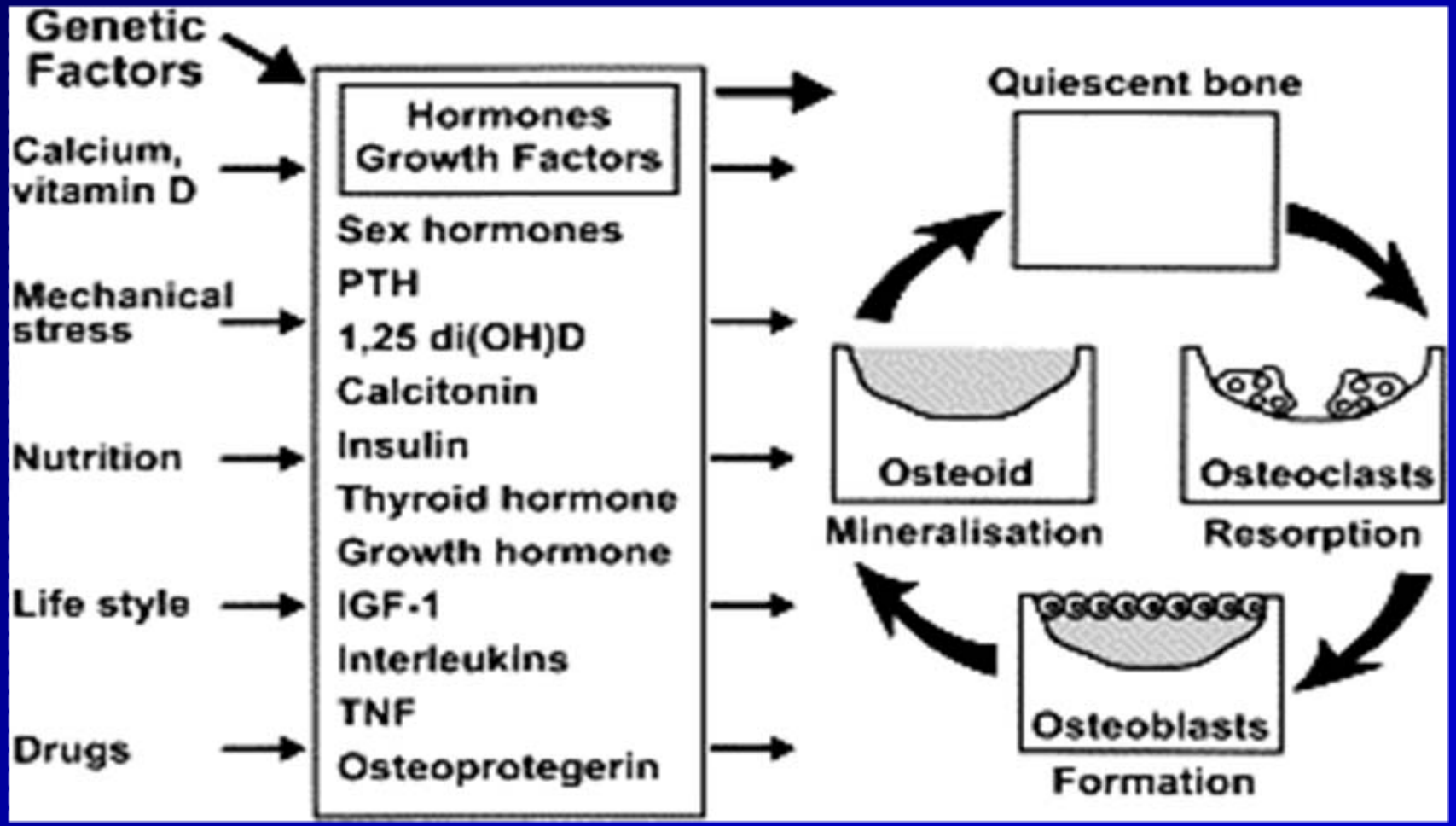
BONE QUANTITY

BONE QUALITY

BONE STRENGHT

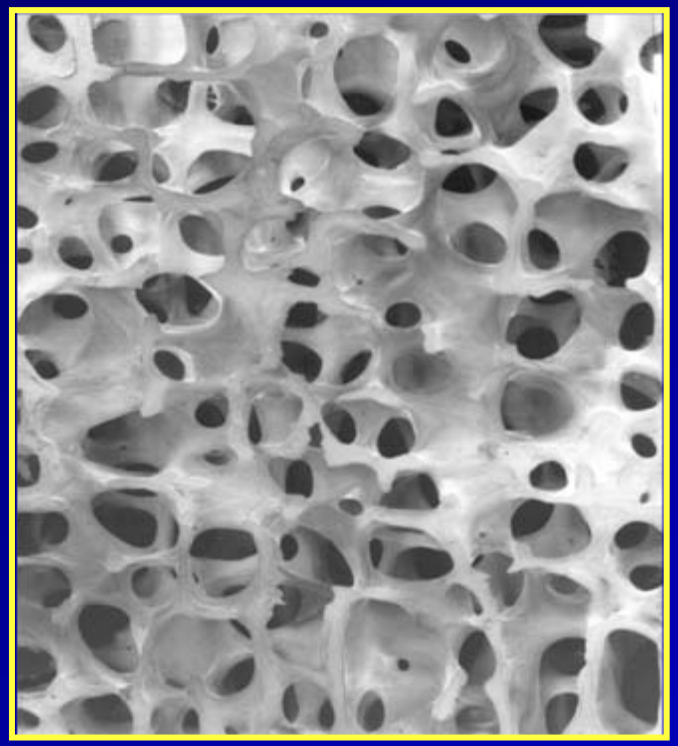
Trauma




Genetic Factors
Calcium, vitamin D
Mechanical stress
Nutrition
Life style
Drugs
Hormones Growth Factors
Sex hormones
PTH
1,25 di(OH)D
Calcitonin
Insulin
Thyroid hormone
Growth hormone
IGF-1
Interleukins
TNF
Osteoprotegerin
Quiescent bone
Osteoid
Mineralisation
Osteoclasts
Resorption
Osteoblasts
Formation

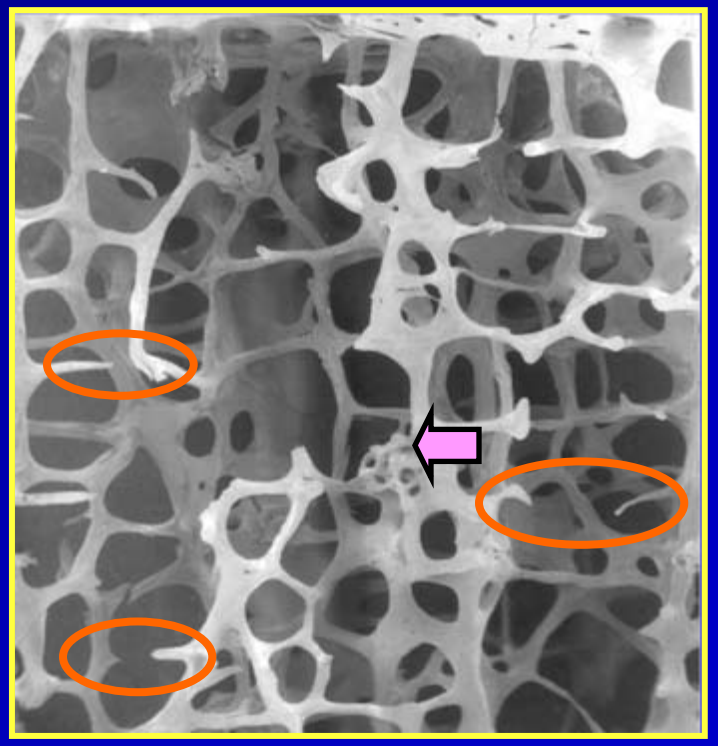
Osteoporosis
Trabecular Micro-architectural Change

Normal



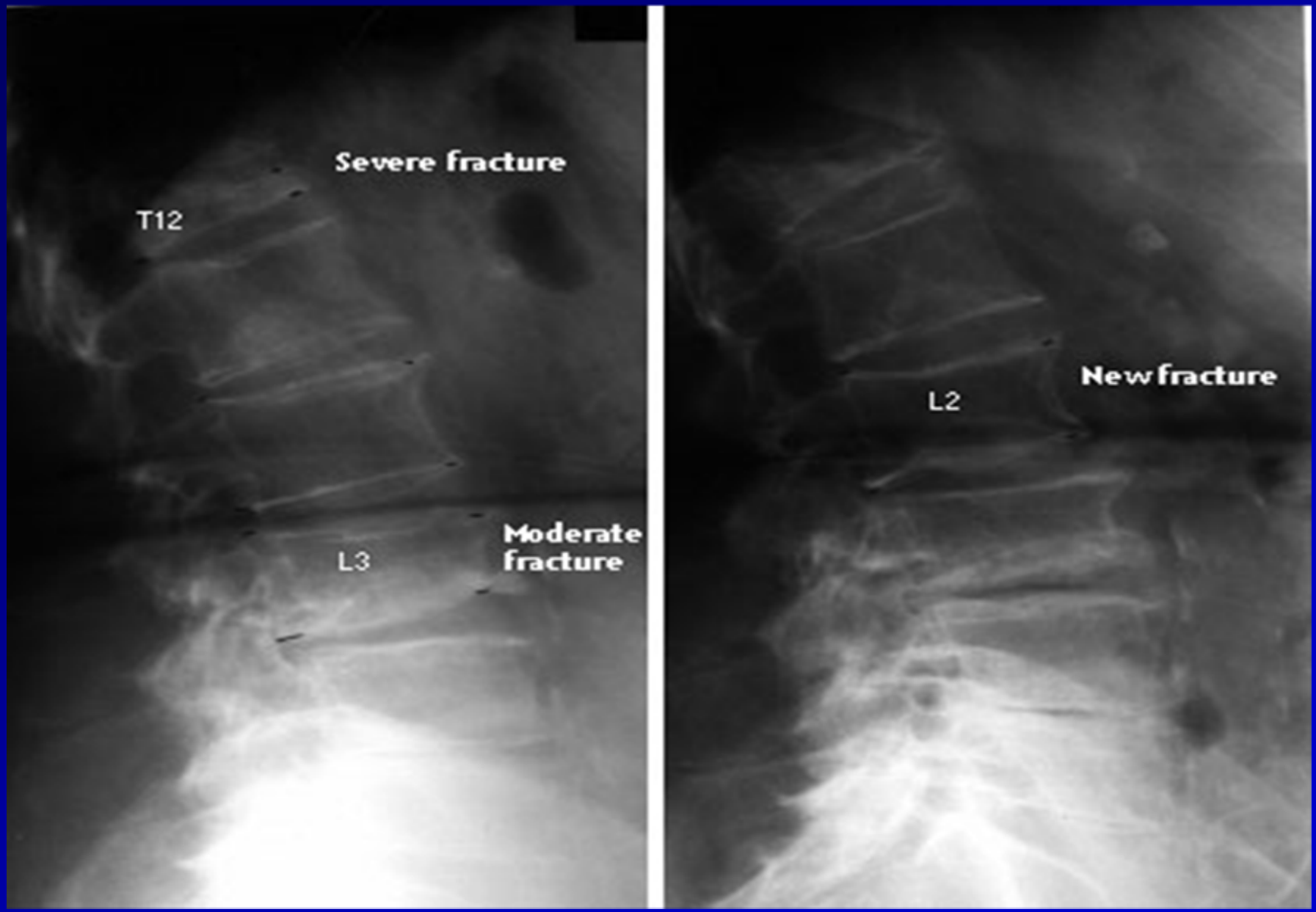
Dempster, 2000

Osteoporosis

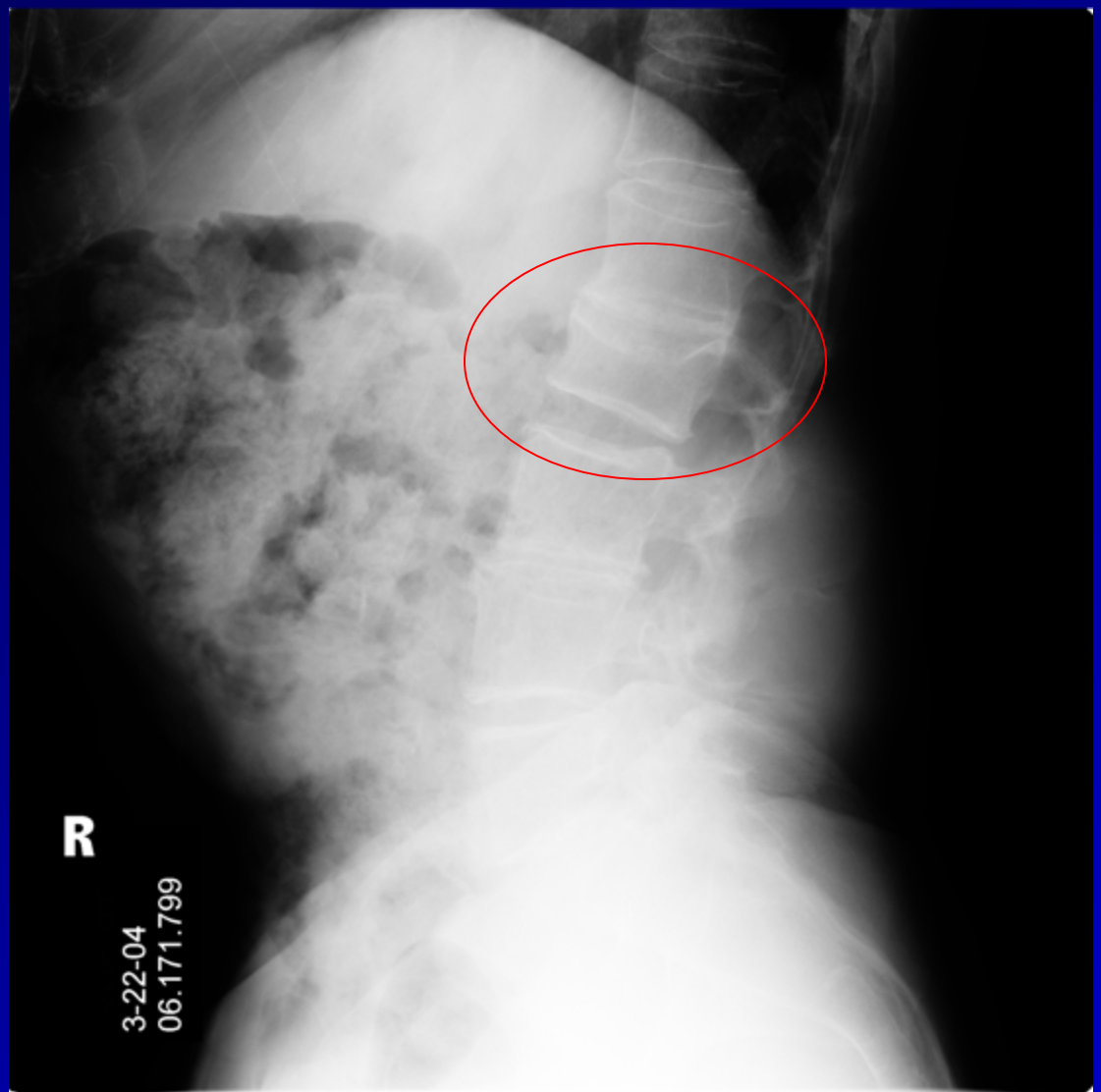


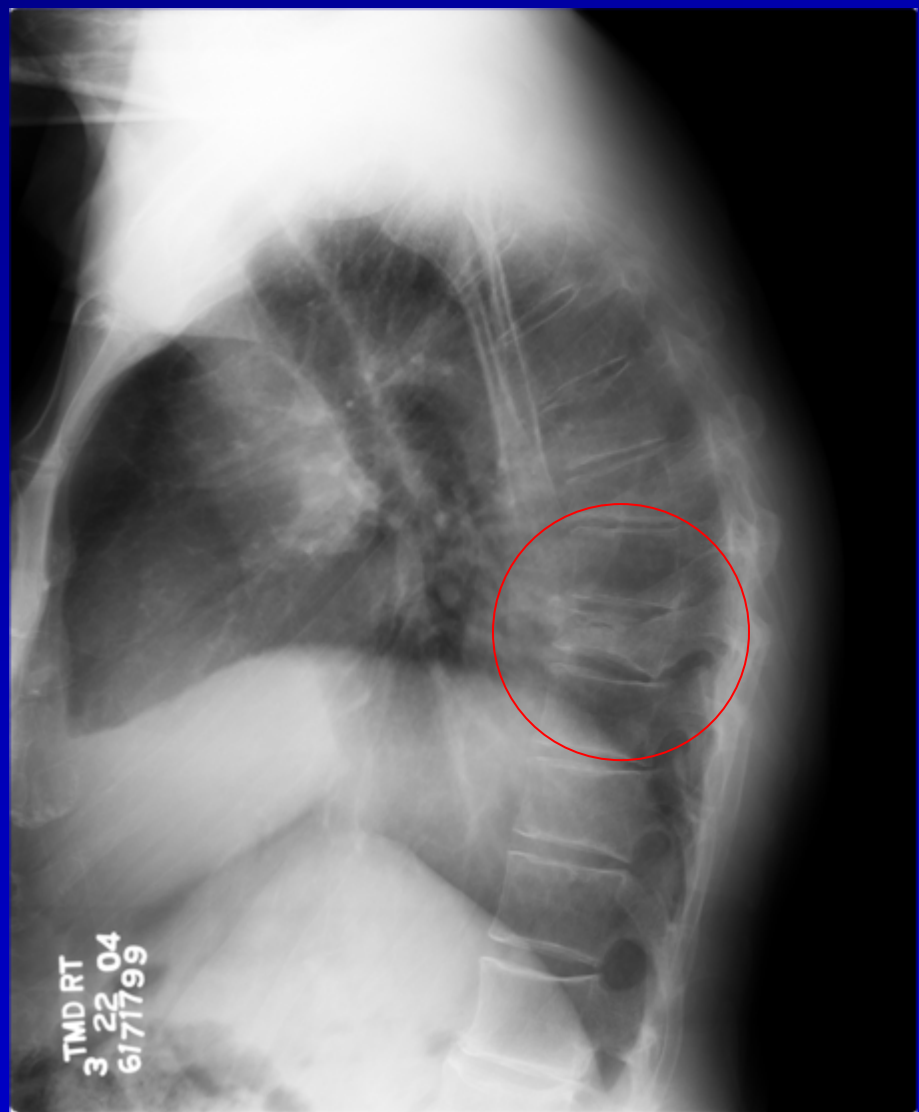
Horizontal Perforations
Micro-callous

Diagnostic tools


Severe fracture
T12
L3
Moderate fracture
L2
New fracture

Osteoporosis

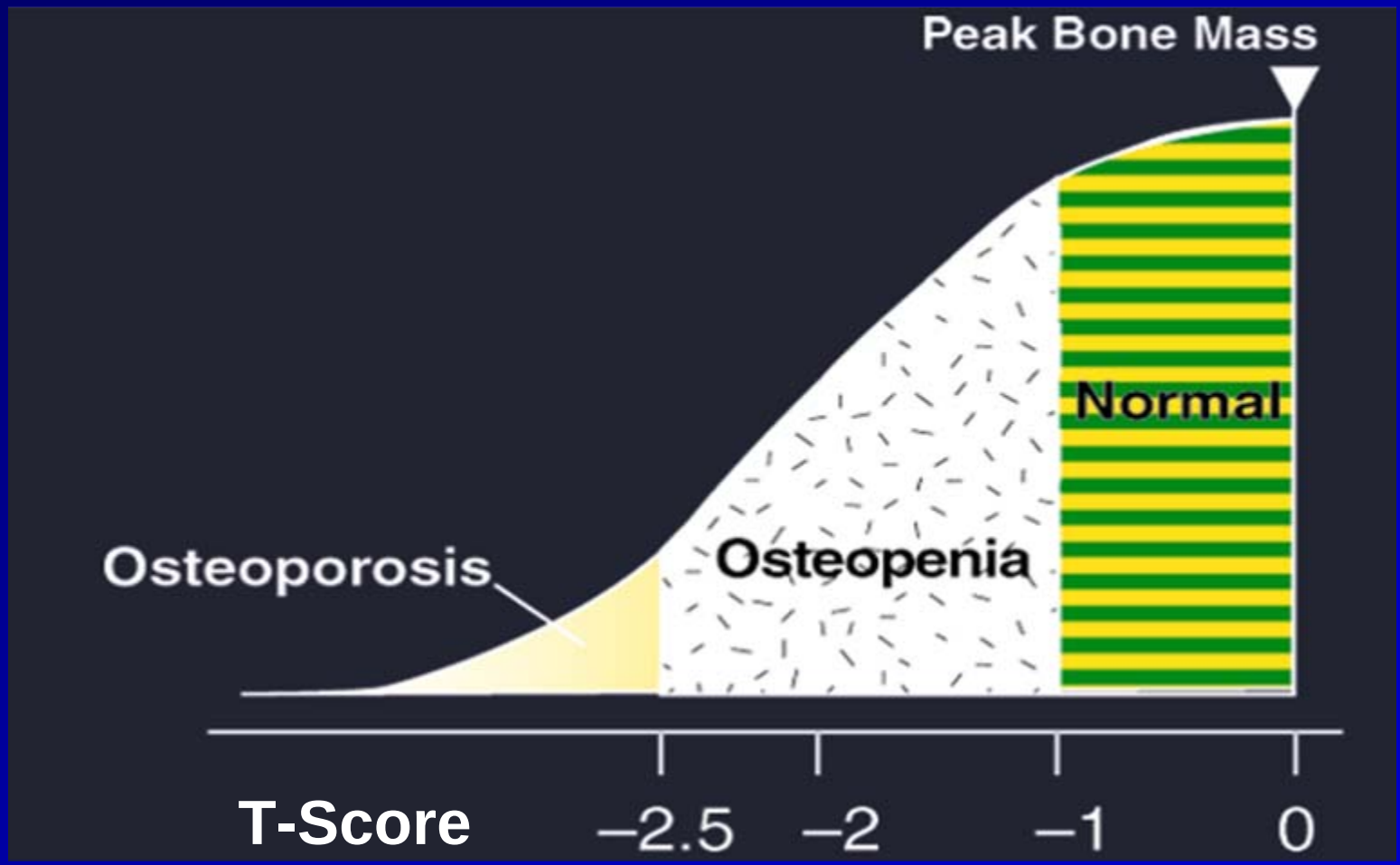




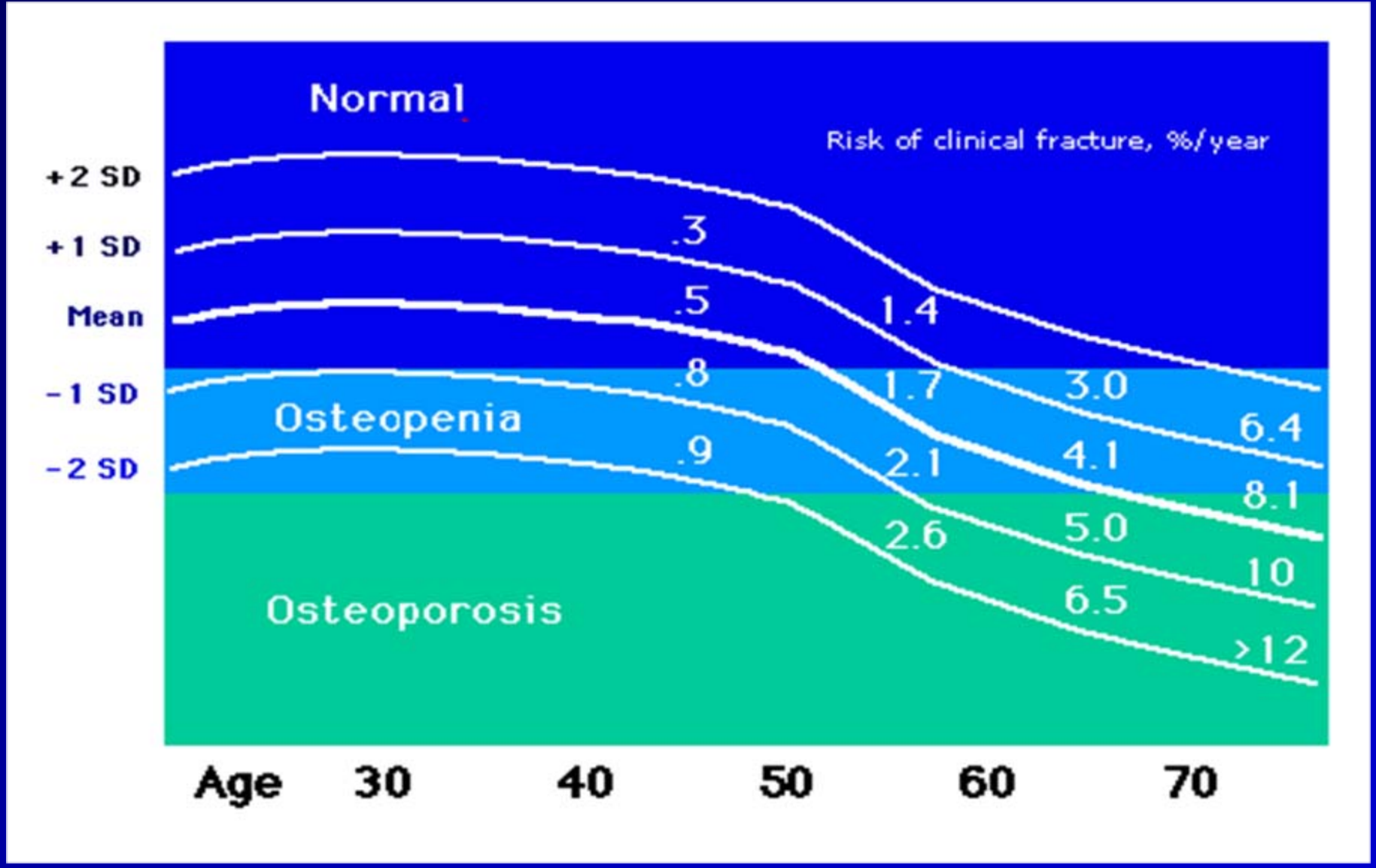
Central Dual-Energy-Xray-Absorptiometry (DXA) Measurement

- Measures multiple skeletal sites
  - ✓ Spine
  - ✓ Hip
  - ✓ Forearm
  - ✓ Total body
- Office based
- DXA bone density measurement considered the clinical standard

World Health Organization (WHO) Diagnostic Criteria for Osteoporosis



The WHO criteria were established for use in a postmenopausal female population

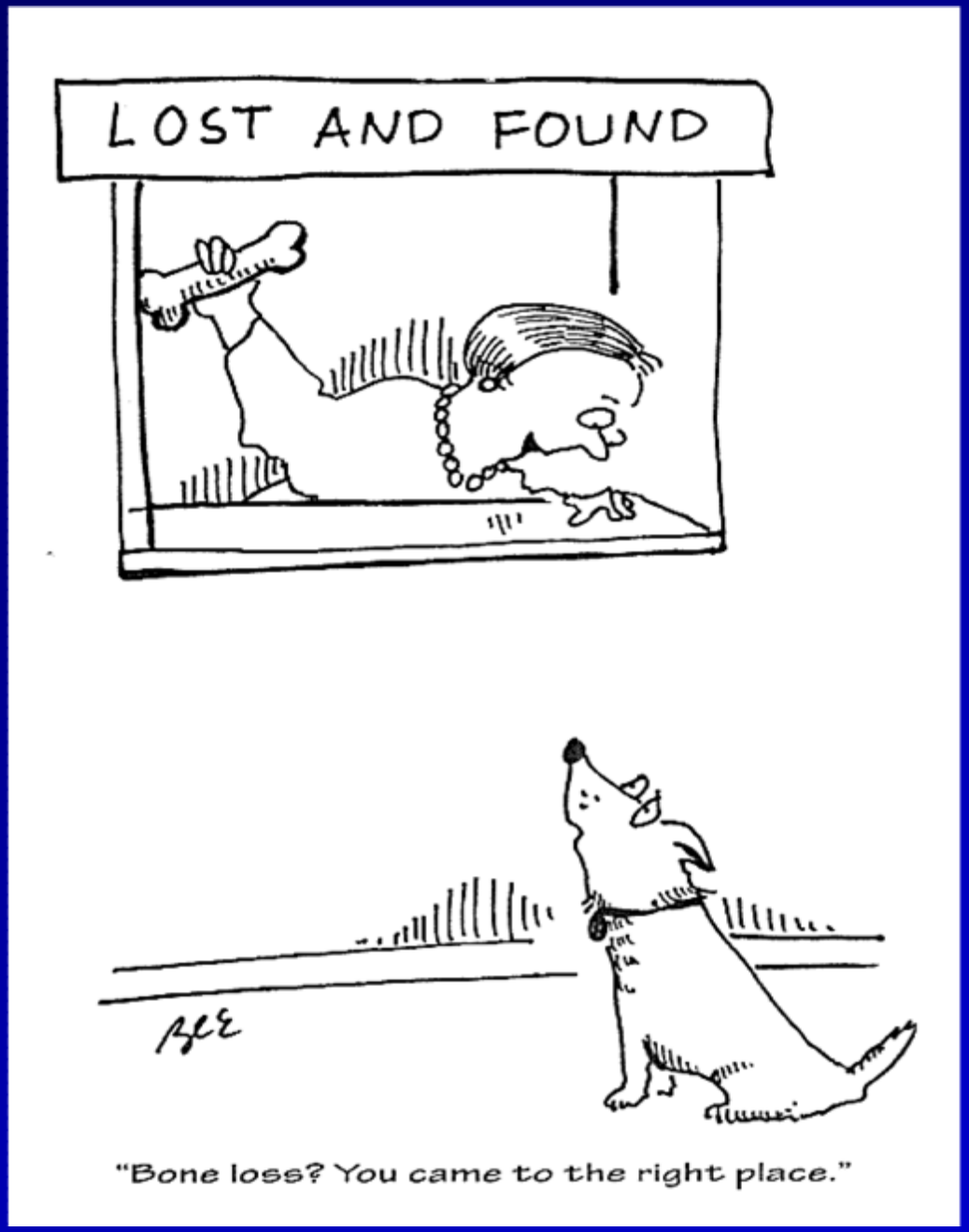

Normal
Risk of clinical fracture, %/year
+2 SD
+1 SD
Mean
-1 SD
-2 SD
.3
.5
.8
.9
1.4
1.7
2.1
2.6
3.0
4.1
5.0
6.5
6.4
8.1
10
>12
Osteopenia
Osteoporosis
Age
30
40
50
60
70

Hepatic Osteodystrophy
(Metabolic Bone Disease)

- Most of the patients have osteopenia / osteoporosis regardless of the cause of liver disease
- Frequently found in patients with PSC and PBC
- Fractures prior to transplantation -35%
- End-Stage Liver Disease is considered an independent factor for bone disease

Risks factors

- Age
- BMD - DEXA
- Alcoholism
- Smoking
- Hypogonadism- post-menopausal
- Abnormal Vitamin D metabolism
- Malabsorption - malnutrition
- Medication: steroids, loop diuretics (lasix)



"Bone loss? You came to the right place."

Treatment

- Begin calcium supplementation
- Multivitamins
- Vitamin D supplementation
- Weight bearing and exercise
- Smoke cessation
- Consider anti-resorptive agents

General Guidelines

Patients with cirrhosis have malnutrition until proven otherwise

Anorexia is a major problem – calorie counts, frequent meals – snack at bedtime – early feeding tube placement

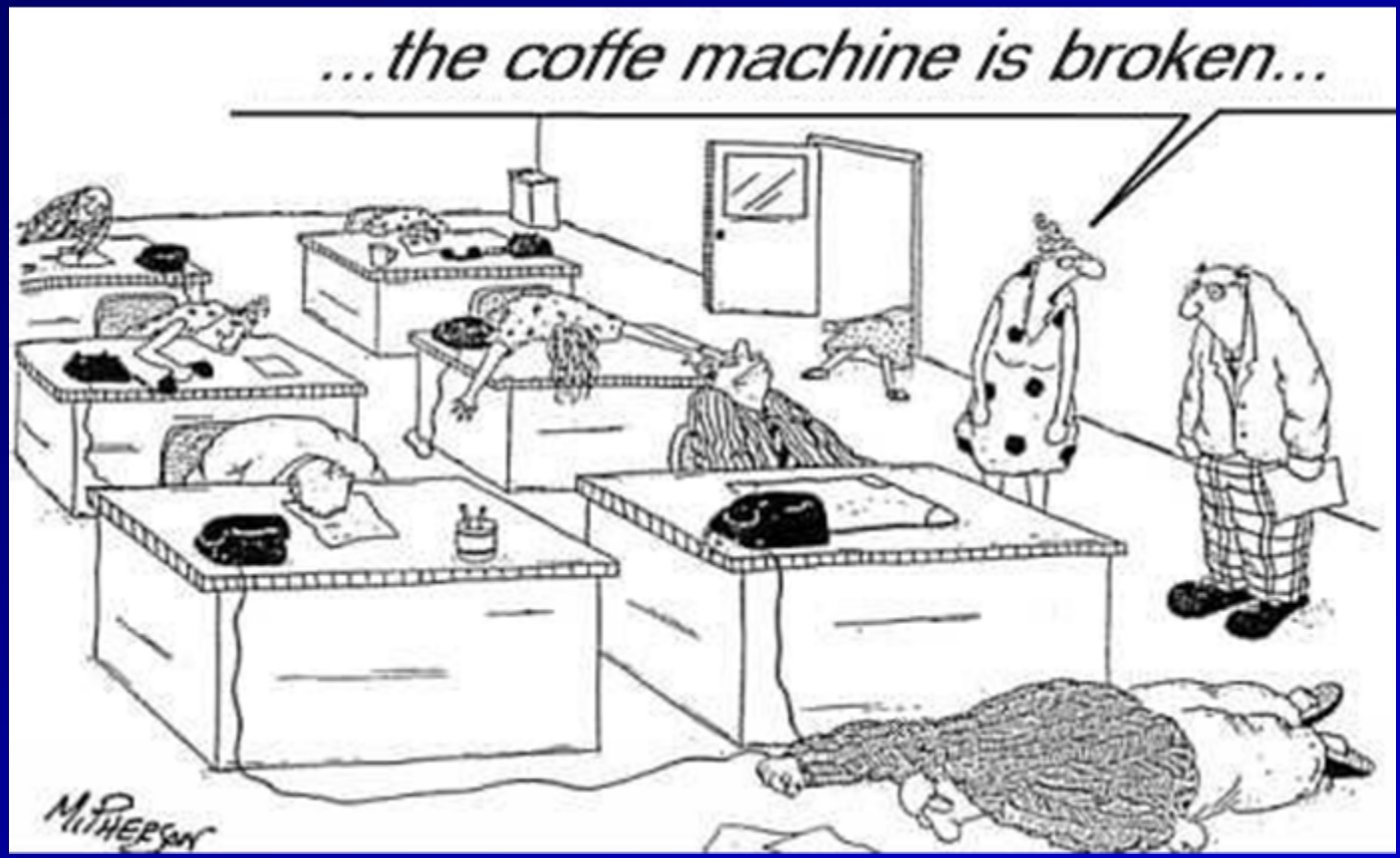
Do not restrict protein even in the presence of encephalopathy

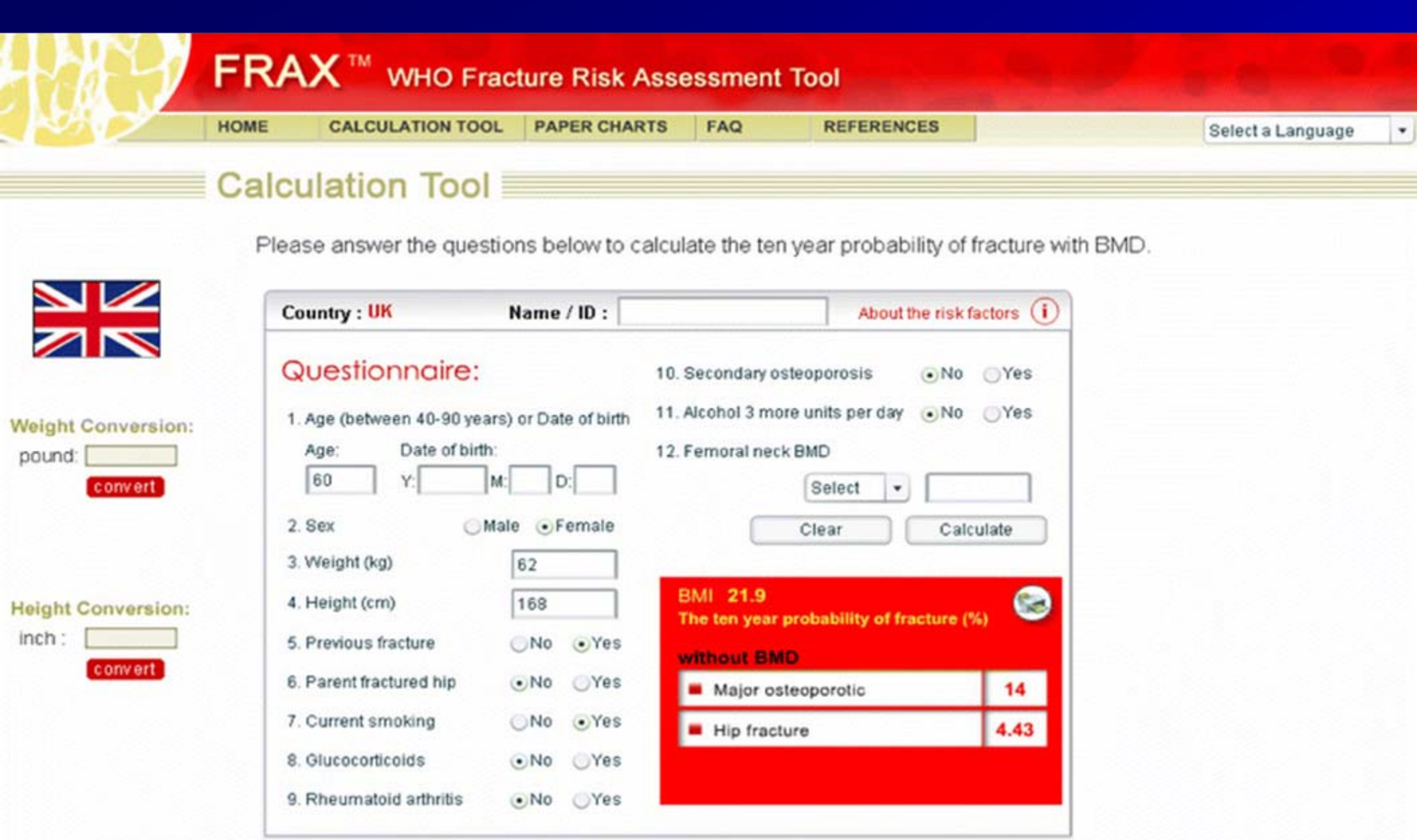
Look for malabsorption– fat soluble vitamins (ADEK) and replace if deficient

Physical activity very important and more aggressive in patients awaiting liver transplantation

All patients with cirrhosis should receive multivitamins

DEXA scan to assess bone density


...the coffe machine is broken...



Kanis JA, et al. Osteoporosis Int 2008;19:385-397.

FRAX™ Calculator

- WHO 10-year fracture risk assessment tool
  - ✓Risk factors: age, BMD, prior fracture, steroids, etc.
- Treatment *guidelines*:
  - ✓Hip fracture risk > 3%
  - ✓Major osteoporotic fracture > 20%

Kanis JA, et al. Osteoporosis Int 2008;19:385-397.
http://www.shef.ac.uk/FRAX/

Osteoporosis Therapy

- Bone Anti-resorptive Agents
  - ✓Calcium and Vitamin-D
  - ✓Bisphosphonates (several oral and intravenous drugs)
  - ✓Estrogen (oral or skin patch)
  - ✓SERMs (Evista® - raloxifene)
  - ✓Calcitonin (Miacalcin®)
- Bone Formative (Anabolic) Agents
  - ✓Parathyroid hormone (Forteo®, teriparatide - rhPTH)
  - ✓Sodium Fluoride (controversial, not FDA approved)
  - ✓Tibolone and Strontium (not FDA approved)
  - ✓Testosterone (hypogonadal men)

Vit.D Deficiency
Lab Assessment of Total 25(OH)D Levels

- Mayo Medical Lab, ng/mL (1.0 ng/mL = 2.5 nmol/L)
  Liquid chromatography tandem mass spectrometry

< 10	severe deficiency
10-25	mild to moderate deficiency
25-80	***"optimal" levels***
> 80	toxicity "possible"
> 150	toxicity likely

A. Nutritional Vitamin D Deficiency

- Vitamin D deficiency is not uncommon
  - ✓The present “usual” practice for vitamin D 400 I.U. daily (RDI) prophylaxis is inadequate
- Vitamin D deficiency is under recognized
  - ✓Clinical symptoms or signs often attributed to another disease process
    - Osteoporosis, “normal-calcemic” HPT, chronic pain syndrome (*not* fibromyalgia), age-related weakness
- Clinical awareness & appropriate testing needed

Subclinical Osteomalacia
Not Uncommon

- 25-50% if in elderly nursing home or housebound
  - ✓Mean age 81 years

  Gloth, *JAMA* 1995;274:1683 and McKenna, *Am J Med* 1992;93:69
- 23% of elderly presenting with hip fractures
  - ✓Mean age 77 years

  Dirschl et al, *Bone* 1997;21:97
- 57% of adult general medicine hospitalized patients
  - ✓Mean age 62 years

Thomas M, *NEJM 1998*;338:777

Prevalence Vit.D "Insufficiency" ≤ 30 ng/ml

White elderly	30%	Curr Opin Endocrinol Diabetes 2002;9:87
Hispanic elderly	42%	(ibid)
Black elderly	84%	(Ibid)
Hospitalized pts	57%	NEJM 1998;338:777
Adolescents	24%	Arch Ped Adoles Med 2004;158:531
Young adults	32%	Am J Med 2002;112:659
NHANES	25-57%	Bone 2002;30:771
Low back pain	83%	Spine 2003;28:177

Prevalence Vit.D "Deficiency" ≤ 15 ng/ml

25-50% of nursing home or housebound residents[º], mean age 81

44% of elderly ambulatory women[1], > 80 yrs

30% of women with osteoporosis[1], age 70-79

23% of patients with hip fractures[2], mean age 77

42% of African American women[3], 15-49 yrs

57% of adult hospitalized patients[4], mean age 62

ºJAMA 1995;274:1683, ºAm J Med 1992;93:69, [1]McClung, NEJM 2001;344:333, [2]Bone 1997;21:97, [3]Am J Clin Nutr 2002;76:187, [4]NEJM 1998;338:777

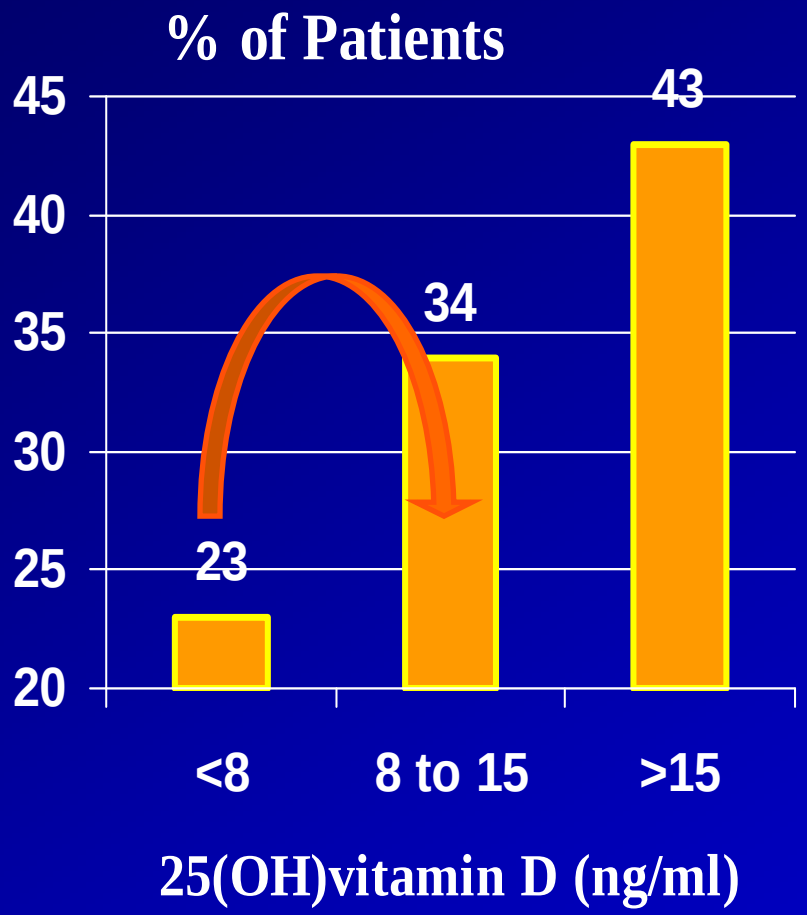
Prevalence of Vit.D Deficiency ≤ 15 ng/ml

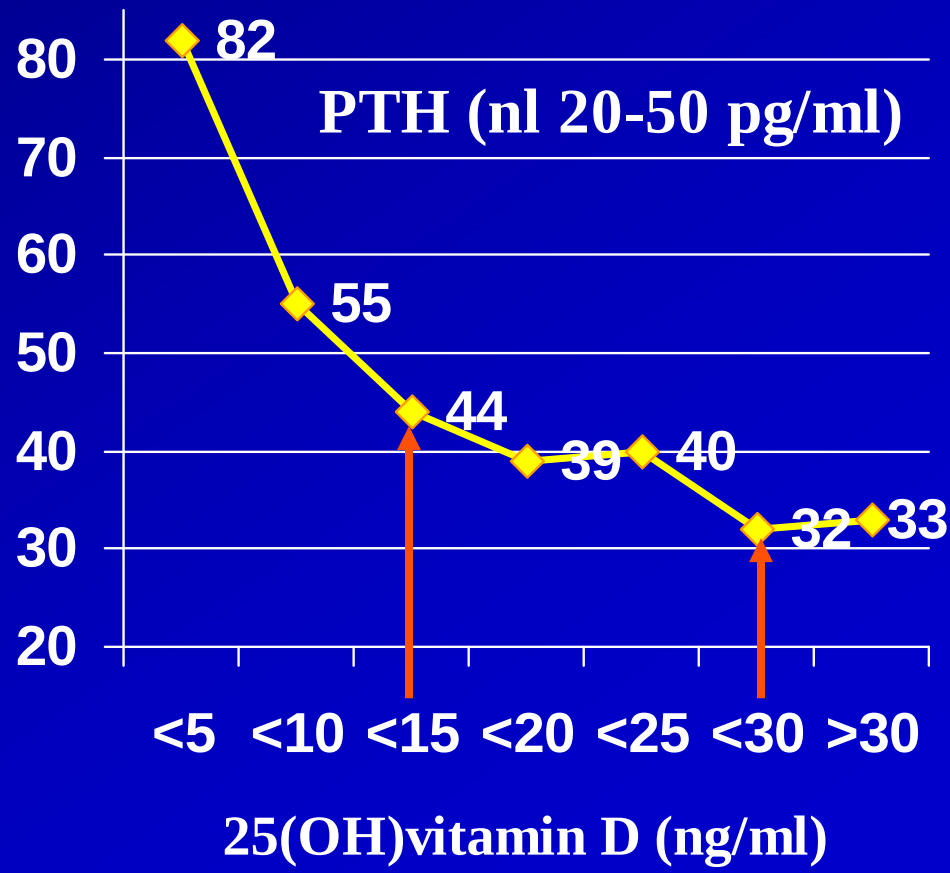
- Thomas, NEJM 1998;338:777
  - ✓57% of 290 men/women, *mean age 62 yrs*, admitted to hospital in March (n=150, 63%) and Sept (n=140, 49%)
    - 23% with *severe deficiency* of vit D (<8 ng/ml)
    - 60% of those *not taking a multivitamin*
    - 46% of those reportedly *taking a multivitamin*

Prevalence of Hypovitaminosis D

Hospitalized Medical Patients (n=290, mean 62 yr)

Thomas M, NEJM *1998*;338:777





B. Drug Induced Vitamin D Deficiency

- Inhibitors of vit.D formation or GI absorption
  - ✓Sunscreens ≥ factor 8, blocks 90% of vit.D formation
  - ✓Cholestyramine (binding of BA salts in short bowel)
- Increased metabolism of vit.D
  - ✓Antiepileptics (induced cytochrome P450 enzymes)

Calcium Recommendations

Optimal:

- Dairy products
- Some greens, crustaceans
- Fortified foods (OJ)

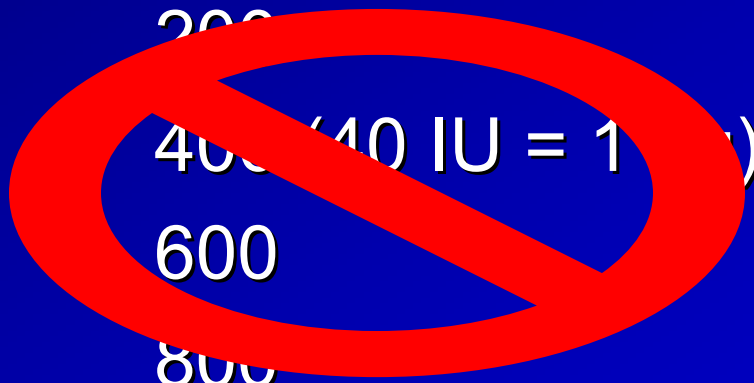
Practical:

- Calcium salts: most exhibit similar bioavailability
- Ca-Carbonate or Ca-phosphate: take with food
- Brand name or chewable products likely best

Vitamin D Recommendations

Present RDI treatment guidelines:

Age	RDI, IU/d
Birth-50	200
51-70	400 (40 IU = 1 µg)
> 70	600
Osteoporosis	800



37-46% of vit.D *deficient* individuals *meet the RDI !*

Sources of Vitamin D

- Nutritional vitamin D deficiency
  - ✓Vitamin D is rare in foods...
    - D2 from plants and yeast
    - D3 from fatty fish (cod liver oil, salmon, mackerel)
  - ✓...and possibly even when "fortified"
    - 400 IU vitamin D per quart of fortified milk (100 IU/cup)…
    - …but, almost 50% of school skim milk carton samples found to contain <50% of stated vitamin D content, and almost 15% of skim milk cartons without any vitamin D (USA/Canada)[1]
  - ✓Daily multivitamin (400 IU) recommended as a minimum RDI daily intake

[1]Holick et al, NEJM 1992;326:1178

Sources of Vitamin D

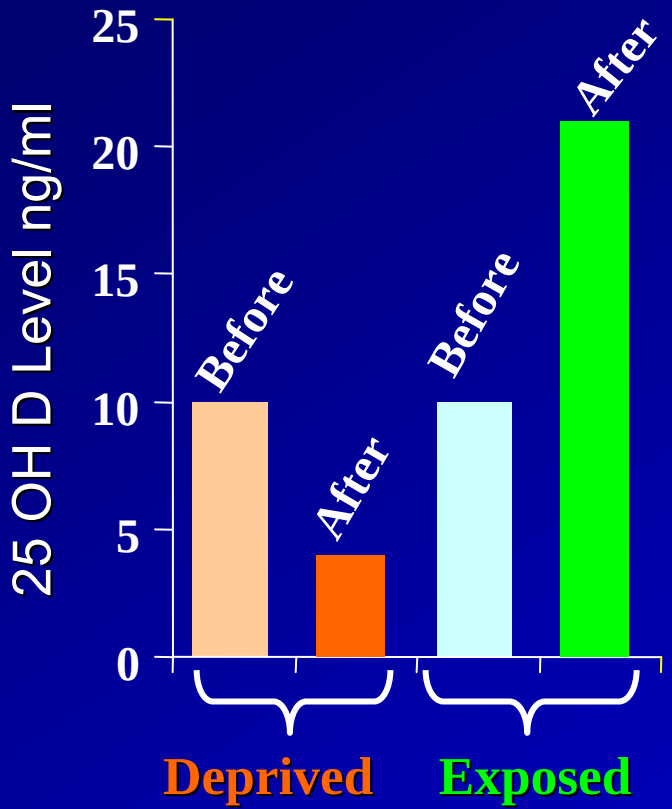
- Food sources generally *poor*; includes fish, fish oil, egg yolks, and fortified milk and foods

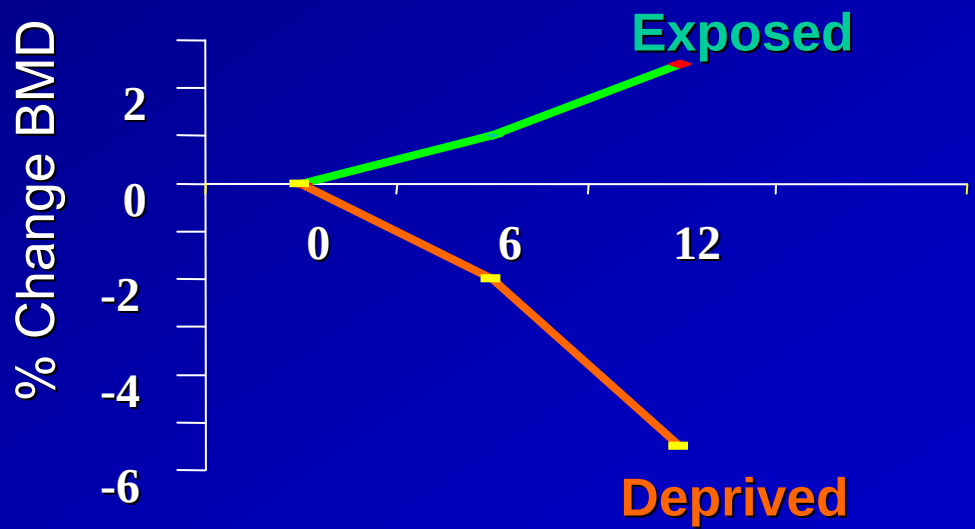
Food Source	Serving	I.U.
Pink salmon, canned	3 ounces	530
Fortified instant oatmeal	1 packet	140
Fortified cow's milk	8 ounces	100
Fortified orange juice	8 ounces	100
Fortified cereal	1 serving	40
Egg yolk	medium	25

- Sunlight vitamin D provision depends upon exposure

Vitamin D Deficiency

Effect of Sunlight





Fractures

11-sunlight deprived

3-sunlight exposed (p=0.03)

JBMR 20:1327, 2005

Vitamin D Requirements

Treatment for Osteoporosis

Calcium: 1200-1500 mg total elemental calcium daily

Phosphate: 2-4 grams daily (supplied by usual-normal diet intake)

Vitamin D (D2 ergocalciferol, or D3 cholecalciferol)

- ✓ ≥ 1000 IU/day vitamin D needed for bodily needs*
- ✓ ≥ 2000 IU/day total intake reported as safe
  - Milk, yogurt or cheese ≤ 100 IU/serving
  - Daily multivitamin: 400 IU (daily)
  - Vitamin D_2 or D_3: 1,000 IU (daily)
  - Vitamin D_2 or D_3: 50,000 IU (1/mos. to 1/wk.)

Vieth R. Am J Clin Nutr 1999;69:842

1 mcg = 40 International Units

Volume	Organ	Exocrine Secretions		Major Functions
+2000 ml ingested +1500 ml	Salivary glands	Ions, water Mucus Amylase IgA, lysozyme	--- --- --- ---	Moisten food Lubrication Polysaccharide digestion Oral hygiene
	Esophagus	Mucus	--- ---	Propels bolus of food Lubrication
+2500 ml	Stomach	HCl Pepsinogen Mucus Intrinsic factor	--- --- --- --- ---	Store, mix food Kill microbes, particle breakdown, pepsinogen activation Protein digestion Lubrication Bind vitamin B_{12}
+1500 ml	Pancreas	Enzymes HCO_3^-, water	--- --- ---	Secretion of enzymes, HCO_3^- Carbohydrate, fat, protein, nucleic acid digestion Neutralization of acidic chyme
+500 ml	Liver	Bile salts HCO_3^-, water Organic waste	--- --- --- ---	Secretion of bile, toxic substances Secretion of bile, absorption of fat Neutralization of acidic chyme Elimination from body
	Gallbladder		---	Storage and concentration of bile
+1000 ml -7500 ml	Small intestine	Ions, water Mucus	--- --- ---	Digestion and absorption of most substances Osmotic equilibrium Lubrication
-1300 ml -200 ml excreted	Large intestine	Mucus	--- ---	Storage, absorption of water Lubrication

Vitamin D Functions (1,25-dihydroxy D)

- Gastrointestinal absorption of calcium
  - ✓Prevents secondary HPT
  - ✓Prevents osteoporosis
- Mineralization of bone collagen matrix
  - ✓Prevents osteomalacia
    - Maximizes bone mineral density & increases bone strength

Vitamin D Deficiency
Musculoskeletal Associations

Skeletal

- 2º HPT
- Osteoporosis
- Mineralization defect
  - ✓ Rickets: children
  - ✓ Osteomalacia: adults

Muscle

- Myopathy
  - ✓ Weakness
  - ✓ Pain

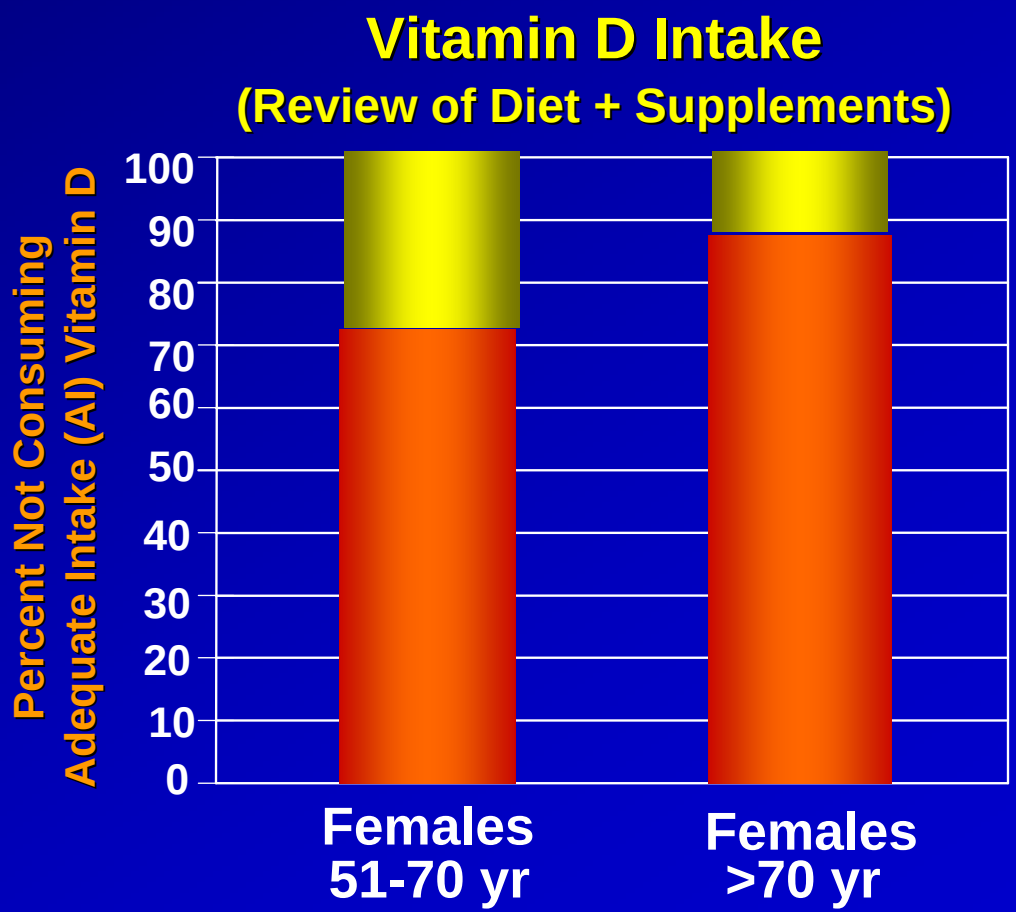
Nutrition and Liver Disease

- Malnutrition adversely affects prognosis in cirrhosis
- Increase Oral supplements
- Naso-enteric feeding tubes are well tolerated
- Nutrition can improve protein balance

Most Americans Are Not Receiving Adequate Vitamin D

NHANES III survey: 3,444 women ≥ 51 years old

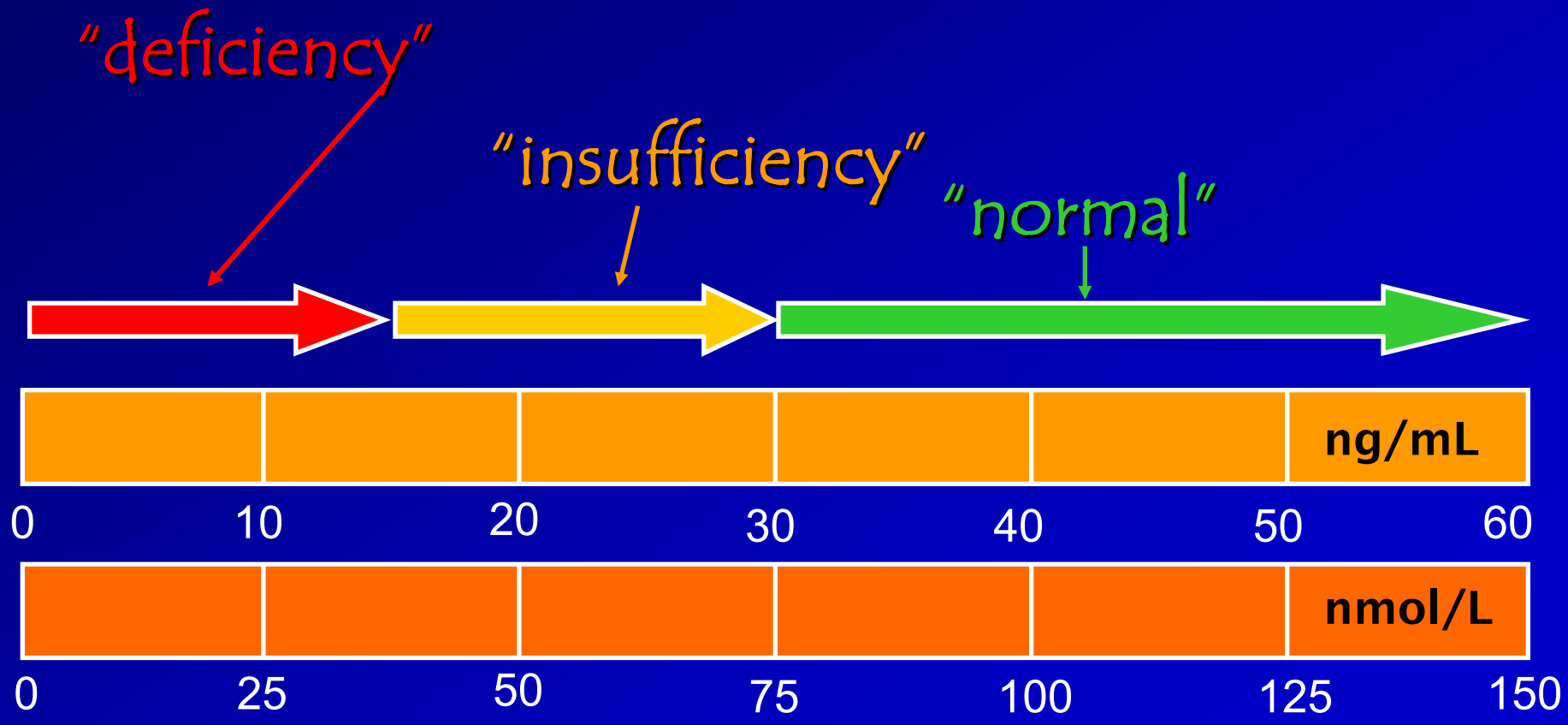
- Over 70% of women 51-70 yrs old were estimated not to meet adequate intake for vit.D (RDI = 400 IU), based on daily diet & vit.D supplements
- Nearly 90% of women > 70 yrs were estimated not to meet NOF vit.D guidelines (600 IU)



Moore C. J Am Diet Assoc. 2004;104(6):980

NHANES = National Health and Nutrition Examination Survey; NOF = National Osteoporosis Foundation

Optimal Vit.D Status?
The 25(OH)D Continuum Controversy



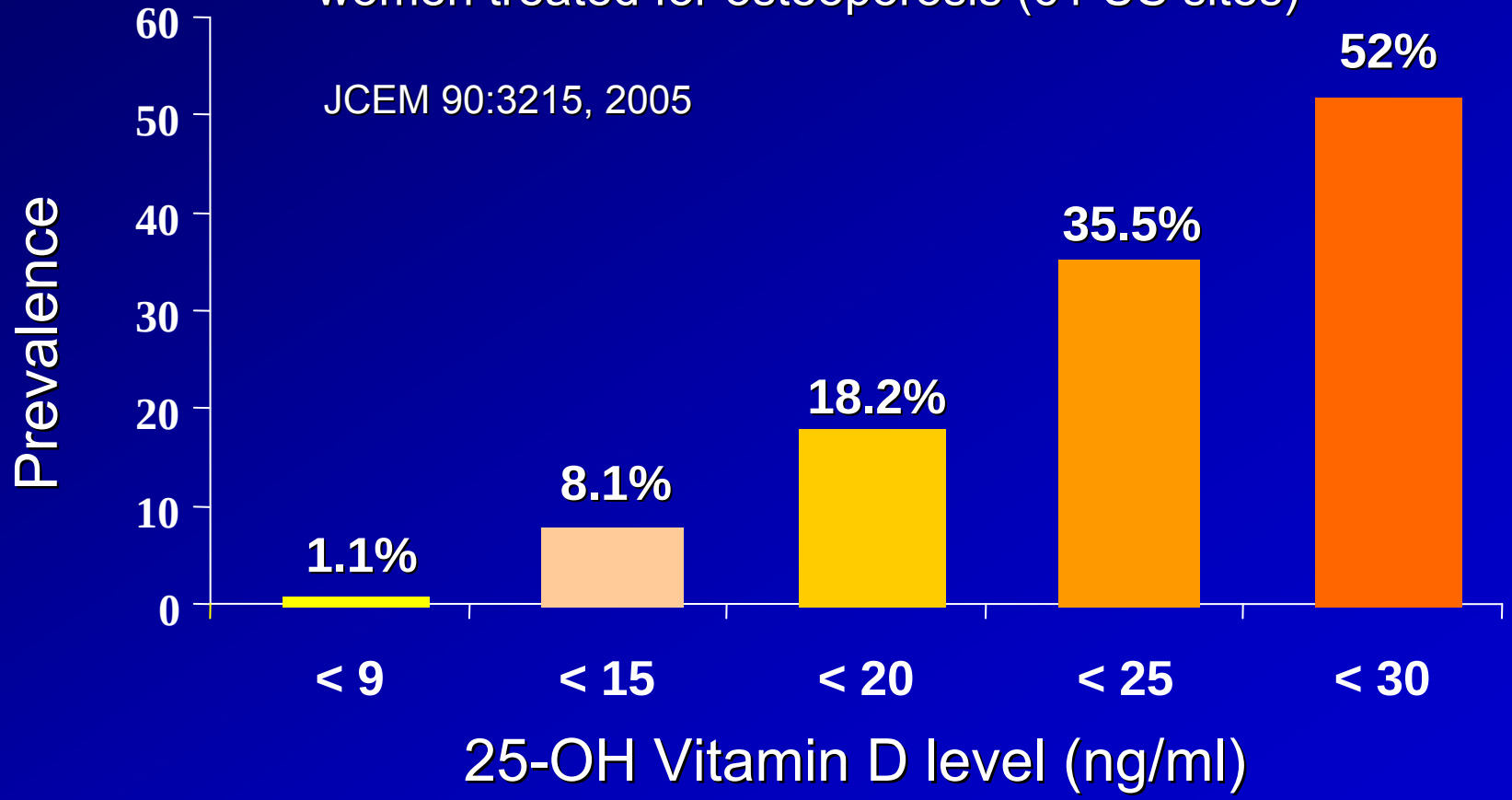
* modified after RP Heaney (10 ng/mL = 25 nmol/L)

Vit D Deficiency In North America

An Endemic Problem

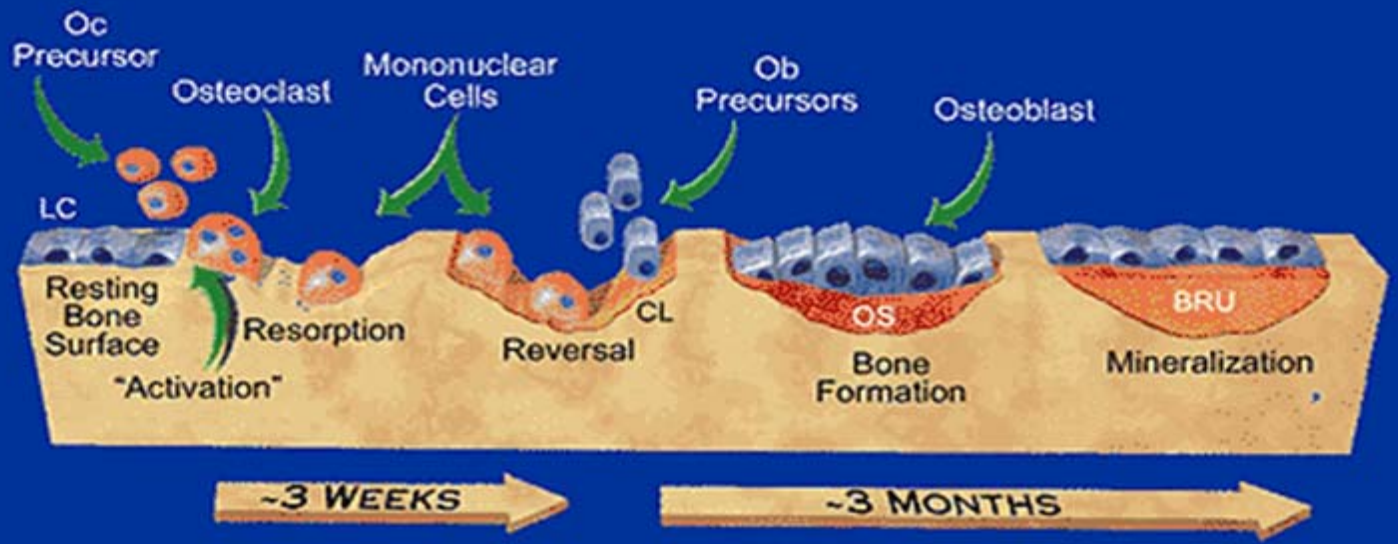
n= 1536 community-dwelling, postmenopausal women treated for osteoporosis (61 US sites)

JCEM 90:3215, 2005



OSTEOPOROSIS

Bone destruction>formation



LC = Lining Cells CL = Cement Line OS = Osteoid BRU = Bone Remodeling Unit