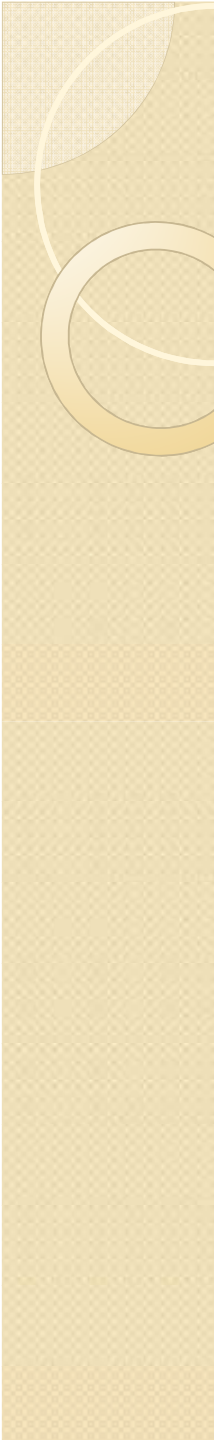


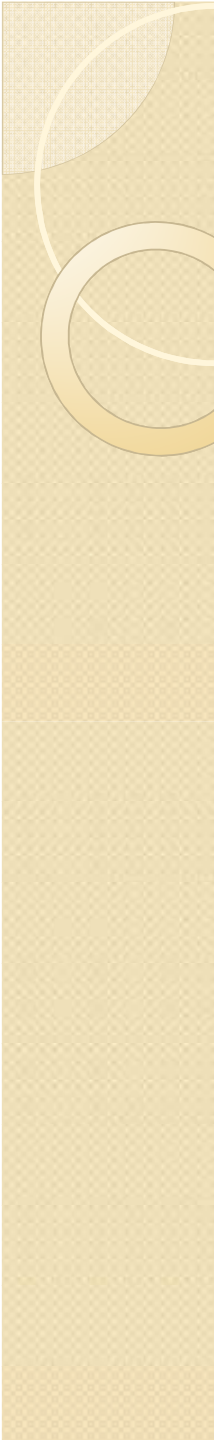


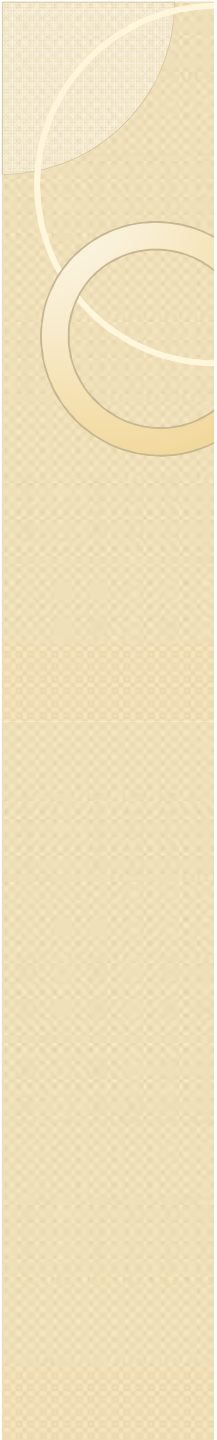
Sunshine is good

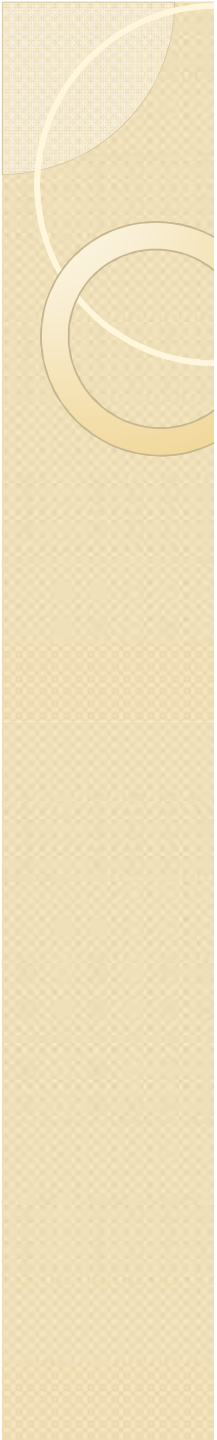


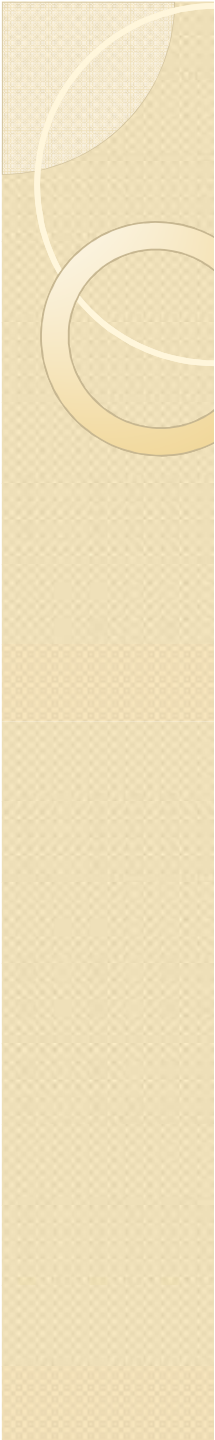
**Dr Chan Man Yan Grace
TWEH
25 Mar 2011**

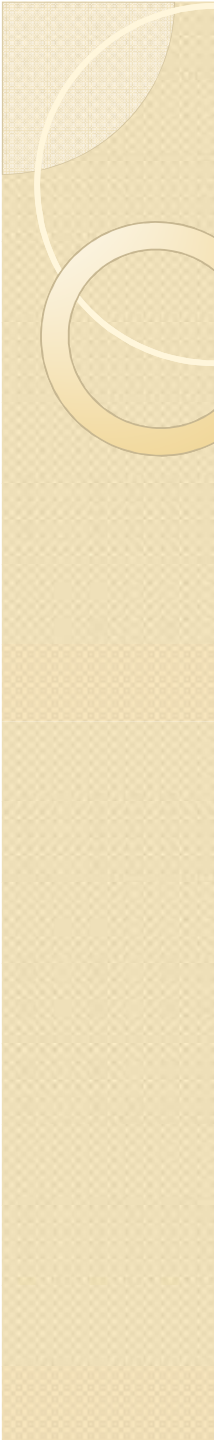
- 
- F / 80
 - Lives with family. Walks with stick. Cared by maid
 - PMH:
 - HT FU in private
 - History of old PTB
 - Osteoporosis
 - On alendronate, Ca supplement, adalat retard, aldomet

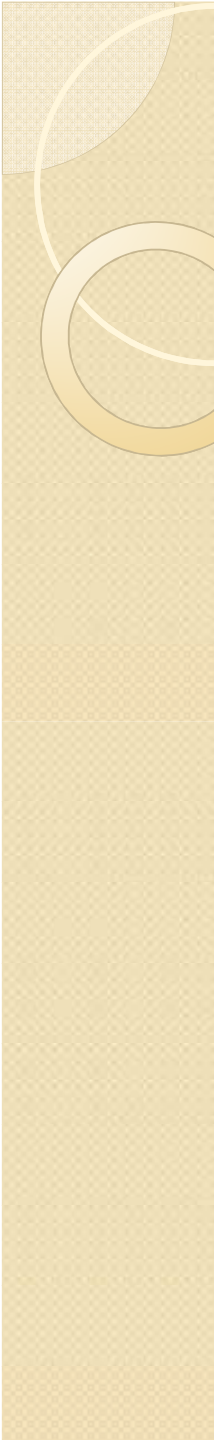
- 
- Presented to orthopedics clinic for low back pain 1/2007
 - XR LS spine showed degenerative changes
 - started on voltaren SR, pepcidine, panadol

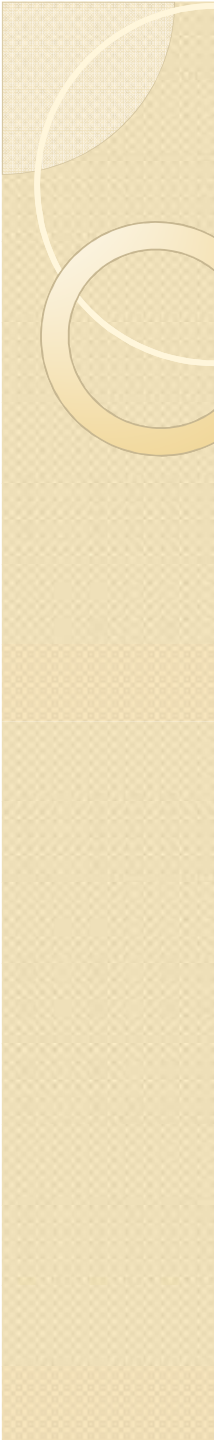
- 
- Admitted to orthopedics ward 2/2007 because of low back pain
 - XR LS spine and pelvis showed collapsed T12 and fracture left inferior pubic ramus
 - Bone scan showed increased uptake in sacrum compatible with pelvic insufficiency fracture
 - Started on dologesic, physiotherapy for pain control

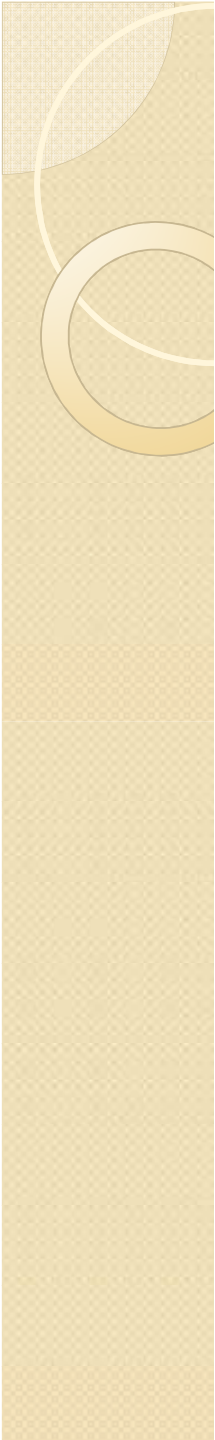
- 
- Blood test showed mild renal impairment with Cr 110
 - Noted Hb drop from 10 to 8, with lowish BP
 - OGD done showed Helicobacter associated gastric ulcer
 - Transfusion given, put on PPI
 - BP improved and anti-HT drugs resumed

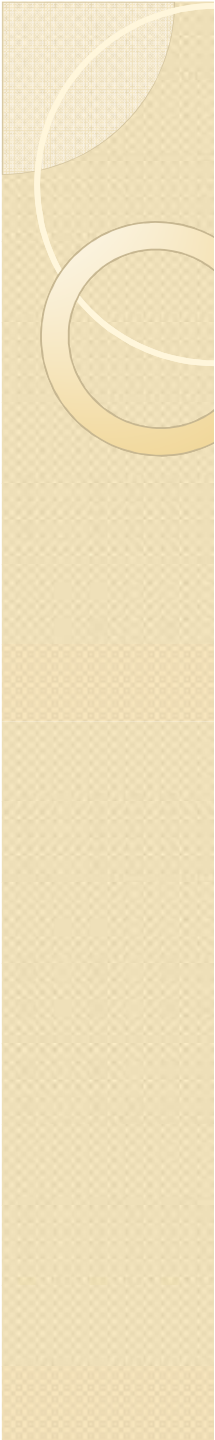
- 
- Medications on discharge:
 - Alendronate 70mg Weekly (SFI)
 - FeSO₄ 300mg BD
 - CaCO₃ 1g BD
 - Calciferol 1.25mg Daily
 - Dologesic 2 tab QID prn
 - Adalat retard 20mg Daily
 - Aldomet 250mg BD
 - Pepcidine 20mg BD

- 
- **FU at Med OPD**
 - BP control well
 - Able to walk with stick indoor; wheelchair outdoor
 - **Blood test 19/12/2009**
 - RFT Cr 160 (from 117), Hb 11.0
 - Ca 2.94, Alb not a/v

- 
- Medications:
 - Alendronate 70mg Weekly (SFI)
 - CaCO₃ 1g BD
 - Calciferol 1.25mg Daily
 - Adalat retard 20mg Daily
 - Aldomet 250mg BD
 - Pepcidine 20mg BD
 - Panadol 500mg QID prn
 - Triact 1 tab TDS prn

- 
- Dose of CaCO_3 reduced to *1g Daily*
 - Continue FU in OPD
 - Blood test the next visit – RFT Cr 154, Ca not checked

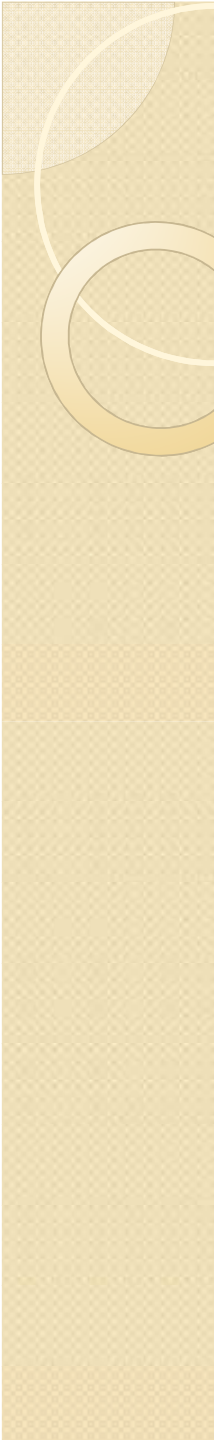
- 
- Admitted 7/2010 for
 - Decreased general condition and responsiveness, generalised weakness for 2 days
 - Poor appetite
 - No fever
 - No chest / urinary symptoms
 - Constipation. No diarrhoea / vomiting
 - No headache. No limb weakness

- 
- Physical examination on admission
 - BP 120/68 P 78. SaO₂ 98% RA. Afebrile
 - H'stix 6.9
 - GCS E2V3M4
 - Clinically dehydrated
 - Chest clear
 - Abdomen soft; no palpable bladder
 - No neck stiffness
 - Power grade 4/5 both sides. Jerks present



- Investigations

- CBP WBC 12.2, Hb 12.9, plt 487
- RFT Ur 16.4, Cr 364, Na 135, K 4.1
- LFT normal
- Ca **4.60**, PO4 1.77
- Alb 46, Globulin 33
- CK 180
- TSH 0.21, FT4 normal 16.9
- PTH 12.7 (15-65)
- Vit B12 / folate normal; VDRL non-reactive

- 
- ECG: SR 70/min
 - CXR: clear
 - Plain CT brain: periventricular ischemia
 - Urine multistix +ve for wbc / nit



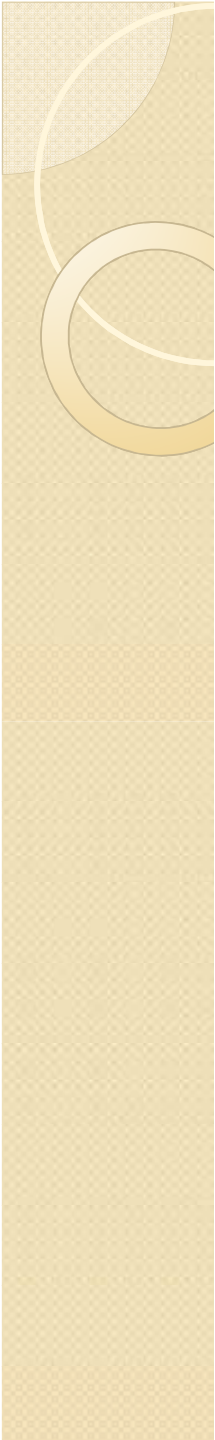
- **Problems**

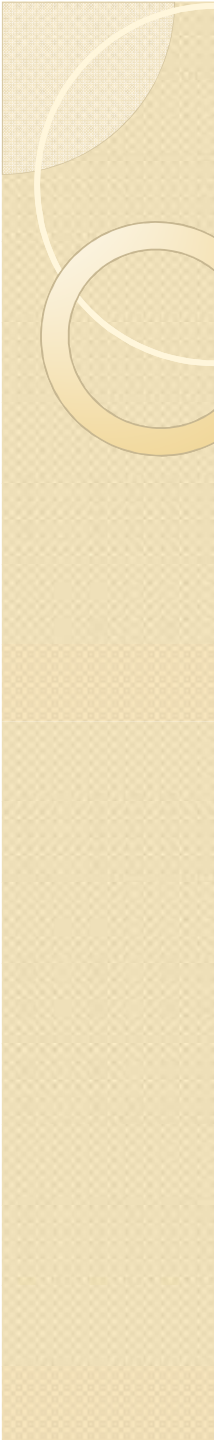
- UTI with acute on chronic renal failure

- Dehydration

- Hypercalcemia

- with symptoms of anorexia, constipation, weakness, change in sensorium

- 
- Cause of hypercalcemia
 - Primary hyperparathyroidism
 - Usually small rise in Ca level
 - PTH suppressed 12.7 (15-65)
 - Secondary and tertiary hyperparathyroidism
 - Usually in CRF
 - Increased Ca intake
 - Malignancy
 - Thyrotoxicosis
 - TSH slightly suppressed, FT4 normal
 - **Hypervitaminosis D**
 - Together with raised PO4

- 
- Medications before admission:
 - Alendronate 70mg Weekly (SFI)
 - CaCO₃ 1g daily
 - ***Calciferol 1.25mg Daily***
 - Adalat retard 20mg Daily
 - Aldomet 250mg BD
 - Pepcidine 20mg BD
 - Panadol 500mg QID prn
 - Triact 1 tab TDS prn



- **CaCO₃**

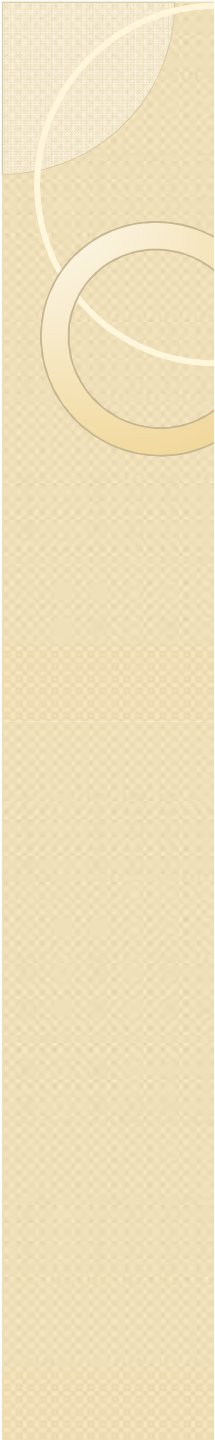
- 40% elemental Ca

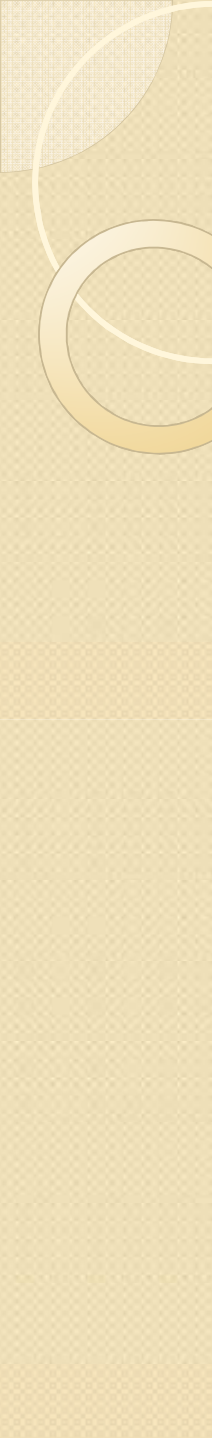
- CaCO₃ 1g daily = 400mg elemental Ca
(*recommended upper level intake 2000mg / day*)

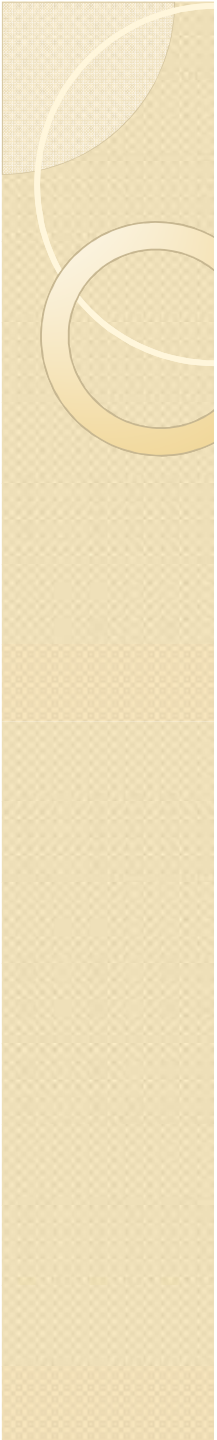
- **Calciferol / vitamin D₂**

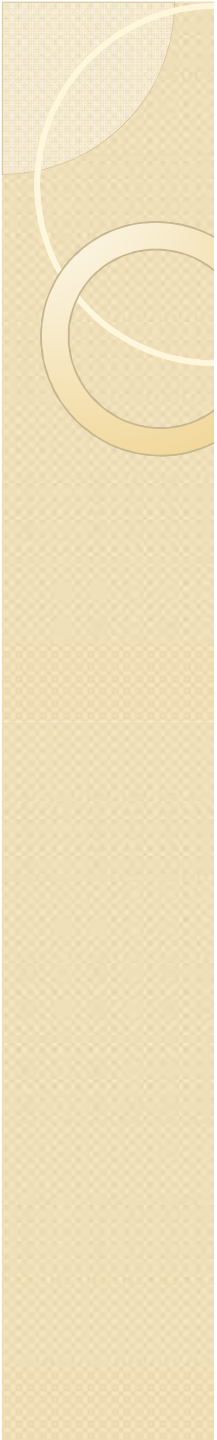
- 1 mcg = 40 IU

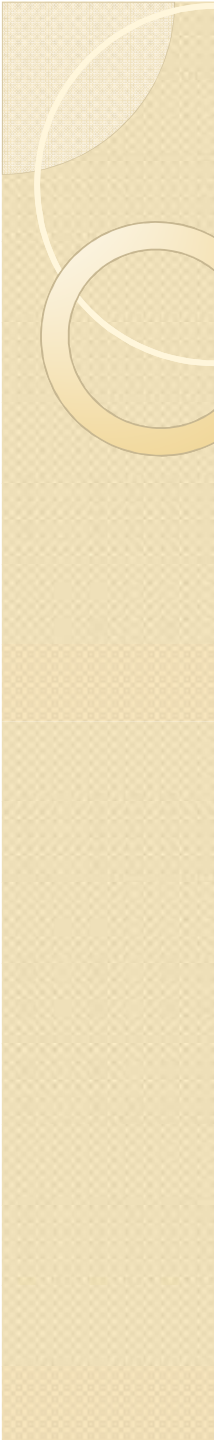
- Calciferol 1.25mg = **50000 IU** (*recommended upper level intake 4000 IU / day*)

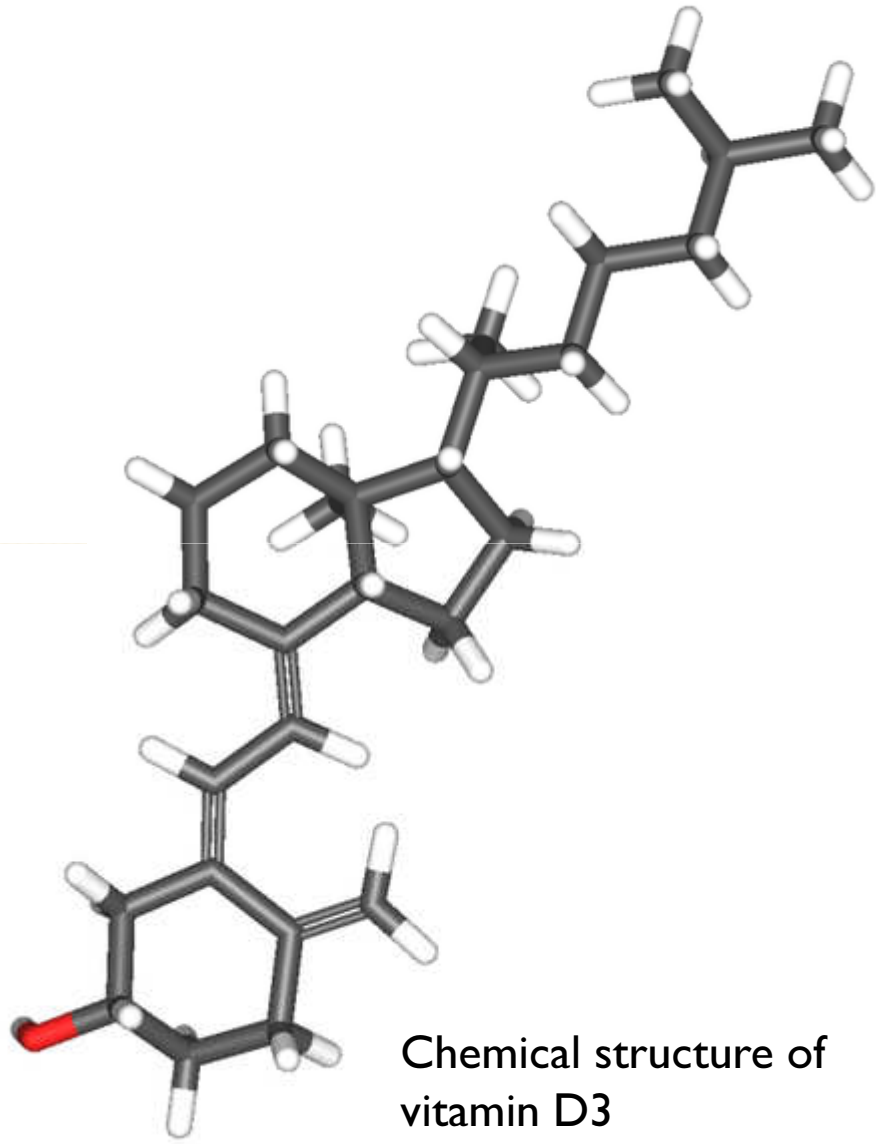
- 
- Treatment
 - Given IVF replacement
 - Calciferol and CaCO₃ taken off
 - Augmentin for E coli UTI
 - Repeated RFT Cr down trend to 330
 - Ca still raised 4.60 -> 4.14 -> 4.11
 - IV pamidronate given

- 
- Ca level down trend to 3.15 -> 2.91 -> 2.81
 - Dull and poor oral intake started on RT feeding

- 
- **Workup for encephalopathy**
 - EEG: unremarkable
 - Repeated CT brain: no catastrophic calcification
 - MM screen –ve
 - Lead normal
 - Toxicology –ve
 - Ammonia normal

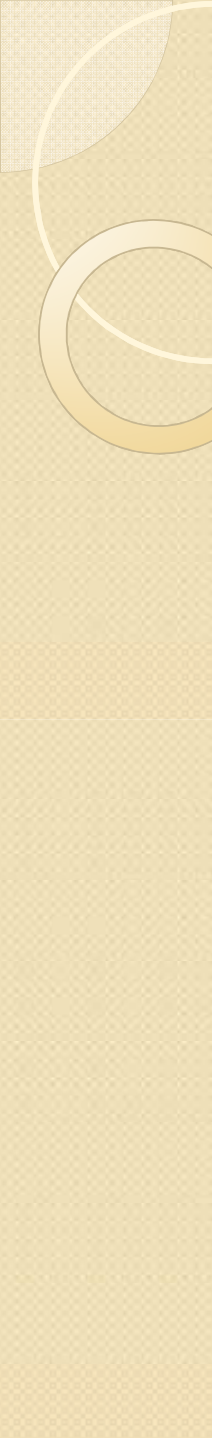
- 
- Hypervitaminosis D is the likely cause of hypercalcemia leading to impaired sensorium in this case

- 
- Transferred to convalescence bed 2 weeks after admission
 - Family reported that patient had been taking Centrum before admission
 - Improved in sensorium gradually
 - Repeated RFT Cr down to 163, Ca adjusted 2.62
 - RT feeding off and oral diet resumed
 - On discharge, able to walk with stick with assistance



Chemical structure of
vitamin D3

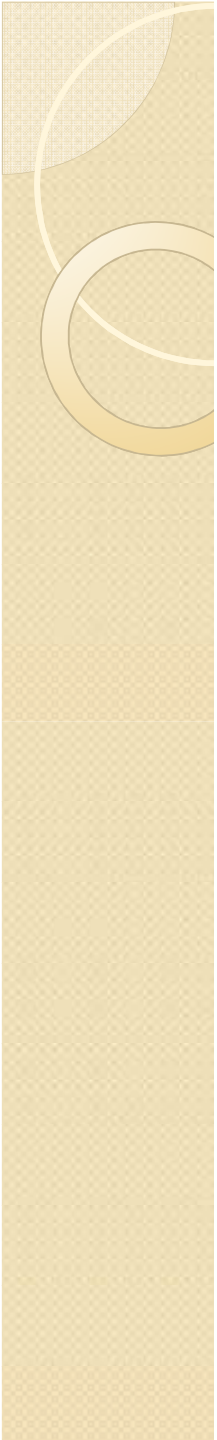
Vitamin D

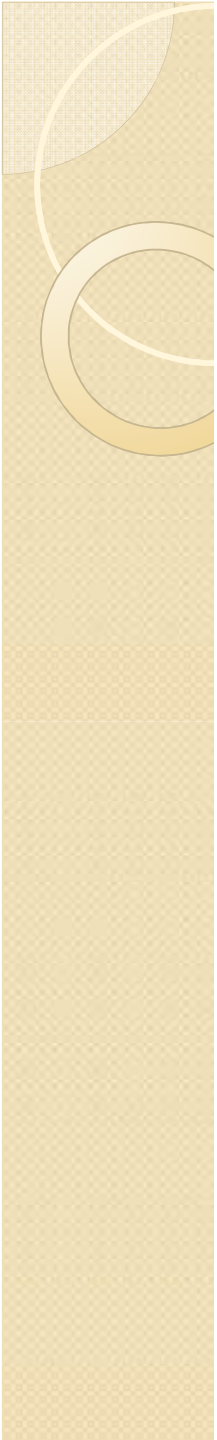
- 
- Fat soluble vitamin
 - Two major forms
 - vitamin D₂ or ergocalciferol
 - vitamin D₃ or cholecalciferol

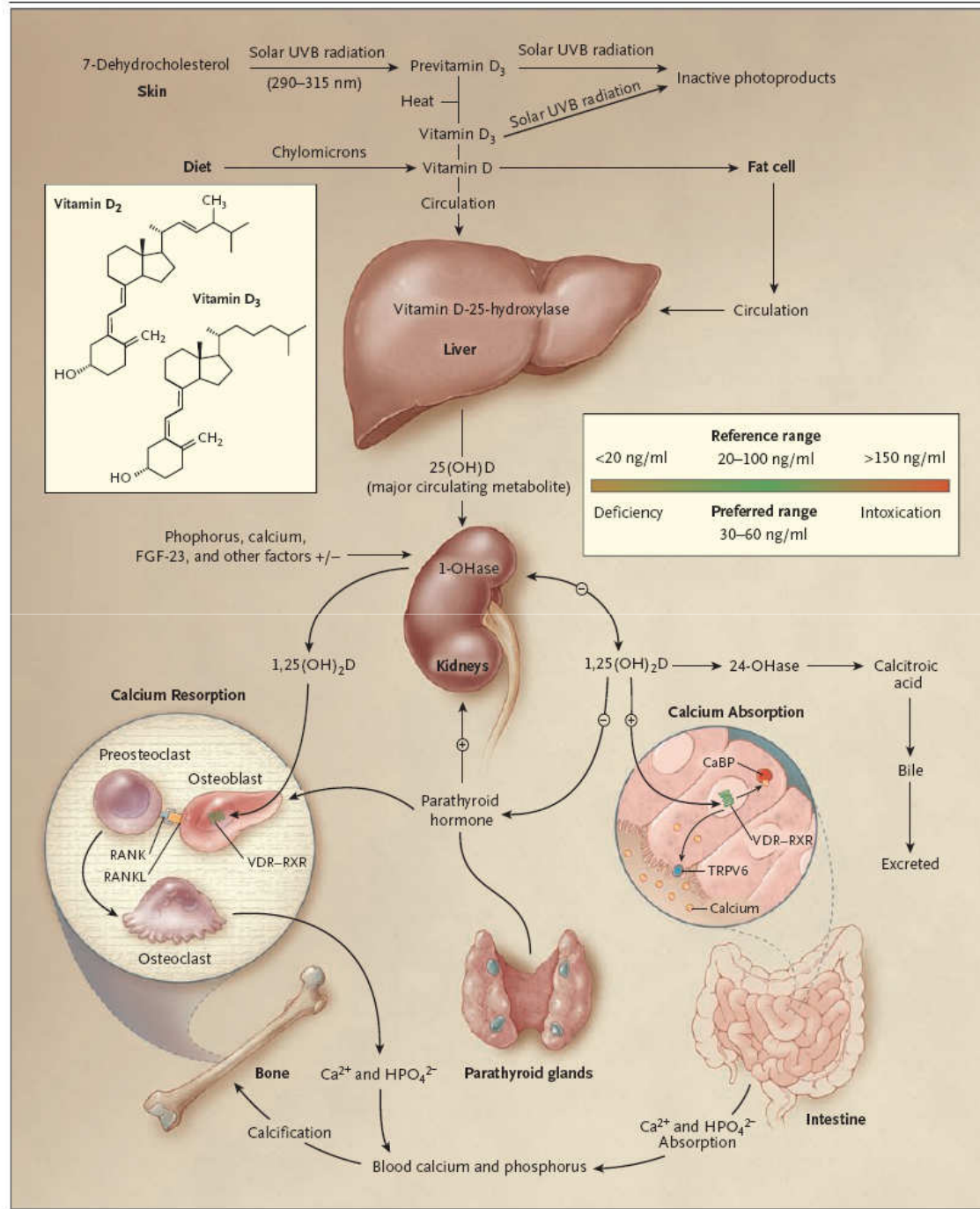


Metabolism of vitamin D

- Absorption and metabolism of dietary vitamin D
 - absorbed by enterocytes, packaged into chylomicrons
 - transported to the liver - vitamin D undergoes a hydroxylation process by 25-vitamin-D hydroxylase to form 25-hydroxy-vitamin-D (25OHD)
 - further hydroxylation of 25-hydroxy-vitamin-D to 1,25-dihydroxy-vitamin D (1,25(OH)₂-vitamin D) occurs in the mitochondria of the proximal tubules of the kidney
 - **1,25(OH)₂-vitamin D** is the physiologically active form of vitamin D

- 
- The synthesis of vitamin D and its metabolism to 1,25(OH)₂-vitamin D is closely related to calcium homeostasis, and is modulated by parathyroid hormone, serum calcium, and phosphorus levels

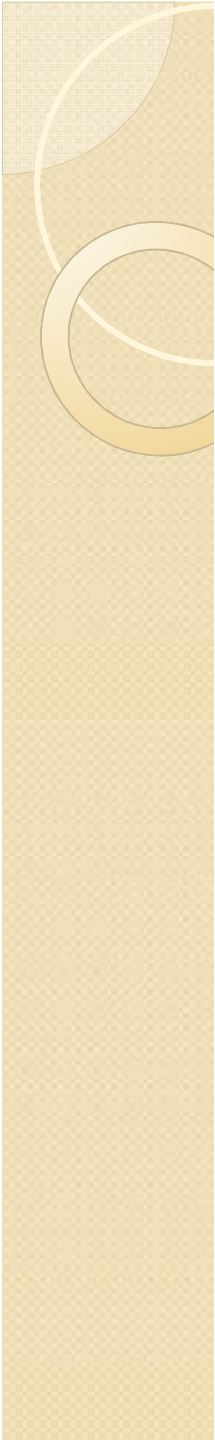
- 
- **Dermal synthesis**
 - Sunlight and ultraviolet light photoisomerize provitamin D to vitamin D3 (cholecalciferol) in the skin
 - Bound by the vitamin D binding proteins and transported via blood to liver / kidney for metabolism and activity

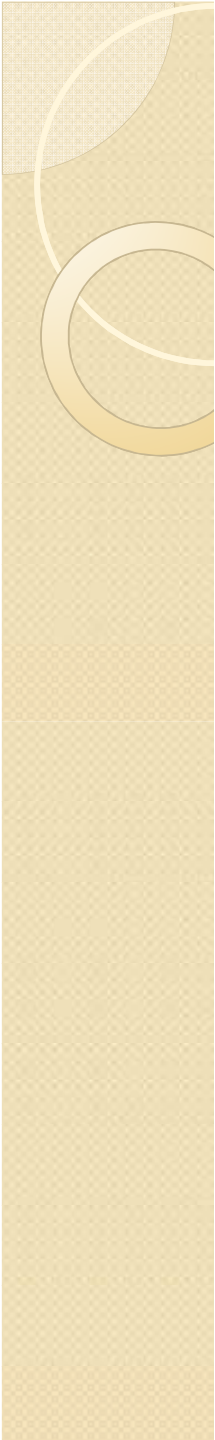


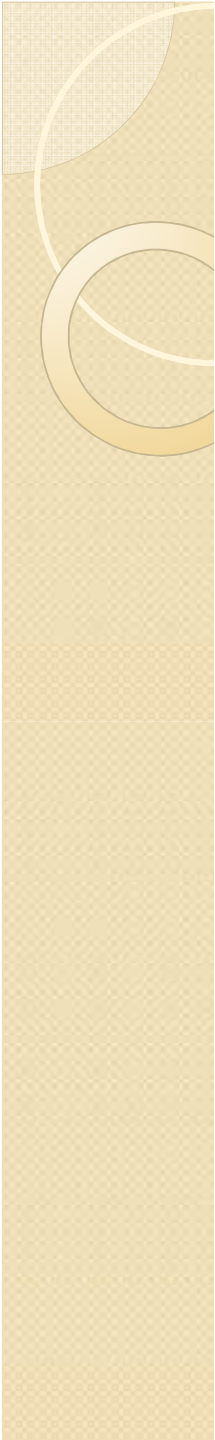
Vitamin D Deficiency; *N ENGJ Med* 2007



**What is the clinical importance of
vitamin D?**

- 
- Vitamin D and risk of fractures
 - Adequate dose of vitamin D supplement can reduce risk of fractures
 - A meta-analysis of some randomized clinical trials that evaluated the risk of fracture in older persons given 400 IU of vitamin D3 per day revealed little benefit with respect to the risk of either nonvertebral or hip fractures
 - In studies using doses of 700 to 800 IU of vitamin D3 per day, the relative risk of hip fracture was reduced by 26% and the relative risk of nonvertebral fracture by 23% with vitamin D3 as compared with calcium or placebo

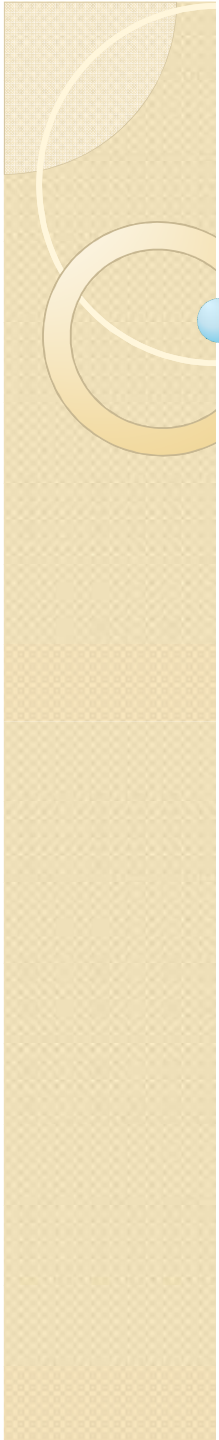
- 
- Vitamin D and fall risk
 - Adequate dose of vitamin D supplement reduces fall risk in the elderly
 - One meta-analysis suggested that supplemental vitamin D in a dose 700-1000 IU daily can reduce risk of falling among older individuals by 19% and to a similar degree as active forms of vitamin D
 - Doses less than 700 IU may not reduce risk of falling

- 
- Vitamin D and cancer
 - A case-control study in European populations, a lower level of 25OHD is associated with a higher incidence of colorectal cancer
 - Lower levels of 25OHD (25.0-49.9 nmol/l) were associated with higher colorectal cancer risk
 - Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations: a nested case-control study; *BMJ*. 2010
 - The results of vitamin D intervention trials on cancer risk are inconsistent
 - In other vitamin D supplementation studies, in which the primary end points are fracture risk, there are no beneficial effects on cancer risks



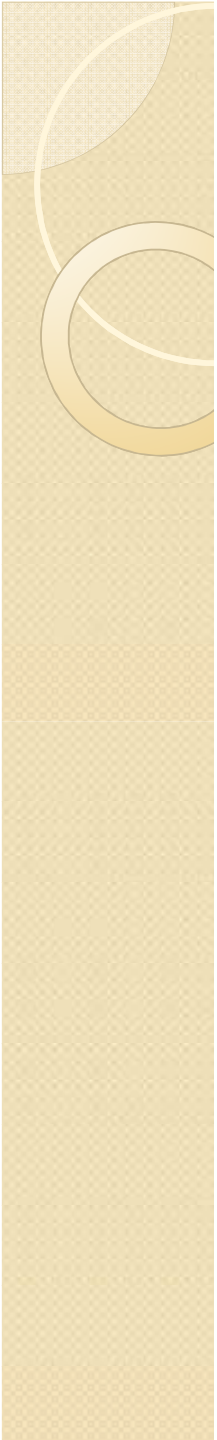
- **Others**

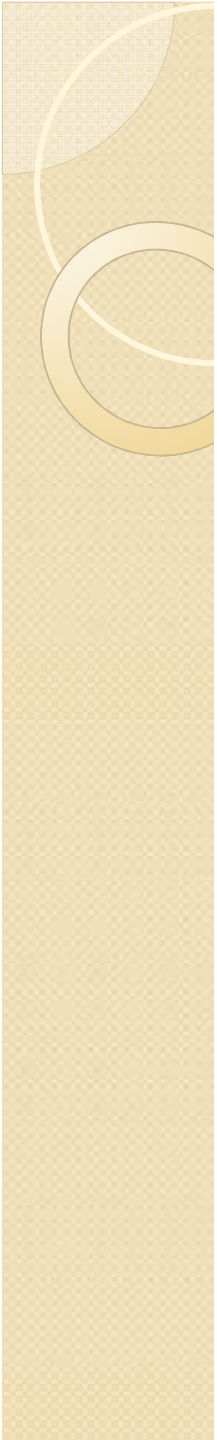
- 1,25-(OH)₂ vitamin D₃ decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation
- Use of 1,25-(OH)₂ vitamin D₃ and its active analogues for the treatment of psoriasis

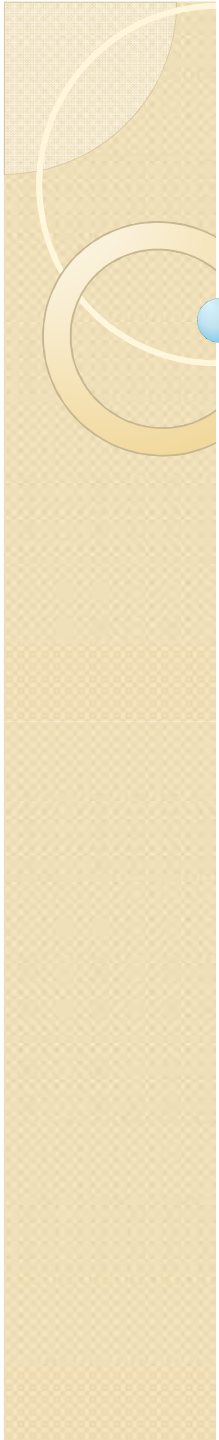


Vitamin D

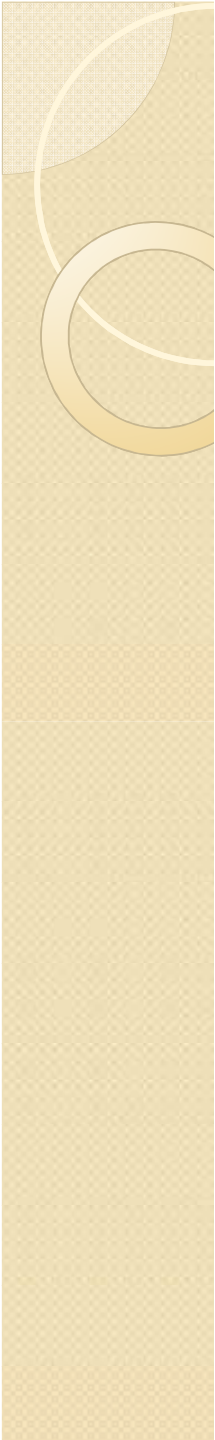
Enough ? Deficient ?

- 
- **Measurement of vitamin D levels**
 - No consensus on optimal levels
 - Vitamin D insufficiency - 25OHD concentration of 20 to 30 ng/mL (50 to 75 nmol/L)
 - Vitamin D deficiency - 25OHD level less than 20 ng/mL (50 nmol/L)
 - Vitamin D sufficiency – 25OHD level above 30 ng/mL
 - Vitamin D intoxication – 25OHD level > 150 ng/ mL (374 nmol/L)

- 
- The 25-OHD assay should never be used for detecting vitamin D deficiency because levels will be normal or even elevated as a result of secondary hyperparathyroidism.
 - Costly
 - Vitamin D supplement

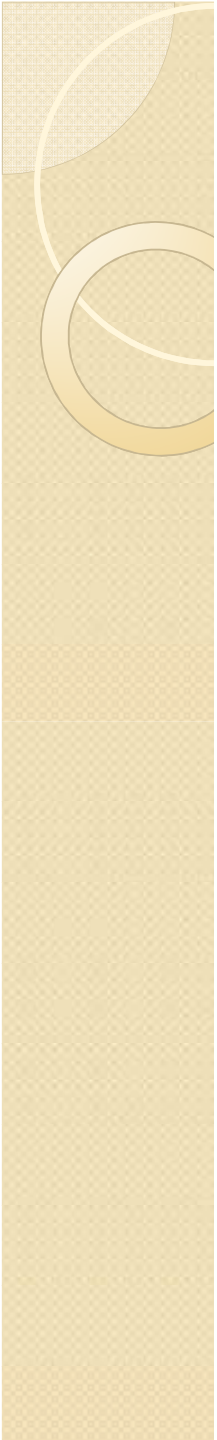


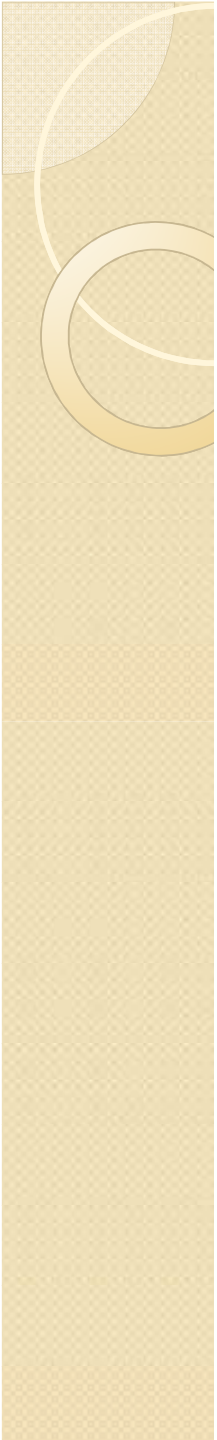
**Is vitamin D deficiency common
in the elder ?**

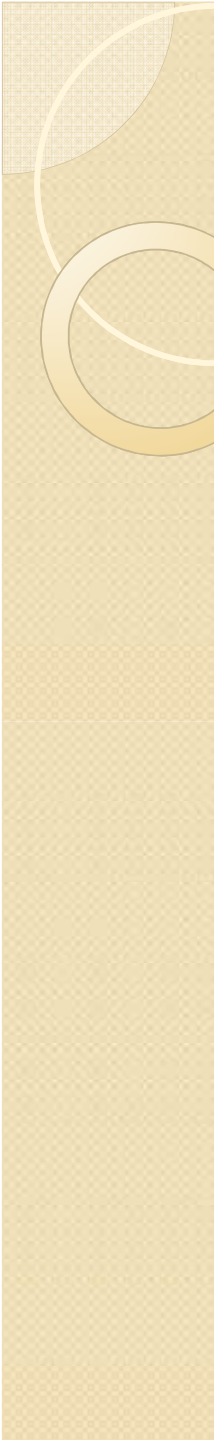
- 
- According to several studies, 40-100% of U.S. and European *community dwelling* elderly have vitamin D deficiency



Why vitamin D deficiency is common in the elder ?

- 
- Impaired vitamin D metabolism and thus decreased calcium absorption in aging
 - Cutaneous vitamin D production and vitamin D stores decline with age
 - Reduces vitamin D₃ synthesis by about 75% in a 70-year-old
 - Impaired conversion of 25-OH to 1,25 (OH)₂ vitamin D in chronic kidney disease
 - Diet
 - Institutionalizaion

- 
- Vitamin D intoxication
 - Rare
 - Can be caused by inadvertent or intentional ingestion of excessively high doses
 - Doses of more than 50,000 IU per day are associated with hypercalcemia and hyperphosphatemia
 - Excessive exposure to sunlight will not cause vitamin D intoxication as excess previtamin D or vitamin D is destroyed by sunlight

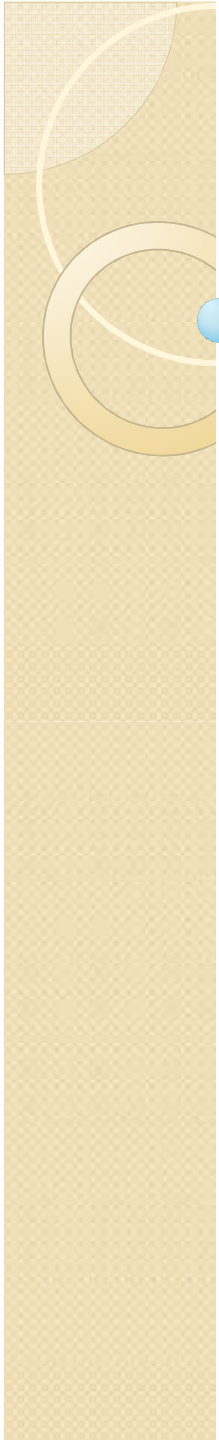
- 
- Treatment for hypercalcemia
 - Intravenous fluid replacement
 - Initial rate of 200 to 300 mL/h that is then adjusted to maintain the urine output at 100 to 150 mL/h
 - Lasix if chronic renal failure / heart failure
 - Calcitonin
 - Corticosteroid
 - Effective in treating hypercalcemia due to some lymphomas, sarcoid, or other granulomatous diseases



- **Bisphosphoates**

- Previous observations have suggested that there is increased bone resorption in hypervitaminosis D
- Pamidronate disodium, a bone resorption inhibitor through osteoclast mediation, has been used to treat chronic hypercalcemia secondary to malignancy and chronic renal failure
- Pamidronate treatment resulted in a brisk reduction in plasma calcium concentration, while corticosteroid treatment was more delayed.

Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate; *Clin Endocrinol* 1995 Nov
The use of pamidronate for hypercalcemia secondary to acute vitamin D intoxication; *J Toxicol Clin Toxicol*. 1998



How much is good enough ?

Dietary reference intake (30 Nov 2010 Institute of Medicine of the U.S. National Academy of Sciences)

Dietary Reference Intakes for Calcium and Vitamin D

Life Stage Group	Calcium			Vitamin D		
	Estimated Average Requirement (mg/day)	Recommended Dietary Allowance (mg/day)	Upper Level Intake (mg/day)	Estimated Average Requirement (IU/day)	Recommended Dietary Allowance (IU/day)	Upper Level Intake (IU/day)
infants 0 to 6 months	*	*	1,000	**	**	1,000
infants 6 to 12 months	*	*	1,500	**	**	1,500
1-3 years old	500	700	2,500	400	600	2,500
4-8 years old	800	1,000	2,500	400	600	3,000
9-13 years old	1,100	1,300	3,000	400	600	4,000
14-18 years old	1,300	1,300	3,000	400	600	4,000
19-30 years old	800	1,000	2,500	400	600	4,000
31-50 years old	800	1,000	2,500	400	600	4,000
51-70 year old males	800	1,000	2,000	400	600	4,000
51-70 year old females	1,000	1,200	2,000	400	600	4,000
>70 years old	1,000	1,200	2,000	400	800	4,000
14-18 years old, pregnant/lactating	1,300	1,300	3,000	400	600	4,000
19-50 years old, pregnant/lactating	800	1,000	2,500	400	600	4,000

*For infants, Adequate Intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.
 **For infants, Adequate Intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.

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31-50 years old	800	1,000	2,500	400	600	4,000
51-70 year old males	800	1,000	2,000	400	600	4,000
51-70 year old females	1,000	1,200	2,000	400	600	4,000
>70 years old	1,000	1,200	2,000	400	800	4,000
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- **Source**

- **Sunlight exposure**

- Exposure of arms and legs for 5 to 30 minutes (depending on time of day, season, latitude, and skin pigmentation) between the hours of 10 a.m. and 3 p.m. twice a week is often adequate.

- **Excessive exposure to sunlight, especially sunlight that causes sunburn, will increase the risk of skin cancer.**

- **Excess vitamin D is destroyed by sunlight**



- **Dietary source**

- **Very few foods contain vitamin D**

- Fortified milk / cereals

- Fatty fish species

- Egg (1 whole egg provides 20 IU)

- Fish liver oils, such as cod liver oil 1 Tbs (15 ml) provides 1360 IU

- Difficult to obtain that much vitamin D on a daily basis from dietary sources

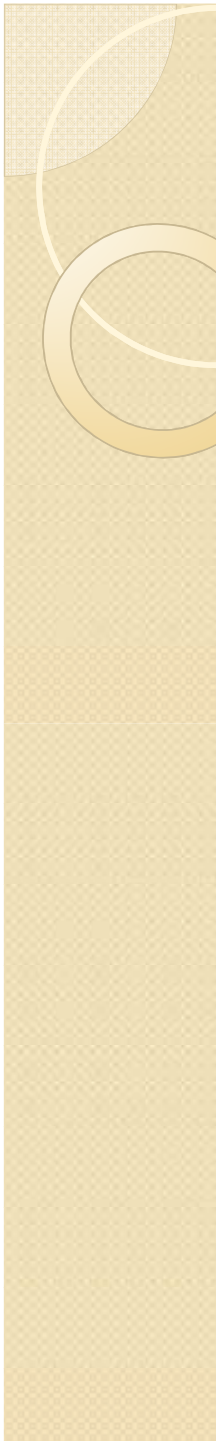


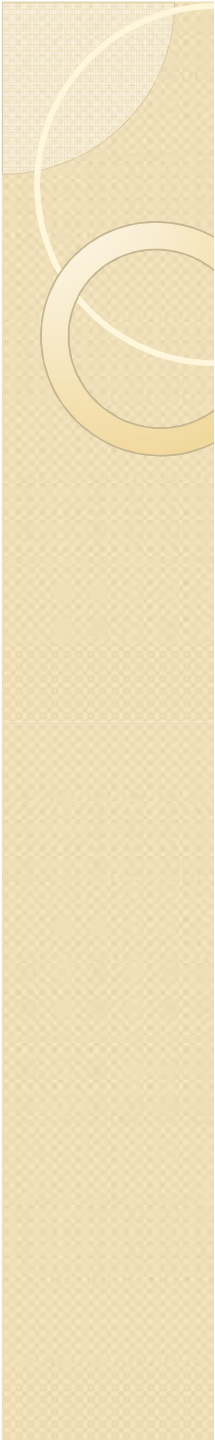
Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D₂ and D₃.^{*†}

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D ₃
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D ₃ or D ₂
Canned (3.5 oz)	About 300–600 IU of vitamin D ₃
Sardines, canned (3.5 oz)	About 300 IU of vitamin D ₃
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D ₃
Tuna, canned (3.6 oz)	About 230 IU of vitamin D ₃
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D ₃
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D ₂
Sun-dried (3.5 oz)	About 1600 IU of vitamin D ₂
Egg yolk	About 20 IU of vitamin D ₃ or D ₂
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythral dose) [†]	About 3000 IU of vitamin D ₃
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D ₃
Fortified orange juice	About 100 IU/8 oz vitamin D ₃
Infant formulas	About 100 IU/8 oz vitamin D ₃
Fortified yogurts	About 100 IU/8 oz, usually vitamin D ₃
Fortified butter	About 50 IU/3.5 oz, usually vitamin D ₃
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D ₃
Fortified cheeses	About 100 IU/3 oz, usually vitamin D ₃
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D ₃
Supplements	
Prescription	
Vitamin D ₂ (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D ₂) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D ₂ , or D ₃ [‡]
Vitamin D ₃	400, 800, 1000, and 2000 IU

* IU denotes international unit, which equals 25 ng. To convert values from ounces to grams, multiply by 28.3. To convert values from ounces to milliliters, multiply by 29.6.

[†] About 0.5 minimal erythral dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure (depending on the time of day, season, latitude, and skin sensitivity) of the arms and legs to direct sunlight.

[‡] When the term used on the product label is vitamin D or calciferol, the product usually contains vitamin D₂; cholecalciferol or vitamin D₃ indicates that the product contains vitamin D₃.

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- Preparations of vitamin D supplement
 - MV (400 IU vitamin D) or other OTC preparations
 - Vit D2 / Calciferol
 - Vit D3
 - More potent than vitamin D2 in some studies
 - Longer duration of action
 - Calcitriol / 1,25(OH)₂-vitamin D
 - Alphacalcidol / 1- α -hydroxycholecalciferol
 - Higher risk of hypercalcemia

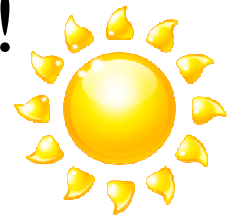
A comparative study of cholecalciferol, dihydrotachysterol and alfacalcidol in the treatment of elderly patients with hypocalcaemia. *Age Ageing.* 1987

May; 16(3):178-80

Vitamin D2 is much less effective than vitamin D3 in humans. *Clin Endocrinol Metab.* 2004

Take home message

- Vitamin D deficiency is likely to be common in the elderly, and under-diagnosed
 - ? Oral supplement, with or without Ca
 - OTC vitamins supplement
 - Polypharmacy in elderly
- Vitamin D intoxication is rare, but
- Iatrogenesis is not uncommon in the elderly
 - NSAID induced gastric ulcers
 - Vitamin D intoxication in this case
- More outdoor exercise under the sun !





**THE END
THANK YOU**