THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"An 82-year-old man with dyspnea and weight loss"

OBJECTIVES

- Differential diagnosis of non-PTH mediated hypercalcemia
- Pathophysiology of hypercalcemia in hypervitaminosis D
- Discuss treatment options for vitamin D toxicity

HPI

- 82yo man with h/o HTN, T2DM, HL, CAD, HFrEF, CKD stage III, BPH, carotid artery stenosis (s/p L enterectomy), AAA (s/p EVAR in 10/2020), and RA who was admitted with fatigue, worsening dyspnea, orthopnea, decreased appetite, and ~15 lbs weight loss over the last two months. Denies cough, chest pain, fever. Reports symptoms started when he was prescribed amlodipine for BP control.
- Diagnosed with RA more than 10 years ago. Has been on methotrexate since then. Currently on 15 mg weekly. CT chest on 2017 showed mild ILD.

Other history and medications

- Past Medical History: HTN, T2DM, HL, CAD, HFrEF (45% 9/2020), CKD stage III, BPH, carotid artery stenosis (s/p L endarterectomy in 01/2019), AAA (s/p EVAR in 10/2020), RA
- Medications: MTX, folic acid, Januvia 100 mg/d, Glipizide 5 mg/d, ASA, Coreg, Lasix 80 mg+40mg, Hydralazine, Isodril, Lipitor, Proscar
- In 06/2020 noted to have Ca 7.8, corrected 8.4, 25(OH)D 21 ng/ml and started on ergocalciferol 50,000 IU/weekly
- SH: long-time smoker, quit 2 years ago, no alcohol or drugs
- FH: no autoimmune or endocrine problems

Physical exam

- PE: T 97.7, HR 62 bpm; BP 159/68, O2 Sat 97%, Wt 69 kg, BMI 22.6
- In no acute distress, deconditioned but comfortable, HEENT: EOMI, dry mucous membranes; No thyromegaly; Lungs: diminished breath sounds bilaterally, CVD: RRR, No hepatosplenomegaly, no pedal edema

Initial labs

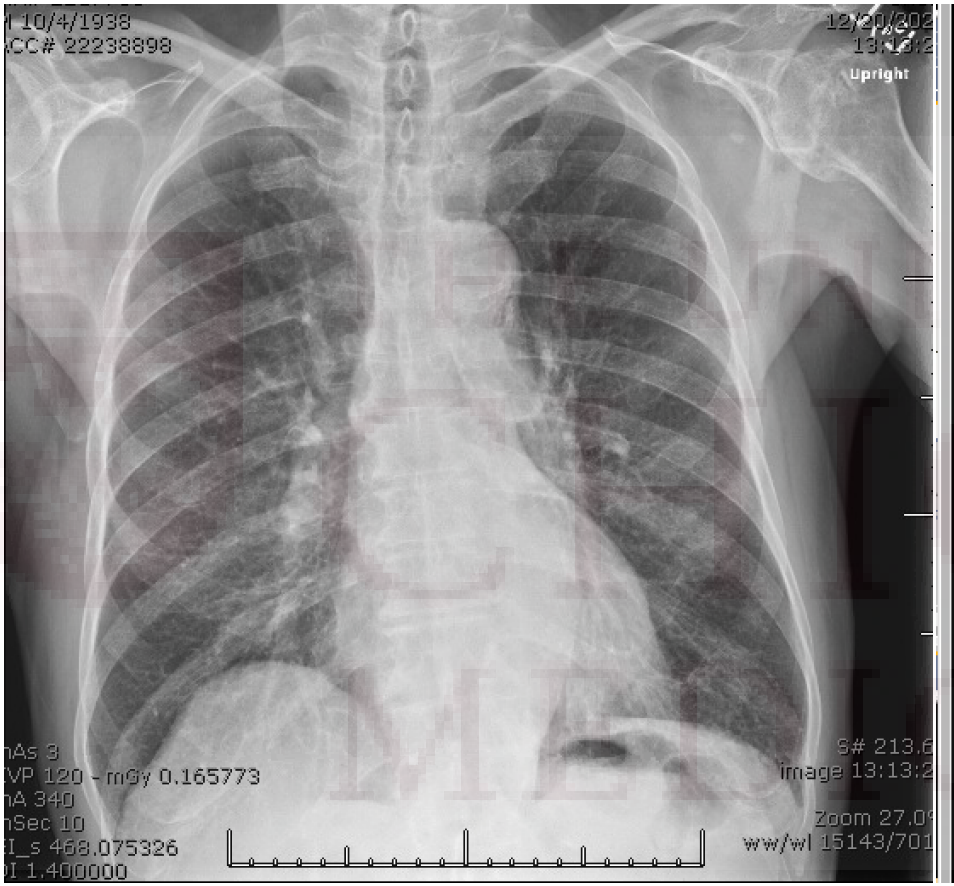
- **LABS**

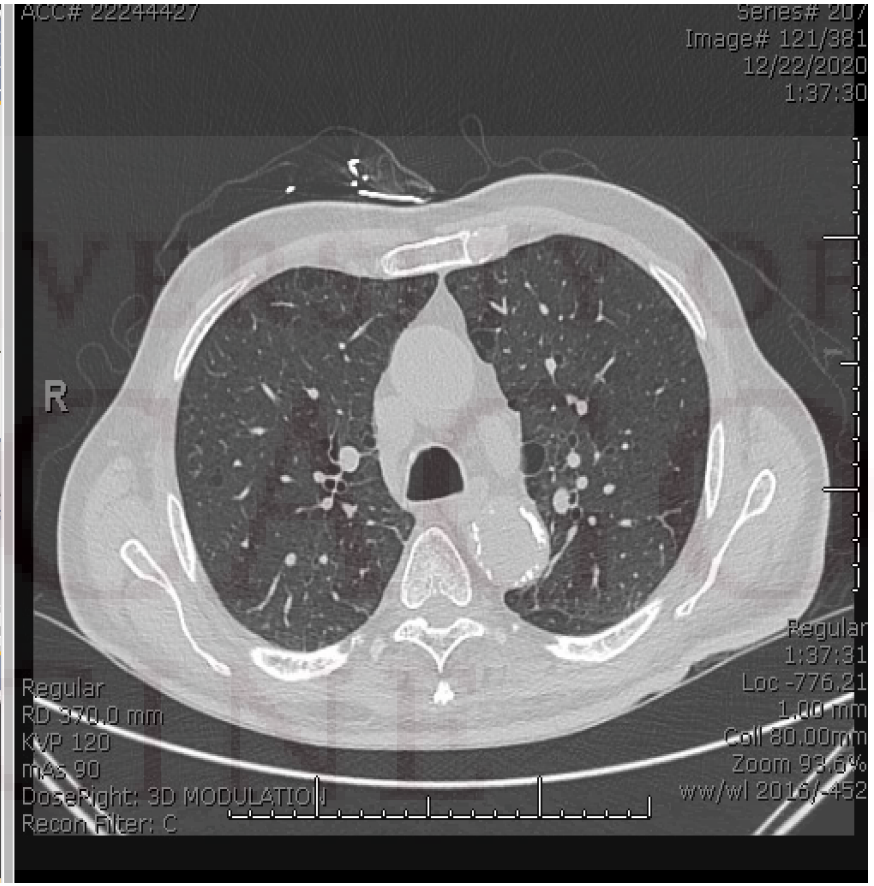
	12/20/20	12/11/20
Sodium	140	141
Potassium	3.9	3.1
Chloride	99	102
Bicarbonate	27	29
BUN	53	56
Creatinine	2.9 (1.7)	2.4
Calcium	11.2	9.0
Phosphorus	3.9	
Albumin	3.4	2.9
Corrected Ca	11.7	9.9
25(OH) Vit D	82	146
Glucose	301	240

	12/21/20
PTH	9
PTHrP	0.8
1,25 (OH)2 Vit D	137
C-telopeptide	700
Osteocalcin	23.5
ALP	79
TSH	1.7

	12/21/20
WBC	6.9
RBC	3.21
Hb	9.8
Ht	31.4
Plt	255

CXR and CT chest





- What is the differential for his hypercalcemia?
- Do we need additional tests?

Non-PTH mediated hypercalcemia

- Non-PTH-Mediated
  - Endocrine
    - Hypothyroidism
    - Hypoadrenalism/Addison's syndrome
    - VIPoma
    - Pheochromocytoma
    - Pregnancy/lactation-associated (PTHrP-mediated
  - Malignancy
    - Humoral hypercalcemia of malignancy
      - PTH-related peptide
      - 1,25-dihydroxyvitamin D
    - Lytic bone lesions
  - Drug-related
    - Thiazide diuretics
    - Vitamin D or vitamin D analogs
    - Vitamin K
    - Calcium
    - Aluminum
    - Beryllium
    - Theophylline
    - Vitamin A intoxication
  - Vitamin D-mediated
    - Excessive cholecalciferol or ergocalciferol indigestion
    - Ingestion or administration of excessive calcitriol (or other 1α-hydroxylated vitamin D analogs)
    - Ectopic 1,25-dihydroxyvitamin D production
      - Granulomatous disease
        - Sarcoidosis
        - Tuberculosis
        - Fungal diseases
        - Leprosy
        - Other granulomatous lesions
      - Lymphoma
    - Inactivating mutations of the *CYP24A1* gene in children and adults
  - Miscellaneous conditions
    - Post-acute renal failure
    - William's syndrome
    - Paget's disease
    - Immobilization
    - Jansen's metaphyseal chondrodysplasia
    - Hypophosphatasia
    - Milk-alkali syndrome

Our recommendation

Start gentle hydration and Lasix

	12/22	12/23	12/24	12/25	12/26	12/27
Creatinine	2.3	2.1	2.4	2.3	2.4	2.3
Calcium	10.8	10.6	10.5	10.2	10.4	10.7
Albumin	3.2	2.9	3.1	2.9	2.8	2.9
Corrected Ca	11.4	11.5	11.2	11.1	11.4	11.6
Phosphorus	3.2	4.0	4.7	3.9	4.3	3.7

Additional tests: ACE 20, RF 16, CCP 92, IgG, IgA, IgM normal, SPEP no monoclonal; Quantiferon test negative

What is the best treatment option and are there alternatives?

Treatment

Started on Prednisone 40 mg/d on 12/27

	12/27	12/28	12/29	12/30	12/31	1/1
Creatinine	2.3	2.2	2.0	2.0	2.0	2.3
Calcium	10.7	10.5	10.3	10.3	10.1	10.1
Albumin	2.9	2.8	2.9	3.1	2.9	3.1
Corrected Ca	11.6	11.5	11.2	11.0	11.0	10.8
Phosphorus	3.7	4.9	3.9	3.6	2.7	3.8
25(OH) Vit D	74				66	
1,25 (OH)2 Vit D	103				24	
PTH					12	

Follow up

Prednisone tapered to 20 mg, 10mg, 5 mg and discontinued

	12/27	12/28	12/29	12/30	12/31	1/1	1/6
Creatinine	2.3	2.2	2.0	2.0	2.0	2.3	2.4
Calcium	10.7	10.5	10.3	10.3	10.1	10.1	9.1
Albumin	2.9	2.8	2.9	3.1	2.9	3.1	3.3
Corrected Ca	11.6	11.5	11.2	11.0	11.0	10.8	9.7
Phosphorus	3.7	4.9	3.9	3.6	2.7	3.8	2.6
25-OH Vit D	74				66		
1,25 (OH)2 Vit D	103				24		16
PTH					12		59

Vitamin D toxicity (VDT)

- VDT due to vitamin D overdosing is diagnosed by markedly elevated 25(OH)D >150 ng/ml and severe hypercalcemia and hypercalciuria and by very low or indetectable PTH activity. 1,25 $(OH)_2D$ can be in reference range, slightly increased or reduced (less frequently).

Epidemiology

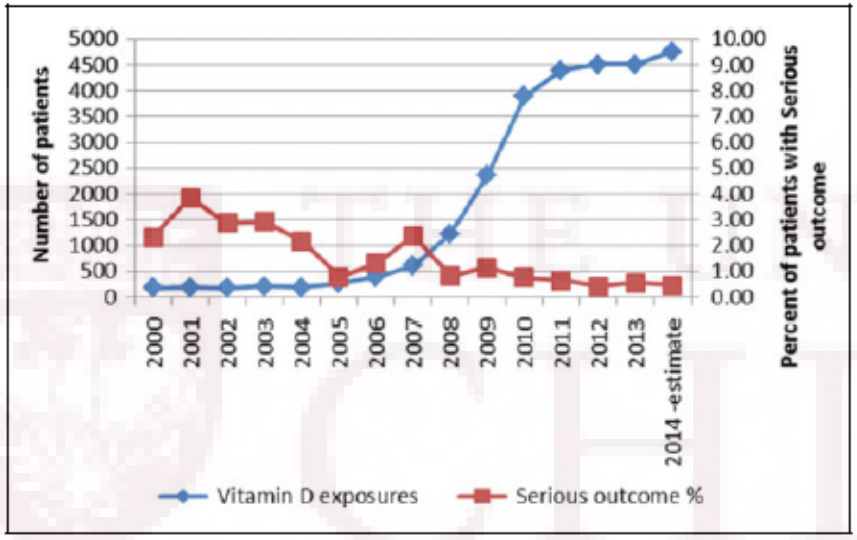


Figure 1. Number of patients who consumed vitamin D and percent with serious outcome by year.

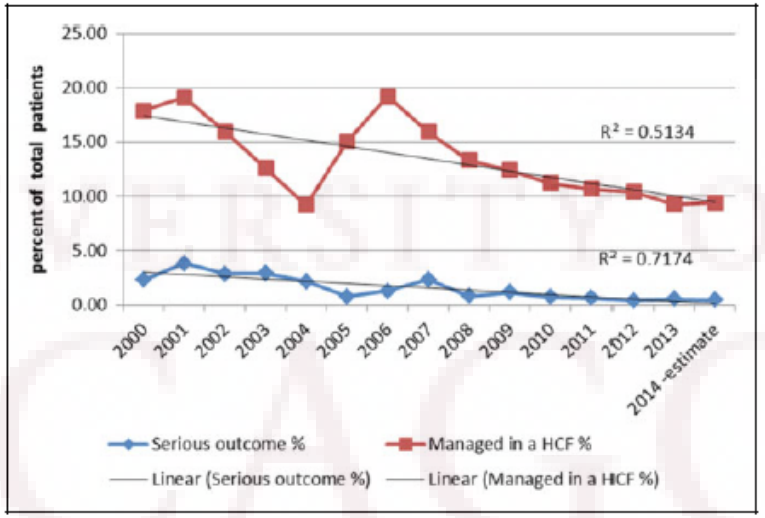
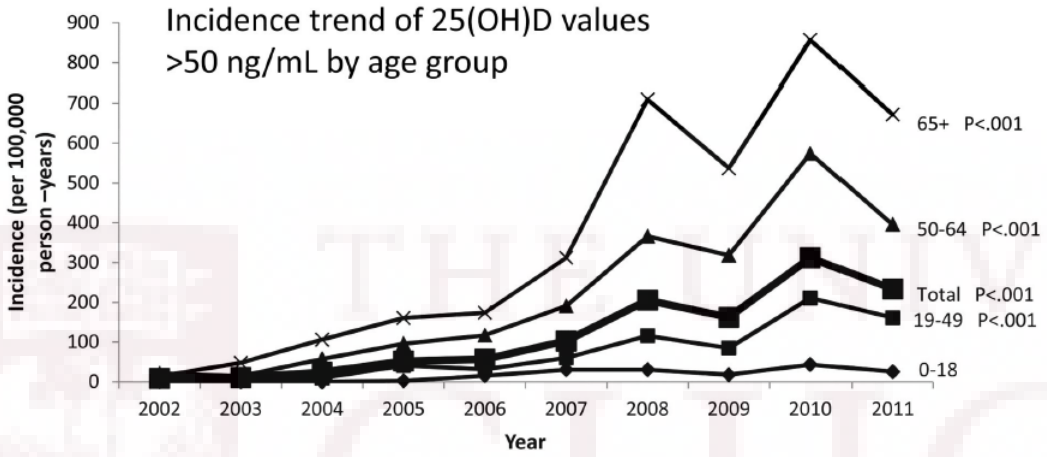
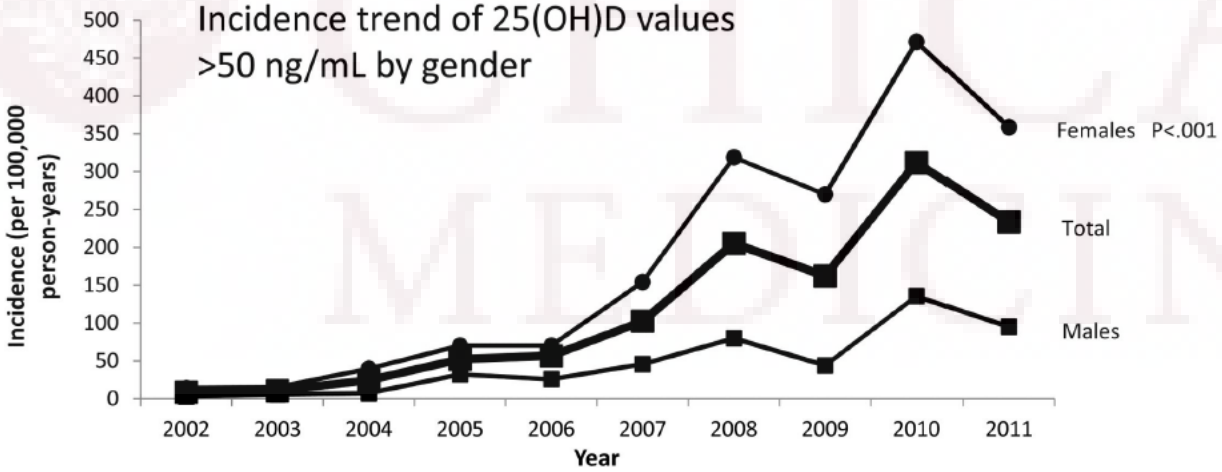


Figure 2. Percentage of total patients managed at an HCF and with serious medical outcome.

From 2000-2014 there were 25,397 reported cases of hypervitaminosis D with marked increase 2005-2011. Decline in serious medical outcomes

Incidence





Total 20,308 measurements,

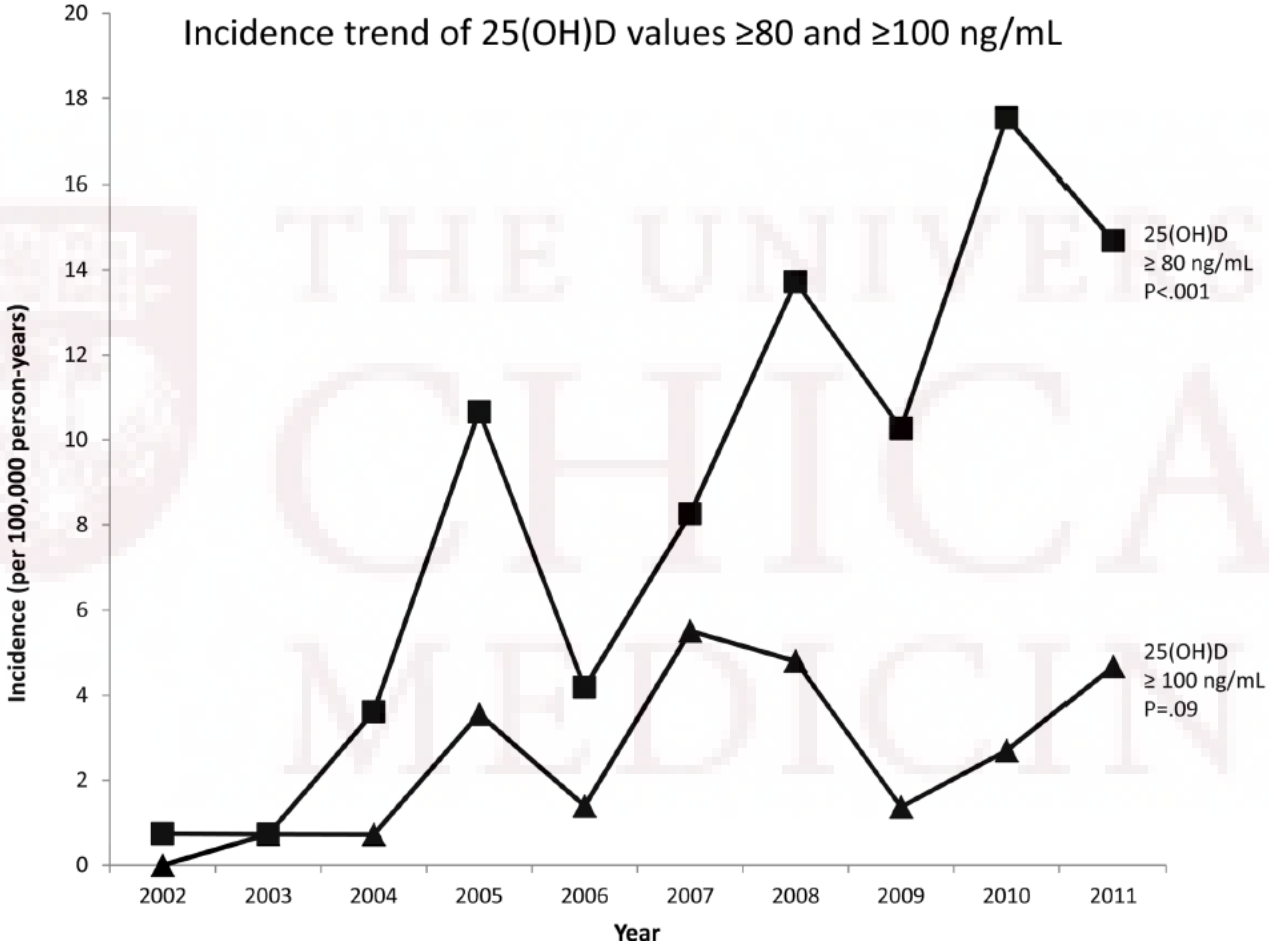
8.4% > 25(OH)D >50, 0.6% >80,

0.2% >100.

Incidence increased for 9 to 233

per 100,000 person-years

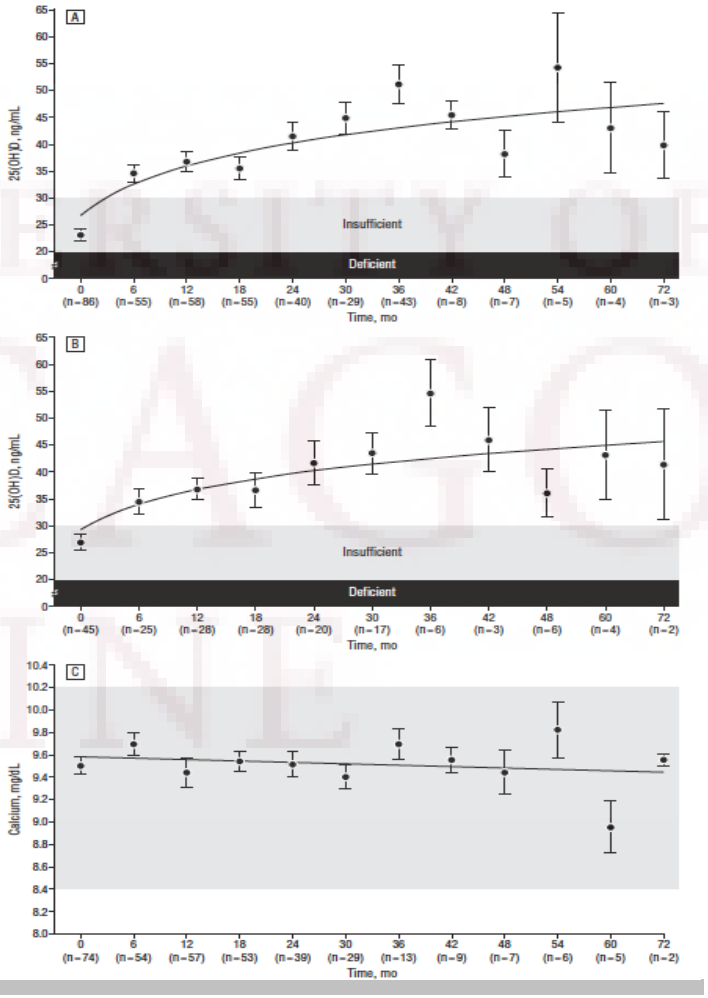
Incidence


Incidence trend of 25(OH)D values ≥80 and ≥100 ng/mL
Incidence (per 100,000 person-years)
20
18
16
14
12
10
8
6
4
2
0
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
Year
25(OH)D
≥ 80 ng/mL
P<.001
25(OH)D
≥ 100 ng/mL
P=.09

Vitamin D2 for Vit D deficiency or insufficiency

- 79 patients with 25(OH)D <30 ng/ml were treated with D2 50,000 IU weekly for 8 weeks and after that, 50,000 IU every other week.
- Mean age 61, mean treatment duration 26 months
- Mean pretreatment 25(OH)D level 26.9,

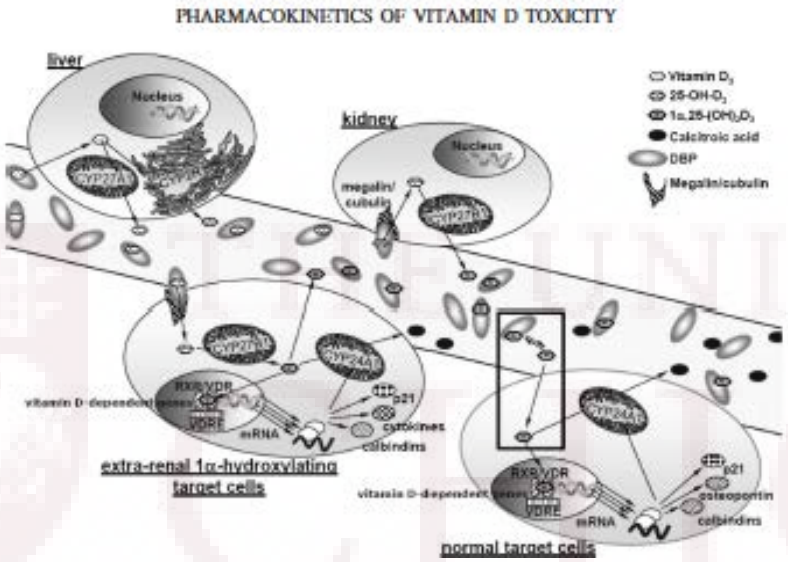
final level 47.1 ng/ml. No change in Ca



Pharmacokinetics

- Adipose tissue distribution
- Half-life of ~ 2 months
- Half-life of 25(OH)D is 15 days, 1,25 $(OH)_2D$ is 15h

Theories about the mechanism of vitamin D toxicity

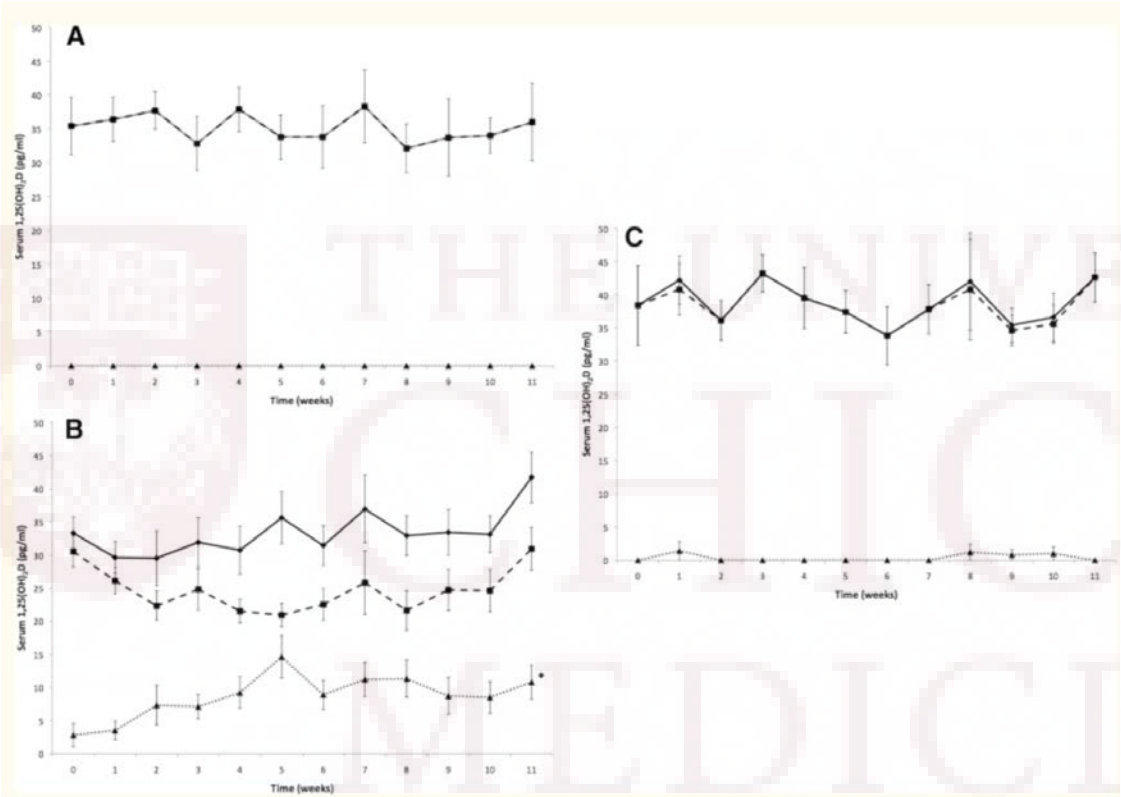


1) Vit D intake rises plasma 1,25 (OH)2 Vit D, which increases its cellular concentration

2) Vit D intake rises plasma 25-OH Vit D that exceeds DBP capacity and it enters the cell where it has direct effect on gene expression

3) Vit D intake rises the concentrations of many D metabolites and this leads to exceed DBP capacity and cause release of free 1,25 (OH)2 D which enters the target cells

Vitamin D2 vs D3 supplementation



Serum concentration of $1,25(OH)_2D3$ and total $1,25(OH)_2D$ did not change in those on Vit D3, but in those on Vit D2 there was a gradual increase in $1,25(OH)_2D2$ mirrored by increase in 25(OH)D2

Initial symptoms and diagnosis

- Nonspecific: weakens, fatigue, anorexia, headache, nausea, vomiting, polydipsia, polyuria, confusion, irritability
- In elderly people, the amount of body fat is usually increased and total body fluid is reduced → higher relative distribution volume, longer half-life, increased accumulation, and prolongation of pharmacological effect.

Treatment

- Discontinuation of Vit D, reduction of dietary Ca intake
- IV Hydration, Lasix
- Short course of steroids: reduce intestinal absorption of Ca, increase Ca urinary excretion, change hepatic Vit D metabolism to inactive metabolites. Ca returns to normal over several days. Usual dose 100 mg/d hydrocortisone or equivalent
- Bisphosphonates: the most effective treatment (better studied in children)
- Second-line treatment: phenobarbital, ketoconazole, aminoquinolones

Steroids vs bisphosphonates?

- Case series of 6 patients with VDT, 2 treated with oral steroids, 3 with pamidronate. Both treatments were equally effective in reducing Ca, but the effect was achieved in a shorter period of time with pamidronate (9 vs 22 days after steroids)

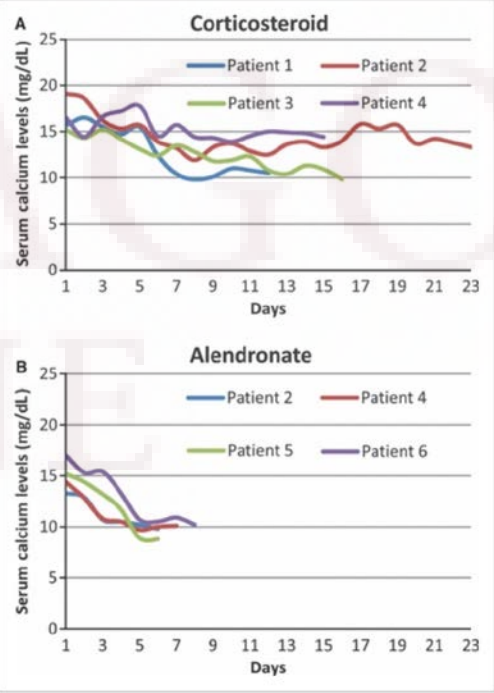
- Case series of 6 children, mean age 8 months, received Vit D3 600,000 IU to 1,500,000 IU.

- Two achieved normocalcemia

7 and 12 days after starting prednisolone,

other two did not despite 23 and 15 days of treatment

Alendronate 3.5 days vs 14.2 prednisolone



Selby et al. Clin Endocrin. 1995
Sezer et al. Acta Pediatrica 2011

Thank you!