Epidemic of Vitamin D Deficiency and Health Hazards

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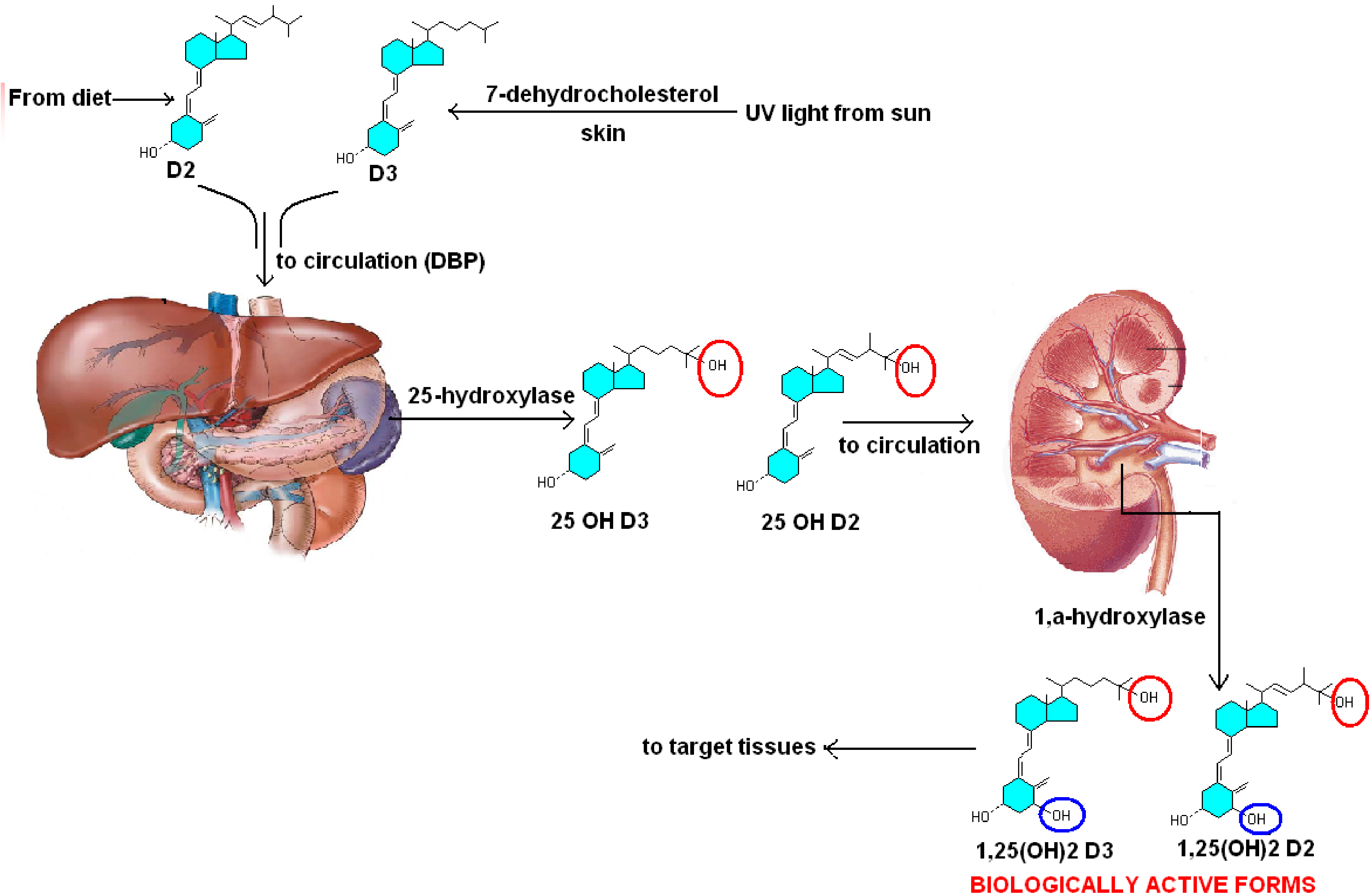
Objectives

- List the main sources of vitamin D
- Describe the endocrine changes associated with vitamin D deficiency
- Know disease risks associated with vitamin D deficiency
- Know how to diagnose and treat vitamin D deficiency

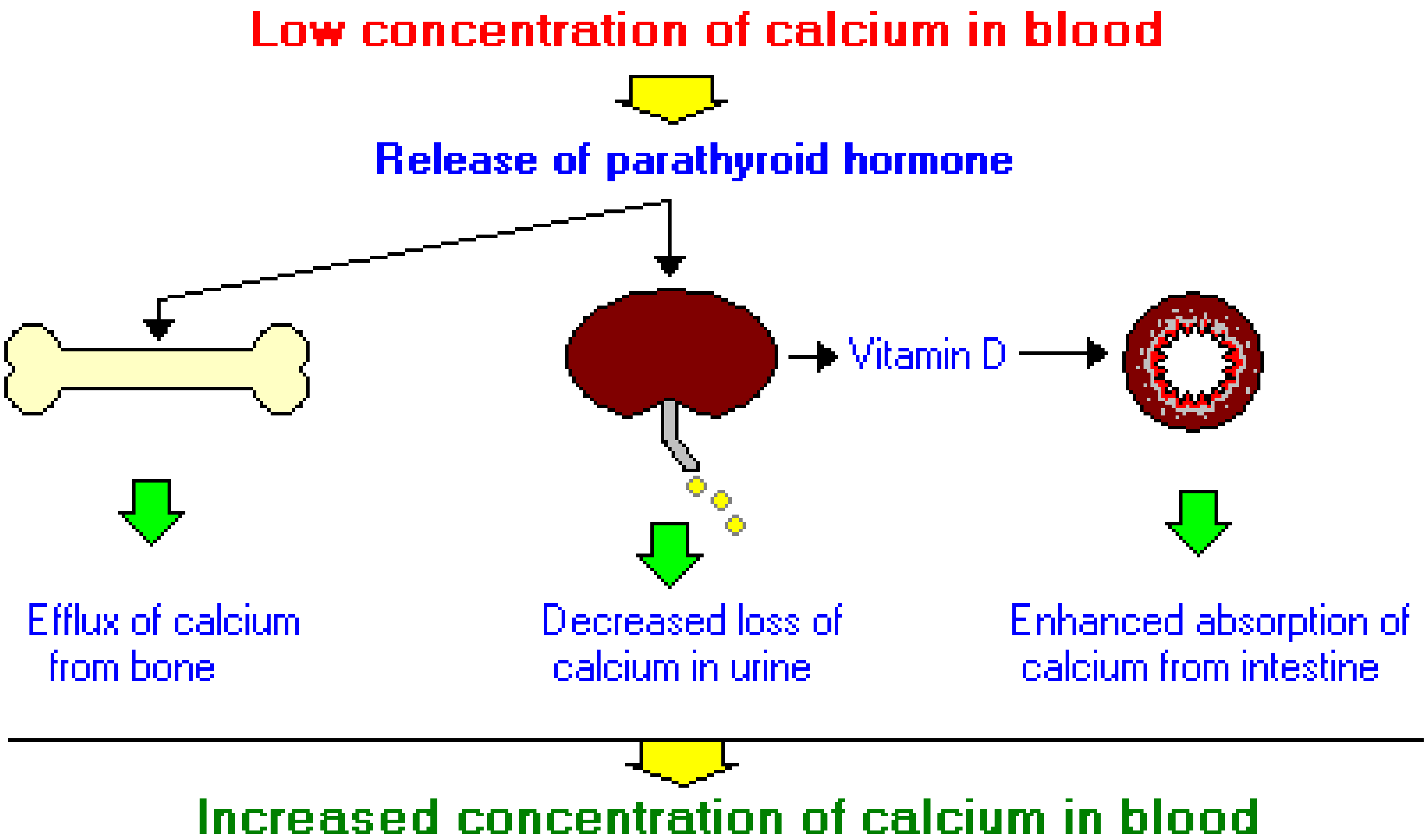
Mechanisms of Calcium Regulation

- PTH
- 1,25 dihydroxy Vit. D
- Calcitonin
- Calcium sensor receptor
- Calcium effects

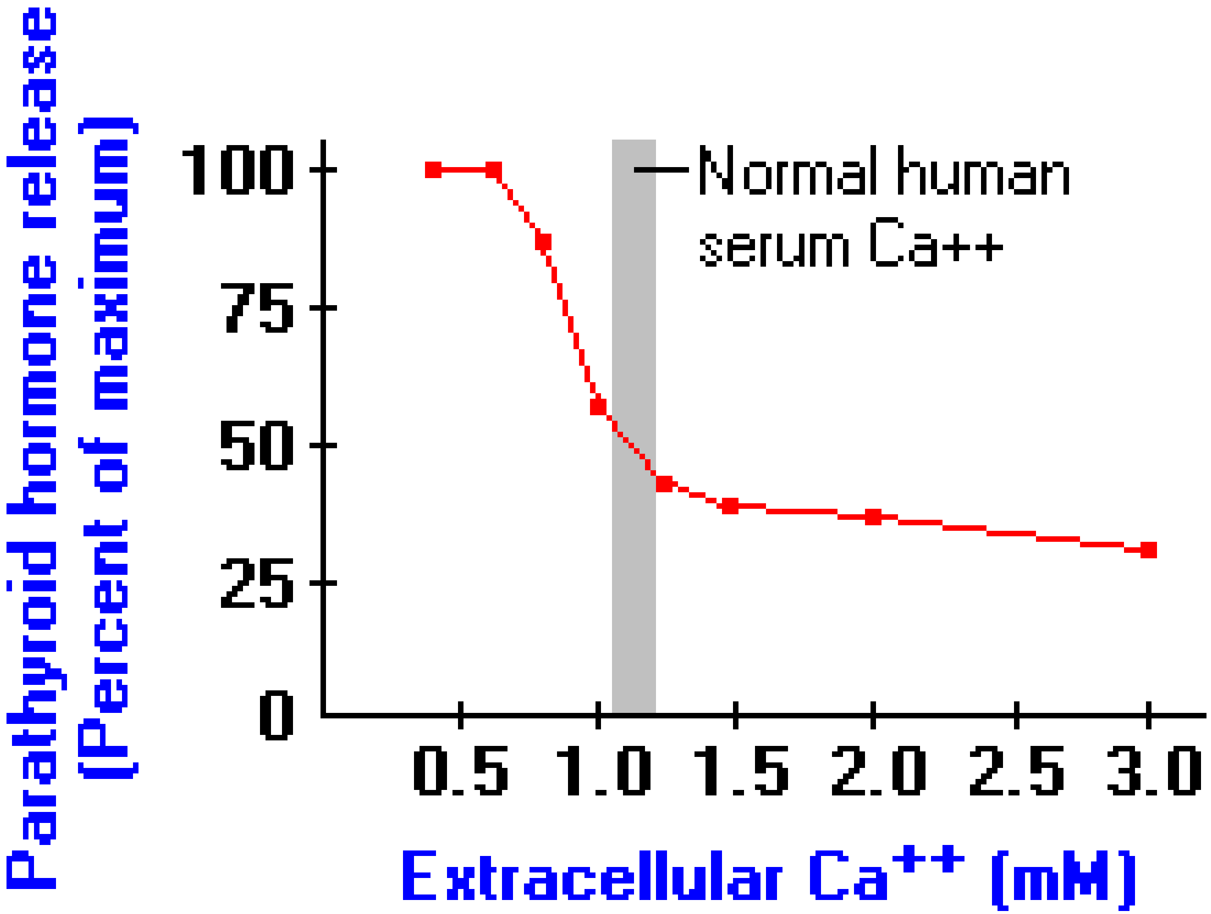
Biological pathway



Control of Serum Calcium



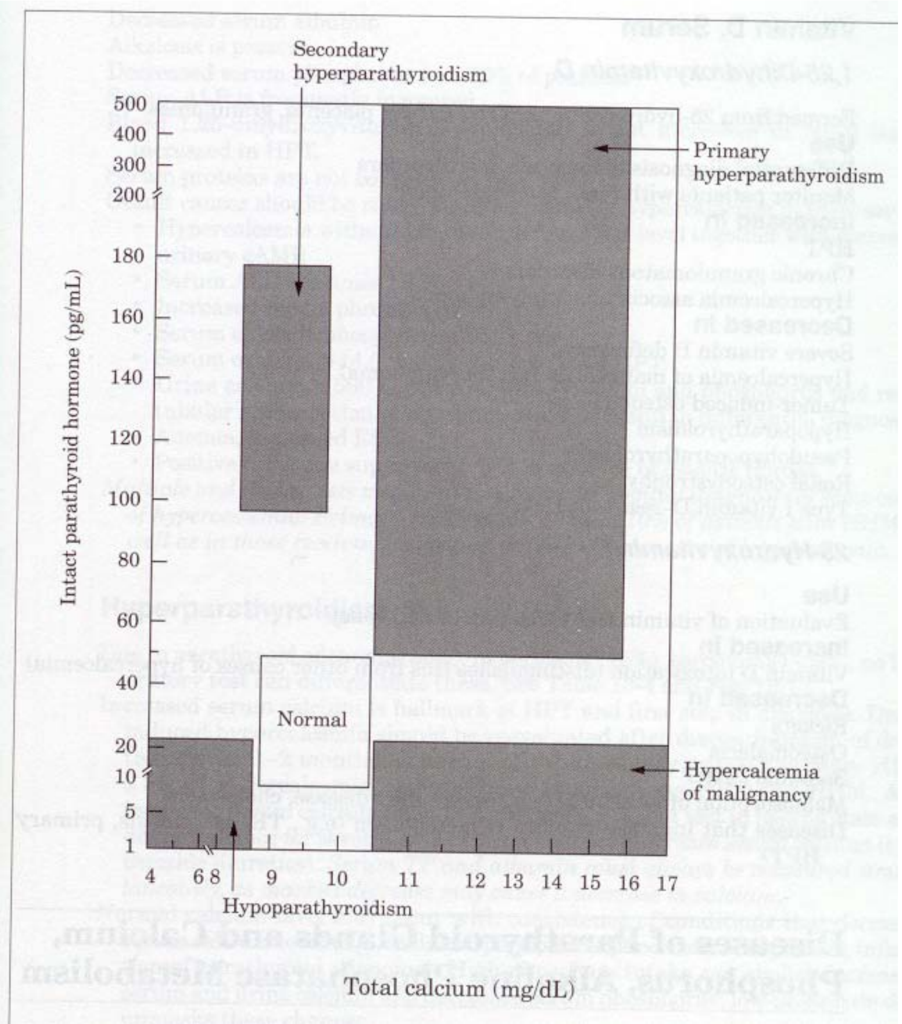
Calcium Regulation of PTH



Main **causes** of hypocalcemia

- 1) loss of calcium from the circulation
- 2) hypoparathyroidism including pseudohypoparathyroidism
- 3) Magnesium deficiency
- 4) vitamin D deficiency.

PTH-Calcium Nomogram



Treatment of Hypocalcemia

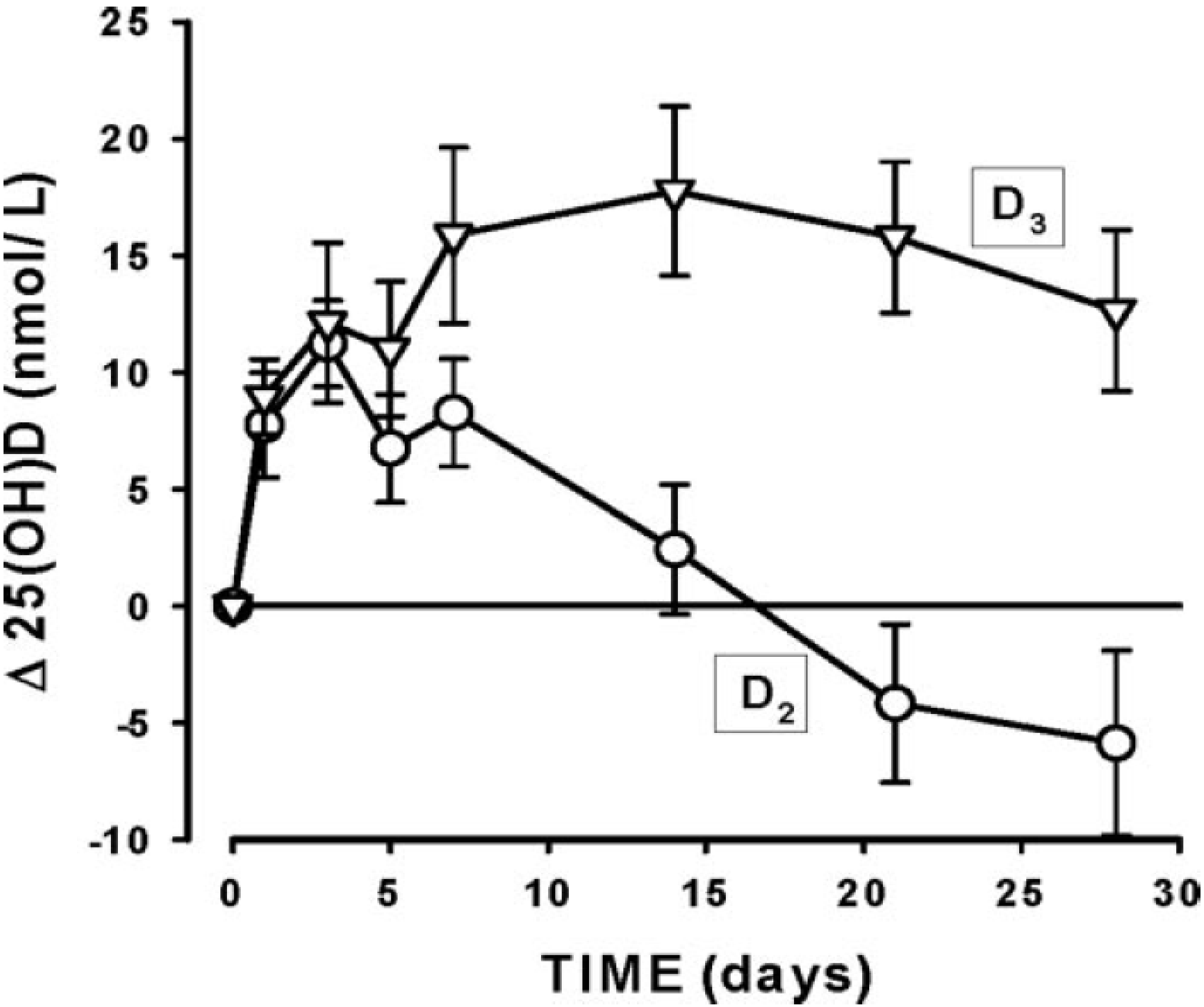
- Hypoparathyroidism, primary or secondary
  - Oral calcium for mild cases plus vitamin D or calcitriol
  - Intravenous calcium if the symptoms are severe
- Vitamin D deficiency
  - Vitamin D plus supplemental calcium
- Magnesium deficiency
  - magnesium

Vitamin D Deficiency Without Hypocalcemia

Secondary Hyperparathyroidism

Osteomalacia

Osteoporosis



Armas et al JCEM 89:5387-91, 2004

25 OH Vitamin D and Vitamin D_3 Dose

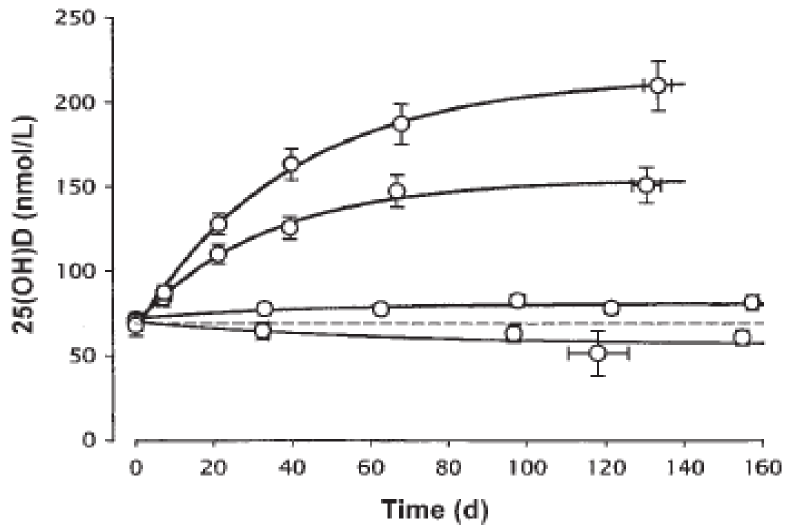


FIGURE 1. Time course of serum 25-hydroxycholecalficerol [25(OH)D] concentration for the 4 dosage groups. The points represent the mean values, and error bars are 1 SEM. The curves are the plot of Equation *1*, fitted to the mean 25(OH)D_3 values for each dosage group. The curves, from the lowest upward, are for 0, 25, 125, and 250 μg cholecalciferol (labeled dose)/d. The horizontal dashed line reflects zero change from baseline.

Heaney et al. Am J Clin Nutr 77:204-10, 2003; Note 40 IU=1ug D_3

Vitamin D production in the skin

- 10000 - 20000 IU maximal daily production
  - i.e. 1 minimal erytheme dose (MED)
  whole body exposition

- provitamin D3 is photolabile and will be converted to vitamin D3 after some time of deposition in the skin

Minimal Erytheme Dose (MED)

- Amount of UVB that produces redness 24 hours after exposure
- Learn your MED to avoid Sunburns

UV-induced Vitamin D

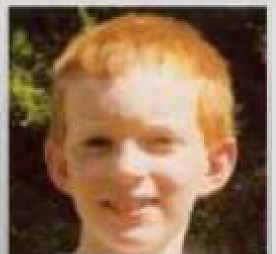
- 90-95% of vitamin D demand is fullfilled by UVB-radiation
- the daily demand is about 1000 IU
- i.e. 25% wholebody exposition with ¼ MED (minimal erytheme dose)

Prudent Use of Sunlight

- sunexposition of 18% body surface with 1/3 - 1/2 MED 2-3 x per week from spring to autumn at high noon according to the skin type for 5-20 min
  - face and arms
  - or lower arms and lower legs
- whole body exposition 1/4 MED (2-5 min)
- UVB therapy in medical light cabin 1 x per week with 1/2 MED

Variable Skin Characteristics

Skin Type I (2%)



- Red/red-blond hair, freckles
- Always sunburned, no tanning of the skin
- 5-10 minutes to develop erythema

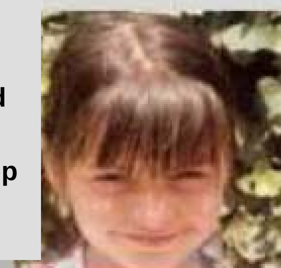
Skin Type II (12%)

- Blond, fair/light colored eyes
- Often sunburned, weak tanning of the skin
- 10-20 minutes to develop erythema

Skin Type III (78%)

- Brunette, light or dark eye color
- Rarely sunburned, good skin pigmentation
- 20-30 minutes to develop erythema

Skin Type IV (8%)



- Dark hair, Mediterranean type
- Never sunburned, dark tan
- Approximately 45 minutes to develop erythema

Optimal and Normal Vitamin D-25OH Concentrations

Optimal 25-hydroxyvitamin D values are: **30-60 ng/mL** **Toxicity >100 ng/mL**	**25-hydroxyvitamin D lab values are:** Insufficiency **20-30 ng/mL** Deficiency <20 ng/mL

Measurement Total Vitamin D 25 OH

- Vitamin D3 25 OH animal sources
- Vitamin D2 25 OH Plant sources
- Mass Spec can measure both forms and provide a total value
- RIA can measure total from both sources
- No known advantage to measure both forms

1,25 DihydroxyVitamin D or Calcitriol

- Circulating Mainly made in the kidney
- Stimulated by PTH and hypophosphatasemia
- Renal failure and PTH deficiency can cause a deficiency and hypocalcemia
- Used to diagnose hypercalcemia
- Monitor therapy of renal failure

Extrarenal Synthesis of Vitamin D $1{,}25\ (OH)_2\ D_3$

- Autonomous production $1{,}25\ (OH)_2\ D_3$
- Colon
- Prostate
- Mammary gland
- Many other tissues

Lechner et al. Molecular and Cellular Endocrinology 263: 55-64, 2006

How is the optimal serum concentration of Vitamin D 25 OH Determined?

Relationship between PTH and Serum Vitamin 25(OH)D

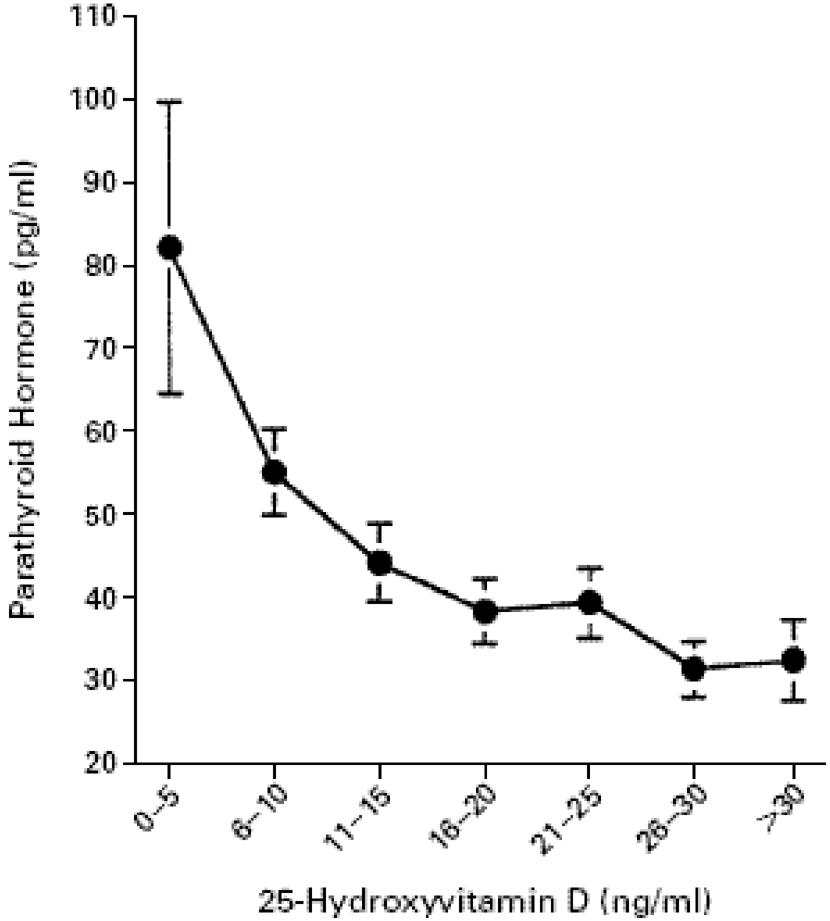


Figure 2. Relation between Serum 25-Hydroxyvitamin D Concentrations and Mean (±SE) Serum Concentrations of Parathyroid Hormone in the Study Patients.

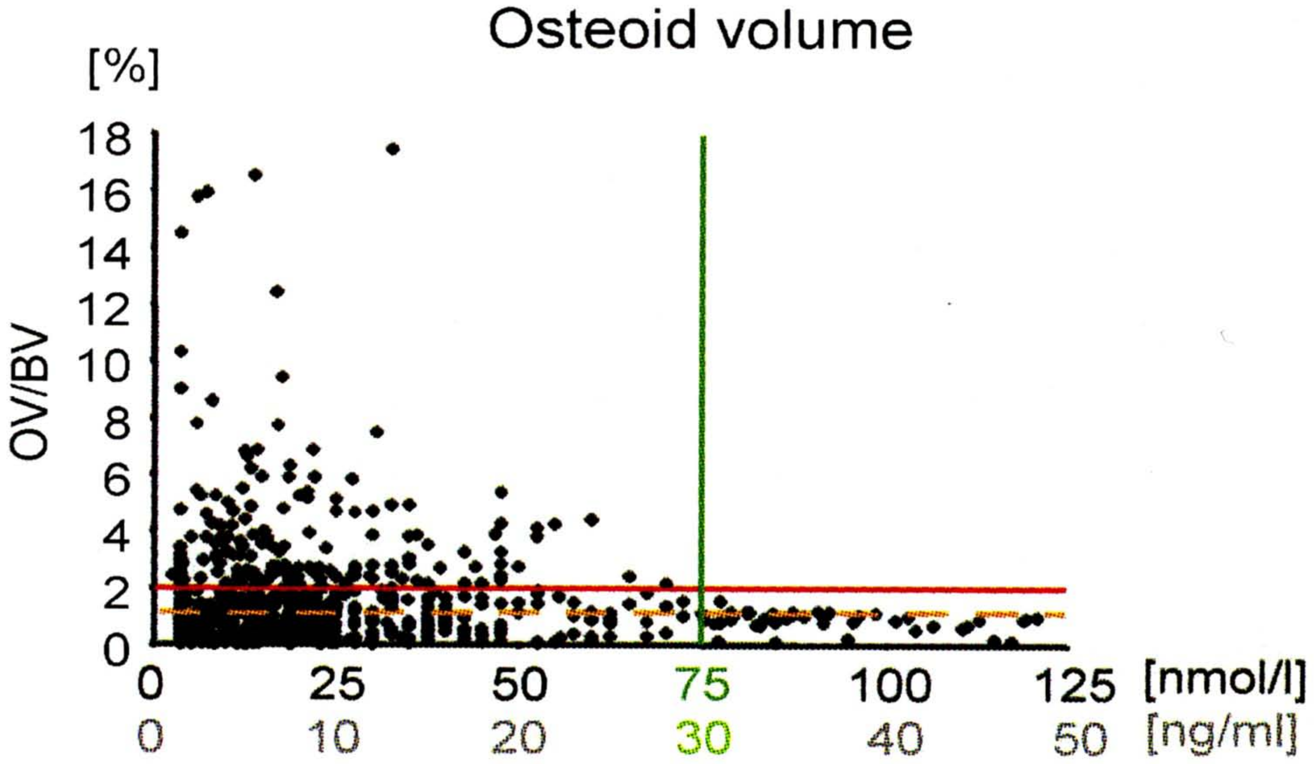
Thomas, NEJM, 338:777-83

Vitamin D Concentration and Calcium Absorption

- Postmenopausal women
- Increase vitamin D 25 OH from 20 ng/ml to 32 ng/ml increased intestinal calcium absorption 65%.
- This led to defining vitamin D insufficiency as a 25(OH)D concentration of 21–29 ng/ml

Heaney et al J Am Coll Nutr. 22:142-6, 2003

Vitamin D 25OH and Osteoid



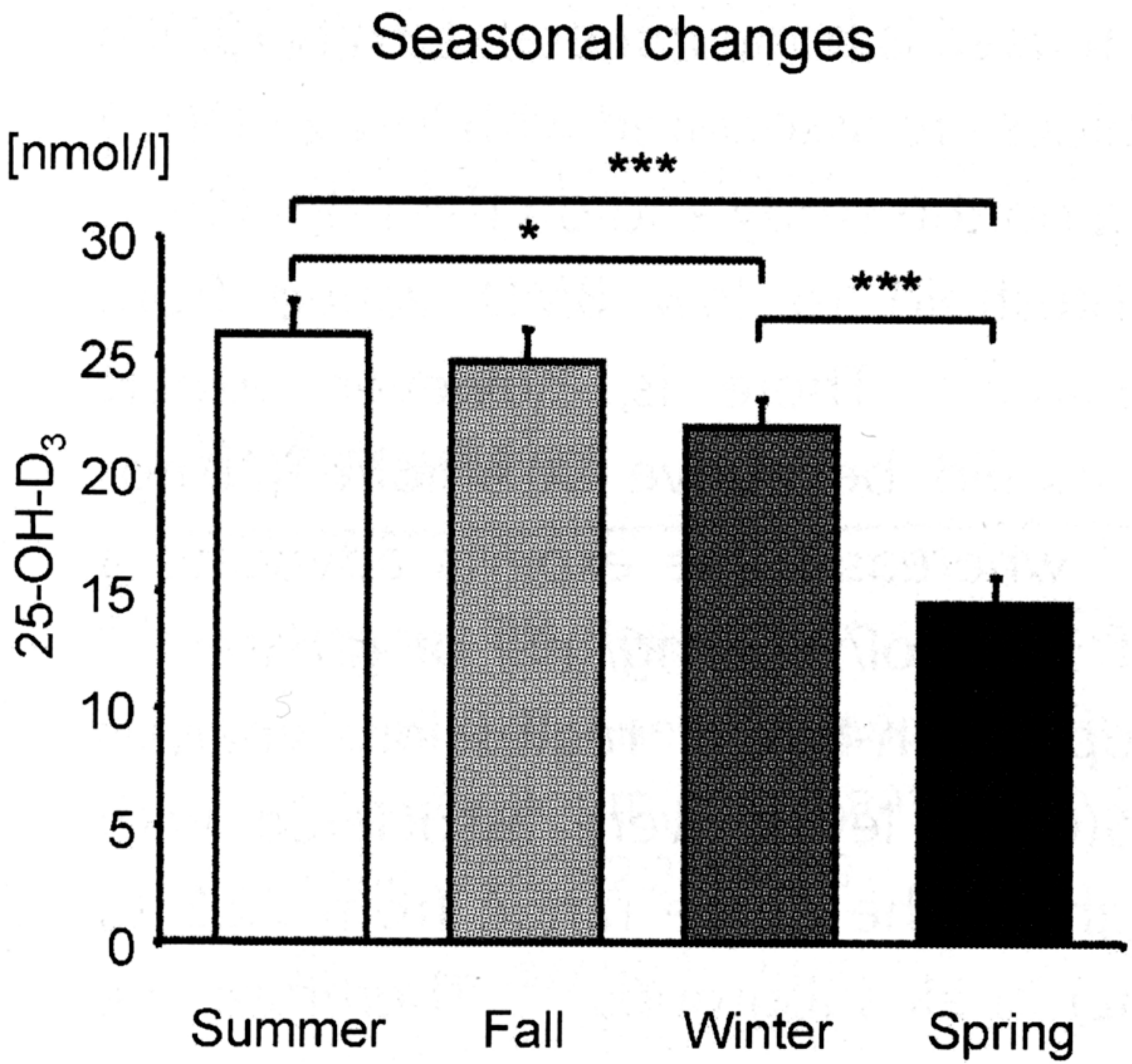
Priemel et al. JBMR 25: 305-12, 2010

How Frequent is Vitamin D Deficiency?

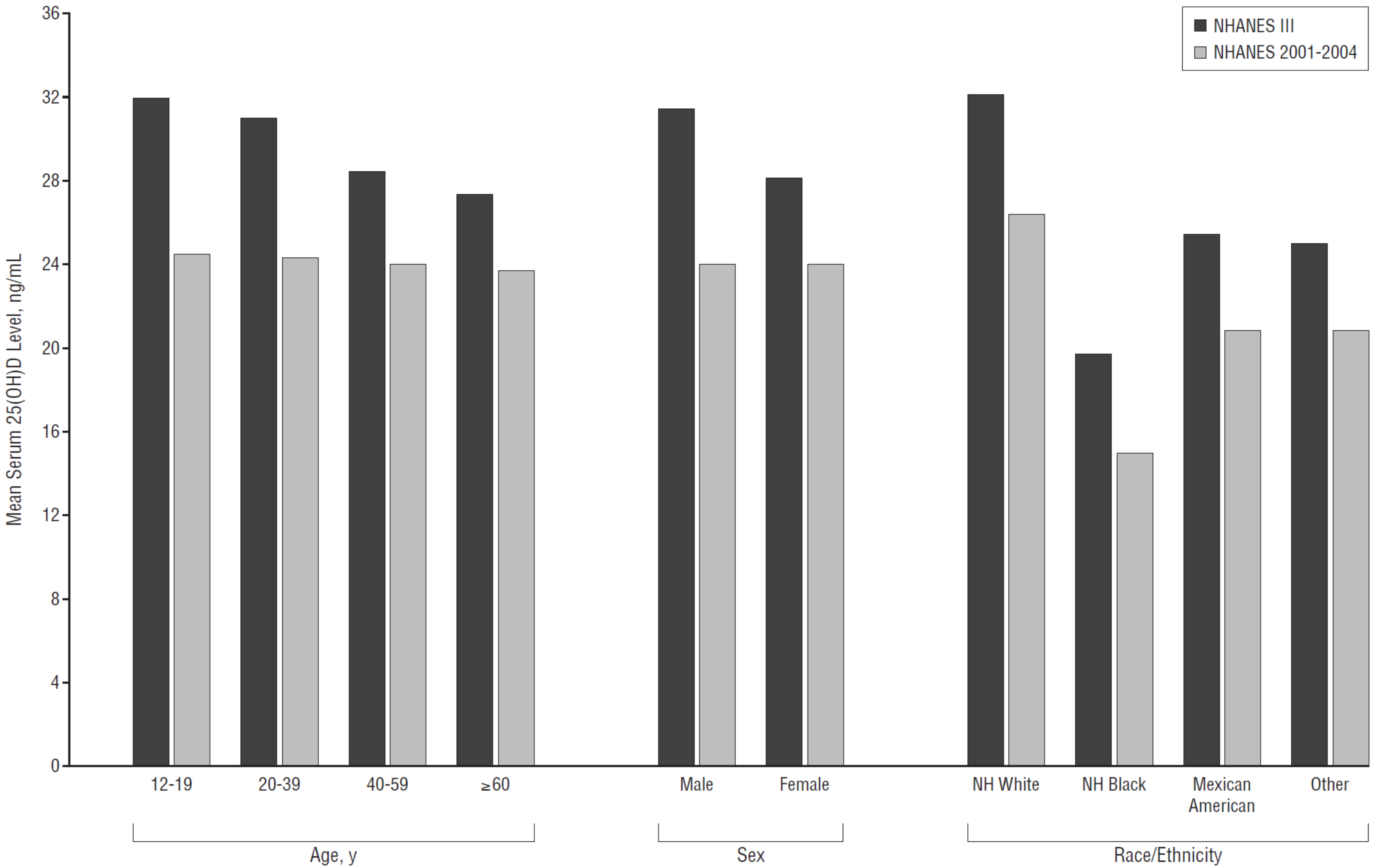
- About 58% of assays for Vitamin D 25 OH at ARUP in 2008 and 2009 were less than 30 ng/mL
- ng/mL=2.5 nMol/L

Vitamin D 25OH

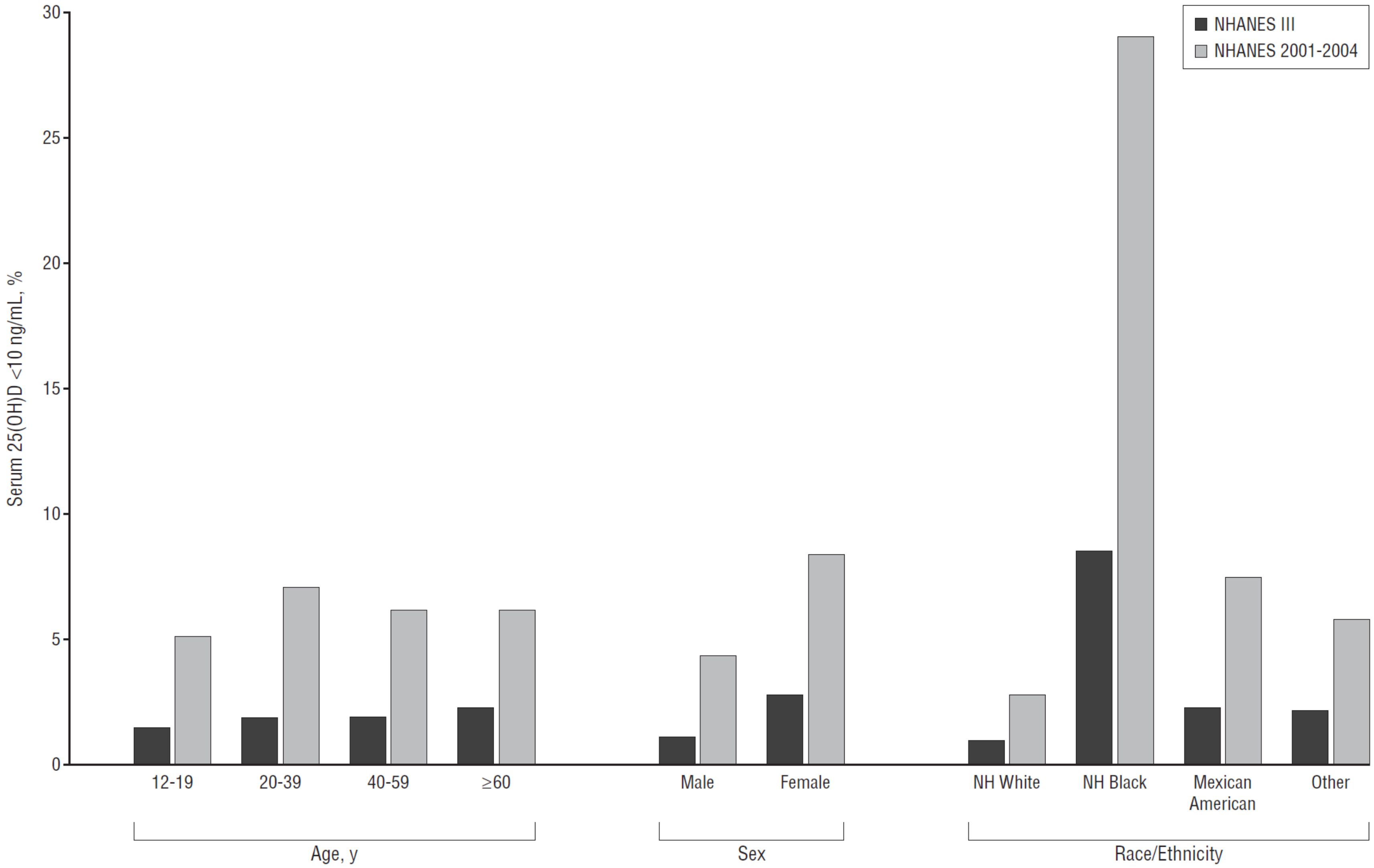
Total Vitamin D 25 Numbers 7-27 to 8-27				
Total #	<10 ng/mL	10-19 ng/mL	20-29 ng/mL	30+ ng/mL
143685	1656	10432	49363	66766
	1.2%	7.3%	34.4%	46.5%



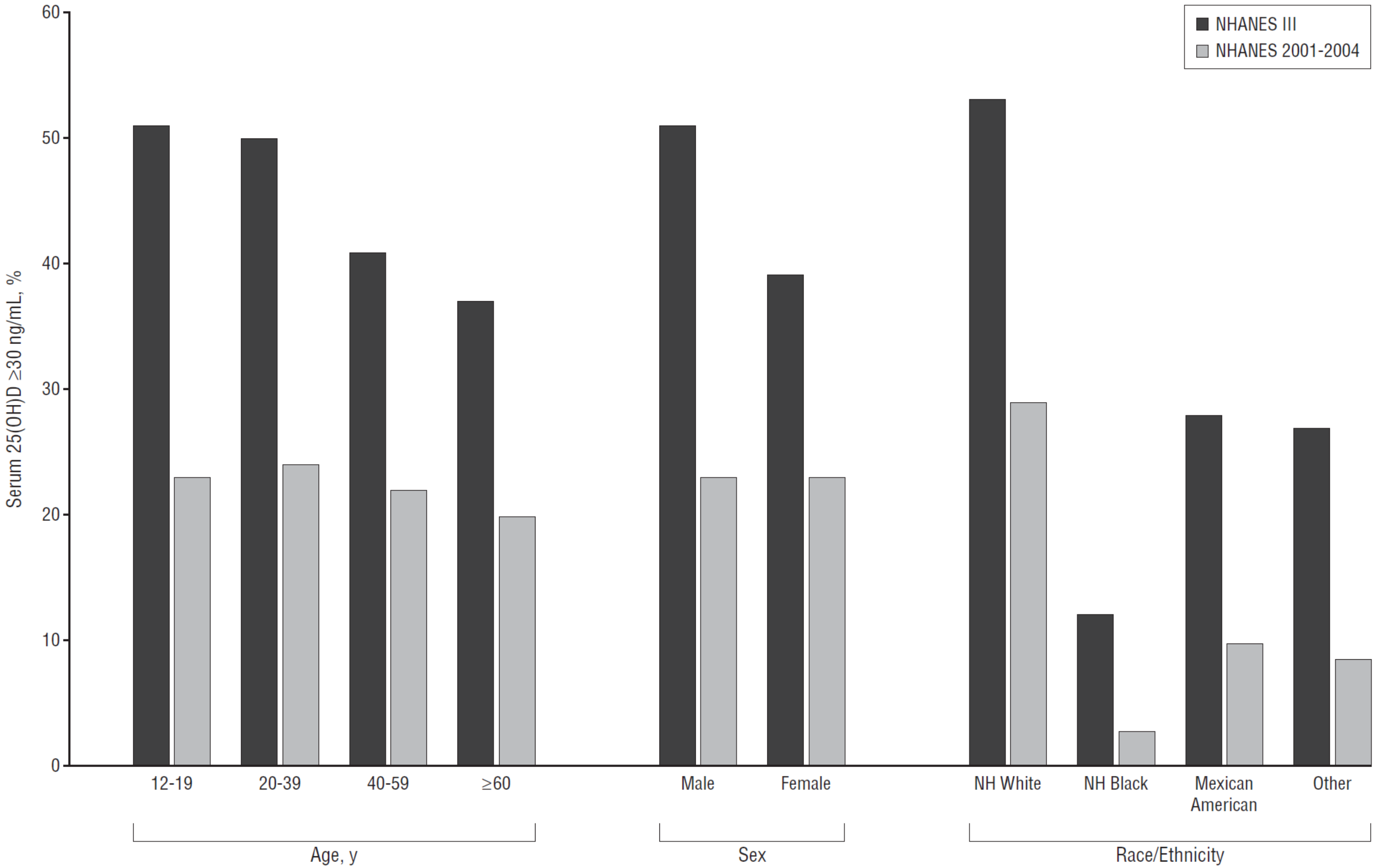
Priemel et al. JBMR 25: 305-12, 2010



Ginde et al Arch Intern Med 169:626-32, 2009



Ginde et al Arch Intern Med 169:626-32, 2009



Ginde et al Arch Intern Med 169:626-32, 2009

Watching Television

- >4 hours daily 38% Vitamin D <15 ng/mL
- No TV 2% Vitamin D < 15 ng/mL

Vitamin D Transport Blood

- Vitamin D binding protein (DBP)-4-8 mM
  - 85-88%, only about 2% saturated
  - 25OH, Ka=5x108M
  - 1,25(OH)2D, Ka=4x107M
- Albumin
  - 12-15%
- Free Vitamin D
  - 25OHD-0.03%
  - 1,25(OH)2D-0.4%

Why has Vitamin D Deficiency Increased?

Sun Exposure

- UV triggers Vitamin D synthesis
- Influenced by
  - Season
  - Geographic latitude
  - Time of day
  - Cloud cover-reduces 50%
  - Smog
  - Sunscreen-SPF 8 or > blocks vitamin D
  - Sunlight-10-15 minutes adequate time for vitamin D synthesis

Hypovitaminosis D

Causes of Vitamin D deficiency

- Dietay
- Sunscreen
- Limited sun exposure
- Malabsorption
- Decreased 25 hydroxylation in the liver
- Kidney can’t convert Vitamin D 25 to 1, 25 dihydroxyvitamin D

Who needs supplemental Vitamin D

- Breast feed infants
- Older adults
- Persons with limited sun exposure
- Darker skin people
- Persons with fat malabsorption
- Anticonvulsants

Vitamin D

- Osteoporosis-silent contributor
- Cancer protection-colon, prostate
- Corticosteroids-decrease vitamin D absorption
- Caffeine-may decrease Vitamin D absorption

Food Sources of Vitamin D

- Milk fortified with Vitamin D, 400 IU/Qt
- One cup supplies
  - 50% recommended for adults 19-50 yrs
  - 25% for 51-70 yrs
  - 15% for 71 and older
- Cheese and Ice cream are not fortified

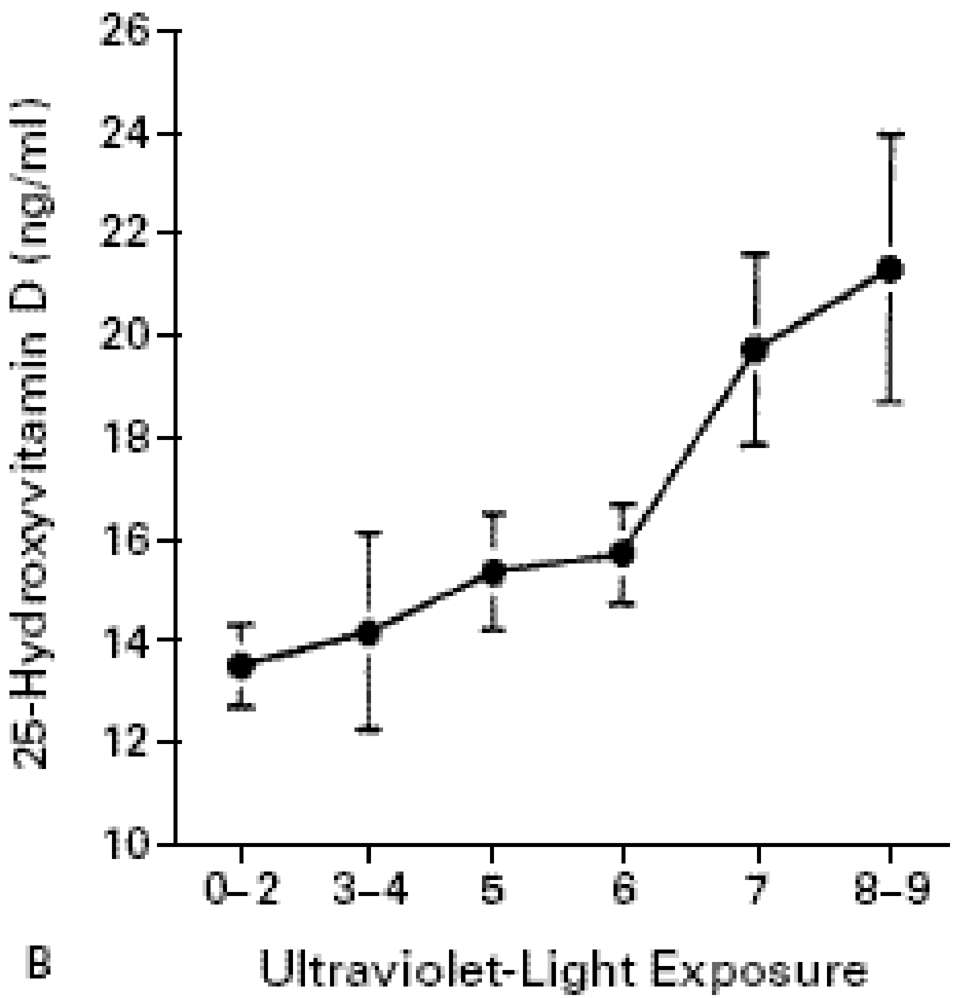
Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D_2 and D_3.*

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 erythemal 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

Holick NEJM 357:266-281, 2007

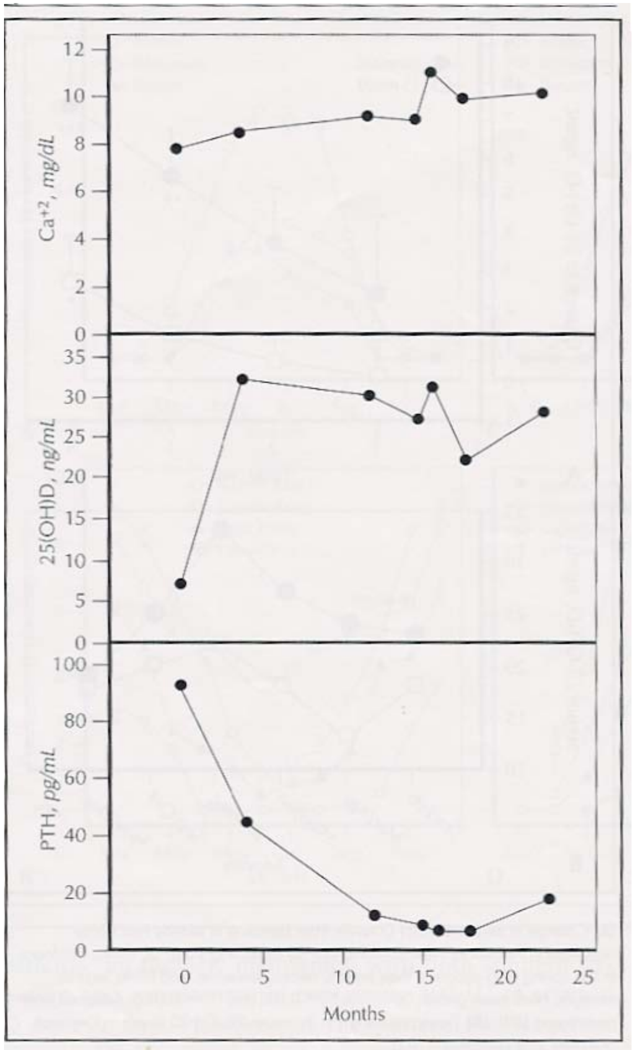
Sun Exposure Scale and Serum 25(OH)D



Thomas, NEJM, 338:777-83

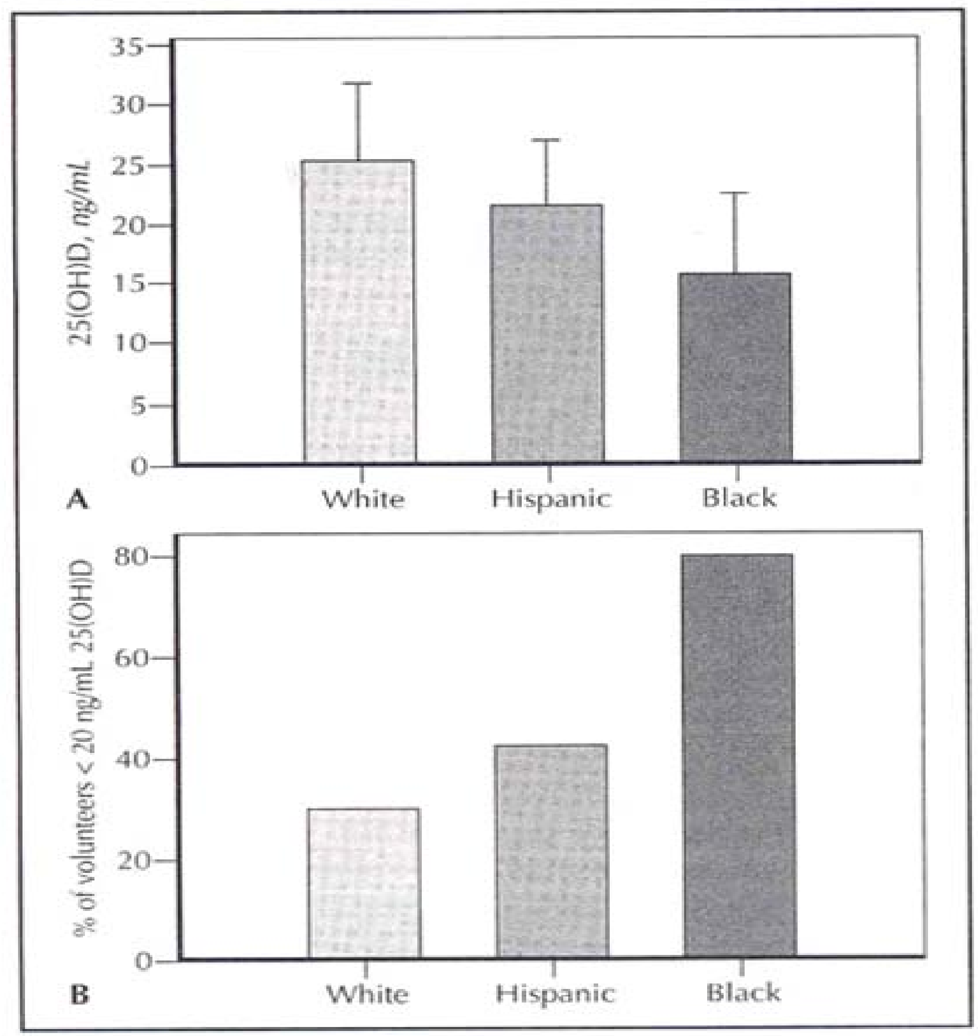
Tanning Bed Effects on 25(OH)D, Calcium and PTH

10 min. 3 times/week for 6 months



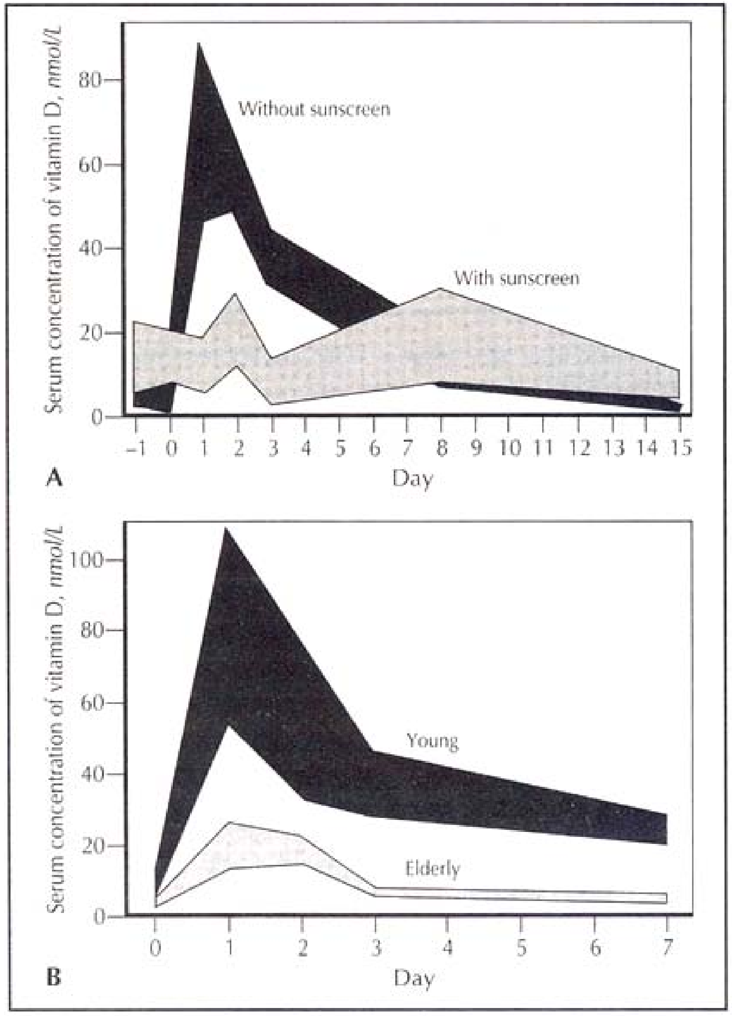
Holick Curr. Opin.Endo Diab. 9:87-98, 2002

Serum 25(OH)D Seniors Boston in August



Holick Curr. Opin.Endo Diab. 9:87-98, 2002

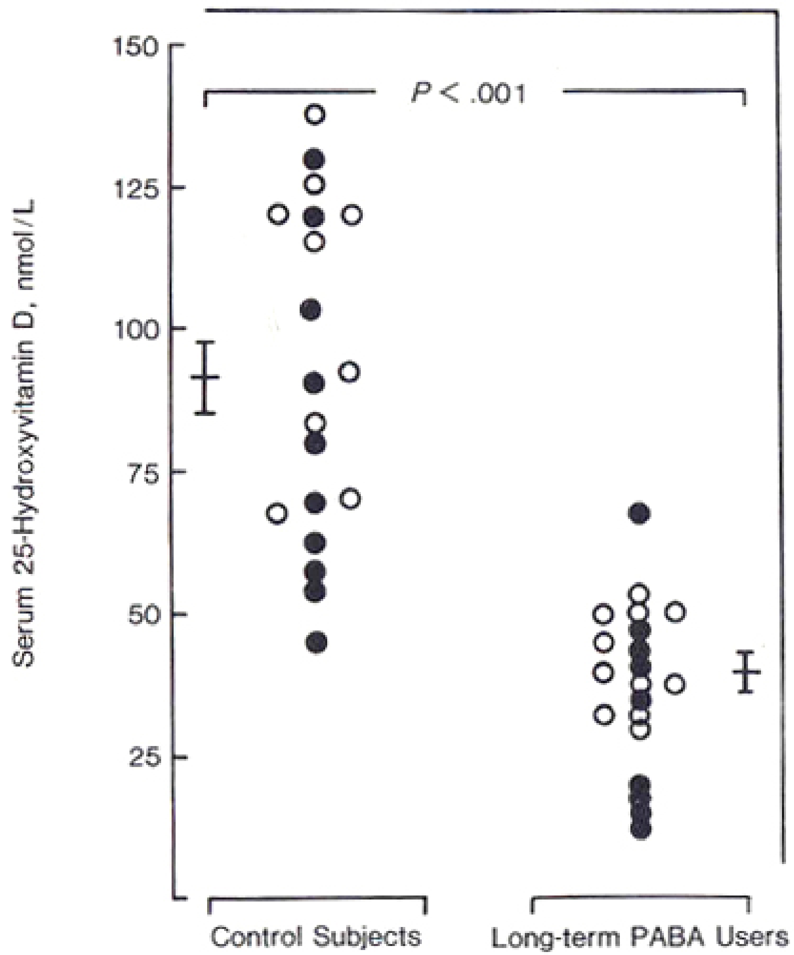
Effect of Sunscreen and Aging on Serum 25(OH)D



Holick Curr. Opin.Endo Diab. 9:87-98, 2002

Serum 25(OH)D in Long-term Sunscreen Users

Matsuoka, Arch Derm 124:1802-04, 1988



What are the health consequences of Vitamin D deficiency?

Vitamin D deficiency Studies in Mice

Mimics Deficiency in Humans and Health Risks

Vitamin D Receptor (VDR) Null Mice

- VRD or vitamin D deficiency
- Immune system is grossly normal
- Increased sensitivity to autoimmune diseases, such as inflammatory bowel disease or type I diabetes after exposure to predisposing factors
- More prone to oncogene or chemocarcinogen-induced tumors

Vitamin D Receptor (VDR) Null Mice

- Increased
  - High renin hypertension
  - Cardiac hypertrophy
  - Thrombogenicity
  - Increased prevalence of diseases in humans

Vitamin D and the Endocrine System

- Fertility decreased in males and females
- Reduced sperm number and motility
- Increased LH and FSH
- Hypergonadotropic hypogonadism
- These are from studies in mice and human studies need to be done.

Health Consequences of Vitamin D Deficiency in humans

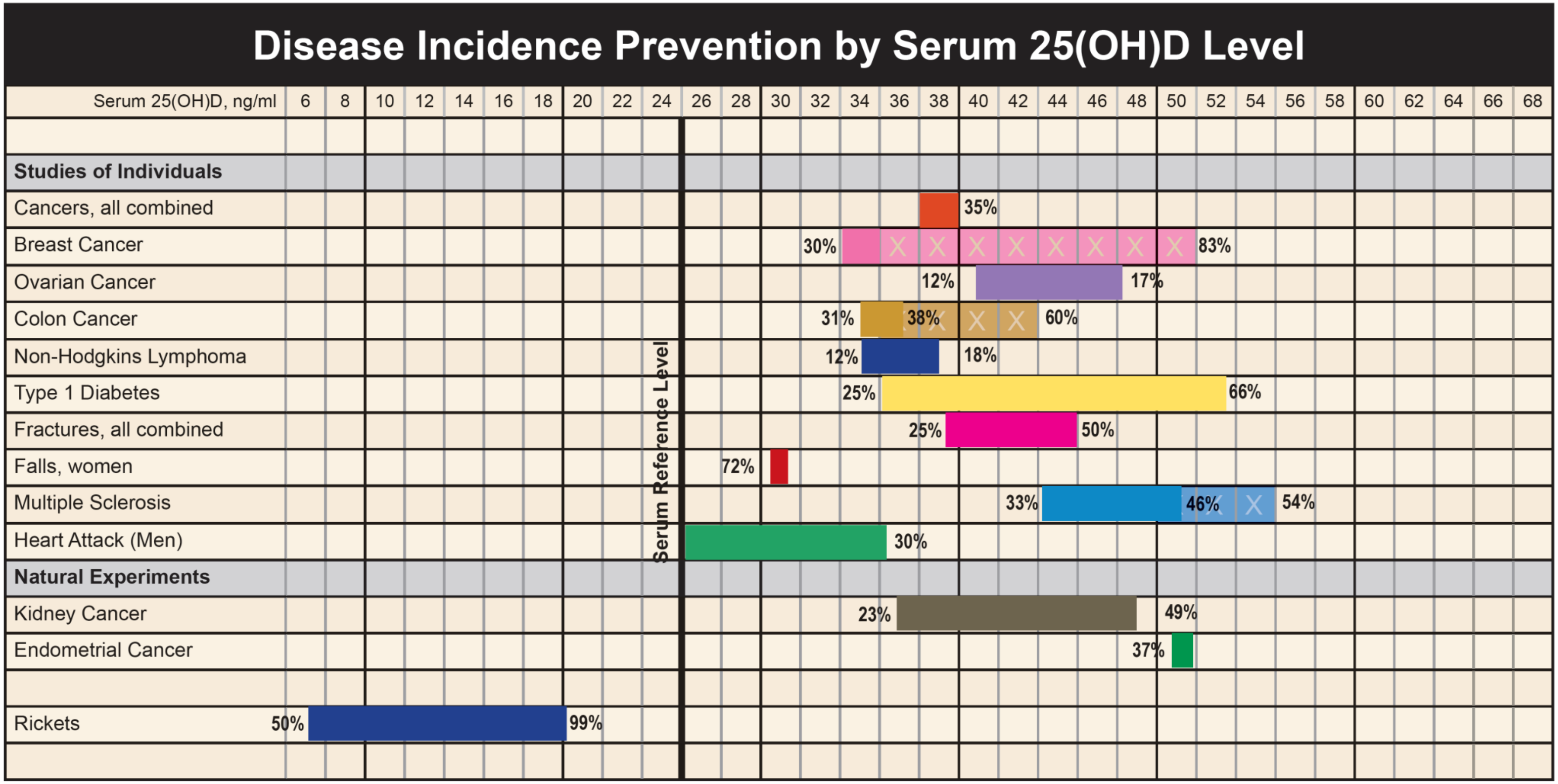


Chart prepared by: Garland CF, Baggerly CA

Age-, Sex- and Race-adjusted Prevalence and ORs of Select CV Disease Risk Factors between the First and Fourth Quartiles of Serum 25(OH)D Levels

Risk factor	Prevalence of CV risk factor: 1st quartile (< 21 ng/ml)	Prevalence of CV risk factor: 4th quartile (≥ 37 ng/ml)	OR	P value
Hypertension	20.46	15.10	1.30	0.001
Diabetes	6.85	3.38	1.98	< 0.001
Obesity	24.69	11.50	2.29	< 0.001
Triglyceride level ≥ 150 mg/dl	32.86	23.84	1.47	< 0.001
ACR ≥ 200 for males / ≥ 300 for females	1.59	0.76	2.54	< 0.001

1991 Mo

Martins D et al., Arch Intern Med 2007; 167: 1159-1165

Obesity and Vitamin D 25 OH Insufficiency

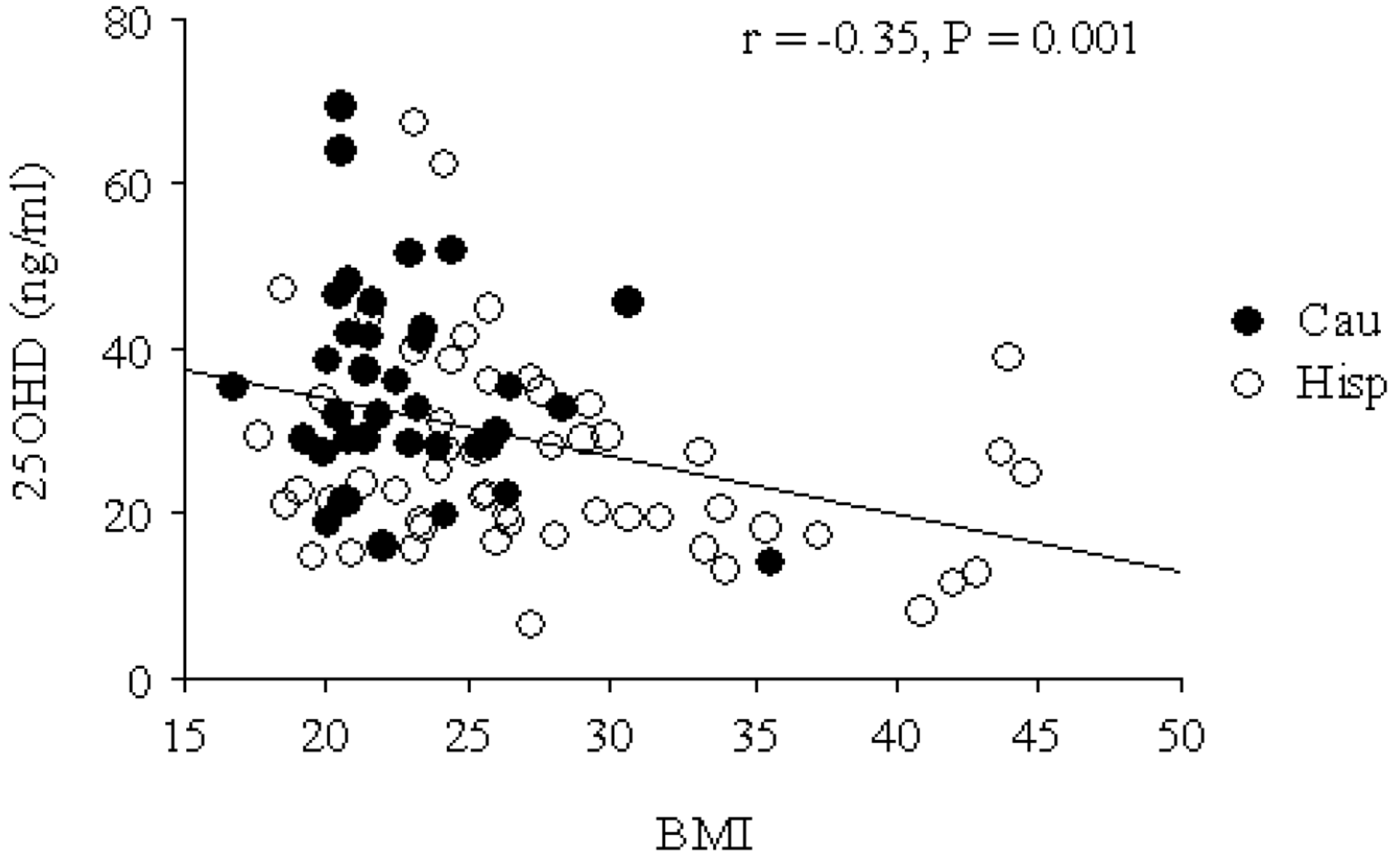
- Common
- Is the vitamin D insufficiency of obesity causally related to health hazards?
- Diabetes
- Cardiovascular disease
- Cancer
- Gonadal dysfunction

Table 2.
25OHD concentrations (ng/ml) of 90 women separated by ethnicity and body mass

	25OHD (ng/ml)		
	All (n = 90)	Hispanic (n = 53)	Caucasian (n = 37)
All BMI (n = 90)	30.1 ± 13.0 (6.7 – 69.6)	26.6 ± 12.3†‡ (6.7 – 67.3)	35.1 ± 12.4 (14.2 – 69.6)
Lean (BMI < 25) (n = 51)	34.3 ± 13.8* (15.2 – 69.6)	31.2 ± 14.6 (15.2 – 67.3)	36.6 ± 12.9 (16.1 – 69.6)
Overweight (BMI ≥ 25) (n = 39)	24.6 ± 9.5 (6.7 – 46.0)	23.3 ± 9.3 (6.7 – 44.9)	29.7 ± 9.3 (14.2 – 46.0)

Values are expressed as mean ± SD and (range).
*Indicates a significant difference between lean and overweight subjects (P <0.001)
† Indicates a significant difference between Hispanics and Caucasians (P = 0.002)
‡ ANOVA analysis indicates no statistical difference between Hispanics and Caucasians when adjusted for BMI (P = 0.09)

Kremer et al JCEM 93, 2008



Kremer et al JCEM 93, 2008

Vitamin D Concentrations and Cancer Risk

- Inverse association between vitamin D 25 OH and colorectal cancers
- Mixed results with association of Vitamin D 25 OH and prostate and breast cancer

Vitamin D and the Immune System

- Vitamin D deficiency associated with
  - Increased susceptibility to infections
  - Autoimmune disease such as type I diabetes

Vitamin D and the Endocrine System

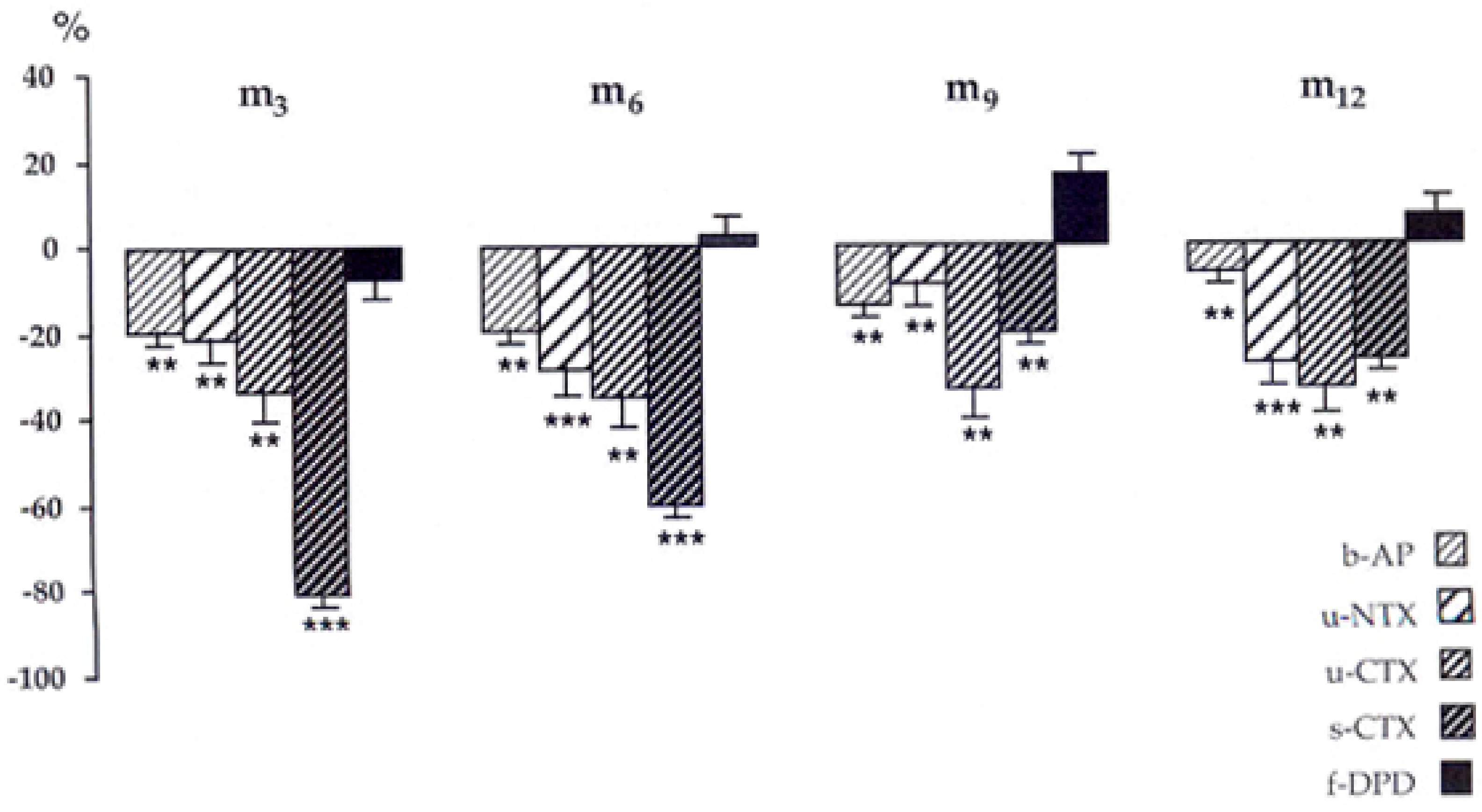
- Vitamin D deficiency
- Impairs
  - Insulin secretion
  - Glucose tolerance
- Increases risk of metabolic syndrome
- Increases cardiovascular risk
- Decreased muscle mass, strength and predisposition to falls in the elderly

Vitamin D and Type 2 Diabetes

- Vitamin D 25OH score and T2D
- Framingham Study-133 T2D cases over 7 years
- Highest quartile vitamin D score compared to lowest quartile at baseline had 40% lower incidence of T2D
- Adjusted for age, sex, waist circumference, prenatal history of T2D, hypertension, low HDL, cholesterol, elevated triglycerides, impaired fasting glucose, and dietary guidelines

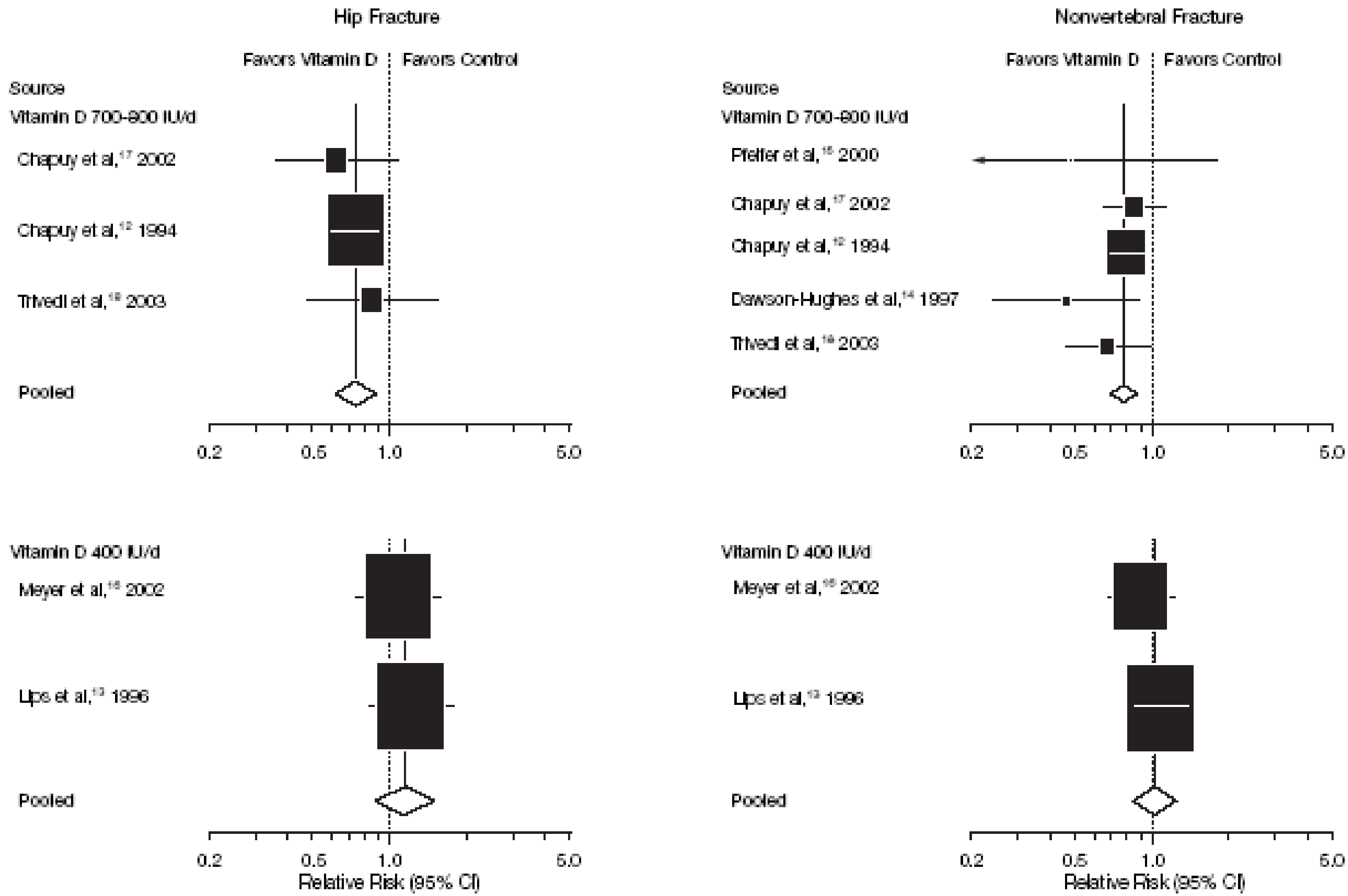
Lin et al, Am J Clin Nutr, 2010

Vitamin D-Calcium Effect on Bone Remodeling Markers



Grados, JCEM 88:5175-79, 2003

Figure 2. Forest Plots Comparing the Risk of Hip and Nonvertebral Fractures Between Vitamin D (700-800 IU/d and 400 IU/d) and Control Groups



Bischoff-Ferrari JAMA 293:2257, 2005

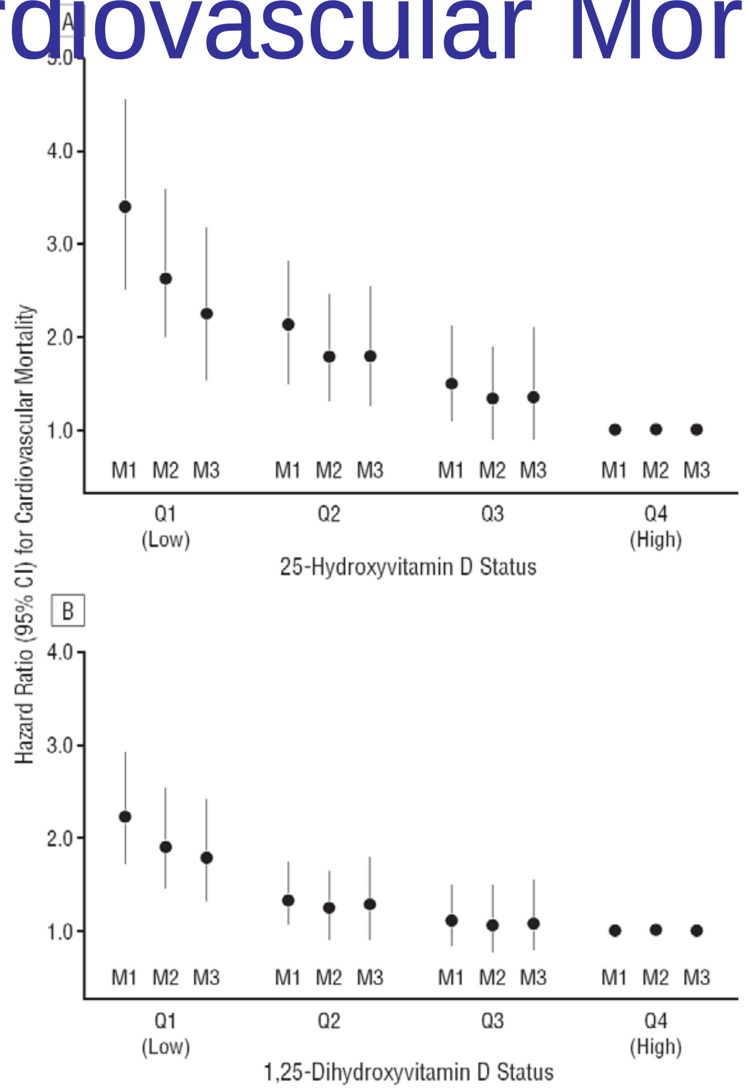
Myocardial Infarction Risk and Vitamin D 25 OH

Table 3. Estimated RRs of MI by Level of 25(OH)D at Baseline During 10 Years of Follow-up

	Plasma 25(OH)D, ng/mL				
Variable	**≤15.0**	**15.1-22.5**	**22.6-29.9**	**≥30.0**	***P* Value (Trend)**
Cases/controls, No.	63/87	156/307	165/299	70/207	NA
RR (95% CI)					
Matching variables	2.42 (1.53-3.84)	1.65 (1.15-2.37)	1.72 (1.22-2.42)	1 [Reference]	<.001
MV1[a]	2.01 (1.22-3.30)	1.45 (0.99-2.12)	1.56 (1.09-2.22)	1 [Reference]	.02
MV2[b]	2.09 (1.24-3.54)	1.43 (0.96-2.13)	1.60 (1.10-2.32)	1 [Reference]	.02

Giovannucci E et al Arch Intern Med 168:1174-1180, 2008

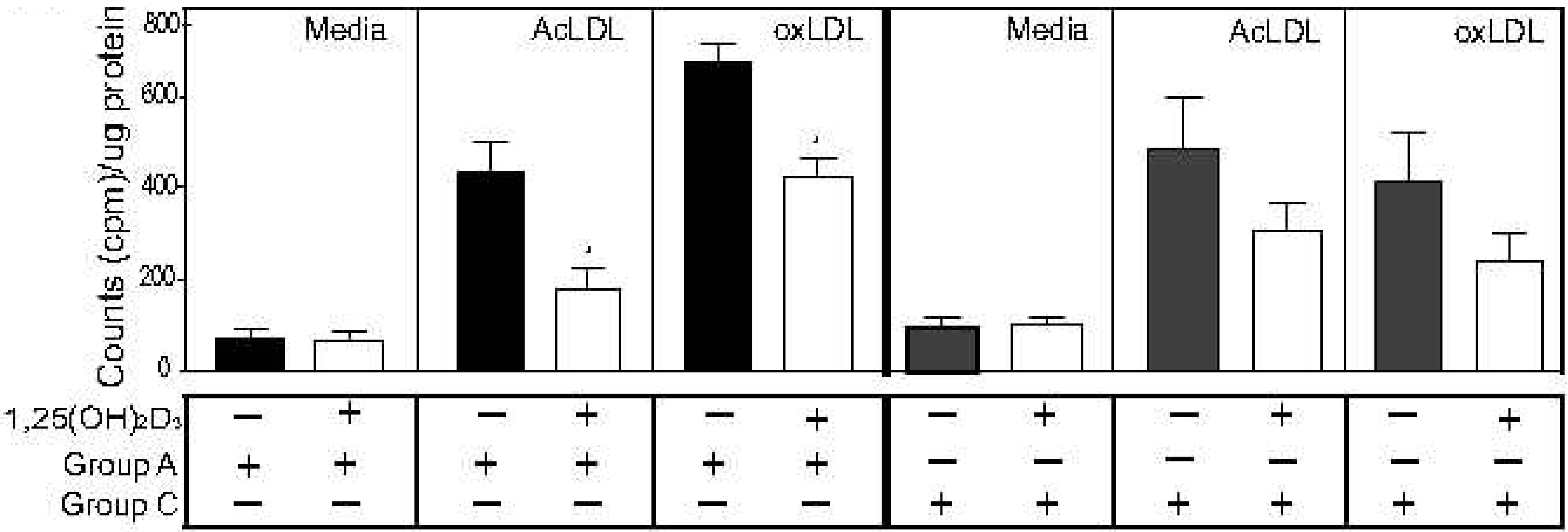
Hazard Ratio (95% CI) Cardiovascular Mortality



Dobmig H et al Arch Intern Med 168: 1340-1349, 2008

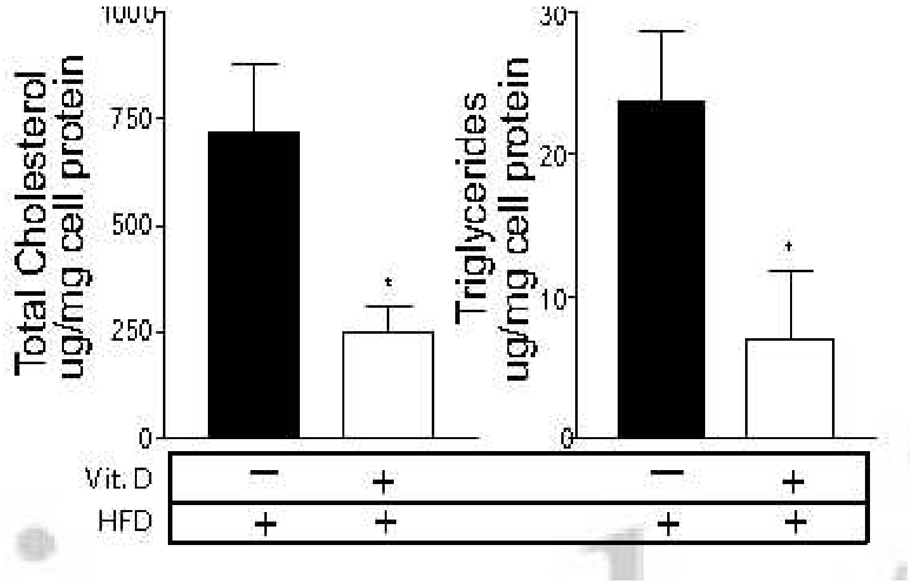
Potential Mechanisms of Vitamin D Health Protection

Effect of Vitamin D, 1, 25 (OH)2 on Foam Cells in Diabetic



Oh et al Circulation 120:687-698, 2009

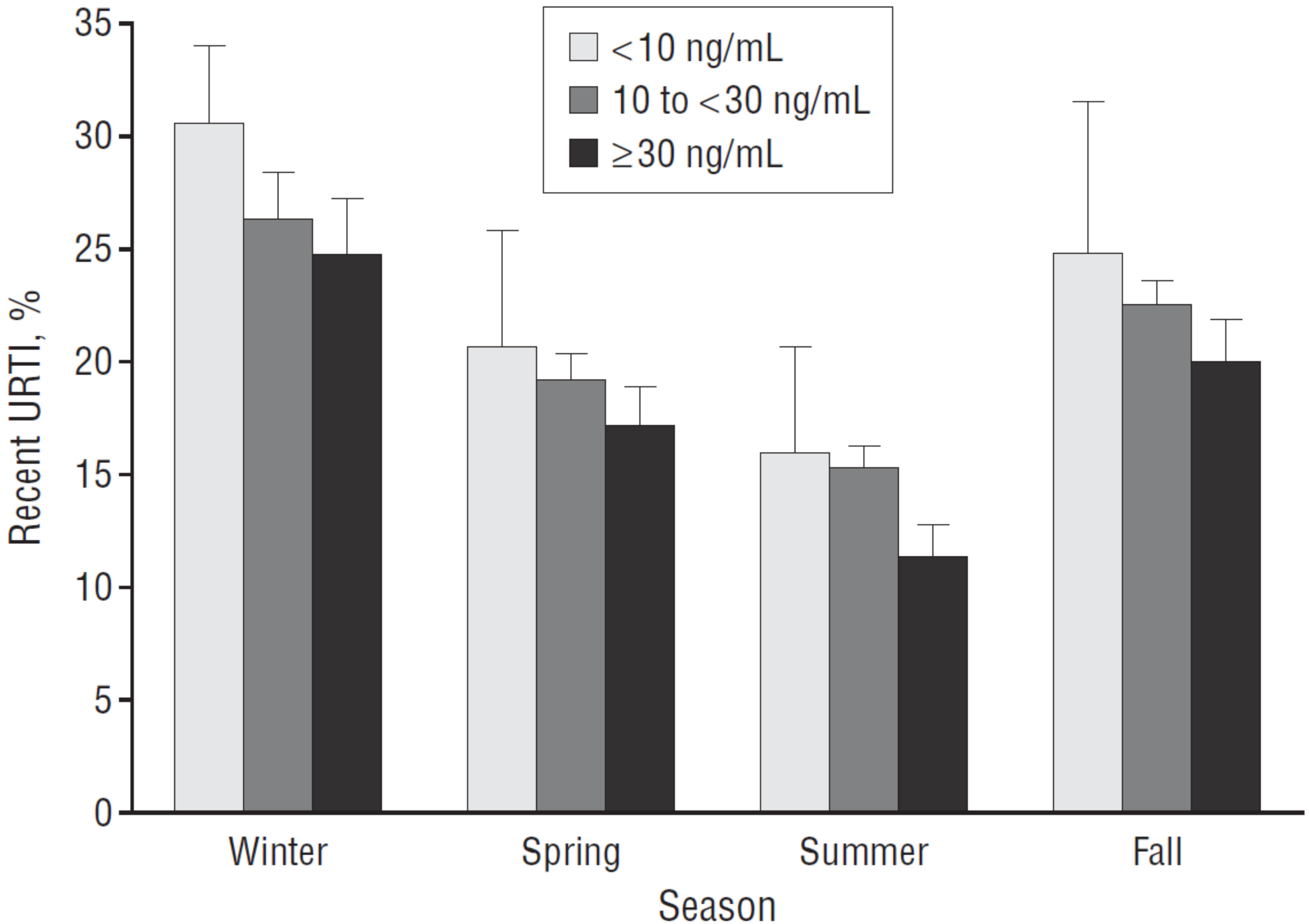
Effect of Vitamin D, 1, 25 (OH)2 on Foam Cells in Diabetic



Oh et al Circulation 120:687-698, 2009

Vitamin D and diabetic cardiovascular disease

- Deletion of vitamin D receptors in macrophages from diabetics accelerated foam cell formation induced by modified LDL.
- Vitamin D receptor signaling is a potential mechanism underlying increased foam cell formation and accelerated cardiovascular disease in diabetic subjects.



Ginde et al Arch Intern Med 384-390, 2009

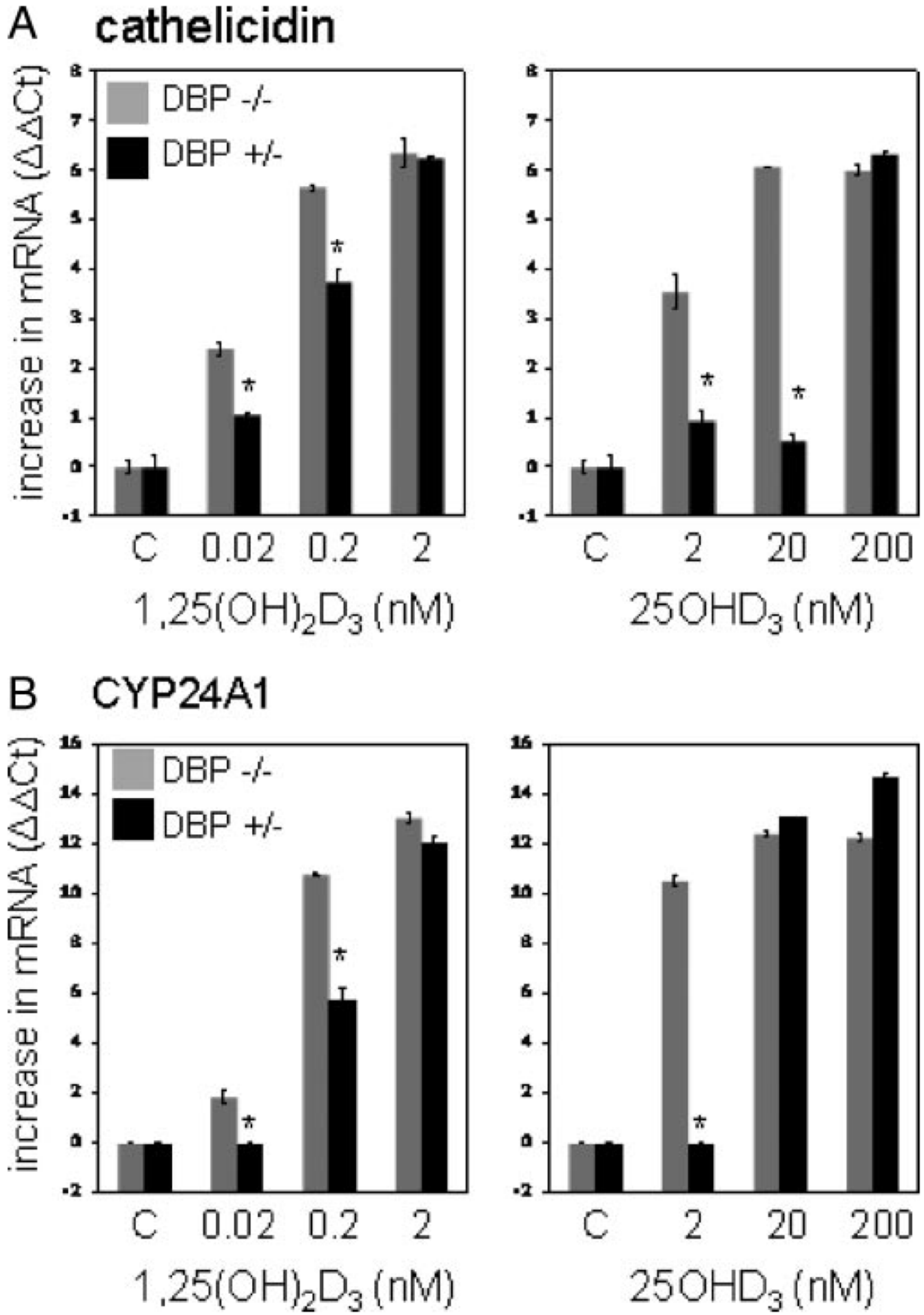
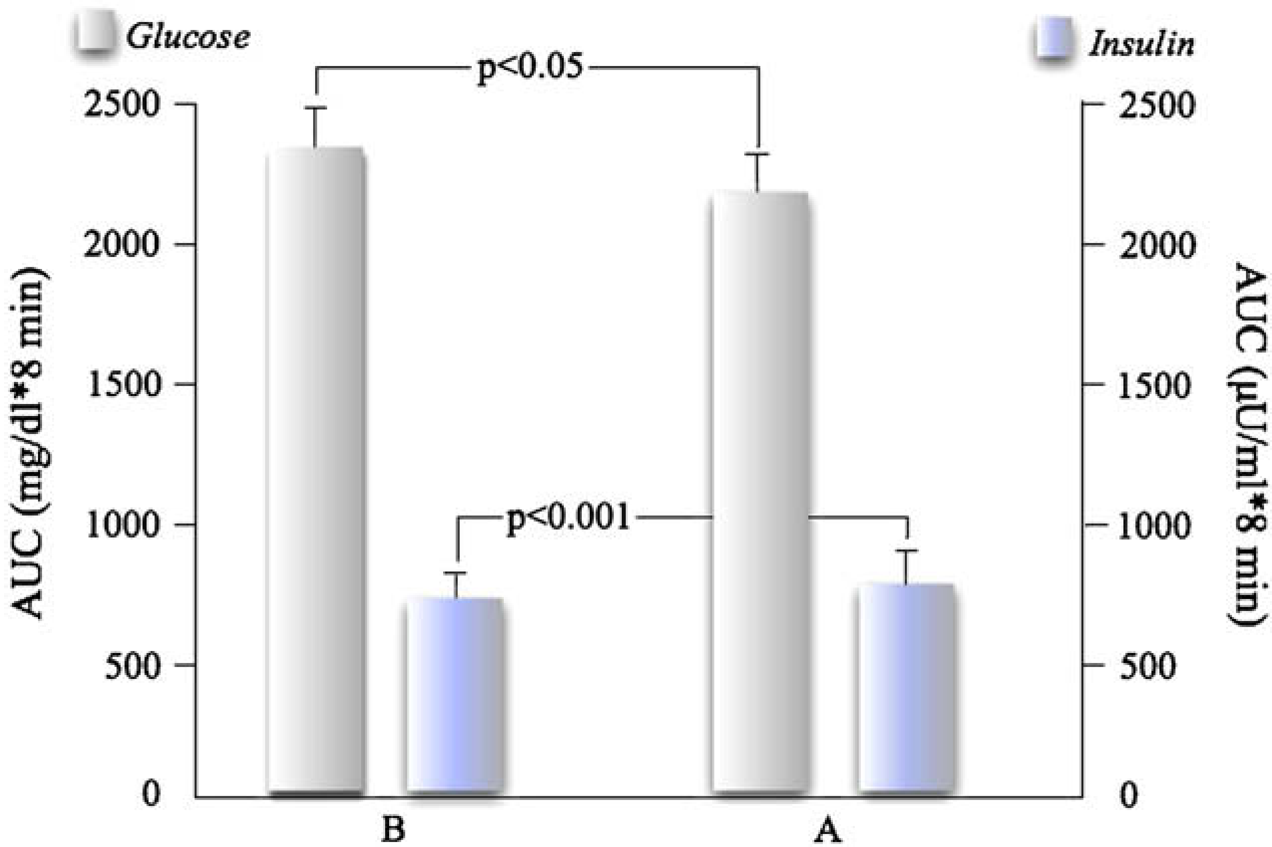


FIG. 1. DBP knockout serum increases monocyte responses to vitamin D metabolites. Human monocytes cultured in medium supplemented with 5% serum from $DBP^{+/-}$ and $DBP^{-/-}$ mice were treated with $25OHD_3$ (2–200 nM), $1,25(OH)_2D_3$ (0.02–2 nM), or vehicle control (C, 0.2% ethanol) for 6 h. RNA from the resulting cells were then analyzed by RT-PCR for cathelicidin (panel A) and 24-hydroxylase (CYP24A1) (panel B). Data are shown as mean (n = 3) changes in RT-PCR ΔΔCt values relative to vehicle-treated cells. *, Statistically different from $DBP^{+/-}$ serum cells at $P < 0.001$.

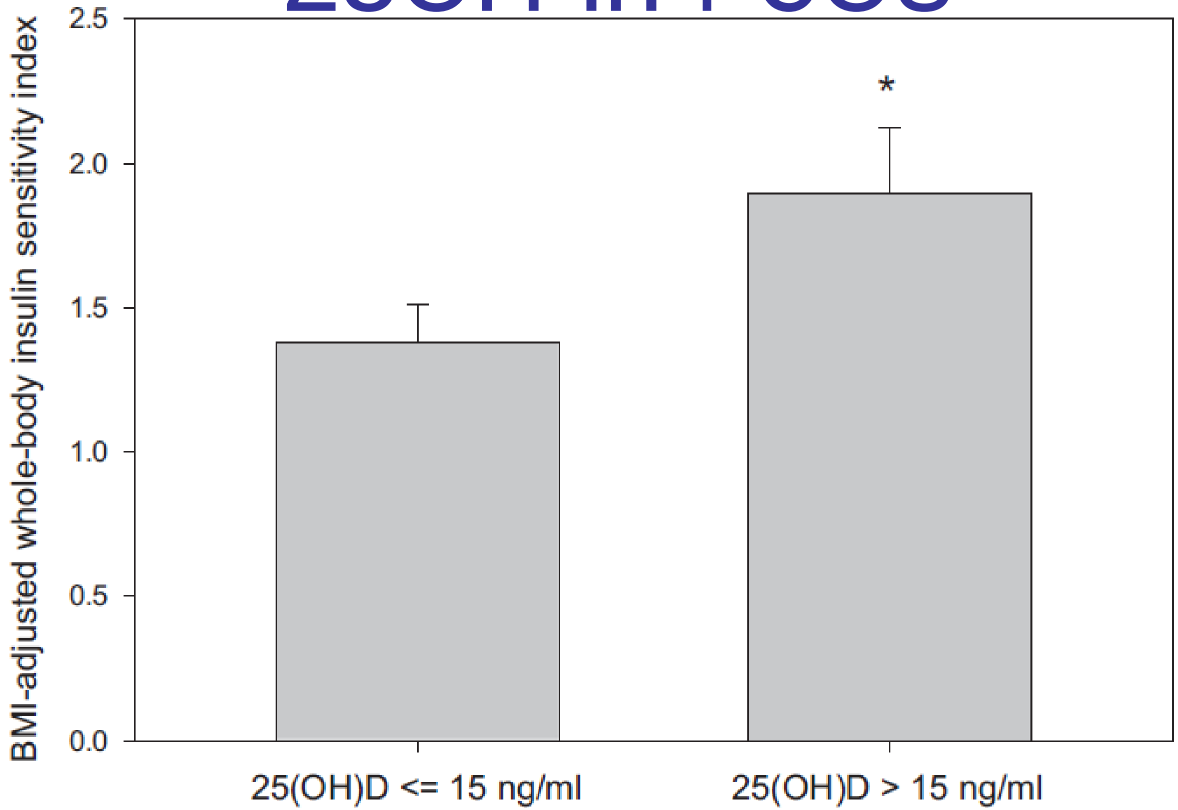
Chun et al JCEM 95:3368-3376, 2010

Changes in glucose and insulin concentration during the first phase of insulin secretion (AUC_{1-8}) before and after treatment with alphacalcidol. Values are mean + SE. B = before treatment; A = after treatment.



Kotsa. Vitamin D treatment and glucose metabolism in PCOS. Fertil Steril 2009.

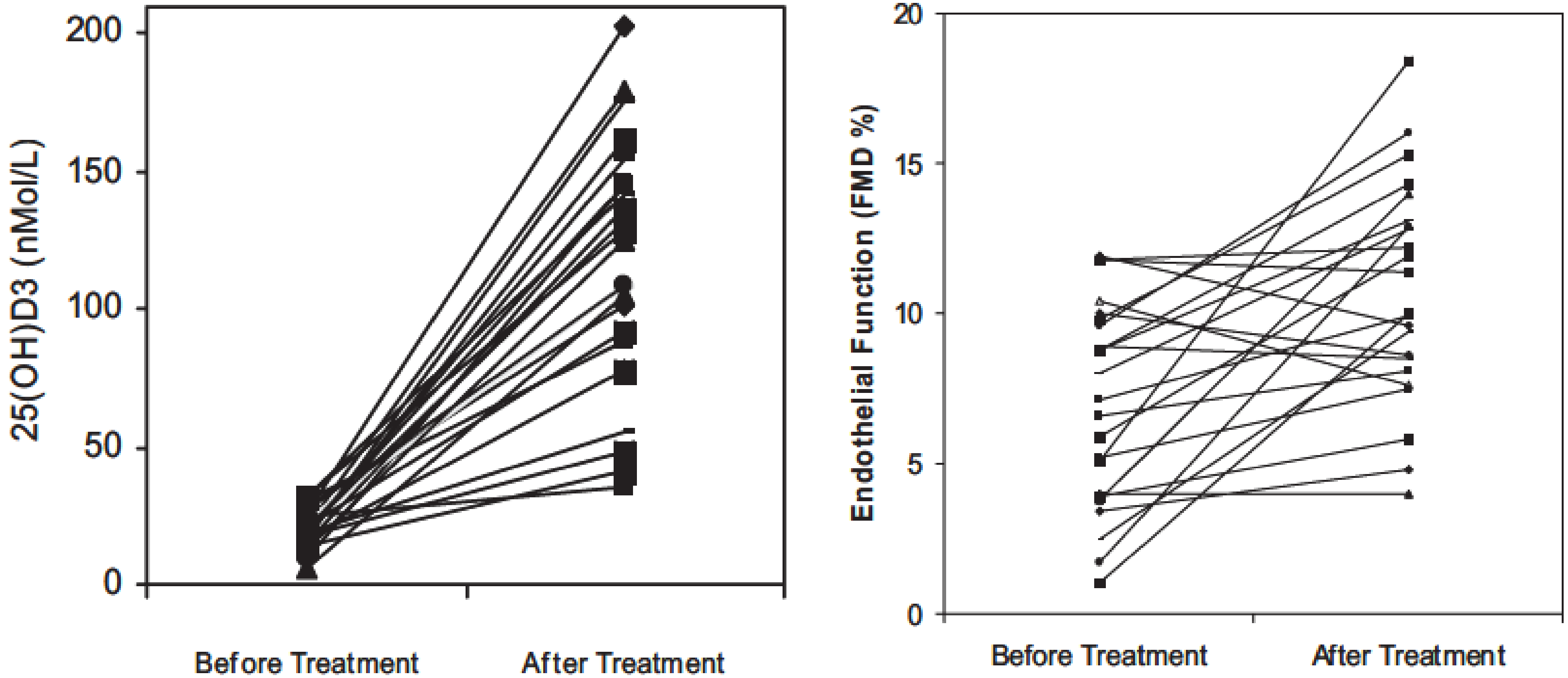
Insulin Sensitivity and Vitamin D 25OH in PCOS



BMI-adjusted WBISI by vitamin D-deficiency status. *, *P* for difference between groups = 0.047.

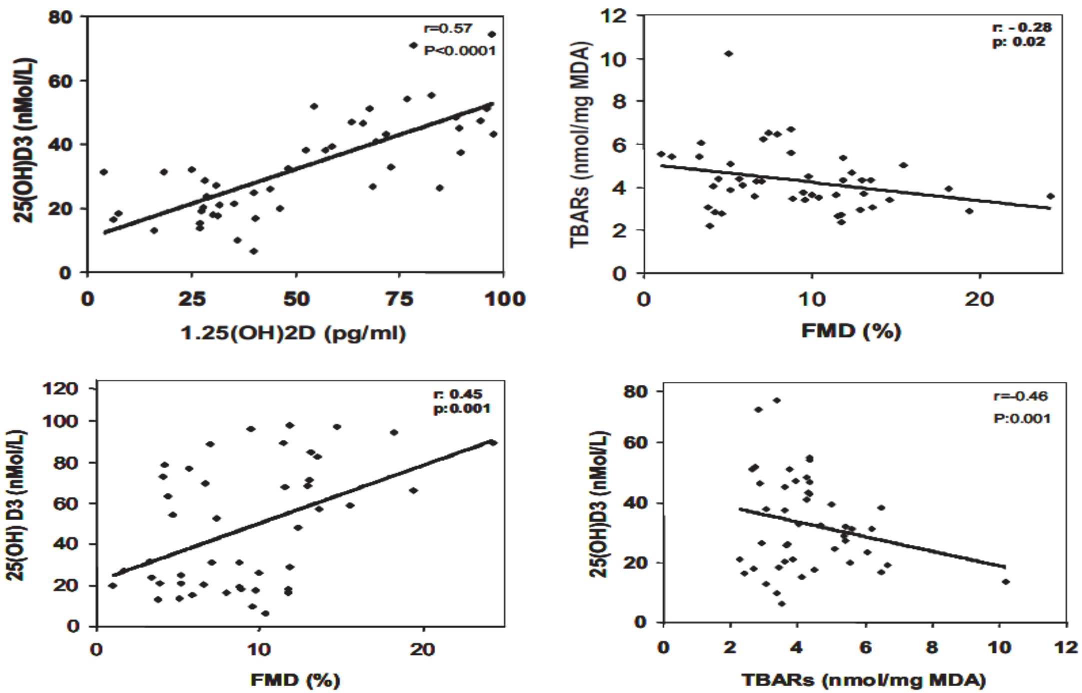
Ashraf et al JCEM (4: 3200-06, 2009

Vitamin D and Endothelial Function



Tarcin JCEM 94: 4023-30, 2009

Vitamin D and Flow Mediated Dilatation



The correlation data of the vitamin D-deficient subjects and the control group showed a positive association between 25(OH)D_3 and FMD values (r = 0.45; *P* = 0.001), also between 25(OH)D_3 and 1,25(OH)$_2$D levels (r = 0.57; *P* < 0.0001). There was a negative correlation between FMD and TBARS (r = −0.28; *P* < 0.05), also between 25(OH)D_3 levels and TBARS (r = −0.46; *P* = 0.001).

Tarcin JCEM 94: 4023-30, 2009

Cancer and Vitamin D

- Randomized control trial in postmenopausal women 1100 IU vitamin D_3 plus 1500 mg of calcium daily for 4 years
- Vitamin D group vitamin D 25OH increased 24 nmol/L
- No change in calcium only or placebo
- >60% reduction in all cancers

Lappe et al. Am J Clin Nutr 85:1586-91, 2007

Vitamin D and Calcium on Cancer Free

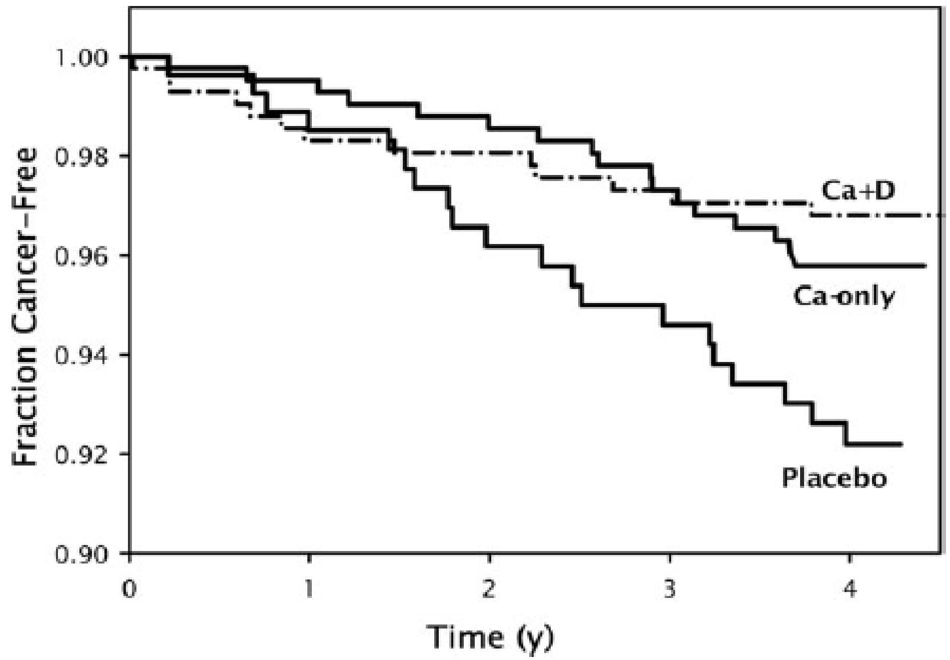


FIGURE 1. Kaplan-Meier survival curves (ie, free of cancer) for the 3 treatment groups randomly assigned in the entire cohort of 1179 women. Sample sizes are 288 for the placebo group, 445 for the calcium-only (Ca-only) group, and 446 for the calcium plus vitamin D (Ca + D) group. The survival at the end of study for the Ca + D group is significantly higher than that for placebo, by logistic regression. (Copyright Robert P Heaney, 2006. Used with permission.)

Lappe et al. Am J Clin Nutr 85:1586-91, 2007

Expression of CYP27B1

- Increased in hyperplastic colon polyps
- Increased in early stage tumors
- Declines in late-stage neoplasia
- CYP24A1 is induced by 1,25 $(OH)_2$ D_3
- Tumor cells determine the extent of Vitamin D catabolism

Lechner et al. Molecular and Cellular Endocrinology 263: 55-64, 2006

Antiproliferative Effects of Vitamin D 25 OH in Colon Cancer

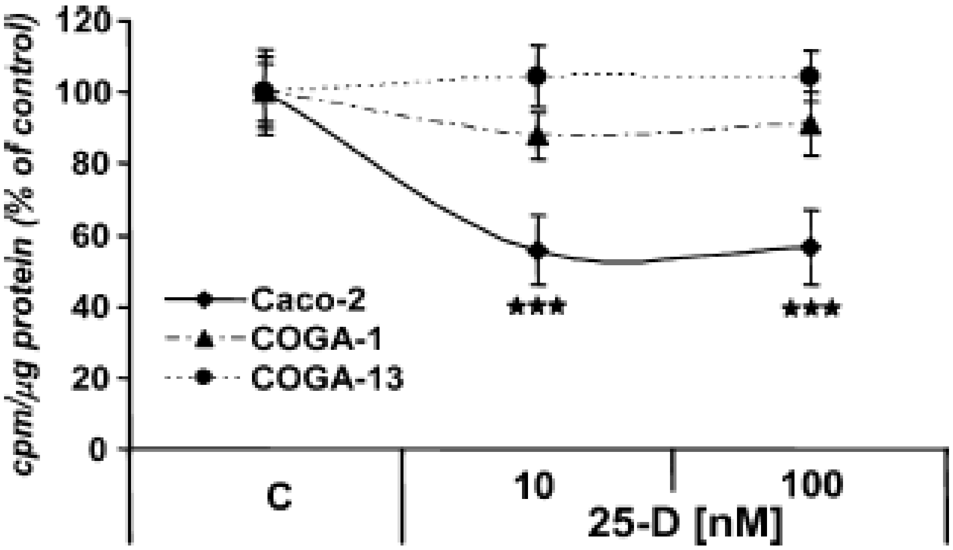


Fig. 4. Evaluation of the antiproliferative effect of 25-OH-D_3 in colon cancer cell lines by [^{3}H]-thymidine incorporation into DNA. Caco-2, COGA-1 and COGA-13 cells were exposed to 100 and 10 nM of 25-OH-D_3 (25-D) for 48 h. Data are presented as percentage of vehicle control (C; $^{***}P < 0.001$).

Lechner et al. Molecular and Cellular Endocrinology 263: 55-64, 2006

Renal and Colon Vitamin D Synthesis and Catabolism

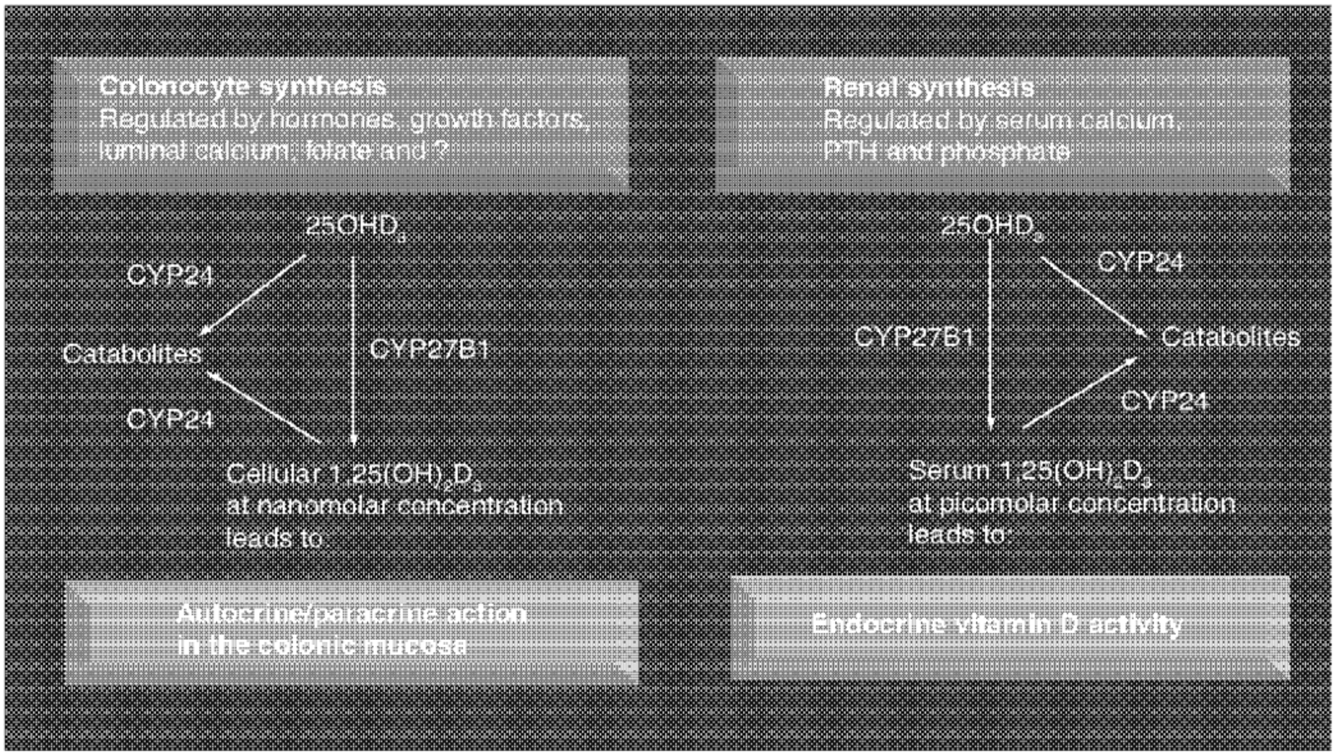
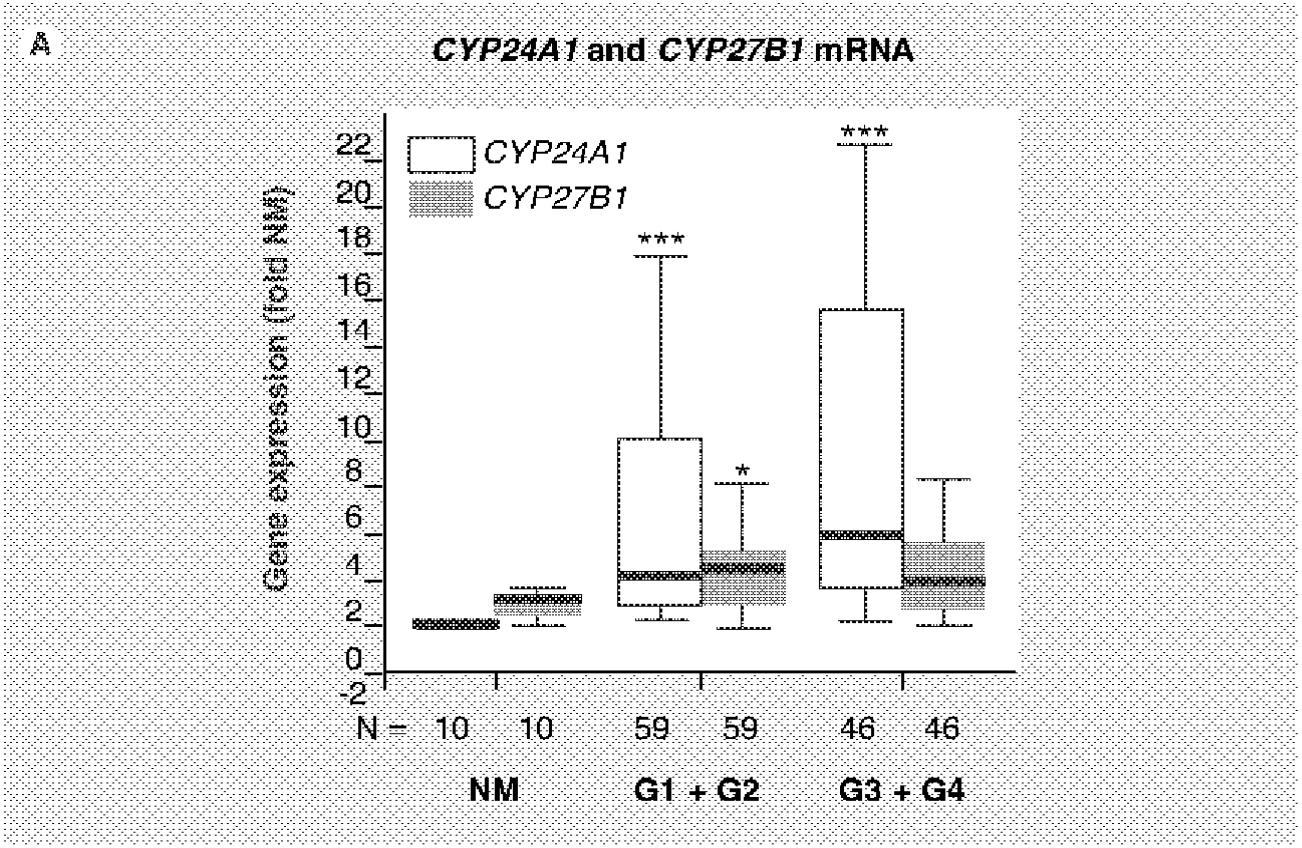


Figure 3. Comparison of colonic and renal vitamin D synthesis and catabolism. Differences in regulation and function are indicated.

Cross and Kallay Futrue Oncol 5: 493-507, 2009

CYP24A1 and CYP27B1 in Normal Colon and Colon Tumor



Lechner et al. Molecular and Cellular Endocrinology 263: 55-64, 2006

Summary of Vitamin 25 (OH)D Deficiency

- Common, particularly in older women
- Generally asymptomatic
- Causes
  - decreased dietary intake
  - decreased sun exposure
  - Sunscreen
- Diagnosis:Serum 25(OH)D <20 ng/mL and Elevated PTH; insufficiency <30 ng/mL
- Benefits-CVD, diabetes, cancer, immune
- Treatment: Vitamin D

Questions