

The Physiological Roles of Vitamin D *A Review of the Old and A Look at the New*

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Care

Forms of Vitamin D

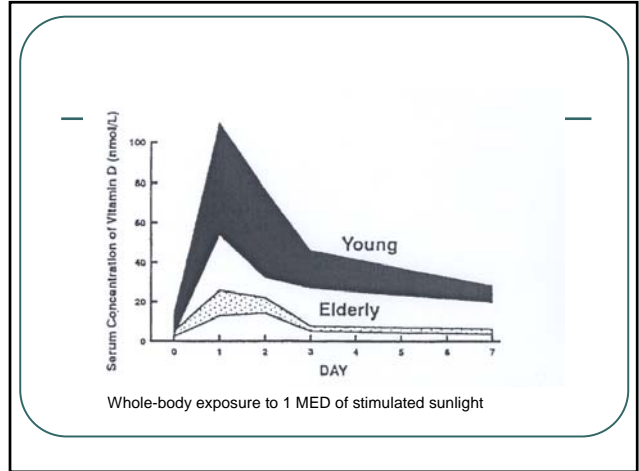
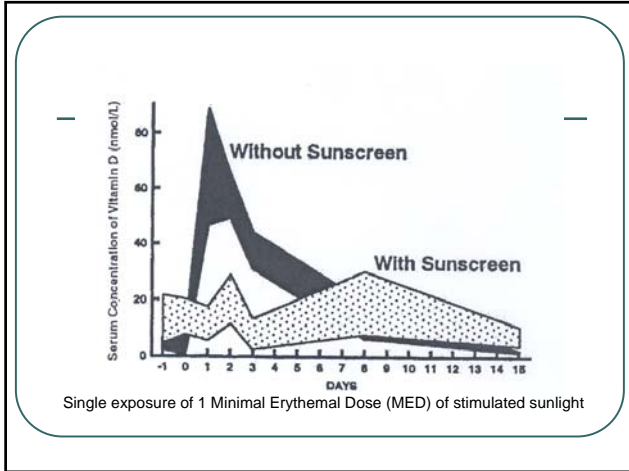
- Vitamin D₂ – Ergocalciferol
 - Vitamin D₃ – Cholecalciferol
 - Exogenous Sources
 - Foods of plant origin
 - Dietary supplements
 - Fortified food stuffs
 - Exogenous Sources
 - Foods of animal origin
 - Dietary supplements
 - Fortified food stuffs
- Milk 400 IU/ quart
Fat soluble vitamin

Endogenous Production

- Formation of D₃ only
- Synthesized in the skin
 - Action of UVB radiation on 7-dehydrocholesterol
 - Prolonged sun exposure does not result in excess production and toxic levels

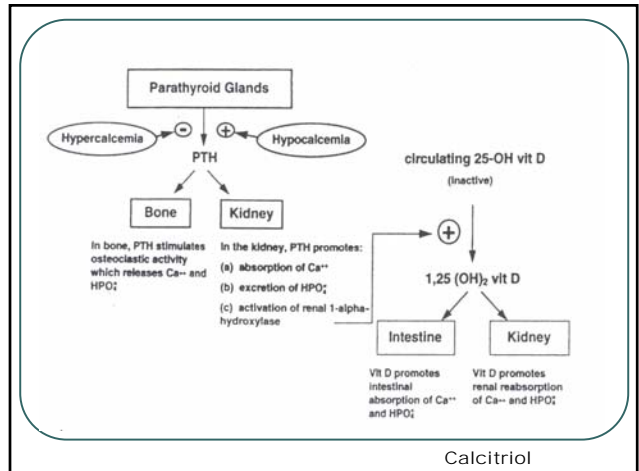
Factors Affecting Cutaneous Production

- Latitude
- Time of year & Time of day
- Skin pigmentation
- Use of sunscreen
 - SPF 8 - >95% reduction
- Age



25-hydroxyvitamin D

- D₂ or D₃ is hydroxylated by hepatic vitamin D 25-hydroxylase
- Major circulating form of Vitamin D
 - Measurement of vitamin D status
- "Inactive" hormone



The "Sunshine" Vitamin & Rickets

Rickets - defined as an interruption in the development and mineralization of the growth plate of bone resulting in growth retardation and skeletal deformities.

Right – bowed legs
Left – knocked knees



Other Causes: Nutritional, renal phosphate wasting...

Osteomalacia

- Adult equivalent of rickets and accompanies that disorder in children
- Defined as inadequate or delayed mineralization of bone with deposition of uncalcified bone matrix
- Complication of chronic renal failure

Decreased 25(OH) Vit D

- Inadequate exposure to sunlight
- Inadequate dietary intake
- Vitamin D malabsorption
- Severe hepatocellular disease
- Increased catabolism intake
- Increased loss
 - Nephrotic syndrome

Increased 25(OH) Vit D

- Vitamin D intoxication
 - Vitamin D or 25(OH) Vit D
 - Hypercalcemia
 - Toxicity usually associated with 25(OH) Vit D concentration >150 ng/mL

Decreased 1,25 (OH)₂ Vit D

- Renal failure
- Hypoparathyroidism
- Hyperphosphatemia
- Hypercalcemia of malignancy

Increased 1,25 (OH)₂ Vit D

- Primary hyperparathyroidism
- Pregnancy
- Lymphoma
- Granulomatous diseases

Assessment of Vit D Status

- 25(OH) Vitamin D
 - ½ life 2 to 3 weeks
 - 10 to 50 ng/mL
 - 25 to 125 nmol/L
 - 0.03% free
- 1,25 (OH)₂ Vitamin D
 - ½ life 4 to 6 hours
 - 15 to 60 pg/mL
 - 36 to 144 pmo/L
 - 0.4% free
 - NOT USEFUL

TABLE 1
Commercially available assays for measuring 25-hydroxyvitamin D³

Assay type and manufacturer	Sample type and volume	Extraction	Range of detection nmol/L	Sensitivity	Intra-assay CV	Inter-assay CV	Assay time	Comments
				nmol/L	%	%		
RIA TherSia	Serum or plasma, 50 µL	Acetonitrile	0-100	≤6	≤8	≤13	2.3 h	Calibrators and controls in serum matrix; no yield determination required
IDS Inc	Serum or plasma, 50 µL	Two-step reagent extraction	4-400	≤3	6.8	8.9	3 h	Calibrators and controls in serum matrix; no yield determination required; 75% cross-reactivity for 25(OH)D ₃
ELISA IDS Inc	Serum or plasma, 25 µL	None	6-360	≤5	≤6	≤9	3 h	75% cross-reactivity for 25(OH)D ₃
Immunofluorescent	Serum or plasma, 30 µL	Proprietary extraction reagent	6.3-250	2	10	8	ON	Monoclonal antibody; 25% cross-reactivity for 25(OH)D ₃
CPR Immunofluorescent	Serum or plasma, 30 µL	Acetonitrile	6.4-250	5.6	11	13	4.5 h	Uses DBP in RIA format; 100% cross-reactivity for 25(OH)D ₃
HPLC Immunofluorescent	Serum, 500 µL	Acetonitrile and C ₁₈ cartridge extraction	Up to 1250	4	5.2	8.4	20 min	Laboratory must have HPLC unit with silica column; 25(OH)D ₃ and 25(OH)D ₂ separated with different column
Chemiluminescence DiaSorin Liaison	Serum or plasma, 25 µL	Automated	7.5-375	≤10	4	6	40 min	Fully automated on Liaison instrument; 100% cross-reactivity for 25(OH)D ₃

¹ RIA, radioimmunoassay; 25(OH)D₃, 25-hydroxyvitamin D₃; ELISA, enzyme-linked immunosorbent assay; ON, overnight; CPR, competitive protein binding; DBP, vitamin D binding protein.

25(OH) Vit D Deficiency

- Validity of reference range
 - 30 ng/mL
- Major health problem for adults >50 y of age
- 38% of nursing home residents
- >50% of African Americans in US
- >40% of hospitalized patients in Boston
 - 32% of students & doctors 18-29 y of age at winter's end

Osteoporosis & Vitamin D Deficiency

- Compensatory 2^o hyperparathyroidism → Mobilizes skeletal calcium → Reduction in bone mineral density → Precipitates or exacerbates osteoporosis

Also a mineralization defect of the collagen matrix increases fracture risk and bone pain

Gene Regulation

- 1,25-Dihydroxy Vitamin D interacts with a specific nuclear receptor
 - Vitamin D receptor – VDR
- VDR complexes with another receptor forming a heterodimeric complex
- Complex seeks out specific DNA sequences known as Vitamin D-responsive elements
- Enhancement or inhibition of transcription of Vitamin D-Responsive Genes

Nuclear Vitamin D Receptor

- 200 human genes contain vitamin D-responsive elements
- Cells
 - Activated B & T lymphocytes
 - Mononuclear cells
 - Beta-islet cell
 - Keratinocytes
- Skeletal muscle
- Small intestine & Colorectal*
- Brain
- Heart
- Skin
- Gonads & Prostate*
- Breast*

*Observational: Latitudinal associations with cancer risks

Treatment of Psoriasis

- Exploits potent anti-proliferative activity of 1,25-dihydroxyvitamin D
 - Keratinocytes growth is markedly inhibited & induced to differentiate
- Topical activated vitamin D analog developed

Regulation of Cell Growth

- Vitamin D concentrations above 30 ng/mL are necessary for maximal extra-renal, intracellular production of 1,25(OH)₂ Vitamin D
- Inverse association established
 - Prostate cancer
 - Colorectal cancer
 - 50% reduction in risk with serum 25(OH) vitamin D concentrations of ≥ 32 ng/mL,

Essential Hypertension & Cardiac Outcomes

- Essential hypertension – inverse correlation between 1,25(OH)₂ vit D levels and plasma renin activity
- Coronary angiography patients with vitamin D levels <10 ng/mL (vs 30 ng/mL)
 - 3X more likely to die of heart failure
 - 5X more likely to die of sudden cardiac death
- Antihypertrophic system in cardiac muscle

Skeletal Muscle

- In mice, activation of VDR in myocytes leads to protein synthesis and muscle cell growth
- In humans, association with higher vitamin D levels and improved muscular function and strength
 - Decreased levels associated with muscle weakness and pain among adults with osteomalacia

Autoimmunity

- T cell-mediated
- Animal & *in vitro* models
- Hypothesis that vitamin D regulates the differentiation and activity of CD4+ T cells
- Inhibits T helper cell development and cytokine production
- Expansion of regulatory T cells
- Decrease in autoimmune response and severity of symptoms

Immunomodulation

- “Adequate” vitamin D concentration might mitigate or prevent the onset of:
 - DM type 1
 - Multiple sclerosis
 - Rheumatoid arthritis
 - Crohn's disease

Recommendations - Institute of Medicine

- Birth – age 50 y
 - 200 IU/d
- 51 – 70 y
 - 400 IU/d
- Aged >70 y
 - 600 IU/d
- Supplemental intake of 400 IU/d increases 25(OH)D levels by 2.8 to 4.8 ng/mL
- Additional intake of approximately 1700 IU/d are required to raise levels from 20 to 32 ng/mL

Tolerable Upper Limit

- 2000 IU/d
 - Established by the Food and Nutrition Board
- “An intake for all adults of ≥ 1000 IU/d is needed to bring vitamin D concentration in no less than 50% of the population up to 75 nmol/L.” (30 ng/mL)
 - Reference 9