

VITAMIN "D"

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Content



- Source
- Physiology & metabolism
- Deficiency & resistance
- Requirements & Treatment
- 'Extra-skeletal' effects

History

- 1600s 1st description of rickets by Whistler & Glisson
- 1918 Sir Edward Mellanby linked with fat-soluble nutrient
- 1923 Goldblatt & Soames demonstrated exposure to sunlight or UV light produced a substance with similar properties
- 1936 Identification of Vitamin D by Windaus

Modern Day Interest

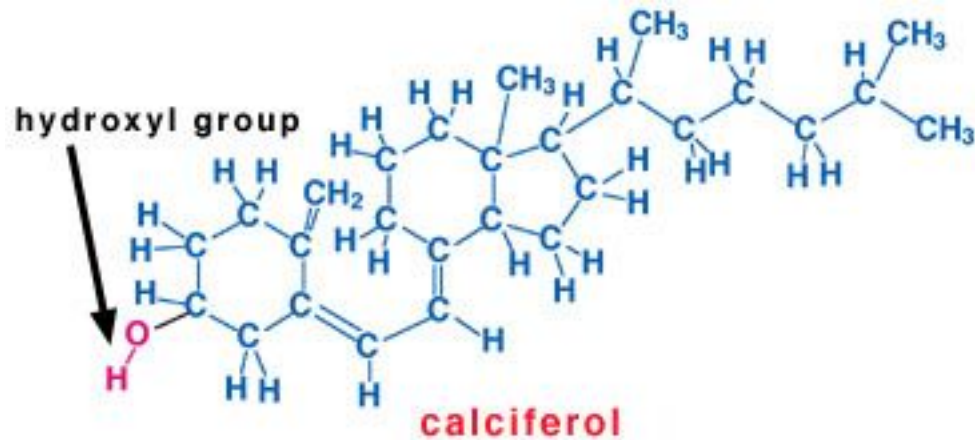
- Vitamin D & metabolites
 - Significant role in calcium homeostasis & bone metabolism
- Deficiency
 - Rickets in children
 - Osteomalacia in adults
- Rickets ? rare in most developed populations

Vitamin D Deficiency

- Subclinical deficiency
 - Silent epidemic.
 - Present in approximately 30% to 50% of the general population.
 - More prevalent in elderly, women of child bearing age and infants.
 - Often unrecognized by clinicians.
 - May contribute to development of osteoporosis & increased risk of fractures related to falls in the elderly.

Vitamin D

- 'Calciferol'
- Generic terms for a group of lipid-soluble compounds with a 4-ring cholesterol backbone



Sources Of Vitamin D

- Sunlight (UV)
- Intestinal absorption (only ~20%)
 - Oily fish
 - Fortified milk / bread / cereal
 - Supplements

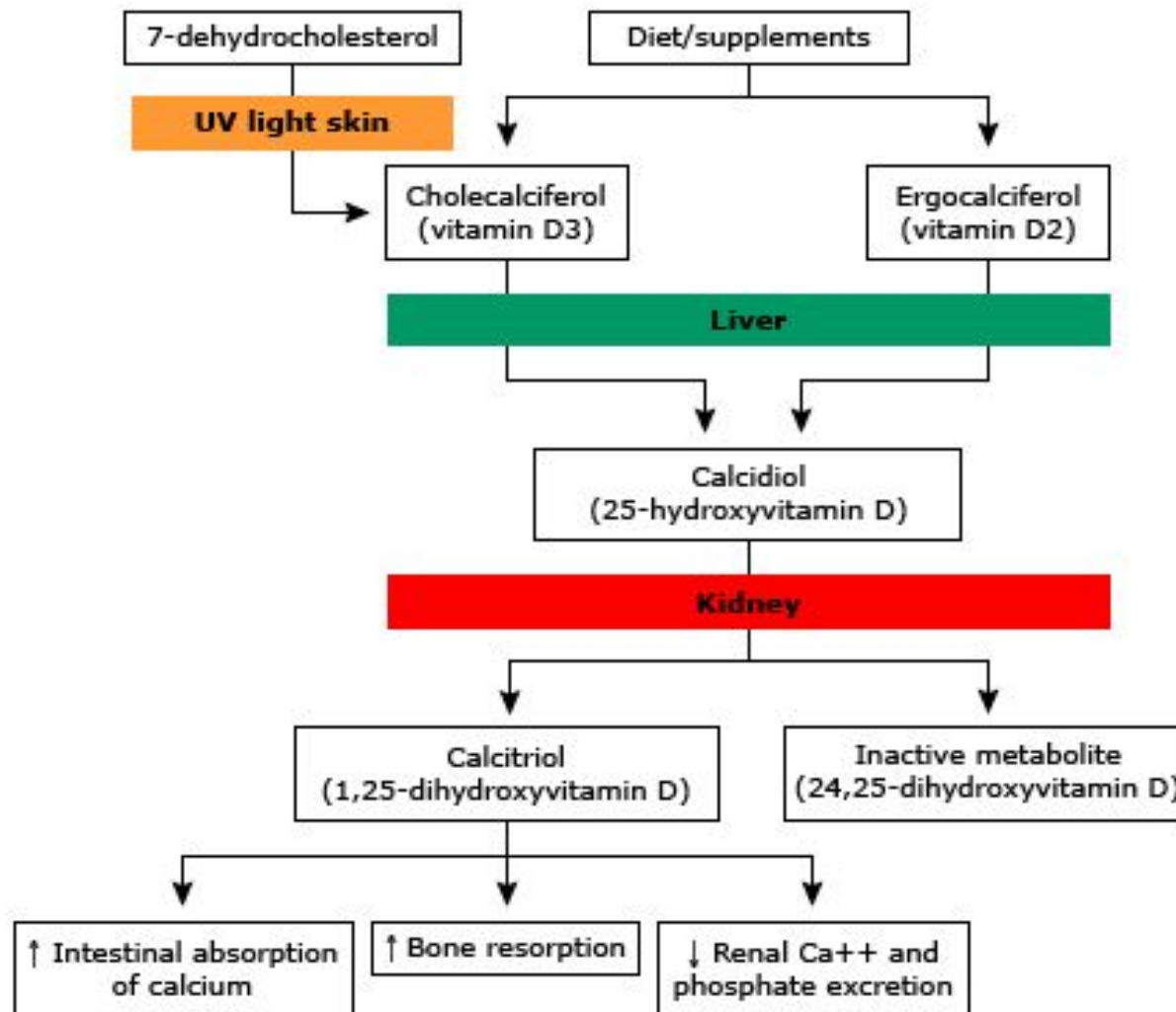
Absorption & Metabolism

- Affected by fat malabsorption
 - Pancreatic insufficiency
 - CF
 - Cholestatic liver disease
 - Coeliac
 - Crohn's

Vitamin D Metabolism

- Skin
 - UV light photo-isomerises provitamin D to D3 (cholecalciferol)
 - Transported by Vit D binding proteins to liver
- Intestine
 - Absorbed by enterocytes & packaged into chylomicrons
 - Transported to liver by portal circulation
 - Hydroxylated in liver to 25-OH
 - Further in kidneys to 1,25-OH
 - Physiologically active

Vitamin D Metabolism



Deficiency & Resistance

- Impaired availability of Vit D
 - Lack of sun exposure, can be seasonal
 - Fat malabsorptive states
- Impaired liver hydroxylation to 25-OHD
- Impaired renal hydroxylation to 1,25-OHD
- End-organ insensitivity to Vit D metabolites
 - Hereditary Vit D resistant rickets
 - Glucocorticoids – inhibit intestinal Vit D dependent calcium absorption

Consequences of Vitamin D Deficiency

- ❑ Reduced intestinal absorption of calcium & phosphorus
- ❑ Hypophosphataemia precedes hypocalcaemia
- ❑ Secondary hyperparathyroidism
- ❑ Bone demineralisation
- ❑ Osteomalacia / rickets

Rickets



Child with Rickets

Osteomalacia

- After closure of epiphyseal plates
- Impaired mineralisation
- Fractures
- Lab tests
 - Low calcium & phosphate
 - High ALP
- X-rays
 - Diffuse bone lucencies

Associated Clinical Conditions

- Muscle Weakness and Falls
 - Proximal muscle weakness
 - Chronic muscle aches
 - Myopathy
 - Increase in falls
 - Recent studies suggest that vitamin D supplementation at doses between 700 and 800 IU/d in a vitamin D-deficient elderly population can significantly reduce the incidence of falls.

Associated Clinical Conditions

- Bone Density and Fractures
 - Risk of osteoporosis may be reduced with adequate intake of vitamin D and calcium.
 - Studies support the concept that vitamin D at doses between 700 and 800 IU/d with calcium supplementation effectively increase hip bone density and reduced fracture risk, whereas lower vitamin D doses may have less effect.

Associated Clinical Conditions

□ Role in Cancer Prevention

- Low intake of vitamin D and calcium has been associated with an increased risk of non-Hodgkin lymphomas, colon, ovarian, breast, prostate, and other cancers.
- The anti-cancer activity of vitamin D
 - a nuclear transcription factor that regulates cell growth, differentiation, & apoptosis, central to the development of cancer
- Vitamin D is not currently recommended for reducing cancer risk

Associated Clinical Conditions

- Autoimmune Disease
 - Vitamin D supplementation is associated with a lower risk of autoimmune diseases.
 - In a Finnish birth cohort study of 10,821 children, supplementation with vitamin D at 2000 IU/d reduced the risk of type 1 diabetes by approximately 78%, whereas children who were at risk for rickets had a 3-fold higher risk for type 1 diabetes.
 - In a case-control study of 7 million US military personnel, high circulating levels of vitamin D were associated with a lower risk of multiple sclerosis.
 - Similar associations have also been described for vitamin D levels and rheumatoid arthritis.

Associated Clinical Conditions

- Role in Cardiovascular Diseases
 - Vitamin D deficiency activates the renin-angiotensin-aldosterone system and can predispose to hypertension and left ventricular hypertrophy.
 - Additionally, vitamin D deficiency causes an increase in parathyroid hormone, which increases insulin resistance secondary to down regulation of insulin receptors and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk.

Associated Clinical Conditions

- Role in Reproductive Health
 - Vitamin D deficiency early in pregnancy is associated with a five-fold increased risk of preeclampsia.
 - Role in All Cause Mortality
 - Researchers concluded that having low levels of vitamin D (<17.8 ng/mL) was independently associated with an increase in all-cause mortality in the general population.

At-Risk Groups

- Elderly
 - Stores decline with age
 - Winter
 - House-bound or institutionalised
 - Poor nutritional intake
 - Impaired absorption
 - CKD

At-Risk Groups

- Children
 - Exclusively breast-fed infants
 - Variable dietary intake
- Vegetarian or fish-free diet
- Ethnic background
- Women treated for osteoporosis

At-Risk Groups

- Healthy adults
 - Immigrants
 - Winter (1 in 6 UK adults)
 - Boston study – Holick et al, 2002
 - 36% vs. 4% of healthy volunteers with normal Vit D concentration at start & end of winter season

At-Risk Groups

- Hospitalised patients
 - Age
 - Sun exposure
 - Intake
 - Renal injury
 - Burns victims
 - 22-42% prevalence in US studies

Assessment

Patient characteristics	Advice and management
Healthy, no risk factors, symptom free	No investigations required Lifestyle advice Consider preventive therapies
Risk Factors Only	Lifestyle advice Consider long term preventative therapies
Risk factors AND symptoms/signs	Lifestyle advice Investigations Therapeutic intervention Long term preventative treatment

Investigations

Test	Reason
Renal function Liver function tests FBC Parathyroid hormone Calcium, Phosphate Alkaline phosphatase	Exclude renal disease Iron deficiency commonly co-exists
25-OH Vitamin D concentrations	Diagnosis

Diagnosis

Serum 25-hydroxyvitamin D concentrations, status and management	
<10 mcg/L (<25 nmol/l)	Deficiency: High dose treatment initially (3200 iu daily for 8-12 weeks), then long term maintenance treatment required (1600 iu/d).
10-20 mcg/L (25-50 nmol/l)	Insufficiency: long term maintenance treatment (1600 iu/d)
20 – 30 mcg/L (50-75 nmol/l)	Healthy, give lifestyle advice
>30 mcg/L(>75 nmol/l)	Optimal

Vitamin D Measurements

Interpretation	Vit D Level (nmol/l)	Action
Deficiency	< 25	Replace Vit D Loading dose followed by maintenance
Insufficient	25-50	Consider replacement if: • Glucocorticoids • Osteopenia/osteoporosis • 2° HPTH • Hypocalcaemia • CKD Maintenance dose
Replete	>50	No need for replacement or continue dose
Toxic	>150	Check calcium Stop treatment

Vitamin D Preparations

- (assuming normal renal function)
- Cholecalciferol
 - D3
 - Natural molecule in man
- Ergocalciferol
 - D2
 - Plant-derived
 - Less effective than D3 preparations

Vitamin D Preparations

Vitamin D products (loading/treatment doses):

Product	Strength	Contents	Approximate Annual Cost per patient*	Suitability for vegans
Colecalciferol capsules	20,000IU	D ₃	Varying (from £15 to ~£90 for 50 capsules)	No
Ergocalciferol i.m. injection	7.5mg (300,000 IU) per 1ml	D ₂	1ml ampoule - £8.50 2ml ampoule - £9.85	Yes

* Based on information in the British National Formulary 60, September 2010 and suppliers quoted

Vitamin D products (maintenance doses):

Products	Strength	Contents	Approximate Annual Cost per patient*	Suitability for vegans
Colecalciferol capsules/ tablets	1,000IU/tablet 400IU/tablet	D ₃	Varying (from £7.15 upwards for 100 tabs/caps) Can also be bought OTC e.g. Solgar, Biolife, Sunvite	Varying, prescribe "gelatin free" if required.
Calcichew D ₃ capsules	200IU/tablet	D ₃	£55.26	No
Calcichew D ₃ Forte chewable tablets	400IU/tablet	D ₃	£56	No
Adcal D ₃ chewable tablets	400IU/tablet	D ₃	£46.68	No
Adcal D ₃ Dissolve tablets	400IU/tablet	D ₃	£59.88	No
Calceos chewable tablets	400IU/tablet	D ₃	£43.44	No
Cacit D ₃ effervescent granules	440IU/sachet	D ₃	£97.44	No
Calfovit D ₃ powder	800IU/sachet	D ₃	£103.68	No

* Based on information in the British National Formulary 60, September 2010 and suppliers quoted

Vitamin D Supplementation

Deficiency (<25 nmol/l or 10 mcg/l)

- **Oral Therapy**

- 1st line agent:

- Fultium-D3[®] (Cholecalciferol) 800 iu capsules x4/d (licensed product) - 3200 iu daily for 8-12 weeks.

- 2nd line:

- Dekristol[®] (Cholecalciferol) capsules 20,000 units (unlicensed import). Prescribe 1 capsule (20,000 units) once per week for 8-12 weeks.

Vitamin D Supplementation

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□ ***Where oral therapy not appropriate (e.g. malabsorption states)***

□ Ergocalciferol 300,000 (or 600,000) iu single dose by intramuscular injection. The injection is gelatin free and may be preferred for some populations.

Vitamin D Supplementation

Insufficiency (25-50 nmol/l or 10-20 mcg/l) or for long-term maintenance following rx of deficiency

- 1st line therapy
 - Fultium-D3[®] 800iu capsules x2/d (licensed) - 1600iu per day (a dose between 1000 – 2000 units daily is appropriate).
- 2nd line:
 - Prescribe Dekristol[®] capsules 20 000 units [unlicensed import]. Prescribe 1 capsule (20,000 units) once per fortnight.
- ***Alternatively where oral therapy not appropriate***
 - Ergocalciferol 300,000 international units single dose by intramuscular injection once or twice a YEAR.

Combined calcium & vitamin D supplements

- Calcium component usually unnecessary in primary vitamin D deficiency
 - Less palatable ? affects compliance
- Dual replacement required where there is severe deficiency accompanied by hypocalcaemia leading to secondary hyperparathyroidism
- appropriate for the management of osteoporosis and in the frail elderly.

Alfacalcidol/Calcitriol

- Alfacalcidol (1 alpha- vitamin D) and Calcitriol have no routine place in the management of primary vitamin D deficiency
- Reserved for use in renal disease, liver disease and hypoparathyroidism.

Monitoring

- 1 month
 - Bone and renal profile
- 3 months
 - Bone and renal profile, vitamin D, and plasma parathyroid hormone.
- Once vitamin D replacement is optimised no further measurement of vitamin D is necessary.

Conclusion

- Commoner than we think!
- Can be prevented:
 - Promote awareness, especially in high-risk groups
 - Sun-exposure
 - Safe, 10-15 minutes per day (longer with darker skin)
 - Adequate intake of fortified products in diet

References:

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- Lappe JM, et al. *Am J Clinical Nutrition*, 2007.
- Mitri J. et al. *Am J Clinical Nutrition*, 2011.