VITAMIN D IN HEALTH AND DISEASE

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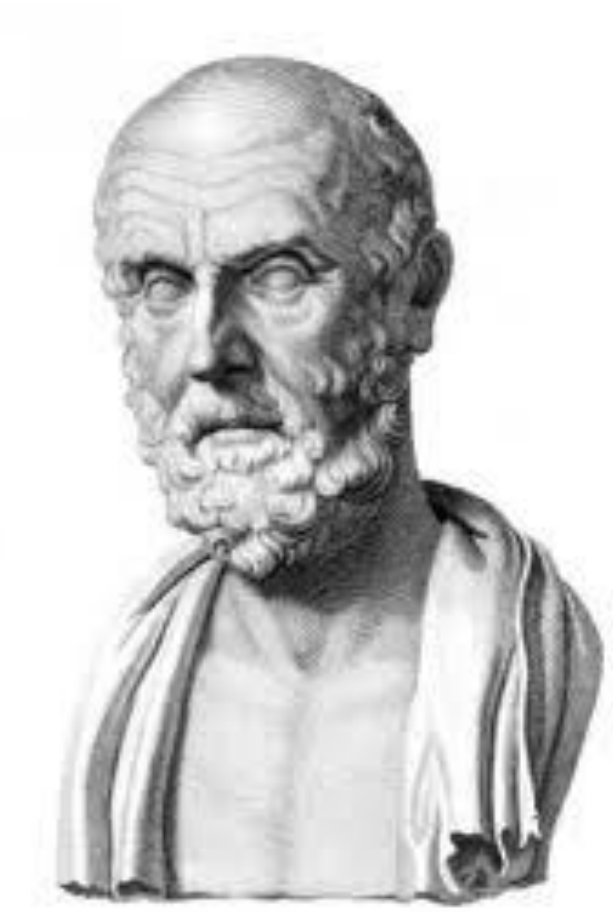


Thefamouspeople.com

- It`s most healthy to live on the southern side of a mountain

- Hippokrates of Kos 460-370 BC

Rickets/Rachitis

- In mid 1600s most children in Northern Europe developed rickets (growth retardation, deformities, weak muscles)
- 1822- effect of Sun on rickets
- Connected to geographical location
- More in towns and cities
- Healing properties of the fish liver oil
- UV induces the synthesis of vitamin D


R

- Vit D has been produced by phytoplankton for more than 500 million years
- Protection of ultraviolet-sensitive macromolecules (incl proteins, DNA, RNA)
- Maintenance of Ca homeostasis in vertebrates
- Evolving into hormone having many extraskeletal effects
- Ethnical and gender differences in skin pigmentation
- Evolutionary selection pressure towards a lighter skin with higher ability to produce vit D

- Vitamin D or D-hormone?
- Organism synthesizes its own vit D (no other vitamins)
- Organism turns vit D into hormone, metabolites are active, receptors needed VDR

Colecalciferol-Vitamin D_3

- biologically inert
- synthesized in the skin upon exposure to UVR
- also contained in certain nutrients
- activates in liver and kidneys

Ergocalciferol- Vitamin D_2

- another inactive type of vitamin D
- is formed by the irradiation of the plant sterol ergosterol
- weaker than D_3
- activates in liver and kidneys

Calcitriol ($1,25[OH]_2D$)

- major biologically active metabolite of vitamin D (= active vitamin D)
- 1000 times more active than any of its precursors
- $1,25(OH)_2D$ is formed by the metabolic conversion of the two inactive forms of vitamin D.

Metabolism of vitamin D

7-dehydrocholestrol (in cell membranes of keratinocytes)→ pre vit D_3 on UVB

→ vit D_3 on heat

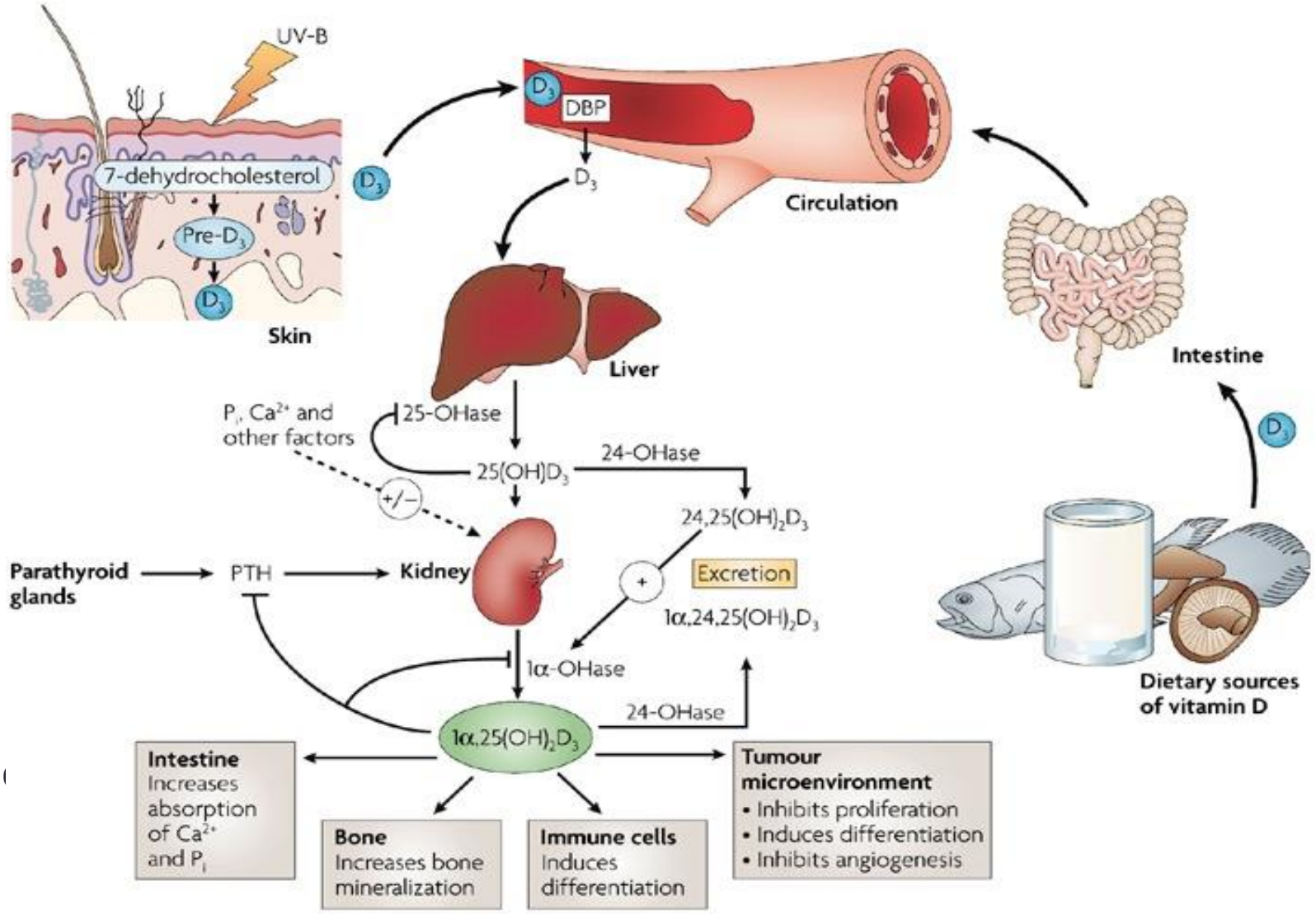
→in liver pro-hormone 25(OH)D

- **25(OH)D is the main circulating metabolite**
- 25(OH)D → in kidneys etc $1,25(OH)_2 D_3$

- Active vit D can penetrate to target cells and bind to specific VDR (VDR is expressed in several organs)

- These complexes translocate to nucleus, where they activate or repress the expression of several genes.

- M H


UV-B
7-dehydrocholesterol
Pre-D3
D3
Skin
D3
DBP
D3
Circulation
Liver
Intestine
D3
P, Ca2+ and other factors
25-OHase
25(OH)D3
24-OHase
+/−
24,25(OH)2D3
Excretion
Parathyroid glands
PTH
Kidney
+
1α,24,25(OH)2D3
1α-OHase
24-OHase
1α,25(OH)2D3
Dietary sources of vitamin D
Intestine
Increases absorption of Ca2+ and Pi
Bone
Increases bone mineralization
Immune cells
Induces differentiation
Tumour microenvironment
• Inhibits proliferation
• Induces differentiation
• Inhibits angiogenesis

Where do we get vitamin D from? 1

- Exposure to sunlight, the cutaneous production of vit D
  - affected by season,
  - latitude (UVB exposure angle over 50 deg)
  - the duration of exposure, sunscreen use
  - skin pigmentation
  - and the ability of the skin to form and process vitamin D

  - in southern areas 2 hr/week of sunshine on face and hands

Sunbathing 1

Sunbathing 2

Where do we get vitamin D from? 2

- Rarely found in foods naturally, dietary intake is a minor source of vitamin D (no more than 100 IU/day)
- Fatty fish and eggs
- Vitamin D–fortified milk
- Multivitamins and supplements


Sunflower
spread
Sunflower
spread
vegetable fat spread
Cod Liver Oil
550mg
1 to 2 a day
30
NUTRITION INFORMATION
SARDINES
IN BRINE
SARDINES
IN BRINE

Measurement of vit D status

- **Serum 25(OH)D** is the main circulating metabolite
- **Level of S- 25(OH)D is taken to assess vitamin D status**

Lips P. In: *Advances in Nutritional Research* 1994:151–65;

Vitamin D levels

	$25(OH)D_3$ (nmol/L)
Deficiency	< 25
Insufficiency	< 50
Optimal	> 75
Toxic	> 370

Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency Am J Clin Nutr. 2004 ;80:1706-9.

- Sometimes concentration of 25(OH) D_3 expressed in ng/mL:

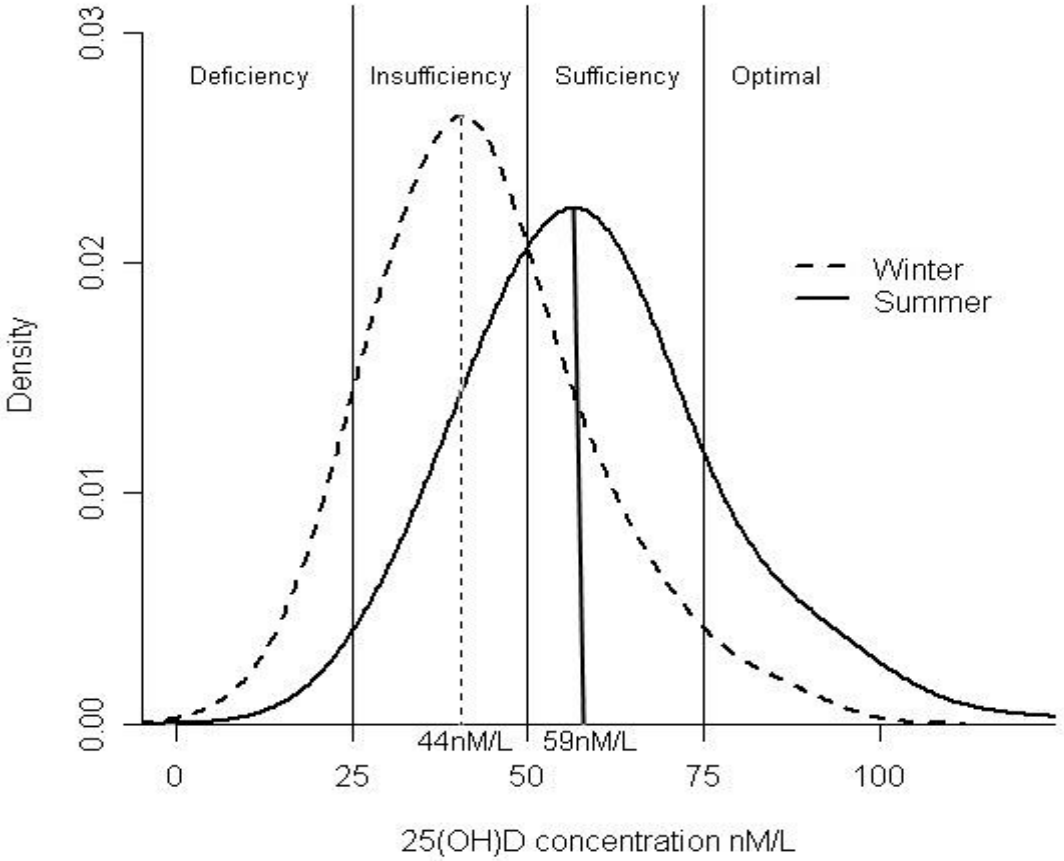
C1 **x 2.5** ng/mL= C2 nmol/L

Population study in Estonia

- N=357 (age 25-70), a random sample in GPs` list
- Average age 48.9±12.2 y
- 200 females, 167 males
- Measured in winter and summer

M.Kull, R.Kallikorm, A.Tamm, M.Lember BMC Public Health, 2009

Seasonal variation



Hypovitaminosis

1/3 in summer, 2/3 in winter

Avitaminosis in winter 8%

M Kull, R Kallikorm, A Tamm, M Lember
BMC Public Health, 2009

Sunbathing and vitamin D

Summer:

- Avoids Sun: average 45 nmol/l
- Sunbathing face, arms: 55 nmol/l
- Sunbathing total body: 63nmol/l

Winter:

- Avoids Sun : 34 nmol/l
- Sunbathing face, arms : 41 nmol/l
- Sunbathing total body : 46 nmol/l

D-vitamin in winter

Estonia (59N)	44 nmol/l
Finland (60N)	46
Belgium (50N)	48
Germany	40-45
Switzerland(46-47N)	50
USA (25-47N)	60-79

Optimal is considered >75 nmol/l

Vit D in Ca metabolism

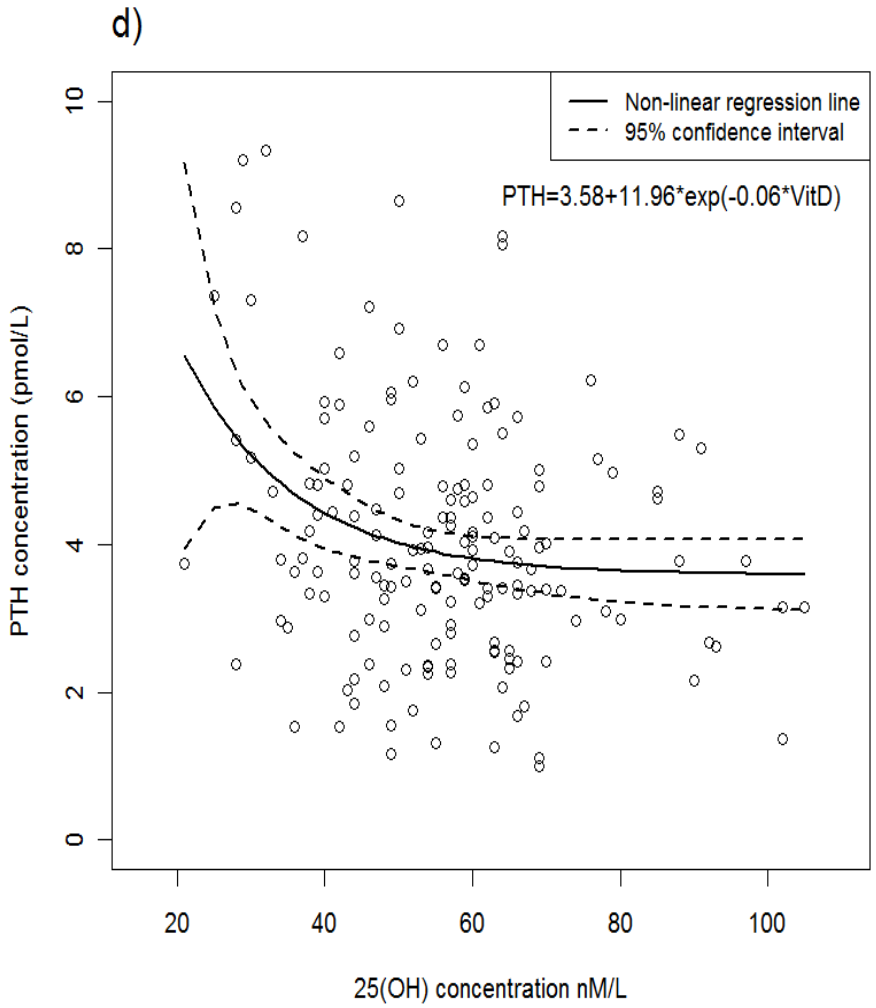
- helps to keep adequate levels of Ca and P
- enhances Ca absorption in intestine
- increases tubular Ca reabsorption
- helps to mobilize skeletal Ca
- Lower vit D→lower serum Ca →stimulates PTH↑
- PTH increases tubular Ca and decreases renal P reabsorption, stimulates osteoclasts to mobilize skeletal Ca stores

Holick M Current Drug Target 2011

Vitamin D vs PTH

- 367 Estonians
- (200 F,167 M)
- Summer PTH and 25(OH) vit D
- PTH plateau ~80 nmol/L

Kull M, Kallikorm R, Lember M. BMC Public Health 2009



Vitamin D and osteoporosis

- Impaired calcium absorption
- Increased PTH, increased bone resorption
- Decreased bone mineral density
- Decreased peak bone mass
- Decreased efficiency of osteoporosis medications
- Impaired muscle function, increased risk for falls

Prevalence of osteoporosis in Estonia

Random sample of population, age 40-70, N= 271

Spinal 5.5-8.6%

Femoral neck 1.3-2.0%

Osteopenia in Estonia:

Spinal 30-34%

Femoral neck 15-39%

Kull M, Kallikorm R, Lember M. Int Med J 2012

Vitamin D and bisphosphonates

Patients with nonsufficient response to treatment with bisphosphonates:

- 51% hypovitaminosis
- With correction of vit D -> in 85% cases positive dynamics of BMD

Ishijima et al. Calcif Tissue Int. 2009

Geller et al. Endocrine practice 2008

Vitamin D and muscles

- VDR expressed on muscle cells
- Vit D level correlated with muscle contractility
- Vit D deficiency- impaired function of 1b type (fast-twich) muscles
- In aging VDR number on muscle cells decreases

Bischoff-Ferrari H, Borchers M, Durmuller, JBMR 2004

M. Pfeifer, B. Begerow and H. W. Minne, Osteop. Int 2002

Vit D and muscle

- Maintaining posture requires adequate sensory-motor signal processing and coordinated muscle contractions as a complex motor response.

- Link between vit D level and muscle power (first of all, contraction velocity, not so much on stregth). Intracellular Ca levels, actin and myosin fibres.

Vitamin D and falls

- Metaanalysis: 5 RCTs
- Subjects: age 60+
- Follow-up: up to 3 years
- Conclusion: Vit D (compared to calcium only or calcium+placebo) decreases the risk for falls by **22%**
- NNT=15

Bischoff-Ferrari HA. *JAMA.* 2004;

Bischoff HA et al. *J Bone Miner Res.* 2003;

Gallagher JC et al. *J Clin Endocrinol Metab.* 2001;

Dukas L et al. *J Am Geriatr Soc.* 2004;

Vit D and central nervous system

- Vit D has demonstrated neuroprotective effects (whatever the mechanism- oxidative stress, degeneration, inflammation, vascular disorders)

- Cognitive function in the elderly

Impact of vitamin D

PubMed papers 57706 (14.01.14)

- Autoimmune diseases
- Cancer
- Cardiovascular diseases
- Diabetes and other metabolic
- Infections
- Falls, fractures, osteoporosis
- Depression
- Pregnancy

Grant WB, Cross HS, Garland CF et al. /Progress in Biophysics and Molecular Biology (2009)104-113

Vitamin D and cancer

- Vit D affects cell proliferation, inhibits cancer cell division, decreases angiogenesis, diminishes risk ofmetastases
- Some tumors produce $1,25(OH)_2D_3$ locally
- Protective effect of vit D from animal models. But in humans?

- Observational studies: vit D over 82.5 vs vit D less than 30: 2-fold difference in risk of colorectal cancer and breast cancer, but not in prostate cancer.

- Interventional studies have not proved so far usefulness of vit D in cancer prevention, methodological problems of the trials.

Obesity

- An independent risk factor for vit D deficiency
- Low dietary intake
- Sedentary lifestyle, limited sun exposure
- Decreased bioavailability of vit D due to sequestration of vit D within adipocytes
- After bariatric surgery vit D deficiency
- Increased dosages for supplementation, guidance on actual vit D measurements in blood

Vit D and immune system

- VDR is expressed by immune cells (lymphocytes, macrophages, neutrophils, dendritic cells)
- Local production of active vitamin D
- Vit D production locally in skin in case of skin barrier damage leads to increased antimicrobial defence

- Clinical data: vit D lower in patients with active tuberculosis
- Vit D deficiency may increase the risk of influenza, other viral and bacterial infections
- DM 1: more spread in countries with less sunshine and more expressed vit D deficiency

- Vit D deficiency and/or VDR absence predisposes to different immune-mediated disorders.

- Baeke F et al Mol Aspects Med 2008

- RA: Greater RA activity in patients with lower vit D levels
- Associations with multiple sclerosis, Crohn`s disease, RA, DM1
- Many confounding factors

- Mixed results of vit D links with infections and sepsis: more studies needed (type of infection, dosage and time for supplementation, outcome measures etc)

Vit D and cardiovascular risk

- Inverse association between vit D levels and cardiovascular risk
- Inverse association between vit D levels and hypertension
- Cerebrovascular events risk higher with low vit D
- Possible antidiabetic effects?

Prevention and treatment

- Screening recommended only for individuals at risk
- Infants: immediate daily supplementation (first year of life) 400 IU/daily

- Institute of Medicine (US):
  Age 1-70 600 IU/daily
  Age 70+ 800 IU/daily

- Endocrine society:
  children 400-1000 IU
  adults 1500-2000 IU

- Obese individuals, patients with malabsorption syndromes, patients on glucocorticoids, anti-seizure and AIDS medications may require 2-3 times higher doses

- Treatment of vit D deficiency: higher doses, 50000 IU/once a week for 8 weeks or 6000 IU /daily for 8 weeks, thereafter maintenence 600-1000 IU /daily

Conclusions

- Vit D level is a powerful biomarker for the overall health status in populations over the age of 50.
- Uncertainties: is it only a marker or contributes directly to induce health conditions (via genomic and cellular effects in imune cells or dysplastic precancerous cells)?
- Convincing evidence of vit D supplementation in preventing falls and fractures

- Low serum vit D levels should lead to a lifestyle evaluation, advice about outdoor activities, a reasonable amount of sunshine, fish consumption, vit D supplementation in winter if needed.
- High-dose vit D supplementation is useful in osteoporosis or severe vit D deficiency
- Uncertain whether supplementation decreases the risk for cancer or cardiovascular disease
- Bouvard B et al Joint Bone Spine 2011; 78: 10-16