

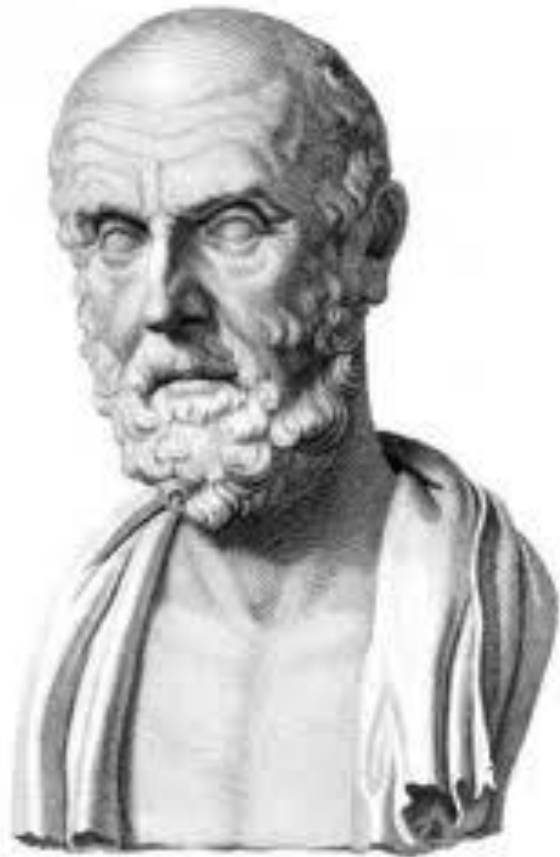
# VITAMIN D RELATED HEALTH PROBLEMS

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- It`s most healthy to live on the southern side of a mountain
- Hippokrates of Kos 460-370 BC

# Rickets/Rachitis

- 17th century- most children in Northern Europe developed rickets
- 1822- effect of Sun on rickets
- Connected to geographical location
- More in towns and cities
- Healing properties of the fish liver oil
- Vitamin D 1922
- UV induces the synthesis of vitamin D

**UM,UM GOOD**





- 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

# Vitamin D metabolism

**Vit D3 (colecalciferol)** in the skin, UVB, biologically inert

**Vit D2 (ergocalciferol)** in plants, biologically inert, weaker than D3

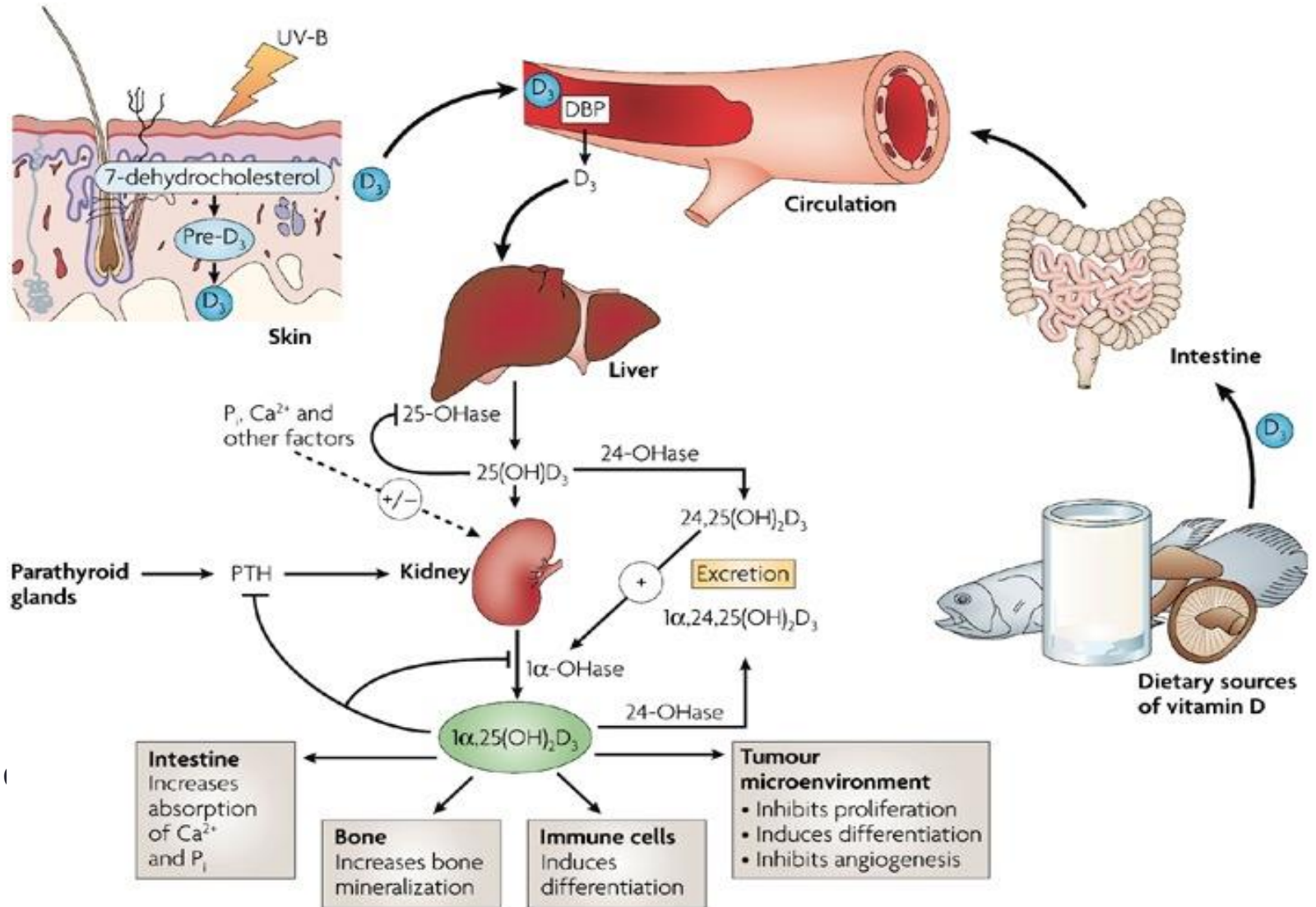
→ **in liver pro-hormone 25(OH)D**

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

→ in kidneys etc **1,25(OH)<sub>2</sub>D (calcitriol)**  
active vit D

- **Active vit D** can penetrate to target cells and bind to specific **VDR**, expressed in several organs
- These complexes translocate to nucleus, where they activate or repress the **expression of several genes**
- Vitamin D or D-hormone?
- Organism synthesizes its own vit D (no other vitamins)





• M H

# Where do we get vitamin D from? 1

## Exposure to sunlight

- affected by season,
- latitude
- the duration of exposure, sunscreen use
- skin pigmentation
- ability of the skin to form and process vitamin D
- in southern areas 2 hr/week of sunshine on face and hands

# Sunbathing 1

[Picture with nice young ladies]

# Sunbathing 2

[Picture with man sitting in seaside]

# 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



Cod Liver Oil  
550mg  
1 to 2 a day  
30

Sunflower spread  
vegetable fat spread



**NUTRITION INFORMATION**  
These eggs have been laid by hens, full and free to reach, large, fresh and incubated in a well ventilated barn. All items have been inspected and produced to high environmental and welfare standards.  
The only quality mark guarantee that these eggs have been laid in the standards of food safety and quality from hatch to farm before they are packed and ready to eat.  
All Lion Quality eggs are produced by Lion Red and are inspected daily. Visit Lion Quality at [www.lion.co.uk](http://www.lion.co.uk)

PER 100g	
Energy	157 kJ (37 kcal)
Protein	12.5g
Carbohydrate	0.7g
Fat	11.1g
of which saturated	3.2g
Monounsaturated	6.1g
Polyunsaturated	1.8g
Fibre	0g
Sodium	0.5g
Cholesterol	210mg
Iron	0.3mg
Calcium	50mg
Phosphorus	100mg



# Measurement of vit D status

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

- Sometimes concentration of 25(OH) D<sub>3</sub> expressed in ng/mL:

$$C1 \text{ ng/mL} \times 2.5 = C2 \text{ nmol/L}$$



# Vitamin D levels

	25(OH)D <sub>3</sub> (nmol/L)
Deficiency	< 25
Insufficiency	< 50
Optimal	> 75
Toxic	> 370

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

Heaney RP. Am J Clin Nutr. 2004 ;80:1706-9.

# Optimal?

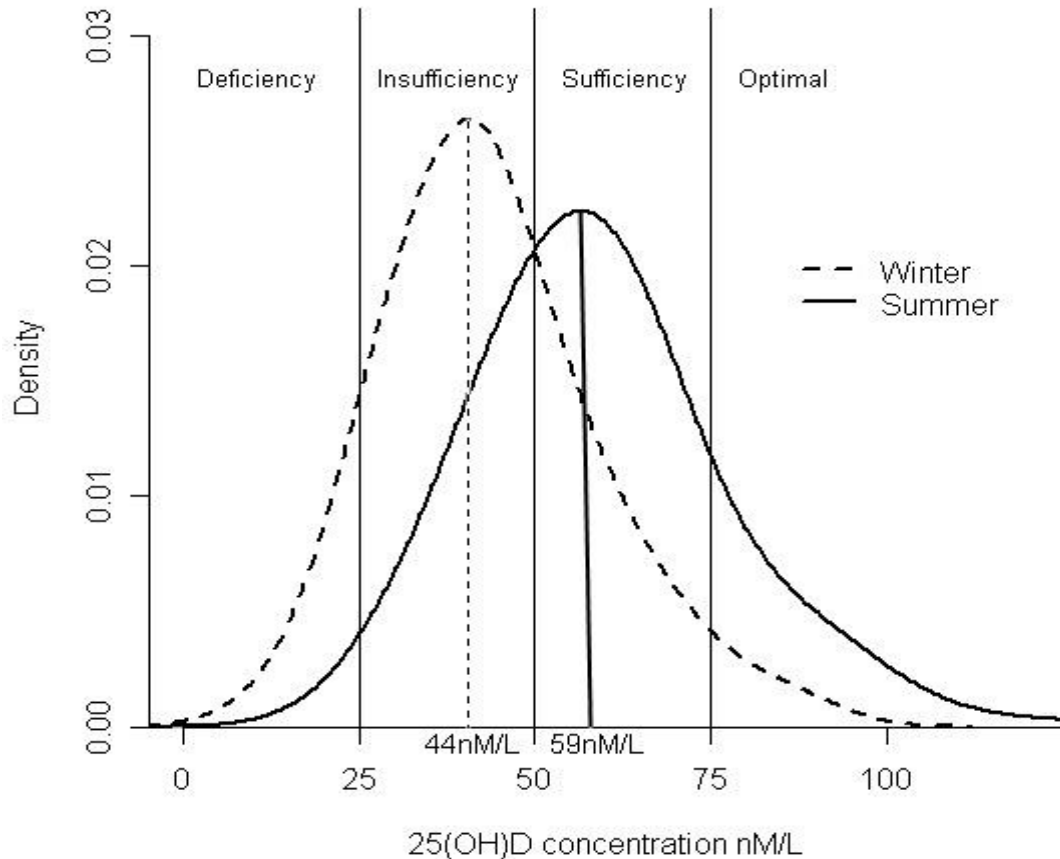
- 50 nmol/L Institute of medicine, Dietary recommendations 2011
- 75 nmol/L Endocrine Society (Holick MF et al 2011)
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# Population study in Estonia

- N=357 (age 25-70), a random sample in GPs` list
- Average age  $48.9 \pm 12.2$  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%

# 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**

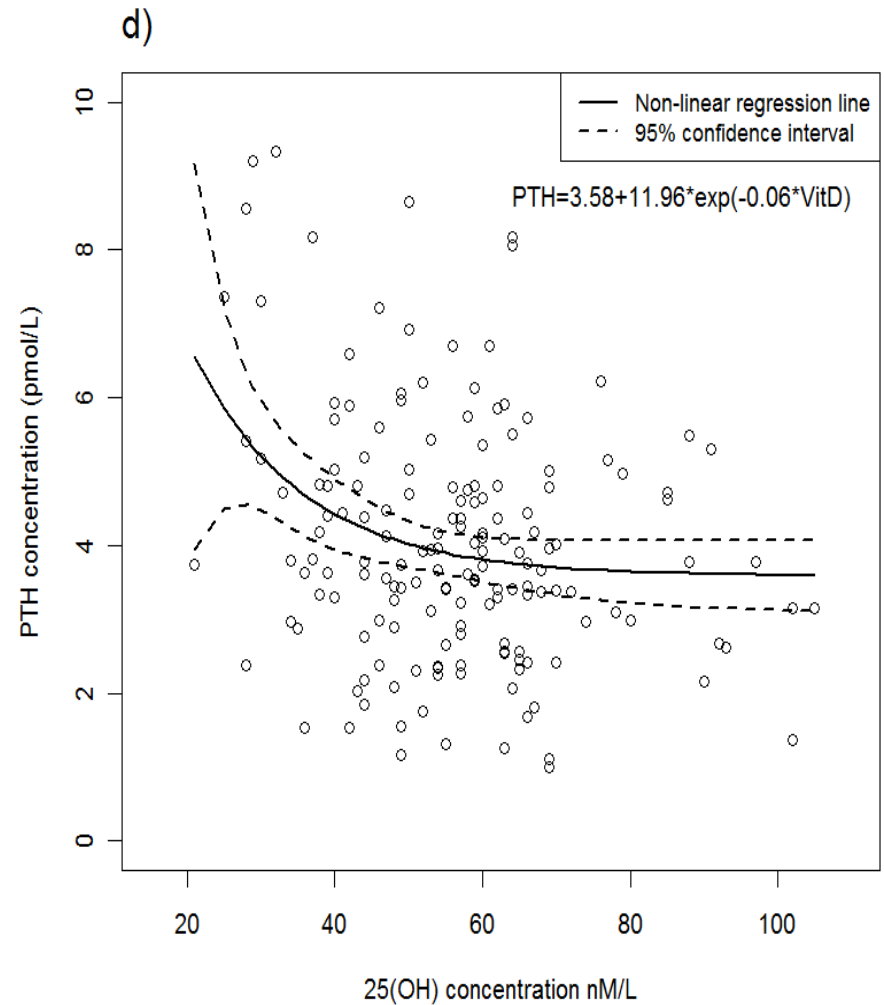
# Vit D in Ca metabolism

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

# 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





# Impact of vitamin D

PubMed papers 65023 (06.10.15)

- Skeletal system: falls, fractures, osteoporosis, muscles
- Extraskkeletal:
  - Autoimmune diseases
  - Cancer
  - Cardiovascular diseases
  - Diabetes and other metabolic
  - Infections
  - Depression
  - Pregnancy

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

# Low vitamin D and osteoporosis

- Impaired Ca 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

# Does vit D replacement improve bone/ prevent fractures?

- Inconsistent results, probably yes.
- Randomised, placebo-controlled trial: vit D and Ca supplementation reduced hip and non-vertebral fractures in a group of elderly vit D deficient women.

Chapuy MC et al N Engl J Med 1992; 327: 1637-1642

- Vit D alone did not reduce total or hip fracture risk.

Bolland MJ et al Lancet Diabetes Endocrinol 2014; 2: 307-320

- Older individuals at increased risk of vit D deficiency: supplement both vit D and Ca

# 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-twitch) muscles
- In aging VDR number on muscle cells decreases
- Maintaining posture requires adequate sensory-motor signal processing and coordinated muscle contractions

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

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

# 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%** in the elderly

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



# Vitamin D and cancer

- Vit D affects cell proliferation, inhibits cancer cell division, decreases angiogenesis, diminishes risk of metastases
- Some tumors produce  $1,25(\text{OH})_2 \text{D}_3$  locally
- Colorectal and breast cancers
- Protective effect of vit D from animal models.
- 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
- Decreased bioavailability of vit D due to sequestration of vit D within adipocytes
- Low dietary intake
- Sedentary lifestyle, limited sun exposure
- 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 vit 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
- Mixed results of vit D links with infections and sepsis: more studies needed
- Inflammatory changes- a reduction in total vit D levels, reduced levels of the binding proteins.
- Reid D et al Am J Clin Nutr 2011; 93: 1006-11

- 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

# Vit D and cardiovascular risk

- Inverse association between vit D levels and cardiovascular risk and hypertension
- Cerebrovascular events risk higher with low vit D
- Vit D supplementation does not improve glycemic indices, blood pressure or lipid status in prediabetes.

Sollid ST et al Diab Care 2014; 37: 2123-2131

- Vit D supplementation might protect against cardiac failure in older people, but not against MI or stroke.

Ford JA et al Am J Clin Nutr 2014; 100: 746-755

# 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 maintenance 600-1000 IU /daily
- Recently questions about „loading doses“



# 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 immune cells or dysplastic precancerous cells)?

- Convincing evidence of vit D in healing rickets and osteomalacia, mostly supporting evidence 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.