

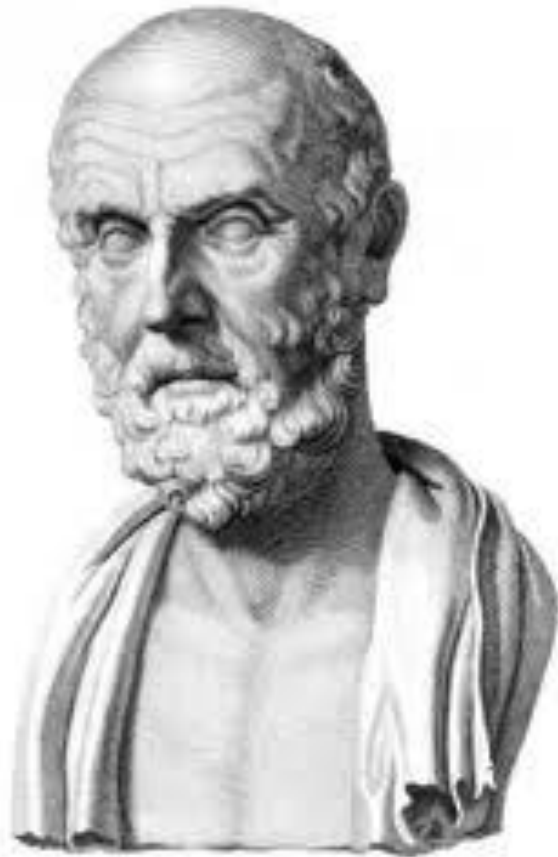
# VITAMIN D RELATED HEALTH PROBLEMS

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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

- 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 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

# 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**

# 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



# 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

# 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

# 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**

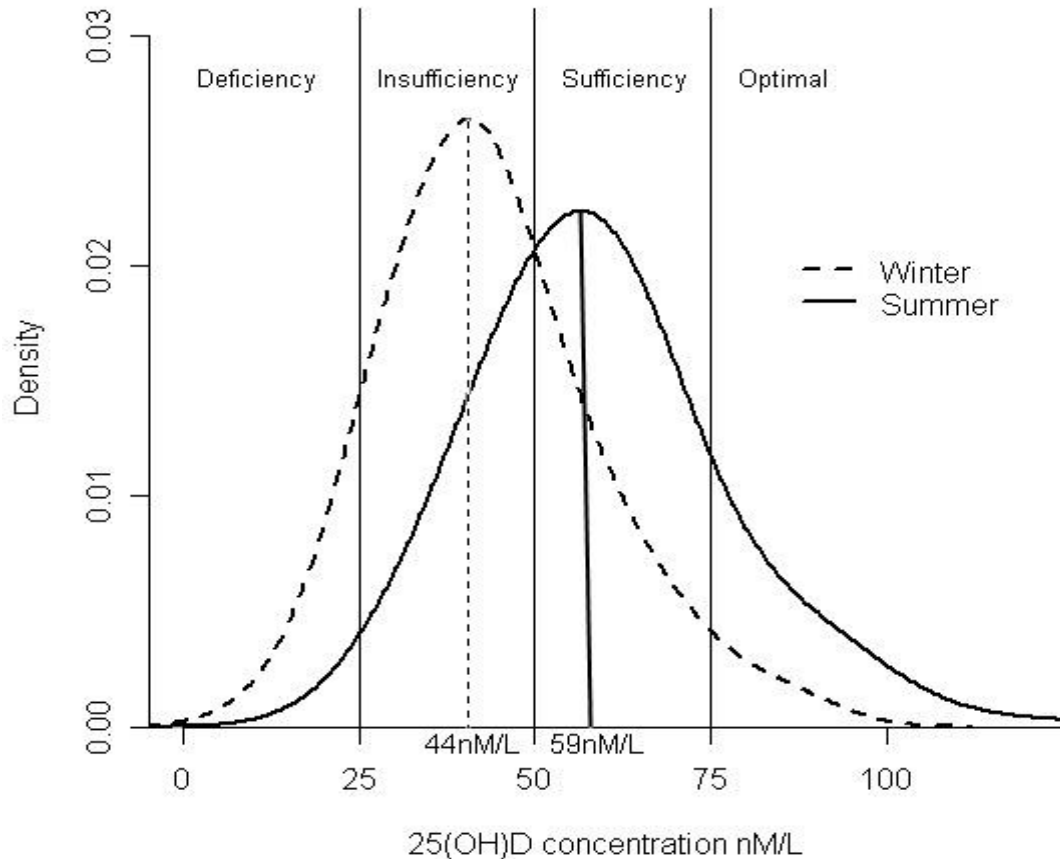
Heaney RP. Am J Clin Nutr. 2004 ;80:1706-9.

# 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**

# Is there really a pandemic?

Manson JE et al NEJM 2016

Wide-scale **misinterpretation and misapplication** of reference values

Values based on bone health studies on vit D supplementation:

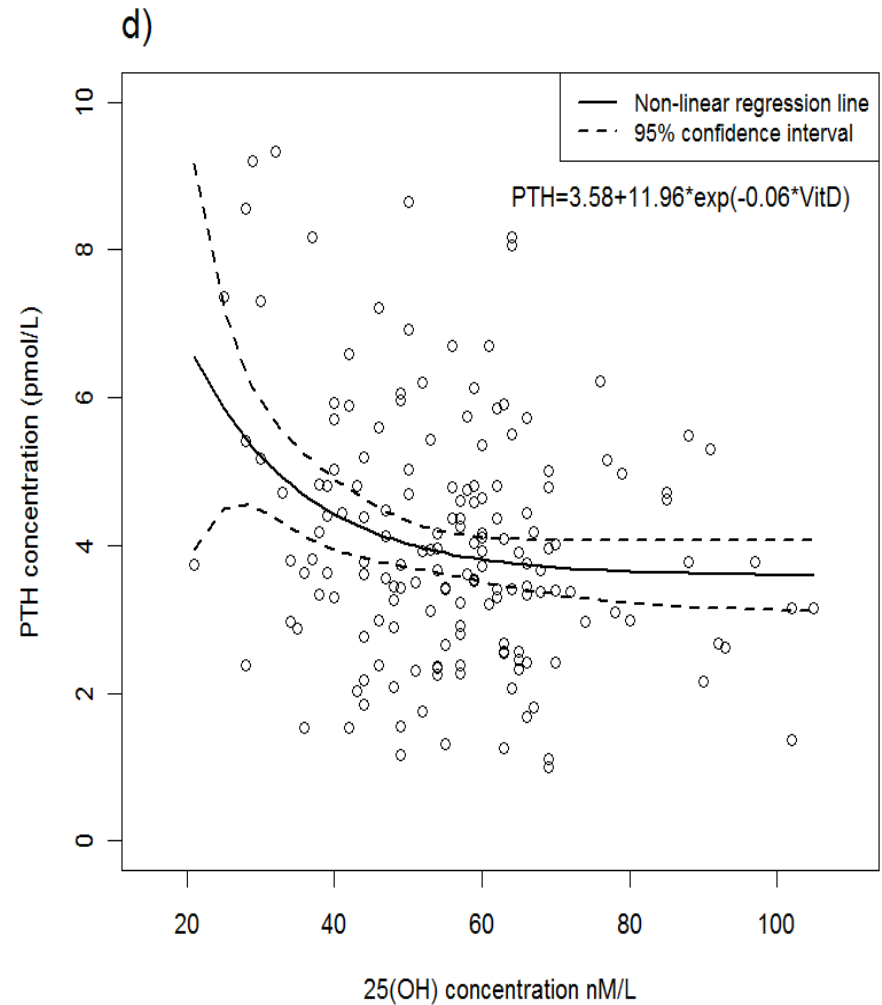
Median of the human requirements 400 IU/d adults, corresponds to 40 nmol/l

With 600 IU/d (corresp. 50 nmol/l) 97.5% population covered

# 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



but

- The utility of using PTH for optimal level of vit D concentration remains controversial
- Relationship between serum vit D and PTH inconsistent, no clear threshold

Manson JE et al NEJM 2016

# Impact of vitamin D

PubMed papers 70711 (05.02.17)

10 papers/day added

- Skeletal system: falls, fractures, osteoporosis, muscles
- Extraskeletal:
  - 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

- 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
  - Recent meta-analysis confirming the risk (Ekmekcioqlu C et al 2017)
- 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

# Screening

- **US Preventive Services Task Force (2015):**  
Community-dwelling nonpregnant asymptomatic adults:  
**no recommendation** (insufficient evidence)
- Screening recommended only for individuals at risk

# Risk factors for vit D deficiency Holick MF et al 2011

- Bone diseases (rickets, osteomalacia, -porosis, -penia)
- Hyperparathyreoidism
- GI diseases (hepatic failure, malabsorption, cystic fibrosis, IBD, bariatric surgery)
- Obesity (BMI over 30)
- African-Americans, Hispanics
- Medications (antiseizure, glucocorticoids, AIDS medications, antifungals, cholestyramine)
- Pregnancy, lactating
- Chronic kidney disease
- Older adults (history of falls, history of nontraumatic fractures)

# Measure before treatment?

- Under discussion
  - Probably not
  - Better follow-up?
  - Better treatment adherence?
  - Additional costs?
- 
- Comparability of lab results? No international standards  
Sempos CT et al 2015

# Treatment effects

- Decrease risk of falls (RCTs), but...
- Observational studies on other effects
- RCTs under way to clarify cardiovascular disease or cancer risk

# Vit D supplementation studies

- Crohn`s disease patients given high dose vitamin D have fewer relapses (Narula N et al Dig Dis Sci 2016)
- Elderly patients (over 70 yrs) given 2000 IU/d for 1 year: average vit D from 50 nmol/L to 107 nmol/L; no hypercalcaemia or kidney stones (Hin H et al 2016 Osteop Int)
- Meta-analysis: vit D no effect on reducing hip and total fractures (Bolland MJ et al Lancet Diab Endocrinol 2014)

- High-dose supplementation to increase risk of falls

Bischoff-Ferrari et al JAMA Internal Medicine 2016

- Umbrella review of systematic reviews: Despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable.

Theodoratou E et al BMJ 2014



- Neither Vitamin D nor Exercise Affected Fall Rates Among Older Women in Finland

Uusi-Rasi K et al JAMA Int Med 2015

Tim Spector: genes play a role

# Prevention and treatment

- 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

# 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.

- Expecting review of the existing recommendations