Beyond Osteoporosis
The Global Impact of Vitamin D deficiency

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Introduction
Vitamin D

- Vitamin D insufficiency is an emerging global health concern.

- There is a worldwide epidemic of vitamin D deficiency in various populations, including infants, pregnant and lactating women, the elderly, individuals living in latitudes far from the equator, persons who avoid the sun or ultraviolet radiation in the blue spectrum (UVB), and populations with dark skin pigmentation.

- Scientific evidence indicates that Vitamin D has a new and more critical role as ubiquitous hormone at the centre of a complex endocrine, paracrine, and autocrine system involved in maintaining general health.
Most tissues and cells in the body have a vitamin D receptor.

Many studies have revealed new insights into the regulation of these receptors and new targets for its action.

Several of these cells possess the enzymatic machinery to convert the primary circulating form of vitamin D to the active form.

Vitamin D was found to play an interesting role in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease.
Vitamin D is a steroid which, in its active form, has a hormone activity.

The major sources of vitamin D in humans are cutaneous synthesis, diet, and supplements.

Vitamin D exists in two forms: D2 or ergocalciferol and D3 or cholecalciferol.

These forms differ in the side chains. These differences alter its metabolism, and overall make D2 somewhat less potent than D3.
Vitamin D

- D 25-OH has a half-life in circulation of approximately 2 weeks, making it the best biomarker of vitamin D status.

- The conversion of vitamin D to 25OHD is under little metabolic control. The conversion of 25OHD to 1,25(OH)2D, however, is tightly controlled.

- D 25-OH is the major circulating form of vitamin D, with concentrations in the blood approximately 1000 times that of 1,25(OH)2D3. 24,25(OH)2D3 circulates at approximately 100 times that of 1,25(OH)2D3, and is therefore the second most abundant vitamin D metabolite in blood.
Vitamin D receptor (VDR), a nuclear receptor found in most organs is activated by the physiologically active form of vitamin D, 1,25-(OH)2-D.

The wide tissue distribution of the VDR led to the recognition of the noncalcitropic actions of 1,25-(OH)2-D.

The calcitropic actions of 1,25-(OH)2-D include enhancement of intestinal calcium and phosphorus absorption, suppression of parathyroid hormone secretion, and stimulation of bone resorption.
THE VITAMIN D ICEBERG

cell cycle regulation

gene control

Ca economy
# Cellular and tissue distribution of vitamin D receptor

<table>
<thead>
<tr>
<th><strong>Endocrine</strong></th>
<th>Parathyroid gland, thyroid, pituitary, adrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central nervous system</strong></td>
<td>Brain neurons</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Alveolar cells</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Esophagus, stomach, hepatocytes, small and large intestine</td>
</tr>
<tr>
<td><strong>Renal/ genitourinary</strong></td>
<td>Kidney, urethra, prostate</td>
</tr>
<tr>
<td><strong>Reproductive</strong></td>
<td>Testis, ovary, uterus, placenta</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td>Osteoblasts, osteocytes, chondrocytes, fibroblasts, striated muscle</td>
</tr>
<tr>
<td><strong>Epidermis</strong></td>
<td>Skin, hair follicle, breast</td>
</tr>
<tr>
<td><strong>Immune</strong></td>
<td>Thymus, T-cells, B-cells, macrophages</td>
</tr>
</tbody>
</table>
Mechanism of action
Vitamin D

**Endocrine**

- 25(OH)D → 25(OH)D
- 1,25(OH)₂D
  - 1-α-OHylase
  - PTH
- Serum Pi
- FGF23

**Autocrine**

- 25(OH)D → 25(OH)₂D
- 1,25(OH)₂D → 1,24,25(OH)₃D
  - 24-OHylase
  - 1,25(OH)₂D
AUTOCRINE ACTION

- 1,25D
- VDR
- RXR

VDRE

Transcription
AUTOCRINE ACTION

- cell proliferation
- cell differentiation
  - apoptosis
- immune response
- 24-hydroxylase
AUTOCRINE ACTION

~ 800 genes have VDREs
AUTOCRINE ACTION

25OHD ➔ 25OHD

1,25D ➔ 1,25D

VDR ➔ VDR

VDR ➔ VDR

RXR ➔ RXR

VDRE ➔ Transcription

1,25D
AUTOCRINE ACTION

25OHD → 25OHD

1,25D → VDR

1,25D → VDR

1,25D → RXR

VDRE

Transcription
HOW A CELL RESPONDS

**Signal/Demand**

1,25(OH)$_2$D is the key that unlocks the DNA library

**Response**

newly synthesized cellular equipment
VIT D - CANONICAL SCHEME

<table>
<thead>
<tr>
<th>skin</th>
<th>liver</th>
<th>kidney</th>
<th>gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₃</td>
<td>25(OH)D₃</td>
<td>1,25(OH)₂D₃</td>
<td>CaBP</td>
</tr>
</tbody>
</table>
VIT D - EXPANDED SCHEME

- **endocrine**
  - skin
  - liver
  - $1,25(OH)_2D_3$

- **autocrine**
  - $D_3$
  - $25(OH)D_3$
  - $85\%$

- **kidney**
  - $1,25(OH)_2D_3$
  - $21\%$

- **gut**
  - $CaBP$
  - $1,25(OH)_2D_3$
  - various tissues
  - cell signals

Various tissues receive $1,25(OH)_2D_3$ through periphery signals.
How much Vitamin D is enough and how can this be achieved?
VITAMIN D - Sources

Body D₃ stores

2000

25(OH)D

typical input, all sources: ~2350 iu

150

200
Vitamin D normal level and supplementation

- Serum 25(OH)D from 50 to ~80 nmol/L (30 ng/ml) is needed to improve Ca absorption, raise BMD, and reduce falls and osteoporotic fracture risk. A concentration of 75-125 nmol/l has been recommended. Heaney in the American Journal of Clinical Nutrition 2004.

- Serum 25(OH)D rises by ~1 ng/mL (2.5 nmol/L) for every 100 additional IU/d of vitamin D₃.

- To raise a patient level from 15 to 30 ng/mL will typically require an additional input of 1500 IU/d, however there is huge variability around this average.
VITAMIN D - Sources

Body D₃ stores → 25(OH)D

Needed input, all sources: ~4000 iu

Sources:
- Sun: 2000 iu
- Foods: 150 iu
- Supplements: 200 iu
A VITAMIN D THRESHOLD

physiological regulation no longer limited by vit D availability
Is replacing vitamin D 1, 25 OH is enough?
Safety
VITAMIN D INTAKE & TOXICITY*

15 studies of adults receiving vitamin D supplementation (means)
8 studies reporting toxicity (individual values)

no toxicity below 30,000 IU/d
no toxicity below 500 nmol/L (200 ng/mL)

Maximum safe Total daily intake: 10,000 IU/d*

D2 Vs D3
D$_2$ vs. D$_3^*$ - AUC

*Armas et al., 2004
Beyond Osteoporosis
**Immunomodulatory Effects of Vitamin D**

- A major noncalcitropic function of 1,25-(OH)2-D is in the regulation of the immune system.

- Vitamin D play an important role in both innate and Adaptive immunity.

- Recent studies showed a potential therapeutic role of vitamin D, its metabolites and its analogues for infectious and auto-immune disorders in humans.

- Patients with rickets have impaired macrophage phagocytic function, which could be reversed by 1,25-(OH)2-D repletion.

- Recent studies have also shed new light on the mechanism of the antimicrobial action of 1,25-(OH)2-D.
Vitamin D and Innate immunity
VITAMIN D & INNATE IMMUNITY*

*Liu et al., Science 2006
VITAMIN D & INNATE IMMUNITY*

*Liu et al., Science 2006
Human Macrophages in fetal calf serum

the Vit D 1-α hydroxylase

the Vit D receptor

Cyp27B1

VDR

*Liu et al., Science 2006*
VI T A M I N  D & I N N N A T E I M M U N I T Y*

- Human macrophages in fetal calf serum
- Fetal calf serum is low in both 25(OH)D & 1,25(OH)₂D

*Liu et al., Science 2006
Human macrophages in fetal calf serum add 1,25(OH)₂D to the system

*Liu et al., Science 2006
VI T A M I N  D & I N N AT E  I M M U N I T Y*  

- Human macrophages in fetal calf serum  
- add 25(OH) D to the system  

*Cathelicidin Cyp24  
Cyp27B1 VDR  
1,25D  
25OHD  

*Liu et al., Science 2006
Human macrophages activated with *M. Tuberculosis* and incubated in human serum
- African-American
- White
- African-American with added 25(OH)D

**Cathelicidin mRNA**

- Serum 25(OH)D: 78 nmol/L
- Serum 25(OH)D: 22 nmol/L

*Liu et al., Science 2006*
VITAMIN D & TUBERCULOSIS

- Vitamin D is an essential mediator in the innate immune response
- Serum 25(OH)D is the critical variable
- 25(OH)D is the rate-limiting
VI TAMI N D & TUBERCULOSIS*

- 67 pts with pulmonary TB
- standard treatment for all
- in addition, randomized to either vit D 10,000 IU/d or placebo
  - $P = 0.002$

*S nursyam et al., Acta Med Indones 2006
Most recent articles

- A single oral dose of 2.5 mg vitamin D2 improve week one level but not week 8. (int J Tuberc lung dis Jan 2009)
- Wagner et al Dec 2008. Dose Vitamin D makes the World go round?
- Cochrane Database syst rev. Oct 2008. There were not enough evidence to assess the effect of vitamin D on TB. Trials in progress
- Enhancing the innent immunity in TB for example is clearly beneficial but potentiating of the pro inflammatory processes can increase tissue destruction.
Vitamin D and the immune response to Mycobacterium tuberculosis
VITAMIN D & INFLUENZA*

- 208 African-American, postmenopausal women
- 3 yr DB-RCT
- placebo or vit D$_3$
  - 800 IU/d – 2 yrs
  - 2000 IU/d – 3rd yr
- basal 25(OH)D: 18.8 ± 7.5
  - $P < 0.002$

* Aloia & U-Ng (2007) Epidemiol & Infect
Vitamin D and auto-immune disorders

- Major effect of 1,25-(OH)2-D on the immune system is the suppression of the adaptive immune.
- This seems to be beneficial in Autoimmunity.
- Epidemiologic reports have correlated limited sunlight exposure, reduced dietary vitamin D intake or 25-OH-D levels with a number of auto-immune diseases.
- Studies have shown effectiveness of 1,25-(OH)2-D and its analogs in a variety of animal models of these autoimmune disorders.
Multiple sclerosis

- The prevalence of multiple sclerosis (MS) is well known to increase with latitude both north and south of the equator.

- The role of sunshine was proposed several decades ago, and recent studies have provided evidence that high levels of vitamin D may decrease the risk of MS.

- Intake of vitamin D from diet and from supplements was inversely associated with risk of MS in the Nurses’ Health Study and Nurses’ Health Study II.
Systemic lupus Erythematosus

- The greater incidence of (SLE) in African-Americans and increased morbidity and mortality compared to Caucasians has been attributed to lower serum 25-OH-D concentrations.

- In a group of lupus patients, severe D deficiency was associated with higher disease activity measures but lower levels of antibodies to double-stranded DNA than in patients with normal serum D.

- On the other hand, vitamin D intake from food and supplements was not associated with risk of SLE in the Nurses’ Health Study and Nurses’ Health Study II.

- The role of vitamin D deficiency in the pathogenesis of SLE and whether vitamin D supplementation can improve the course of the disease is still not entirely proven.
Multiple sclerosis

- The risk of MS significantly decreased with increasing levels of 25-OH-D. This was found in a study done on stored serum samples for more than 7,000,000 US military personnel in D.O.D.

- Studies in experimental animal model for human MS disease, also suggest a protective role of active D in MS, through inhibition of monocyte trafficking to the central nervous system, and suppression of chemokine synthesis.

- In a recently published small, uncontrolled pilot study, administration of high doses of vitamin D (up to 280,000 IU per week) to MS patients was associated with a tendency toward a decrease in the number of gadolinium-enhancing lesions per patient.

- Jan 2009 in Mult Scler: a study concluded that higher levels of vitamin D OH are associated with lower incident of MS in women only.
Antiproliferative properties of vitamin D
Antiproliferative properties of vitamin D

- A major noncalcitropic action of 1,25-(OH)2-D is its modulation of benign and malignant hyper proliferative conditions.

- The antineoplastic properties of 1,25-(OH)2-D include regulating apoptosis and angiogenesis, and promoting cellular proliferation of normal and cancerous cells while inducing their terminal differentiation.

- Calcipotriol (calcipotriene), a synthetic 1,25-(OH)2-D analog, has become first-line therapy for plaque psoriasis, either as monotherapy or in combination.
Antiproliferative properties of vitamin D

- In a 4-year study of 1179 community-dwelling postmenopausal women randomly assigned to calcium supplementation alone, calcium and vitamin D supplementation, or placebo, cancer incidence was significantly lower in the calcium and vitamin D supplemented women than in the placebo control subjects (P < 0.03),

- Serum 25-OH-D level was a significant independent predictor of cancer risk in the same study

- The role of vitamin D supplementation in the prevention and treatment of cancer is still not entirely clear
1179 healthy women
aged 66.7 ± 7.3
four year trial
1032 finished (87.5%)
baseline 25(OH)D: 71.8 nmol/L ± 20.3
three treatment groups:
- control
- Ca (1400–1500 mg/d)
- Ca plus D₃ (1100 IU/d)
achieved 25(OH)D: 96 nmol/L ± 21.4

*Lappe et al. AJCN 2007*
VITAMIN D & CANCER

Time (yrs)

Fraction Cancer-Free

0.90
0.92
0.94
0.96
0.98
1.00

Ca+D
Ca-only
Placebo

RR < 0.002

*Lappe et al. AJCN 2007
VITAMIN D & CANCER*

*Lappe et al. AJCN 2007
VI TAMI N D & CANCER*

*Lappe et al. AJCN 2007
Vitamin D and Colon Cancer

- Epidemiologic studies have described inverse associations between biomarkers of sunlight exposure, dairy products, or dietary vitamin D and the risk of various malignancies including colon cancer, prostate cancer, breast cancer, and pancreatic cancer.

- The largest randomized placebo-controlled study of vitamin D and the risk of colon cancer is the Women’s Health Initiative. The incidence of invasive colorectal cancer after 7 years did not differ significantly. N Engl J Med Feb 2006.

- In the (NHANES) III, serum 25-OHD levels was not associated with total cancer mortality, although in the same study, individuals with higher 25-OH-D levels had significantly lower risk of colon cancer mortality.
COLORECTAL CANCER

- Nurses’ Health Study
- ages 46–78
- nested case-control study
- 193 incident cases
- 25(OH)D measured twice, prior to diagnosis
- Feskanich et al., Cancer Epidemiol Biomarkers Prev 2004 13:1502–08

**Odds Ratio**

25(OH)D Quintiles (with medians*)

*ng/mL

P = 0.02
COLORECTAL CANCER

- 5 prospective studies
- > 200,000 individuals
- 430 cases
- ORs computed for 25(OH)D quintiles
- Garland et al, 2005

![Graph showing odds ratio vs Serum 25(OH)D levels with P < 0.001](image)
Vitamin D and Prostate Cancer

- Epidemiological studies have yielded inconsistent associations between vitamin D status and prostate cancer risk.

- A nested case control study as part of the Prostate, lung, colorectal and ovarian cancer screening trial project concluded that Vitamin D is not associated with decreased prostate cancer risk, higher circulating vitamin D was associated with increased risk of aggressive disease. J Natl cancer Inst. June 2008

- In men with advanced, androgen-insensitive prostate cancer treatment, the use of a Vitamin D analog, was associated with improved survival, although it did not produce a statistically significant improvement in the PSA response rate.
VITAMIN D & PROSTATE CA*

- Nested Case control study in the Helsinki heart Study
- 19,000 men
- F Up for 13 years
- 149 cases prostate CA

*Ahonen et al., CancerCauses&Control 11:847-852 (2000)
Those below the median 25(OH)D level were 70% more likely to develop prostate CA than those above.

*Ahonen et al., Cancer Causes & Control 11:847-852 (2000)
Vitamin D and Breast Cancer Risk

- WHI again reported that a vitamin D supplement did not decrease the risk of Breast cancer.

- Epidemiological studies from premenopausal women suggest that vitamin D supplementation may prevent breast cancer in these women. Lin et al Arch Intern Med 2007

- Further studies to address the issues of higher dose of vitamin D and the risk of breast cancer are needed.
BREAST CANCER RISK

- Case-control study
  - 1394 cases
  - 1365 controls
  - Pre menopausal
- Odds ratio for CA inversely associated with vit D status [25(OH)D]

69% decrease in risk

Hazard Ratio

Serum 25(OH)D (nmol/L)
MAMMOGRAPHIC DENSITIES

- 543 women aged 40–60
- 1989–90
- dietary intakes assessed with FFQ
- odds ratios developed for <30% vs. >70% of film with densities
- [Berube et al., 2004; Cancer Epidemiol Biomarkers Prev 13:1466–72]
Vitamin D and cardiovascular disease/ risk factors

- In the Framingham Offspring Study, 25-OH-D deficiency was associated with incident cardiovascular disease, particularly in hypertensive individuals.

- This may be due to the association of lower 25-OH-D levels with a number of traditional cardiovascular risk factors.

- The association between obesity and hypovitaminosis D may be in part due to reduced vitamin D bioavailability from sequestration in adipose tissue.

- From a cross-sectional analysis of data from the third national health and nutrition examination indicated a strong and independent relationship between vitamin D deficiency and the prevalence of CVD. Atherosclerosis Nov 2008
**VIT D & CARDIOVASCULAR DISEASE**

- 1739 Framingham Offspring members
- age: 59 yrs
- follow-up: 5.4 yrs
- 120 individuals developed a CV event
- HR calculated against 25(OH)D values > 15 ng/mL
- *Wang et al. Circulation 2008*

**Graph:**
- Hazard Ratio
- 80% increase in risk
- 53% increase in risk

**Bar Graph:**
- < 10 ng/mL
- < 15 ng/mL
- > 15 ng/mL
Recent reports on the relationship between vitamin D and the risk of hypertension from three large independent prospective cohorts, the Nurses’ Health Study I and II, and the Health Professionals Follow-up Study have yielded conflicting results.

While intake of vitamin D was not associated with the risk of developing hypertension, lower serum 25-OH-D levels conferred a greater risk for the incident hypertension.

Forman et al. Nov. 2008 in Hypertension found that in young women vitamin D level was inversely and independently associated with the risk of developing hypertension.
VIT D & BLOOD PRESSURE*

- 148 women, aged 74 ± 1
- DB-RCT
- baseline 25(OH)D < 50 nmol/L
- treated for 8 wks with:
  - Ca 1200 mg/d or
  - Ca + 800 IU vit D/d

*Pfeifer et al., JCEM 2001; 86:1633–37
1811 men & women with measured 25(OH)D levels**
4 yrs’ observation
97 cases of incident hypertension
RR computed for 25(OH)D <15ng/mL vs. >30 ng/mL

*Forman at al., 2007; Hypertension 49:1063
** Health Profs Follow-up Study & Nurses Health Study
Scragg et al., 2004
Diabetes Care 27:2813–18

NHANES-III
6,228 adults
plasma glucose independently predicted by BMI & serum 25OHD (fasting and 2 hr post load)
NEONATAL VIT D & DIABETES*

- 10,366 northern Finnish children
- 2000 IU Vit D/d 1st year of life
- prevalence of type I diabetes assessed at age 21
- RR calculated vs. no supplementation

*Hypponen et al., Lancet 2001;358:1500–03
**OTHER CHRONIC DISEASES?**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Status of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteoporosis</td>
<td>++++</td>
</tr>
<tr>
<td>osteoarthritis</td>
<td>+</td>
</tr>
<tr>
<td>falls/ neuromusc. fcn</td>
<td>++++</td>
</tr>
<tr>
<td>multiple sclerosis</td>
<td>++</td>
</tr>
<tr>
<td>fibromyalgia-like syndrome</td>
<td>++</td>
</tr>
<tr>
<td>type I diabetes</td>
<td>++</td>
</tr>
<tr>
<td>insulin sensitivity</td>
<td>++</td>
</tr>
<tr>
<td>cardiovascular disease</td>
<td>+++</td>
</tr>
<tr>
<td>periodontal disease</td>
<td>++++</td>
</tr>
<tr>
<td>various cancers</td>
<td>++++</td>
</tr>
<tr>
<td>tuberculosis</td>
<td>++++</td>
</tr>
<tr>
<td>hypertension</td>
<td>++++</td>
</tr>
</tbody>
</table>
Bone health and Skeletal health
Serum 25(OH)D and Hip BMD

- NHANES-III
- Adults Age 20 - 49 yrs
- Lowest plot of difference from lowest quintile

VITAMIN D & FRACTURE RISK

- N = 2,686
- ages 65–85
- 5 yr RCT
- Vit D \( \cong 800 \) IU/d
- Trivedi et al. BMJ 2003; 326:469

Fracture relative risk (hip, forearm, spine)

- 33% decrease

(nmol/L)
VIT D & NEUROMUSCULAR FUNCTION*

- 1359 men & women; mean age 75.5
- Amsterdam longitud. aging study
- neuromuscular performance measured on a scale of 0 to 12 (higher is better)
- each step statistically significant

*Wicherts et al. JBMR. 2005.
VITAMIN D & RISK OF FALLING

- 122 women
- Age: 63–99
- DB-RCT
  - Ca 1,200 mg/d
  - Ca + 800 IU Vit D
- 12 week duration
- 25(OH)D 12 ng/mL at baseline

Thank you

Special thanks to Dr. Robert Heaney for allowing me to use some of his slides