Vitamin D to Improve Health Outcomes?

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Overview (1):

- The major evidence for vitamin D activities concern two distinct bone diseases, osteomalacia and osteoporosis.

- To prevent osteomalacia vitamin D exerts endocrine activities to maintain plasma calcium and phosphate homeostasis, regulating intestinal calcium absorption, kidney reabsorption of calcium and, most importantly, resorb bone.
Overview (2):

- To prevent osteoporosis, Vitamin D exerts **autocrine** activities in bone, in conjunction with adequate dietary calcium, to reduce bone resorption and stimulate bone formation.

- These vitamin D activities for bone health provide information of the potential activities of vitamin D for broader health outcomes.
Overview (3):

- Vitamin D exerts activities across a wide range of tissues modulating expression of least 900 genes.

- Many of these activities involve autocrine activities highlighting the importance for maintaining adequate levels of 25-hydroxyvitamin D, the prohormone.
Vitamin D Synthesis and Activity

Vitamin D₃

Skin

UV

7-dehydrocholesterol

Vitamin D₃

Liver

CYP2R1

25D [INACTIVE]

CYP24

Kidney

CYP27B1

Plasma

24,25(OH)₂D₃ [INACTIVE]

1,25D [ACTIVE]

Endocrine Activity

Ca homeostasis

1,25D

VDRE

VDR

+1
The Endocrine Action of Vitamin D Regulates Intestinal Calcium Absorption
Critical serum 25D Level for Osteomalacia amongst Indian Females New Delhi (Lat. 29ºN)

<table>
<thead>
<tr>
<th></th>
<th>Female patients</th>
<th>Siblings</th>
<th>Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(90)</td>
<td>Sister (51)</td>
<td>Mother (49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brother (74)</td>
<td>Father (47)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24 (9.5)</td>
<td>18 (7)</td>
<td>43 (9)</td>
</tr>
<tr>
<td>Serum 25D (nmol/L)</td>
<td>14.4 (5.7)</td>
<td>18.3 (9.9)</td>
<td>24.5 (17.6)</td>
</tr>
<tr>
<td>Serum 25D (ng/mL)</td>
<td>5.8 (2.3)</td>
<td>7.3 (4.0)</td>
<td>9.8 (7.0)</td>
</tr>
<tr>
<td>Serum PTH (pmol/L)</td>
<td>26.1(16)</td>
<td>8.7 (8.6)</td>
<td>5.5 (3.8)</td>
</tr>
<tr>
<td>Biochemical Osteomalacia</td>
<td>90/90</td>
<td>11/45</td>
<td>5/42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/61</td>
<td>5/40</td>
</tr>
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</table>

Critical level for plasma 25D ≥ 8 ng/mL (20 nmol/L )

Hip fracture patients arising from osteoporosis have provided new insights into requirements for vitamin D.
Vitamin D plus Dietary Calcium but Not Vitamin D alone Protects against Fracture

Data from 68,500 patients

DIPART Group Brit Med J 2010; 340: b5463
Serum 25D less than 20 ng/mL (50 nmol/L) stimulates bone loss and increases risk of fracture

- The rate of bone loss in older, community dwelling men was significantly less (-0.35%/yr) when serum 25D levels were between 20 to 30 ng/mL (51 to 75 nmol/L) compared to -0.54%/yr when levels were 15 to 20 ng/mL (37.5 to 50 nmol/L) (Ensrud et al JCEM 2009;94:2773-2780)

- Postmenopausal women with serum 25D levels < 19 ng/mL (47.5 nmol/L) increased their risk of hip fracture by 71% compared with women with serum 25D levels ≥ 28 ng/mL (70 nmol/L) (Cauley et al Ann Intern Med 2008;149:242-250)
Clinical and pre-clinical studies indicate different activities for the serum 25D and 1,25D metabolites on bone mineral status.

All evidence suggests that the effect of serum 25D arises from within-tissue synthesis of 1,25D.
Vitamin D Synthesis and Activity

Skin (UV) → Vitamin D₃ → CYP2R1 (Liver) → 25D \text{[INACTIVE]} → CYP24 (Kidney) → Plasma → CYP27B1 (Liver) → 24,25(OH)₂D₃ \text{[INACTIVE]} → Plasma → CYP27B1 → 1,25D \text{[ACTIVE]} → VDR → VDRE → Ca homeostasis

Ca homeostasis
What is the evidence in humans for bone autocrine activities of vitamin D?

Ms Deepti Sharma,
PhD student
Structural characteristics of Fracture Patients and Non-fracture controls

MicroCT Images

Non-fracture Control 86 year old female

BV/TV = 9.96
BS/BV = 22.8 mm⁻¹
Tb.Th = 0.16 mm
Tb.Pf = 5.2 mm⁻¹

Hip fracture 87 year old female

BV/TV = 10.5
BS/BV = 27.1 mm⁻¹
Tb.Th = 0.12 mm
Tb.Pf = 6.4 mm⁻¹

Age is not associated with any of the bone mass or quality variables
Serum 25(OH)D and its impact on Bone Quality parameters

Serum 25(OH)D is positively associated with Trabecular Thickness (Tb.Th)

No association was observed between circulating 1,25(OH)_2 D, the biological active form of Vitamin D
Patients with 25(OH)D > 60nmol/L have lower BS/BV as compared to patients with 25(OH)D < 60nmol/L.

BS/BV (mm⁻¹) was significantly lower in patients with 25(OH)D > 60nmol/L, indicating higher bone strength.
Determinants of bone-derived $1,25(OH)_2D$:

**Serum 25(OH)D, Bone CYP27B1 and Bone CYP24A1** are independent predictors of BS/BV

- Serum 25(OH)D, Bone CYP27B1, Bone CYP24A1 - 19% variance in BS/BV along with gender.
- Effect on BS/BV is independent of age, $s_{1,25(OH)_2D}$ and PTH

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Adj. $R^2$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS/BV = -0.04 x 25(OH)D</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>-8.3 x Bone CYP27B1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+19.6 x Bone CYP24A1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+2.3 x Gender</td>
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</table>

$\uparrow$ Vitamin D status

$\downarrow$ BS/BV = Plate-like trabecular configuration

Diagram:
- Serum 25(OH)D → Bone Cell
  - CYP27B1
  - CYP24A1 → Degradation
- 1,25(OH)2D
- Plate-like trabecular structure

$\uparrow$ Vitamin D status

$\downarrow$ BS/BV

Plate-like trabecular configuration
Is there a cellular mechanism for the plate-like structure?

Mean Wall Thickness (MWT) – A measure of bone formation period

- Indicator of how long osteoblast work during each remodelling cycle
- Measured as the distance between the cement line and last completed bone packet
- Preliminary data suggest that serum 25(OH)D levels are strongly related to MWT

High Vitamin D (78.5nmol/L)

Low Vitamin D (16.8nmol/L)

![Graph showing mean wall thickness vs serum 25(OH)D intervals with statistical comparisons.](image)

- a vs b, p=0.8, NS
- a vs c, p=0.001
- a vs d, p<0.0001
- b vs c, p=0.04
- b vs d, p=0.00018
- c vs d, p=0.20

- n=10
- n=7
- n=9
- n=11
• These data provide evidence for assessing serum 25-hydroxyvitamin D as a biomarker for bone quality

• The critical level for serum 25-hydroxyvitamin D is 20 to 24 ng/mL (50 – 60 nmol/L)
In vivo bioluminescence pCYP27B1-luciferase in the transgenic mouse tissues

Anderson et al, Molec Cell Endocrinol, 2008
Are strong data available to support vitamin D status exerting non-skeletal health benefits?

All Cause Mortality – Vitamin D plus calcium but not Vitamin D alone

RCT’s involving 70,528 patients;
151 patients needed to be treated to prevent one death within 3 years

Rejnmark L et al., J Clin Endocrinol Metab 2012; 97: 2670-2681
Adequate Vitamin D Status Associates with Premature Mortality


<table>
<thead>
<tr>
<th>Total plasma 25(OH)D§ nmol/L Quintile</th>
<th>Mean</th>
<th>IQR</th>
<th>n</th>
<th>Deaths</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>30.3</td>
<td>12</td>
<td>7.6</td>
<td>1067</td>
<td>545</td>
<td>7885</td>
</tr>
<tr>
<td>Q2</td>
<td>41.3</td>
<td>16.5</td>
<td>8.9</td>
<td>1008</td>
<td>485</td>
<td>7977</td>
</tr>
<tr>
<td>Q3</td>
<td>51.6</td>
<td>21</td>
<td>11.8</td>
<td>992</td>
<td>458</td>
<td>8020</td>
</tr>
<tr>
<td>Q4</td>
<td>61.0</td>
<td>24.4</td>
<td>14.9</td>
<td>958</td>
<td>417</td>
<td>8056</td>
</tr>
<tr>
<td>Q5</td>
<td>77.0</td>
<td>31</td>
<td>21.1</td>
<td>939</td>
<td>402</td>
<td>8150</td>
</tr>
</tbody>
</table>

Per 25 nmol/l increase

‡Adjusted for age, socio-economic disadvantage, education, total energy intake, Mediterranean diet pattern, alcohol intake, smoking status, physical activity, waist measurement, diabetes mellitus at baseline, history of hypertension, history of angina, history of myocardial infarction, history of stroke, and stratified by sex and Southern European migrant status.
Pre-diagnosis Vitamin D status Associates with Improved Survival in Cancer Patients

Cancer mortality and pre-diagnostic vitamin D status

Risk of death from colorectal cancer is reduced by 50% if serum 25D is ≥ 30 ng/mL compared with < 20 ng/mL at diagnosis

1,202 Colorectal Cancer patients with 444 CRC-specific deaths and overall mortality 541

Fedirko V, et al., Cancer Epidemiol Biomarkers Prev. 2012 April; 21(4): 582-593
Does vitamin D supplementation improve treatment of TB patients? Meta-analysis data

- 8 studies with 898 patients receiving vitamin D and 889 receiving placebo as adjunctive therapy
- Wide range of dosages and length of studies
- Vitamin D increased the proportion of sputum smear conversions (OR 1.21, (95%CI 1.05-1.39), $P = 0.007$) and sputum culture conversions (OR 1.22, (95%CI 1.04-1.43), $P = 0.02$)
- Vitamin D decreased the mean no. of zones involved observed on chest radiograph (MD -0.33, − 0.57 − 0.08, $P = 0.01$)

Wu, H et al BMC Pulmonary Medicine 2018;18: 108
Vitamin D deficiency in Iran

- Prevalence of vitamin D deficiency (<20 ng/mL) (<50 nmol/L)
  - Male 46% (95% CI: 29.63 to 61.65)
  - Female 62% (95% CI: 48.85 to 74.96)
  - Pregnant women 61% (95% CI: 23.73 to 97.16)

Meta-analysis of 48 studies (2000-2016) identified 18,531 individuals with vitamin D deficiency (<20 ng/mL)

### Iranian Maternal Outcomes according to Vitamin D Supplementation and Baseline Vitamin D Status


<table>
<thead>
<tr>
<th>Vit D Status</th>
<th>Suppl. N (%)</th>
<th>Non-suppl. N (%)</th>
<th>OR (95% CI)</th>
<th>Number Needed to Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite adverse pregnancy outcomes# deficiency</td>
<td>Moderate 62 (16)</td>
<td>94 (23)</td>
<td>0.6 (0.4-0.9)</td>
<td>20 (13-55)</td>
</tr>
<tr>
<td>Severe deficiency</td>
<td>71 (18)</td>
<td>129 (39)</td>
<td>0.3 (0.2-0.5)</td>
<td>8 (5-13)</td>
</tr>
</tbody>
</table>

# Includes pre-eclampsia, gestational diabetes and pre-term delivery

### Vitamin D Deficiency Levels

- **Moderate deficiency**: 25-hydroxyvitamin D 10-20 ng/mL (25-50 nmol/L)
- **Severe deficiency**: 25-hydroxyvitamin D < 10 ng/mL (<25 nmol/L)
Conclusions:

Vitamin D and dietary calcium are essential nutrients. Adequate dietary calcium is 1300 mg/day for postmenopausal women and men >70 yrs; 1000 mg/d for adults.

Current clinical trial data indicate that serum 25D levels above 20 ng/mL (50 nmol/L) reduce the risk of fractures, falls, premature mortality, TB, adverse maternal outcomes, …

There is no evidence of benefit for serum 25D levels >40 ng/mL (>100 nmol/L)