Vitamin D and cardiovascular disease

Thomas J. Wang, MD
Massachusetts General Hospital, Harvard Medical School
Framingham Heart Study
Disclosures

- **Funding support**: NIH/NHLBI, NIH/NIDDK, AHA
- **Industry relationships**: Brahms (support for assays), Siemens Diagnostics (assays), Diasorin (advisory board)
Prevalence of cardiovascular disease

- Estimated 80 million people in U.S. have some form of CVD (1 in 3 adults)
- Most common: coronary heart disease, stroke
- Lifetime risk (Framingham data)
  - ~70% in men, ~50% in women
- Most common risk factor is hypertension
  - Lifetime risk 90%
- Even small gains in prevention are important from a public health perspective
Types of Vitamin D

**Vitamin D₂**
- Formed by irradiation of ergocalciferol, found in plants
- Provided by some dietary sources and multivitamins
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form
- D₂ is less potent than D₃

**Vitamin D₃**
- Naturally occurring form in humans
- Formed by action of ultraviolet light on vitamin D precursors in skin
- Present in certain nutrients
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form

Cutaneous vitamin D3 synthesis

7-Dehydrocholesterol ↔ Previtamin D₃

Skin Temperature

Vitamin D₃

SKIN

BLOOD

DBP

DBP-D₃
Vitamin D activation

Vitamin D3 → 25-Hydroxyvitamin D3 → 1,25-Dihydroxyvitamin D3 or Calcitriol

Storage Form → Active Form
Classical actions of 1,25-OH vitamin D

- Genomic actions of vitamin D mediated by nuclear VDR
- Non-genomic actions have been described

Holick, AJCN 2004
Vitamin D and its receptor

From B. Hollis
VITAMIN D SUFFICIENCY

Lowered concentration of plasma concentration of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D

Increased synthesis and secretion of PTH

Further decrease in 25-hydroxyvitamin D through increased turnover and increased consumption

Failure to absorb calcium
Calcium resorbed from bone
Bone unable to mineralise

VITAMIN D INSUFFICIENCY

Insufficient 25-hydroxyvitamin D to form adequate 1,25-dihydroxy vitamin D

VITAMIN D DEPLETION
osteomalacia and rickets

Vitamin D supply diminished by lack of dietary vitamin, malabsorption of dietary vitamin or decreased exposure to sunlight

Decreased intestinal absorption of calcium

Increased synthesis of 1,25-dihydroxyvitamin D corrects defective calcium absorption; gives normocalcaemia at expense of ↑PTH

From B. Hollis
# Vitamin D receptor (VDR) distribution

<table>
<thead>
<tr>
<th>System</th>
<th>Tissue and Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Esophagus, stomach, small intestine, large intestine, colon</td>
</tr>
<tr>
<td>Arterial vessels</td>
<td>Vascular smooth muscle cells</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Liver parenchymal cells</td>
</tr>
<tr>
<td>Renal</td>
<td>Proximal and distal tubules, collecting duct</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Parathyroid, pancreatic $\beta$-cells, thyroid $C$ cells</td>
</tr>
<tr>
<td>Exocrine</td>
<td>Parotid gland, sebaceous gland</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Testis, ovary, placenta, uterus, endometrium, yolk sac</td>
</tr>
<tr>
<td>Immune</td>
<td>Thymus, bone marrow, B cells, T cells</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Cardiac myocytes, vascular smooth muscle, endothelial cells</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Lung alveolar cells</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Osteoblasts, osteocytes, chondrocytes, striated muscle</td>
</tr>
<tr>
<td>Epidermis/appendage</td>
<td>Skin, breast, hair follicles</td>
</tr>
<tr>
<td>Central nervous</td>
<td>Brain neurons</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Fibroblasts, stroma</td>
</tr>
</tbody>
</table>
Vitamin D Modulates the RAS: VDR Knockouts

+/- = wild-type (WT) mice; -/- = vitamin D receptor (VDR) knockout mice.

VDR Knockout Mice: Renal and Cardiac Effects

Kidney Cortex With Anti-Renin Antiserum

- VDR Knockouts:
  - sHPT
  - RAS activation
  - LVH

- VDR Knockout + rescue diet:
  - NO sHPT
  - YES RAS activation
  - YES LVH

Effect of 1,25D & not PTH

1,25-(OH)_{2}D_{3} Supresses Renin Expression in Wild-Type Mice

Li et al. JCI 2002
Relationship Between Serum $1,25(\text{OH})_2\text{D}_3$ and Plasma Renin Activity

1,25 vitamin D suppresses expression of lymphokines in cultured PBMCs

Rigby et al, JCI 1987
VSMCs express VDR, and 1,25 OH vitamin D inhibits cell proliferation.

Somjen et al, Circulation 2005
VSMCs express 1α-hydroxylase, and its activity is regulated by PTH

Somjen et al, Circulation 2005
1,25 vitamin D inhibits VEGF-induced endothelial cell proliferation

Mantell et al Circ Res 2000
Rats overexpressing 24-hydroxylase exhibit increased atherosclerosis

Kasuga et al, BBRC 2002
Hierarchy of clinical studies

- Ecological data
- Retrospective/cross-sectional
- Prospective/longitudinal
- Randomized studies
Prevalence of hypertension and ischemic heart disease increases with distance from the equator

Rostand, HTN 2007
Patients with MI have lower 25-OH vitamin D levels compared with matched controls

<table>
<thead>
<tr>
<th>Time of year</th>
<th>Distribution of case-control pairs</th>
<th>Relative risk* (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole year (179 pairs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>≥32nmol/L</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>&lt;32nmol/L</td>
<td>24</td>
</tr>
<tr>
<td>Case</td>
<td>≥32nmol/L</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>&lt;32nmol/L</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.43 (0.27, 0.89)</td>
</tr>
</tbody>
</table>

Scragg et al, Int J Epi 1990
Acute stroke patients have lower 25-OH vitamin D levels compared with healthy elderly controls

Poole et al, Stroke 2005
25-OH vitamin D levels are lower in individuals with heart failure

N = 54 for CHF, 34 controls

Zittermann et al JACC 2003
Framingham Heart Study

1948 → 2008
Original cohort
N = 5209

1971 → 2008
Offspring study
N = 5124

Exams 6-7 (1996-2001): ~2000 people had 25-OH D measured

2002 → 2008
Gen 3 study
N=4200
### Framingham baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>≥15 ng/mL (n=1258)</th>
<th>&lt;15 ng/mL (n=481)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59±9</td>
<td>59±9</td>
<td>0.53</td>
</tr>
<tr>
<td>Women, %</td>
<td>54</td>
<td>55</td>
<td>0.91</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.5±4.9</td>
<td>29.6±6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>12</td>
<td>17</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>127±18</td>
<td>130±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive therapy, %</td>
<td>26</td>
<td>30</td>
<td>0.13</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>11</td>
<td>14</td>
<td>0.16</td>
</tr>
<tr>
<td>ARB, %</td>
<td>2</td>
<td>1</td>
<td>0.12</td>
</tr>
<tr>
<td>Thiazide diuretic, %</td>
<td>8</td>
<td>10</td>
<td>0.16</td>
</tr>
<tr>
<td>Loop diuretic, %</td>
<td>1</td>
<td>1</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>39</td>
<td>42</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>7</td>
<td>11</td>
<td>0.002</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>4.1±1.3</td>
<td>4.5±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.2±0.2</td>
<td>1.1±0.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Total vitamin D intake, IU</td>
<td>483±328</td>
<td>278±203</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vitamin D supplement, %</td>
<td>5</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivitamin, %</td>
<td>48</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical activity index†</td>
<td>36.1±6.6</td>
<td>35.6±6.3</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Cumulative incidence of CVD, according to 25-OH vitamin D status

Wang et al, Circulation 2007
25-OH D levels and risk of incident CVD

Wang et al, Circulation 2007
Vitamin D and risk of CVD, according to hypertension status
25-OH D and risk of myocardial infarction: Health Professionals Follow-up Study

- N = 51,529 US male doctors followed from 1986
- Blood collected in ’93 – ’95 on 18,225
- 454 fatal or non-fatal MI
- 1:2 case:control ratio, total 900; matched by age, timing of blood collection, smoking
- Events by self-report, validated with hosp records, death certificates

Giovanucci et al Arch Int Med 2008
25-OH D Levels and Myocardial Infarction

Giovanucci et al Arch Int Med 2008
Vitamin D and mortality in NHANES

Ginde et al JAGS 2009
Correlation of 25-OH vitamin D with arterial compliance and brachial reactivity

London et al. JASN 2007
1,25 OH vitamin D and coronary calcification

Possible mechanisms

Vitamin D deficiency

- Increase RAAS activation
- Promote inflammation
- Direct effects on cardiac and vascular tissue
- Association with CV risk factors
Prevalence of hypertension according to vitamin D status, in Framingham Gen 3 (n~4000)

Cheng et al
Obesity and vitamin D

After total body irradiation

After oral dose of vitamin D

Worstmann et al, AJCN 2000
Visceral versus Subcutaneous Fat

- Hypocaloric diet
- Physical activity
- Antiobesity drugs
- Adiposopathy regulators

VAT, a target for early intervention

- ↑ TNF-α
- ↑ IL-6
- ↑ CRP
- ↑ FFA
- ↓ Adiponectin
Additive effects of subcutaneous and visceral adiposity (Framingham Gen 3)

Cheng et al, Diabetes 2009
Increasing VAT is associated with lower 25-OH D, even in lean individuals.
Fasting HOMA-IR, according to tertile of 25(OH)D, in Framingham Gen 3

Liu et al, J Nutr 2009

**Graph:****

- **Y-axis:** HOMA-IR
- **X-axis:**
  - Unadjusted
  - Adjusted for age, sex
  - Adjusted for age, sex, BMI, WC

- **Legend:**
  - Low 25(OH)D
  - Middle 25(OH)D
  - High 25(OH)D

- **Statistical Significance:**
  - p<0.001

Liu et al, J Nutr 2009
Is there any evidence from randomized trials?

- No completed prospective RCT’s of vitamin D supplementation and cardiovascular endpoints
- Need large numbers for adequate statistical power
- Difficult to prohibit vitamin D use in the control arm, especially with increasing awareness of vitamin D deficiency
- Target everyone or just those with deficiency?
- Adequate treatment dose debated
What is the “optimal” vitamin D level: evolutionary perspective

Major source of vitamin D is from sun exposure

Vitamin D is virtually absent from natural foodstuffs

Vieth 2007
Number of months that UVB insufficient to produce vitamin D3 in skin

- No vit D > 6 mos
- No vit D 1-6 mos
- Vit D all year
- No vit D 1-6 mos
- No vit D >6 mos

From B. Hollis
Vitamin D and mortality: meta-analysis of RCTs

Autier et al Arch Intern Med 2007
Women’s Health Initiative: analysis of CV outcomes

- Vitamin D dose: 400 IU/d
- Supplements allowed in control group, such that large proportion had >400 IU/d intake
- No prospective assessment of vitamin D status

Hsia et al, Circulation 2007
Circulating 25-OH vitamin D and response to supplementation

From Vieth et al
The VITamin D and OmegA-3 Trial (VITAL)

Mean Treatment Period = 5.0 years
Primary Outcomes: Cancer (total) and CVD (MI, stroke, CVD death)

From J. Manson
Small trials with CV intermediates: blood pressure

- 145 women aged >70 years
- 25-OH D less than 20 ng/ml
- Randomized to 800 IU vitamin D vs placebo
- In 8 weeks: SBP reduced 13 mm Hg in vitamin D arm vs. 5 mm Hg with placebo (p=0.02)
UVB radiation and blood pressure

UVB: 6 mm Hg drop in SBP
162% increase in 25-OH D

UVA: No change in BP or 25-OH D

Krause et al, Lancet 1998
Intravenous calcitriol and LV mass in dialysis patients

Park et al, AJKD 1999
Mendelian randomization

- Random allocation to therapy versus no therapy is the gold standard for clinical studies
- In observational studies, exposures are generally distributed non-randomly
- Genetic exposures are one potential exception: due to random (Mendelian) assortment of alleles
Use of population genetics to assess causality (Mendelian Randomization)

Vitamin D deficiency → ? → CVD risk
Use of population genetics to assess causality (Mendelian Randomization)

- Genetic variant
- Vitamin D deficiency
- CVD risk
Use of population genetics to assess causality (Mendelian Randomization)

- Vitamin D deficiency
- Genetic variant
- Winter

The diagram illustrates the relationship between Vitamin D deficiency and Winter, with Genetic variant shown as causally related to Vitamin D deficiency and Winter.
Is vitamin D status influenced by genetic factors?

- In Framingham Gen 2: season, vitamin D intake, waist circumference, and HDL cholesterol explained ~24% of variation of 25(OH)D levels
- Residual heritability ~29% (p<0.01)

Common variants in vitamin D binding protein (VDBP) and 25(OH)D levels

<table>
<thead>
<tr>
<th>rs No.</th>
<th>Genotype</th>
<th>Subjects $^j$</th>
<th>Crude mean ± SE $^j$</th>
<th>P value $^2$</th>
<th>Adjusted mean ± SE $^3$</th>
<th>P value $^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>nmol/L</td>
<td></td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td>rs7041</td>
<td>GG</td>
<td>228 (31.1)</td>
<td>67.3 ± 1.3</td>
<td>—</td>
<td>67.5 ± 1.1</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>GT</td>
<td>377 (51.4)</td>
<td>65.0 ± 1.0</td>
<td>0.16</td>
<td>64.5 ± 0.8</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>128 (17.5)</td>
<td>60.2 ± 1.7</td>
<td>0.0010</td>
<td>60.8 ± 1.5</td>
<td>0.0003</td>
</tr>
<tr>
<td>rs4588</td>
<td>CC</td>
<td>370 (50.5)</td>
<td>67.2 ± 1.0</td>
<td>—</td>
<td>67.2 ± 0.9</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>CA</td>
<td>296 (40.4)</td>
<td>63.2 ± 1.1</td>
<td>0.0081</td>
<td>63.2 ± 0.9</td>
<td>0.0018</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>67 (9.1)</td>
<td>59.0 ± 2.4</td>
<td>0.0016</td>
<td>58.4 ± 2.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Sinotte et al, AJCN 2009
Framingham Heart Study

Original cohort
N = 5209

Offspring study
N = 5124

1971 → 2008

Exams 6-7 (1996-2001): ∼2000 people had 25-OH D measured

Exam 1 (2001-2005): ∼4000 people had 25-OH D measured

Gen 3 study
N=4200
Conclusions

- Large body of observational data linking vitamin D deficiency with higher burden of CV risk factors and increased CV risk
- RCT’s are needed but will be challenging
- Genetic studies may provide some insight although statistical power will be a barrier
- The public health implications are substantial
Framingham Heart Study/BU
  Vasan Ramachandran
  Josee Dupuis
  Martin Larson
  Emelia Benjamin
  Caroline Fox
  Joe Massaro
  Michelle Keyes

Tufts
  Sarah Booth
  Paul Jacques

Hebrew Rehab
  Doug Kiel
  David Karasik

MGH
  Myles Wolf
  Susan Cheng
  Elizabeth McCabe
  Jose Florez
  Christopher Newton-Cheh
  Heather Swales
  Ravi Thadhani

BWH
  JoAnn Manson