Vitamin D & Orthopedics

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Disclosure

No financial interests or other relationships with manufacturers of any commercial products discussed during this presentation.
Objective: To identify the major vitamin D metabolite, its source(s), and how it relates to inflammatory cytokines and muscle strength in various orthopedic conditions

Outline:
- Introduction
- Few studies
  - Vitamin D
    - muscular strength
    - inflammatory cytokines
- Summary
- Questions
STUDIES ON EXPERIMENTAL RICKETS.

XXI. AN EXPERIMENTAL DEMONSTRATION OF THE EXISTENCE OF A VITAMIN WHICH PROMOTES CALCIUM DEPOSITION.

By E. V. McCollum, Nina Simmonds, and J. Ernestine Becker,

(From the Department of Chemical Hygiene, School of Hygiene and Public Health, the Johns Hopkins University, Baltimore.)

And P. G. Shipley.

(From the Department of Pediatrics, the Johns Hopkins University, Baltimore.)

- Elmer Verner McCollum (Kansas, 1879-1967)
- University of Kansas (BS & MS) &
- Doctorate from Yale (Chemistry)
- College of Agriculture, University of Wisconsin
- Chairman of the Department of Chemical Hygiene at John Hopkins (1917-1944)
- Rats fed only cereal grains developed a condition similar to rickets in children
- Small amounts of cod-liver oil ‘cured’ rickets in rats
- Italian immigrants in NY
1,25-dihydroxyvitamin D (1,25(OH)D; calcitriol; plasma ≈ 10-20 hr)

Sunlight (UVB)

Dietary intake
- Milk
- Orange juice
- Salmon
- Beef

Supplements
- Vitamin D3 (cholecalciferol)
- Vitamin D2 (ergocalciferol)

VDBP

Chylomicrons

(peripheral tissues)

Vitamin D3
(Cholecalciferol; plasma ≈ 4-6 hr; whole body ≈ 2 mo)

Epithelial cells
- Osteoblasts
- Myocytes
- Immune cells
- APC
- Cortical neurons & glia

Vitamin D Receptor (VDR)

Deficient < 20 ng/ml
Insufficient 20-29 ng/ml
Target 30-60 ng/ml
Normative 30-100 ng/ml
Toxic > 150 ng/ml

25-Hydroxyvitamin D (25(OH)D; calcidiol; plasma ≈ 15 d)

CYP27A1
CYP2R1
CYP2J2/3
CYP3A4
CYP2D25
CYP2C11
CYP2D11

High calcium diet
- High serum calcium
- High serum phosphate

Low calcium diet
- Vitamin D deficiency
- Elevated PTH
- Low serum calcium
- Low serum phosphate

24,25-dihydroxyvitamin D (24,25(OH)D)

CYP27B1
CYP24A1

Role of vitamin D in skeletal muscle

1,25(OH)D

Effects on intestine, parathyroid glands, bone, kidney

Systemic calcium and phosphate homeostasis, parathyroid hormone levels

Intracellular calcium, phosphate homeostasis

Effects via the VDR

Alternate dimer

Genomic effects

Contractile protein expression

METABOLISM, STRUCTURE, & FUNCTION

Re-drawn Girgis et al. (2012) *Endo Rev*
Risk factors for low vitamin D

- Decreased skin production
- Increasing latitude
- Darker skin pigment
- Use of sunscreen
- Increasing age
- Decreased bioavailability and production
- Liver or kidney dysfunction
- Obesity
- Malabsorption disorders
- Primary hyperparathyroidism
- Hyperthyroidism

- Exclusive breast feeding
- Medications
- Cholesterol-lowering agents
- Glucocorticoids
- Anti-seizure medications
- Genetic disorders
- Pseudovitamin D-deficiency rickets
- Vitamin D-resistent rickets
- Autosomal dominant hypophosphatemic rickets
- X-linked hypophosphatemic rickets
- Acquired disorders

Patton et al. (2012) *Ortho Adv*
Low vitamin D is associated with…

- Bone Health
- Schizophrenia & Depression
- Cardiovascular Health
- Osteoarthritis
- Cancer
- Skeletal Muscle Strength
- Immune System & Inflammatory Cytokines
- Lung Function
- Oxidative/Nitrative Stress
Vitamin D and muscular function or physical performance

Association Between Vitamin D Status and Physical Performance: The InCHIANTI Study

Denise K. Houston, Matteo Cesari, Luigi Ferrucci, Antonio Cherubini, Dario Maggio

Low Vitamin D Status Has an Adverse Influence on Bone Mass, Bone Turnover, and Muscle Strength in Chinese Adolescent Girls

Improving the Vitamin D Status of Vitamin D Deficient Adults Is Associated With Improved Mitochondrial Oxidative Function in Skeletal Muscle

Akash Sinha, Kieren G. Hollingsworth, Steve Ball, and Tim Cheetham

Inflammation-related muscle weakness and fatigue in geriatric patients

I. Beyer, R. Njemini, I. Bautmans, C. Demanet, P. Bergmann, T. Mets
Vitamin D supplementation influences muscular strength or physical performance

Muscle strength, functional mobility and vitamin D in older women


Hypovitaminosis D Myopathy Without Biochemical Signs of Osteomalacic Bone Involvement


International Journal of COPD

Supplemental vitamin D and physical performance in COPD: a pilot randomized trial


Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function


Impact of vitamin D supplementation during a resistance training intervention on body composition, muscle function, and glucose tolerance in overweight and obese adults

Andres E. Carrillo, Michael G. Flynn, Catherine Pinkston, Melissa M. Markofski, Yan Jiang, Shawn S. Donkin, Dorothy Teegarden
Review Articles...

**Athletic Performance and Vitamin D**

John J. Cannel, Bruce W. Hollis, Marc B. Sorenson, John J. B. Anderson

1 Atascadero State Hospital, Atascadero, CA; 2 Departments of Biochemistry and Medical University of South Carolina, Charleston, SC; 3 University of North Carolina, Chapel Hill, NC; 4 Departments of Orthopedics and Sports Medicine, University of North Carolina, Chapel Hill, NC.

**Vitamin D and Athletes**

D. Enette Larson-Meyer and Kentz S. Willis

1 Departments of Family and Consumer Sciences (Human Nutrition), University of Wyoming, Laramie, WY; 2 Cooperative Extension Service, Sheridan, WY.

**Vitamin D and Athletic Performance: The Potential Benefits**

Bruce R. Zidek

Calcif Tissue Int (2013) 92:151-162

DO 10.1007/s00223-012-9645-y

**Vitamin D and Its Role in Skeletal Muscle**

Lisa Ceglia, Susan S. Harris

**Vitamin D Effects on Bone and Muscle**

Heike Bischoff-Ferrari, Hannes B. Stähelin, and Paul Walter

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.nrjournal.com
..., but results are conflicting!

Serum 25-hydroxyvitamin D concentration and physical function in adult men
Lisa Ceglia*,†, Gretchen R. Chiu‡, Susan S. Harris† and

Effects of Vitamin D Supplementation on Strength, Physical Function, and Health Perception in Older, Community-Dwelling Men
Anne M. Kenny, MD,* Bradley Biskup, BS,* Bertha Robbins, RN,† Glenn Marcella, BS,* and Joseph A. Burleson, PhD‡

Is Vitamin D a Determinant of Lower Limb Kinematics?
Isabel Marantes,1,2 Sara J Achenbach,3 Elsa L Joseph Melton III,1,4 and Shreyasee Arulkumaran5
1Division of Epidemiology, Department of Health Sciences, Rush University Medical Center, Chicago, IL, USA
2Department of Hygiene and Epidemiology, Oporto Medical School, Oporto, Portugal
3Division of Biomedical Statistics and Informatics, Department of Biomedical Informatics, School of Medicine, University of Minnesota, USA
4Division of Endocrinology, Diabetes, Metabolism and Nutrition, University of California, San Francisco, CA, USA
5Division of Rheumatology, Department of Medicine, Oregon Health and Science University, Portland, OR, USA

Vitamin D concentration in 342 professional football players and association with lower limb isokinetic function
Bruce Hamilton1,*, Rod Whiteley2, Abdulaziz Farooq3, Hakim Chalabi4
Low vitamin D is associated with...

- Bone Health
- Skeletal Muscle Strength
- Immune System & Inflammatory Cytokines
- Lung Function
- Oxidative/Nitrative Stress
- Schizophrenia & Depression
- Cardiovascular Health
- Osteoarthritis
- Cancer

[Image of a pie chart with the above categories]
Vitamin D and inflammatory cytokines

Redrawn from Cantorna et al. (2008) *Mol Aspects Med*
Inflammatory cytokines

• Regulatory peptides that participate in host defense, repair processes, and cell signaling
• Secreted by a variety of inflammatory (i.e., monocytes/macrophages, lymphocytes, etc.) and non-inflammatory (i.e., skeletal muscle, endothelial, etc.) cells

Pro-inflammatory cytokines
TNF-α, IL-1β, IL-6

Promote inflammation
control tissue damage
killing infective organisms
induce repair processes
Inflammatory cytokines

- Regulatory peptides that participate in **host defense**, **repair processes**, and **cell signaling**
- Secreted by a variety of inflammatory (i.e., monocytes/macrophages, lymphocytes, etc.) and non-inflammatory (i.e., skeletal muscle, endothelial, etc.) cells

**Pro-inflammatory cytokines**  
TNF-α, IL-1β, IL-6

**Anti-inflammatory cytokines**  
IL-10

- Promote inflammation  
control tissue damage  
killing infective organisms  
induce repair processes

- Provide protection against  
uncontrolled or excessive pro-inflammatory cytokines

Dinarello (2000) *Chest*  
Opal & DePalo (2000) *Chest*
TNF-α mediates muscular weakness

- Transgenic mice with cardiac-restricted overexpression of TNF-α
- TNF-α was elevated in the circulation but not in the diaphragm muscle
- in vitro diaphragm contractile properties

Li et al. (2000) Circulation
IL-10 deficiency exacerbates time to fatigue

- Wild type (IL-10 \(^{+/+}\)) and IL-10 deficient (IL-10 \(^{-/-}\)) mice
- Intraperitoneal injection of LPS or saline
- Time to fatigue was measured 24-hr after injection

Kryszton et al. (2008) *AJP - RIC*
Cytokines and muscular weakness

- **Obstructive lung disease** (Yende et al. (2006) *Thorax*)
- **Chronic heart failure** (Toth et al. (2006) *Int. J Cardiol.*)
- **Obese elderly** (Shrager et al. (2007) *J Appl Physiol*)
- **Hip facture patients** (Miller et al. (2008) *J Am Geriatr Soc*)
- **Parkinson’s disease** (Scalzo et al. (2010) *Neurosci Lett*)
- **Knee osteoarthritis** (Levinger et al. (2011) *Arthritis Rheum*; Santos et al. (2011) *Arch Gerontol Geriat*)
- **Acute infection-induced inflammation** (Beyer et al. (2012) *Exp Gerontol*)
Vitamin D

Insufficient vs. Sufficient
Lower serum 25(OH)D concentration following vitamin D status demarcation

Data presented as mean ± SEM

Barker et al. (2013) *EJAP*
Pro-inflammatory cytokines were significantly increased in the circulation with vitamin D insufficiency

Data presented as mean ± SEM

A

Vitamin D insufficient
Vitamin D sufficient

B

*  

C

D

Barker et al. (2013) *EJAP*
...but no difference in an anti-inflammatory cytokine

Data presented as mean ± SEM

Barker et al. (2013) EJAP
Peak isometric force and power output were not significantly different groups.

Data presented as mean ± SEM

Barker et al. (2013) *EJAP*
Summary

Vitamin D Insufficiency

↑ Pro-Inflammatory Cytokines

↔ Muscle Strength

 ↔ Anti-Inflammatory Cytokine
Vitamin D

Insufficient vs. Sufficient

Supplementation
Experimental protocol

- Data was collected during the winter in Salt Lake City, UT (latitude ≈ 40° N).
- Subjects were not taking any supplements
- Subjects were recreationally active males and females (18-45 y)

Barker et al. (2012) *Nutr Metab*
Supplemental vitamin D at 4000 IU increased 25(OH)D

Barker et al. (2012) Nutr Metab

Serum 25(OH)D (ng/ml)

placebo  200 IU  4000 IU

1P < 0.001 vs. Pre
2P < 0.001 vs. Pre and 7-d
3P < 0.001 vs. Pre, 7-d, 14-d and 21-d
*P < 0.05 vs. placebo
#P < 0.05 vs. 200 IU
Mean ± SEM
Low-dose supplemental vitamin D modulated IL-5?

Data presented as mean ± SEM Barker et al. (2012) Nutr Metab

$^{1}P < 0.05$ vs. 7-d in Placebo

$^{2}P < 0.05$ vs. 7-d and 14-d in 200 IU

*P < 0.05 vs. corresponding placebo

Barker et al. (2012) Nutr Metab
Despite a increase in serum 25(OH)D concentrations after 28-d, supplemental vitamin D at 4000 IU…

\[ \text{Placebo} \quad \text{200 IU} \quad \text{4000 IU} \]

Data presented as mean ± SEM

\[ ^1 p < 0.05 \text{ vs. Pre} \]

Barker et al. (2012) *Nutr Metab*
Summary

200 IU/d

Serum 25(OH)D

Anti-inflammatory Cytokine

Muscle Strength

↑

4000 IU/d
Vitamin D

Insufficient vs. Sufficient

Muscle damage / injury

Supplementation
Does vitamin D influence strength recovery following muscle damage / injury?

Research Article
Vitamin D Status Is Not Associated with Outcomes of Experimentally-Induced Muscle Weakness and Pain in Young, Healthy Volunteers

Susan M. Ring, Erin A. Dannecker, and Catherine A. Peterson
Experimental design and protocol

Randomization

Placebo
n=13

4000 IU/d
n=15

Baseline (Bsl)

35 days

Blood draw

Strength testing

Barker et al. (2013) Nutr Metab
Experimental design and protocol

Randomization

Placebo
n=13

4000 IU/d
n=15

Blood draw
Strength testing
Blood draw
Strength testing
Blood draw
Strength testing
Blood draw
Strength testing
Blood draw
Strength testing
Blood draw
Strength testing
Blood draw
Strength testing
Blood draw
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Strength testing
Blood draw
Strength testing

Barker et al. (2013) Nutr Metab
Experimental design and protocol

CON vs. SSC leg

Barker et al. (2013) *Nutr Metab*
Supplemental vitamin D increased serum 25(OH)D concentrations

Data presented as mean (SD).

Barker et al. (2013) *Nutr Metab*

1\(^P < 0.05\) vs. Bsl, Pre, 1-h, 48-h, 72-h, and 168-h
2\(^P < 0.05\) vs. Pre and 72-h
3\(^P < 0.05\) vs. Bsl
\(*P < 0.05\) vs. Placebo

Bsl Pre Post 1-h 24-h 48-h 72-h 168-h
Supplemental vitamin D improved strength recovery within the damaged / injured leg…

Barker et al. (2013) *Nutr Metab*
... increased TNF-α and tempered the fluctuation in IL-10

Data presented as mean ± SEM.

Barker, unpublished observation
Summary

Supplemental Vitamin D (4000 IU/d)

- Serum 25(OH)D
- TNF-α
- Strength Recovery
- IL-10
Vitamin D

Insufficient vs. Sufficient

Supplementation

Muscle damage / injury

Knee surgery
To identify strength gains after an ACL injury and surgery in subjects with disparate vitamin D levels.
Following vitamin D status demarcation,…

Data presented as mean ± SEM

Barker et al. (2011) *JEBCAM*

*P < 0.05 vs. corresponding values in the < 30 ng/ml group

Data presented as mean ± SEM
Greater improvement in peak isometric force from pre-surgery to post-surgery in patients with...
Plasma 25(OH)D < 30 ng/ml
- 4 partial meniscectomies

Plasma 25(OH)D ≥ 30 ng/ml
- 1 partial meniscectomy
- 5 meniscus repairs

Barker et al. (2011) *JEBCAM*
Vitamin D Deficiency and an ACL injury impairs strength and recovery.
It has been suggested…

…that an ACL injury and surgery can age the knee 30 years!!!
Vitamin D

- Insufficient vs. Sufficient Supplementation
- Muscle damage / injury
- Knee surgery
- Knee osteoarthritis (OA)
102 subjects assessed for eligibility

29 subjects excluded
- 19 Co-morbidities
- 9 Previous knee or hip arthroplasty on the symptomatic or non-symptomatic limb
- 8 Dietary or vitamin supplement user

73 subjects enrolled

56 subjects included

17 subjects excluded
- 3 WOMAC pain < 2
- 7 No knee extension muscular weakness
- 13 Kellgren-Lawrence grade < 2

17 deficient (≤ 20 ng/mL)
21 insufficient (21 to 29 ng/mL)
18 sufficient (≥ 30 ng/mL)
### Table 1. Subject characteristics and clinical chemistries

<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>Deficient</th>
<th>Insufficient</th>
<th>Sufficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (males:females)</td>
<td>17 (9:8)</td>
<td>21 (9:12)</td>
<td>18 (7:11)</td>
<td>0.536</td>
</tr>
<tr>
<td>age (y)</td>
<td>51 ± 3</td>
<td>48 ± 2</td>
<td>47 ± 3</td>
<td>0.487</td>
</tr>
<tr>
<td>height (cm)</td>
<td>167 ± 2</td>
<td>170 ± 2</td>
<td>168 ± 2</td>
<td>0.536</td>
</tr>
<tr>
<td>body mass (kg)</td>
<td>100.6 ± 5.4</td>
<td>99.7 ± 4.6</td>
<td>81.4 ± 3.3</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>36.0 ± 1.8</td>
<td>34.2 ± 1.3</td>
<td>28.6 ± 0.8</td>
<td>0.001</td>
</tr>
<tr>
<td>serum 25(OH)D (ng/mL)</td>
<td>16.3 ± 0.7</td>
<td>24.7 ± 0.6(^a)</td>
<td>36.0 ± 0.8(^a,b)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rheumatoid factor (IU/mL)</td>
<td>9.18 ± 0.46</td>
<td>8.95 ± 0.44</td>
<td>8.83 ± 0.45</td>
<td>0.599</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>50.1 ± 3.8</td>
<td>44.1 ± 3.6</td>
<td>33.6 ± 2.2</td>
<td>0.004</td>
</tr>
<tr>
<td>calcium (mg/dL)</td>
<td>9.35 ± 0.13</td>
<td>9.29 ± 0.1</td>
<td>9.49 ± 0.1</td>
<td>0.632</td>
</tr>
<tr>
<td>WOMAC pain (0-20)</td>
<td>9.47 ± 1.03</td>
<td>7.60 ± 0.63</td>
<td>6.69 ± 0.82</td>
<td>0.320</td>
</tr>
<tr>
<td>WOMAC function (0-68)</td>
<td>30.1 ± 3.4</td>
<td>24.7 ± 2.4</td>
<td>19.7 ± 2.5</td>
<td>0.461</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade</td>
<td>2 (n) 1</td>
<td>4 (n) 0</td>
<td>0 (n) 0</td>
<td>0.468</td>
</tr>
<tr>
<td></td>
<td>3 (n) 14</td>
<td>9 (n) 15</td>
<td>4 (n) 3</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean ± SEM unless otherwise noted

All subjects were Caucasian

\( ^a \) p < 0.05 vs. deficient

\( ^b \) p < 0.05 vs. insufficient

\( ^c \) p = 0.07 vs. insufficient

Barker et al. (2014) *Redox Biology*
Vitamin D deficiency impaired quadriceps strength (concentric knee extension at 60°/sec)

Data presented as mean ± SEM
# p < 0.05 vs. symptomatic leg
○ non-symptomatic leg
◊ symptomatic leg

Barker et al. (2014) Redox Biology
...but did not increase serum cytokine concentrations

GM-CSF, TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, or IL-13
Summary

Vitamin D Deficiency and Knee OA

Quadriceps Dysfunction

↔

Inflammatory cytokines
Overall Summary

Vitamin D insufficiency or deficiency:
• Increased circulating pro-inflammatory cytokines in young, reportedly healthy adults
• Impaired leg strength recovery after ACL surgery
• Impaired quadriceps (muscular) strength in patients with knee OA

Supplemental vitamin D in young, reportedly healthy adults:
• Increased an anti-inflammatory cytokine (i.e., IL-5)
• Increased TNF-α and tempered the fluctuation in IL-10 after muscular damage / injury
• Improved the immediate (i.e., post to 24-h) recovery in muscular strength after damage / injury
Acknowledgements

Intermountain Healthcare
Lindell K. Weaver, MD
Roy H. Trawick, MD
G. Lynn Rasmussen, MD
Nathan Momberger, MD
Vanessa T. Henriksen, MS, AT-L
Victoria E. Rogers, AT-L
Kimberley B. Brown, AT-L
Ronda Ingram, MS, ATC
Graham Burdett, PA
Dale Aguirre, MBA, AT-L
Penny Snow
Kristi Thunell
Michelle (Shelly) Oliver

University of Utah
& ARUP Laboratories
Harry R. Hill, MD
Carl R. Kjeldsberg, MD
Thomas B. Martins, MS

USANA Health Sciences, Inc.
Brian M. Dixon, PhD
Mark Levy, PhD
John Cuomo, PhD
Jenna Templeton
Adam Dern
Erik D. Schneider
Toni McKinnon

Funding Support
Intermountain Research & Medical Foundation
USANA Health Sciences, Inc.

Customized Supplements
USANA Health Sciences, Inc.
Thank you for your time!

Questions/Discussion?