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Department of Laboratory Medicine and Pathobiology, and the
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Canada.

Vitamin D beyond bone health:
Primary prevention and therapeutic potentials in the contexts of Multiple Sclerosis and Prostate Cancer.
Vitamin D is the only nutrient that Canada’s Food Guide tells adults to take as a supplement. The amount of vitamin D that adults should be taking for disease prevention or treatment remains highly disputed, ranging from 600 IU (15 micrograms) per day, toward even 10,000 IU/day. The lower range of advice is intended to optimize the accepted utility of vitamin D for bone health, while the higher range of advice relates to evolving roles of vitamin D in a variety of conditions, which include conditions as diverse as prostate cancer and multiple sclerosis.

This presentation will:
1. Summarize knowledge about vitamin D in the context of prevention and treatments for bone health, prostate cancer and multiple sclerosis
2. Differentiate unresolved issues pertinent to prevention and treatment of these diseases
3. Address the risk and benefits profiles about the use of vitamin D supplementation/treatment
4. Explain why it is unrealistic to expect that double blind randomized trials will ever provide evidence that vitamin D can prevent prostate cancer or multiple sclerosis.
Hypovitaminosis D Myopathy Without Biochemical Signs of Osteomalacic Bone Involvement

H. Glerup,1 K. Mikkelsen,2 L. Poulsen,2 E. Hass,2 S. Overbeck,2 H. Andersen,3 P. Charles,1 E. F. Eriksen1

1Department of Endocrinology and Metabolism C, Aarhus Amtssygehus, University Hospital of Aarhus, Tage Hansensgade 2,

Journal of Pediatric Endocrinology & Metabolism, 18, 719-722 (2005)

Treatment of Malabsorption Vitamin D Deficiency Myopathy with Intramuscular Vitamin D

Saif Alyaarubi and Celia Rodd

Department of Endocrinology and Metabolism, Montreal Children’s Hospital, Montreal, Quebec, Canada

Muscle Weakness in Infants with Rickets: Distribution, Course, and Recovery.

Carlos F. Torres, MD *, Gilbert B. Forbes, MD *, and George H. Decancq, MD *

We describe the distribution, progression, and resolution of muscle weakness, wasting, and hypotonia in three infants with rickets due to different causes. Progressive muscle weakness affecting preferentially the proximal muscles of the legs and failure to gain weight in the first 4 months of life led to a diagnosis of rickets. At 1 year of age he could not bear weight on his legs, sat using his hands for support. He could not bear weight on his legs or raise his arm above his head. The weakness and hypotonia had become progressively more severe, particularly in the lower extremities, shoulder girdle muscles, and neck flexors. His quadriceps and gluteal muscle masses were barely palpable and the patellar reflex was absent.
The Children's story
HEIDI

Her friend Clara who lived in the city probably suffered from

- Rickets
- Weak muscles
- Infection-prone

Probable serum 25(OH)D < 25 nmol/L

She regained her health after time in the mountains with Heidi

Probable serum 25(OH)D > 75 nmol/L
The basic background to vitamin D nutrition
7-dehydrocholesterol

Skin & UVB → Cholecalciferol (Vitamin D3)

Liver → 25(OH)D

Kidney → 1,25(OH)₂D

25(OH)D-1-hydroxylation is stimulated by:
- PTH ↑
- Calcium ↓

1,25(OH)₂D Hormone control to increase calcium absorption and bone development (via Calcium)
The 1,25(OH)2D produced within non-renal tissues do NOT normally spill out into the bloodstream. This 1,25(OH)2D provides autocrine/paracrine regulation of cellular biology within the tissue.
25(OH)D is like a blank paper that does nothing by itself.

A hormone is a message molecule.

Made in Multiple Tissues

- BONE
- BREAST CELLS
- PROSTATE CELLS
- COLON CELLS
- SKIN
- LYMPH NODES
- BRAIN (CEREBELLUM AND CORTEX)
- THYROID TISSUE
- PARATHYROID TISSUE
- DENDRITIC CELLS
- VASCULAR ENDOTHELIUM
- MACROPHAGES
WHAT IS NORMAL?
The conditions for which our human genome was selected offer a reasonable basis for optimal nutrition.

Anatomically “Modern” humans have existed for 100,000 years.
Maasai median 25(OH)D = 104 nmol/L

Luxwolda and Muskiet, submitted manuscript
What is “Normal”?

Humans exposing full skin surface to Sunshine’s UVB

Winter 43° N Latitude

Serum 25(OH)D nmol/L

Old-World Primates 0

Humans 80

Blood Levels when taking 1000 IU/day 25 mcg/day

“Normal”

Baseline 120

Physiological adult intake

80

Rickets

Northern People Taking 4000 IU/day

Sources, include Cosman, Osteoporosis Int 2000; Fuleihan NEJM 1999; Scharla Osteoporosis Int 1998; Vieth AJCN 1999, 2000
University of Toronto students of various ancestries
25(OH)D measured last winter

Below this is Diagnostic of vitamin D deficiency rickets in infants
Effect of UV at index=10 exposure time and skin colour on Vitamin D production:

White skin

Very Dark skin

Same capacity for vit D, different exposure-time requirements

Yield of vitamin D

20 min

120 min
The role of sunshine:
full-skin exposure to UVB
= 10,000 IU daily of vitamin D3
Implicit evidence that 10,000 IU/day of vitamin D is safe, because it matches the potential effect of UV light exposure.
If shadow TALLER than you are tall, you CANNOT make vitamin D

(UV index = 3)
World Distribution of Nonhuman Primates

Regions shaded white are the natural habitat of non-human primates.

*from; Primate Behavior: Field studies of monkeys and apes. I DeVore 1965*
How low does the vitamin D supply have to be before it makes you unhealthy?

- NO Vit D for >6 mo/yr
- NO Vit D for 1-6 mo/yr
- Vit D all year

The map shows the global distribution of vitamin D supply, with different regions marked for various durations of vitamin D deficiency.
Lack of UVB is the reason why human skin phenotype varies with latitude.

Fig. 3. Nonlinear piecewise regression results for 102 male samples ($R^2 = 0.85$) using the reduced model (equa-

From JH Rethelford, Am J Physical Anthropology 1997; 104: 449
Childhood lack of vitamin D causes rickets.

Contracted pelvis, in a case of osteomalacia (adult rickets). Normal childbirth would be impossible.

Normal shape of female pelvis.
WHAT IS VITAMIN D GOOD FOR?
All By Itself, Vitamin D Increases Bone Density

NHANES Study of the US Population

Each line shows average bone densities for 2500 men and women < age 50

0 is set to cancel out density differences among the groups of White, Black, Spanish Americans)

The Lines are local averages of BMD for the 25(OH)D levels along the horizontal axis

FRACTURE-PREVENTION STUDIES WITH VITAMIN D3

Figure 3. Hip and Nonvertebral Fracture Efficacies by Achieved 25-Hydroxyvitamin D Levels in 400 IU/d and 700-800 IU/d Vitamin D–Treated Groups

Vitamin D Dose

- 400 IU/d
- 700-800 IU/d = 20 mcg/d

Bischoff-Ferrari et al. JAMA. 2005;293:2257-2264
Meta-analysis of data on all-cause MORTALITY in randomized controlled trials with vitamin D.

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>PLACEBO</th>
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</thead>
<tbody>
<tr>
<td>Chapuy et al, 1992</td>
<td>258/1634</td>
<td>274/1636</td>
</tr>
<tr>
<td>Lips et al, 1996</td>
<td>223/1291</td>
<td>251/1287</td>
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<td>Chapuy et al, 2002</td>
<td>71/393</td>
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<td>Meyer et al, 2002</td>
<td>169/569</td>
<td>163/575</td>
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<td>Trivedi et al, 2003</td>
<td>224/1345</td>
<td>247/1341</td>
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<td>Porthouse et al, 2005</td>
<td>57/1321</td>
<td>68/1993</td>
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<td>RECORD Trial, 2005</td>
<td>438/2649</td>
<td>460/2643</td>
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<td>Flicker et al, 2004</td>
<td>76/312</td>
<td>85/313</td>
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<tr>
<td>Jackson et al, 2006</td>
<td>744/18176</td>
<td>807/18106</td>
</tr>
</tbody>
</table>

Summary relative risk (95%). 0.92 (0.86-0.99)

Autier and Gandi 2007 Arch Intern Med;167(16):1730-1737
To raise an Adult’s 25(OH)D by 50 nmol/L requires about 2000 IU/day of vitamin D3.

Our clinical evidence against smoking is largely based on Prospective Cohort Epidemiology.
Survival after age 35 years among nonsmokers and cigarette smokers smoking different amounts at the time their last questionnaire was returned.

Richard Doll. *Statistical Methods in Medical Research* 1998; 7: 87±117 (published when author was 88 years young)

THE LASA STUDY

STATISTICS ABOUT VITAMIN D AND LIFE EXPECTANCY
Cardiovascular Health
Health Professionals Follow-up Study; the men were aged 40 to 75 years and were free of diagnosed cardiovascular disease at blood collection.

- Samples taken at Baseline
- Monitored for 10 Years
- Prospective **Relative Risk** of MI shown

![Graph showing the relative risk of MI based on serum 25(OH)D levels.](image)
Gestational Diabetes
At 16 Weeks, blood was obtained and serum stored frozen.

At 24 Weeks, Pregnant women with a one-hour plasma glucose value between 7.8 and 10.2 mmol/L subsequently underwent an oral glucose tolerance test (OGTT), either following a 3-hour 100-gram protocol or a 2-hour 75-gram protocol (depending on the preference of the ordering physician). GDM was diagnosed if at least two glucose criteria were met or exceeded during the OGTT. The glucose criteria for the 3-hour 100-gram protocol were fasting ≥ 5.8 mmol/L, one hour ≥ 10.6 mmol/L, two hours ≥ 9.2 mmol/L and three hours ≥ 8.1 mmol/L.
TWO WAYS OF LOOKING AT THE SAME DATA

Odds Ratios for Gestational Diabetes

1\textsuperscript{st} Trimester Glucose Levels vs 25(OH)D

TWO WAYS OF LOOKING AT THE SAME DATA

Odds Ratios for Gestational Diabetes

1\textsuperscript{st} Trimester Glucose Levels vs 25(OH)D
WHAT DO OHIP AND HEALTH CANADA THINK?
Dietary Reference Intakes for Calcium and Vitamin D

Calcium and vitamin D are two essential nutrients long known for their role in bone health. Over the last ten years, the public has heard conflicting messages about other benefits of these nutrients—especially vitamin D—and also about how much calcium and vitamin D they need to be healthy.
WHY ARE THERE DIFFERENT VITAMIN D INTAKE RECOMMENDATIONS?

IOM (i.e. Health Canada) VS ENDOCRINE SOCIETY VS OSTEOPOROSIS CANADA

**Dietary Reference Intakes for Calcium and Vitamin D**

Calcium and vitamin D are two essential nutrients that play a critical role in bone health. Over the last ten years, there has been an increased awareness of other benefits of these nutrients beyond bone health, including their role in immune function, muscle health, and overall health.

**Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline**

**Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada**

David A. Hanley MD, Ann Cranney MB BCh, Glenville Jones PhD, Susan J. Whiting PhD, William D. Leslie MD, David E.C. Cole MD PhD, Stephanie A. Atkinson PhD,
<table>
<thead>
<tr>
<th>Life stage group</th>
<th>IOM recommendations</th>
<th>Committee recommendations for patients at risk for vitamin D deficiency</th>
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<tbody>
<tr>
<td></td>
<td>AI</td>
<td>RDA</td>
</tr>
<tr>
<td>Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 6 months</td>
<td>400 IU (10 μg)</td>
<td>1,000 IU (25 μg)</td>
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<tr>
<td>6 to 12 months</td>
<td>400 IU (10 μg)</td>
<td>1,500 IU (38 μg)</td>
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<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 yr</td>
<td>400 IU (10 μg)</td>
<td>2,500 IU (63 μg)</td>
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<tr>
<td>4–8 yr</td>
<td>400 IU (10 μg)</td>
<td>3,000 IU (75 μg)</td>
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<tr>
<td>Males</td>
<td></td>
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<tr>
<td>9–13 yr</td>
<td>400 IU (10 μg)</td>
<td>4,000 IU (100 μg)</td>
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<tr>
<td>14–18 yr</td>
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<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
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<tr>
<td>14–18 yr</td>
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<td>400 IU (10 μg)</td>
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</tr>
</tbody>
</table>
“Risk of vitamin D deficiency osteomalacia in bone maintenance”

KEY TEACHING POINT
What does this minimal risk actually mean in IOM context???
The key Figure from Priemel et al 2010: The IOM Report claims that based on the figures below, 25(OH)D > 50 nmol/L prevents osteomalacia in 97.5% of people (i.e. claim is Risk < 2.5%). Below is the evidence they specify IT SHOWS >18% RISK

11 osteomalacia 17 OK Risk = 6/28 = 39%

7 osteomalacia 22 OK Risk = 6/28 = 25%

5 osteomalacia 23 OK Risk = 5/28 = 18%
DENOMINATOR DISPUTE

In a study of 675 people (blue dots), 7 people with vitamin-D blood levels of 50 nmol/L or more had weak bones. The Institute of Medicine (IOM) panel concluded that this level met the needs of 99% of the population. But others have disputed the calculation, and recommend a higher level.

BECAUSE AVERAGE 25(OH)D = 65 nM, the IOM LOGIC COMMITS THE AVERAGE PERSON TO A 21% RISK OF LOW BONE!
The actual data summarized by Bischoff-Ferrari et al AJCN2006

IOM claims that this graph represents the relationship between Serum 25(OH)D and Bone Mineral Density

NB: SAME SCALE as above
The Nutrition Source

Comment on the IOM Vitamin D and Calcium Recommendations

For Adult Bone Health, Too Low on Vitamin D—and Too Generous on Calcium

By Heike Bischoff-Ferrari and Walter Willett

Vitamin D and Bone Health

Most evidence on vitamin D and calcium is available for bone health. Thus the recommendations of the Institute of Medicine (IOM) panel released on November 30, 2010 (1) are largely based on bone health and call for 600 IU of vitamin D daily for all ages up to age 70 and 800 IU after age 71. This assumes that most people get little sun exposure. The panel raised the safe upper limit of 2,000 IU daily to 4,000 IU for adults, and declares a safe upper limit of 1,000 to 2,000 IU per day in children depending on their age. According to the IOM, a serum concentration of 50 nmol/l (20 ng/ml) is sufficient for 97 percent of the population, including bone health as the main endpoint.

The vitamin D–lemma

A vociferous debate about vitamin–D supplementation reveals the difficulty of distilling strong advice from weak evidence.

BY Amy Maxmen

With his skull-and-crossbones bow-tie tied tight, Clifford Rosen strides to the podium at the Metropolitan Bone Club, a meeting of researchers and clinicians in New York City concerned with all things skeletal. He begins by raising himself: “If you want to ask a question, just yell.” Challenged that view, Blood levels of vitamin D need not be as high as many physicians and testing companies had been advocating, it said, and high doses of the vitamin could actually cause harm. Since the report was released, Rosen says he’s received about 150 e-mails critical of the panel’s decisions. About one...
Why is policy slow to adapt to evidence?

Metaanalysis of RCT’s

Primary vs 2° outcomes

Levels of Evidence

RCTs

Cohort Studies

Case Control Studies

Case Series

Case Reports

Ideas, Opinions

Most Non-Bone Health Evidence Is Ecological / Epidemiological
The shades of grey of health/medical decisions

1. Personal care decisions (flexible and possibly only during sickness).
2. Physician care of patient (flexible and possibly only during sickness).
3. Government Health policy: for all society and for years to come.

Certainty = “Causality” = RCT only
TWO KEY ONGOING PLACEBO-CONTROLLED CLINICAL TRIALS WAITING FOR RESULTS... 2016??

1. The “VITAL” STUDY (2000 IU/d)
2. The New Zealand Vit D trial (3000 IU/d)
New national guidelines for vitamin D intake highlight the need for the VITAL study

You may have heard about a new report from the respected Institute of Medicine (IOM), released in late 2010, that made recommendations about the amount of vitamin D that most Americans should consume. The IOM recommended 600 international units (IU) per day for people aged 1 to 70 and 800 IU per day for those aged 71 and older (an increase from the 400-600 IU/day previously recommended for adults at midlife and older).

To develop its recommendation, the IOM reviewed nearly 1000 scientific studies of vitamin D in relation to not only bone health but also many other health outcomes. It concluded that there is clear evidence that vitamin D has bone benefits but that current research is inconclusive as to whether higher vitamin D intake can cut the risk for cancer, heart disease, stroke, or other chronic diseases. We simply don’t know whether vitamin D supplements are beneficial in non-bone health outcomes.

Given the current lack of evidence for non-bone benefits of vitamin D, the IOM based its vitamin D recommendation on the amount required for bone health only. The new guidelines call for a daily intake—or “recommended dietary allowance” (RDA)—that will meet the needs of the vast majority of Americans who are at risk of developing vitamin D deficiency. The RDA is 600 IU per day for people aged 1 to 70 and 800 IU per day for those aged 71 and older.

Will evidence EVER be convincing enough? Even after 2017?
Vitamin D3 (cholecalciferol) 100,000 IU oral capsule monthly for 4 years

PI Robert Scragg, New Zealand

3000 men and women randomized to vit D3 or placebo.

Primary outcome: Incidence rate of fatal and non-fatal cardiovascular disease, as assessed by mortality, hospital discharges and family doctors.

Secondary outcome 1: Incidence rate of respiratory disease, as assessed by mortality, hospital discharges and consultations with family doctors.

Secondary outcome 2: Incidence rate of non-vertebral fractures, as assessed by hospital discharges, consultations with family doctors and self-reported questionnaires.

Key inclusion criteria: 1. age 50-84 years; 2. ability to give informed consent; 3. resident in Auckland at recruitment; 4. anticipated residence in New Zealand for the 4-year study period. Minimum Age: 50 Years Maximum Age: 84 Years Gender: Both males and females
CONCLUSIONS

- RDA = 600 IU VIT D DAILY (average) for public health and food policy. Targets 50 nmol/L as an average
- Medical advice does and should differ, to ensure 75 nmol/L (800-2000 IU/d)
- Stay aware of evidence of osteomalacia (proximal muscle weakness)
- Evolving evidence that 25(OH)D plays a preventive or therapeutic role in Multiple Sclerosis and in diabetes.
Potential Effect for DRUG RCT

“Evidence Based Medicine”

• Persons at high risk or with existing condition
• Treat existing condition
• High likelihood to show effect in an individual.

Relative Dose Difference

Response Outcome

CLASSIC DRUG CLINICAL TRIAL

PLACEBO - TREATMENT

Potential Effect for DRUG RCT

“Evidence Based Medicine”
Healthy persons at low risk
• Prevent future condition
• Low likelihood to show effect in an individual

White response curve is the “index”, classic effect of the nutrient.

Green represents a new, putative effect.

Relative Dose Difference

Potential For Non-Index Nutrition RCT

X

Y

CLASSIC NUTRIENT CLINICAL TRIAL

Response Outcome

RDA TREATMENT

Relative Dose Difference
Wirkung von Vitamin D auf Muskulatur und Fitness

Harald Dobnig, MD

Diagnostikinstitut Prof. Dr. H. Dobnig GmbH

Klinische Abteilung für Endokrinologie und Stoffwechsel
Medizinische Universität Graz
The „Waddling Gait“ of Osteomalacia

62 yr old patient

<table>
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<th>Value</th>
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<tr>
<td>S.creatinine</td>
<td>2.13 mg/dL (-1.3)</td>
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<tr>
<td>S.calcium (corr)</td>
<td>1.50 mmol/L (2.2-2.6)</td>
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<tr>
<td>S.phosphate</td>
<td>1.81 mmol/L (0.84-1.45)</td>
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<tr>
<td>S.magnesium</td>
<td>0.65 mmol/L (0.7-1.1)</td>
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<tr>
<td>1,25(OH)2D</td>
<td>163 pg/ml (30-70)</td>
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<tr>
<td>25(OH)D</td>
<td>15 nmol/L</td>
<td>(&gt;50 or &gt;75 nmol/L)</td>
</tr>
<tr>
<td>PTH</td>
<td>1082 pg/ml (&lt;65)</td>
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</table>

CKD stage III
PAOD stage II
arterial hypertension
chronic pancreatitis (MRI diagnosis)
Acknowledgements

VitD4MS Study Group

St. Michael’s
Jodie Burton
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MS Patients

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MSSOC – student support
A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis

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R. Vieth, PhD
A. Bar-Or, MD, MSc, FRCPC
H.-M. Dosch, MD, PhD
R. Cheung, MSc
D. Gagne
C. D’Souza, PhD
M. Uswell, MS, MSc

ABSTRACT

Objective: Low vitamin D status has been associated with multiple sclerosis (MS) prevalence and risk, but the therapeutic potential of vitamin D in established MS has not been explored. Our aim was to assess the tolerability of high-dose oral vitamin D and its impact on biochemical, immunologic, and clinical outcomes in patients with MS prospectively.

Methods: An open-label randomized prospective controlled 52-week trial matched patients with MS for demographic and disease characteristics, with randomization to treatment or control groups. Treatment patients received escalating vitamin D doses up to 40,000 IU/day over 28 weeks to raise serum 25-hydroxyvitamin D [25(OH)D] rapidly and assess tolerability, followed by 10,000 IU/day (12 weeks), and further downtitrated to 0 IU/day. Calcium (1,200 mg/day) was given throughout the trial.

24 PATIENTS, 12 MONTH PROTOCOL, AVERAGING 12,000 IU/ DAY

Burton et al. Neurology 2010
Case Report

Urinary calcium response to high dose vitamin D3 with calcium supplementation in patients with multiple sclerosis

Samantha M. Kimball a,*, Jodie M. Burton b, Paul G. O'Connor c, Reinhold Vieth d

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b St. Michael's Hospital, Division of Neurology, Toronto, ON, Canada M5B 1W8 416-864-6060
c St. Michael's Hospital, Division of Neurology, and University of Toronto, Department of Neurology, Toronto, ON, Canada M5B 1W8
d University of Toronto, Departments of Laboratory Medicine and Pathology and Nutritional Sciences, Mount Sinai Hospital, Department of Pathology & Laboratory Medicine, Toronto, ON Canada M5G 1X5
Treatment Group

* p<0.05 wrt baseline
Urine calcium / creatinine ratio vs 25(OH)D

Range to which vitamin D helps increase calcium absorption

Range of no effect on Ca absorption

First evidence that higher 25(OH)D is driving on Ca absorption. This is NOT YET TOXIC
## Relapse Events During Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Relapse # (McNemar)</th>
<th>Proportion with Relapse (Fisher’s exact)</th>
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<tbody>
<tr>
<td>6 relapses (in 4 pts)</td>
<td>10 relapses (in 9 pts)</td>
<td>p=0.09</td>
<td>p=0.11</td>
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</table>

The table shows that:
- There were 6 relapses in the Treatment group (16%) compared to 10 in the Control group (37%).
- The proportion of relapses was not statistically significant, with p-values of 0.09 and 0.11 for McNemar and Fisher’s exact tests, respectively.
### Disease Progression: EDSS Change

**Visual disturbances**
- Blurred vision, color distortions, loss of vision in one eye, eye pain

**Mental changes**
- Decreased concentration, attention deficit, memory loss

**Loss of sensation**
- Speech impediment, tremors, or dizziness

**Depression**
- Paranola
- Uncontrollable laughter and weeping

**Limb weakness**
- Loss of coordination and balance

**Muscle spasms**
- Fatigue, numbness, prickling pain

**Bladder and bowel dysfunction**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS change</td>
<td>1.15</td>
</tr>
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</table>

**EDSS Change over Trial**

- **Control**
  - EDSS pre: 1.23
  - EDSS post: 1.45
- **Treatment**
  - EDSS pre: 1.46
  - EDSS post: 1.15
Proportion of Patients with EDSS Increase During the Trial

Visual disturbances (blurred vision, color distortions, loss of vision in one eye, eye pain)
Loss of sensation, speech impediment, tremors, or dizziness
Limb weakness, loss of coordination and balance
Muscle spasms, fatigue, numbness, prickling pain
Bladder and bowel dysfunction
Mental changes (decreased concentration, attention deficit, memory loss)
Depression
Paranoia
Uncontrollable laughter and weeping

% with EDSS Increase over Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>8.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>37.5</td>
</tr>
</tbody>
</table>

p=0.018
## Adverse Events

<table>
<thead>
<tr>
<th>AE</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation*</td>
<td>4</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Breast calcification**</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Responded to change in form of **calcium** supplement

**Not associated with treatment
1. Collect fresh blood sample, isolate the lymphocytes
2. Incubate the lymphocytes with neuronal and diabetes-related antigens, to provoke an immune response
3. Measure the proliferation of the lymphocytes based on their incorporation of radioactive nucleic acid into the cellular DNA

DOES VITAMIN D TREATMENT SUPPRESS IMMUNE RESPONSE TO AUTOANTIGENS?
DOES VITAMIN D TREATMENT SUPPRESS IMMUNE RESPONSE TO AUTOANTIGENs?

At baseline, and at the end of the year of study, for each patient:

- **Control**
  - MBP
  - BSA
  - BSAP193
  - Pro-Insulin

- **Treatment**
  - MBP
  - BSA
  - BSAP193
  - Pro-Insulin

Significant changes are indicated by *p* < 0.05.
Supplementation of VigantOL® Oil Versus Placebo as Add-on in Patients With Relapsing Remitting Multiple Sclerosis Receiving Rebif® Treatment (SOLAR)

This study is currently recruiting participants.

Verified on April 2011 by Merck KGaA
Serum 25-hydroxyvitamin D status as a determinant of MS outcome following acute demyelination in children

H.E.C. Hanwell¹, R. Vieth¹, A. Bar-Or², D. Sadovnick³, D. Arnold² and B. Banwell⁴ and the Canadian Pediatric Demyelinating Disease Study Group

¹Nutritional Sciences, University of Toronto, Toronto, Ontario, ²Montreal Neurological Institute, Montreal, Canada, ³University of British Columbia, Vancouver, Canada, ⁴Division of Neurology, The Hospital for Sick Children, Toronto, Ontario.
University of Toronto students of various ancestries
25(OH)D measured last winter

![Box plot showing serum 25(OH)D levels for different ancestries.

- African
- East Asian
- European
- South Asian
- Other

Women of Lappe Study after vit D given
(average in Lappe Vit D group where cancer was prevented)

Women of Lappe control group

The box demarks:
- 75\text{th} percentile
- 50\text{th} %ile
- 25\text{th} %ile

For the group
Indicated below the box

Below this is
Diagnostic of vitamin D deficiency
rickets in infants
Drug Name(s) | DRISDOL (Brand Name Drug)
FDA Application No. | (NDA) 003444
Active Ingredient(s) | ERGOCALCIFEROL
Company | SANOFI AVENTIS US
Original Approval or Tentative Approval Date | November 11, 1911
ADHERENCE IS A PROBLEM FOR ANY MEDICATION, INCLUDING VITAMIN D
A year after hip fracture few patients still take calcium and vitamin D, but most of them still take bisphosphonate.

Table 1. Characteristics of study population.

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Discharge</th>
<th>6 weeks</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>174</td>
<td>174</td>
<td>174</td>
<td>121</td>
</tr>
</tbody>
</table>

Pitrella and Jones. *BMC Family Practice* 2006, 7:31
“disclose to the program audience any real or apparent conflict(s) of interest that may have a direct bearing on the subject matter of the continuing education program. This pertains to relationships within the last two years with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the presentation topic. The intent of this policy is not to prevent a speaker with a potential conflict of interest from making a presentation. It is merely intended that any potential conflict should be identified openly so that the listeners may form their own judgments about the presentation with the full disclosure of facts. It remains for the audience to determine whether the speaker’s outside interests may reflect a possible bias in either the exposition or the conclusions presented.”

I have/had financial interest/arrangement or affiliation with one or more organizations that could be perceived as a related or apparent conflict of interest in the context of the subject of this presentation.

<table>
<thead>
<tr>
<th>Affiliation/Financial Interest</th>
<th>Name of Organization(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Dairy Farmers of Canada</td>
</tr>
<tr>
<td>Consultant</td>
<td>Ddrops Company, DiaSorin, Cytochroma, Merck &amp; Co, Novartis</td>
</tr>
<tr>
<td></td>
<td>DSM Nutritionals, Council for Responsible Nutrition.</td>
</tr>
<tr>
<td>Speakers’ Bureau</td>
<td>Merck, Carlson Vitamins, DiaSorin, Wyeth/Centrum, Yoplait/Agropur Dairies</td>
</tr>
</tbody>
</table>