Vitamin D and Neurological Disease

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Objectives

• To understand the mechanism of Vitamin D metabolism
• To discuss the neurologic correlation of disease and Vitamin D, especially multiple sclerosis
• To discuss treatment and its ramifications of Vitamin D
Understanding the Molecule and Its Function
Introduction

• Vitamin D is a fat soluble vitamin present in several molecular forms
  – Acts more like a hormone (related to steroid hormones) than vitamin
  – Exists in 2 forms
Introduction

- Cutaneous 7-dehydrocholesterol and pre-vitamins are inert
- Cholecalciferol needs 2 or more hydroxylations to become active in the body
7-dehydrocholesterol in skin

Sun exposure

Cholecalciferol (D₃)

25-hydroxyvitamin D

25-hydroxylase in liver

1-alpha-hydroxylase in kidney

1,25-dihydroxyvitamin D (1,25-dihydroxycholecalciferol or calcitriol - active)

Binding to vitamin D receptors

Biological actions

From www.vitaminddeficiencysymptomsblog.com/theinfluence-of-vitamin-d-deficiency.html with permission.
Vitamin D (1,25-dihydroxyvitamin D3) receptor. Vitamin D acts intracellularly at the high-affinity receptor, which when stimulated alters gene transcription. (en.wikipedia.org/wiki/calcitriol_receptor with permission)
Calcium regulation in the human body. The role of vitamin D is shown in orange. Receptors in small bowel enterocytes enhance calcium and phosphorus absorption, and bone receptors stimulate mineralization of newly formed bone. (from en.wikipedia.org/wiki/vitaminD with permission)
In the presence of bile salts, orally ingested Vit D is packaged and absorbed in small intestine. Vit D is bound to lipoproteins and transported in chylomicrons to the liver the lymphatic system. In the liver, it is hydroxylated to 25 (OH) Vit D. Further hydroxylated in the kidney to 1,25 (OH) Vit D, the active form. With permission from Janssen H C et al. Am J Clin Nutr 2002;75:611-615.
Vit D hydroxylation is increased by parathormone. If too much hydroxylated 3rd time to 24, 25 (OH)2 Vit D and excreted in bile and urine. Therefore, a diseased liver or kidney causes abnormal hydroxylation of Vit D. (from en.wikipedia.org/wiki/vitaminD with permission)
Introduction

- 1,25 dihydroxyvitamin D is the physiologically active form

BUT

- The inactive 25-hydroxy-VitD3 most often measured clinically in the serum
Introduction

• Enzyme for activation not only in kidney, but:
  – Skin
  – Prostate
  – Breast
  – Colon
  – Lung
  – Brain
  – Macrophages
  – Placenta
Causes for Deficiency
Causes for Deficiency

• Lower circulating Vitamin D
  – Inadequate sun exposure in chronically ill, institutionalized or homebound
  – Aging
  – Obesity
  – Sun protective clothing/sunblock
Causes for Deficiency

• Lower circulating Vitamin D
  – Malnutrition/malabsorption (i.e. celiac disease, cholestatic liver disease, Crohn’s disease, gastric bypass, partial gastrectomy)
  – Pancreatic disease
  – Advanced liver-kidney disease
  – Chronic AED use especially Dilantin and Phenobarb
Causes for Deficiency

• People with darker skin such as African-Americans have much lower Vit D levels than those with lighter skin
Prevalence of Vitamin D deficiency in a cohort of 2,955 American adolescents

From Arch Pediatric Adolescent Med 2004;158(6);531-7. With permission.
Causes for Deficiency

• Living greater distances from the equator
  – Live: in a line from the northern border of California to the city of Boston
    • i.e. > 42° north latitude
  – The UV energy is insufficient for cutaneous Vitamin D synthesis from November thru February
Causes for Deficiency

– Live: in a line from the border of Los Angeles to South Carolina
  • i.e. < 34° north latitude
– The UV energy is sufficient for cutaneous Vit D synthesis all year long
Clinical Significance of Vitamin D
Clinical Significance of Vitamin D

- Vitamin D deficiency best known for defective mineralization of newly formed bone and hypocalcemia with secondary hyperparathyroidism which further impairs normal bone mineralization
Rickets

- Stunted growth
- Odd curve to spine or back
- Odd shaped arms & breast bones
- Large Abdomen
- Wide joints at elbow or wrist
- Odd shaped legs
- Wide Bones
- Wide ankles

From www.bing.com/search?q=rickets+photos&from=QSRRE1 with permission.
Clinical Significance

• But other roles in human health include
  – Modulation of immune function
  – Reduction of inflammation
Clinical Significance

– Modulation of immune function and reduction of inflammation!

• Decreased vitamin D associated with multiple autoimmune diseases (rheumatoid arthritis, SLE, diabetes-type I, irritable bowel disease, multiple sclerosis), as well as cancers, heart disease, lung disease, schizophrenia, and depression
How Vitamin D and its Receptor (VDR) Affect Immune Regulation
How Vitamin D and Its Receptor Affect Immune Regulation (In Vitro in Mice)

- Vitamin D can increase expression of:
  - interleukin (IL-4)
  - Transforming growth factor (TNF-β)

Both play a pivotal role in immune regulation
How Vitamin D and Its Receptor Affect Immune Regulation (In Vitro in Mice)

• VDR inhibits expression of cytokines:
  – IL-2 in T cells
  – IL-12 in monocytes
  – Interferon-\(\gamma\)
  – Tumor necrosis factor-\(\alpha\) in peripheral blood mononuclear cells
How Vitamin D and Its Receptor Affect Immune Regulation (In Vitro in Mice)

• Vitamin D modulate T-helper cells (Th) and the balance of Th1/Th2 towards less inflammation in EAE in mice

• Vitamin D inhibits Th-17 development in EAE, a key factor in MS
How Vitamin D and Its Receptor Affect Immune Regulation in Humans

• What’s important in humans:
  – Vitamin D increases TGF-β, IL-10
  – Vitamin D decreases IL-12, IL-17
  – Vitamin D linked to Th-17 in multiple sclerosis patients
  – Vitamin D affects B-cell differentiation
The immunomodulatory effects of vitamin D on immune cells. After binding to VDR, the biologically active 1,25-(OH)₂ vitamin D₃ can induce a conformational change on VDR and increase its affinity to RXR. The VDR-RXR heterodimer becomes a transcriptional factor, interacts with VDREs in the promoter regions of different genes, and ultimately leads to functional changes in multiple immune cell lineages, including Th1, Th17, Th2, Treg, and NKT cells.

Clinical Association with Multiple Sclerosis as a Autoimmune Model
Clinical Association with Multiple Sclerosis as a Autoimmune Model

• Increased relapse risk with low Vitamin D serum levels (low vitamin D at MS onset...even lower at exacerbation than at remission)

• An increase in serum 25(OH) Vit D levels with 10 nmol/L were associated with a 9-12% risk reduction for relapses
Clinical Association with Multiple Sclerosis as a Autoimmune Model

- In a pediatric population, 14% decrease in relapsing risk
- A low level of Vit D was associated with a higher disability and increased brain atrophy as measured by MRI
- But, its is unknown if Vit D supplementation prevents multiple sclerosis
Facts of Vitamin D Levels
Facts of Vitamin D Levels

• 25(OH) Vit D best indicator of Vit D status due to its stability in the serum and its correlation with Vit D sufficiency in the body
Facts of Vitamin D Levels

• Vit D levels based on bone health measures
  – IS THAT THE SAME FOR ALL DISEASES?
• Vit D level 30-100 Normal [25(OH)Vit D]
  – although, is higher or lower numbers within that range optimal for all Vit D ranges?
• 77% of Americans are considered deficient
Facts of Vitamin D Levels

• Dose of supplementation to achieve good levels theoretically unknown
  – But twice the upper limit of normal Vit D would not cause any toxicity
  – Unknown long term effects of Vit D supplementation or long term effects of Vit D toxicity
Facts of Vitamin D Levels

• 25 (OH) Vit D
  – Produced by sun exposure, obtained from food, obtained from supplements
  – Long serum half life of 15 days
  – Does not indicate the amount of Vit D stored in the body tissue
Facts of Vitamin D Levels

• 1,25 (OH)2 Vit D
  – Active form of Vit D
  – Short half life of 15 hours
  – Not a good indicator of Vit D status!!
  – Levels do not decrease until severely deficient!
  – Regulated by parathyroid hormone, calcium, and phosphate
  – Serum concentrations are regulated by parathyroid hormone, calcium, and phosphate
Facts of Vitamin D Levels

• Vit D2 (ergocalciferol)
  – Naturally occurring
  – In phytoplankton and fungi/yeast
  – In several food products like dairy, cereals, and orange juice
  – Less effective in raising 25 (OH)Vit D in people than Vit D3
Facts of Vitamin D Levels

• D2 is derived from ergosterol, a precursor molecule of VitD2 found in phytoplankton, fungi, and invertebrates

↓ UV radiation

Vitamin D2 (ergocalciferol)
Facts of Vitamin D Levels

- No D2 in vertebrates since they don’t have ergosterol

SO

only get as a pharmaceutical or in diet (i.e. 50,000 IU weekly x 3 months to correct)
Assessment Needs
New Advice on Vitamin D & Calcium

### Vitamin D

<table>
<thead>
<tr>
<th>Age</th>
<th>RDA (IU)</th>
<th>Upper Level (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 3 years</td>
<td>600</td>
<td>2,500</td>
</tr>
<tr>
<td>4 to 8</td>
<td>600</td>
<td>3,000</td>
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<tr>
<td>9 to 70</td>
<td>600</td>
<td>4,000</td>
</tr>
<tr>
<td>71 and older</td>
<td>800</td>
<td>4,000</td>
</tr>
</tbody>
</table>

### Calcium

<table>
<thead>
<tr>
<th>Age</th>
<th>RDA (mg)</th>
<th>Upper Level (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 3 years</td>
<td>700</td>
<td>2,500</td>
</tr>
<tr>
<td>4 to 8</td>
<td>1,000</td>
<td>2,500</td>
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<tr>
<td>9 to 18</td>
<td>1,300</td>
<td>3,000</td>
</tr>
<tr>
<td>19 to 50</td>
<td>1,000</td>
<td>2,500</td>
</tr>
<tr>
<td>51 to 70 (men)</td>
<td>1,000</td>
<td>2,000</td>
</tr>
<tr>
<td>51 to 70 (women)</td>
<td>1,200</td>
<td>2,000</td>
</tr>
<tr>
<td>71 and older</td>
<td>1,200</td>
<td>2,000</td>
</tr>
</tbody>
</table>
The Significance of Clinical Disease with Vitamin D Deficiency
The Significance of Clinical Disease with Vitamin D Deficiency

• In addition to its role in regulating calcium physiology, also shown to affect
  – Brain development and function
  – Cell proliferation and apoptosis
  – Immune cell differentiation
  – Modulation of immune responses
  – Neuroprotective properties of Vit D
The Significance of Clinical Disease with Vitamin D Deficiency

• Proposed neuroprotective properties of Vitamin D
  – Vitamin D simultaneously targets several factors leading to neurodegeneration
    • Immunoregulatory, antioxidant, anti-ischemic factors
    • Neurotrophic factors
    • Acetylcholine neurotransmitters
    • Clearance of amyloid beta peptide
    • Prevention of hyperparathyroidism

Multiple Sclerosis
Multiple Sclerosis

• Etiology of MS is multi-factorial; genetic susceptibility and environmental exposure
  – One environmental factor associated with development of multiple sclerosis is vitamin D
  – Vitamin D came to light about three decades ago
Multiple Sclerosis

• “Vitamin D has been shown to regulate the expression of the MS associated HLA-DRB1*15 allele, HLA-DRB1 and smoking in the risk of MS, further advocating that HLA determines the impact of environmental triggers.”

Multiple Sclerosis

• However,
  – “in untreated patients with MS, increasing levels of Vit D 25 (OH) are inversely associated with radiologic disease activity irrespective of their HLA-DRB1*15 status”

Multiple Sclerosis

• Each 10 nmol/L increase in 25 (OH) Vit D was associated with
  – 12.7% reduced odds of new T1 gad enhancing lesions
  – 11.7% for new T2 lesions
  – 14.1% for combined activity

Multiple Sclerosis

- No association between 25 (OH) Vit D and disease activity were detected after initiation of IFN-β

Multiple Sclerosis

• “Class III evidence that IFN-β is associated with reduced risk of relapse and this effect may be modified by a positive effect of IFN-β on serum 25(OH) D levels”

Multiple Sclerosis

• IFN-β associated with greater production of Vit D from sun exposure, suggesting that part of the therapeutic effects on MS relapses may be through modulation of Vit D metabolism!

Multiple Sclerosis

- IFN was only protective against relapse among persons on IFN-β
  - Did not differ for IFN-β type
- IFN-β was only protective against relapse among persons with the higher 25 (OH) D (not in insufficient persons)

Multiple Sclerosis

- So patients on IFN-β should have Vit D levels maintained in the sufficiency range by monitoring

Multiple Sclerosis

- Why this association with the IFN-β and Vitamin D?
  - How they work unknown but thought to
    - Increase IL-10 expression
    - Reduce antigen presentation
    - Restore the blood-brain barrier
    - Work against Herpes viruses

Multiple Sclerosis

- Epiphenomenon with IFN-β in RRMS and cancer patients “is a drop in serum cholesterol”
- Other drugs like statins that reduce serum cholesterol can increase Vit D 25 (OH)...so a reciprocal relationship between serum cholesterol and Vit D

Multiple Sclerosis

- Higher Vitamin D levels are associated with decreased exacerbation risk in RRMS
- "For each doubling of the serum Vit D 25 (OH) concentration, the relapse risk in MS decreases by 27%"

Runia TF, Hop WCJ, Buljevac D, Hintzen RQ. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology* 2012;79:261-266.
Multiple Sclerosis: The Bottom Line on Vit D 25(OH)

- Appears to influence MS risk and course of disease
- It is cheap, safe and easy to administer and could be a valuable addition to treatment
- Need to interpret cautiously; questions remain
Multiple Sclerosis: The Bottom Line on Vit D 25 (OH)

- 25 (OH) Vit D and MS
  - Exact nature of the association (dose-response, effects of seasonal variation) requires further clinical trials to address
    - High levels are protective?
    - Low levels are potentially pathogenic?
    - Safety of Vitamin D
    - Monitoring frequency because of seasonal variability
Multiple Sclerosis: The Bottom Line on Vitamin D 25 (OH)

• Are the IOM recommendations correct for MS?
  – they were written for food fortification

IOM=Institute of Medicine
Besides MS, What Does Vit D Effect?
**Vitamin D: A nutrient for the entire body**

**Multiple sclerosis**
Lack of sun exposure and vitamin D are major risk factors for MS. Studies suggest that sun exposure is important in the prevention of MS and some studies suggest that vitamin D can play a hand in delaying progression of the disease and maybe even decreasing relapse rates.

**For the lungs**
Randomized controlled trials show that being sufficient in vitamin D can reduce flare-ups in the lungs for patients with diseases that affect the lungs, like cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). Furthermore, in one trial, vitamin D reduced the risk of mortality in people with CF.

**Breast cancer**
Preliminary research suggests that vitamin D plays a hand in preventing breast cancer. Does a lack of sun exposure explain the increase in incidence the last few decades? Research is underway to find out.

**Grip strength**
Vitamin D improves hand grip strength in elderly women.

**Bone health**
Vitamin D’s importance for bone health has long been known. Cod liver oil – which contains vitamin D – was used to treat rickets in the 19th and early 20th centuries, while UV therapy was used in the early 20th century. Today, vitamin D by itself is used to treat rickets and the adult form, osteomalacia. Besides preventing and treating rickets, studies show that vitamin D in higher doses prevent fractures and may improve bone mass density alongside calcium.

**Sun exposure**
In response to sun exposure, your body can produce 10 to 25 thousand IU of vitamin D per day.

**Allergies**
A randomized controlled trial found that vitamin D helps reduce sneezing, congestion and nasal drip in people with allergic rhinitis.

**Blood pressure**
Studies show that vitamin D supplementation during winter – when vitamin D is hardest to get – reduces blood pressure.

**Skin disease**
UV exposure is an effective treatment for a variety of skin diseases, including psoriasis, vitiligo and eczema.

**Prostate cancer**
A randomized controlled trial showed that vitamin D supplementation for a year, at 4,000 IU/day, improved the prognosis of low-grade prostate cancer.

**Falls**
Several studies show that vitamin D reduces the incidence of falls in the elderly. How? Possibly by improving balance and strength.

From [www.vitaminday.net/why-vitamin-day/a-nutrient-to-the-entire-body.com](http://www.vitaminday.net/why-vitamin-day/a-nutrient-to-the-entire-body.com) with permission.
Other Effects of Vitamin D

• Most tissues and cells in body have Vit D receptor
• Serum Vit D influences the expression levels of up to one third of the human genome
• Numerous studies associate Vit D deficiency with
  – Cancer
  – Heart disease
  – Gut microbiome
Other Effects of Vit D

• Arthritis 2° dysregulation of calcium and phosphate
  – Therefore decreasing bone growth and remodeling resulting in pathologic fractures and bone pain
  – Defective bone mineralization with hypocalcemia secondary to hyperparathyroidism
Other Effects of Vit D

• Cutaneous hyperalgesia
  – Resistant to antidepressants and opiates
  – Responds to Vit D correction
Other Effects of Vit D

• Memory impairment
  – Recent study ID 40% increased risk for Alzheimers
  – Vitamin D may protect brain by reducing amyloid-beta and inflammation
Other Effects of Vit D

• Vit D and BP
  – Possibly may lower BP in African-Americans
  – African-Americans normally have lower Vit D and increased BP
  – Recent study ID 1.4 point drop for every 1,000 IU of Vit D
  – Blood pressure fell the most in those whose Vit D levels rose the most
Other Effects of Vit D

• Peripheral neuropathy
  – Has been associated with type I and II diabetes as well as both the microvascular and macrovascular complications of diabetes
  – Has been shown to be common in diabetic patients who have symptoms of distal symmetrical polyneuropathy
  – Often diagnosed in those with established diabetes and replacement may prevent or delay the onset of diabetic complications
Other Effects of Vit D

• Secondary compression of spinal cord, plexus, or peripheral nerves from rickets or osteomalacia
Other Effects of Vitamin D

• Myopathy
  – Vitamin D is important to maintain healthy muscles
  – Vitamin D deficiency doesn’t normally cause a significant myopathy, but can cause muscle weakness
    • In the elderly, muscle weakness is usually increased in pelvic and thigh musculature more than arms resulting in a waddling gait and increased tendency to fall
Other Effects of Vitamin D

• Myopathy
  – Cholesterol, Vitamin D, and statins
    • 7-dehydrocholesterol can be metabolized to cholesterol or Vitamin D
    • It is known that statins decrease cholesterol and there is a paradoxical increase in Vit D 25 (OH)
    • Therefore, treating with Vit D 25 (OH) would not be expected to improve statin-induced myotoxicity (opposite of the current hypothesis/study at Cedar Sinai)
Recommendations and Conclusions
Recommendations and Conclusions

• Assess the levels of Vitamin D with seasonal variation and maintain normal accepted levels
• Supportive tests: serum calcium, phosphorus, alkaline phosphastase, PTH level, bone density
Recommendations and Conclusions

• P.O. supplementation
  – 25 (OH) Vit D levels checked during winter months (Jan & Feb in Northern Hemisphere-the seasonal trough)
  – Supplement Vit D3 at 600-4000 IU (with 1000-1200 mg of calcium per day) to target range of 30-40 ng/mL (check level 2-4 months)
Recommendations and Conclusions

- The Vitamin D Council recommended a minimal serum Vit D 25 (OH) of 75 nmol/L for health in MS (30-100 nmol/L normal range)
  - A strong correlation between Vit D and VDR binding in CD4 + T cells
  - VDR binding sites were highly enriched for genes associated with MS in individuals with levels > 75
  - Level > 75, 4500 receptor binding sites; level < 75, approximately 500 binding sites
Recommendations and Conclusions

• Below latitude of LA-summer
  – Check levels twice a year
  – Level < 30 ng/ml, treat, recheck level 2-4 months

• Vitamin D2 when treatment failure with lower doses of Vit D3 (1000 to 4000 IU/d)
  – (due to easy availability of D3 and controversy to D2 deficiency)
Recommendations and Conclusions

• D2-50,000 IU every week x 3 months-safe but monitor calcium levels to be safe
  – Recheck Vit D 25 (OH), once stable switch to Vit D3 maintenance (600-4000 IU daily)
Recommendations and Conclusions

• Drawbacks: variable absorption based on body fat
  – More body fat need 2-3x more Vit D to maintain level
Recommendations and Conclusions

• Alternative Supplementation
  – 15 minutes of noon day sunlight or
  – Artificial UVB radiation (in some tanning bed biweekly in the buff)
    • Gives us 10,000 IU of 25 (OH) Vit D in fair skinned people
  – Draw backs
    • Inconsistent dosing
    • Sunburn
    • Skin cancers
Recommendations and Conclusions

- UV treated mushrooms
  - Potent source up to 75% of daily requirement in a single 3.5 ounce serving

UV Treated Mushrooms Pop with Vitamin D. Environmental Nutrition. The Newsletter of Food, Nutrition, and Health. 2013;36(9); pg 2.
Recommendations and Conclusions

• Vitamin toxicity
  – Rare
  – Levels > 100 to 150 ng/ml
  – Hypercalcemic effects on organs, hypercalcuria, and renal failure
  – Can’t get toxic with sun exposure
  – Monitor serum and urine calcium, serum 25 (OH) D, if urine calcium excretion > 100 mg /24 hours. Decrease Vitamin D dose
  – Phosphate level (if ↑suggests 2° hyperparathyroidism
Human Dose Response for vitamin D

Vitamin D Intake  IU/day

Serum
25(OH)D ng/ml
400
40

25(OH)D nmol/L
1000
100

Vitamin D µg/day

UL

TANNING

X = reported toxicity = HYPERCALCEMIA

X = Individuals with Vit D2 Hypercalcemia

Study Group Mean Data
Vit D2-Treated Group Mean Data

Recommendations and Conclusions

• Contraindications
  – Vit D toxicity
  – Allergy to Vit D or its carrier agents
Recommendations and Conclusions

• Vit D hypersensitivity syndromes
  – Occur with unregulated production of 1,25 (OH) Vit D with
  • Sarcoidosis
  • Tuberculosis
  • Certain cancers like lymphoma
  – But must watch closely since they can get deficient
Recommendations and Conclusions

• Vit D hypersensitivity syndromes
  – Sunlight-prohibiting dermatologic conditions
    • Medications
    • Skin cancers
Conclusions

• Vit D not an orphan vitamin
• Important functions being identified
• IOM recommendations for Vit D supplementation recommended, but these are dietary recommendations and not for disease states
  – These levels are still not known
Conclusions

• Interpreting the findings of Vit D studies still warrants more investigation
  – In MS, there is a complex interplay among diverse multiple environmental factors, including viral infections, hygiene, UV sunlight exposure, smoking, and nutrition on genetic vulnerability being implicated as potential risk for the development of MS
  – Vitamin D and VDR especially may affect gene expression and risk of developing MS! as well as other diseases
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