



Shining a Light on Vitamin D & MS

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Objectives

- Understand the role of vitamin D in the body and how it effects immune function
- Appreciate the role of vitamin D in altering the risk of MS
- Be aware of the rationale for Vitamin D supplementation as a primary prevention strategy in MS
- Be familiar with the evidence suggesting a role for vitamin D in the treatment of MS

Vitamin D Basics

Sources of Vitamin D

- Major Source: Sunlight



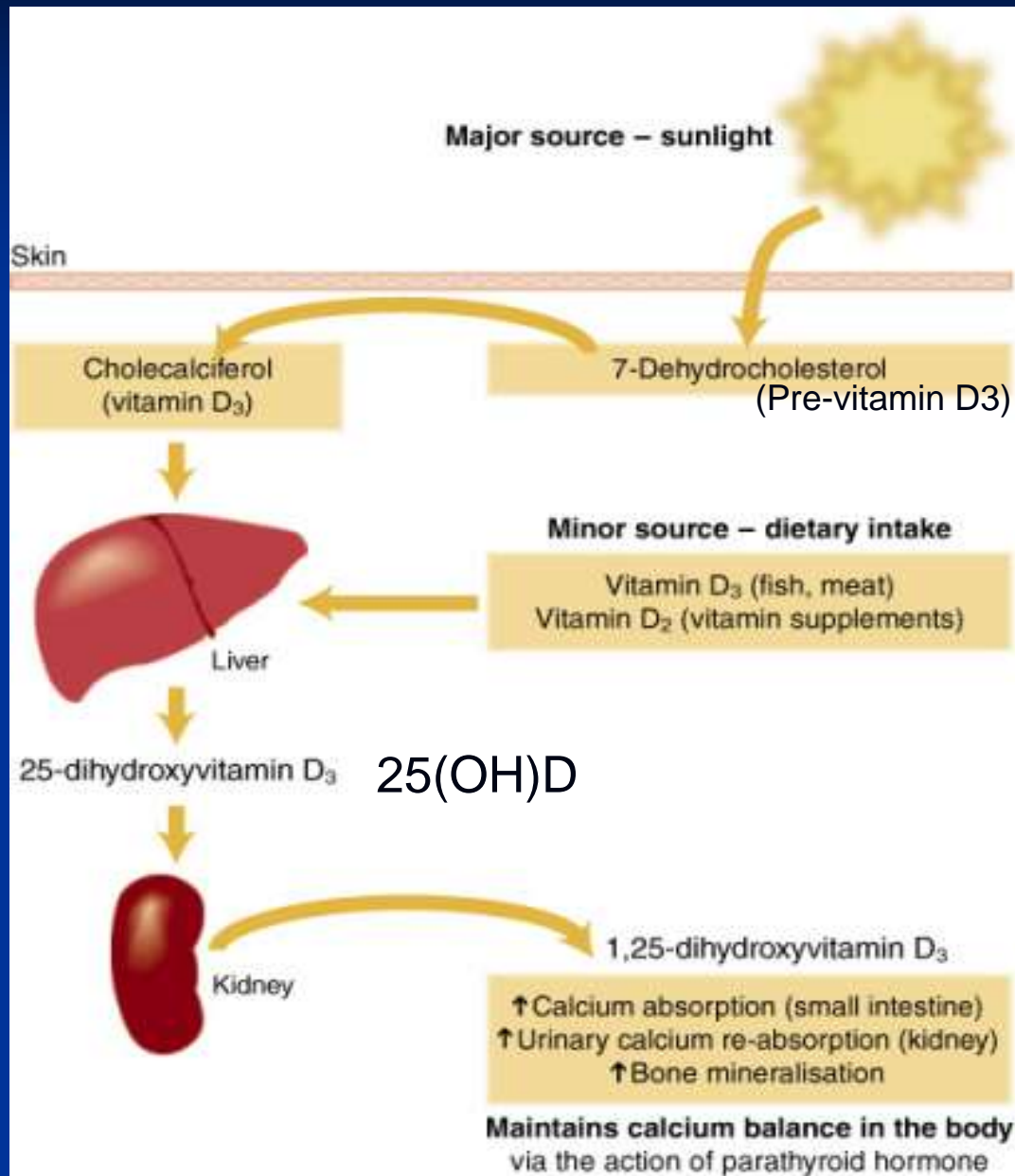
- Minor Source: Certain foods



- Other: Supplements



Vitamin D Metabolism



Vitamin D in The Body

- Vitamin D is a steroid hormone
- Has multiple regulatory and functional effects throughout the body
- Transported through the body bound to vitamin D-binding protein
- Biological effects primarily mediated through the vitamin D receptor (VDR)
- VDR found in the brain and on immune cells, as well as multiple other tissues

Vitamin D in the Body

- Regulates calcium and phosphorus metabolism
- Maintenance of adequate bone mass
- Immunomodulatory effects
- May have neuroprotective effects

Measuring Vitamin D Status

- The best indicator of vitamin D status, reflecting intake from all sources, is serum 25(OH)D₃
- Levels < 25 nmol/L considered “severely deficient”
- Levels >25 but <80 nmol/L considered insufficient or “mildly to moderately deficient”
- Levels \geq 80 nmol/L considered sufficient

Optimum Vitamin D Levels

- Review of research in multiple health outcomes (bone mineral density, lower extremity function, dental health, risk of falls, admission to nursing home, fractures, cancer prevention, incident hypertension) suggested the most advantageous serum level for 25(OH)D appeared to be at least 75 nmol/L*
- For cancer prevention, most desirable levels between 90-120 nmol/L*

•Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. Adv Exp Med Biol. 2008;624:55-71.

How Do We Measure Up?

- Study of healthy young Canadian adults of diverse ancestry revealed that 93% were below 75 nmol/L and almost 3/4 below 50 nmol/L *
- In a study of healthy western Canadian adults living in Calgary 97% fell below the generally recommended level of 80 nmol/L on at least one of four seasonal measurements.**

* Gozdzik A et al. Low wintertime vitamin D levels in a sample of healthy young adults of diverse ancestry living in the Toronto area: associations with vitamin D intake and skin pigmentation. BMC Public Health 2008. Sept 26;8:336

** Rucker D et al. Vitamin D insufficiency in a population of healthy western Canadians. CMAJ 2002;166(12):1517-24.

Vitamin D Toxicity

- Current recommended upper limit is 250 nmol/l*, though toxicity may not occur until levels are much higher (possibly >600-750 nmol/L)**
- Certain diseases (certain cancers, granulomatous diseases, primary hyperparathyroidism) increase risk
- Body has protective mechanism with sunlight

* Jones G Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr. 2008;88(2):5825-5865.

**Vieth R. Vitamin D toxicity, policy and science. J Bone Miner Res. 2007 Dec;22Suppl2:V64-8.

Adverse Effects of Too Much Vitamin D

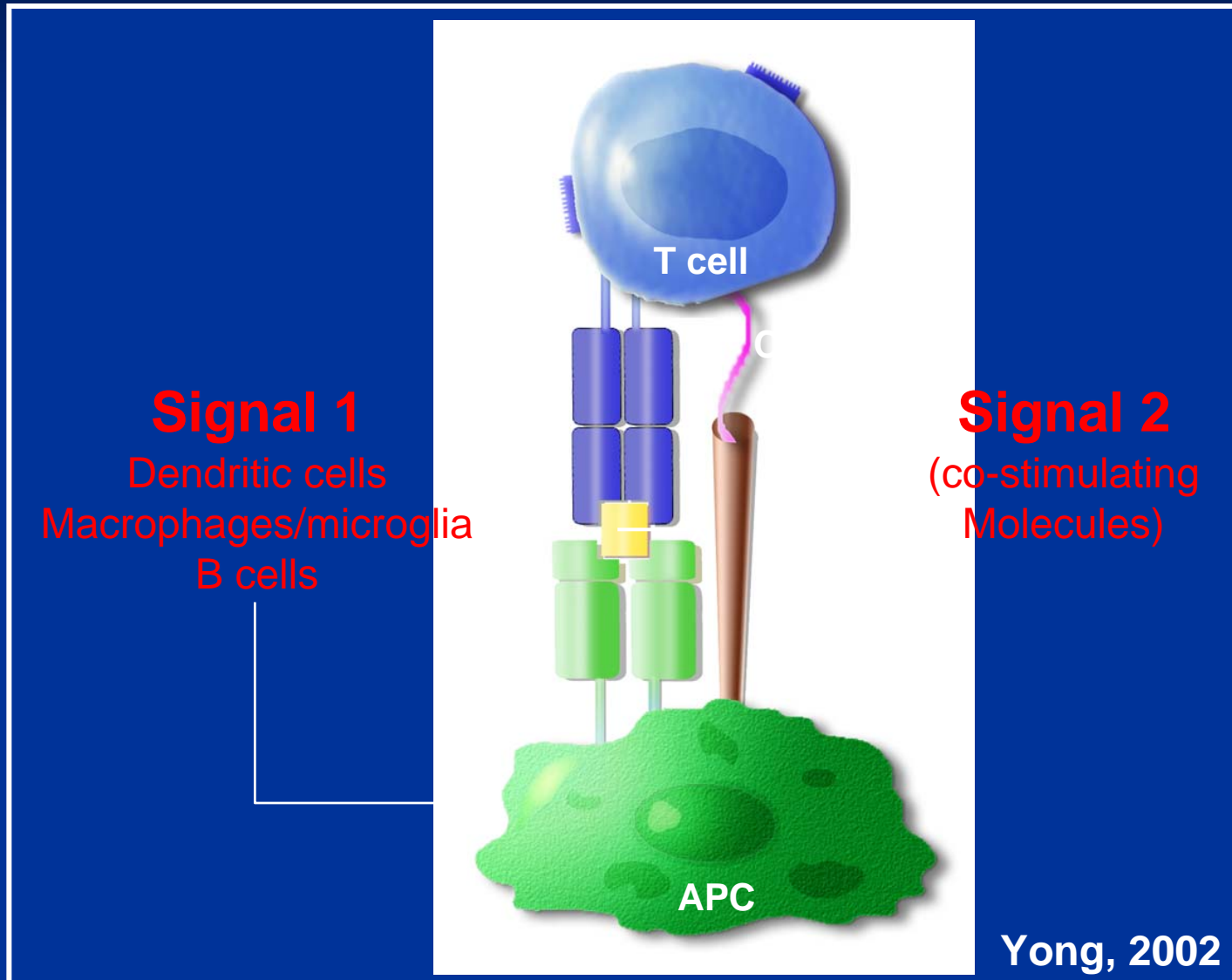
- Potential complications include:
 - Nausea and vomiting
 - Metallic tastes
 - Hypercalcemia (too much calcium in blood)
 - Calcium deposits in the blood vessels or kidneys
 - Renal (kidney) failure
 - Heart failure
 - Pancreatitis

Immunology & Vitamin D

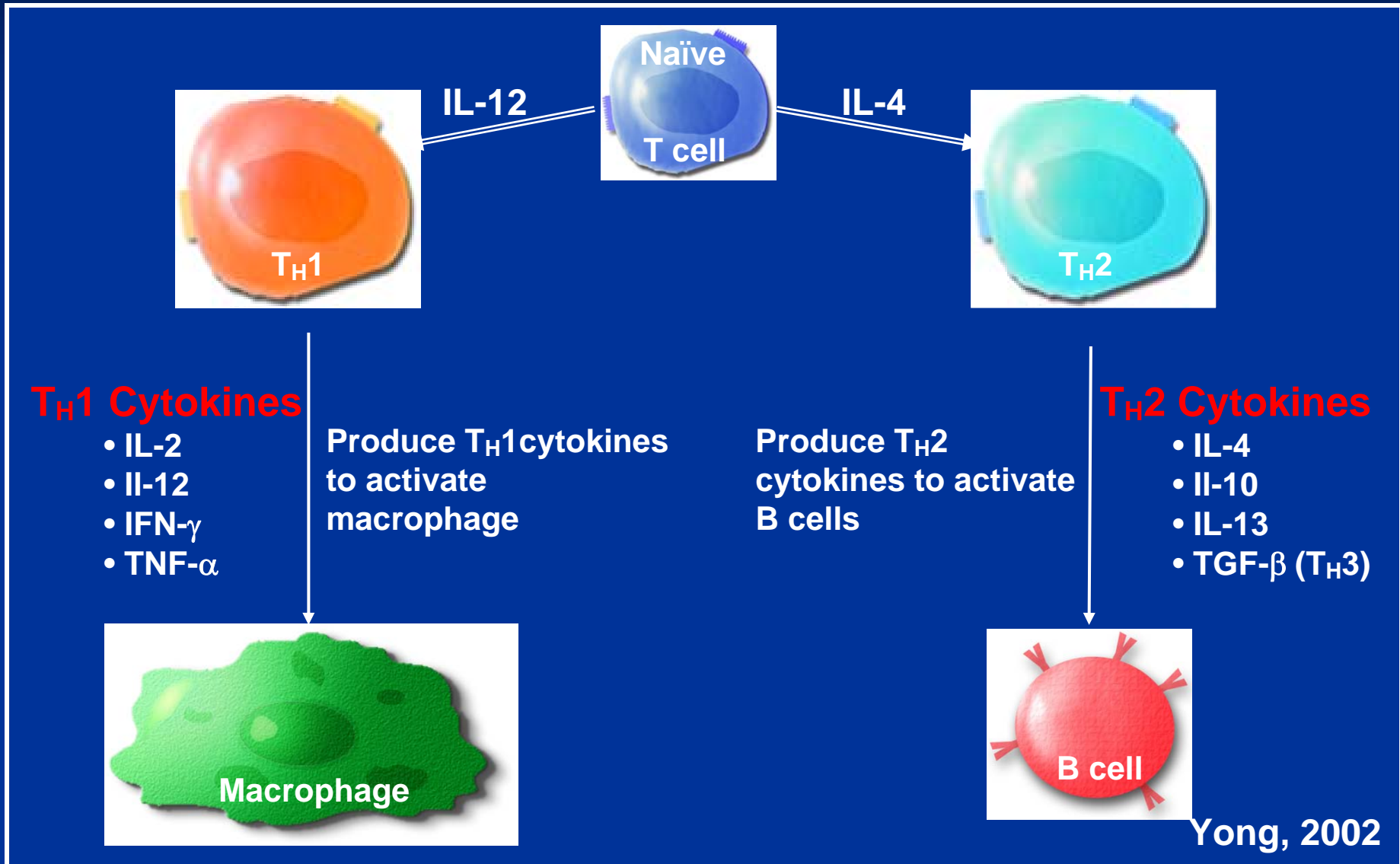
Simplified Immunology of MS

- Activated T cell directed against components of myelin play a key role in MS
- Antigen presenting cells and stimulation by co-stimulatory molecules initiates this immune response
- Th1 pro-inflammatory T cells predominate and drive the inflammatory process
- Disruption of normal regulatory/suppressor T cell function also occurs
- B cells, which coordinate antibody responses also play a role

Antigen presentation is necessary to activate T cells



Naïve CD4 T cells differentiate into T_H1 and T_H2 cells



T_H1 and T_H2 Imbalance In MS

(reviewed in Yong, Neurol 2002)

- MS relapses are often preceded by increased T_H1 and decreased T_H2 cytokines. Conversely, cells isolated at the time of remission express T_H2 cytokines
- Thus, aims of therapy include decreasing the activation of T_H1 cells, or causing a T_H1 to T_H2 deviation

Immune Effects of Vitamin D

T cells

- Reduces T cell activation by reducing expression of major histocompatibility complex (MHC) class II & surface co-stimulatory receptors in antigen presenting cells
- Reduces T cell proliferation
- Shifts T cells to a TH2 (anti-inflammatory) profile
- Inhibits production of pro-inflammatory cytokines (chemical messengers)
- Promotes T regulatory cells

Immune Effects of Vitamin D

B cells

- Reduces proliferation of activated B cells
- Reduces immunoglobulin (antibody) production
- Induces cell death of activated B cells
- Some of these effects may be indirect and via mediation by T cells and other immune cells

Immune Effects of Vitamin D

Immunomodulatory effect



Reduces pro-inflammatory processes

AND

Enhances anti-inflammatory and
regulatory functions

Vitamin D may have Neuroprotective Effects

- Evidence that Vitamin D can be converted to active form by certain brain cells
- Vitamin D important in fetal brain development
- Vitamin D found to have an effect on neurotransmitters and nerve growth factors

*Kalueff AV et al. The Vitamin D Neuroendocrine System as a Target for Novel Neurotropic Drugs. CNS & Neurological Disorders-Drug Targets. 2006 Vol.5, No.3, 363-371.

Vitamin D may have Neuroprotective Effects

- Vitamin D has effects that reduce cell death in the brain by multiple mechanisms*
- Vitamin D abolishes T cell killing of neurons in culture**

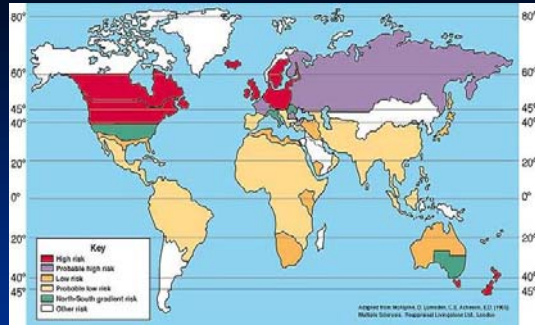
*Kalueff AV et al. The Vitamin D Neuroendocrine System as a Target for Novel Neurotropic Drugs. CNS & Neurological Disorders-Drug Targets. 2006 Vol.5, No.3, 363-371.

**Slovka S et al Environmental risks for multiple sclerosis: quantitative analyses and biological Mechanisms. Poster 533 ECTRIMS Sept 2009

Vitamin D as a Risk Factor for MS

Vitamin D & Risk of MS

- Latitude
- Sunlight Exposure
- Vitamin D levels



Latitude and Risk of MS

- The geographical distribution of MS with low prevalence in equatorial regions and increasing prevalence with increasing latitudes in both hemispheres correlates with sun exposure/vitamin D levels
- Five fold difference in MS between Tasmania and Queensland, Australia despite similar genetics
- Migrating populations seem to acquire the MS risk of the areas they move to but individuals keep risk of country of origin if move after adolescence.

Sunlight & Risk of MS

- There is an inverse correlation between MS prevalence and sunlight found in multiple studies
- Also inverse correlation between altitude (marker of sunlight intensity) and MS
- Higher childhood sunlight exposure and higher actinic damage in skin associated with lower MS risk
- Twin studies suggest MS developed in twin with less sun exposure
- Lower incidence of non-melanoma skin cancer in MS

Vitamin D Levels & Risk of MS

- Prospective nested case control study among more than 7 million US military personnel
- Vitamin D levels stored from time of entry
- Cases of MS identified and paired with two matched controls (age, race/ethnicity, sex, time of collection)
- Strong relationship between vitamin D levels and risk of MS
- Lowest risk with level of $>99\text{nmol/L}$

Vitamin D and Childhood MS

- Canadian study of 153 children with a first demyelinating event
- Vitamin D level at baseline was a significant predictor of risk of developing definite MS
- Each incremental 10 nmol/L rise in 25(OH)D was associated with a 20% reduction in the likelihood of an MS diagnosis

Hanwell, H et al Vitamin D status as a predictor of MS outcome following an initial paediatric Demyelinating event. Poster 173 ECTRIMS September, 2009

Other Evidence

- Birth month effect on risk of MS (May highest risk and November least risk) - hypothesized to be related to lower vitamin D levels in later pregnancy
- Quantitative analytical review of different potential environmental risk factors for MS using global population data and NASA satellite data found:**
 - lack of available UV radiation was the single most important risk for developing MS
 - This outweighed other factors by at least 20 fold

**Sloka S, Silva C, Pryse-Phillips W, Patten S, Metz L & Wong, Y et al. A Quantitative Analysis of Suspected Environmental Causes of MS 2009 In press. From: Dr. Wee Yong, University of Calgary

Interaction of Vitamin D & Genetics

- Vitamin D response element (VDRE) found in the promotor region of HLA-DRB1*1501, the main susceptibility locus for MS
- Direct functional interaction between vitamin D and this major locus of genetic susceptibility found
- Authors concluded their results implied that “vitamin D supplementation at critical time periods may be key to disease prevention”*

* Ramagopalan SV et al. Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D. PLoS Genetics 2009Feb;5(2):e1000369

Partially funded by MS Society of Canada

Vitamin D & Prevention of MS

Primary Prevention of MS

- Vitamin D supplementation
 - Vitamin D supplements found to reduce the risk of MS by about 40% comparing women with intake of >400 IU/day to those with no supplemental vitamin D (Nurses Health Study)*
 - A dose of 1000 to 4000 IUs daily to achieve a serum level of >99nmol/L is safe and may reduce risk by as much as 62% (especially in late teens/early twenties)**

*Munger KL et al. Vitamin D intake and incidence of multiple sclerosis. Neurology 2004; Vol62(1):60-65.

** Ascherio A & Munger K. Epidemiology of MS: From Risk Factors to Prevention. Semin Neurol 2008;28:17-28.

Pregnancy and Vitamin D

- Vitamin D deficiency may be associated with increase in pregnancy complications (e.g. pre-eclampsia, insulin resistance and gestational diabetes)
- Vitamin D is critical for fetal brain development, fetal skeletal formation and immunological functions
- Vitamin D status may affect chronic disease susceptibility in offspring (type I diabetes, MS)
- No intervention studies have been done

Lessons from Animal Studies

Experimental allergic/autoimmune encephalomyelitis (EAE)



Vitamin D in EAE

- Treatment with vitamin D before induction of disease shown to completely prevent disease
- This effect not seen in vitamin D receptor knock-out mice
- Treatment after induction but before clinical symptoms found to result in milder disease and longer survival
- Treatment with vitamin D after the onset of clinical symptoms halted disease progression and even reduced disability scores

Smolders J et al. Vitamin D as an immune modulator in multiple sclerosis: a review. *Journal of Neuroimmunology* 2008. 194:7-17.

Vitamin D as an MS Treatment

Vitamin D and Disease Activity: Relapses

- RRMS patients found to have significantly lower levels of 25(OH)D during relapses compared with those in remission*
- Immunological analyses revealed activated vitamin D reduced the proliferation of myelin reactive T cells and resulted in a favourable shift in the cytokine profile of T cells* isolated from patients with MS
- Demonstrated T cells were capable of metabolizing 25(OH)D to 1,25(OH)₂ vitamin D, which in turn demonstrated effects on T cell function

* Correale J et al. Immunomodulatory effects of Vitamin D in multiple sclerosis. Brain 2009;132;1146-1160.

Vitamin D and Disease Activity: Pregnancy Effects

- In pregnancy there is a reduction in relapse rates as pregnancy advances and an increase in relapse rates post-partum
- Vitamin D levels rise as pregnancy advances and abruptly fall post-partum
- Vitamin D may therefore be one of many factors that explains the relative protective effect of pregnancy
- Vitamin D may interact with estrogen to produce beneficial response

Vitamin D Supplementation as a Treatment

- Important to consider form and dose of vitamin D, patient numbers (enough to show a statistically significant benefit) and whether or not there is a control group
- Small preliminary clinical trials have had many challenges
- Preliminary results are encouraging

Vitamin D and the Cytokine profile in MS


- 39 MS patients with baseline vitamin D level of less than 50 nmol/L
- Treated with 1000 IU/day or placebo
- Analysis of blood samples done
- Vitamin D supplementation significantly increased TGF-B1 levels (correlated with inhib of MS in EAE) and one of the pro-inflammatory cytokines (IL-2) but not three

Maier et al. Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. J Neuroimmunol 2003;134:128-32.

Pilot Study of Calcitriol (1,25-dihydroxyvitamin D3)

- Pilot study with 15 pts with RRMS and at least one clinical relapse in previous year
- Oral calcitriol (target dose 2.5 ug/d) for 48 weeks
- Calcitriol is the metabolically active form of vitamin D
- Symptomatic hypercalcemia in two patients
- Reduced relapses (27% from baseline) but no control group

Wingerchuk DM et al. A pilot study of oral calcitriol (1,25-dihydroxyvitamin D3) for relapsing-remitting MS J Neurol Neurosurg Psychiatry 2005;76:1294-1296.
Partially funded by MS Society of Canada



A Phase I/II dose escalation trial of oral vitamin D3 with calcium supplementation in patients with multiple sclerosis J. Burton et al.

- **Objective:** To characterize the safety profile of high-dose vitamin D3 (VD3) in MS
- 49 pts (25tx/24control) Rx:
 - VD3 ~14,000IU/day over 52 wks (4,000IU/dayx8wks, escalated over 28wks to 40,000IU/dayover 28 wks then maintenance with 10,000IU/d x12wks, 4000IU/dx8wks and 4 wk wash-out) and calcium 1200 mg /day
- **Primary endpoint:**
 - Change in calcium level at each level of VD3 and between treated and controls
 - No significant differences in calcium, PTH or urine Ca/creatinine
- **Adverse effects:**
 - No significant clinical or biochemical adverse events, even at levels >400 nmol/L
 - Few people with constipation - relieved with change in calcium dose



Results continued

■ Relapses:

- significant difference in change in annualized relapse rate between treated (-41%) and controls (-17%);
- proportion with relapses 16% versus 37%

■ Progression:

- greater proportion of treated pts with stable/ improved EDSS ($p=0.018$)

■ Immunology:

- T cell reactivity reduced on a lymphocyte assay in those with serum levels of $>100\text{nmol/L}$; other immunological markers to be reported later

■ Conclusion:

- High dose VD3 ($\sim 10,000$ IU/day and possibly higher is “safe & tolerable with evidence of clinical improvement”

■ Preliminary but encouraging

Vitamin D and Progression in MS

- Several studies have demonstrated a correlation between lower serum 25(OH)D levels and higher EDSS (disability) scores.
- One study showed that those with higher levels of disability had lower vitamin D levels than controls while those with lower disability had similar vitamin D levels as controls*
- Statistical analysis revealed that reduced sun exposure accounted for half of this excess risk of higher disability in those with low vitamin D levels*
- No prospective studies looking at progression

*Van der Mei I at al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. Journal of Neurology 2007, 254:581-590.

Other Health Benefits of Vitamin D

Vitamin D and Other Autoimmune Diseases

- Reduced risk of type I diabetes in children (80% reduction with 2000 IU daily but not with lower doses)*
- Vitamin D supplementation (at least 400 IU daily) associated with reduced risk of rheumatoid arthritis**
- Vitamin D analogues and UVB light used in treatment of psoriasis

*Hyppponen E et al. Intake of vitamin D and risk of type I diabetes: a birth-cohort study. Lancet 2001;358(9292):1500-3.

** Merlino LA et al. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. Arthritis Rheum 2004;50(1):72-7.

Vitamin D & Bone and Muscle Health

■ Bone health

- Prevention of osteomalacia/osteoporosis
- Reduced risk of fractures (mixed results)
- Reduced tooth loss in elderly (vitamin D & calcium)

■ Muscle Health

- Vitamin D deficiency can produce muscle weakness
- Vitamin D supplementation found to improve muscle strength
- Vitamin D associated with a modest reduction in risk of falls in meta-analysis of treatment studies

Vitamin D and Infectious Diseases

- Vitamin D supplementation associated with lower rate of upper respiratory tract infections
- Vitamin D deficiency associated with increased risk of viral and bacterial infections*
- Role of Vitamin D in reducing severity of influenza, including H1N1 flu, being investigated**

*Cannell JJ et al Epidemic influenza and vitamin D. Epidemiol Infect. 2006Dec;134(6):1129-40.

**Yamshchikov AV et al. Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. Endocr Pract 2009July-Aug;15(5):438-49

Vitamin D and Cancer

- Higher levels of vitamin D associated with a reduced risk of certain cancers including
 - breast,
 - colon,
 - pancreatic,
 - prostate,
 - ovarian
 - non-Hodgkin's lymphoma
- Higher vitamin D associated with increased survival in several types of cancer including melanoma (most feared type of skin cancer)

Vitamin D & Other Chronic Disease

- Increasing vitamin D levels above 75 nmol/L associated with improved blood sugar control/insulin sensitivity (may be as effective as some of the common drugs used for diabetes)*
- Vitamin D might help to reduce blood pressure (mixed results)
- Beneficial effects on cardiovascular disease are unclear

* Chiu KC et al. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr* 2004;79(5):820-825.

Possible Additional Benefits

- Higher vitamin D levels associated with improved cognitive function (study in middle aged men)
- Higher vitamin D levels may reduce risk of dementia
- Possible role in treating depression/seasonal affective disorder
- Possible role in aches/pains, fibromyalgia and “chronic widespread pain” syndrome
- May help wound healing and reduce risk of infection



Vitamin D Supplements in MS

Getting it Right

Vitamin D Supplements

Which One?

- Vitamin D2 is not a suitable supplement for many reasons including absorption, differences in efficacy at raising vitamin D levels, diminished binding to proteins in blood, shorter shelf-life etc.*
- **D3 (cholecalciferol)** is the best supplemental form of vitamin D
- Vitamin D3 (cholecalciferol) is cheap and effective

•Houghton LA & Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr. 2006 Oct;84(4):694-7.

Vitamin D Supplements

What is the Right Dose?

- Ideally the dosage should be guided by blood levels of 25(OH)vitamin D
- Genetic differences in response to supplements
- Other factors determine Vitamin D needs:
 - Baseline vitamin D
 - Age
 - Skin colour
 - Obesity
 - Sunlight exposure (time of year depending on latitude)
 - Dietary intake
 - Medications (e.g. some anticonvulsants, diuretics, etc)

My Current Recommendations

- No uniform recommendations by Canadian neurologists on vitamin D dose for those with MS
- Evidence suggests that the health benefits in MS prevention and treatment are greatest with supplementation to maintain a

vitamin D level of ≥ 100 nmol/L

- The benefit of higher doses (beyond those required for a blood level of ≥ 100) is uncertain

Conversion from ng/ml (quoted in American studies) is 2.496. Equivalent optimum therefore ≥ 40 ng/ml.



Dosages of Vitamin D Supplements

- Supplementation should be at least 2000 IU daily in most people in Alberta, at least in fall to spring
- Doses as high as 4000 IU daily are definitely safe
- Some experts suggest doses up to 10,000 IU are safe* , though not necessarily optimum or necessary for maximum benefit
- No studies in any disease type showing an additional benefit with blood level above ~ 125 nmol/L

**Vieth R. Vitamin D toxicity, policy and science. J Bone Miner Res. 2007 Dec;22Suppl2:V64-8.

Summary

- The maintenance of adequate vitamin D levels has very important implications for many facets of health and well-being
- Vitamin D deficiency is a modifiable risk factor for MS
- Vitamin D supplementation can be used as a primary prevention strategy
- Vitamin D almost certainly has some beneficial effects on disease course in MS
- Oral supplementation with vitamin D3 is necessary in Alberta to maintain adequate blood levels

Some Suggested Sources (Reviews)

- Smolders J et al. Vitamin D as an immune modulator in multiple sclerosis: a review. *Journal of Neuroimmunology* 194(2008) 7-17.
- Niino M et al. Therapeutic Potential of Vitamin D in Multiple Sclerosis. *Current Medicinal Chemistry*, 2008, 15, 499-505.
- Pierrot-Deseilligny C. Clinical implications of a possible role of vitamin D in multiple sclerosis. *Journal of Neurology* Published on-line April 28, 2009.

Some Suggested Sources Continued

- Myhr K. Vitamin D Treatment in multiple sclerosis. *Journal of the Neurological Sciences*, 2009, doi:10.1016/j/jns.2009.05.002

QUESTIONS

