Vitamin D & MS: developments

Michael Hutchinson
Outline of talk

• Evidence that vitamin D deficiency
  • contributes to the susceptibility to MS
  • increases disease activity in MS

• Evidence that vitamin D supplementation
  • will be of benefit in people with MS.

• NEW DATA, ON-GOING TRIALS

• What should you do at present?
environment and MS

the changing face of multiple sclerosis
Changing epidemiology of MS: increasing prevalence of MS (Denmark)

Denmark; increased prevalence 1951-2005 due to: increased survival, improved diagnosis, and also increased incidence. Bentzen et al., Mult Scler J 2010
Prevalence of MS in women in Denmark 1950-2005 has increased four fold, in men two-fold.

Bentzen et al., Mult Scler 2010

Increased incidence in women is not explained by Improved diagnosis or longevity. Environment must play a role.
In Canada the sex ratio has almost doubled in last 50 yrs

Orton SM et al. 2006

Figure: Female to male ratio of multiple sclerosis patients from the CCPGMS by year of birth, spanning a 50 year period (n=27 074). Spearman rank correlation, r=0.84. Logistic regression analysis showed the increasing trend was significant (p<0.0001).
Environment and increased MS incidence in women

- Delayed pregnancy?
- Increased use of oral contraceptives?
- Increase in cigarette smoking?
- Lower levels of vitamin D in women? No
- Differential effects of Vitamin D on immune system in women? - possibly

- Other unidentified environmental agent?
Evidence that vitamin D is the environmental factor in MS

- **Vitamin D deficiency and susceptibility to MS**
  - Migration studies
    - UK to South Africa, West Indies to UK, India to UK
  - MS prevalence and latitude
    - Australia, NZ, France, North America

- Vitamin D deficiency predisposes to MS
  - Nurses’ observational study (Munger et al 2004, 2006)
Immigration before age 15 causes one to acquire the risk for MS of the new country.
There is a seven-fold difference in the prevalence of MS over the eastern coast of Australia.

McLeod et al., Med J Aust 1994
Incidence of first ever demyelinating event (CIS) increases with latitude in Australia

Rate of increase in incidence of CIS is 9.6% per higher degree of latitude (Brisbane to Hobart)

Taylor et al., Mult Scler 2010
New Zealand
Pronounced prevalence gradient for RRMS, women > men
Latitudinal factors that influence prevalence act differentially by
*gender*
*ethnicity*
and MS phenotype
Latitude and prevalence of MS: linked to sunshine in France

The latitudinal anomaly of MS prevalence in Norway

Ebers, Lancet neurol, 2008
Multiple sclerosis prevalence in Ireland: relationship to vitamin D status and HLA genotype

R Lonergan,¹ K Kinsella,¹ P Fitzpatrick,² J Brady,³ B Murray,³ C Dunne,⁴ R Hagan,⁴ M Duggan,¹ S Jordan,¹ M McKenna,³ M Hutchinson,¹ N Tubridy¹ JNNP 2011

Vitamin D deficiency (< 25 nmol/L)
28% MS patients v 19% controls
(p < 0.004)

Vitamin D deficiency alone does not explain prevalence difference

prevalence
Donegal: 290/10⁵
mean vit D: 37 nmol/L

prevalence
Wexford: 145/10⁵
mean vit D: 40 nmol/L
Vitamin D sufficiency protects against MS

Prospective study, 1992-2004, of 7 million military personnel, serum stored at entry.

• 148 whites developed MS, 296 controls.

• Risk of subsequently developing MS decreased with higher vitamin D levels at the time of entry to the military.

• Munger et al., JAMA  2006
Vitamin D deficiency relates to disease activity in MS

- Seasonal variation in relapse activity and MRI activity
- Seasonal variation in the onset of MS and month of birth of people with MS
- Vitamin D deficiency is more marked in relapses of MS than in remission.
MS relapses are more common in March - June each year in the Northern hemisphere & September - December in the Southern hemisphere (the lowest point of vitamin D levels)

Spelman et al., 2014
Nadir of relapse rate was in February over a 3 year period and RR correlated with environmental UV exposure.

Tremlett et al., 2008
Gadolinium + lesions in MS MRI scans / month and serum vitamin D levels

Embry et al., Ann Neurol 2000
Variation in susceptibility to MS by month of birth

- MS patients are more frequently born in the spring than the autumn.
  - 22% more in spring; 16% less in autumn (W Scotland)
  - Similar pattern in Sweden, Canada, Denmark, UK.
    (Willer et al., 2005)

- Spring births in MS patients HLA-DRB1*15 positive are more prevalent than those negative.

Does vitamin D deficiency at birth or in utero, prime the immune system?
Vitamin D deficiency increases risk of MS relapse

• 110 paediatric onset MS/CIS patients
  • Followed mean of 1.7 years, 52% relapsed
  • Baseline vitamin D was $22\pm9$ng/ml (adequate $>30$)
  • Only 15% had adequate vitamin D levels
  • Every 10ng/ml increase in the baseline Vit D level was associated with a 34% reduction in the risk of subsequent relapse (RR 0.66, 95% CI; 0.46,0.95)

Mowry et al., Ann Neurol 2010
Tasmania, Australia
Prospective study of 145 pts with RRMS and six monthly vitamin D levels
Risk of relapse in a six month period was inversely related to vitamin D level
Each 10 nmol/L increase in serum vitamin D was associated with a 12% reduction in risk of a subsequent relapse

Ascherio et al., 2014

patients with a first MS symptom in in a clinical trial of Betaferon and followed for 5 years

higher vitamin D levels reduce new brain lesions in multiple sclerosis over 5 years

\[ \text{Percentage change of T2 volume from year 1 to year 5 in } \geq 50 \text{ nmol/L vs } < 50 \text{ nmol/L: } -9.0 \text{ (-15.0 to -2.5), } P = .008 \]
higher vitamin D levels partially protect against brain atrophy in early multiple sclerosis over 5 years

Ascherio et al., 2014
Genetics of MS & vitamin D metabolism

- People with MS inherit from their parents multiple genetic variations including genes affecting vitamin D metabolism which increase their risk of MS.

Genome-wide association study identifies new multiple sclerosis susceptibility loci on chromosomes 12 and 20

The Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene)¹

Nature Genetics 2009
genetically lowered vitamin D levels increase the risk of MS two-fold

RESEARCH ARTICLE

Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization Study

Lauren E. Mokry¹, Stephanie Ross¹, Omar S. Ahmad¹,², Vincenzo Forgetta¹,², George Davey Smith³, Aaron Leong⁴,⁵, Celia M. T. Greenwood⁶,⁷,⁸,⁹, George Thanassoulis²,¹⁰, J. Brent Richards¹,²,⁷,⁸,¹¹*

PLOS Medicine August 2015

<table>
<thead>
<tr>
<th>Clinically Relevant 25OHD Threshold</th>
<th>25OHD Level Required to Decrease Odds of MS by 50% a</th>
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<tbody>
<tr>
<td>Vitamin D deficient (25 nmol/l)</td>
<td>36.86 nmol/l</td>
</tr>
<tr>
<td>Vitamin D insufficient (50 nmol/l)</td>
<td>73.72 nmol/l</td>
</tr>
<tr>
<td>Vitamin D sufficient (75 nmol/l)</td>
<td>110.6 nmol/l</td>
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</table>
PwMS metabolise vitamin D faster

Patients with MS and healthy control participants took vitamin D 5000 IU daily over 90 days.

Over 90 days the rise in serum vitamin D was about 20 nmol/L less in the MS patients than in controls.

MS patients are genetically more susceptible to vitamin D deficiency

September 2015  Bhargava et al., 2015
Immunological effects of Vit D

- $1,25(\text{OH})_2\text{D}$ interacts with the intracellular vitamin D receptor (VDR)

- VDR present in monocytes, dendritic cells, B cells and CD4+ T cells.

- a VDR element is found in HLA-DRB1*1501
  - vitamin D deficiency in such a setting could reduce the central deletion of auto-reactive T cells
Vitamin D - basics

- Vitamin D3 (cholecalciferol) is produced by sunlight acting on 7-dehydrocholesterol in the skin.
- Also available in foods and tablets.
- Foods: fatty fish (herring 1300 IU/100g; egg 20 IU; fortified milk)
- Vitamin D3 is not biologically active
  - it is hydroxylated in the liver to 25(OH)D (calcifediol)
  - then hydroxylated in kidney to 1,25 (OH)₂D (calcitriol)
- 1,25 (OH)₂D (calcitriol) is the biologically active form
four genetic variations in the metabolism of vitamin D which cause lower vitamin D levels and increase the susceptibility to multiple sclerosis
## Vitamin D deficiency is common

<table>
<thead>
<tr>
<th>country</th>
<th>latitude</th>
<th>Number Controls</th>
<th>Winter serum vitamin D mean levels (nmol/L)</th>
<th>controls deficiency % &lt; 25nmol/L</th>
<th>controls insufficiency % &lt; 50nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>53 ° N</td>
<td>226</td>
<td>36</td>
<td>46</td>
<td>86</td>
</tr>
<tr>
<td>Belgium</td>
<td>50 ° N</td>
<td>126</td>
<td>48</td>
<td>No data</td>
<td>34</td>
</tr>
<tr>
<td>Estonia</td>
<td>59 ° N</td>
<td>367</td>
<td>44</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>Finland</td>
<td>60 ° N</td>
<td>328</td>
<td>46</td>
<td>26-28</td>
<td>56-86</td>
</tr>
<tr>
<td>Italy</td>
<td>40 ° N</td>
<td>90</td>
<td>43</td>
<td>18</td>
<td>70</td>
</tr>
<tr>
<td>Japan</td>
<td>35 ° N</td>
<td>197</td>
<td>38</td>
<td>No data</td>
<td>87</td>
</tr>
</tbody>
</table>
How much vitamin D do we need?

- No universally agreed level of intake
- Everyone in high latitudes is Vitamin D deficient in winter/spring
- Calcichew D3 contains 400iu/ tablet
- Tolerable official upper limit is 2000 iu/day
- Sunlight safely provides 20,000 iu/day
- Older adults are advised to have serum levels of 75 nmol/L for bone health thus need 4000iu/day
- For the immunological effects of vitamin D serum levels > 100nmol/L probably needed
<table>
<thead>
<tr>
<th>Food Safety Authority Ireland</th>
<th>Vitamin D council</th>
<th>Food &amp; Nutrition Board (US)</th>
<th>Endocrine Society</th>
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<tr>
<td>800 IU</td>
<td>5000 IU</td>
<td>600-800 IU</td>
<td>2000 IU</td>
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</table>

markedly divergent recommendations for daily allowance from various authorities
Vitamin D and health in multiple sclerosis

Lonergan et al., 2011

- AIM: take 5000 IU/day
- Bone health: 4000 IU/day
- Mean level of Irish MS patients
- 30% of Irish MS patients

25(OH)D nmol/L

- Sufficient for immune effects
- Insufficient
- Deficient
10,000 iu of vitamin D daily will produce a serum 25(OH)D level of >200 nmol/L within 3 months.
Clinically isolated Syndrome (CIS)

- patients presenting with the first symptom of demyelination, ie optic neuritis.
- NOT MS yet – no dissemination in time (DIT).
- CIS patients with two + asymptomatic lesions on MRI are at high risk of further relapse
  - 45% over next 24 months have a clinical relapse
  - BUT 85% have MRI evidence of DIT in 24 months
  - At 6 months: 51%
  - at 12 months: 74%
- One can use the power of the MRI to detect DIT in a CIS cohort to increase frequency of endpoint and the effect of a drug on the endpoint.

September 2015
What evidence do we need?

1) a double-blind randomised controlled trial of vitamin D versus placebo in the prevention or delay of the development of MS in patients at risk of MS.

2) a double-blind RCT of vitamin D plus a standard disease modifying therapy in reducing relapses and MRI activity in multiple sclerosis.
13 control participants: placebo
13 control participants: 5,000 IU vitamin D
13 control participants: 10,000 IU vitamin D
15 CIS patients: placebo
15 CIS patients: 5,000 IU vitamin D
15 CIS patients: 10,000 IU vitamin D
28-30 weeks follow-up
0 4 8 12 16 20 24 weeks visits to clinic
pilot study of vitamin D dosing in patients with first MS symptom and controls with vitamin D at 5000 IU & 10,000 IU over 6 months

a) people at risk of MS, given large doses of vitamin D, achieve significantly lower serum levels of vitamin D than healthy control participants

b) 50% PwMS are deficient in vitamin D at first presentation

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what does all this mean for MS?

1) vitamin D levels are deficient in the general population for 9 months of the year.

2) people with a genetic susceptibility to MS have even lower levels of vitamin D.

3) this lower serum vitamin D level increases the likelihood of developing MS and having more active disease.

4) vitamin D sources (sun & food) are poor in Ireland (unless eating salmon & mackerel).

5) PwMS should take vitamin D supplements.
Proving that vitamin D is an effective therapy for MS: trials in process (1)

- **Clinically Isolated Syndrome:** delaying a development of a second episode or new MRI lesion
- **PrevANZ:** Australia, New Zealand & Ireland
  - Doses: Placebo, 1000, 5000 or 10,000 IU daily in four arms.
- **D-LAY:** France (completion June 2019).
  - 316 patients randomised to
    - a) Vitamin D 100,000 IU every 14 days
    - b) Placebo
Proving that vitamin D is an effective therapy for MS: trials in process (2)

- relapsing MS (vit D + interferons / glatiramer).
  - EVIDMS (December 2018)
  - SOLAR (completed - no results yet, poor recruitment)
  - + others

- NO DEFINITIVE STUDY RESULTS

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Vitamin D supplements: how much? (1)

- WE NEED DEFINITIVE EVIDENCE THAT VITAMIN D SUPPLEMENTATION WORKS:
  - TO PREVENT MS
  - TO AMELIORATE MS

VITAMIN D IS NOT A SUBSTITUTE FOR DISEASE MODIFYING THERAPIES - IT IS COMPLEMENTARY
CHECK WITH YOUR GP THAT YOU DO NOT HAVE ANY CONTRAINDICATION TO VITAMIN D
- there are a number of rare disorders to be excluded

DOCTORS CAN ONLY PRESCRIBE 800 IU daily

THIS WILL RAISE YOUR VITAMIN D LEVELS BY ONLY 10-15 nmol/L.
Vitamin D supplements: how much? (3)

- YOU WILL HAVE TO BUY VITAMIN D IN A ‘HEALTH-FOOD STORE’.
- BUY THE CHEAPEST FORM
- TAKE 2000 IU (at least) to 5000 IU daily
- IF YOU MISS A DAY TAKE THEM ALL TOGETHER

- OBESITY IS BAD FOR MS AND VITAMIN D LEVELS (LOSE WEIGHT- STOP THE CARBS).

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SIX THINGS YOU CAN DO FOR YOUR (RELAPSING) MS

- AVOID BEING OVER-WEIGHT
- STOP SMOKING
- ATTEND A NEUROLOGIST YEARLY (at least)
- HAVE A YEARLY MRI SCAN
- TAKE YOUR PRESCRIBED MEDICATION
- EXERCISE - KEEP REASONABLY FIT
- TAKE A VITAMIN D SUPPLEMENT

September 2015