Emerging Role of Dietary Factors in Multiple Sclerosis

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Disclosures

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  – Other:
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  – Advisory Board: Biogen Idec
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Learning Objectives

- At the conclusion of this activity, the participant will be able to learn about:
  - Popular diets, Dietary Factors and Supplements in MS and evidence of their effectiveness
  - Plausible mechanisms by which dietary interventions and supplements may influence MS
  - Guidance on clinical application of available data
What people with MS are talking about?

Alternative versus Traditional Treatment Topics Mentioned in Social Media (July 2014–June 2015)

- Diet
- Cannabis
- Exercise
- Vitamins/Supplements
- Stem cells
- Copaxone
- Tysabri
- Tecfidera
- Avonex
- Gilenya
- Aubagio
- Mindfulness
- Rebif
- Lemtrada
- Betaseron

Wellness and Healthy Living in MS

- Huge interest among patients
- Patients want self control over disease
- Side effects of MS drugs and symptomatic drugs
- Over emphasis on MS drugs by conventional care providers
- Symptom management often inadequate
Emerging role of Vascular diseases in MS

• Vascular co-morbidity - > 50%
  – Hypercholesterolemia – 37%
  – Hypertension -30%
  – Heart disease - 7%
  – Diabetes – 6%
  – Peripheral Vascular Disease – 2%

• 16% had 2 vascular co-morbidity; 4% had 3
• Obese children more likely to get MS
• Vascular disease risk factors appear to accelerate disease

Marrie R et al. Neurology 2010;74:1041-1047
Vascular Risk Factors Increase Risk of MS Disability

Marrie R et al. Neurology 2010;74:1041-1047
Obesity Trend Among US Adults

Changing MS Epidemiology

Koch-Henriksen & Sorensen, Lancet Neurology 2010. meta-regression analysis of studies on MS prevalence and incidence in Europe and North America (178 studies meeting inclusion criteria)
Increasing Evidence That Obesity Influences MS

- National MS Society-launched International MS Genetics Consortium
- Researchers identified 70 genetic predictors of weight (BMI) by analyzing obesity-related genes
- Analyzed these gene variations in data compiled from > 14,000 MS and 24,000 people non-MS
- **Increase in body mass from being “overweight” to “obese” associated with significant increase (41%) in risk of developing MS**
- Supports growing body of evidence - obesity is a risk factor for developing MS
- Being overweight is also known to worsen MS symptoms

Body Mass Index and Risk of MS Progression

- 5 year follow up, 150 people with MS
- Retrospective, observational study

- Associations between body weight, MRI, and disability (Expanded Disability Status Scale- EDSS)

- Overweight and obese MS patients - more likely to show a significant progression of MS disease markers or symptoms than people with normal weight

Zacharia et al, June 2015, CMSC Annual meeting abstract
Metabolic syndrome: abdominal obesity, high triglyceride level, low HDL cholesterol level, high blood pressure, and high fasting blood sugar
Adverse lipid profile is associated with disability and its progression in MS

- Australian study, N=178, prospective, 2002 – 2005
- Associations between serum lipids and MS disability
- Serum: Baseline and 6 months, Annual change in disability
- Total cholesterol (p = 0.037) independently associated with a higher EDSS
- Higher BMI - Independently associated with higher EDSS (p = 0.013)
- Total cholesterol/ High density lipoprotein ratio (p = 0.029) prospectively associated with subsequent change in EDSS

Diet and MS – Is there a relationship?
Diet and MS: Swank work

- “Good dieters” (n=70)
  - Followed a low-fat diet (Consuming less than 20 g/d of fat)
  - 34 years later: 23 deaths
  - In year 2000: 15 survivors
  - 13/15 were still ambulatory and otherwise healthy

- “Bad dieters” (n=74):
  - Consumed more than 20 g/d of fat
  - 34 years later: 58 deaths
  - In year 2000: no survivors

A Randomized-Controlled Study of Diet & Multiple Sclerosis

- 61 people with MS participated
- 29 randomized to control group
- 32 randomized to vegan diet
- Trained in McDougall Diet and followed diet for one year
- Age – 41; Females – 90-97%; EDSS 2.22-2.72
- Disease duration – 5.3 yrs
- No of relapses in the previous 2 yrs – 1.4-1.7

Changes in BMI during 1-year trial

Changes in Blood Lipids during 1-year trial

Low Fat Plant Based Diet Improves MS Fatigue

Yadav et al, Effects of a Low Fat Plant Based Diet in Multiple Sclerosis (MS): Results of a 1-Year Long Randomized Controlled (RC) Study. P6.152. AAN 2014 Annual Meeting, Philadelphia, USA
Low fat dietary intervention with omega-3 fatty acid supplementation in MS

"Fish Oil" (FO) group

- Low fat diet (15% fat) + omega-3 FOs
- At 6 months –
  - PCS/SF-36 (P = 0.050) and MHI (P = 0.050) improved
- At 1 year – Relapse rate (relative to the rates during the 1 year preceding the study)
  - Decreased : mean change
  - -0.79 +/- SD 1.12 (P = 0.021)

"Olive Oil" (OO) group

- AHA Step I diet (fat 30%) + OO supplements
- At 6 months -
  - Reduced fatigue (P = 0.035)
- At 1 year –
  - Decreased: mean change
  - -0.69 +/- SD 1.11 (P = 0.044)

1 yr PC, DB, Primary outcome : QOL, Physical Components Summary Scale (PCS) of the Short Health Status Questionnaire (SF-36); Secondary Outcome: MS specific QOL questionnaires, neurological status and relapse rate

Paleo diet with a multimodal intervention for secondary progressive MS

Paleo diet with a multimodal intervention for secondary progressive MS

- Single-arm, open-label intervention study, outpatient setting
- Multimodal intervention - Modified Paleolithic diet with supplements, stretching, strengthening exercises with electrical stimulation of trunk and lower limb muscles, meditation, and massage
- Outcomes: Adherence, side-effects, blood analyses, Fatigue - Fatigue Severity Scale
- Data collection - baseline and months 1, 2, 3, 6, 9, and 12

Results

- 10/13 continue in the 12-month main study
- 8/10 completed the study and 6 subjects showed full adherence
- Average adherence to diet exceeded 90% of days, and to exercise/muscle stimulation exceeded 75% of days
- Nutritional supplements intake was variable
- Group daily average duration:
  - Meditation - 13.3 minutes
  - Massage - 7.2 minutes
- FSS scores decreased from 5.7 to 3.32 (p=0.0008)
- No adverse side-effects were reported

Mediterranean diet and MS
Mediterranean diet adherence and risk of MS

- Iran, Hospital-based, case–control, MS (N=70); Healthy controls (N=142), face to face interview
- Study relationship of Mediterranean diet and risk of MS
- Adherence to Mediterranean diet (9-unit dietary score)
- Higher consumption of fruits (OR=0.28, p-value: 0.002) and vegetables (OR=0.23, p-value: 0.001) significantly associated with reduced MS risk

Dietary Intake of Sodium and Risk of MS

- High Sodium intake - increased disease severity in mouse model of MS
- Study - risk of MS and dietary intake of sodium, potassium, magnesium, calcium, phosphorus, iron
  - Different minerals from diet and supplements validated by Food Frequency Questionnaire (FFQ) every 4 years
  - 81,757 nurses in Nurses’ Health Study (1984-2004) and 95,452 in Nurses’ Health Study II (1991-2009)

Marianna et al. Dietary Intake of Sodium and Other Minerals and the Risk of Multiple Sclerosis. 2016 Annual AAN Abstract
Risk of MS and dietary sodium and minerals

- **High dietary intake of sodium** (p=0.84) at baseline **not associated with MS risk**
- Potassium (p=0.38), magnesium (p=0.12), calcium (p=0.21), phosphorus (p=0.99) and Iron (p=0.81) intake **not associated with risk of development MS**

Marianna et al. Dietary Intake of Sodium and Other Minerals and the Risk of Multiple Sclerosis. 2016 Annual AAN Abstract
Lipoic Acid: Dietary supplement, Natural Anti-Oxidant

Lipoic acid

\[
\begin{align*}
\text{Oxidized} & : & \begin{array}{c}
\text{S-S} \\
\text{Lipoic acid}
\end{array} \\
\text{Reduced} & : & \begin{array}{c}
\text{SH SH} \\
\text{Dihydrolipoic acid}
\end{array}
\end{align*}
\]

Lipoic acid
Alpha lipoic acid
R-lipoic acid
Lipoic Acid Trial in SPMS

- SPMS
- Randomized to lipoic acid (1200 mg once a day) or to placebo
- On treatment for 2 years
- Measurement of brain atrophy

Spain et al. Lipoic Acid for Neuroprotection in Secondary Progressive Multiple Sclerosis, AAN Annual Meeting 2016 abstract
Lipoic Acid for Secondary Progressive MS

2 year, DB, RCT
1200mg daily LA versus placebo

*Primary outcome:* MRI whole brain atrophy

Secondary outcomes: atrophy of brain substructures, spinal cord atrophy, retinal and macular atrophy, changes in neurological exam, walking, cognition, fatigue, and quality of life

Pharmacokinetic labs - Baseline and month 12

Adverse events and safety laboratory measurement

Spain et al. Lipoic Acid for Neuroprotection in Secondary Progressive Multiple Sclerosis, AAN Annual Meeting 2016 abstract
Lipoic Acid for Secondary Progressive MS

54 subjects, 51 subjects took at least 1 dose of study drug and were included in analysis
Average age - 58.5 ± 5.9 (40-69) years, F - 61%, 96% Caucasian
Average disease duration - 29.6 ± 9.5 (9-51) years
Median EDSS 6.0 (3.0-9.0)
Compliance, > 90% in 93% of subjects and >80% for all subjects

Spain et al. Lipoic Acid for Neuroprotection in Secondary Progressive Multiple Sclerosis, AAN Annual Meeting 2016 abstract
Brain Atrophy Occurs over Time in MS
Lipoic Acid reduces brain atrophy

Spain et al. Lipoic Acid for Neuroprotection in Secondary Progressive Multiple Sclerosis, AAN Annual Meeting 2016 abstract
As health care providers – what can we advise now?

• **Vascular disease risk factor reduction**
  – Diet and life style interventions

• **Obesity – optimal BMI**
  – Fatigue improvement and weight reduction

• **Potential Role of anti-oxidants**
CE/CME Credit

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Thank You
Lipoic acid consumption affects the cytokine profile in MS

- Double-blind, placebo-controlled, randomized clinical trial
- Assess the effect of daily consumption of LA on the cytokine profiles in MS patients
- N = 52 Relapsing Remitting Multiple Sclerosis patients
- Age 18-15
- 2 groups: LA (1,200mg/day) or placebo
- 12 week supplementation
- Fasting blood samples collected for cytokine profile at baseline and after intervention

Lipoic acid affects the cytokine profile in MS

- INF-γ, ICAM-1, TGF-β and IL-4 were significantly reduced in the LA group compared to the placebo group
- No significant changes in TNF-α, IL-6, EDSS and MMP-9

Low-fat diet with antioxidant supplementation on biochemical markers of MS

- Randomized prospective placebo-controlled study
- Institutionalized patients with progressive MS
- long-term care residents
- 42 days
- \( N = 9, \) 5 in intervention group (low-fat diet and antioxidant supplementation), 4 assigned to placebo group (low-fat diet)
- Examined daily - measuring anthropometric, biochemical parameters and oxidative stress markers in blood at baseline (day 0), intermediate (day 15) and end (day 42) stages of the treatment

Mauriz et al. AAN Annual Meeting 2016 abstract
Results

• Intervention group had significantly lower C reactive protein levels
• Oxidative stress and inflammatory markers isoprostane 8-iso-PGF2α and interleukine IL-6 values also diminished after dietary intervention in the intervention group
• Catalase activity increased significantly in the intervention group prior antioxidant supplementation
• No significant differences were observed in other oxidative stress markers
Simvastatin 80mg in SPMS: randomized, placebo-controlled, phase 2 trial

- 0.56% per year
- 0.29% per year

Placebo n=70  Simvastatin n=70

Chataway et al. Lancet 2014
Ocrelizumab: Significant reduction in rate whole brain volume loss PPMS

17.5%
$p=0.02$

Ocr = -0.40 % per year

Pl = -0.55 % per year
Table 1. Socio-demographic characteristics of the multiple sclerosis patients and controls (n=209)*

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=140)</th>
<th>Multiple sclerosis patients (n=69)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>26 (18.6)</td>
<td>12 (17.4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Women</td>
<td>114 (81.4)</td>
<td>57 (82.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>71 (50.7)</td>
<td>35 (50.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>30-39</td>
<td>53 (37.9)</td>
<td>22 (31.9)</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>16 (11.4)</td>
<td>12 (17.4)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24.9</td>
<td>93 (66.9)</td>
<td>35 (50.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>25-29.9</td>
<td>28 (20.1)</td>
<td>26 (37.7)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>18 (12.9)</td>
<td>8 (11.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Age of mother at birth (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤18</td>
<td>14 (10.0)</td>
<td>11 (15.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>18-29.9</td>
<td>76 (54.3)</td>
<td>34 (49.3)</td>
<td></td>
</tr>
<tr>
<td>30-39.9</td>
<td>40 (28.6)</td>
<td>21 (30.4)</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>10 (7.1)</td>
<td>3 (4.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Age of father at birth (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-29.9</td>
<td>41 (29.3)</td>
<td>23 (33.3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>30-39.9</td>
<td>64 (45.7)</td>
<td>31 (44.9)</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>35 (25.0)</td>
<td>15 (21.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin D supplementation before diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>110 (78.6)</td>
<td>56 (81.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Yes</td>
<td>30 (21.4)</td>
<td>13 (18.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>130 (92.2)</td>
<td>65 (94.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78 (55.7)</td>
<td>43 (62.3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Yes</td>
<td>62 (44.3)</td>
<td>26 (37.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Hometown</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tehran (capital)</td>
<td>69 (49.3)</td>
<td>36 (52.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Other</td>
<td>71 (50.7)</td>
<td>33 (47.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Season of birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>41 (30.4)</td>
<td>27 (39.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Summer</td>
<td>50 (35.7)</td>
<td>12 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Autumn</td>
<td>18 (13.3)</td>
<td>17 (24.6)</td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>26 (19.3)</td>
<td>13 (18.8)</td>
<td></td>
</tr>
<tr>
<td><strong>History of Rabella</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77 (55.0)</td>
<td>38 (55.1)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Yes</td>
<td>63 (45.0)</td>
<td>31 (44.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of multiple sclerosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>140 (100)</td>
<td>59 (85.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>10 (14.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of fat used</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetable oil</td>
<td>75 (53.6)</td>
<td>13 (18.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat (Ghee)</td>
<td>14 (10.0)</td>
<td>25 (36.2)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>51 (36.4)</td>
<td>31 (44.9)</td>
<td></td>
</tr>
</tbody>
</table>

* p-values are derived using chi-squared analysis.
†Current vitamin D supplementation or former vitamin D consumption.
‡Yes means current smokers, No means never or former smokers.
§Physical activity means leisure time physical activity.
‖Family history refers to both first and second relatives.
Table 2. Characteristics of participants across the Mediterranean Dietary Pattern Score (MDS) tertile categories in a case-control study of multiple sclerosis in Iran

<table>
<thead>
<tr>
<th></th>
<th>Cases MDS tertiles</th>
<th>p trend</th>
<th>controls MDS tertiles</th>
<th>p trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>31 (44.9)</td>
<td>34 (49.3)</td>
<td>4 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>27 (47.4)</td>
<td>28 (49.1)</td>
<td>2 (3.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age, yr</td>
<td>26.0 (9.0)</td>
<td>32.0 (17.0)</td>
<td>32.0 (12.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5 (5.4)</td>
<td>25.2 (4.2)</td>
<td>21.8 (7.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Energy, kcal</td>
<td>2214 (841)</td>
<td>2349 (672)</td>
<td>2550 (5937)</td>
<td>0.91</td>
</tr>
<tr>
<td>Smoking (yes), n (%)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>0.44</td>
</tr>
<tr>
<td>Vitamin D supplement (yes), n (%)</td>
<td>3 (23.1)</td>
<td>9 (69.2)</td>
<td>1 (7.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tehran</td>
<td>21 (56.8)</td>
<td>14 (37.8)</td>
<td>2 (5.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Physical activity (yes), n (%)</td>
<td>12 (46.2)</td>
<td>12 (46.2)</td>
<td>2 (7.7)</td>
<td>0.75</td>
</tr>
<tr>
<td>Season of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>9 (64.3)</td>
<td>4 (28.6)</td>
<td>1 (7.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Vitamin D intake (μg)</td>
<td>1.1 (2.1)</td>
<td>0.9 (2.1)</td>
<td>0.9 (0.7)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or median (IQR)

**The p value for trend was determined using the linear regression coefficient for MDS scores for continuous variables and the logistic regression coefficient for the dichotomous variables.

Table 3. Univariate and multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for multiple sclerosis risk by components of the Mediterranean Dietary Pattern in a case-control study in Iran

<table>
<thead>
<tr>
<th></th>
<th>Univariate MS risk</th>
<th>Multivariate adjusted MS risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Vegetables</td>
<td>0.25</td>
<td>0.13-0.59</td>
</tr>
<tr>
<td>Fruits</td>
<td>0.28</td>
<td>0.14-0.54</td>
</tr>
<tr>
<td>Nuts</td>
<td>0.70</td>
<td>0.39-1.25</td>
</tr>
<tr>
<td>Legumes</td>
<td>0.74</td>
<td>0.41-1.33</td>
</tr>
<tr>
<td>Fish</td>
<td>0.86</td>
<td>0.48-1.52</td>
</tr>
<tr>
<td>Unsaturated/saturated lipids</td>
<td>1.54</td>
<td>0.84-2.73</td>
</tr>
<tr>
<td>High fat dairy product</td>
<td>0.65</td>
<td>0.36-1.18</td>
</tr>
<tr>
<td>Red meat/White meat</td>
<td>0.95</td>
<td>0.45-1.73</td>
</tr>
<tr>
<td>Refined grain</td>
<td>1.83</td>
<td>1.09-3.33</td>
</tr>
</tbody>
</table>

Reference (median)

Values are mutually adjusted for age, multiple sclerosis family history, season birth and energy intake and other variables in the table.

Table 4. Multivariate adjusted odds ratios for multiple sclerosis risk across the Mediterranean Dietary Score (MDS) tertile categories in a case-control study of multiple sclerosis in Iran

<table>
<thead>
<tr>
<th>MDS</th>
<th>Controls (n)</th>
<th>Cases (n)</th>
<th>Age adjusted OR</th>
<th>95% CI</th>
<th>p-trend</th>
<th>Multivariate adjusted OR*</th>
<th>95% CI</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile1</td>
<td>49</td>
<td>31</td>
<td>1</td>
<td></td>
<td>0.017</td>
<td>1</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Tertile2</td>
<td>62</td>
<td>34</td>
<td>0.85</td>
<td>0.46-1.5</td>
<td>1.07</td>
<td>0.53-2.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile3</td>
<td>29</td>
<td>4</td>
<td>0.21</td>
<td>0.06-0.67</td>
<td>0.23</td>
<td>0.06-0.89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Age, multiple sclerosis family history, season birth and energy intake were also included in the regression models as covariates.
Vitamin D and Its Role in Multiple Sclerosis

Walter Royal, III, M.D.
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VA Multiple Sclerosis Center of Excellence-East
Professor of Neurology
University of Maryland School of Medicine
Director, Maryland Center for Multiple Sclerosis Treatment and Research
Disclosures

- Dr. Royal has the following interest to disclose:
  - Grant/research: Veterans Administration, NIH, National MS Society, Teva Neuroscience, Biogen Idec, Mallinckrodt, MedImmune, Novartis, Genzyme, EMD-Serono, Alexion
  - Speakers Bureau: None
  - Advisory Board: None

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Explain the importance of vitamin D deficiency in MS
2. Describe effects of vitamin D that underlie its impact in MS
3. Discuss approaches to treating vitamin D deficiency in MS
Vitamin D and MS

- Vitamin D suppresses experimental MS-like disease in animals (Experimental Allergic Encephalomyelitis – EAE)

- MS is
  - More common within inland (vitamin D-poor)
  - Less common in coastal areas (fatty fish, fish oils, and vitamin-D rich)

- Less sunlight = higher risk of MS (sunlight required for vitamin D synthesis)
Vitamin D: Historical Aspects

- First Description of Vitamin D Deficiency (Rickets)
  - Dr. Daniel Whistler (1645) – first publication
  - Prof. Francis Glisson (1650) – original observations
  - Sir Edward Mellanby (1919) – studies in dogs raised indoors; cod liver oil identified as an antirachitic; vitamin D as treatment
Sources of Vitamin D

- Sunlight
- Diet
- Dietary Supplements
Multiple Sclerosis Risk and Geography

U.S. Mean Daily Solar Radiation

McDowell T-Y et al. Neuroepidemiology 2010;34:238–244.
Vitamin D Synthesis in Humans

7-Dehydrocholesterol → Pre-Vitamin D3 → Vitamin D3 → 25-Hydroxyvitamin VD3 → 1, 25-Dihydroxyvitamin VD3

Sunlight: UVB (290-315 nm)

25-hydroxylase
(Primarily liver; also skin, intestine and kidney)

25-hydroxyvitamin D-1α-hydroxylase
(Produced in kidney and numerous other tissues; contribute to blood levels only in pregnancy and in pathological conditions)
Factors that Effect Sun-Induced Vitamin D Synthesis

- Duration and quality of sun exposure
  - UV Index
  - Over-exposure: degradation of vitamin D synthetic enzymes

- Skin pigmentation
  - Darker pigment blocks UV radiation
  - Lower vitamin D levels in Blacks and Hispanics
Enzymatic Control of Vitamin D Metabolism

- 25-hydroxyvitamin D-1α hydroxylase (CYP27B1)
  - 25-hydroxyvitamin D $\rightarrow$ 1, 25-dihydroxyvitamin D
- 25-hydroxyvitamin D-24-hydroxylase (CYP24)
  - 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D $\rightarrow$ calcitroic acid
25-hydroxyvitamin D-1\(\alpha\) hydroxylase (CYP27B1)

- Expression documented in
  - Renal epithelial cells
  - Monocyte/macrophage lineage cells

- Production is increased by
  - Parathyroid hormone (PTH)
  - Hypocalcemia
  - Hypophosphatemia
  - Fibroblast growth factor 23 (inhibits phosphate transport by renal tubules)
25-hydroxyvitamin D-24-hydroxylase (CYP24)

- Expressed by mitochondria in multiple cell types including peripheral blood mononuclear cells and renal and skin cells
- Production is stimulated by
  - 1, 25-dihydroxyvitamin D (promoter regulated by VDR binding)
  - 25-hydroxyvitamin D
Vitamin D Levels and Risk of MS: Study of U.S. Military Personnel

7 million persons → 257 cases definite MS

Whites (n=148)  
Blacks (n=77)

Error bars indicate 95% confidence intervals.

* 30 cases among Hispanics

Vitamin D Deficiency: Risk Factors

- Age
- Race/Ethnicity
- Mobility
- Diet
- Medications
What are Some of the Causes of Vitamin A Deficiency?

- Sunscreen use
- Skin pigmentation
- Aging
- Season, latitude, time of day
- Malabsorption, obesity
- Drug effects
- Liver failure
- Renal disease

- Rickets
  (Pseudovitamin D def. rickets; VitD-resistant rickets; etc.)
- Malignancy
- Primary hypoparathyroidism
- Granulomatous disorders
- Hyperthyroidism
Vitamin D Levels and Race

Yetley EA. Am J Clin Nutr 2008;88(Suppl):558S.
Medications Associated with Induction of Vitamin A Deficiency

- Anticonvulsants (e.g., phenytoin, phenobarbital)
- Glucocorticoids
- HAART
- Anti-rejection drugs
- Other Inducers of CYP3A4 (CYP3A4 is a 25-hydroxylase): antibiotics, St. John’s Wort,
Vitamin D and MS Risk: Other Factors

- Vitamin D receptor polymorphisms
  - Associations with increased MS risk, reduced disability
- Vitamin D receptor expression levels
  - Higher in women (estrogen effect)
- Alterations in vitamin D target genes
  - Increase HLA-DRB1*15 promoter binding of vitamin D, increased expression of the gene (Ebers et al)
- Altered expression of vitamin D degradative enzymes
  - Lower expression women
Immune Effects of Vitamin D

- Increased anti- and decreased pro-inflammatory cytokine secretion by activated T cells
- Direct suppression of CD4+ and CD8+ T cell proliferation (1,25-dOH VitD)
- Induction of Th2 cells and tolerance mediated by regulatory T cells in several models of autoimmunity
- Suppression of Th1 and Th17 cell production
- Increase Th2 and regulatory T cells
Smolders et al: Correlation Between Treg Cell Numbers and 25(OH)D Levels (86% +IFN-β Treatment)

Vitamin D Status and Regulatory T cell Function in Patients with MS (Rx-Naïve and IFN-β Treated)

T Regulatory Cell Analysis in MS

CD4+

CD4+ Treg

1.1% (~3.0%)

Suppressive effect in MS
Vitamin D Measurements and Regulatory T Cell Percentages (~90% Treatment Naïve)

Vitamin D Measurements and CXCR3+ T cell Percentages (~90% Rx-Naïve Patients)

Studies of Effects of Vitamin D Metabolites on Treg Cells Induced In Vitro

PBMCs → Column purification → CD4+or CD4+CD25+ T cell

αCD3/αCD28 Beads
αIFN-γ/αIL-4
TGF-β

5-day cultures

Treg T cell

No VitD
OR
25(OH)D
OR
1,25(OH)2D
Staining for FoxP3+ Cells in Treg Cell Cultures
Staining for CD127+ Cells in Treg Cell Cultures
Vitamin D Metabolite Effects on Treg Cell (CD4+CD25^{hi}FoxP3+) Percentages in Vitro

25-OH VitD

10 nM 29.65
100 nM 33.37
1.0 μM 35.93

1, 25-dOH VitD

15 pM 37.36
150 pM 33.55
1.5 nM 32.09

CD3/CD28 Bead: 13.65%
CD3/CD28 Bead/Abs/Cytokine: 24.02%
Induction of FoxP3+ Cells in Treg Cultures

1. Medium
2. +TGF-β, IL-2, αIFN-γ/αIL-4 Abs
3. +Cytokines, Abs, 25(OH)D

10 nM 25(OH)D

100 nM 1,25(OH)2D

15 pM 25(OH)D

150 pM 1,25(OH)2D

FoxP3+
Treg Cell suppression Assay

$\alpha$CD3 Concentration = 2.0 $\mu$g/ml

<table>
<thead>
<tr>
<th>Treg:Tresp</th>
<th>Medium</th>
<th>25(OH)D 100 mM</th>
<th>1, 25(OH)2D 150 pM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:0</td>
<td>0.53</td>
<td>0.47</td>
<td>0.40</td>
</tr>
<tr>
<td>1:0.5</td>
<td>35.72</td>
<td>43.72</td>
<td>71.45</td>
</tr>
</tbody>
</table>

1. Treg Cells
2. Tresp Cells

CD3 Concentration = 2.0 $\mu$g/ml
Percentages of CXCR3+CD45RO+ CD25(hi)+ T Helper Cells in Chronic Cultures

- 25-OH VitD
  - 10 nM: 55.48%
  - 100 nM: 50.88%
  - 1 μM: 57.97%

- 1, 25-dOH VitD
  - 15 pM: 49.04%
  - 150 pM: 52.29%
  - 1.5 nM: 53.80%

CD3/CD28 Bead: 18.97%
CD3/CD28 Bead/Abs/Cytokine: 26.91%
Induction of CXCR3+ Expression by Memory T Cells in Treg Cultures

1. Medium
2. +TGF-β, IL-2, αIFN-γ/αIL-4 Abs
3. +Cytokines, Abs, 25(OH)D

1. Medium
2. +TGF-β, IL-2, αIFN-γ/αIL-4 Abs
3. +Cytokines, Abs, 1,25(OH)2D

CXCR3+
Induction of CXCR3 Expression by Naïve T Cells in Treg Cultures

1. Medium
2. +TGF-β, IL-2, αIFN-γ/αIL-4 Abs
3. +Cytokines, Abs, 25(OH)D

1. Medium
2. +TGF-β, IL-2, αIFN-γ/αIL-4 Abs
3. +Cytokines, Abs, 1,25(OH)2D
Clinical Evaluation of Vitamin D Deficiency

- Measurement of 25-OH vitamin D levels
  - Deficiency = levels ≤20 ng/ml
  - Healthy levels (bone health, etc): >30 ng/ml
- Also measure
  - Serum PTH
  - Serum Ca
Vitamin D Supplementation and MS Incidence: The Nurses’ Health Studies

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NHS*</th>
<th>NHS II*</th>
<th>Pooled*</th>
<th>Pooled†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D from supplements, IU/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>64/1,120,418</td>
<td>0</td>
<td>63/436,790</td>
<td>Ref.</td>
</tr>
<tr>
<td>&lt; 400</td>
<td>228 (5/153,468</td>
<td>228</td>
<td>16/147,326</td>
<td>0.68 (0.42–1.08)</td>
</tr>
<tr>
<td>≥ 400</td>
<td>400</td>
<td>7/325,394</td>
<td>18/165,960</td>
<td>0.59 (0.38–0.91)</td>
</tr>
<tr>
<td></td>
<td>76/1,599,281</td>
<td></td>
<td>97/750,075</td>
<td></td>
</tr>
</tbody>
</table>

• NHS (1976): 121,700 nurses aged 30 to 55 years
• NHS II (1989): 116,671 nurses aged 25 to 42 years
• First dietary assessment:
  • NHS: 1980
  • NHS II: 1991

*Adjusted for age in 5-yr groups
†Further adjusted for smoking and latitude at birth

Study of Safety of Vitamin D Supplementation in MS Patients

- 12 patients with RRMS
- 25-OH vitD in escalating doses over 28 wks
  - 0 to 7000 μg/day
  - (280,000 IU/day)
  - Calcium 1200 mg/day

- No effect on relapses or disability
- Decrease in enhancing lesions
  (p=0.03)

Pilot Study of 1, 25-Dihydroxyvitamin D3 (Calcitrol) in RRMS

- 15 patients
- Rx: oral calcitrol 2.5 μg/day for 48 wks.
- Restricted dietary Ca
- Results
  - Mild hypercalcemia sx in dietary compliant patients
  - On-study exacerbation rate 27% less than baseline

Vitamin D Supplementation and MS Clinical Course

- None
Effects of Vitamin D on MRI Measures

- Higher vitamin D levels are associated with a lower risk of new T2 lesions
- In patients with CIS, higher vitamin D levels were associated with higher gray matter volumes
Seasonal Variation in Serum Vitamin D Levels

25(OH)D levels in 50-80 yr olds

Seasonal Variation in MRI activity

Average no. of active MRI lesions
[Auer DP et al, Ann 2000;47:276]
Variation in MRI and Serum Vitamin D Levels

25(OH)D levels in 50-80 yr olds

Average no. of active MRI lesions
[Auer DP et al, Ann 2000;47:276]
Race/Ethnicity and Vitamin D Levels in a Pediatric MS Cohort

Circulating 25(OH)D3 Levels And Oral Vitamin D3 Intake

The Institute of Medicine (IOM) recommends an Adequate Intake (AI) of vitamin D for normal bone health and calcium in healthy men and women:

- 200 IU/day (available in combination dietary supplements) for ages 19 to 50 years;
- 400 IU/day for ages 51 to 70 years;
- 600 IU/day for ages >70 years.

Within the VA, from March 1, 2007 to September 8, 2009, 30 adverse event reports associated with Vitamin D use (all formulations) were submitted to the VA Adverse Drug Event Reporting System (VA ADERS). Of the 30 reports, 14 were associated with ergocalciferol or cholecalciferol use, out of which 7 occurred with a high dose (i.e., ≥50,000 IU every week). No deaths or hospitalizations were reported for cholecalciferol or ergocalciferol ≥50,000 IU oral.

### III. PROVIDER RECOMMENDATIONS

Daily supplementation of 400 IU to 2000 IU of vitamin D has been recommended for the prevention of vitamin D deficiency in those at high risk, and doses of 700 IU to 1000 IU per day combined with calcium have been shown to reduce the risk of fractures in older patients. It has been suggested that doses of 800 IU to 1000 IU per day are necessary for those individuals with inadequate sun exposure, or who have vitamin D insufficiency. Short courses of high dose therapy (e.g., 50,000 IU weekly for 4 to 12 weeks) are reserved for those with more severe vitamin D deficiency. Daily doses of high dose vitamin D (50,000 IU) should NOT be prescribed unless required under rare conditions as determined by clinical experts.
Current Recommendations for the Treatment of Vitamin D Deficiency

- Rapid correction of the deficiency (adults)
  - 50,000 IU 25-OH vitamin D weekly for 8 weeks
  - Maintain with 50,000 IU q 2-4 weeks
  - Alternative: 50,000 IU 1-2x per year (Europe)

- Routine supplementation
  - Adults: 1,000 – 2,000 IU daily (400 UI not enough)
  - Children: 400 IU daily
Vitamin D₃ in Humans: Are we Getting Enough?

- During winter months in high latitudes, insufficient vitamin D₃ synthesized

- Currently recommended daily intake for all healthy females, males and pregnant/lactating women
  - Age < 50 years: 200 IU (5 micrograms)
  - Age 50-70 years: 400 IU (10 micrograms)
  - Age > 70 years: 600 IU (15 micrograms)

- Established daily upper limit for vitamin D₃ intake
  - Infants up to 12 months of age: 1,000 IU (25 micrograms)
  - Children, adults, pregnant/lactating women: 2,000 IU (50 micrograms)

- Should the tolerable upper intake level for vitamin D₃ be raised?

(1) Adapted from MSForum Slideset. (2) MayoClinic.com
Dietary Sources of Vitamin D

<table>
<thead>
<tr>
<th>Fortified Foods</th>
<th>Vitamin Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>~ 100 IU/8 oz, usually D3</td>
</tr>
<tr>
<td>Orange juice</td>
<td>~ 100 IU/8 oz D3</td>
</tr>
<tr>
<td>Infant formulas</td>
<td>~ 100 IU/8 oz D3</td>
</tr>
<tr>
<td>Yogurts</td>
<td>~ 100 IU/8 oz, usually D3</td>
</tr>
<tr>
<td>Butter</td>
<td>~ 50 IU/3.5 oz, usually D3</td>
</tr>
<tr>
<td>Margarine</td>
<td>~ 430 IU/3.5 oz, usually D3</td>
</tr>
</tbody>
</table>
## Dietary Sources of Vitamin D

### Natural Sources

<table>
<thead>
<tr>
<th>Food</th>
<th>Amount of Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmon</strong></td>
<td></td>
</tr>
<tr>
<td>Fresh, wild (3.5 oz)</td>
<td>~ 600–1000 IU of D3</td>
</tr>
<tr>
<td>Fresh, farmed (3.5 oz)</td>
<td>~ 100–250 IU of D3 or D2</td>
</tr>
<tr>
<td>Canned (3.5 oz)</td>
<td>~ 300–600 IU of D3</td>
</tr>
<tr>
<td>Sardines, canned (3.5 oz)</td>
<td>~ 300 IU of D3</td>
</tr>
<tr>
<td>Mackerel, canned (3.5 oz)</td>
<td>~ 250 IU of D3</td>
</tr>
<tr>
<td>Tuna, canned (3.6 oz)</td>
<td>~ 230 IU of D3</td>
</tr>
<tr>
<td>Cod liver oil (1 tsp)</td>
<td>~ 400–1000 IU of D3</td>
</tr>
<tr>
<td><strong>Shiitake mushrooms</strong></td>
<td></td>
</tr>
<tr>
<td>Fresh (3.5 oz)</td>
<td>~ 100 IU of D2</td>
</tr>
<tr>
<td>Sun-dried (3.5 oz)</td>
<td>~ 1600 IU of D2</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>~ 20 IU of D3 or D2</td>
</tr>
</tbody>
</table>
## Supplemental Sources of Vitamin D

<table>
<thead>
<tr>
<th>Prescription</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D2 (ergocalciferol)</td>
<td>50,000 IU/capsule</td>
</tr>
<tr>
<td>Drisdol (vitamin D2) liquid supplements</td>
<td>8000 IU/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Over the Counter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamin</td>
<td>400 IU vitamin D, D2, or D3</td>
</tr>
<tr>
<td>Vitamin D3 (cholecalciferol)</td>
<td>400, 800, 1000, and 2000 IU</td>
</tr>
</tbody>
</table>
Vitamin D2 versus Vitamin D3: Does it Matter?

Vitamin D2 = Ergocalciferol
Vitamin D3 = Cholecalciferol

Vitamin D2 vs. Vitamin D3 Effects on Serum Vitamin D levels

Vitamin D Effects on Cytokine Expression in Patients with MS

Double-blind, placebo-controlled

- 39 Patients
  - 17 pts: 1,000 IU vitD/800 mg Ca
  - 22 pts: /Placebo/800 mg Ca

In MS Higher Levels of 25-OH VitD May be More Protective in Women

<table>
<thead>
<tr>
<th>Measure/Season</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-OH vitD summer</td>
<td>0.87 (0.77–0.98)</td>
<td>0.91 (0.80–1.05)</td>
</tr>
<tr>
<td>25-OH vitD winter</td>
<td>0.81 (0.69–0.95)</td>
<td>0.75 (0.62–0.91)</td>
</tr>
<tr>
<td>1,25-dOH vitD summer</td>
<td>0.97 (0.90–1.05)</td>
<td>1.00 (0.91–1.10)</td>
</tr>
<tr>
<td>1,25-dOH vitD winter</td>
<td>0.97 (0.88–1.07)</td>
<td>0.97 (0.86–1.09)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-OH vitD summer</td>
<td>1.07 (0.94–1.23)</td>
<td>1.13 (0.96–1.32)</td>
</tr>
<tr>
<td>25-OH vitD winter</td>
<td>1.00 (0.86–1.17)</td>
<td>1.00 (0.82–1.22)</td>
</tr>
<tr>
<td>1,25-dOH vitD summer</td>
<td>1.01 (0.86–1.18)</td>
<td>1.01 (0.86–1.18)</td>
</tr>
<tr>
<td>1,25-dOH vitD winter</td>
<td>1.13 (0.96–1.32)</td>
<td>1.13 (0.95–1.35)</td>
</tr>
</tbody>
</table>

Vitamin D Suppresses EAE in Female Mice

Spach KM and Hayes CE. J Immunol 2005;175:4119.
Conclusions

- Vitamin D appears to have a significant role in determining MS disease risk.
- The effects of vitamin D are mediated by the modulation of immune mechanisms that hold relevance to MS disease pathogenesis.
- Carefully designed clinical trials will provide guidance for appropriate clinical management approaches that involve vitamin D supplementation.