Diet & MS: A Neurologist’s Perspective

November 8, 2016

Presented by:

Teva Pharmaceuticals | Acorda Therapeutics
Mallinckrodt Pharmaceuticals Autoimmune and Rare Diseases | US Bank
United Way of Eagle River Valley
Thank you for joining Can Do MS and the National MS Society tonight!
How to Ask Questions During the Webinar:

- **Chat Feature** – Type in your questions using the chat box on the lower left hand side of your screen.
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Why study the effect of diet in MS?
Why study the effect of diet in MS?

MS prevalence continues to rise...

...as does the prevalence of obesity
Obesity is a risk factor for MS

Obesity at age 18/20 is linked to increased MS risk (Munger, 2009)

Higher BMI at ages between 7 to 13 linked to increased MS risk

Langer-Gould et al., Neurology 2013
How Might Diet Influence MS Risk or Prognosis?

**Direct effects on the immune system**
- metabolism of immune cells can influence their function
- immune cells have receptors for Vitamin D, fatty acids

**Altering the gut microbiota**
- gut bacteria may be associated with MS
- diet can alter the gut bacterial composition

**Effects on components of the central nervous system**
- certain foods might be protective for cells in the CNS
Gut Bacteria

- 100 Trillion bacteria in the intestines

- **Normal** bacteria help to “teach” the immune system what belongs and what is an invader

- **Altered** [numbers or types of] bacteria → increase risk of some autoimmune diseases, asthma

- Changes in bacteria may be due to dietary changes, use of antibiotics
Vitamin D
Vitamin D Levels and MS Risk

Munger et al, JAMA 2006
Higher vitamin D levels → Less MS activity

Risk per 10 units higher vitamin D level

New brain lesions | Active lesions | Relapses

0.9 | 0.8 | 0.7 | 0.6 | 0.5 | 0.4 | 0.3 | 0.2 | 0.1 | 0

Adult | Child

Slide courtesy: Ellen M. Mowry MD, MCR

Scientific “Levels of Evidence”

Example

Level I: Well-designed, randomized controlled trial
Level II-1: Well-designed trial without randomization
Level II-2: Cohort/case-control study
Level II-3: Comparing times (or places) with and without the intervention
Level III: Opinions of experts, committees, etc.

To prevent “chicken or the egg” problem and other major bias
Why Are Impacts of Diets and Supplements Reported by Media So Confusing?

Vitamin D and MS

Example 1.

We think:
Low vitamin D → MS risk → Worse outcomes for people who already have MS

What if:
More severe MS → less time in sun → low vitamin D

Example 2.

People with lower vitamin D levels also have lower levels of …. (sodium, zinc, chocolate intake)

AND

Chocolate intake → improved MS
Cautionary Lessons from Supplements for Other Diseases

<table>
<thead>
<tr>
<th></th>
<th>Folic Acid</th>
<th>Beta Carotene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational</td>
<td>↓ Colon cancer</td>
<td>↓ Heart disease</td>
</tr>
<tr>
<td>(overall population)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized Trial</td>
<td>↑ Advanced pre-cancerous</td>
<td>↑ Lung cancer</td>
</tr>
<tr>
<td>(at-risk populations)</td>
<td>colon lesions</td>
<td>↑ Heart disease deaths</td>
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</table>
Recent results from vitamin D trials

SOLAR trial
• 14,000 IU cholecalciferol vs placebo for 48 weeks in addition to Interferon
• Enrolled 229 patients of whom 81% completed the study.
• There was a 31% reduction in new MRI lesions over the study period

French trial
• 100,000 IU cholecalciferol twice monthly for 2 years in 129 patients
• 20% reduction in relapse rate in the entire population
• In completers there was a significant reduction in relapses (60% lower) and new MRI lesions (almost 80% lower)

Hupperts R et al. ECTRIMS 2016.
Camu W et al. ECTRIMS 2016.
VIDAMS trial

Screening

Patient meets eligibility criteria

Patient begins glatiramer acetate for one month

Meets compliance criteria

Randomized to oral vitamin D₃ 5000 IU/day plus glatiramer acetate

Randomized to oral vitamin D₃ 600 IU/day plus glatiramer acetate

Does not meet compliance criteria

Patient not randomized

MS patients have a diminished response to vitamin D supplementation compared to healthy individuals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Multiple Sclerosis (n=27)</th>
<th>Healthy controls (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.2 ± 9.2</td>
<td>37.9 ± 12.1</td>
<td>0.44</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3 ± 2.9</td>
<td>23.6 ± 2.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D (ng/mL)</td>
<td>22.1 ± 7.9</td>
<td>22.4 ± 8.0</td>
<td>0.91</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.3 ± 0.3</td>
<td>9.5 ± 0.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Oral contraceptive use (n(%))</td>
<td>4 (14.8)</td>
<td>9 (30)</td>
<td>0.17</td>
</tr>
<tr>
<td>Dietary vitamin D intake (IU/day)</td>
<td>117.8 ± 184</td>
<td>77.3 ± 97</td>
<td>0.31</td>
</tr>
<tr>
<td>Fat Intake Score</td>
<td>18.1 ± 7.9</td>
<td>19.1 ± 6.6</td>
<td>0.61</td>
</tr>
<tr>
<td>Sun exposure (hours per week)</td>
<td>12 ± 10.6</td>
<td>9.3 ± 5.8</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Vitamin D supplementation also affects the gut microbiome

Cantarel BL et al. Journal of Investigative Medicine, 2015

Involved in “immune tolerance”

Prevents inflammation
Summary

- Vitamin D deficiency: increased risk for MS and with worse disease activity in established MS.

- Optimal dose of vitamin D and effect on clinical disease activity are being investigated

- Results from ongoing trials suggest decreased radiological disease activity with high-dose vitamin D supplementation.

- MS patients may not have the same response to vitamin D supplementation as healthy controls.
Polyunsaturated fatty acids (PUFAs)
PUFAs

• Derived from both plant and animal sources

• PUFAs contain 2 or more double bonds beginning at the third or sixth carbon (ω-3 or ω-6)

• They are involved in the biogenesis of multiple inflammatory molecules both anti- and pro-inflammatory

• Various immune cell populations have receptors for PUFAs
PUFAs and MS risk

- Women in the “Nurses Health Study” and “Nurses Heath Study II” were included and data on diet was derived from a standardized questionnaire.

- Higher baseline PUFA intake was associated with 34% lower MS risk.

- Higher linoleic and linolenic acid intake was associated with lower MS risk.

Bjornevik K et al. ECTRIMS 2015.
**PUFAs and MS risk**

- **Case-control study from Australia included 267 cases and 517 controls**

- **Higher intake of ω-3 PUFA (39% lower) especially those from fish (46% lower) associated with lower risk of MS**

<table>
<thead>
<tr>
<th>(a)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>p for trend</th>
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<tr>
<td><strong>Total fat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>62/103</td>
<td>53/103</td>
<td>52/104</td>
<td>43/103</td>
<td>57/104</td>
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<tr>
<td>Median (range)</td>
<td>38 (13–47)</td>
<td>55 (47–60)</td>
<td>67 (60–75)</td>
<td>85 (76–97)</td>
<td>122 (98–559)</td>
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<tr>
<td>AOR (95%CI)</td>
<td>1.00</td>
<td>0.83 (0.49–1.41)</td>
<td>0.83 (0.46–1.49)</td>
<td>0.65 (0.32–1.35)</td>
<td>1.00 (0.38–2.66)</td>
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<tr>
<td><strong>Saturated fat</strong></td>
<td></td>
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<td></td>
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<td>0.36</td>
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<td>Cases/controls</td>
<td>57/103</td>
<td>51/103</td>
<td>58/104</td>
<td>41/103</td>
<td>60/104</td>
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<tr>
<td>Median (range)</td>
<td>15 (5–18)</td>
<td>22 (18–24)</td>
<td>28 (25–32)</td>
<td>35 (32–41)</td>
<td>51 (41–224)</td>
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<tr>
<td>AOR (95%CI)</td>
<td>1.00</td>
<td>0.92 (0.54–1.55)</td>
<td>1.22 (0.70–2.12)</td>
<td>0.92 (0.47–1.79)</td>
<td>1.86 (0.79–4.35)</td>
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<tr>
<td><strong>MUFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.32</td>
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<td>Cases/controls</td>
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<td>49/103</td>
<td>49/103</td>
<td>43/103</td>
<td>57/104</td>
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<tr>
<td>Median (range)</td>
<td>14 (5–17)</td>
<td>19 (17–21)</td>
<td>23 (21–27)</td>
<td>30 (27–35)</td>
<td>44 (35–213)</td>
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<tr>
<td>AOR (95%CI)</td>
<td>1.00</td>
<td>0.82 (0.47–1.41)</td>
<td>0.73 (0.41–1.31)</td>
<td>0.61 (0.30–1.23)</td>
<td>0.87 (0.33–2.31)</td>
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<tr>
<td><strong>PUFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.18</td>
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<tr>
<td>Cases/controls</td>
<td>56/103</td>
<td>60/103</td>
<td>58/104</td>
<td>44/103</td>
<td>49/104</td>
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<tr>
<td>Median (range)</td>
<td>4 (1–6)</td>
<td>7 (6–8)</td>
<td>10 (8–11)</td>
<td>13 (11–15)</td>
<td>18 (15–84)</td>
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<tr>
<td>AOR (95%CI)</td>
<td>1.00</td>
<td>1.11 (0.65–1.90)</td>
<td>1.06 (0.59–1.89)</td>
<td>0.68 (0.37–1.37)</td>
<td>0.74 (0.34–1.57)</td>
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<tr>
<td><strong>Omega-3 PUFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
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<td>Cases/controls</td>
<td>60/103</td>
<td>58/103</td>
<td>58/104</td>
<td>50/103</td>
<td>41/104</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.7 (0.2–0.9)</td>
<td>1.0 (0.9–1.1)</td>
<td>1.3 (1.1–1.4)</td>
<td>1.7 (1.4–2.0)</td>
<td>2.4 (2.0–16.9)</td>
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</tr>
<tr>
<td>AOR (95%CI)</td>
<td>1.00</td>
<td>1.09 (0.64–1.86)</td>
<td>0.81 (0.45–1.46)</td>
<td>0.60 (0.31–1.16)</td>
<td>0.38 (0.16–0.88)</td>
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<tr>
<td><strong>Omega-6 PUFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Cases/controls</td>
<td>51/103</td>
<td>65/103</td>
<td>54/104</td>
<td>47/103</td>
<td>50/104</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.7 (0.9–4.7)</td>
<td>6.0 (4.8–7.1)</td>
<td>8.0 (7.1–9.3)</td>
<td>10.6 (0.3–12.2)</td>
<td>15.3 (12.3–66.9)</td>
<td></td>
</tr>
<tr>
<td>AOR (95%CI)</td>
<td>1.00</td>
<td>1.29 (0.75–2.20)</td>
<td>1.02 (0.57–1.81)</td>
<td>0.82 (0.44–1.55)</td>
<td>0.83 (0.39–1.75)</td>
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</tbody>
</table>

Studies of PUFA and PUFA rich diets in MS

• Trial of low-fat diet supplemented with ω-3 PUFAs (fish-oil) compared to olive oil supplemented diet in 31 patients. There was an improvement in quality of life scores and a reduction in relapse rate compared to pre-diet disease activity.

• OFAMS trial tested two PUFAs (EPA + DHA) in addition to interferon in 46 patients in each arm – no change in MRI or clinical disease parameters over the course of the study.

Weinstock-Guttman B et al. Prostaglandinds Leukot Essent Fatty Acids. 2005
Summary

- Low PUFA intake especially ω-3 is linked to an increased risk for developing MS

- PUFAs can directly act on immune cells and have immunosuppressive effects

- Trials of PUFA supplementation or PUFA-rich diets have had conflicting results and further studies are needed to clarify the role of PUFAs in MS treatment
Salt intake and MS
Salt promotes inflammatory cells and worsens disease in a mouse model of MS.

Does high salt intake increase MS disease activity?

Farez MF et al. J Neurol Neurosurg Psychiatry. 2015.
Salt intake does not predict development of new MRI lesions

*Consistent results using quintiles and deciles to assess dose-response*

<table>
<thead>
<tr>
<th>Quintile Median (g/day)</th>
<th>RR of Cumulative New Active Lesions</th>
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<tr>
<td>1 [3.9]</td>
<td>1.00</td>
</tr>
<tr>
<td>2 [4.5]</td>
<td>1.05</td>
</tr>
<tr>
<td>3 [5.0]</td>
<td>1.14</td>
</tr>
<tr>
<td>4 [5.4]</td>
<td>1.07</td>
</tr>
<tr>
<td>5 [6.3]</td>
<td>1.03</td>
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</table>

<table>
<thead>
<tr>
<th>Decile of 24hr sodium excretion</th>
<th>RR of Cumulative New Active Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [3.2]</td>
<td>1.00</td>
</tr>
<tr>
<td>2 [3.8]</td>
<td>1.02</td>
</tr>
<tr>
<td>3 [4.1]</td>
<td>1.00</td>
</tr>
<tr>
<td>4 [4.5]</td>
<td>0.94</td>
</tr>
<tr>
<td>5 [4.8]</td>
<td>0.95</td>
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<tr>
<td>6 [5.1]</td>
<td>0.96</td>
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<tr>
<td>7 [5.4]</td>
<td>0.96</td>
</tr>
<tr>
<td>8 [5.8]</td>
<td>0.97</td>
</tr>
<tr>
<td>9 [6.3]</td>
<td>0.98</td>
</tr>
<tr>
<td>10 [7.2]</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Slide courtesy: Kathryn Fitzgerald ScD
Salt intake does not predict change in T2 lesion and brain volumes

Slide courtesy: Kathryn Fitzgerald ScD
Summary

• High sodium chloride concentrations promote development of inflammatory T cells

• A high-salt diet leads to more severe disease activity in a mouse model of MS

• In a retrospective study there appeared to be increased risk for relapses with increased salt intake

• However, in an analysis of the BENEFIT trial, salt intake appeared to have no relation to clinical or MRI disease activity

• Further studies, including controlled trials are required to clarify the role salt may play in MS
Diets in MS
Long term diet is linked to gut enterotype

Gary D. Wu et al. Science 2011;334:105-108
Diet can rapidly alter gut microbiome

Diets that have been proposed for MS

• Paleolithic diet
• Mediterranean diet
• McDougall diet
• Gluten free diet
• Swank diet
Diets that have good evidence for an effect in MS
Diets that have good evidence for an effect in MS

NONE
Paleo diet

• Attempting to eat a diet – pre-agricultural revolution

• Elimination of processed foods

• Animal protein makes up 30-35% of daily caloric intake

• High fiber intake (45-100 g/day) that is not cereal based

• Low ratio of saturated fats to PUFA
Paleo diet

• Consume 3 servings each day of green leafy vegetables, sulfur rich vegetables and intensely colored fruits or vegetables.

• Consume 2 tablespoons of omega-3 oils; 4 oz. or more each of animal protein and plant protein; only non-lactose containing milks; no more than 2 servings per week of gluten-free grains/starchy foods.

• Do not consume any dairy or gluten containing grains.
Studies on the paleo diet in MS

• One small study of 10 patients of whom 6 completed the study.

• There appeared to be reduction in fatigue scores; however, the diet was coupled with exercise and other interventions.

• The Paleo diet can result in deficiencies in folic acid, thiamine and vitamin B6 (due to reduced intake of cereals), calcium and vitamin D (due to lack of dairy intake) and insufficient caloric intake.

McDougall Diet

• Low-fat, high carbohydrate, moderate sodium, vegan diet
• Suggested diet staples: wheat flour products, corn, rice, oats, barley, quinoa, potatoes, sweet potatoes, beans, peas, and lentils
• Fresh fruits and non-starch green or colored vegetables
• Low sodium intake encouraged and small amounts of sugar and spices may be used
• No animal-derived foods allowed: dairy, eggs, meat, poultry and fish are excluded. Oils are not allowed (including vegetable oils)
Studies on McDougall diet in MS

- Trial of 61 patients (diet vs wait-listed) – 20% drop-out in diet group,
- Reduction in weight, improved lipid profile and fatigue scores
- No change in MRI and disease parameters
- Diet training was provided in a residential program (10 day)

- The McDougall diet could result in deficiencies in iron, vitamin B12, vitamin D, calcium and ω3-fatty acids

Mediterranean diet

• Extensively studied for its beneficial effects on cardiac health

• High intake of whole grains, vegetables, fruits, legumes, olive oil and fish

• Low intake of saturated fats (butter and other animal fats), red meat, poultry, dairy products

• Regular but moderate intake of ethanol mainly consisting of red wine during meals
Figure 1: Pyramidal representation of the components of the Mediterranean diet and lifestyle (adapted from Ostan et al. 21)
Swank diet

• Saturated fats < 15 gm/day, while unsaturated fats/oils < 20-50 gm/day.
• No processed foods containing saturated fats and dairy products < 1% fat.
• Whole grain cereals and pastas are recommended.
• Two cups each of fruits and vegetables are recommended.
• No red meat for the first year after which 3 oz. weekly.
• White fish and shellfish permissible in any amount. Skinned trimmed poultry meat is permissible.
• A cod liver oil and multivitamin supplement recommended.
Studies on Swank diet in MS

- 144 patients followed over 34 years
- Less deterioration and lower death rates in low fat diet compared to high fat diet
- Study conducted prior to introduction of disease modifying therapies
- Lacks appropriate controls

Gluten-free diet

- Gluten is composed of gliadin and glutenin found conjoined with starch in wheat, rye, and barley.

- Major component of the proteins found in wheat.

- Gluten sensitivity is a feature of celiac disease and GFD is a common treatment for this disorder.

- “Wheat-free” is not the same as “gluten-free”.

- No evidence that this is beneficial in MS patients without gluten sensitivity.
What is common to most of the proposed diets for MS?

- Eat food
- Not too much
- Mostly plants

Michael Pollan
What is common to most of the proposed diets for MS?

Eat food

Not too much

Mostly plants

Michael Pollan
Does the amount of calories we eat matter?

• Mouse models of other neurological disorders improved by calorie restriction, with less inflammation in the brain

• In mouse models of MS restricting calories or fasting prior to disease induction:
  ➔ Lower risk of disease
  ➔ Less severe disease in the mice that do get it

2. Piccio L, J Leukocyte Biology 2008
3. Sanna V, J Clinical Invest 2003
Fasting mimicking diet reduces the severity of a mouse model of MS

Caloric restriction and the immune system

Caloric restriction may promote remyelination in a mouse model

Intermittent caloric restriction trial

Slide courtesy: Ellen M. Mowry, MD, MCR. Johns Hopkins University
Summary

• Various diets have been proposed for MS, but evidence for a clear benefit for any of them is lacking.

• Rigorous studies that include measures of adherence, disease activity, and quality of life are required.

• Caloric restriction or fasting appears to lead to reduction of inflammation and perhaps promotes repair in mouse models.

• Trials of fasting diets are ongoing and will provide more information on the feasibility and efficacy of this intervention.
Future directions for Diet in MS

• There is a need to study diet and supplements in MS

• Currently insufficient high-quality data to recommend a specific diet or supplement for the treatment/prevention of MS

• Though studies are challenging to do, they are necessary in the light of prior experience with other supplements
Questions/Comments

Pavan Bhargava, M.B.B.S., M.D.

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Johns Hopkins University School of Medicine
Baltimore, MD
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your best life update

Q&A

Can Do Library


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Food for Thought – MS and Nutrition

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People affected by MS can live their best lives as we stop MS in its tracks, restore what has been lost and end MS forever.

NATIONALMSSOCIETY.ORG/DIET
Sleep in MS: Strategies for Improving Your Zzz’s
December 13, 2016

Presented by:
Teva Pharmaceuticals | Acorda Therapeutics
Mallinckrodt Pharmaceuticals Autoimmune and Rare Diseases | US Bank
United Way of Eagle River Valley