Food for Thought

Diet, BMI & MS?

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Main Questions in MS & Diet/BMI

+ Is a high BMI is associated with developing MS?
+ Is a high BMI associated with MS progression?
+ Is there any association between diet & MS?
+ Is there association between the microbiome, the diet in MS & the progression of MS?
“Let food be thy medicine and medicine be thy food” Hippocrates

1826 - Anthelme Brillat-Savarin "Dis-moi ce que tu manges, je te dirai ce que tu es.” - Tell me what you eat and I will tell you what you are

1863 - Ludwig Andreas Feuerbach wrote: "Der Mensch ist, was er ißt.” 'man is what he eats’
Body Mass Index (BMI) –> 25 & 30
Objective: To examine whether obesity during childhood, adolescence, or adulthood is associated with an increased risk of MS.

Methods:
- Women in the Nurses’ Health Study (n=121,700) and Nurses’ Health Study II (n=116,671) provided information on weight at age 18 and weight and height at baseline, from which body mass index was derived.
- Women selected silhouettes representing their body size at ages 5, 10, and 20.
- Over the total 40 years of follow-up in both cohorts combined, we confirmed 593 cases of MS.
- Statistical models, adjusting for age, latitude of residence, ethnicity, and cigarette smoking, were used to estimate the rate ratios and 95% confidence intervals (CI).

Nine silhouettes women selected to best describe their body size at ages 5, 10, and 20

Those who were obese by age 18 had double the risk for MS - These illustrations represent a BMI of 30 or more

Obesity at age 18 (body mass index 30 kg/m²) was associated with a greater than twofold increased risk of MS as compared to women with a BMI between 18.5 and 20.9 kg/m².

MS risk among women who were overweight, but not obese, at age 18 (BMI 25–29.9 kg/m²) was only moderately increased. Obese adolescents have an increased risk of developing multiple sclerosis (MS).

The mechanisms of this association is uncertain, but this result suggests that prevention of adolescent obesity may contribute to reduced MS risk.

Obesity & Risk of MS – Nurses’ Study

**Obesity at Age 18 and Risk of Multiple Sclerosis**

- **Relative risk**
  - 18.5 – <21: 1
  - 30+: 3

**Body mass index (kg/m²)**

*Munger et al. Neurology® 2009;73:1543–1550*
<table>
<thead>
<tr>
<th>Body Mass Index, kg/m²</th>
<th>Multivariate-Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>0.96 (0.73 – 1.27)</td>
</tr>
<tr>
<td>18.5 – &lt;21</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>21 – &lt;23</td>
<td>1.13 (0.91 – 1.40)</td>
</tr>
<tr>
<td>23 – &lt;25</td>
<td>0.97 (0.72 – 1.31)</td>
</tr>
<tr>
<td>25 – &lt;27</td>
<td>1.44 (0.87 – 2.39)</td>
</tr>
<tr>
<td>27 – &lt;30</td>
<td>1.40 (0.92 – 2.14)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>2.25 (1.50 – 3.37)</td>
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</table>

CI = confidence interval

Women with a BMI 30 kg/m² at age 18 had a 71% increased risk of MS as compared to women with BMI between 18.5 and 20.9 kg/m².

As smoking was the main confounder of the association between obesity at age 18 and MS risk, we also restricted analyses to never smokers in the NHSII (there were too few never smokers in the NHS cohort to do a comparable analysis);

The twofold increased risk of MS persisted among never smoking women with a BMI at age 18 30 kg/m² (RR 2.34, 95% CI 1.21–4.53, p 0.01).
In a Swedish population-based case-control study (1571 cases, 3371 controls), subjects with different BMIs were compared regarding multiple sclerosis (MS) risk, by calculating odds ratios (OR) with 95% confidence intervals (95% CI).

Subjects whose BMI exceeded 27 kg/m\(^2\) at age 20 had a two-fold increased risk of developing MS compared with normal weight subjects.

The obesity epidemic may explain part of the increasing MS incidence as recorded in some countries. Measures taken against adolescent obesity may thus be a preventive strategy against MS.

Hedström et al., Multiple Sclerosis, 2012 Sep;18(9):1334-6
BMI & Progression of MS

**OBJECTIVES:**

- To assess the potential of an online platform, PatientsLikeMe.com (PLM), for research in multiple sclerosis (MS)
- The role of body mass index (BMI) on MS disease course was conducted to illustrate the utility of the platform

**METHODS:**

- Compared the demographic characteristics of subjects from PLM and from a regional MS center
- Validated PLM's patient-reported outcome measure (MS Rating Scale, MSRS) against standard physician-rated tools
- Analyzed the relation of BMI to the MSRS measure

BMI & Progression of MS - Results

- Compared with 4,039 MS Center patients, the 10,255 PLM members were younger, more educated.

- Disease course RRMS, with younger symptom onset and shorter disease duration.

- MSRS scores for 121 MS Center patients revealed acceptable agreement between patient-derived and physician-derived composite scores (weighted kappa = 0.46). The Walking domain showed the highest weighted kappa (0.73) and correlation (rs = 0.86) between patient and physician scores.

- Using PLM data, a modest correlation between BMI and cross-sectional MSRS (rho = 0.17) and no association between BMI and disease course.

What is a Healthy Diet for MS?

Swank Diet?
Dairy food?
Vegetarian?
Paleo Diet?
Mediterranean Diet??
Low saturated fat diet?
Gluten Free Diet?
All Raw?

Even Lisa is confused!
Dietary Key Points

- Dietary changes & supplements are used by patients with MS without reliable evidence for their risks & benefits
- Low vitamin D is associated with a worse course of disease in observational studies
- Polyunsaturated fatty acids & a low fat diet attenuate MS immune responses in vitro & in animal studies but limited data in MS
- Antioxidants, probiotics & vitamin B12 supplementation attenuate MS immune response in vitro & animal models but limited data in humans
- Milk proteins & Gluten are thought to worsen the outcomes in MS, but no randomized controlled trials re dietary restrictions

Swank Low Saturated Fat Diet

+ 144 patients with MS – DSS 4-5, ambulatory but with difficulty – fatigue & low endurance – all had ~124 g/d saturated fat

+ 70 patients – low fat diet – 20 g/d saturated fat – “Good Dieters” - overall fat consumption 16 ± 2.8 g/d

+ 74 patients with MS - >20 g/d saturated fat – “Poor Dieters” – overall fat consumption 38 ± 18 g/d

+ Followed frequently initially = visits & then Phone FU

Swank Low Saturated Fat Diet

- Followed for 34 years
- 23 deaths - 14 (20%) due to MS – in “Good Dieters”
- 58 deaths - 48 (61%) due to MS – in “Poor Dieters”
- 63 surviving patients continued the study up to 50 years
- 2000 – 15 patients were seen who started the study 1950s
- 15 patients ages 72 – 84 year old – 13 ambulatory & care for themselves & 2 with difficulty walking

Swank Low Saturated Fat Diet

- Low fat diet proposed by Swank – 10-15 g/d of saturated fat during 50 years study
- 20% of patients with MS on the lowest fat diet showed little or no neurologic deterioration as a result of the progress of the disease
- Higher percentage than the 4% of “Mild MS” cases expected within a large group of patients

Low Saturated Fat Diet

+ Restriction of saturated fat induces remission of the disease & produces beneficial effects in MS patients

+ Saturated fat decrease membrane fluidity, lead to the synthesis of cholesterol, activate the CD14/TLR4 leading to formation of TNF-α

+ Fat influences transcriptional level, gene expression, cell metabolism & cell growth & differentiation

Swank & Goodwin, Nutrition, 2003, 19(5), 478
Essential Fatty Acids & MS

+ Ω-3 (α-linoleic fatty acid) – fish oil & Ω-6 (linoleic fatty acid) – plants

+ Hypothesis: Diet high in meat & dairy & low in fish increases the risk of MS

+ Swank 1950 – Norway – higher incidence of MS among those that had high consumption of animal fat & dairy products than fish consumption

+ No association between animal fat or saturated fat & the risk of MS – case control studies

  Swank et al. NEJM, 1952, 246, 721.
Prospective cohort study

The amount & type of dietary fat did not affect the risk of developing MS

Ω-3 (α-linoleic fatty acid) was associated with a reduced risk of MS but it did not reach statistical significance

No significant association between fish consumption & MS risk in one case control study but fish consumption was significantly associated with a reduced risk of MS in women

Zhang et al., Am J Epidemiology, 2000, 152, 1056.
Ghadirian et al., J. Epidemiology, 1998, 27, 845
Polyunsaturated Fatty Acids (PUFA)

- Nordvik – fish oil supplements & progression of MS in 16 newly diagnosed patients – significant reduction in relapse rate and improvement on EDSS

- Weinstock-Guttman – low fat diet supplemented with Ω-3 PUFA has moderate benefits in RRMS but the potential therapeutic effects may be related to the low fat diet

- Increased intake of Ω-3 fatty acids reduce the synthesis of pro-inflammatory leukotriene B4 and prostaglandin E2

Nordvik et al., Acta Neurol Scand. 2000, 102, 143.
There is evidence that omega-3 fatty acids reduce the risk of cardiovascular events.

There is not enough definite proof available to recommend omega-3 fatty acids for MS, but findings suggest beneficial effects from unsaturated fatty acids.

Justifiable to consume foods rich in omega-3 fatty acids, high-quality vegetable oils (containing high amounts of unsaturated fats), and 2 or more seafood meals per week.

High consumption of milk was associated with increased incidence of MS.

The incidence of MS in Japan rose between the years 1950 – 1969 in parallel with increased consumption of milk.

Meat & dairy products were associated with incidence of MS in the USA.

Schwarz & Leweling, Multiple Sclerosis, 2005, 11, 24-32.
Cow Milk – Saturated Fat

- Milk proteins with effect in MS are the proteins of the milk fat globule membrane (MFGM proteins)
- The most representative of MFGM is Butyrophilin (BTN)
- BTN is similar to MOG (myelin oligodendrocyte glycoprotein)
- BTN blocks MOG-induced EAE but also induces inflammatory responses in the CNS
- Antibody cross-reactivity between MOG & BTN has been observed in MS

Riccio et al., Autoimmune Diseases, 2010.
Gluten Free Diet & MS

- Open label trial
- End Points: ARR, EDSS
- 42 patients on a gluten free diet

Results
- No change in relapse rate
- No change in disease progression based on EDSS

Paleo Diet Food Pyramid
Vitamin D & MS

- Studies indicate that vitamin D alters immune function in a way that may be desirable in MS.

- Many people with MS have risk factors for developing osteoporosis:
  - Female gender, decreased physical activity, decreased exposure to sunlight, and frequent treatment with steroids.

- People who have these risk factors may consider supplements of vitamin D and calcium.

- Recommended intake of vitamin D is based on blood test level.

Vitamin D & MS

- Double blind placebo controlled randomized trial
- End Points: ARR, EDSS, MSFC
- 35 patients received vitamin D3 20,000 IU weekly vs. 33 patients getting placebo

Results
- No change in relapse rate or EDSS score

Kampman et al., Multiple Sclerosis, 2012, 18, 1144-1451.
Vitamin D - Nurses’ Study

- Nurses’ Health study (20yrs) and Nurses’ Health study II (10yrs) – 40% reduced risk of MS found in women in the highest quintile of vitamin D intake compared with those in the lowest quintile.
- Vitamin D supplementation showed correlation with increased risk of development of MS.
- Vitamin D deficiency may lead to increased intensity of the symptoms in MS due to enhancement of inflammatory cytokines.
- Polymorphisms in certain genes for the vitamin D receptor have been associated with increased likelihood of MS.
Vitamin B12 & MS

+ Vitamin B12 is a prerequisite for the synthesis of myelin
+ Vitamin B12 & MS share clinical & MRI characteristics
+ High dose therapy with vitamin B12 over 6 months trial in 6 severely disabled patients with MS – no clinical benefit
+ Placebo control trial with 138 patients – small without significance - beneficial effect of parenteral therapy of vitamin B12
+ No scientific basis to recommend vitamin B12 supplementation unless has deficiency

Schwarz & Leweling, Multiple Sclerosis, 2005, 11, 24-32.
Kira et al., Internal Medicine, 1994, 33, 82-86.
Wade et al., J Neurol Neurosurg Psychiatry 2002, 73, 246-249.
Probiotics & MS

- Open label single blind trial
- Primary end point: Gadolinium enhancing lesions on MRI
- Secondary end point: serum cytokine levels (IL4, IL10, IL17)

Results:
- RRMS - naive patients - Decreased numbers of lesions on GAD MRI as compared to pre study
- Increased levels of IL4 & IL10

- Administration of probiotics to Mice EAE model
  - Reduction in IL17 & increased IL10

Uric Acid – BBB Integrity

+ Study Design: Double blind placebo controlled randomized – 16 patients with RRMS taking inosine for 12 months vs. 6 months of placebo followed by 6 months of inosine

+ End Points: RR, EDSS, MRI

+ Results:
  + Decreased number of Gad enhanced lesions seen on MRI
  + Decreased EDSS score

Markowitz et al., J Alternative Complementary Medicine, 2009, 15, 619-625
Uric Acid & MS

Study Design: Multicenter - Double blind placebo controlled randomized – 159 patients – inosine vs. placebo as add on to IFN-β

End Points:
- Primary: change in EDSS at 24 months
- Secondary: time to confirmed disability progression, time to first relapse, mean EDSS change, ARR, MSFC & number of relapses

Results:
- No change in relapse rate
- No change in EDSS scores

Gonsette et al., Multiple Sclerosis, 2010, 16, 455-462.
Attempt to answer patients’ questions about dietary recommendations and their impact of prognosis for people with MS

Selection criteria limited to MS and trials that had a comparison arm

Results:

- No specific recommendation for diet & supplements – adopt healthy eating habits
- PUFAs seem to have no effect on disease progression & the risk of clinical relapses over 2 years
- Low level of vitamin D is associated with lower subsequent disability – authors noted no cause-effect relationship

Farinotti et al., Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004192.
Guts, bugs and MS

Did you know that...

- We are made up of more microbes than human cells?
- Bacteria account for 1-3% of body mass?
- Only 1% of bacteria can be cultured in the lab?
- Most bacteria are non-pathogenic?
- There are more bacterial than human genes?

Dr. Sergio Baranzini – Microbiome Project / UCSF MS EPIC Study
The link between dietary intake and host immune system is not direct, but mediated by the commensal bacteria residing in the walls of the intestine called the microbiome.

Commensal bacteria can be classified based on their unique DNA sequences.

Commensal bacterial – responsive for dietary manipulations, regulating metabolism, nutrient absorption and modulation of immune activity.

The importance of the intestinal microbiome & its interactions with the immune system are recognized with regard to the development of autoimmune diseases.

### Known Core & Number of Species

<table>
<thead>
<tr>
<th>Species</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td>Lactobacillus lactis</td>
<td>1</td>
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<tr>
<td>Lachnobacterium spp.</td>
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<tr>
<td>Lachnospira pectinoschiza</td>
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</tr>
<tr>
<td>Parabacteroides spp.</td>
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<tr>
<td>Prevotella spp.</td>
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</tr>
<tr>
<td>Roseburia intestinalis</td>
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<tr>
<td>Ruminococcus spp.</td>
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<tr>
<td>Streptococcus spp.</td>
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<tr>
<td>Subdoligranulum variabile</td>
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<tr>
<td>Sutterella wadsworthia</td>
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<tr>
<td>Uncultured Phylotypes</td>
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<tr>
<td>Akkermansia muciniphila</td>
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<tr>
<td>Alistipes finegoldii</td>
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<tr>
<td>Anaerotruncus colihominis</td>
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<tr>
<td>Bacteroides spp.</td>
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<tr>
<td>Bifidobacterium spp.</td>
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<td>Clostridium spp.</td>
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<td>Colinsella spp.</td>
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<tr>
<td>Dorea spp.</td>
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<tr>
<td>Eubacterium spp.</td>
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<tr>
<td>Faecalibacterium prausnitzii</td>
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</tr>
</tbody>
</table>
Rise in the incidence of Japanese patients developing RRMS was associated with “Westernized” dietary habits.

EAE models suggest that the gut flora contribute to the development of disease.

Sterilization of the gut by treatment with a mixture of antibiotics reduced the severity of EAE.


Microbiome & extra-intestinal autoimmune diseases

Kamada et al., Nature Reviews Immunology 13, 321-335 (May 2013)
Summary
No specific diet has proven beneficial in MS

- Principles of healthy diet
- No basis for recommendations to avoid particular foods (e.g., alcohol, meat, wheat/gluten, coffee, animal fat, dairy products)
- Low saturated fat
- Fish or Omega 3 supplementation
- Probiotics / Vitamin D

Thank You!

Questions / Comments