Western Lifestyle and Autoimmunity

- Genetic Predisposition
- Low Concordance rates in Monozygotic Twins
- Environmental Factors (modulation of gut bacteria)
  - Hygiene hypothesis
  - Psychosocial Stress
  - Smoking/Alcohol
  - Lack of Physical Activity
  - Excess caloric intake/obesity
Lifestyle Related Autoimmune Disorders

- Inflammatory Bowel Disease
- Rheumatoid Arthritis
- Multiple Sclerosis
- Type 1 Diabetes
Inflammatory Bowel Disease
IBD

- 1.6 million Americans
- 70,000 new cases annually
- 80,000 children
- 500/100,000 persons
- Similar Trend in Westernized nations
## Summary

<table>
<thead>
<tr>
<th></th>
<th><strong>ULCERATIVE COLITIS</strong></th>
<th><strong>CROHN’S DISEASE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCIDENCE (NORTH AMERICA)</strong></td>
<td>2.2-14.3:100000</td>
<td>3.1-14.6:100000</td>
</tr>
<tr>
<td><strong>MALE TO FEMALE RATIO</strong></td>
<td>1:1</td>
<td>1.1-1.8:1</td>
</tr>
<tr>
<td><strong>MONOZYGOTIC TWINS</strong></td>
<td>6% Concordance</td>
<td>58% Concordance</td>
</tr>
<tr>
<td><strong>DIZYGOTIC TWINS</strong></td>
<td>0% Concordance</td>
<td>4% Concordance</td>
</tr>
<tr>
<td><strong>SMOKING</strong></td>
<td>Found more in non smokers</td>
<td>More in smokers</td>
</tr>
<tr>
<td><strong>OCP</strong></td>
<td>No increased risk</td>
<td>Increased risk</td>
</tr>
<tr>
<td><strong>APPENDECTOMY</strong></td>
<td>Protective</td>
<td>Not protective</td>
</tr>
</tbody>
</table>
Sulfur

- Epigenetic modulation via Microbiome
- Sulfur containing amino acids (methionine/cysteine) and sulfur additives (food preservation)
- Fermentative sulfidogenesis produces hydrogen sulfide gas
- Linear relationship

Foods High in Sulfur

- Meat and fish
- Eggs
- Cheese
- Tea
- Cocoa
- Dried apricots

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Hydrogen Sulfide

- DNA hypomethylation
- Apoptosis
- Crypt architectural distortion
- Mucosal Ulceration (cancer pre-cursor)

- 2.7 mmol/day vs 16.6 mmol/day
H2S and UC

- H2S main factor responsible for UC relapse
- Elimination of cow’s milk can improve symptoms/reduce relapses
- Meat consumption = 3 fold risk
- Processed meat consumption = 5 fold risk
- Alcohol consumption = 2.7 fold risk
Crohn’s Disease

- Dramatic increases in Japan over the last century
- Strong positive correlation with increases in dietary fat (total, animal, PUFA) and protein (animal and milk)
- Inverse association with vegetable protein.
Inflammatory Bowel Disease: A Growing Global Problem

0.5%
of people in the Western world are now affected by either Crohn's disease or ulcerative colitis

1960-2015

Areas where IBD cases have been reported.
Inflammatory Bowel Disease: A Growing Global Problem

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1960-2015

Areas where IBD cases have been reported.
IBD and Sucralose

- Aspartame → methanol → formaldehyde
- Sucralose reduces #'s of beneficial bacteria
- Sucralose mutagenic at high temperatures
- → chloropropanols
Butyrate and IBD

- Butyrate: SCFA produced via carbohydrate metabolism by beneficial gut microbes
- Plays an important protective role in intestinal homeostasis acting in both adaptive immunity and innate immunity

- PBD high in fiber promote butyrate producing bacteria
- PBD play a role in both prevention and treatment
Fiber, Butyrate and UC

- Topical butyrate (enemas) is effective in UC treatment
- 60 grams oat bran daily for 3 months increases butyrate by 36%
- Effect seen after 4 weeks
- No relapse and improved symptoms in intervention group
Diet and Crohn’s

- 2 year clinical trial 22 Crohn’s patients s/p inpatient remission- SVD
  - Remission rates on SVD 100% at 1 year; 92% at 2 years
  - 4/6 omnivores relapsed by end of year 2

- Compared to drugs
  - Higher remission rates (61%/41%/36%)
  - Less expense
  - No side effects
Additional Therapies

- 2000 IU Vitamin D3
- 75 nm/L = 44% reduced risk of Crohn’s related surgery
- 40 ng/ml = improved QOL scores and reduced disease activity.
Additional Therapies

- Curcumin alone 4/5 with UC remission
- 1 gram curcumin BID plus sulfasalazine or mesalamine
  - 2/43 with relapse (5%)
  - 8/39 with relapse for those with no curcumin (20%)
- Endoscopic improvement in curcumin group
Rheumatoid Arthritis
(Epi)genetics of RA

- HLA-DR4
  - 70% of RA patients
  - 30% of general population
  - Subtypes = 90%
- Monozygotic concordance rate 15%
- Smoking triggers HLA production and seroconversion to HLA positive RA
Microbes and RA

- Role of microbial infections in rheumatic disease
  - GAS in rheumatic fever
  - Spirochetal infections in Lyme disease
  - Campylobacter, Salmonella, Shigella, Yersinia and Chlamydia in reactive arthritis

- Now...occult Proteus UTI and RA
Microbes and RA

- P. mirabilis amino acid sequence resembles type XI collagen
- Isolation rates of P. mirabilis in RA patients is double that of E. coli
- Proteus isolated in 63%/50% of RA patients compared to 32%/11% controls
- Urine from RA patients have elevated levels of Proteus antibodies
RA Treatment

- Proteus is a member of the Bacteroides enterotype (associated with animal food diets)
- Prevotella enterotype (associated with plant based diets)
- Shifting from animal foods to PBD reduces risk of occult Proteus UTI
- AND reduces anti-Proteus antibodies
- PBD also increases urine lignans which are anti-microbial
PBD for RA Treatment

- 1999 randomized trial
- 13 months
  - 27 intervention
  - 26 controls
- 12/27 intervention patients with 50% reduction in symptoms (responders)
- 2/26 control “responders”
- Intervention group
  - 13 pound weight loss
  - Improved sed rate, CRP and WBC count
- After the intervention period, patients were allowed to change diet however all “responders” stayed with the diet and half of all “non-responders” as well.
Turmeric and RA

- 2012- 8 week randomized pilot
  - 45 patients/2 groups
    - Group 1: 500mg curcumin BID
    - Group 2: 500 mg curcumin and 50mg diclofenac BID
    - Group 3: 50mg diclofenac BID

- Primary endpoint reduction in disease activity and joint swelling/tenderness

- Results
  - Group 1: 44.5% improvement
  - Group 2: 44.4% improvement
  - Group 3: 42.1% improvement

- Adverse events only in diclofenac groups
Multiple Sclerosis
MS Distribution

- Most diagnosed ages 20-40
- 400,000 in US and 2.5 million globally
- Prevalence increases with distance from equator
- 57-78/100,000 below 37th parallel
- 110-140/100,000 above it
- Higher incidence in colder climates and people of Northern European descent regardless of where they live
- Women: men 2:1
1-3% chance of MS if you have a sibling or parent with MS
Monozygotic concordance rate of 30%
Roy Swank at OHSU hypothesized that the distribution might be because people in northern latitudes tend to eat more animal foods.
1952 study: Frequency of MS in Norway directly related to amount of saturated animal fat consumed.
Vitamin D and MS

- Those in northern latitudes also get less sun exposure
- MS patients have lower $1,25(\text{OH})_2\text{D}$ levels at time of relapse
- In Norway, inland MS is higher than in fishing villages.
- Oily fish may compensate for relative lack of UV exposure
Vitamin D and MS

- $\text{1,25(OH)}_2\text{D}$ moderates demyelination, remyelination, and stops oligodendrocyte apoptosis
- Upregulates genomic activity on the strongest susceptibility allele
- Homozygosity of the CYP27B1 gene causes a form of rickets.
- 3 individuals in Norway with this genetic rickets also developed MS
- Heterozygosity increases risk of MS by 4.7 times
Dairy and MS

- Molecular mimicry between butyrophilin and myelin oligodendrocyte glycoprotein
- Anti-BTN antibodies attack myelinated structures in the CNS and have been isolated in those with MS
MS Treatment

- Safe and effective treatments are elusive

- Interferon
  - Side effects
  - $30,000 per year
  - No evidence of a reduction in disability progression

- Mitoxantrone
  - NNH 8 for irreversible systolic dysfunction and 123 for therapy-related acute leukemia
Dr. Swank

- 1951- 100 patients limited to 10-15 grams of saturated animal fat per day
- 3 ½ year, 5 ½ year, 7 year, 20 year, 34 year and 50 year follow up reports
- After 34 years (1990), 95% of the patients were without progression of their disease
- Increase in fat to 25-42g/day was accompanied by increased disability and 3-fold increased risk of death to 79%
- In 2000, 15 patients identified (50 year follow up)
  - All could care for themselves independently
  - 15 could ambulate as needed; 13 truly ambulatory
Study on Vitamin D treatment in MS did not look at clinical outcomes.

High dose Vitamin D supplementation did reduce helper T cells believed to be major contributors in immunopathogenesis of MS.

Dose was 10,400 IU daily and 21% of had to stop because of adverse effects.
Type 1 Diabetes
Molecular Mimicry

Fig. 1: Diagram showing Molecular Mimicry Hypothesis. The molecular mimicry hypothesis suggest that a certain antigen (Viral / Bacterial) has a great degree of similarity with endogenous structures. Mistaken identity triggers the host immune system (autoantibodies) to attack the foreign as well as endogenous targets when infected with organism.
Genetic Factors
- alone cannot explain etiology

Environmental Factors
- Cow’s milk antigens
- Viruses
- Enterovirus
- Coxackievirus B
- Rotavirus
- Mumps
- CMV
- Congenital Rubella
MYCOBACTERIUM PARATUBERCULOSIS
HSP 65
Islet Cell and Glutamic Acid Decarboxylase Antibodies and Heat-Shock Protein 65 Responses in Children With Newly Diagnosed Insulin-Dependent Diabetes Mellitus

T Scheinin et al. Immunol Lett 49 (1-2), 123-126. 11996. more

Abstract
Islet cell antibodies (ICA) were detected in 66% and glutamic acid decarboxylase (GAD) antibodies in 64% of children (n = 47) with newly diagnosed insulin-dependent diabetes mellitus (IDDM). Fifteen percent of the patients had neither GAD nor ICA antibodies. Responses to mycobacterial heat-shock protein 65 (Hsp65) were detected in all patients. There was a significant correlation between anti-GAD antibodies and proliferation of peripheral blood mononuclear cells to Hsp65, and between ICA and antibodies to Hsp65.
Figure 5. Percentage of Operations in Which at Least One Environmental Sample Cultured Positive for MAP in 2007, by Herd Size

Percent

- Small (fewer than 100): 63.2%
- Medium (100 to 499): 75.1%
- Large (500 or more): 95.0%
- All operations: 68.1%

Herd Size (Number of Cows)
Protein chain showing amino acids in A1 and A2 beta-casein

One amino acid difference at position 67 in the protein chain
PREVENTING TYPE 1 DIABETES
autoimmune diabetes Accelerator Prevention Trial
adAPT
PBD in T1D

- Type 1’s can develop insulin resistance with a high fat diet
- PBD can reduce insulin requirements by 30-50%
- PBD can reduce risk of diabetic comorbidities
- Latent autoimmune diabetes
- Adult onset; non-obese
- Present without ketoacidosis and weight loss
- Anti-body positive
- Gradual insulin-dependence
<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 1.5</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical age of onset</td>
<td>Youth</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>Progression to insulin dependence</td>
<td>Rapid (days/weeks)</td>
<td>Latent (Months/years)</td>
<td>Slow (Years)</td>
</tr>
<tr>
<td>Presence of Autoantibodies</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Insulin dependence</td>
<td>At diagnosis</td>
<td>Within 6 years of diagnosis</td>
<td>Over time, if at all</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>No</td>
<td>Sometimes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Thank you!
References


References


References


- Rashid T, Ebringer A. Autoimmunity in rheumatic diseases is induced by microbial infections via crossreactivity or molecular mimicry. Autoimmune Dis. 2012; 2012: 539282.


References


References


- Swank MS Foundation. 2009. Dr. Roy Laver Swank.


References


