October 8th 2015, Lausanne

Nutrition – Microbiome – Immune System

Gerhard Rogler, Division of Gastroenterology and Hepatology, UniversitätsSpital Zürich
The exposome in IBD

Rogler G, Vavricka S. Exposome in IBD: Recent Insights in Environmental Factors that Influence the Onset and Course of IBD. Inflamm Bowel Dis. 2014
The role of the exposome (environment) in IBD

- Air pollution
- Diet
- Drugs
- Stress
- Infections
- Food additives
- Water pollution

Direct effects on intestinal epithelial cells, mucosal immune cells, extraintestinal cells

Indirect effects via modulation of the intestinal microbiota

Rogler G, Vavricka S. Exposome in IBD: Recent Insights in Environmental Factors that Influence the Onset and Course of IBD. Inflamm Bowel Dis. 2014


**“Environmental” factors known to play a role**

<table>
<thead>
<tr>
<th>“risk factor”</th>
<th>Disease</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D¹</td>
<td>Crohn’s disease</td>
<td>0.55 (0.30 – 1.00) (Q4 vs. Q1)</td>
</tr>
<tr>
<td>NSAR ≥ 15d/mo²</td>
<td>Crohn’s disease</td>
<td>1.59 (0.99 – 2.56) (vs. non-users)</td>
</tr>
<tr>
<td>NSAR ≥ 15d/mo²</td>
<td>Ulcerative colitis</td>
<td>1.87 (1.16 – 2.99) (vs. non-users)</td>
</tr>
<tr>
<td>Depressive Symptoms³</td>
<td>Crohn’s disease</td>
<td>2.36 (1.40 – 3.98) (vs. MHI-5 86-100)</td>
</tr>
<tr>
<td>Fibers⁴</td>
<td>Crohn’s disease</td>
<td>0.62 (0.40 – 0.95) (Q5 vs. Q1)</td>
</tr>
<tr>
<td>Oral Contraceptives⁵</td>
<td>Crohn’s disease</td>
<td>2.66 (1.52 – 4.64) (current vs. non-users)</td>
</tr>
<tr>
<td>Hormon-substitution-therapy⁶</td>
<td>Ulcerative colitis</td>
<td>1.74 (1.09 – 2.77) (current vs. non-users)</td>
</tr>
</tbody>
</table>

The evidence that diet may play a role

Observational studies

- IBD becomes more prevalent after Westernisation
- Meat and fats increase risk
- High fibre, fruits, vegetable lower risk

Animal models

- Numerous nutrients studied in rodent models
- High fat diets increase colitis severity
- PUFAs prevent / reduce colitis severity
- Amino acids eg glutamine, arginine, and tryptophan
- Plant polysaccharides and fibres

Reviewed in Richman E et al APT 2013;38:1156-1171
EEN probably affects the microbiome

Small studies

- Paediatric - 11 children
- Paediatric - 1 child
- Paediatric 6 CD, 6 healthy
- Adult 33 CD, 17 healthy

All confounded by inflammation

Diet – possible mechanisms

Unfavorable
Whole food
Red meat and fat
Iron
n-6 PUFA

n-3 PUFA

Microbiota

Metabolites
MAMPs
Direct interaction

Host M

Immune response

Shape microbiota composition
Substrate for microbiota metabolite production
Nutrients & Xenobiotics
Vitamins & Minerals

Lee D et al Gastroenterology Jan 2015
The evidence: EEN as induction therapy

- Cochrane\(^1\) review of 7 studies of EEN vs steroids for remission induction
- 352 patients (37 children)
- CDAI or PCDAI

**ITT analysis remission rates vs steroids were:**

<table>
<thead>
<tr>
<th></th>
<th>EEN</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission rate</td>
<td>49%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Available induction medicines are better

Steroids

- Induction of remission between 60-80%\(^1,2,3\)
- Well tolerated in short courses – side-effects are reversible if they occur

Anti-TNF

- Response rates 80-90\(^4,5\), remission 40-50%\(^5\)
- Well tolerated – only 10% stop therapy due to AE\(^6\)
- Safe over the longterm\(^7\)
- Can be continued as maintenance therapy

3. Summers RW et al Gastroenterology 1979;77:847-69
Effect of EEN is transient

High relapse rate on returning to normal diet

Approximately 50% within 6 months\(^1\)

Contrast this with azathioprine withdrawal – can expect 75% to remain well for at least 18 months\(^2\)

The evidence for other diets

Exclusion diet\(^1\)

- 136 patients – \(1/3\)\(^{rd}\) did not tolerate elemental diet
- The remaining 93 achieved were randomised to tapering 12 weeks steroids or an exclusion diet

<table>
<thead>
<tr>
<th></th>
<th>Exclusion diet</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median remission</td>
<td>7.5 months</td>
<td>3.8 months</td>
</tr>
<tr>
<td>Relapse rates at 2 years</td>
<td>79%</td>
<td>62%</td>
</tr>
</tbody>
</table>

**BUT**

- Remission based on clinical score
- No CRP or faecal calprotectin
- Omitted foods typically wheat, dairy

Riordan JO et al Lancet 1993;342:1131-4
Improvement of clinical symptoms in patients with IBD upon gluten free diet

Reported symptom improvements in IBD patients attempting a GFD (n=314)

“Testing a GFD in clinical practice in patients with significant intestinal symptoms, which are not solely explained by the degree of intestinal inflammation, has the potential to be a safe and highly efficient therapeutic approach”

Potential mechanisms of diet: Inflammasome-activation via nanoparticles (not just microbiota)
How much titanium dioxide (TiO2) do we eat?

<table>
<thead>
<tr>
<th>source</th>
<th>mg/person/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee whitener</td>
<td>0.52</td>
</tr>
<tr>
<td>Pastry</td>
<td>0.32</td>
</tr>
<tr>
<td>Tooth paste</td>
<td>0.30</td>
</tr>
<tr>
<td>Chewing gum</td>
<td>0.28</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.27</td>
</tr>
<tr>
<td>Marshmallows</td>
<td>0.27</td>
</tr>
<tr>
<td>others</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Total (Median)</strong></td>
<td><strong>2.5</strong></td>
</tr>
</tbody>
</table>
Summary

- **Environmental (lifestyle) factors such as diet** most likely contribute to **onset** and **disease course** of IBD (and are more important than genetic factors).
- **EEN** may be an **alternative to steroids in children**
- Results on **other diets** are conflicting
- Effects may be mediated via the **intestinal microbiota** or directly via **innate immune mechanisms** in epithelial cells.
- **Further studies are most urgently needed**
General recommendations

• **During flares:**
  – More and lighter meals
  – Avoid fruit juices (orange juice, lemon juice)
  – Avoid fibres, uncooked vegetables, food additives
  – Avoid coffee, avoid nicotine

• **During remission**
  – Don’t care about any special diet restrictions and have fun with your food!!!
  – Avoid food additives, «convenience products»
  – Eat fibres and vitamins
Thank you for your attention!
How fibers might influence epigenetics in the immune system

Dietary fibers → Microbiota → SCFAs

Epithelial and immune target cells

Gene expression

Promotion of Treg cells, tolerance

Chemokines
Cytokines
Anti-inflammatory effects/Inhibition of NF-kB
Antimicrobial peptides

Regulation of enteric nervous system and behavior through gut-brain axis
Stimulation of mucous production
Stimulation of cell growth and differentiation

Anionic diffusion
Mono carboxylate transporters
G protein
Inhibition of HDACs
The diet hypothesis

- TLR5
  - Energy absorption
- Vitamin A
  - Vitamin D
  - AHR ligands
  - Folate
- Fermentation
  - Nutrient uptake
- Vitamin A
  - Fibre
  - Fat
- Diet
- TLRs
  - Antimicrobial peptides
  - Mucins
  - IgA
- Immunity
- Gut microbiota
- Short-chain fatty acids
  - TLR and NOD ligands
  - T_{REG} cells
  - T_{H17} cells
  - ILC induction

N. Jain and W. A. Walker; Nat. Rev. Gastroenterol. Hepatol. 12, 14–25 (2015);
Diet and gut microbiota during lifetime

Mode of delivery
- Vaginal
  - Lactobacillus
  - Prevotella
  - Atopobium
- Caesarean
  - Staphylococcus
  - Corynebacterium
  - Propionibacterium spp.

Early colonizers
- Firmicutes
  - Staphylococcus
  - Streptococcus
  - Enterobacteriaceae
- Enterococcus
  - Lactobacillus
- Bifidobacterium
  - Clostridium

Enterotypes
- Bacteroides
  - Influenced by protein and animal fat content of diet
- Ruminococcus
- Prevotella
  - Influenced by carbohydrate content of diet

Birth
Infancy (0–2 years)
Adulthood

Unstable → Stable

Diet
- Breast milk
  - Bifidobacterium
  - Bacteroides
- Formula milk
  - Clostridium difficile
  - Escherichia coli
  - Bacteroides spp.
- Solid weaning foods
  - Bacteroides spp.
  - Clostridium
  - Streptococcus

Microbial eubiosis

Existence of a core microbiome at the gene level rather than at the organismal level, sharing a group of functions. Changes in core set of genes alters disease susceptibility.
How the microbiome may modulate carcinogenesis

- Dysbiosis
- Bacterium
- Translocation
- NLRs
- Inflammasomes
- TLR
- Myofibroblast
- EREG, AREG
- IL-1, TNF, IL-23
- T_{\mu}17 cell signature
- ERK, NF-\kappaB, STAT3
- Proliferation, Prevention of apoptosis
- Cancer

- Colibactin or CDT producers
- Genotoxin
- MAMP
- ROS, RNS
- Bacterial H_{2}S and ROS production
- CARCINOGEN inactivation
- Bile acid metabolism
- ROS, DCA
- Testosterone and oestrogen metabolism
- Generation of short-chain fatty acids
- Biological activation of cancer-preventing phytochemicals
- Ethanol
- Acetaldehyde
- Nitrosamine production
- CARCINOGEN activation
- Increased energy harvest in obesity

Targeting the microbiome for cancer therapy

- Antibiotics
- Prebiotics or probiotics
- Drugs targeting genotoxins
- Drugs targeting bacterially-induced inflammation
- Genetically modified microbiota with or without change to diet
- Microbiome transplantation
- Dysbiosis or increased translocation
- Carcinogenic effector mechanisms

Cancer