Nutritional interventions for the treatment of inflammatory bowel disease

JAMES D. LEWIS, MD, MSCE
DIVISION OF GASTROENTEROLOGY
CENTER FOR CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS
PERELMAN SCHOOL OF MEDICINE AT THE UNIVERSITY OF PENNSYLVANIA
Nutritional Interventions and IBD

Additions

Exclusion

Modified

Lewis JD. Inflamm Bowel Dis. 2017; 23(2):181-191
Cochrane evidence: Nutritional therapy in IBD

References:


Enteral Formulas for IBD

Meal replacement liquid formulas:
- Protein/Nitrogen source- elemental, semi-elemental, or polymeric
- Variable fat content, often including medium chain triglycerides
- Carbohydrates- predominantly glucose, fructose and sucrose
- No or minimal fiber content

Uses:
- Caloric supplement - <50% of calories from formula
- Partial enteral nutrition - ~50-60% of calories from formula
- Exclusive enteral nutrition - ≥90% of calories from formula
Cochrane reviews: Enteral nutrition for induction and maintenance of CD

Purpose

• To assess the efficacy and safety of enteral nutrition for the treatment of CD

Databases searched

• MEDLINE, EMBASE, CENTRAL, clinicaltrials.gov (July 5, 2017)

Inclusion criteria

• CD patients of all ages

Types of studies

• Randomized controlled trials
Outcomes: Enteral nutrition for induction and maintenance of remission in CD

**Primary outcomes**

**Induction**
- Clinical remission

**Maintenance**
- Clinical relapse
- Endoscopic relapse

**Secondary outcomes**

**Induction**
- Adverse events
- Serious adverse events
- Withdrawals due to adverse events

**Maintenance**
- Quality of life
- Adverse events
- Serious adverse events
- Withdrawal due to adverse events
- Anthropometric measurement
Cochrane review: Dietary interventions for IBD

Purpose
• To assess the efficacy and safety of dietary interventions for the treatment of IBD

Databases searched
• MEDLINE, EMBASE, CENTRAL, Web of Science, Clinicaltrials.gov and Cochrane IBD Specialized Trials Register (January 9, 2018)

Inclusion criteria
• IBD patients of all ages

Types of studies
• Randomized controlled trials
Cochrane review: Dietary interventions for IBD

**Primary outcome**
- Induction of clinical remission
- Maintenance of clinical remission

**Secondary outcomes**
- Clinical improvement
- Corticosteroid free remission
- Surrogate biomarkers for inflammation
- Endoscopic endpoints
- Histologic endpoints
- Health related quality of life
- Hospitalizations
- Need for surgery
- Disease progression
- Therapy escalation
- Adverse events
- Serious adverse events
- Withdrawals due to adverse events
PRISMA flow diagram

7025 records identified

6430 records after duplicates removed

6430 records screened

6373 records excluded

57 full text articles assessed

40 records excluded with reasons

17 studies included in meta-analysis
Clinical remission: Elemental vs. non-elemental enteral nutrition in CD at 10 days-6 weeks

11 RCTs: 378 participants included; GRADE: very low
Clinical remission: Enteral nutrition vs. corticosteroids in CD at 4-10 weeks

8 RCTs: 409 participants included; GRADE: very low
Clinical remission: Enteral nutrition vs. corticosteroids in CD at 4-10 weeks

8 RCTs: 409 participants included; GRADE: very low
Clinical remission: Enteral nutrition vs. corticosteroids in CD at 4-10 weeks

8 RCTs: 409 participants included; GRADE: very low
## Secondary outcomes: Induction

<table>
<thead>
<tr>
<th>Secondary outcome</th>
<th>Comparison</th>
<th>Pooled proportions</th>
<th>Pooled risk ratio (95% CI)</th>
<th>P value</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>Elemental vs. non-elemental</td>
<td>17% vs. 17%</td>
<td>RR 1.01 (0.62, 1.65)</td>
<td>P = 0.95</td>
<td>⊕⊝⊝⊝ ⊝ VERY LOW</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>Elemental vs. non-elemental</td>
<td>22% vs. 17%</td>
<td>RR 1.37 (0.83, 2.25)</td>
<td>P = 0.22</td>
<td>⊕⊝⊝⊝ ⊝ VERY LOW</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Enteral nutrition vs. corticosteroids</td>
<td>25% vs. 16%</td>
<td>RR 1.39 (0.62, 3.11)</td>
<td>P = 0.42</td>
<td>⊕⊝⊝⊝ ⊝ VERY LOW</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>Enteral nutrition vs. corticosteroids</td>
<td>23% vs. 6.4%</td>
<td>RR 2.95 (1.02, 8.48)</td>
<td>P = 0.05</td>
<td>⊕⊝⊝⊝ ⊝ VERY LOW</td>
</tr>
</tbody>
</table>
## Primary outcomes: Maintenance

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Comparison</th>
<th>Pooled proportions</th>
<th>Pooled risk ratio (95% CI)</th>
<th>No. of participants (studies)</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical relapse</td>
<td>Elemental diet vs. free diet</td>
<td>35% vs. 64%</td>
<td>RR 0.54 (0.30, 0.99)</td>
<td>51 (1 RCT)</td>
<td>⊕⊝⊝⊝ VERY LOW</td>
</tr>
<tr>
<td>Clinical relapse</td>
<td>Elemental diet versus 6-MP</td>
<td>38% vs. 23%</td>
<td>RR 1.61 (0.73, 3.53)</td>
<td>62 (1 RCT)</td>
<td>⊕⊝⊝⊝ VERY LOW</td>
</tr>
<tr>
<td>Clinical relapse</td>
<td>Non-elemental (polymeric) diet versus mesalamine</td>
<td>42% vs. 55%</td>
<td>RR 0.76 (0.49, 1.19)</td>
<td>83 (1 RCT)</td>
<td>⊕⊕⊝⊝ LOW</td>
</tr>
</tbody>
</table>
Nutritional Interventions and IBD

Lewis JD. Inflamm Bowel Dis. 2017; 23(2):181-191
### Types of diets: CD induction trials

<table>
<thead>
<tr>
<th>Diet</th>
<th>N</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination diets for 30 food components vs conventional nutritional diet</td>
<td>51</td>
<td>Dariel 2007</td>
</tr>
<tr>
<td>Low-microparticle diet vs exclusion of fibre-rich foods</td>
<td>20</td>
<td>Lomer 2001</td>
</tr>
<tr>
<td>Low-calcium, low-microparticle diet vs low-calcium, normal-microparticle vs normal-calcium, normal-microparticle</td>
<td>82</td>
<td>Lomer 2005</td>
</tr>
<tr>
<td>Restricted organic diet vs unrestricted low-fat, high-carbohydrate diet</td>
<td>14</td>
<td>Bartel 2008</td>
</tr>
<tr>
<td>High-fibre diet vs low-fibre diet</td>
<td>7</td>
<td>Brotherton 2014</td>
</tr>
<tr>
<td>Low-carbohydrate diet vs high-carbohydrate diet</td>
<td>9</td>
<td>Brandes 1981</td>
</tr>
</tbody>
</table>
Clinical remission: Intervention diet vs. control diet in CD at 4-16 weeks

6 RCTs: 185 participants; GRADE: very low
### Types of diets: CD maintenance trials

<table>
<thead>
<tr>
<th>Diet</th>
<th>N</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>High vs low red and processed meat</td>
<td>214</td>
<td>Albenberg 2018</td>
</tr>
<tr>
<td>Elemental diet with reintroduction of single food each day vs fiber-rich diet</td>
<td>20</td>
<td>Jones 1985</td>
</tr>
<tr>
<td>Elemental diet with reintroduction of single food each day + placebo tablet vs usual diet + prednisolone tablet</td>
<td>78</td>
<td>Riordan 1993</td>
</tr>
<tr>
<td>Unrefined carbs vs. refined carbs</td>
<td>352</td>
<td>Ritchie 1987</td>
</tr>
<tr>
<td>Low- vs high-carbohydrate</td>
<td>11</td>
<td>Brandes 1981</td>
</tr>
<tr>
<td>Low-carbohydrate vs. usual diet (w/ or w/out supplement)</td>
<td>204</td>
<td>Lorenz-Meyer 1996</td>
</tr>
<tr>
<td>Anti-IBD diet vs FOS supplement vs placebo (usual diet)</td>
<td>54</td>
<td>Mutlu 2016</td>
</tr>
</tbody>
</table>
Clinical relapse: Intervention diet vs. control diet in CD at 6-24 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention Diet Events</th>
<th>Total</th>
<th>Control Diet Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M.H, Random, 95% CI</th>
<th>Risk Ratio M.H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albenberg 2018</td>
<td>63</td>
<td>96</td>
<td>75</td>
<td>118</td>
<td>26.8%</td>
<td>1.03 [0.85, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Ernandes 1981</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td>1.2%</td>
<td>1.20 [0.10, 14.69]</td>
<td></td>
</tr>
<tr>
<td>Jones 1985</td>
<td>3</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>7.5%</td>
<td>0.33 [0.14, 0.80]</td>
<td></td>
</tr>
<tr>
<td>Lorenz-Meyer 1986</td>
<td>45</td>
<td>93</td>
<td>90</td>
<td>135</td>
<td>26.5%</td>
<td>0.92 [0.75, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Nduu 2016</td>
<td>0</td>
<td>15</td>
<td>10</td>
<td>36</td>
<td>1.9%</td>
<td>0.11 [0.01, 1.76]</td>
<td></td>
</tr>
<tr>
<td>Riordan 1963</td>
<td>12</td>
<td>40</td>
<td>25</td>
<td>38</td>
<td>14.5%</td>
<td>0.46 [0.27, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Ritchie 1987</td>
<td>66</td>
<td>190</td>
<td>52</td>
<td>162</td>
<td>22.7%</td>
<td>1.08 [0.80, 1.46]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 426 / 507 = 100.0%  
Risk Ratio: 0.81 [0.61, 1.07]

Heterogeneity: $\tau^2 = 0.06$, $\chi^2 = 17.14$, df = 5 ($P = 0.009$); $I^2 = 55$
Test for overall effect: $Z = 1.51$ ($P = 0.13$)

7 RCTs: 933 participants; GRADE: Low
Clinical remission: Intervention diet vs. control diet in UC at 4-6 weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention Diet</th>
<th>Control Diet</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candy 1995</td>
<td>4</td>
<td>11</td>
<td>1.63 [0.69, 3.87]</td>
</tr>
<tr>
<td>Strisciuglio 2013</td>
<td>13</td>
<td>14</td>
<td>1.16 [0.67, 1.95]</td>
</tr>
<tr>
<td>Wright 1995</td>
<td>18</td>
<td>53</td>
<td>0.825 [0.50, 1.36]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>78</strong></td>
<td><strong>49</strong></td>
<td><strong>1.51 [0.68, 3.39]</strong></td>
</tr>
</tbody>
</table>

Total events: 35, 17

Heterogeneity: Tau^2 = 0.23; Chi^2 = 4.79, df = 2 (P = 0.09); I^2 = 58%
Test for overall effect: Z = 1.01 (P = 0.31)

3 RCTs: 127 participants; GRADE: very low
Clinical relapse: Intervention diet vs. control diet in UC at 6-12 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention Diet</th>
<th>Control Diet</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhattacharya 2017</td>
<td>3</td>
<td>5</td>
<td>46.5%</td>
<td>0.50 [0.15, 1.64]</td>
</tr>
<tr>
<td>Keshteli 2016</td>
<td>5</td>
<td>4</td>
<td>53.5%</td>
<td>1.25 [0.42, 3.70]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>24</td>
<td>19</td>
<td>100.0%</td>
<td>0.82 [0.33, 2.02]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.09; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 0.44 (P = 0.66)

2 RCTs: 43 participants; GRADE: very low
Endoscopic improvement: Intervention diet vs. control diet in UC at 6 weeks

2 RCTs: 35 participants; GRADE: very low
Conclusions: Enteral nutrition in CD

- No significant difference in
  
  - Clinical remission rates:
    - elemental and non-elemental enteral feed groups at 10 days-6 weeks and 4-10 weeks
    - enteral nutrition and corticosteroids groups at 4-10 weeks

  - Clinical relapse rates:
    - any of the treatment and control groups at 6-12 months
Conclusions: Dietary interventions in IBD

- A higher clinical remission rate observed in the intervention diet compared to the control diet in CD patients at 4-6 weeks.

- No significant difference in clinical remission between the intervention and control groups in UC patients at 4-6 weeks.

- A higher endoscopic improvement rate observed in the intervention diet compared to the control diet in UC patients at 6 weeks.
Types of diets: UC trials

**UC Induction Trials**
Exclusion of foods that provoke symptoms versus usual diet (Candy 1995)
Cow’s milk protein elimination diet versus usual diet (Strisciuglio 2013)
Milk-free, low-roughage diet versus exclusion diet with ad libitum milk and milk products (Wright 1965)

**UC Maintenance Trials**
Carrageenan-free diet + placebo (dextrose) vs. carrageenan-free diet + carrageenan-containing capsules (Bhattcharayya 2017)
Alberta-based anti-inflammatory diet (anti-inflammatory diet designed to increase patients' intakes of probiotics, prebiotics, soluble fibres, and omega-3 polyunsaturated fatty acids and decrease red meat intake) vs diet based on Canada's Food Guide (Keshteli 2016)
## Secondary outcomes: Maintenance

<table>
<thead>
<tr>
<th>Secondary outcome</th>
<th>Comparison</th>
<th>Pooled proportions</th>
<th>Pooled risk ratio (95% CI)</th>
<th>No. of participants (studies)</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal due to adverse events</td>
<td>Elemental diet vs. non-elemental diet</td>
<td>32% vs. 0%</td>
<td>RR 9.75 (0.59, 159.93)</td>
<td>33 (1 RCT)</td>
<td>⊕⊝⊝⊝ VERY LOW</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Elemental diet vs. 6-MP</td>
<td>3% vs. 13%</td>
<td>RR 0.23 (0.03, 1.98)</td>
<td>62 (1 RCT)</td>
<td>⊕⊝⊝⊝ VERY LOW</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>Condition</td>
<td>Comparison</td>
<td>Pooled proportions</td>
<td>Pooled risk ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>-----------------------------</td>
<td>--------------------</td>
<td>---------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Need for surgery</td>
<td>CD</td>
<td>Intervention vs. control diet</td>
<td>4.2% vs. 8.8%</td>
<td>RR 0.50 (0.22, 1.10)</td>
<td>P = 0.09</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>UC</td>
<td>Intervention vs. control diet</td>
<td>45.5% vs. 10%</td>
<td>RR 4.55 (0.63, 32.56)</td>
<td>P = 0.13</td>
</tr>
<tr>
<td>Endoscopic improvement</td>
<td>UC</td>
<td>Intervention vs. control diet</td>
<td>68.8% vs. 15.8%</td>
<td>RR 4.09 (1.39, 12.07)</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Histologic improvement</td>
<td>UC</td>
<td>Intervention vs. control diet</td>
<td>27.3% vs. 30%</td>
<td>RR 0.91 (0.24, 3.51)</td>
<td>P = 0.89</td>
</tr>
</tbody>
</table>
Case 2
Nutritional interventions for the treatment of IBD

- 18 year old non-smoking male
- Mother is a dietitian
- Lower abdominal pain and diarrhea for 3 months
- 5 kg weight loss
- Colonoscopy showed patchy Crohn’s colitis without deep ulcers
- Patient and family have read about diet and IBD
- Can he be treated with elemental diet or other nutritional therapy?
- Do adults and children respond the same to these therapies?
- Does it make a difference for small vs. large bowel disease?