Diet as a trigger or as a therapy for IBD: Research updates – Year in review
Current dietary studies at CHOP

Lindsey Albenberg, D.O.
Background
Global Increase of IBD

Importance of environmental factors in IBD – Leading to changes in the microbiome?

Kaplan and Ng.
Present Medical Therapies for IBD

Aminosalicylates
- Decrease inflammation through inhibition of COX and lipoxygenase

Corticosteroids
- Block immune cell recruitment and regulation of NF-kappaB

Immunomodulators

Thiopurines:
- Block lymphocyte proliferation and protein/nucleotide synthesis and lead to apoptosis of activated T-lymphocytes

Methotrexate:
- Block purine and pyrimidine synthesis and anti-inflammatory effects

Biologics
- Block inflammatory cytokines (e.g. TNF-alpha and adhesion molecules)

Antibiotics
- Microbiota balance and anti-inflammatory properties

Enteral nutritional therapy
- Unknown mechanism

IBD Therapies
Diet Research Updates: Year in Review

- Impact of the environment in pediatric IBD
- General food intake patterns in patients with IBD
- Defined formula diets -- ENT
- The specific carbohydrate diet
- Fiber
Diet Research Updates: Year in Review

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Impact of Environmental and Familial Factors on Pediatric IBD

• Study which enrolled 264 children with IBD and 203 healthy children

• All patients underwent a questionnaire asking about
  – Family history of IBD and autoimmune diseases
  – Perinatal period
  – Home amenities and domestic hygiene
  – Childhood diseases and vaccination
  – Diet

Mediterranean Diet!

- Number of patients who showed a low adherence to a Mediterranean diet was higher for CD and UC cases as compared to healthy cases.
- Most striking finding in the study!

Diet Research Updates: Year in Review

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Food Intake and Adequacy in Pediatric Patients with IBD

• Study of children and adolescents with CD and UC
• Patients enrolled into the study, disease characteristics documented (thorough history and physical examination), disease activity by symptoms measured, extensive nutritional evaluation
• Nutritional evaluation – growth parameters, blood work reflecting nutritional status, dietary history

Food Intake and Adequacy in Pediatric Patients with IBD

• Results:
  – Compared with recommended daily allowance, significantly poor intake of carbohydrates, calcium, magnesium, vitamin A, vitamin E, and fiber and higher intakes of protein and iron
  – Lower intakes of calories in children with IBD compared to healthy
  – Children treated with enteral nutritional therapy had better intakes of calories, carbohydrates, all minerals, and all micronutrients

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Enteral Nutritional Therapy For Crohn’s Disease (CD)

• A therapy which has been used for almost 4 decades

• Involves the use of a specific formula as nutritional therapy (food = medicine)
  – Replacing all or the majority of daily calories with formula and excluding or limiting food

• First-line treatment for Crohn’s disease in many parts of the world with similar or even better remission rates than many medications

• Disease location possibly important

CHOP Enteral Nutritional Therapy Protocol

**Induction**
- 8-12 weeks
- 80-90% of estimated needs from formula
- 10-20% food
  - Need to be strict
  - Not all food considered equal
- NG tube/oral/combo

**Maintenance**
- Post induction to . . . ?
- Lower % calories from formula by 10-15%
  - ↓ # of days
  - ↓ volume
- Simultaneously increase % of calories from food
- Closely monitor!
How Does Enteral Nutritional Therapy Work?

• Thought #1 - Regular diet is unable to adequately supply an essential nutrient
• Thought #2 - Regular diet contains something harmful that leads to inflammation
• Thought #3 – Diet alters the gut microbes
Differences in gut microbes in children who have a long-term response to nutritional therapy

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The Specific Carbohydrate Diet

- Principle that specifically selected carbohydrates, requiring minimal digestion, are well absorbed and leave virtually none to be used for furthering microbial overgrowth in the intestine
- Exclusion diet (very restrictive)
- Mostly anecdotal evidence supporting efficacy
- Scientific literature includes only small, uncontrolled studies in children (10-12 patients)
- Concerns regarding growth and nutrition particularly in children

Clinical and Fecal Microbial Changes with Diet Therapy in Active IBD

• Study:
  – Pediatric patients with mild to moderate IBD (Crohn’s and UC)
  – Patients started on the SCD with symptoms and blood work and stool samples measured at 2, 4, 8, and 12 weeks

• Results:
  – 12 patients ages 10-17 enrolled
  – Improvement in symptoms in 8 patients
    • 2 did not improve
    • 2 could not maintain diet
  – Overall moderate decrease in CRP

Clinical and Fecal Microbial Changes with Diet Therapy in Active IBD

• Results:
  – “Dysbiosis” or abnormal microbiome at baseline which corrected in some patients after just 2 weeks of the diet
  – Stool microbiome overall looked more healthy-like at the end of the study

• Limitations:
  – Very small!
  – Baseline disease activity scores were low – patients included were not very sick
  – Missing stool sample data

SCD – CHOP Experience

• Offer providers and dieticians who have experience treating patients with SCD
• Works for some patients – NOT ALL!
• Many patients are not appropriate candidates
  – Severe disease, stricturing disease, malnutrition, picky eaters, difficulty coping
• Very strict monitoring protocol – labs, calprotectin
  – Look for response within 4-8 weeks and remission within 12 weeks and if this is not achieved – move on!
First-Ever National Study of Dietary Interventions to Treat Crohn's Disease Receives Funding

March 24, 2016
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Dietary Fiber: Helpful or Harmful?

• Efficacy of dietary fiber was first investigated over 30 years ago
  – Beneficial effects on GI tract function
  – Production of the fiber metabolites short chain fatty acids (butyrate in particular)
• Systematic review of RCT’s by Wedlake and colleagues in 2014 showed no effect of supplementation of dietary fiber in 12 studies on CD, possible weak effect in UC in 3/10 studies
• Importantly, no evidence that fiber intake should be restricted!
• Still today, most IBD patients are advised to reduce fiber consumption

Wedlake et al. Inflamm Bowel Dis 2014.
Avoidance of Fiber is Associated with Greater Risk of CD Flare in 6-Month Period

<table>
<thead>
<tr>
<th>IBD type</th>
<th>Effect</th>
<th>No. cases flare</th>
<th>Median intake (fiber g/day, whole g oz Eq/day)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
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Noteworthy Current Dietary Studies at CHOP
CEASE

Crohn disease Exclusion diet After Single medication de-Escalation

PI: Ronen Stein, MD
Aims

• Primary Aim:
  – To determine the proportion all subjects with sustained relapse-free remission 1 year after withdrawal of biological or immunomodulator therapy

• Secondary Aim:
  – To determine differences in time-to-relapse between subjects on the Crohn’s Disease Exclusion Diet (CDED) and those on an unrestricted diet after withdrawal of therapy
Crohn’s Disease Exclusion Diet

- Structured diet that reduces or eliminates exposure to:
  - Animal fats
  - Dairy products
  - Gluten
  - Packaged foods
  - Canned goods
  - Emulsifiers
Inclusion/Exclusion

• Inclusion
  – Ages 10-21
  – Normal Growth Velocity, or Tanner 5
  – Steroid-free Remission (PCDAI <10  without the height component) for at least 12 months prior to enrollment
  – Colonoscopy during the preceding 3 months with complete mucosal healing or only few apthous ulcerations located in one segment
  – Stool calprotectin <250µg/g during the preceding 3 months

• Exclusion
  – Discontinuation of biologic or immunomodulator therapy by the subject without the approval of the primary gastroenterologist.
Outcome Measures

• Main outcome measure
  – Sustained relapse-free response
    • Stool calprotectin
    • PCDAI
    • CRP
UC Diet Study

PI: Lindsey Albenberg, DO
Why the diet works

• Recent studies suggest that UC is associated with:
  – Increased mucosal sulfides, sulfate or sulfide reducing bacteria impair butyrate production, causing dysbiosis
  – Defective production of SCFA

• A dietary intervention could induce remission in UC by:
  – Reducing exposure to foods that allow sulfide reducing bacteria to thrive & foods that impair mucous layer
  – Increasing exposure to foods that enhance butyrate production
UC Diet

• 12-week diet with a step down phase at week 6
• There are allowed foods, disallowed foods, and mandatory foods
• The UC Diet excludes foods that contain
  – Sulfated proteins and thickeners
  – Sulfite as additives
  – Animal fat, red meats, processed meats
  – Emulsifiers
Pilot Study Data

• Prof. Arie Levine, MD at Wolfson Medical Center in Israel performed a pilot study in 8 patients to evaluate benefit of protocol
• 7/8 participants had improved symptoms with decreased diarrhea and bleeding
• 4/8 (50%) patients were in remission by 6 weeks
Inclusion Criteria

- Informed consent
- Established diagnosis of UC
- Age: 8-19 (inclusive)
- Mild to moderate active disease, $10 \leq \text{PUCAI} \leq 45$
- Stable medication (IMM/5ASA) use or no medication use for the past 6 weeks.
- Participant has agreed to follow the UCD for 12 weeks
Exclusion Criteria

• Any proven current infection such as positive stool culture, parasite or C. difficile within the past 4 weeks
• Antibiotic or corticosteroid use in the past 2 weeks
• Use of biologics in present or in the past
• PUCAI>45
• Acute severe UC in the previous 12 months
• Current extra intestinal manifestation of UC
• PSC or liver disease
• Pregnancy
• Known food allergy to mandatory foods in the UCD
What’s Involved?

- 3 in-person visits & 3 telephone calls
- Information sessions about the diet at baseline & at week 6 prior to start of phase 2
- Stool collection at baseline, week 6, and week 12
  - For the analysis of microbiome, metabolomics & SCFA
- Stool calprotectin at baseline, and weeks 3, 6, and 12
- Urine test at baseline and week 6
  - For analysis of metabolomics
- Rectal swab at baseline and week 6
  - For analysis of microbiome
- 24 hour diet recalls will be completed at baseline, week 6, week 24, and if a flare occurs
Thank You!