



# **Evolving Research**

Diet, the Microbiome, and  
Inflammatory Bowel Disease

# Summary of Findings from the Diet and IBD Workshop

Co-hosted by the Helmsley Charitable Trust  
and Kenneth Rainin Foundation

April 19-20, 2018

New York, NY

## Executive Summary

### Overview

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition that can affect the entire gastrointestinal tract. The cause of IBD is thought to be multifactorial, involving the interplay between genetics, the environment, the microbiome and the immune system.<sup>1,2</sup> Multiple environmental risk factors for IBD have been identified, including maternal influences on the fetus, pathogen infections, antibiotic treatment, air pollution, stress, and smoking.<sup>1,2</sup> However, imbalance of the intestinal microbiota (dysbiosis) is a major driver of IBD<sup>3</sup> and gut microbiota composition and function, gut barrier, and host immunity are largely impacted by diet.<sup>4</sup>

IBD is a global public health epidemic with millions of people affected worldwide.<sup>5</sup> The number of newly diagnosed IBD patients is rising steadily in countries with urbanization and shifts towards a "Westernized" diet. Increasing evidence indicates that food habits are implicated in disease development through disrupted intestinal homeostasis leading to decreased tolerance towards commensal bacteria and a concomitant reduction in microbial diversity.

IBD is a lifelong illness that may require indefinite treatment in many patients. Current treatment options are largely targeted at immune suppression; although effective for many patients, these systemic treatments can cause significant adverse effects and are insufficient to alter the course of the disease. Even if patients respond initially to pharmacotherapy, they may become refractory or intolerant over time. Furthermore, pharmacotherapies for IBD target the inflammatory response but do not seek to modulate the root cause of the inflammation. Thus, patients with IBD are becoming increasingly interested in non-pharmacologic approaches, including dietary interventions that can modulate the composition of the intestinal microbiota and have the potential for long-lasting effects.

The Helmsley Charitable Trust and Kenneth Rainin Foundation fund basic and clinical research with the goals of increasing understanding of the pathogenesis of IBD; developing prediction and prevention strategies; and evaluating new treatments with the aim of curing these diseases. A key topic of interest for both organizations is the role of diet and nutrition and the microbiome in preventing and treating IBD. On April 19-20, 2018, the two organizations co-hosted a workshop to review research on diet and nutrition as it relates to IBD with the following main goals:

- Discuss the current state of research in dietary interventions in IBD;
- Advance understanding of dietary interventions to improve patient outcomes and how diet contributes to the development of the disease;
- Discuss potential barriers that may impede advancement of diet and IBD research, and identify mechanisms to overcome these barriers; and
- Explore the gaps and future solutions to better understand the potential roles that the funding organizations can play to advance thinking about diet as therapy in IBD.

## Key Findings

*The following summarizes the key findings from the workshop, with an emphasis on gaps in knowledge, potential answers to address these gaps, and priorities for future research.*

### Dietary Interventions for IBD

Numerous epidemiological studies have demonstrated associations between dietary patterns or the intake of specific dietary factors and the risk of developing IBD.<sup>6</sup> In particular, dietary factors commonly found in the Western diet have been shown to adversely affect the composition of the gut microbiota as well as host barrier function and immunity, thus increasing intestinal inflammation.<sup>6</sup>

Diet, a modifiable environmental contributor to IBD, has been incorporated into current treatment options for IBD. The three principle modes of dietary interventions for IBD are: 1) use of dietary formulas in place of a normal diet, 2) whole-food diets that eliminate or restrict selected dietary components, and 3) supplementation with selected dietary components.<sup>7</sup> Dietary therapy is not effective for all patients. It can be utilized as stand-alone monotherapy or concomitant with immunosuppressive drugs.<sup>8</sup> Like drugs, future personalization of dietary therapy is an opportunity for improving efficacy.<sup>8</sup>

The most compelling evidence for the role of diet in CD is the high efficacy of exclusive enteral nutrition (EEN), which involves the exclusive use of liquid formulations as nutrition over a period of 6-8 weeks for treatment of active pediatric CD.<sup>9</sup> Studies have shown that EEN is a potent induction therapy in mild-to-moderate pediatric CD and at least as effective as corticosteroids for inducing remission and more likely to result in intestinal healing.<sup>10-12</sup> Studies evaluating the efficacy of EEN in adult CD patients have been less conclusive as compliance to EEN is more difficult for adults. Factors that hinder the

widespread use of EEN include patient non-adherence and poor understanding of the therapy's mode of action in treating CD-associated inflammation.

Because initiation of EEN poses significant challenges and maintaining EEN over long periods is not practical,<sup>6,13</sup> partial enteral nutrition (PEN) was developed to achieve the effects of EEN while allowing access to whole foods.<sup>6</sup> Several studies have shown that PEN combined with the Crohn's disease exclusion diet (CDED) is effective for inducing clinical remission in children and adults with active CD and reduces inflammatory biomarkers and enhances mucosal healing during the maintenance phase.<sup>14,15</sup>

Defined diets are whole-food dietary regimens prescribed based on an underlying theory of how food interacts with the body. Table 1 lists defined diets of greatest interest for the treatment of IBD. Presently, evidence supporting the efficacy of defined diets as adjunctive to standard of care for IBD is largely based on small observational studies. The implementation of effective dietary strategies and approaches in clinical practice has been slow and limited perhaps due to lack of experimental evidence of efficacy and mechanisms of action. Well-designed and specific nutritional interventions are urgently needed to test the safety and efficacy of these diets for treating IBD and define the precise role of each diet in the prevention and management of IBD.

**Table 1. Defined Diets for IBD**

- Autoimmune diet
- Crohn's disease exclusion diet (CDED)
- Low fermentable oligo-, di-, mono-saccharides and polyols (FODMAP) diet
- IBD anti-inflammatory diet (IBD-AID)
- Mediterranean diet
- Semi-vegetarian diet (SVD)
- Specific carbohydrate diet (SCD)

Dietary supplements, such as probiotics, prebiotics, and fish oil, have been utilized to treat established IBD and influence the microbiota of children at risk of developing IBD. Thus far, probiotics and prebiotics have been shown to have only modest effects in patients with IBD.<sup>16</sup> Maternal supplementation with probiotics appears to result in short-lived and limited changes to the infant gut microbiome.<sup>17</sup> Neonatal probiotic supplementation has been associated with both benefits and harmful effects.<sup>17,18</sup>

## Challenges in Evaluating Dietary Interventions

Evaluating whole-diet therapies in IBD presents a number of challenges. First, since most natural foods are complex and the different combinations in which these foods can be consumed are largely diverse, dietary factors and their health effects may be difficult to isolate and specify.<sup>7</sup> It is hard to capture dietary patterns and exposure to individual food ingredients. Second, due to the intermittent activity of IBD, a strong placebo response is often observed in clinical trials,<sup>19</sup> and therefore, placebo controls are important to include in the study design. However, it is difficult to design a placebo for a dietary therapy so that it is nutritionally matched to the intervention while lacking the active component being investigated. Third, there is no consensus defining the composition of dietary interventions such as a

“standard diet” for use as a reference group in randomized clinical trials.<sup>20</sup> Finally, it is difficult or nearly impossible to blind participants to the forms of whole foods that comprise their meals.<sup>21</sup>

## **Gaps in Knowledge about the Microbiome and Dietary Interventions for IBD**

There is a significant need for preclinical and clinical research to address gaps in knowledge regarding the role of the microbiome in the pathogenesis of IBD; the mechanisms of action and key components of effective dietary interventions in IBD; and the optimal use of diet to treat IBD. Below, we summarize the most pressing questions regarding these gaps in knowledge.

### ***Basic Research***

- What is a “healthy” microbiome?
- How can we more precisely measure the composition of the gut microbiota and its functional capacity and activity, and how are these changes associated with clinical outcomes?
- How does early life exposure to diet and other environmental factors affect the composition of the microbiota and, subsequently, the onset of IBD?
- Is microbial dysbiosis a cause and/or consequence of IBD?
- Which types of dietary interventions are most effective at restoring intestinal homeostasis?

### ***Clinical Research***

- What is the specific mode of action of diet in treating IBD-associated inflammation?
- What are the direct effects of diet or dietary factors on the microbiome, the intestinal mucosa, and the immune system?
- Are dietary interventions for IBD that seek to exclude or remove something “bad” (e.g., toxins) more effective than interventions that seek to add something “good” (e.g., prebiotics)?
- Can we identify biomarkers to develop disease predictive tools?
- How can patient adherence to dietary therapy be improved?
- Are there any personalized methods available to help patients make and maintain dietary lifestyle change?
- How can long-term outcomes be improved with dietary therapy?
- Are there patient subgroups or clinical disease phenotypes that are more responsive to dietary intervention?

## **Considerations and Studies to Address Gaps in Knowledge**

Below, we summarize important considerations and specific study topics recommended by panel participants for future research on the microbiome and dietary interventions in IBD.

## ***Key Considerations***

- Research on diet should account for inherent inter- and intra-individual variability and the plethora of environmental factors that may affect the composition of the gut microbiota.
- To resolve conflicting findings in rodent studies, researchers should increase the consistency of experimental protocols in terms of diet composition, treatment duration, and the type of rodent models used in these studies.
- Confirmatory studies must be performed to ensure the reproducibility of diet study outcomes.
- Well-designed, prospective, controlled dietary clinical trials are needed to demonstrate cause and effect between microbiome dysbiosis and IBD.
- Research tools should be developed to distinguish between the acute digestive effects versus systemic effects of foods. Patients can report the acute effects of foods, which reflect the digestion and absorption processes. However, the systemic effects (e.g., anti-inflammatory, inflammatory), which are more important to assessing the disease process, are less reliably self-reported by patients.
- Integrated “omics” technology can be utilized to better understand the composition of the gut microbiota and its functional capacity and activity.
- It is important to assess the timing of food intake and the response of the microbiome as well as the duration of effect (if diet is continued) after dietary change.

## ***Study Topics***

- Conduct randomized, double-blind, controlled studies of whole-diet alterations.
- Conduct studies to elucidate the mechanisms of action of dietary interventions shown to be effective in large groups of IBD patients.
- Evaluate whether manipulating the microbiome during pregnancy and/or early life with diet, dietary supplements, and precision probiotics can prevent IBD in at-risk children.
- Develop and utilize experimental models (e.g., M-SHIME, humanized gnotobiotic mice) as a platform for testing the effect of dietary ingredients on gut inflammation.
- Evaluate the effectiveness of the low FODMAP diet, a collection of foods categorized by their chemical structure, used for the management of irritable bowel syndrome (IBS) in people with inactive IBD.

## **Key Ongoing Studies**

The field is moving towards examining the mechanisms of interventions, especially their effects on the microbiome, and conducting more comparative clinical trials of dietary interventions. Below, we briefly summarize important ongoing studies in the IBD field.

- The MECONIUM (Exploring MEchanisms Of disease traNsmission In Utero through the Microbiome) study is a prospective case-control study designed to investigate the role that IBD

plays in the composition of the maternal microbiome during pregnancy and the effect on the infant's microbiome.<sup>22</sup>

- The FARMM (Food And Resulting Microbial Metabolites) study is a controlled feeding experiment among healthy volunteers with the objective of examining how different diets (the “Western” diet, EEN, and a vegan diet for two weeks) influence the gut microbiota and fecal metabolomics.<sup>23</sup>
- The GEM (Genetic Environment Microbial) Project is recruiting healthy first-degree relatives of CD patients and focuses on assessing genetic and environmental factors and the gut microbiome.<sup>24</sup> Participants are followed longitudinally to determine the risk of developing CD and factors associated with the disease.
- The PREDICTS (PRoteomic Evaluation and Discovery in an IBD Cohort of Tri-service Subjects) study is focused on identifying predictive preclinical serologic and proteomic biomarkers for CD that can be identified before disease development.<sup>25</sup>
- The “Holiday” study is a randomized, placebo-controlled study designed to determine the effect of 15 days of adjunctive non-immune suppressant therapy (combination oral antimicrobials) in modifying the gut microbiota in pediatric and adult patients with refractory CD.<sup>26</sup>
- The Multiplex Families Study aims to develop a predictive biomarker panel based on the discovery of the specific genetic, serologic, and/or microbial alterations that occur in high-risk individuals prior to the onset of IBD that can inform rational preventive or very early interceptive strategies.<sup>27</sup>
- The PRODUCE (Personalized Research on Diet in Ulcerative Colitis and Crohn’s Disease) study aims to compare the effectiveness of a strict specific carbohydrate diet (SCD) versus a modified SCD in reducing symptoms and inflammatory burden in children with IBD.
- The CD-DINE study is a 12-week randomized trial in 194 adult CD patients designed to determine whether the SCD or Mediterranean-style diet results in higher remission rates.<sup>28</sup>

## Conclusion

IBD is a chronic debilitating gastrointestinal disorder for which there is no cure. Dietary patterns are associated with incidence of IBD and have been shown to dictate microbiome composition and the integrity of the intestinal mucosal layer. Dietary interventions can therefore address the root cause of inflammation by promoting intestinal homeostasis and thus hold the potential for long-lasting therapeutic benefits for IBD patients. Diet is also the most readily modifiable of the likely environmental triggers, thereby representing an ideal therapeutic target. Conducting rigorous dietary

intervention research is challenging but not beyond the reach of the IBD community. Nonetheless, it will likely require adapting commonly used study designs to address special challenges that are unique to dietary interventions and utilizing next-generation technologies (e.g., multi-omics) to accelerate understanding of the role of the gut microbiota and diet-host-microbiota interactions in IBD. Ultimately, identification of dietary interventions that can improve the course of IBD could have immediate and long-lasting impact on the management of these diseases.

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