REVIEW ARTICLE

Implementing Personalized Dietary Interventions for Immune-Mediated Inflammatory Diseases

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Abstract

The epidemiological association between various dietary patterns and the risk for chronic diseases is reasonably well established, including those for autoimmune and immune-mediated inflammatory diseases (IMIDs). However, when population data used to develop these associations for particular groups are used to predict risk in specific individuals, other complicating factors often affect the risk assessment. Additionally, understanding which components of any given dietary pattern are responsible for or protect against the risk of a specific health/disease outcome is complicated and hotly debated. This is especially true for autoimmune disorders and IMIDs. Furthermore, when these dietary associations are tested as preventative or interventional therapies in clinical trials, the results are often equivocal or difficult to interpret. Predictably, guideline recommendations for dietary intervention (for IMIDs and other chronic diseases) are limited and are often ignored in clinical practice, an oversight that prevents patients with IMIDs from realizing lasting remission and tissue healing. Emerging data on the mechanisms connecting dietary intake with changes in the gut microbiome, intestinal permeability, and dysfunctional immune reactivity have shed light on the role of dietary intervention as adjunctive therapies for IMIDs. However, leveraging this emerging data involves personalized dietary assessments and recommendations, often requiring the services of a nutritional specialist trained to understand the complexity of food-driven systemic inflammation. This paper summarizes the published data connecting diet patterns, individual dietary assessment, and dietary interventions for specific IMIDs. When personalized and implemented with other lifestyle interventions (e.g., stress reduction, movement, etc.), nutritional interventions should be considered foundational therapy for chronic immune-mediated inflammation.

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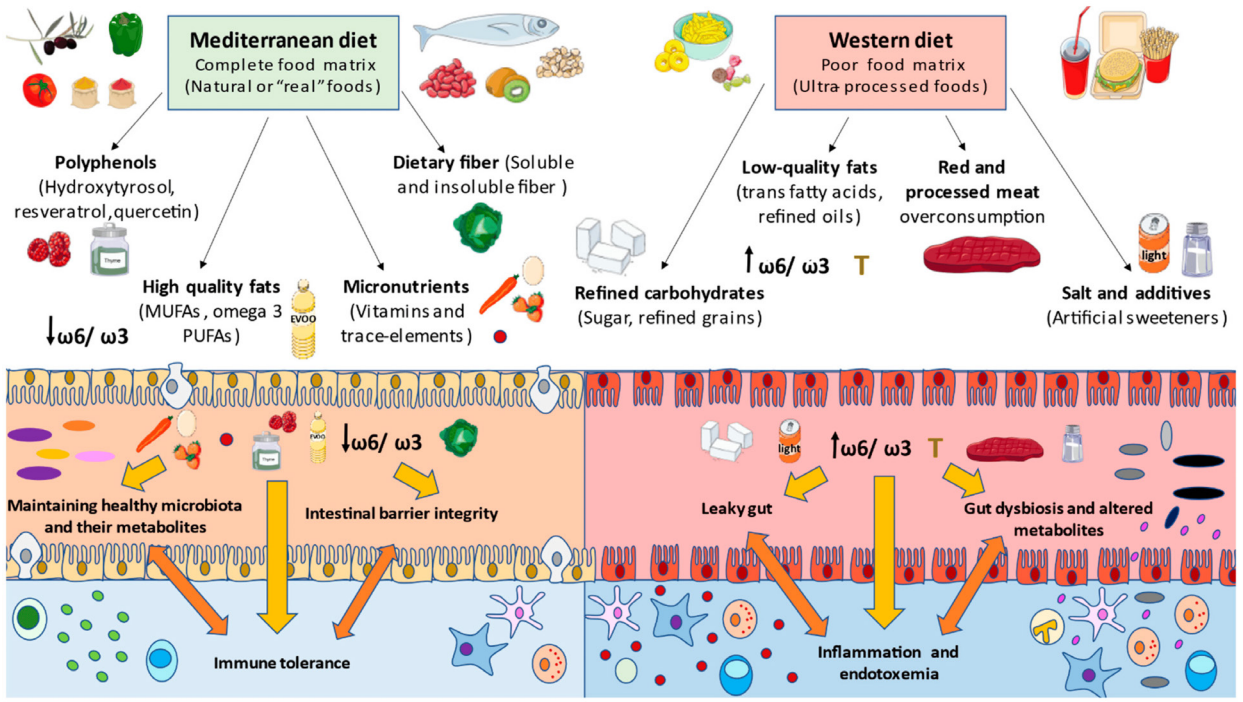
Introduction

Immune-mediated inflammatory diseases (IMIDs) describe a wide range of conditions in which dysregulated immune responses mediate destructive chronic inflammation in different tissues and organs. While often still categorized as autoimmune disorders, IMIDs are multifactorial inflammatory conditions that often lack specific or causal auto-reactive T-cells or antibodies. Nonetheless, once initiated, IMIDs are commonly mediated by core signaling components of both the innate and adaptive immune systems and can involve the activities of dendritic cells, mast cells, macrophages, and T-cells (particularly TH1 and TH17 cells). The cytokine signatures of these conditions are particularly notable, which most often involve TNF-α, IL-6, IL-1β, IL-17, IL-12, and IL-23.[1] These debilitating conditions can target a variety of common organs and tissues, such as the gut (e.g., inflammatory bowel diseases), joints (e.g., rheumatoid arthritis), and skin (e.g., psoriasis).

Growing evidence suggests that many IMIDs, especially those with common immune-signaling mediators, share common predisposing factors (i.e., antecedents) and triggers. The simple triad of genetics, environment, and immune dysregulation often describes these factors.[2] However, it is now recognized that there is a wide range of exogenous and endogenous signals derived from an individual's environment and lifestyle that act as antecedents and triggers for the risk, severity, or frequency of relapse of many IMIDS.[3] In recent years, signals that directly influence the gut-immune interface, such as those that cause gut microbiota and intestinal permeability alterations, have received the greatest attention.[4-9] A

Figure 1. Beneficial and Harmful Dietary Patterns that Affect Microbiome and Immune Signaling[28]



person's diet is one such factor that significantly influences their gut microbiota and intestinal permeability. It has been the focus of much research as a modifiable factor for IMIDs.

For decades, dietary recommendations were mostly omitted from therapeutic guidelines for complex autoimmune and immune-mediated inflammatory conditions. This was partly due to the need to understand the connection between dietary components with gut microbiome and immune system alterations and the lack of consistent evidence from epidemiological and interventional studies. Today, there is a robust understanding of the influence of many dietary components on the gut microbiota and immune system and more published clinical evidence linking specific dietary patterns and nutrients with IMID-related outcomes. These advances have resulted in several recent dietary guideline recommendations for complex immune-mediated inflammatory diseases.[10,11] Nevertheless, while these guideline recommendations help summarize the available research, they still offer minimal guidance in assisting a clinician in choosing personalized dietary therapies for such patients.[12-15] This paper will also summarize the evidence that links certain dietary patterns or specific dietary components with the prevention or intervention of common IMIDs while exploring the proposed mechanisms that explain these associations. More importantly, we highlight implementable principles for prioritizing individualized dietary recommendations from clinical trials, which often reach heterogeneous conclusions.

Mediterranean Dietary Patterns (Avoiding Western Dietary Patterns)

Epidemiological data suggest that a person's dietary choices strongly influence their gastrointestinal microbiota, inflammatory burden, and nutrient availability, all affecting their risk for a wide range of immune-mediated inflammatory conditions.[16-18] However, while epidemiological and dietary intervention studies are often heterogeneous or difficult to interpret, several important principles have emerged from these investigations. Perhaps the least controversial is that non-Western, prudent nutritional patterns (e.g., Mediterranean, Paleo, Nordic) are almost always associated with lower autoimmune and inflammatory disease burden than Western dietary patterns.[19-21]

Generally, processed and animal-derived foods create a pro-inflammatory environment as markers of diet quality. In contrast, plant-derived foods and fish create an anti-inflammatory environment.[22] Intake of dietary polyphenols, higher in the Mediterranean dietary (MedDiet) pattern than in Western dietary patterns, is likely to be a critical factor in this benefit.[23] In a large epidemiological study, individuals who adhered most closely to the traditional MedDiet had 20 percent lower c-reactive protein (CRP) levels than individuals with the least adherence.[24] Also, a small trial showed that a single Mediterranean-style meal decreased postprandial CRP levels, while a Western-style meal did not.[25] More importantly, a longer controlled study has demonstrated a beneficial effect of the MedDiet on markers of inflammation. Individuals with metabolic syndrome experienced a significant drop in levels of CRP

and other markers of inflammation after two years on a MedDiet compared to individuals on a control diet.[26] Interestingly, healthy subjects realized significant reductions in fecal calprotectin (a commonly used biomarker of gastrointestinal inflammation in IBD patients) just 4 weeks after increasing their adherence to the MedDiet.[27] As Figure 1 illustrates, diets rich in plant-based nutrients such as polyphenols, high-quality fats (MUFAs and high omega 3 PUFAs), micronutrients (vitamins and trace elements), and dietary fiber that, in an adequate and complete food matrix, create beneficial signals for maintaining a healthy gut microbiota, intestinal barrier integrity, and immune tolerance.[28] On the other hand, a Western dietary pattern of ultra-processed foods is characterized by low levels of dietary fiber or micronutrients. It contains many harmful nutritional signals, including refined carbohydrates (sugar and refined grains), low-quality fats (trans fatty acids and an excessive omega 6/omega 3 ratio due to the refined oils), salt, and unhealthy additives (mainly sweeteners). These poor food signals can prevent intestinal barrier maintenance, leading to "leaky gut," and drive gut dysbiosis and altered microbial metabolites, leading to local and systemic chronic inflammation.

The overall benefit of the MedDiet, consistent with similar prudent dietary patterns, is multifactorial. Compared to the Western diet, it is characterized by an increased intake of fresh and cooked vegetables and fresh fruits, legumes/plant proteins and whole grains, fresh fish, nuts, and olive oil, moderate intake of wine, dairy (mainly yogurt and cheese), and low consumption of red meat, refined grains, sugary and highly processed foods. Consistent with the dietary relationship of almost all other chronic and/or inflammatory conditions, increased intake of fruits and vegetables is also associated with decreased incidence of IBD.[29-31] This relationship has also been linked with increased intake of omega-3 fatty acids,[32-34] vitamin D,[35-39] and a host of phytochemicals.[40,41] Many of these nutrients have been further explored as therapeutic agents for which specific recommendations to increase consumption (often through supplementation) may be appropriate.

Not surprisingly, recent studies have reported that greater adherence to the MedDiet (using a variety of metrics) is associated with better quality of life and is inversely related to disease severity in subjects with different IMIDs. This includes Crohn's disease,[42,43] ulcerative colitis,[44] Sjogren's syndrome,[45] multiple sclerosis,[46] psoriasis,[47,48] and psoriatic arthritis,[47] though this relationship is inconsistent in rheumatoid arthritis.[50] Since the MedDiet is the dietary pattern that is best proven to reduce metabolic comorbidities in patients with immune-mediated inflammatory diseases,[51-53] and has been shown to alter the gut microbiota in IBD patients favorably,[54] this is the dietary pattern that should function as the foundation for a personalized dietary plan for patients with any IMID (modified as needed). Other prudent dietary practices such as the Nordic diet, Okinawan diet, and the so-called "Paleo" diet may have similar benefits in patients with IMIDs. However, they have not been systematically tested in clinical trials. The Wahls diet, a modified version of the Paleo diet, has successfully benefited patients with multiple sclerosis.[55] The autoimmune protocol diet (AIP), a strict form of the paleo diet, is discussed further below.

Finally, before delving into various therapeutic diets, it is essential to mention the role food processing, additives, and added sugar may play in the inflammatory process. Research has implicated many negative consequences of consuming various food additives or altered food components resulting from food processing. A recent publication compiling data from 21 countries discovered that higher intake of ultra-processed food was strongly associated with risk for IBD (hazard ratio 1.82 for >5 servings per day compared to <1 serving per day).[56] Also, consuming more than one sugar-sweetened soda increases a woman's risk of seropositive RA by 63%, compared to women consuming less than one per month.[57] While several mechanisms are proposed to explain these relationships, many involve changes in gut microbiota composition, alteration of tight junction integrity, aggravation of inflammatory processes, and the loss of immune tolerance.[58-62] It is important to understand that commercial products designed to facilitate particular diet trends (e.g., gluten-free) are often highly processed foods that may contain less-known but equally problematic food additives. Helping patients choose real (mostly unprocessed) foods is a hallmark of a diet promoting healing in all tissues.

Anti-Inflammatory Dietary Patterns

While the MedDiet is considered an anti-inflammatory diet, several other experimental dietary patterns have been designed to target inflammatory pathways and biomarkers.[63,64] They are often based upon a prudent dietary pattern (like the MedDiet) but emphasize the exclusion of foods known to create inflammatory outcomes or to exclude foods for which the patient has known reactions.[65]

To measure the potential inflammatory burden of a person's diet, researchers have developed various indices for scoring the inflammatory components from diet diaries, including the Dietary Inflammatory Index (DII) and the Empirical Dietary Inflammatory Index (EDII or EDIP).[66,67] These indices have been successfully used to predict biomarkers of inflammation and the burden of various inflammatory-mediated diseases.[68-73] In a recent study, both indices were used to measure the impact of dietary changes in participants of the Manitoba Living with IBD Study.[74] Each inflammatory index was measured at baseline and after one year. Those who decreased their inflammatory measure using the EDII saw statistically improved fecal calprotectin levels and lower IBD symptom

scores. In contrast, an increased inflammatory action using the EDII was associated with higher fecal calprotectin and symptom scores (a similar relationship was unrelated to this cohort's DII score).

Anti-inflammatory diets have been therapeutically tested in various clinical trials in patients with IBD or other IMIDs. While the diets used in these multiple trials were not identical, they follow a similar pattern whereby patients are instructed to increase the consumption of certain foods (e.g., fruits, vegetables, spices, cultured dairy, nuts, whole grains, fiber, fatty fish) and to avoid or reduce the consumption of certain foods (e.g., added sugar, red meat, highly processed and fast foods).[75] In most clinical trials, the control diet is based either on the general dietary guidelines in the country where the trial is being performed or a typical Western diet.

While most trials evaluating anti-inflammatory diets are small, and some did not find statistically significant differences, anti-inflammatory diets have shown positive clinical effects in patients with many different inflammatory conditions such as rheumatoid arthritis,[76-79] IBD,[80,81] multiple sclerosis,[82] cardiometabolic diseases,[83] and premature aging.[84,85] It is important to note that these trials did not customize the dietary recommendations for each individual nor report baseline inflammatory dietary scores for each patient.

Clinicians treating patients with immune-mediated inflammatory diseases should ensure that a full dietary assessment is completed for each patient by a trained nutritional specialist. This process should include a measure of the inflammatory burden of their diet (using a validated index, if possible) as well as a comprehensive plan to help each patient with the implementation of a customized and sustainable anti-inflammatory diet (e.g., recipes, grocery lists, training, and motivation).

Elimination Diets

Most clinical studies that attempt to use diet to induce or sustain remission in subjects with an immune-mediated inflammatory disease investigate diets that exclude particular foods or food components. These exclusion (or elimination) diets can be specifically designed for one specific condition (i.e., the Crohn's disease exclusion diet-CDED) or are applied across several different conditions (i.e., gluten-free diet). For the most part, these diets typically consist of 3 phases: induction (most restrictive), introduction or re-introduction (more foods allowed or re-challenge with foods that were specifically eliminated), and maintenance (a less stringent diet intended to be the new dietary pattern). In summarizing most of these common diets (below), it is important to point out that while specific diets "fail" to show statistical improvements when compared to control diets in some studies (i.e., comparing group A with group B), most often there are individuals who realize significant benefits in the intervention group. Therefore, the goal in personalizing a successful dietary intervention for IMIDs is not simply choosing the correct diet for each condition. Instead, it involves identifying suitable dietary recommendations for every individual patient. This task requires significant input from a trained nutritional specialist.

Gluten-Free Diets

Gluten-free diets are a vital therapeutic recommendation for individuals with celiac disease and are highly recommended for those with various levels of gluten intolerance.[86] However, Fasano et al. have proposed that gluten (specifically the protein gliadin) can initiate changes in tight junction integrity in non-celiac subjects, which increases gut permeability and triggers several non-celiac immune-mediated inflammatory conditions such as type 1 diabetes, asthma, multiple sclerosis, and inflammatory bowel disease.[87] Nevertheless, the cause/effect relationship between gluten intake and various IMIDs is still heavily debated.[88] For instance, while population studies don't show a statistically significant association between gluten intake and risk for IBD, RA, psoriasis, or psoriatic arthritis,[89,90] the incidence of non-celiac gluten sensitivity is higher in subjects with IBD, and several studies have reported that nearly 2/3 of IBD patients report subjective improvements in their symptoms when avoiding gluten.[91,92]

Investigations using gluten-free diets for non-GI immune-mediated inflammatory conditions are limited.[93] A recent report of cases (n = 4) from a hospital in Rome suggests that rheumatoid arthritis patients may see improvements in symptoms when initiating a gluten-free diet. Still, there have yet to be controlled trials to investigate this further.[94] In another study, 13 of 97 subjects with psoriasis had elevated gliadin IgA antibodies compared to 2 of 91 subjects in the control group.[95] They reported that all 13 patients were started on a strict gluten-free diet without any other modifications to their treatment for psoriasis. Improvement of psoriatic lesions was observed in all patients with positive anti-gliadin IgA antibodies. Still, the decline in the Psoriasis Area and Severity Index score and reduced pharmaceutical treatment was more pronounced in the 5 patients with strong positive anti-gliadin IgA.

All IMID patients should be screened for gluten/gliadin sensitivity and celiac disease using standard laboratory methods. Patients with celiac disease or non-celiac gluten sensitivity should be instructed to implement a healthy gluten-free diet. Subjects who maintain a gluten-free diet to maintain subjective alleviation of disease symptoms (with or without a diagnosed gluten insensitivity) should be screened for nutritional deficiencies common in those on a long-term gluten-free diet.[96,97]

Sugar Elimination or Modification Diets

Several dietary recommendations alter the types or

amounts of sugar consumed. Many of them have been investigated for their role in altering the gut microbiota, affecting gut permeability, triggering inflammatory signaling, and/or the severity of one or more immune-mediated inflammatory diseases.[98] Many of these diets have been explored for their effect on GI symptoms (similar to the gluten-free or FODMAPs recommendations), so there is more research focus related to outcomes of IBD than other IMIDs. Nonetheless, since inflammation in the gut can trigger increased gut permeability and systemic inflammation, this information may be useful for clinicians treating various autoimmune and IMID patients. Not surprisingly, diets high in simple sugar (i.e., sucrose, fructose, and high-fructose corn syrup) have been implicated as inhibiting immune system functions, increasing autoimmunity, and contributing to excessive inflammation.[99,100]

Low FODMAPs Diet

The acronym FODMAP stands for Fermentable Oligosaccharides (e.g., fructans), Disaccharides (e.g., lactose), Monosaccharides (i.e., fructose), and Polyols (e.g., sorbitol, xylitol, mannitol, etc.). These represent a heterogeneous group of short-chain carbohydrate molecules poorly absorbed along certain individuals' GI tract.[101] Consumption of FODMAPs has been associated with increased luminal distention, leading to symptoms of abdominal bloating, pain, and altered bowel habits in certain individuals. These symptoms may lead to the diagnostic signature of irritable bowel syndrome (IBS) or other functional gastrointestinal disorders.[102-104]

Essentially, the low FODMAP diet is an "elimination and re-challenge" diet, where patients identify foods in their current diet that are high in FODMAPs and replace them with alternatives low in FODMAPs.[105] The elimination portion of the diet begins with the "induction phase," where the patient adheres to a stringent and restricted diet eliminating all high FODMAP foods for 4 to 6 weeks.[106] The status of symptoms at the end of the "induction phase" determines whether or not a re-challenge phase is necessary. If an adherent patient's GI symptoms are not improved following the "induction phase," the patient should discontinue the low FODMAP diet and seek other dietary or appropriate therapies. However, if the patient experiences symptom improvement after eliminating foods high in FODMAPs, the patient is advised to follow an individualized, "step-down" food reintroduction plan to determine tolerance of certain FODMAP-containing foods. Different groups of FODMAPs (i.e., monosaccharides, polyols, oligosaccharides) may have different osmotic and fermentative potentials based largely on their molecular weight and degree/rate of absorption, resulting in heterogeneity among various FODMAP components. At the same time, there may be heterogeneity in responses to different FODMAP components or FODMAP-containing foods across individuals. The reintroduction, or re-challenge, phase aims to diversify and minimize unnecessary dietary restrictions for an individual as much as possible and restrict only to the level needed for symptomatic control.

The Low FODMAPs diet has become a standard recommendation for patients with functional bowel disorders, especially irritable bowel syndrome, and is not generally recommended as a dietary intervention for IMIDs. However, a recent meta-analysis of 27 studies (3169 subjects) reported that 25 percent of IBD patients in remission have IBS-like symptoms.[107] Additionally, survey data suggest that functional gastrointestinal disorders are more prevalent in subjects with autoimmune diseases such as psoriasis and rheumatoid arthritis.[108] Therefore, patients with IMIDs should be screened for functional bowel disorders such as IBS and given suitable therapy and dietary recommendations (including a low FODMAP diet recommendation if appropriate). Patients lacking classic symptoms of functional gastrointestinal disorders are unlikely to benefit from a low FODMAP diet.

The Specific Carbohydrate Diet (SCD)

This diet eliminates most polysaccharides and disaccharides, allowing only monosaccharides like fructose and glucose.[109] This diet is designed to prevent carbohydrate-driven bacterial fermentation, which is thought to drive inflammatory symptoms in susceptible individuals (like the FODMAPs Diet). This diet excludes lactose and a host of common grains, vegetables, and tubers but allows most fruits, meat, and nuts. While SCD has been investigated for IBD, limited studies suggest it may be more successful at reducing IBD symptoms in children than adults.[110] SCD is not generally recommended for patients with IMIDs, but it may be helpful to reach remission in some patients with IBD, especially children. The SCD is not intended to be an ongoing dietary pattern to maintain health.

Autoimmune Protocol (AIP) Elimination Diet and ITIS Diet

The autoimmune protocol diet is based on the paleo diet framework, which emphasizes the initial removal of a host of foods reported to cause flairs in IBD subjects. These foods include things like gluten, grains, legumes, nightshades, dairy, eggs, coffee, alcohol, nuts and seeds, refined sugars and oils, and food additives of all sorts. A few small clinical trials of the AIP diet have been performed in IBD patients at the Scripps Clinic in La Jolla. An uncontrolled trial in IBD patients (n = 15) given the AIP (elimination phase weeks 1-6, maintenance phase from weeks 7-11) saw improvements in disease scores, fecal calprotectin, and, when performed, endoscopy scores.[111] Follow-up studies show that these subjects experienced improved quality of life and even beneficial gene expression (i.e., anti-inflammatory, etc.) within the gut due to implementing the AIP diet.[112,113]

The ITIS diet was designed by researchers at the University of California, San Diego, as an anti-inflammatory version of the MedDiet, tailored for subjects with rheumatoid arthritis.[114] Developed in several phases to include patient feedback on its feasibility and accessibility, this diet emphasizes specific dietary components to increase (e.g., omega-3 fatty acids, daily green juice, pre-biotics, anti-inflammatory spices) and to avoid (e.g., red meat, gluten, nightshade vegetables, sugar). The ITIS diet incorporates a wide range of common features of other anti-inflammatory diets but also includes instructions on reducing inflammatory signals through cooking methods and food combinations. This diet was evaluated in a prospective, open-label pilot trial in 20 patients with rheumatoid arthritis.[115] While only implemented for two weeks, pain scores improved in subjects after the ITIS diet, as did several anti-inflammatory metabolites derived from the gut microbiota.

While a larger clinical trial still needs to be performed, these dietary approaches fit with our general recommendation to implement a prudent (MedDiet-like) approach that reduces foods known to trigger inflammatory responses. Since these diets have been published, several tools may be available to the patient to help implement these diets, which may be helpful for clinicians who still need a dedicated nutritional professional on their team.

Crohn's Disease Exclusion Diet (CDED)

As the name implies, this diet was designed specifically for patients with Crohn's disease and is mainly intended to help induce remission. It is often used with enteral nutrition (exclusive or partial).[116] The CDED is designed to reduce exposure to dietary components that could adversely affect the microbiome and intestinal barrier and combines a specific whole-food diet with partial enteral nutrition (PEN). This diet is conducted in 3 phases.[117] Phase 1 is used for remission induction during the first 6 weeks, providing 50 percent of energy in strictly determined food types and quantities. Enteral formulas supplement the remaining 50 percent. The second phase lasts for 6 weeks and allows consumption of a broader spectrum of permitted foods, which is further enriched during phase 3 (maintenance phase), which lasts ideally for 9 months and continues after that more flexibly. Several clinical trials have demonstrated that the CDED can be helpful to induce and/or maintain remission in adults and children with Crohn's disease.

Apart from enteral nutrition, the list of foods excluded in the CDED overlaps significantly with the various lists included in many other exclusion/elimination diets designed for IBD or other IMIDs. Currently, the published literature includes only Crohn's disease-related interventions using the CDED, though it is likely to benefit a broader array of patients. Another advantage of the CDED is that the list of permitted and excluded foods is readily available online.

Exclusion Diets Related to Food Allergy Testing (IgG Exclusion Diets)

Food allergies can be described as any adverse immune-mediated reaction to food components. Allergenic food components can trigger systemic reactions in susceptible individuals, though symptoms may mimic other dysfunctions and remain undiagnosed for many years. Among other proposed mechanisms, food allergens can trigger inflammation within specific immune cells along the GI tract, which leads to signals that increase intestinal permeability.[118]

While allergic reactions are characterized mainly by IgE-mediated responses, IgG antibodies against various food antigens are elicited in many non-allergic people.[119] While the implications of this phenomenon are hotly debated, clinical studies have attempted to investigate the benefit of removing foods that produce IgG antibodies from patients' diets to reduce immune-mediated symptoms. One such study performed a double-blinded randomized sham-controlled trial to examine the efficacy of an IgG4-guided exclusion diet in improving the quality of life in patients with Crohn's disease.[120] Patients with a Crohn's disease activity index (CDAI) of 80-400 had IgG4 titers tested against 16 common food types using ELISA. They were told to exclude 4 food types with the highest antibody titers for 4 weeks. The sham group excluded the 4 foods with the lowest antibody titers. Of the 145 patients screened, 96 had initial food antibody testing performed, and 76 patients completed the study. Milk, beef, pork, and eggs were the most commonly excluded food types in the true diet group. After 4 weeks, there was a notable improvement in mean scores on the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores by 3.05 points ($P < .05$) as well as a significant 41-point improvement in the Crohn's disease activity index (CDAI, $P = .009$).

While exclusion diets based on food allergy testing (IgG or another method) is a largely untested therapeutic approach, it aligns with a common theme practiced by many functional medicine practitioners (i.e., remove signals known to harm the patient). The most commonly used methods to identify foods to which the patient may be intolerant (e.g., wheat, gluten, dairy, corn, shellfish, nuts, eggs, etc.). is to include elimination and rechallenge diets. These diets can help direct a patient to avoid foods that exacerbate symptoms or trigger a relapse. It is recommended that every patient with an IMID be screened for common food allergens (minimally by elimination/rechallenge) and be instructed to limit dietary intake of those components that trigger inappropriate immune reactions.

Fasting (and Fasting-Mimicking Diets) and IMIDs

While we have primarily focused on the role of dietary components and their ability to influence disease risk and

severity in patients with IMIDs, the increasingly popular practice of fasting is getting more research attention. Though mainly investigated for its effects on weight and cardiometabolic outcomes, fasting (of various types) has more recently been studied for its effects on other body systems, including the gut microbiome and immune-related diseases.[121-123] In the past few decades, researchers have explored different ways to leverage the health benefits of calorie restriction using various methods, including extended calorie restriction, prolonged fasting, intermittent fasting, time-restricted feeding, ketogenic diets, and the fasting-mimicking diet (FMD). Prolonged fasting (greater than 72 hours) causes cells to initially utilize liver glycogen as their primary energy source before switching to a metabolic mode in which non-hepatic glucose, fat-derived ketone bodies, and free fatty acids are used for energy.[124] This process also dramatically reduces certain growth factors, particularly insulin-like growth factor 1 (IGF-1), signaling growth but inhibiting cell regeneration. Based on these and other effects of prolonged fasting, it is believed to contribute to the death of fast-growing cancer and immune cells (often associated with autoimmunity) and the stimulation of the tissue self-maintenance, which removes damaged cells and promotes new cell growth through the process known as autophagy.[125] When this fasting process is followed by nutrient availability, hemopoietic stem cells (HSCs) are activated, stimulating the regeneration of damaged tissues.

Ironically, few studies have investigated traditional fasting methods and the risk or severity of autoimmune diseases or IMIDs. Instead, recent research has focused on the fasting-mimicking diet (FMD). The FMD signals prolonged fasting in cells and tissues while providing some calories to the subject in a controlled sequence over 5 days. Many benefits have been recorded for the FMD after one "cycle" of 5 days, though many studies use 3 cycles of 5 days (i.e., 5 days of FMD followed by 25 days of a "normal" diet, repeated for 3 months). Studies of the FMD have been used in several animal and human subjects for various outcomes. However, animal models of autoimmune conditions such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and psoriasis have been a recent focus.[126-130]

L-Nutra, the ProLon® 5-day FMD program distributor, currently has 3 ongoing clinical trials in subjects with IBD and plans to introduce trials for psoriasis soon.[131]

Fasting can be an important adjunct diet-related therapy in some IMID patients. Choosing a fasting approach for their IMID-related symptoms can be incorporated into other goals for fasting (i.e., weight loss). The fasting-mimicking diet is currently being studied for its immune benefits, and early reports are promising as it relates to different IMIDs. Since the FMD is a complete protocol, it can be a simple way to initiate a "fast" and elimination diet simultaneously. However, patients must maintain a healthy anti-inflammatory diet after a 5-day FMD.

Personalizing and Prioritizing: The Role of a Nutritional Specialist

While current therapies for IMIDs focus almost exclusively on blocking the mediators of inflammation, official guidelines mostly lack serious discussions of the antecedents and triggers driving the inflammatory process. A patient's diet introduces a myriad of different compounds, many known to modulate the gut microbiome, intestinal permeability, and immune reactivity, acting as a protective or risk-inducing factor. A comprehensive approach to treating patients with IMIDS must include a significant focus on therapeutic dietary interventions, along with other lifestyle assessments and interventions.

As clinical research and practice have made very clear, a particular dietary intervention that works for one patient may differ from that for the next. Therefore, successful dietary interventions for IMIDs require a personalized and prioritized approach, which is best implemented with the help of a well-trained nutritional specialist functioning within a multi-disciplinary care team. Their skills must include creating a personalized dietary plan that is prioritized to meet the shared goals of the patient and medical care team. This includes understanding the patient's past dietary habits, exploring how past dietary changes have affected their disease journey, screening the patient for undiagnosed food reactions, and providing the necessary tools to allow the patient to implement necessary dietary modifications successfully (e.g., education, recipes, grocery lists, encouragement, etc.). While some patients will realize noticeable improvements within a few weeks of dietary change, studies suggest that dietary interventions that last longer than 3 months typically show better results than those shorter than 3 months; therefore, sustainability is a critical component of success with IMID patients.[132] Finally, the ultimate goal for clinicians employing dietary therapies for IMIDS should be to help each patient discover a healthy dietary pattern that they can maintain for a lifetime, which functions as a foundation for lifestyle management of their diagnosed condition and allows them to pursue their full health potential.

Author Disclosure Statement

TG and JW are both consultants for AndHealth, LLC. Columbus, OH.

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