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The Influence of Anti-Inflammatory Diets on the Reduction of Symptoms of Inflammatory Bowel Disease



**The Influence of Anti-Inflammatory Diets on the Reduction of Symptoms of
Inflammatory Bowel Disease**

A thesis submitted in partial satisfaction
of the requirements of the University Honors Program
of Loyola Marymount University

by

Kelly Stanton

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Bowel Disease**

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Introduction

A person's diet is a highly modifiable facet of lifestyle someone can change in order to alter their internal bodily processes. One of these processes is inflammation. While inflammation is beneficial as part of an acute immune response, it can become detrimental to a person's health if it becomes chronic. There are many dietary factors that can be examined in order to avoid or diminish chronic, unwarranted, inflammation. This paper focuses on how people can change their dietary patterns to control symptoms of Inflammatory Bowel Disease (IBD), an immune-mediated inflammatory condition that is heavily influenced by excessive inflammation in the digestive tract. Day-to-day dietary changes that can create an anti-inflammatory effect include an overall elimination technique through following The Autoimmune Protocol, limiting residue within the diet, and meeting adequate requirements of omega-3 polyunsaturated fatty acids (n-3 PUFAs).

Inflammation and its Regulation

Inflammation is a normal response within the body, as an integral part of the innate immune system. The initiation of inflammation aims to eliminate pathogens that may cause tissue damage. Inflammation is essential in the immune response as it allows for many types of immune cells, such as neutrophils, to migrate to an infected area and recognize a pathogen they need to attack. While this beneficial reaction is meant to be acute, some people can experience chronic inflammation as well. This chronic inflammation can cause tissue damage and, if left untreated, organ damage. This may seem counterintuitive due to the fact that inflammation is a mechanism of the immune system, used to protect the body, but a response is not always warranted (Bauman, 2017).

One common reason for unwanted inflammation in the body, as seen in many chronic diseases, is the formation of immune complexes. These immune complexes are constructed when multiple antibody-antigen units bind to each other and become a mesh-like network (Bauman, 2017). If these complexes are large, they can get stuck in blood vessels, and thus activate an immune response, inducing inflammation, even though there is no pathogen threatening a person's tissues. Over time, these immune complexes can cause chronic, widespread, inflammation (Bauman, 2017). This is only one of the many ways in which there is an abnormal T cell immune response stimulated within the body. There are many causes of abnormal T cell function, which typically lead to inflammation. When T cells are not regulated correctly, they begin to recognize a pathogen, or even non-pathogenic cells, as foreign, and then induce more inflammation with a positive feedback loop (Bauman, 2017). These abnormalities cause the type of inflammation that worsens chronic diseases. One chronic disease that displays a dysregulation of T cells is IBD. In IBD, the microbiome of the gut is thrown off balance and the lack of diversity of bacteria in this microbiome can lead to the misregulation of T cells (Kostic et al., 2014).

The microbiome is the collection of microorganisms such as bacteria, fungi, genetic material, or even viruses that live in and on your body (Bauman, 2017). Each individual has a unique microbiome within their gastrointestinal (GI) tract, or their gut. This microbiome can help synthesize vitamins, absorb vitamins and minerals, digest food, enhance nutrition, inhibit the growth of pathogens, prevent infection, and even keep your immune system healthy. Fermentation is carried out by the bacterial colonies that are part of this microbiome. Fermentation is the process by which microorganism such as bacteria in the gut break down foods such as carbohydrate or fiber into usable acids such as short-chain fatty acids. The

byproducts of fermentation by the gut microbiota are helpful in providing energy for epithelial cells lining the GI tract and can aid in enhancing the integrity of the epithelial barrier of the gut (Bauman, 2017). This epithelial integrity is important because it prevents any leakage of contents from the gut inside the body, which may cause an immune response led by T cells. Gut dysbiosis occurs when this microbial community is altered in a way that decreases the number and diversity of bacteria. Gut dysbiosis is associated with many chronic health conditions, one of which is IBD (Bauman, 2017).

IBD

IBD is a group of disorders that lead to the chronic inflammation of the GI tract. Two types of IBD include Chron's Disease and Ulcerative Colitis. Chron's Disease mainly affects the final portion of the small intestine but can ultimately affect any part of the GI tract. Ulcerative Colitis is defined by the long-term inflammation and formation of ulcers in the lining of the large intestine and rectum (Kostic et al., 2014). A major factor in the possible development of IBD is the microbial community of the gut. It is suggested that IBD can be due to the dysregulation of the mucosal immune system as a result of specific changes in the microbiome (Knox et al., 2019). This then causes dysbiosis in the intestinal lining, which leads to chronic inflammation. Dysbiosis in the lining of the intestines begins with a genetic abnormality that makes the host more susceptible and is followed by the ways in which the microbiome of the gut responds to its environment (Knox et al., 2019).

Until recently, IBD was thought of as an autoimmune disease because it was originally assumed that the chronic inflammation seen with this condition was due to the immune system attacking itself, but this is not actually the case (Kostic et. al., 2014). Instead, the microbiome of the gut is attacking "harmless" viruses, bacteria, or food products that pass through the GI tract,

which is causing the chronic swelling and damage to the intestines that characterize IBD. Experts now believe that IBD results from altered interactions between intestinal microbes and the mucosal immune system (Kostic et al., 2014). Because of these factors, IBD is no longer classified as an autoimmune disease. Instead, it is considered an immune-mediated inflammatory disease (Knox et al., 2019).

Immune-mediated inflammatory diseases lack any definitive etiology. They are identified by common inflammatory pathways leading to inflammation, which is triggered by a dysregulation of the normal immune response. In the case of IBD, this dysregulation is caused by dysbiosis within the gut. These diseases have been seen to occur in people who have specific genetic mutations which make them more susceptible when they have an overactive immunological response which is initiated and then later reactivated by exposure to environmental stimuli. The presence of overactive immunological responses makes these diseases similar to autoimmune diseases because the host has an overactive immune response, but they are different because the response is not to a stimulus that originates within the body, but one that comes from the environment (Knox et al., 2019).

Dietary Intake and IBD

Recent studies have shown that the rates of patients with IBD is increasing greatly over the years, suggesting that genetics and a person's immune response are not the only major factors that determine whether or not a person develops this disease (Kostic et al., 2014). Instead, environment is playing a large role in this determination, and diet is one way in which a person can change the environment and the microbiome which resides in their digestive system. Long-term dietary decisions impact the types of microorganisms that grow and flourish in a person's gut, whether they be healthy or not (Kostic et al., 2014). Because of the large environmental

impact on IBD, a person's dietary patterns can very easily influence inflammation and have a negative impact on their symptoms and reoccurrence of IBD. Luckily, a healthier and more structured diet can be a possible solution to help decrease systemic inflammation and manage, or even decrease, symptoms of IBD (Richards et al., 2016). The focus of dietary patterns used to decrease gut inflammation should be on anti-inflammatory foods. This includes, but is not limited to, foods allowed through an elimination-based diet, a focus on nutrient-dense foods, lowering the amount of residue in the diet and meeting adequate requirements of n-3 PUFAs. Nutrient dense foods contain high amounts of nutrients, such as essential vitamins and minerals, and have relatively low calories compared to other foods in the same proportions.

A major contributing factor of dietary patterns which increase systemic inflammation has to do with a person's gut microbiome. Although humans are born with very unique microbiomes, these microbiomes constantly adapt over time, and diet can play a central role in the alterations within the microbiome (Richards et al., 2016). A person's digestive tract is one of many large mucosal surface areas within the body, which means it is also home to many T cells and other immunoregulatory cells. It has been recognized that what a person puts into their body can affect the microbiome of their gut by changing the types of bacteria that may be growing there (Richards et al., 2016). The specific bacteria that grow in a person's gut can then affect the health of these mucosal layers, which can help maintain healthy function of T cells and other immunoregulatory cells.

Autoimmune Protocol Diet

The Autoimmune Protocol Diet (AIP) is a dietary protocol meant to mimic ideas behind following the "Paleolithic Diet", to eliminate any foods that do not seem to be tolerated well by the bacteria in many people's gut microbiome and may cause it to be compromised. The main

goal of the AIP is to eliminate any factors of the Western diet that cause inflammation or other immune responses and to replace them with more nutrient-dense foods that have healthier effects on our gut microbiome and body in general. While IBD is not an autoimmune disease, it is triggered by a dysregulation of the body's normal immune response and acts like an autoimmune disease of the gut.

The first part of this protocol is considered an elimination phase, in which a person cuts out many foods within their diet that may be harming their microbiome (Konijeti et al., 2017). The food groups that are eliminated during this initial phase include grains, legumes, eggs, dairy, nuts and seeds, coffee, alcohol, refined/processed sugars, nightshades, industrial seed oils, as well as food additives and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen. Nightshades are foods that may appear healthy at first but are not tolerated well by all individuals, such as tomatoes, eggplant, peppers, and more. During the elimination phase, it is essential for participants to also focus on eating nutrient-dense foods and probiotics, and to pay attention to how their foods are prepared to avoid losing nutrients. Some of the foods that are still options for people to eat once they are going through this elimination phase would be lean meats and fish, vegetables (excluding nightshades), fruits, plant-based milks such as coconut milk, fermented foods, and other foods which do not fall into the categories listed above. The second phase of this diet is a maintenance phase, when a person should continue with this new diet from the initial phase until their symptoms improve. At this point, a person moves into the reintroduction phase by slowly reinstating specific foods in stages to determine which foods or food groups are symptomatic triggers (Konijeti et al., 2017).

A study done by Konijeti et al. (2017) investigated how the AIP specifically affects IBD. Although this study only followed participants during the elimination phase (6 weeks) and the

maintenance phase, not the reintroduction phase, the results were still very informative. By the end of the 6-week elimination phase, 11 out of 15 (73%) of the participants were in remission from IBD altogether. This is a significant discovery, especially considering that the most effective IBD drug treatments only have an average of a 50% remission rate (Konijeti et al., 2017). Along with these results, there was also a reduction in fecal calprotectin (FC) and refinement in mucosal inflammation as viewed through endoscopy in patients after following this diet. FC is used as a measure to determine the number of neutrophils that travel to the intestinal mucosa, which is caused by inflammation (Konijeti et al., 2017). So, this means that, implementing this dietary change can help people with IBD alleviate some of their symptoms, and possibly even move into remission.

In 2019, a follow-up study was performed by Chandrasekaran et al. This was a randomized control trial which was performed on 9 participants with Crohn's disease, and 6 who had Ulcerative Colitis that was focused on examining the quality of life changes between participants. Like the previous study, this new trial examined participants through the 6-week elimination phase of the AIP, in which certain foods were eliminated in a staged fashion over time. It also followed participants for a 5-week maintenance phase after the eliminations, in order to assess the outcomes of the eliminations. Participants filled out the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) at baseline and weeks 3, 5, 9, and 11 to assess how the dietary changes may have improved their quality of life. The results of this study showed that in both Chron's disease and ulcerative Colitis patients, while the questionnaire scores were different between these two subgroups, the scores for each subgroup significantly improved by week 11 of the trial. Results of the improved quality of life were significant as early as week 3 of the dietary

intervention, showing how diet can not only help alleviate symptoms of such an uncomfortable disease, but also improve a patient's quality of life (Chandrasekaran et al., 2019).

The AIP diet can be followed in contrast to diets like the Western diet which include excess of certain food groups, and are specifically high in saturated fats, which have been commonly linked to increased systemic inflammation. A high-fat Western diet leads to extra fat stores and adipose tissue within the body which chronically manipulate regulatory T cells of the immune system. As explained previously, the dysregulation of these regulatory T cells can create an unwanted inflammatory response, and in this case, it creates a low-grade response. This would not typically be a problem, except in the case of diet. Consuming a Western diet is a chronic pattern that makes this inflammatory response chronic as well (Manzel et al., 2014).

Without changes in dietary habits, there is no change within the body to help with this chronically increasing inflammation. Even if a person decides to change their eating habits for a week or two, this will not be enough. The inflammation stimulated by an excessively high-fat diet stems mainly from the adipose tissue cells that form within the person's body (Manzel et al., 2014). To decrease these inflammatory responses, a person needs to change their dietary habits for an extended period of time in order to give their bodily systems time to adjust.

Low Residue Diets

One food component that has been shown to have a great effect on the microbiome and the mucosal layers of the gut is fiber. Although the body cannot digest fiber, the gut bacteria can ferment some forms of fiber, creating helpful metabolites such as short-chain fatty acids (SCFAs) (Richards et al., 2016). SCFA have anti-inflammatory effects by controlling the number of regulatory T cells and their functioning abilities within the colon. Along with direct gut health, the article written by Richards et al. (2016), explains how SCFAs can help increase the

generation of T regulatory cells via epigenetic effects. This allows immune cells to work throughout the whole body in order to have more power over autoreactive lymphocytes, which can help prevent the development of or decrease the symptoms of immune-mediated inflammatory diseases (Richards et al., 2016).

SCFAs can help keep the mucosal layer of the gut healthy. Without an adequate production of SCFA, the function of the intestinal mucosal barrier will begin to break down, making it “leaky” (Richards et al., 2016). When there is a leakage in this barrier, an immune response will be created by T cells and immunoglobulin-A (IgA) antibodies. This immune response will also create an increase in inflammation. Along with this immediate immune response, there is a greater likelihood that pathogenic bacteria will attach to the gut mucosal surface when it is not protected as well. This will also cause an inflammatory immune response (Dolan & Chang, 2017). While there is currently much controversial evidence as to whether or not leaky gut syndrome is a real diagnosis, there is evidence that shows that permeability of the intestinal lining does still occur and lead to inflammation (Fasano, 2012).

There are many different types of fiber, and it is very important for people with IBD to know which types of fiber they are eating in order to gain the desired effects. A study by Kuo (2013), compared previous clinical trials in which fermentable fibers were incorporated into the diet and inflammatory markers within the body were measured. Kuo’s review explained the previous discrepancies as to why certain studies were not showing significant results and ultimately suggested that an introduction of adequate amounts of fermentable fiber into a person’s diet decreases the number of inflammatory markers present (2013). Fermentable fibers can be found mainly in beans and legumes. The current adequate intake recommendation of fiber is between 25-38 grams per day of total fiber (Institute of Medicine, 2005). Along with

fermentable fiber, soluble fiber has also been seen to decrease inflammation. A study done by Morrison et al. in 2019, demonstrated how diets without adequate soluble fiber were shown to increase systemic inflammation and to promote a poor nutritional environment of the gut in mice. This study was performed because previous research overlooked the role of soluble fiber on different diseases. In this study, mice were transferred from a chow diet to a low-soluble fiber diet. This shift was seen to increase the systemic inflammation of the rodents, and they lost specific taxa of bacteria in the gut microbiome which were important to the environmental health of the gut (Morrison et al., 2019).

The low-residue diet focuses on digestibility of food intake and emphasizes consumption of different types of fiber. In the case of a low-residue diet, residue is an umbrella term for any type of food that is poorly digested (Hwang et al., 2014). While people automatically assume that this means fiber as a whole and attempt to cut fiber out of their diet completely, it specifically refers to insoluble fibers. Soluble and fermentable fibers are still beneficial to digestion and are recommended within a person's diet. While this is the case, many foods that have one type of fiber also have others, this is why a person following a low-residue diet should limit their insoluble fiber intake and they should try to focus on what kind of fiber is in the foods they are preparing. Studies on this diet suggest that a lower recommendation of fiber, specifically 10-15 grams per day, is more beneficial in order to avoid taking in too much insoluble fiber which can be found in foods that also contain soluble and fermentable fiber types. Beneficial soluble fibers can be found in food such as oatmeal, peeled fruits, nuts, seeds, and more (Hwang et al., 2014). Below is a chart that shows how many of the foods that are high in soluble fiber, have a large amount of insoluble fiber as well.

Table 1: Shows the amount of soluble and insoluble fiber in high fiber foods (adapted from Jackson GI Medical, 2020)

Food	Serving Size	Total Fiber (Grams)	Soluble Fiber (Grams)	Insoluble fiber (Grams)
Apple (Peeled)	1 Apple	2.40	0.70	1.70
Black Beans	1 Cup	5.30	1.40	3.90
Broccoli (Fresh Cooked)	1 Cup	4.60	2.30	2.30
Brussel Sprouts (Cooked)	1 Cup	6.40	3.90	2.50
Carrots (Raw)	1 Cup	3.30	1.60	1.70
Green Peas (Cooked)	1 Cup	8.80	2.60	6.20
Lentils	1 Cup	7.30	1.10	6.40
Lima Beans (Cooked)	1 Cup	13.20	7.00	6.20
Oatmeal	1 Cup	4.00	1.90	2.10
Soybeans (Roasted)	1 Cup	30.40	13.70	16.70
Sunflower Seeds	1 Cup	13.40	2.70	10.70
Whole Wheat	1 Slice of Bread	0.20	0.10	0.10

Omega-3 Enriched Diets

Another main element of the typical Western diet that leads to systemic inflammation is the overconsumption of saturated fatty acids (SFA). These types of fatty acids can typically be found in animal foods such as different types of meat or high-fat dairy products. As mentioned before, dietary habits have a direct effect on the microbiome within a person's gut. High-fat foods, specifically foods high in saturated fat, increases the release of lipopolysaccharides (LPS) from the gut bacteria into the bloodstream and can lead to metabolic endotoxemia. This then

causes the activation of toll-like receptor-4 (TLR4) complexes and their subsequent inflammatory pathways. This can lead to a more chronic form of inflammation, which is the type of inflammatory reaction that is seen in IBD and other chronic inflammatory diseases (Rocha et al., 2016).

One way to reduce systemic inflammation is to lower consumption of SFAs. While this can help with the problem of systemic inflammation, many people replace these fats with unhealthy, high glycemic index carbohydrates. A healthier, and even anti-inflammatory, alternative to this approach is to replace SFAs with unsaturated fatty acids. More specifically, a person should replace SFAs with n-3 PUFAs which have a very positive effect of antagonizing unnecessary systemic inflammation (Calder & Grimble, 2002).

While it is important to consume both n-6 and n-3 PUFAs, many people do not consume these products in correct proportions (Simopoulos, 2008). Most people eat many more n-6s which is most likely due to their abundance in commonly consumed foods such as nuts, seeds, and oils (Mayo Clinic, 2019). Fish and fish oils are the main sources of n-3s, which many people do not incorporate into their diets enough. In order to eat the correct proportions of n-3s to n-6s, the World Health Organization recommends that people incorporate two servings of fish into their diet each week as an adequate source of n-3s (Kris-Etherton et al., 2009). It has also been determined that n-6s compared to n-3s should be consumed in a ratio of 4:1, so the recommended amount of n-6s that a person should eat will depend on their n-3 intake (Simopoulos, 2008).

The common discrepancy between how much of each nutrient is eaten is important because n-6s increase the amount of arachidonic acid in the body, and n-3s increase eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Arachidonic acid increases a

person's eicosanoids which can help regulate the intensity and duration of inflammation during an immune response (Calder & Grimble, 2002). These eicosanoids can have many different effects, some of which can be pro-inflammatory, and others which can be immunosuppressive. In contrast to this, EPA from fish oils has been seen to competitively inhibit the oxygenation of arachidonic acid. After the inhibition, EPA-derived eicosanoids are produced instead of the eicosanoids produced by arachidonic acid. These EPA eicosanoids have anti-inflammatory effects and they can enhance immune function (Calder & Grimble, 2002).

There are two separate ways in which n-3 and n-6 PUFAs battle over whether or not an inflammatory response will be induced. These two methods are through the activation of TLRs and the formation of different types of eicosanoids. A study done by Weatherill et al. in 2005 was aimed at determining whether or not either saturated or unsaturated fatty acids alter immune responses as a result of the regulation of TLR signaling pathways and the genes they helped express within dendritic cells. Although the main aim of this study was not focused on the inflammatory effects of these fatty acids, these responses were discussed in the results. This study compares the SFA lauric acid, and the n-3 PUFA, DHA. Within this study, it was determined that lauric acid activates TLR4 and DHA was an antagonist to this activation. The activation of these TLR4s is the main mechanism of initiating an immune response within the body, and the main component of this immediate immune response is inflammation. This is why it is important to recognize that DHA fails to stimulate unhealthy receptors, but it also antagonizes their activation. By incorporating more n-3 PUFAs into the diet, a person can reduce any systemic inflammation which may be causing them harm. (Weatherill et al., 2005)

Like the study explained above, Calder and Grimble (2002) directly examined the effects of n-3 PUFA supplementation and its effects on diseases that may owe their pathogenesis to

chronic inflammation. This study focused more on the types of eicosanoids that are produced by each type of fatty acid, and how they lead to, or inhibit, inflammation. As explained in the previous section of this paper, the n-6 PUFA, arachidonic acid, is what stimulates the growth of inflammatory eicosanoids, and the n-3 PUFAs, DHA and EPA, are arachidonic acid antagonists (Calder & Grimble, 2002). A person can use this information to recognize that it is necessary to meet the recommended amount of n-3 PUFAs each week to counteract the inflammatory effects of arachidonic acid.

While dietary n-3s are mainly found in seafood, there are many people that do not incorporate any seafood into their diet. Because of this, many people have studied the effects of n-3 supplementation in order to create the correct balance of n-3s and n-6s that they are consuming. A study done by Costenbader et al. in 2019 performed a randomized clinical trial to study the effects of marine n-3 and vitamin D supplements. These trials were not able to find any definitive positive effects of either supplement on biomarkers of systemic inflammation (Costenbader et al., 2019). While this is the case, there were many flaws within this study that were recognized, and which should be reviewed.

Despite the lack of findings, it is still a high possibility that n-3 supplements can be beneficial for those who do not already include fish within their diet, and more randomized control studies must be done to determine whether or not this is the case (McKinley, 2019). There are also no known adverse health effects of these supplements which is why they are better than no source of n-3s at all (McKinley, 2019).

Conclusion:

As described above, changing a person's diet can ultimately change the way in which their immunoregulatory cells function. While decreasing inflammation in the gut is not a cure for

immune-mediated inflammatory diseases like IBD, it can greatly improve symptoms for people diagnosed with this disease. The best way to use diet as a regulatory tool is to follow the AIP, limit the consumption of poorly digested foods, and incorporate adequate n-3 PUFAS, while limiting SFAs, in their daily meals. People who change their dietary patterns in this way are able to incorporate more nutrient-dense foods and avoid foods that their body cannot tolerate. Each of these changes has its own anti-inflammatory effect, and all together these changes create a significant decrease in systemic inflammation. This can greatly improve chronic inflammation and symptoms of IBD.

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