Inflammation and Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is an idiopathic disease and includes a group of chronic, relapsing inflammatory gastrointestinal condition. The two most common in this group are Ulcerative Colitis (UC) and Crohn's Disease (CD). The distinct difference being that Crohn's can affect any part of the gastrointestinal tract, from mouth to anus, with most beginning in the terminal ileum; while Ulcerative Colitis is restricted to the colon.[1] Despite CD being first seen in 1623,[2] and Ulcerative Colitis first described in 1859[3], the exact causes of both are still a mystery. Recently, research has achieved a better understanding of the pathogenesis of this disease through advances in three areas: IBD-specific genes, environmental factors, and the immunopathology.[4] The impact of diet in all of these areas continues to be a topic of great interest in researching the causes and treatments of IBD.

One popular theory of the etiology of IBD is that the body's immune system reacts abnormally in some people mistaking bacteria, foods, and other substances as foreign. This causes a complex, sequential progression of events for protection from suspected intruders. Normally, these processes attack intruders such as viruses, harmful bacteria, and pathogens. However, in IBD, the attacks are also triggered by benign substances in the lumen of those who are genetically susceptible.[5] As a result, white blood cells accumulate in the lining of the intestine, producing chronic inflammation, which leads to ulcerations and bowel injury.[4]

To better understand, leading this cascade of events by the immune system is the production of antibodies by humoral response, acting mostly through the lymphatic system. Secondly, the cell mediated immune system is triggered and believed to play a major role in the development and relapse of IBD.[5] The cell mediated immune system protects against foreign organisms that have maneuvered to infect tissue cells. One type of white blood cells (lymphocytes) called T-cells, is part of the cell mediated immunity defense, and is actively involved in the disposal of antigens. Genetic abnormalities in IBD cause overly aggressive T-cell responses to commensal enteric bacteria.[5] T-cells cause lymphocytes to produce antibodies often activated by cytokines which include the interleukins, lymphokines, and tumor necrosis factor. Interestingly, the tumor necrosis factor (TNF) has been found at high levels in people with Crohn's disease.[6]

Whether the cause of the inflammation in IBD is the body's reaction to antigens, or that the antigens themselves are the case for the inflammation is unknown. It is known however, that the distal ileum and colon are colonized with an extremely complex microbiota that is metabolically active.[7] It is hypothesized that this commensal enteric bacteria and possibly fungi are the stimulants that provide the constant antigenic immune responses in IBD for genetically susceptible individuals.[8] And that it may be that a variety of genetic defects in either the mucosal barrier function or bacterial killing that could lead to the increased numbers of microbial antigens that overwhelm usual regulatory mechanisms in IBD. It is quite likely that microbe alterations may interact with genetic defects to cause epithelial injury of the mucosal barrier in IBD allowing damage to the intestinal wall.[8] IBD research continues to explore the immune response and it's regulation to better understand the damaging inflammatory processes of IBD.

Incidence

IBD is found in greater proportions in industrialized countries and rates are rising in developing countries.[9,11] In North America, the prevalence rates of Crohn's disease are highest for Caucasians, followed by African-Americans, Asians, and Hispanics.[9,10,12] IBD is believed to affect over 1 million people in the United States alone.[11] Crohn's disease in particular is more prevalent in urban areas and in higher socioeconomic classes, and after immergence in a region, over time it becomes more prevalent across all socioeconomic classes.[12] It is generally believed that chronic IBD occurs in genetically predisposed individuals who are exposed to unknown environmental and microbial triggers.[13] However, the genetic links provide only a partial explanation for disease development as the majority of patients with IBD have neither a family history nor a known genetic defect.[13]

Another area of recent interest is the role of obesity and inflammation in IBD. Obesity is considered a low-grade chronic inflammatory state due to increased levels of C-reactive protein (CRP)[14] and the secretion of proinflammatory cytokines by adipose tissue.[6,15] Supporting the idea that obesity and inflammation affect IBD, Florin et al[16] found that CD patients with low levels of CRP had significantly lower body mass index (BMI), compared to the group with raised

CRP levels. In addition obesity produces oxidative stress and insulin resistance, which combine to prevent the anti-inflammatory effect of insulin.[17] Finally, Ley et al[18] have shown that obese individuals have altered enteric flora, with fewer proportion of Bacteroidetes and increased butyrate-producing Firmicutes compared to lean people. The finding that butyrate levels are significantly increased in obese subjects is confounding given that levels are known to be low in IBD. Future investigations should look for any association between the increase in obesity and the rising incidence of IBD.

Environmental Impact

Research continues to explore the role of potential environmental factors in IBD related to modernization including: diet, a lack of exposure to particular microorganisms, increased stress, exposure to pollutants, and lack of Vitamin D.[19] In particular diet may be important. Dietary changes associated with the Western world include increased consumption of animal protein, fat, refined carbohydrates, and decreased consumption of whole grains and fruits and vegetables.[20] It has long been suspected that this type of diet plays a significant role in the etiology of IBD, possibly through several different mechanisms. One such mechanism could be a direct effect of specific dietary components on the epithelium and immune function; others could be nutrient-induced epigenetic modifications or alteration in the composition of the gut microflora. [20,21,27]

Specific Dietary Components

1. **Sugar**

Chapman-Kiddell et al[20] cautions accepting a relationship between sugar consumption and IBD. They found no studies that used appropriate methodology or took other risk factors into consideration (e.g. smoking). Chapman-Kiddell goes on to state that any relationship with sugar is not currently supported by epidemiology, and that interventional studies have been inconclusive. Lacking a proven mechanism to explain any such association, Chapman-Kiddell suggests that the only possible relationship between increased sugar intake and IBD may be by influencing insulin resistance and its known positive relationship to chronic inflammation.[22] However, Lee and Sartor[23] observed sucrose and fructose potentiated colitis in IL-10 deficient

mice, and demonstrated that several invasive E. coli strains that were capable of causing experimental colitis in mice grew with fructose but were incapable of metabolizing sucrose. Also protective enteric species (*Faecalibacterium prausnitzii)* did not grow with fructose, glucose, or sucrose but proliferated in the presence of maltose as a carbon source. This evidence suggests that diet could contribute to the composition of intestinal bacteria, and thus affect IBD. In summary, there is an increased growth and function of aggressive species with refined sugars, while growth of protective bacteria is promoted by complex carbohydrates such as prebiotics.

2. Fiber

Fermentable dietary fiber, also known as soluble fiber, is metabolized by bacteria present in the gastrointestinal tract to produce lactate, short-chain fatty acids (acetate, proprionate, and butyrate) and gas. Butyrate (the preferred energy substrate of GI cells) has also been shown to have anti-inflammatory effects by preventing transcription of pro-inflammatory cytokines, and it is thought to reduce colonic permeability.[24] Increasing permeability may predispose a genetically susceptible person to CD.[24] Several case-control studies have investigated the association between fiber intake and IBD however the results are conflicting. For example Lomer et al[25] found CD patients consumed less fiber. One explanation could be that people avoid high fiber foods due to the onset of symptoms such as diarrhea or discomfort. And Sakamoto et al[26] found no significant difference in fiber intakes of pre-illness diet of those with IBD. Asakura et al. agree that assessment of long- term effects of dietary habits are difficult to obtain before the development of IBD.[27] Although fiber shows a strong potential anti-inflammatory role, studies have not yet proven this in development and treatment of IBD.

3. Fat

The role of increased intake of total fat, animal fats, dietary n-6 polyunsaturated fatty acids (PUFA) and decreased intake of n-3 PUFA have been associated with a higher incidence of IBD in epidemiological studies.[28] One common example is fatty acid intake. Chronic inflammatory diseases are associated with increased production of the pro-inflammatory eicosanoids, prostaglandin E2 and leukotriene B4, both of which are derived from the n-6 fatty acid, arachidonic acid.[29] Conversely, n-3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) alter the production and release of inflammatory eicosanoid mediators, suppress the

production of inflammatory cytokines, and downregulate many genes involved in inflammation.[30] Although an intake ratio of 4:1 (n-6:n-3 PUFA) is considered optimal, the Westernized diet has ratios of 15-16:1 (n-6:n-3).[31] Interestingly, this increase of n-6 fatty acids in the Western diet has paralleled the increase of chronic and autoimmune inflammatory disorders[32] which include IBD. In addition a high-fat diet may alter the composition of the gut microflora[33,34] but well controlled case studies are inconsistent in showing a direct correlation with IBD. Thus a Western-style diet, high in n-6 PUFA and saturated fatty acids, could potentially trigger the onset of inflammation in genetically-predisposed individuals.

4. Protein

Western-style diets have a high amount of meat, cheese, milk, fish, nuts, and eggs as the major sources of protein. A recent prospective study by Jantchou[35] involving over 60,000 women, demonstrated an association between high animal protein intakes and increased risk of developing IBD. When large quantities are consumed, a proportion of heme and amino acids can reach the colon where they can be metabolized by the resident microflora.[36] This can result in the production of a number of possibly toxic end products, including hydrogen sulfide, phenolic compounds, amines and ammonia.[36] Christl[37] demonstrated that increased levels of hydrogen sulfide are associated with UC.

Another mechanism by which animal protein may trigger inflammation is through an effect on intestinal energy metabolism. Chronic intestinal inflammation such as that in IBD, is characterized by energy-deficiency with alterations in oxidative metabolism seen in epithelial cells and ER stress in enterocytes, mucus-producing goblet cells, and definsin-secreating cells.[13,32] Dietary iron has been shown to induce ER-associated stress responses and produce inflammation in genetically predisposed mice, while feeding an iron-deficient diet completely prevented the development of inflammation.[38] Overall there appears to be accumulating evidence of a relationship between increased protein intake and an increased incidence of IBD as seen through the induction of ER-stress and/or alteration in gut microbial metabolism.

5. Pre- and Probiotics

Prebiotics are dietary carbohydrates that are usually nondigestable and stimulate the growth and metabolic activity of beneficial bacteria present in the GI tract. This stimulation of protective commensal bacteria may prevent intestinal inflammation. Specifically, commensal species such as Bifidobacterium may enhance production of short chain fatty acids, decrease stool pH (which inhibits growth of detrimental bacteria), and increase the water holding capacity of the stool. [8,39] However, there are limited human studies using prebiotics in treatment of IBD. Fructose-oligosaccharides including inulin, have demonstrated protective activity in experimental colitis.[39,40] Lindsay found an apparent clinical benefit to the use of fructo-oligosaccharide in active Crohn's disease.[41]

Probiotics (beneficial bacteria) have shown some potential in prevention of relapse and possibly treatment of mild to moderately active UC but no significant benefit was found in CD.[8,39,42] However, Gionchetti[43] found dramatic improvement in preventing relapse of pouchitis treating with a combination of 8 different probiotic species. Sartor contends that there is a need for large, multicenter, double blind, placebo controlled trials for treatment of active UC and Crohn's disease with probiotics to best clarify its role in IBD.[8] Sartor also states that the difficulty in studying these patients is that individual responses to prebiotics and probiotics differ, and this may have obscured the results in groups of heterogeneous patients.[8] The hope is that an optimal mix of probiotics, and/or prebiotics will be determined by dietary regulation. This could potentially be the best physiological and least toxic approach to treating IBD for long-term use.

Summary

Currently there seems to be insufficient evidence to support a direct relationship between diet and IBD. However, there is some evidence to suggest that specific dietary components and obesity have a proinflammatory effect, either directly or by effects on gastrointestinal bacteria. Perhaps links between diet and IBD can be found in genetically susceptible individuals if future research focuses on the whole diet prior to development of the disease; and if links can be recognized between diet and the microbiota of susceptible individuals with "proinflammatory" eating habits. It appears that the key to prevention and treatment will lie in the progress of

genetics and gut microflora research in identifying those individuals who are susceptible and discovering their individual pre-programmed responses to specific dietary components and treatments.

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