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Inflammatory Bowel Disease, Etiological Factors and Role of Diet and Environment

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Abstract: **Inflammatory bowel disease (IBD) has been an international health care problem with a sustained increasing incidence. It includes two significant kinds, Crohn's disease (CD) and ulcerative colitis (UC), which are distinct chronic bowel-relapsing inflammatory conditions. The aim of this review was to discuss and overview the roles of environment and diet in altering inflammatory bowel disease (IBD), also to review the etiological factors that contribute in IBD from different aspects. Electronic comprehensive search was performed through medical databases; PubMed/ MIDLINE, Embase, and science-direct, for relevant articles discussing the pathogenesis and etiology of inflammatory bowel disease (IBD), as well as studies showing the roles of environment and diet in the pathogenesis of IBD, search was to identified studies that were published through past period to December,2016, in English and containing only human subjects. The key factors responsible for IBD consist of hereditary parts, environmental elements, microbial flora and immune reactions. It is tough to dispute the common belief that IBD emerges from an extremely intricate interaction among genetic and environmental elements, dysregulated immune reactions and changes of the microbiome, and that none of these factors alone is likely to trigger the disease. Numerous patient-targeted dietary suggestions from the internet and specified diets parallel those of irritable bowel syndrome and functional food poisonings.**

Keywords: **IBD, Crohn's disease, ulcerative colitis.**

1. INTRODUCTION

Inflammatory bowel disease (IBD) has been an international health care problem with a sustained increasing incidence [(1)]. It includes two significant kinds, Crohn's disease (CD) and ulcerative colitis (UC), which are distinct chronic bowel-relapsing inflammatory conditions. CD can cause transmural inflammation and impact any part of the gastrointestinal tract (most commonly, the terminal ileum or the perianal area) in a non-continuous type. Unlike UC, CD is commonly related to complications such as abscesses, strictures and fistulas. In contrast, UC is typified by mucosal inflammation and limited to the colon [(2)]. The etiology of IBD stays mainly unknown, recent research study indicated that the person's hereditary susceptibility, external environment, intestinal microbial plants and immune actions are all involved and functionally integrated in the pathogenesis of IBD [(3,4)].

The recognition of hereditary determinants has supplied insight into the pathogenesis of IBD but have actually not totally discussed disease pathogenesis. This is highlighted by a Swedish twin research study [(5)], which demonstrated a more powerful genetics consider CD over UC among monozygotic twins, with a concurrence rate of 58% for CD and only 6% for UC. Incomplete gene penetrance recommends that extra factors affect disease pathogenesis [(6)]. Additionally, genetic susceptibility does not describe the rise in occurrence of IBD observed in established and, now, in establishing nations [(7)]. Inflammatory Bowel Disease (IBD) is hypothesized to result from an environmental trigger in a genetically vulnerable person. The incidence of both Crohn's disease (CD) and ulcerative colitis (UC) are rising in Europe and North America, as well as nations where IBD was formerly thought to be unusual (e.g., China, South Korea, Puerto Rico) [(8)]. Fast shifts in the public health of IBD point to an environmental trigger to IBD. The spread of the "western" diet plan, high in fat and protein but low in veggies and fruits, has actually been proposed as a possible description of the boost in IBD incidence [(9)]. The bowel lumen is continuously exposed to many antigens, including the food that we consume and the huge population of organisms that compose the gut microbiome. There countless proposed systems through which diet might

affect the incidence of IBD, consisting of direct dietary antigens, modifying the gut microbiome, and affecting intestinal permeability [10]. IBD was primarily acknowledged in westernized countries following the rise of the commercial revolution. The incidence of IBD considerably increased throughout the 20th century [11]. IBD is most widespread in industrialized countries such as Canada, the United States and Western Europe [11,12]. The occurrence of IBD in these developed nations is as high as 20 and 24 cases per 100,000 person-years for CD and UC, respectively [12]. Several studies have actually explored the relationship between IBD and environment; nevertheless, these studies have actually not entirely elucidated the association between the environment and IBD [13].

The aim of this review was to discuss and overview the roles of environment and diet in altering inflammatory bowel disease (IBD), also to review the etiological factors that contribute in IBD from different aspects.

2. METHODOLOGY

Electronic comprehensive search was performed through medical databases; PubMed/ MIDLINE, Embase, and science-direct, for relevant articles discussing the pathogenesis and etiology of inflammatory bowel disease (IBD), as well as studies showing the roles of environment and diet in the pathogenesis of IBD, search was to identified studies that were published through past period to December,2016, in English and containing only human subjects.

3. RESULTS

Familial clustering of cases and twin studies have actually established a role for hereditary factors, which are likely to play a more popular function in Crohn's disease than in ulcerative colitis [14]. The observation that cases of both these diseases can take place within the exact same family suggests that some of the genes may be common to both conditions. As with other complex congenital diseases, inflammatory bowel disease requires the interaction of genetic and non-genetic factors. Modifications in diet, antibiotic usage, and intestinal colonization (e.g., the elimination of intestinal helminths) have most likely added to the increased occurrence of inflammatory bowel disease throughout the past century [15,16].

- ***Genetics factor behind IBD:***

Recent studies have brought the number of IBD-associated gene loci to 163, which 110 are related to both diseases, 30 CD specific and 23 UC specific [17]. Studies of gene loci shared by UC and CD may offer brand-new way to find their typical pathogenesis. The era of modern IBD hereditary research began in 2001 with the discovery of NOD2 (nucleotide-binding oligomerization domaincontaining, the first vulnerability gene for CD [18]. The NOD2 gene codes for a protein that was originally referred to as an intracellular receptor recognizing the muramyl dipeptide (MDP), a saved concept present in peptidoglycan from both Gram-positive and -negative germs [19]. MDP stimulation induces autophagy which manages bacterial replication and antigen presentation [20,21], and modulates both inherent and adaptive immune actions [22]. NOD2 participates in distinct MDP-independent pathways such as the regulation of the T-cell response [23]. The association in between CD and NOD2 has currently been duplicated at the genome-wide significance level (24). Genetic analyses have revealed an essential function for autophagy in immune actions in IBD, and reported 2 autophagy-related genes named ATG16L1 and IRGM [25]. Autophagy is associated with intracellular homeostasis, adding to the degradation and recycling of cytosolic contents and organelles, as well as to the resistance against infection and removal of intracellular microorganisms [26]. ATG16L1 is vital for all types of autophagy, and the coding mutation T300A is associated with an increased risk of CD. IRGM comes from the p47 immunity-related GTPase family. CD-associated polymorphisms in IRGM lead to lowered protein expression. Epithelial cells and dendritic cells including ATG16L1 and NOD2 variants show flaws in anti-bacterial autophagy [21,27]. With the widespread use of GWAS and SNPs, a considerable association between IBD and the IL23R gene has just recently been described [28]. The IL23R gene encodes a subunit of the receptor for the pro-inflammatory cytokine interleukin (IL)-23, a peptide associated with the generation of Th17 cells. The Th17 and IL-23 path is well established in the pathogenesis of IBD, with vulnerability gene loci IL23R, IL12B, JAK2, and STAT3 having been recognized in both UC and CD [29]. Versions in IL12B, which encodes the p40 subunit of IL-12 and IL-23, have actually been associated with IBD and other immune conditions. Defects in the function of IL-10 have likewise been related to CD and UC [30].

Current progress in the genetics of IBD holds numerous essential messages in regard to the underlying mechanism of the disease. On one hand, the broadening variety of susceptibility gene loci explained in IBD suggests that hereditary influences are vital components of the disease pathogenesis; while on the other hand, explainable vulnerability loci found

so far represent just 20%-25% of the heritability discovered in those research studies. This is not just real for IBD, however likewise real for many other polygenetic diseases, and the phenomenon has actually been called "the secret of missing heritability of typical qualities" or "hereditary vacuum" [31].

- ***The Inflammatory Response in IBD:***

The intestinal lamina propria contains a complex population of immune cells that stabilize the requirement for immune tolerance of luminal microbiota with the have to resist pathogens, the extreme entry of luminal microbiota, or both (**Figure 1**) [2]. The hallmark of active inflammatory bowel disease is a pronounced infiltration into the lamina propria of inherent immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells) and adaptive immune cells (B cells and T cells). Increased numbers and activation of these cells in the intestinal mucosa raise local levels of tumor necrosis factor α (TNF-α), interleukin-1β, interferon-γ, and cytokines of the interleukin-23 - Th17 pathway (**Figure 2**) [2].

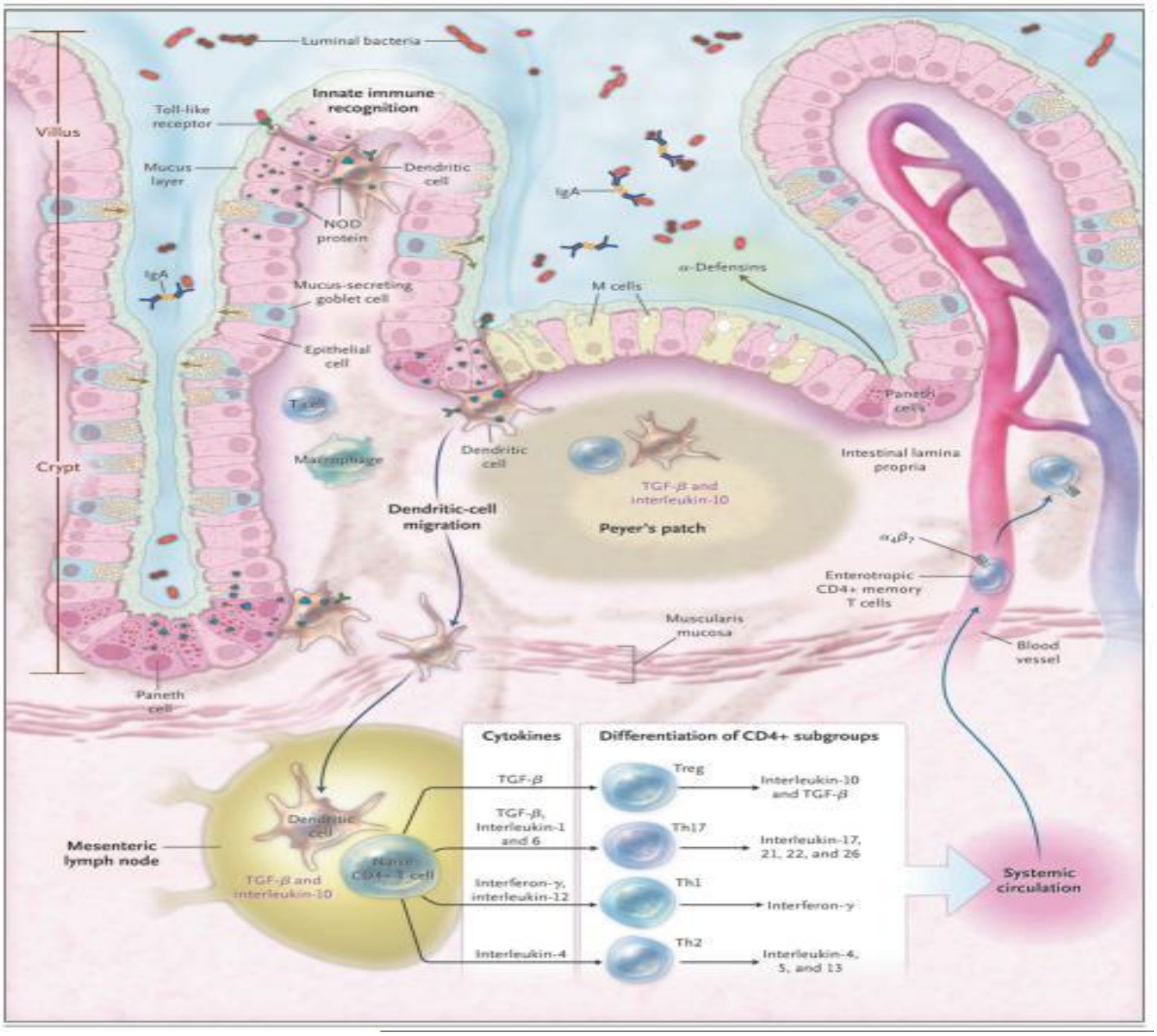

Figure1: The Intestinal Immune System

In the healthy state, the goblet cells secrete a layer of mucus that limits exposure of the intestinal epithelial cells to bacteria. Both the secretion of antimicrobial peptides (e.g., *α*-defensins) by Paneth cells and the production of immunoglobulin A (IgA) provide additional protection from luminal microbiota. Innate microbial sensing by epithelial cells, dendritic cells, and macrophages is mediated through pattern-recognition receptors such as toll-like receptors and nucleotide oligomerization domain (NOD) proteins. [2]

The initial immune response to intestinal microbiota is firmly managed, and this policy determines whether immune tolerance or a defensive inflammatory action ensues. Disruption of the balance of these reactions can lead to inflammatory bowel disease: in mouse designs, perturbation of the proteins vital to immune function can prompt intestinal inflammation [2,3].

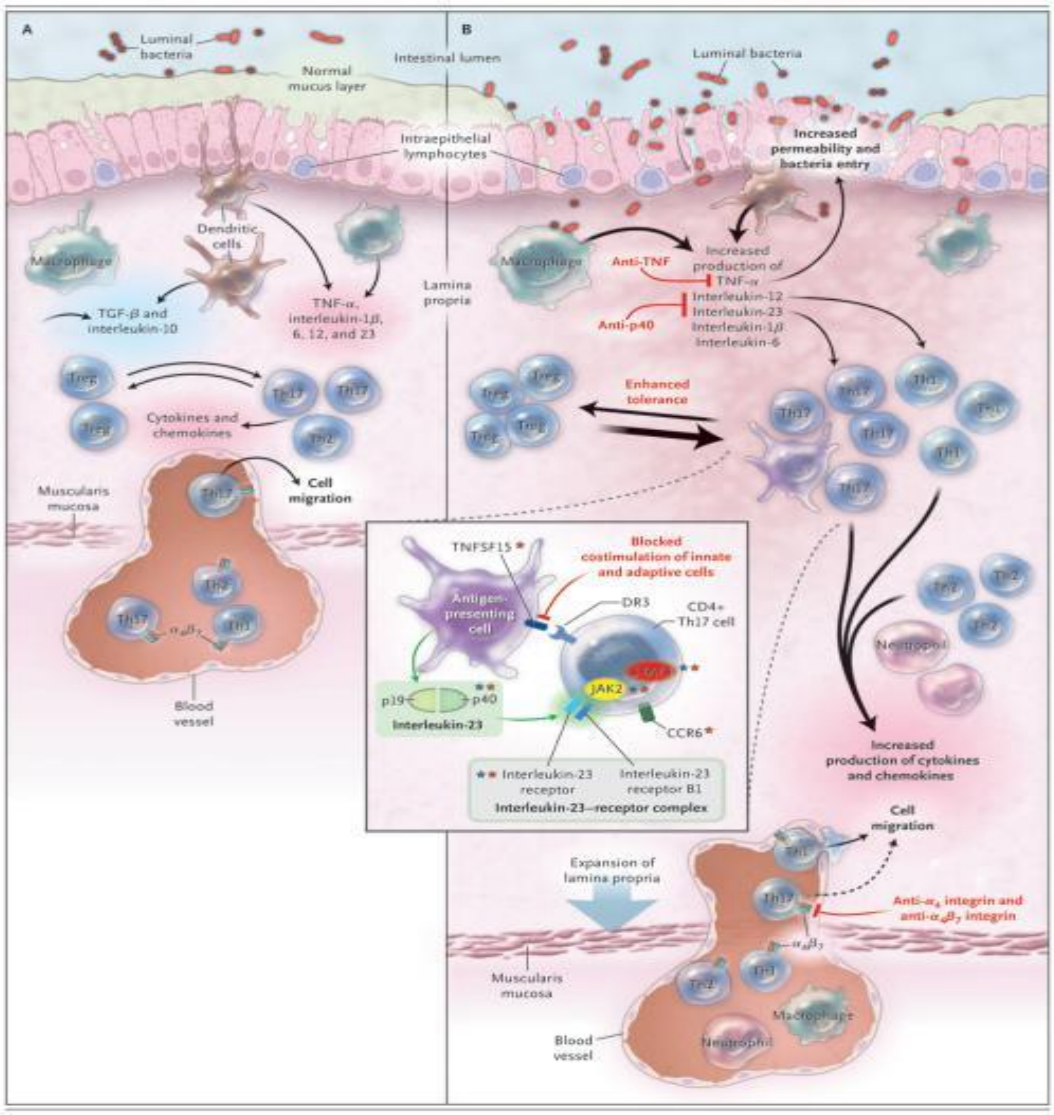

Figure 2: The Intestinal Immune System in Health and Disease [(2)]

With the acknowledgment of T-cells as central effector cells and their soluble conciliators as key modulators of resistance, the focus of immune examination in IBD moved to T assistant (Th) cell subsets and the soluble arbitrators they produce. A large number of cytokine problems have actually been described, consisting of pro-inflammatory and immune-regulatory particles [(32)]. In CD, intestinal CD4+ T cells produce big amounts of INF-γ and display significant overexpression of the Th1-cell-specific transcription factor, T-bet [(33)], while mucosal macrophages produce large amounts of IL-12 and IL-18 [(34)]. Additionally, CD mucosal T-cells are resistant to apoptosis and cycle faster than control cells [(35)].

- ***Microbial Factors as etiology of IBD:***

It is possible that classical infectious agents are the reason for IBD, but present evidence supporting this hypothesis is rather weak. Throughout the years, several microbes, such as Listeria monocytogenes, Chlamydia tracomatis, Escherichia coli, Cytomegalovirus, Saccharomyces cerevisiae, in addition to others, have been proposed as having an etiologic function. In particular, Mycobacterium paratuberculosis as the agent of CD has received and continues to get significant attention. This bacterium is the reason for Johne's disease, a persistent granulomatous ileitis in ruminants that carefully resembles CD. M. paratuberculosis was at first separated from a few CD tissues [(36)], however follow up research studies attempting to validate its existence by histological assessment, tries to culture it from tissue homogenates, search for its genome in intestinal tissues with highly specific probes, and evaluation of serum antibodies have all yielded contrasting or inconclusive outcomes. Furthermore, regulated trials have actually cannot show a helpful impact of antituberculous treatment in CD patients [(37)]. One of the last germs to be linked to CD is an adherent-invasive pressure of E coli which is particularly associated with ileal CD [(37)], but its prospective etiological function, if any, stays uncertain.

Commensal bacteria

In contrast to the decreasing evidence that CD or UC are contagious diseases, proof continues to install that the indigenous commensal plants of the gut is the target of the immune reaction in IBD [38]. A big body of information from animal designs of IBD indicates that the normal enteric plants is needed to establish experimental colitis. In fact, gut inflammation just develops in animals kept in a traditional however not a germ-free environment [39], allegedly because an immune reaction directed against enteric bacteria is essential to disease pathogenesis [40]. Thus, the paradigm "no bacteria, no colitis" was developed to underscore the central function of the intestinal microbiota in IBD pathogenesis. This paradigm is supported by a range of medical observations in IBD patients. There is an increased number of bacteria in close contact with the mucosa in IBD patients [41]; IBD lesions take place preferentially in sectors with the highest concentrations of bacteria (the ileo-cecal valve and the colon); surgical diversion of the fecal stream prevents reappearance of CD whereas repair of the fecal flow causes disease reoccurrence [42]; modulation of the enteric plants with probiotics and prescription antibiotics attenuates inflammation. In addition, pouchitis establishes in a significant proportion of UC patients, and is associated with a dysbiosis brought on by the contact of the once near sterile small bowel mucosa with an abundant colon-like plants repopulating the pouch soon after proctocolectomy [43].

Helicobacter pylori as most disastrous microbial for IBD:

H pylori, a pathogen involved in peptic ulcer disease, is a germ that is associated with larger family size, multiple siblings and poor sanitary conditions [44]. A meta-analysis [45] reported that CD and UC are adversely related to H pylori. H pylori increases the expression of T cell regulatory genes, such as Foxp3, resulting in an anti-inflammatory response [45]. H pylori might not be causally associated to IBD, but instead is a proxy marker of the 'health hypothesis'. Decreased colonization of H pylori in IBD patients may be secondary to more frequent antibiotic usage before the diagnosis of IBD or a consequence of enhanced childhood hygienic living conditions [46].

- ***Roles of Environment in altering IBD:***

There is no doubt that environmental factors play an important role in the pathogenesis of IBD. A a great deal of environmental factors are thought about risk factors for IBD, including smoking cigarettes, diet, drugs, location, social stress, and psychological aspect [47]. Amongst them, smoking remains the most extensively studied and duplicated environmental prompter for IBD. Given that the first explained inverse association between UC and smoking in 1982, subsequent research studies have actually confirmed the protective effect of heavy cigarette smoking on the development of UC with a lower rate of relapse [48,49,50]. Contrary to its effect on UC, smoking cigarettes increases the risk of CD and is associated with a greater rate of postoperative disease [51].

Conventional conception for vitamin D's function is focused in calcium metabolism and bone health. Nowadays, there has been increasing acknowledgment of the immunologic function of vitamin D [52]. Recent literature suggests that the role of vitamin D is numerous and connected with diverse diseases including IBD. Leslie et al [53] found that vitamin D shortage had been common in diagnosed IBD patients and pointed out that low vitamin D had actually added to the increased risk of IBD. In mouse models, vitamin D deficiency is connected with an increased vulnerability to dextran sodium sulfate-induced colitis and 1,25(OH)2D3 supplements ameliorates the seriousness of intestinal inflammation [54].

The effect of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) in the gastrointestinal system is well recognized. However, limited high quality evidence is available to support the notion that aspirin and NSAIDs have an impact in triggering beginning or relapse of IBD. Ananthakrishnan et al [55] discovered no association between the dosage, duration, or frequency of aspirin usage and the risk for CD or UC; but the high dose, prolonged using period, and regular use of NSAIDs had been connected with an increased risk of CD and UC. A current research study has actually found that making use of antibiotics is an essential environmental factor, influencing the risk of IBD through their result on the microbiome. Antibiotic use within the very first year of life is more typical amongst pediatric IBD cases compared to controls [56].

Recent ecological and epidemiologic evidence recommends that air pollution may contribute to the risk of CD and UC. The rising incidence of CD and UC in developing nations parallels the development of industrialization [57]. Raised air pollution is related to an augment in distributing polymorphonuclear leukocytes and plasma cytokines [58,59]. Kaplan et al [60] utilizing The Health Improvement Network Database in the United Kingdom, discovered that high levels of NO2 and SO2 correlate with the increased risk of CD and UC. In another research study, overall pollutant emission has actually

been linked to increased rates of hospitalizations for both CD and UC, recommending that ambient air contamination may likewise influence these established diseases [61].

- ***Roles of Diet in IBD:***

Various dietary components have been proposed to increase the risk of establishing or worsening symptoms of IBD One of the very first dietary components connected with establishing IBD was intake of sugar and improved carbohydrates [62,63]. Nevertheless, an environmental study in North America, Europe and Japan cannot reveal an association between refined sugar consumption and CD incidence rates [64]. There correspond associations in between both fat and protein composition in the diet plan with the development of IBD in both prospective and environmental friend research studies [65,66]. Dietary fiber consumption has been associated with a lower risk of establishing CD, but not UC (HR 0.59; 95% CI 0.39-- 0.90) [67].

2 research studies of patients who underwent ileocolonic resection supply the greatest evidence for the function of intestinal contents on the course of CD. Both research studies demonstrated that reoccurrence of inflammation after ileal resection depends on exposure of the neo-terminal ileum to the fecal contents. Inflammation recurred within 8 days of exposure to the luminal contents [68,69]. However, the fecal stream is a complex mix of bacteria, other microbes, absorbed food content, and the metabolic products of food digestion of food elements by the host and microbiota. This makes it really challenging to recognize the parts of the luminal material that drives the underlying inflammation. Furthermore, these components are not independent of each other [69].

There are surprisingly couple of observational research studies examining the association of diet with the nature of IBD. Jowett et al. performed a prospective study of patients with ulcerative colitis (UC). Jowett observed that patients who reported higher levels of meat, eggs, protein and alcohol intake were most likely to have a regression of UC [70]. Significantly, the association was much more powerful for red and processed meats than for other meats and there was no association with fish consumption. Jowett hypothesized that these dietary patterns led to higher intestinal concentration of sulfate which in turn led to disease regression. Another research study discovered a connection between sulfite consumption and endoscopic activity in UC [70].

Dietary intervention to change the course of IBD

In CD, exclusive enteral nutrition with elemental, semi-elemental, and specified formula diets has actually been commonly studied for induction of remission and is thought about first line therapy in Europe [70,71]. Special enteral nutritional therapy does not act through immunosuppression, but it has actually been shown to induce mucosal recovery and lengthen clinical remission of CD [72]. The functionality of preserving exclusive enteral dietary treatment over long periods of time is skeptical. In head-to-head randomized medical trials, the degree of hydrolysis of proteins does not appear to impact the response rate with special enteral nutrition therapy [73]. In general, action rates to enteral treatment surpass 80% among children with CD. For maintenance of remission, a diet plan in which half of the everyday calories were from an essential supplement led to a nearly 50% reduction in CD regression rates compared with a routine diet plan [74]. Some proof suggests that response rates are higher among those with little bowel disease. Exclusive enteral nutrition has actually not been effective for UC [75]. The factor for this is uncertain, however raises interesting hypotheses about the prospective system of action of exclusive enteral treatment.

Several small trials of diet plan restriction using routine food have likewise demonstrated enhanced disease activity and extended time to relapse [76,77,78]. In a recent unrestrained trial, food specific IgG4 levels were used to select which foods to omit instead of omitting nearly all foods and gradually adding back selected foods [79]. Eggs and beef were the most common foods with high IgG4 antibody levels and were therefore left out by the greatest variety of patients. The 29 patients on the exemption diet experienced a considerable decrease in signs based on a modified Crohn's Disease Activity Index and decrease in the ESR as compared with pretreatment levels. The major restriction of this study was the absence of a control group. In another small study (n=22), Chiba et al. demonstrated supremacy of the semi-vegetarian versus an omnivorous diet to preserve scientific remission over 2 years (94% vs. 33%) [80]. This research study included patients with medically or surgically caused remission who received a lacto-ova-vegetarian diet in hospital. After discharge, the semi-vegetarian diet plan permitted fish when weekly and meat once every 2 weeks. Eggs were permitted without constraint. It ought to be noted that this was not a randomized trial but rather allowed patients to choose whether or not to advance the diet after discharge [80].

Other dietary intervention studies have actually not recommended a benefit. Omega-3 fat supplements have been evaluated and were not effective in preventing CD relapse in 2 large placebo-controlled trials [81]. One of the largest dietary trials (n=352) compared recommendations for a diet high in refined carbs to one high in unrefined carbohydrates and low in sugar amongst patients with CD. Although there were distinctions in sugar and fiber consumption between the study hall, rates of clinical degeneration were not statistically various [82].

4. CONCLUSION

There is no doubt that an unmatched progress in our understanding of IBD pathogenesis has been achieved during the past couple of years. The key factors responsible for IBD consist of hereditary parts, environmental elements, microbial flora and immune reactions. It is tough to dispute the common belief that IBD emerges from an extremely intricate interaction among genetic and environmental elements, dysregulated immune reactions and changes of the microbiome, and that none of these factors alone is likely to trigger the disease. Numerous patient-targeted dietary suggestions from the internet and specified diets parallel those of irritable bowel syndrome and functional food poisonings. The existing information do not support these suggestions as a means of reduction of intestinal mucosal inflammation, the anecdotal reaction reported by patients to these dietary limitations might highlight a practical part of GI symptoms amongst patients with IBD.

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