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The Impact of Diet changes on the outcome of Inflammatory Bowel Disease: A systematic review

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Abstract:
Introduction: Inflammatory bowel disease consists of two clinical subtypes: Crohn's disease and ulcerative colitis, a pathology of the gastrointestinal tract indicated mainly by chronic inflammation of gastrointestinal mucosa. Diet is considered a potential modifiable factor influencing the disease's progression and patient quality of life. Understanding the role of dietary changes can provide insights into non-pharmacological interventions for IBD management.
Purpose: This systematic review aims to evaluate the impact of dietary modifications on the outcomes of patients with IBD, focusing on symptom management, disease activity, and quality of life.
Methodology: We conducted a comprehensive search of all literature with the keywords "diet", "inflammatory bowel disease", "Crohn's disease", and "ulcerative colitis" in databases such as PubMed, Scopus, and Science Direct Library. A total of 64908 articles were screened, with 9 studies meeting our inclusion criteria. The review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
Results/Findings: Our review indicates that certain dietary interventions, and practices as mentioned in the research articles chosen show promise in reducing disease activity, and improving symptoms, and quality of life for patients. The 9 studies also highlighted the beneficial effects of adhering to a FODMAP diet recommended for IBD.
Conclusion: Dietary changes significantly impact the outcomes of IBD, particularly in reducing symptoms and enhancing the quality of life. Tailored dietary interventions could serve as a complementary approach alongside conventional therapies. Further research is required to establish standardized dietary guidelines for IBD management.

Keywords: Diet, Inflammatory bowel disease, Crohn's disease, and Ulcerative colitis

Introduction-

Inflammatory Bowel Disease (IBD) refers to conditions marked by chronic inflammation in the digestive tract. Types of IBD include Ulcerative Colitis, which causes inflammation and ulcers in the lining of the large intestine and rectum, and Crohn's Disease, which involves inflammation that can penetrate deeper layers of the digestive tract. While Crohn's Disease most commonly affects the small intestine, it can also impact the large intestine and, less frequently, the upper gastrointestinal tract. [1].

The exact cause of IBD remains unknown. However certain aggravating factors include diet, stress, immune system malfunction, several gene mutations and family history of IBD [2]. Risk factors for this disease comprise of non-modifiable factors such as old age and white race to modifiable factors such as cigarette smoking and non-steroidal anti-inflammatory medications [3].

The clinical manifestations such as diarrhoea, fatigue, abdominal pain, cramping, blood in stool, decreased appetite and weight loss are generally seen [4].
Complications include colon cancer, skin and eye inflammation, primary sclerosing cholangitis, blood clots and severe dehydration [5].

The diagnosis of IBD is made using imaging techniques such as Computer Tomography and Magnetic Resonance Imaging as well as procedures such as colonoscopy and capsule endoscopy [6].
Treatment covers medications such as anti-inflammatory drugs (mesalamine), immune system suppressors (methotrexate) and antibiotics (ciprofloxacin) [7].

1) Materials and methods-

This systematic review was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).The PRISMA 2020 diagram is attached.

2.1. Search Strategy

The aim of the systematic search was to identify the association of diet in inflammatory bowel disease. The search was restricted to long term and short-term randomized control

trials in which analysis was carried out and was published between 1 January 2019 and 1 February 2024. The comprehensive search was executed within the electronic databases PubMed, Scopus and Science direct. Publications evaluating the association of diet in inflammatory bowel disease were identified using the terms “Diet”, “Inflammatory bowel disease”, “Crohn’s disease”, “Ulcerative colitis”.

2.2. Selection of Studies

The selection of studies was conducted independently by two reviewers (S.S. and B.V.) and then discussed. Both reviewers screened all identified records by title, abstract, and full text, following a standardized procedure. Conflict of Interest was resolved by a third reviewer (S.S.S).

2.3. Eligibility criteria

We considered only randomized control trials. Observational studies, reviews, guides, case reports and handbooks were not included. The study population was restricted to adults between the age of 18-65. Papers written in the last 5 years (2019-2024), Studies looking at solely diet as an intervention, observing a change in the symptoms and those written in English were only considered. Animal studies, pediatric and geriatric population were not considered.

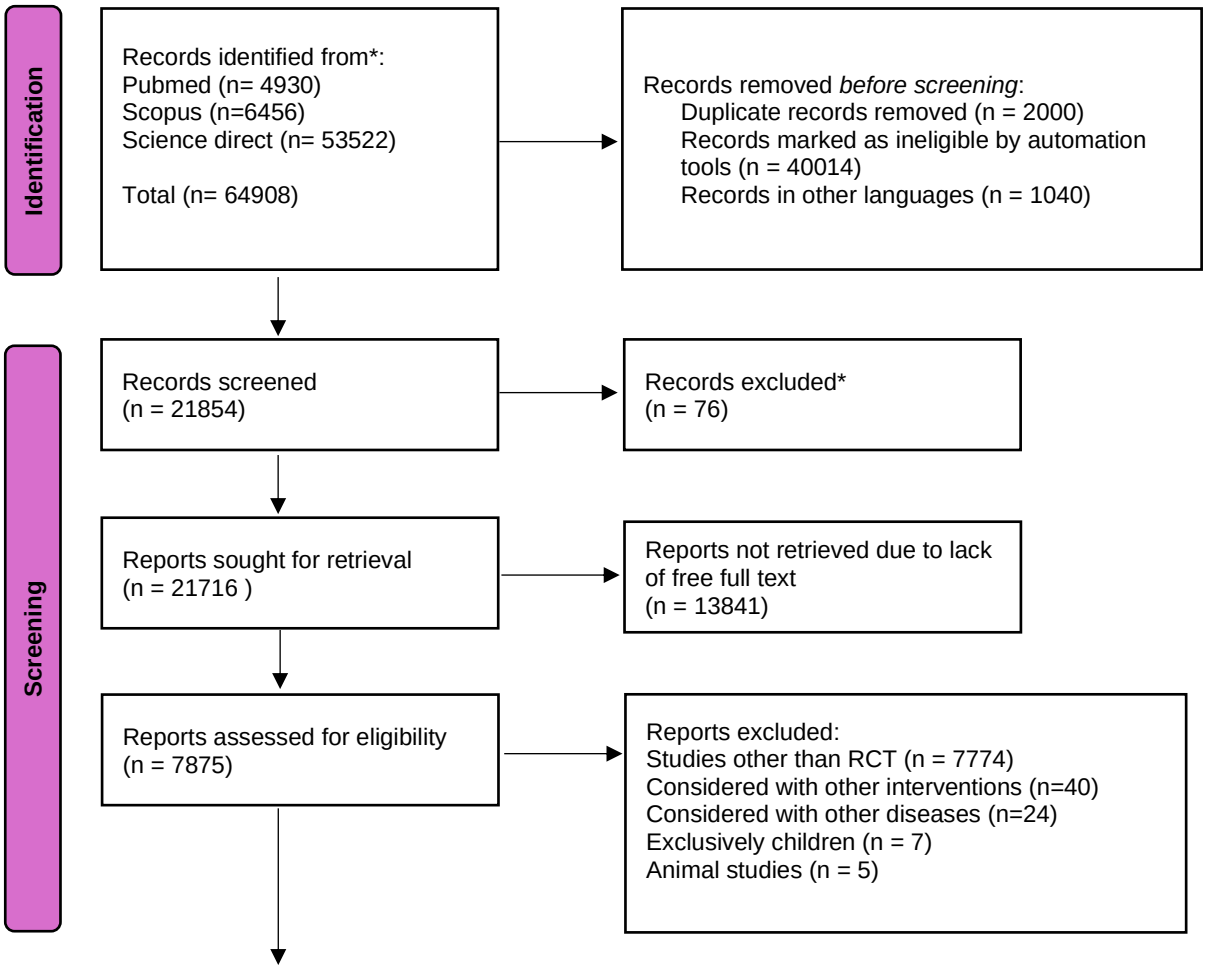
2.4. Data extraction and Risk of Bias Assessment

Data were extracted from all studies that met the inclusion criteria based on a previously established framework. We contacted authors for additional data or clarification when necessary. The risk of bias for each outcome was independently assessed by two reviewers (S.S. and B.V.) using the WHO's risk of bias assessment tool for systematic reviews [8]. For each of the six domains, a risk level of low, moderate, or high was assigned. Following recommendations, these dimensions were evaluated separately, and no overall score was calculated. All studies, regardless of their bias rating, were included in the systematic review. Any discrepancies were resolved through discussion.

3) Results-

3.1. Comprehensive literature search

Figure 1 illustrates the selection process for all records obtained from the literature search. A grand total of 64,908 records were screened, of which 4930 articles were from PubMed, 6456 from Scopus and 53522 articles from Science Direct. Off these, 2000 records were removed after being found duplicated, 40014 records being marked ineligible by the automation tools, while 1040 articles had to be rejected due to non-availability of English versions. From the remaining 21854 studies,13841 were excluded due to inability in acquiring the full text. 7875 reports were assessed for eligibility, since our systematic review focusses on RCT, 7774 directly became ineligible for review, as 12 studies were done on children and animal those studies were excluded due to non-relevance to the topic. 24 studies were in concurrence with other diseases, in 40 studies the investigators had opted to sought for other investigations and hence those articles were beyond the scope of this study. After applying the required filters, screening articles a total of 9 articles were considered for review.



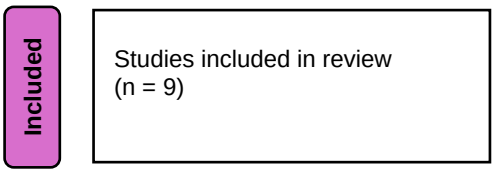


Figure 1: PRISMA flow diagram of the selection process of records

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3.2. Risk of Bias of Included studies

Overall, the studies were assessed as having a low to moderate risk of bias, with none being rated as high risk. All types of bias, including confounding, selection, exposure assessment, outcome measurement, missing data, and selective reporting, were categorized as low to moderate only.

3.3. General study characteristics

Table 1 gives an overview of the 9 studies included in the systematic review. Majority of the studies were conducted in USA, followed by Canada and the rest were conducted in Europe. Publication years ranged from 2019 to 2023.

Sl No.	Reference	Country	Design	Sample size	Association	Effect of diet on symptoms of IBD	Diet recommendations
1	Ammar Hassanzadeh Kashteli et al, 2022 [9]	Canada	RCT	53	Yes	6 months trial period showed decreased inflammatory markers and a reduction in symptoms. Thus, it was concluded that diet has a positive association with improving symptoms of IBD.	Increase the consumption of dietary fibre, probiotics, antioxidants, and omega-3 fatty acids, while reducing the intake of red meat, processed meat, and added sugars.
2	James D Lewis et al, 2022 [10]	USA	RCT	191	Yes	2 months trial period showed improved symptoms among the participants after following the diet	Mediterranean diet
3	Julia Fritsch et al, 2021 [11]	USA	RCT	17	Yes	2 month trial period showed improved symptoms among the participants after following the diet strictly. It was also noted that diet helped patients in remission to lead	Low fat, high fibre diet

						good quality of life	
4	Vaios Svolos et al, 2018 [12]	Scotland	RCT	25	Yes	1 month trial period showed decreased gut inflammation. Further, pH was increased and the short	Exclusive enteral nutrition
5	Lacerda JF et al, 2021 [13]	Portugal	RCT	53	Yes	2 months trial evaluated symptomatology, nutritional status and biochemical parameters. A trend in the reduction of inflammation was noticed but the effect of specific food components were inconclusive.	A personalized diet plan tailored to individual energy needs, following the principles of the Mediterranean diet.
6	Selina R Cox et al, 2022 [14]	United Kingdom	RCT	50	Yes	3 months trial evaluated FR QoL, quality of life and clinical disease activity was assessed. Diet was found to be effective in increasing the quality of life by	Decreased level of processed meat and red meat

						decreasing disease activity.	
7	Albenburg L et al, 2019 [15]	USA	RCT	214	Yes	12 months trial period showed a decrease in symptoms. However on adding red meat to diet, symptomatic relapse was noted, thus dietary components alter remission.	Decreased level of red and processed meat consumption
8	Melgaard D et al,2022 [16]	Denmark	RCT	19	Yes	2 months trial showed decrease in pain and bloating.	Low fermentable carbohydrates (FODMAPS)
9	Haskey N et al, 2023 [17]	Canada	RCT	28	Yes	3 months trial showed alteration in gut microbiota and was associated with decreased symptoms.	Decreased level of red and processed meat consumption

Table 1: Provides a summary of the nine studies featured in this paper.

3.4. Conceptualization, operationalization, Rationale and discussion of results

All the 9 studies showed that introducing changes in a patient diagnosed with IBD will have a positive effect on the outcome of the disease. Another common feature among these studies was, follow up done to the patients ranging from 1 month in the case of Vaios Svolos et al 2018, to Albenburg L et al, 2019 with 12 months of long term follow up,

likewise the sample size of the study varying from 19 in Melgaard D et al,2022 and 214 in Albenburg L et al, 2019.

Ammar Hassanzadeh Kashteli et al, 2022 conducted this research with 53 subjects in Canada and documented improvements in symptoms of IBD along with decrease in IBD markers [9]. James D Lewis et al, 2022 in his trial over 2 months with 191 participants conducted in USA showed alleviation in symptoms with overall lifestyle improvement [10]. Julia Fritsch et al, 2021 who also conducted a similar study in the US with 17 participants over 2 months reaffirmed the positive impact of diet modification in IBD patients and helped in obtaining complete remission, thereby improving their overall quality in life [11].

Vaios Svolos et al, 2018 with his study in Scotland conducted with 25 participants and 1 months follow up revealed decreased gut inflammation, further the pH was increased, and the short chain fatty acid levels were decreased [12]. Lacerda JF et al, 2021, being the only Southern American trial from Portugal with 53 participants and evaluated over 2 months studied the symptomatology, nutrition status and biochemical parameters, a trend in the reduction of inflammation was noticed but the effect of specific food components were inconclusive [13].

The only article in this lot to have quantitatively estimated the quality of life was Selina R Cox et al, 2022 conducted in the UK with 50 participants over 3 months assessing QoL, with assessment of disease activity, the diet was found to be effective in increasing the quality of life by decreasing activity [14]. The Albenburg L et al, 2019 trial conducted in USA with 214 participants over the year recorded a decrease in symptoms with diet modification being a key factor in improving the disease condition.

However on adding of red meat to diet, a relapse of the symptoms were noted [15]. Melgaard D et al,2022 study conducted in Denmark with only 19 participants over 2 months recorded a decrease in vomiting and bloating complaints of patients [16]. Haskey N et al, 2023, another study from Canada with 28 participants showed alteration gut micro bacteria and an associated decrease in symptoms over 3 months of diet modifications, hinting towards the role of gut micro bacteria in remission of IBD [17].

All the trials conducted so far with a combined patient population of 650 and an average study duration of 4-5 months, it was established that by introducing diet modifications, a positive impact was seen on the patient, either quantitatively documenting it by a decrease in the inflammatory factor levels or by bringing down the complaints of vomiting, abdominal pain and discomfort. This along with change in the gut micro bacteria is collectively to have thought to be the influencing factor impacting IBD patients as introducing older diet patterns has increased the disease incidence again.

4) Discussion-

Inflammatory bowel disease has 2 main expressed forms, ulcerative colitis, and Crohn's disease. Though both mimic a similar clinical picture, each possess their own set of unique features based on symptoms, disease location, and histopathological characteristics different from the other [1]. To understand the impact of diet on IBD remission, one must have a deep understanding of the aetiopathogenesis, risk factors, triggers, and pharmacological management. The solution to every complex clinical problem lies at its base, which makes understanding this section very important-the pathology [3].

GUT- Embryologically divided into the foregut, midgut and hind gut. However, when it comes to the physiology of digestion the stomach, small bowel and large bowel are the epicentres of discussion. As the name suggests, IBD deals with changes happening at the level of small bowel and large intestine. The gut mucosa is formed by epithelial cells, stromal cells, goblet cells, Paneth cells and local macrophages[2].

Changes happen at the level of the epithelial cell layer, which flare up and trigger an episode, Ulcerative colitis manifests because of chronic irreversible ulceration of the gut mucosa, while Crohn's is a transmural disease [4]. The goblet cells present in the gut epithelium are responsible for mucous production in the intestine.

The gut epithelium interacts with food and the gut microbiome once the goblet cells get destroyed, the underlying stroma gets exposed to the external environment resulting in the fibrosis of the underlying layers by the action of fibroblasts and macrophages, this is the phenomenon behind Crohn's disease, which later builds up to form strictures, resulting in intestinal obstructions and life-threatening complications. While in ulcerative colitis, the

ulceration of the bowel mucosa results in production of excess mucosa by the action inflammatory chemokines and cytokines released from the gut macrophages and neutrophils [5].

Whenever there's a layer of exposed mucosa, body's immune cells reach to the site and seal off the site of damage by releasing pro inflammatory mediators and immunoglobulins particularly the IgA, which aid in healing via fibrosis [4]. When there's repeated ulceration, inflammation and fibrosis, there comes the triad of chronic intestinal bowel inflammation. This builds up over days when the immune system acts as the reason for the exposed epithelium from gut bacteria while being simultaneously responsible for this. Whenever there's an insult, there'll be a compensatory mechanism to overcome it, and IBD is no exception, the gut starts overacting to the ongoing series of insults and becomes hyper defensive of what happens, resulting in over production of reactive oxygen species in the process this whole cascade is orchestrated via interleukins, cytokines, and chemokines.

Hence, the reason behind alternative diarrhoea, constipation and passage of loose stools accompanied with pain in the abdomen and bloating. Few with ulcerative colitis have reported relief of symptoms following lifestyle modifications. Of these, one of the most common beliefs is the change in the quality of gut micro bacteria. Several studies have reported that IBD always associated with degradation in the quality of gut microbiome and vice versa.

Few studies have hinted that with the ongoing immune war inside the intestine, along with intestinal epithelial destruction, there's a change in the pH of the biome which accompanies it, the quality of the gut bacteria is the first to be affected, long before the onset of ulcers, fibrosis, polyps, and strictures [11]. Gut bacteria help in the digestion of food by acting on them and releasing by products. When there's a sudden shift in the quality of gut bacteria, the whole chain of digestion gets affected. The symptoms slowly start developing and flare up with a strong acute episode, which leads to the diagnosis of IBD.

Anyone is at risk of developing IBD. More so are the people who have a genetic predisposition, those who abuse antibiotics and on chronic immune suppression [2]. All these are factors that lead to the immune system going hay wire and prove disastrous to the patient.

This where the role of diet modifications step in. Now that the problem and the cause for it are identified, minimising further exposure to the risk factor is of paramount importance. This can be done by consumption of foods which promote the proliferation of normal healthy gut bacteria and food which help in restoring the normal of the gut bacteria, which again help in the proliferation of gut bacteria, foods which decrease the inflammation at the gut level, food rich in antioxidants and foods that help with gut motility normalisation [7].

Interestingly, foods rich in red meat are involved in trigger the symptoms of IBD, while bland foods are thought to help with the relief of symptoms of IBD. The RCTs discussed in this review article also reflect the same. Foods rich in FODMAPs are contra indicated in IBD as they give more room for the action of bacteria on the gut while the gut is still healing from the existing insult. FODMAP stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which are short-chain carbohydrates (sugars) that the small intestine absorbs poorly [18].

Some people experience digestive distress after eating them. Symptoms include Cramping , abdominal pain, bloating and Diarrhoea. the key to this lies in consuming food rich in fibre, fermented foods, those which are bland, less oily and in particular the processed foods. Foods processed with nitrosamine compounds are found to be linked with triggering colitis and serve as a predisposition for colorectal malignancies. The key to overcoming IBD lies with consuming the right diet, and at the right time.

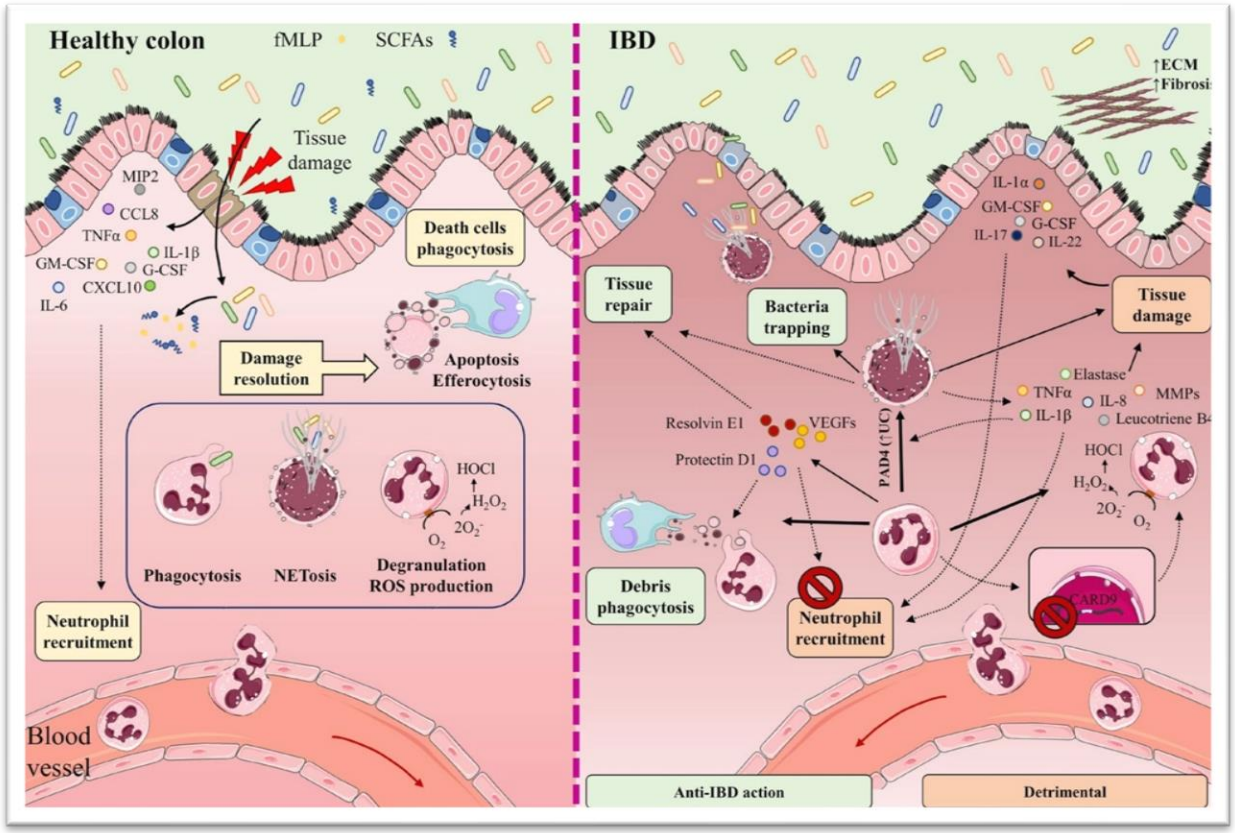

Figure 1. *In healthy intestine (**left**), damage to the intestinal barrier triggers the recruitment of neutrophils from the circulation to the inflamed tissue along a chemotactic gradient formed by cytokines (IL-1β, IL-6, TNF-α), chemokines (CCL8, CXCL10, MIP-2), and growth factors (GM-CSF, G-CSF). Neutrophil recruitment is also mediated by bacteria-derived molecules such as formyl-methionyl-leucyl-phenylalanine (fMLP) and short-chain fatty acids (SCFAs). The recruited neutrophils participate in the elimination of microorganisms through phagocytosis, degranulation, reactive oxygen species (ROS) generation, and the release of neutrophil extracellular traps (NETs). Once their functions are completed, neutrophils undergo apoptosis and efferocytosis, facilitating the resolution of inflammation, tissue repair, and a return to normal tissue homeostasis. The participation of neutrophils and NETs in IBD is a double-edged sword (**right**). Neutrophils cooperate in wound healing and the resolution of inflammation by releasing vascular endothelial growth factors (VEGFs) and lipid mediators (protectin D1, resolvin E1). These factors impede neutrophil recruitment and promote phagocytosis. NETs impede the spread of microorganisms by trapping them in an environment of microbicidal components and stimulate the healing of the intestinal mucosa. Neutrophils directly cause tissue damage by releasing neutrophil elastase, proteases (MMPs), pro-inflammatory cytokines (IL-8, TNF-α, IL-1β), leukotriene B4, and ROS. These factors provoke not only injury to the epithelial barrier, but also the recruitment of neutrophils and other immune cells to the inflamed tissue. Neutrophil recruitment is also promoted by the cytokines IL-1α, IL-17, IL-22, G-CSF, and GM-CSF. Lack of the IBD protective gene CARD9 in neutrophils enhances ROS generation. IL-8, TNF-α, and PAD4 (increased in UC patients) contribute to NET production. Accumulation of NETs in the colon is accompanied by the induction of tissue damage and inflammation, as NETs also boost TNF-α and IL-1β production. Part of the figure was generated by using pictures from Servier Medical Art*. [18]

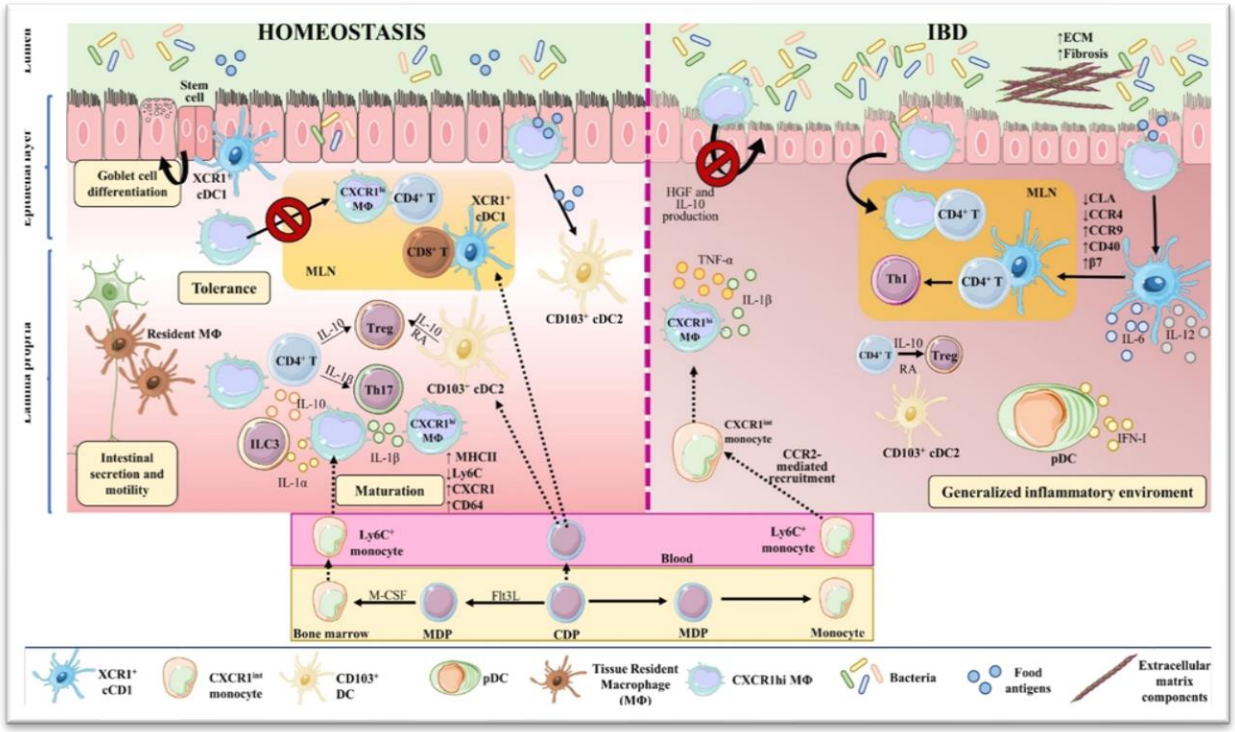

Figure 2. *Macrophages and dendritic cell in homeostasis and IBD. Macrophages and DCs play important roles in homeostasis and in the development of IBD by phagocytosing cellular debris, producing cytokines, regulating tissue repair, and interacting with other cells. In the intestine, monocyte-derived macrophages (MΦ) are more abundant than tissue-resident macrophages of embryonic origin. Both perform phagocytosis, produce cytokines, and interact with other cells. Upon weaning, bone marrow-derived monocytes egress from the circulation and extravasate into the tissue, where they undergo differentiation and maturation (downregulation of Ly6C, production of MHCII, and increased expression of CX3CR1). In homeostasis, tissue-resident macrophages in the muscularis externa interact with enteric and myenteric neurons controlling intestinal secretion and motility, while in the lamina propria, macrophages provide signals to intestinal stem cells that give rise to goblet cells, Paneth cells, and intestinal epithelial cells. These macrophages also modulate T cell activities and functions, via the secretion of IL-10 for Tregs and IL-1β for Th17 cells. In addition, they affect ILC3 cells through the production of IL-1α and IL-1β. The migration of antigen-loaded CX3CR1^{high} intestinal macrophages to mesenteric lymph nodes is impaired by intestinal microbiota, thus affecting antigen presentation to T cells and effectively sustaining tolerance towards commensal bacteria. On the other hand, XCR1^{+} DCs play a tolerogenic role upon recognizing commensal bacterial components, while CD103^{+} cDC2s seem to be important for initiating oral tolerance through their capacity to generate RA and IL-10. In IBD, large numbers of Ly6C^{high} inflammatory monocytes are recruited to the intestine in a CCR2-dependent manner, becoming pro-inflammatory effector cells. These inflammatory macrophages produce TNFα, IL-6, and iNOS, and directly cause the onset and development of fibrosis through a disproportionate accumulation of ECM. The intestinal microbiota is impaired during chronic colitis, and CX3CR1^{high} macrophages can change their habits and migrate to lymph nodes. CD103^{+} cDC numbers are significantly reduced in the inflamed and uninflamed intestine in IBD; however, activated DCs can release inflammatory cytokines, in addition to type I IFN produced by pDCs. All these phenomena contribute to a generalized inflammation. Part of the figure was generated by using pictures from Servier Medical Art.* [18]

5) Strengths and limitations-

Strengths of this systematic review encompasses a transparent methodology which was applied to the data collection process and predefined criteria for inclusion, exclusion and quality, which were followed by two different reviewers. We also put

in a great deal of effort to identify as many studies as possible. Three databases were subjected to the search strategy.

A major limitation in this study was that we were unable to conduct a meta-analysis. All the studies had a different diet that was applied to the participants and there was no standardized approach. Further, there was non-uniformity of participant cohort in terms of their age and other comorbids.

6) Conclusion-

In conclusion, this review has examined the current level of research on the impact of diet changes on the outcome of inflammatory bowel disease. Through a comprehensive analysis and review of the articles shortlisted for this study, it is evident that all the studies have mentioned dietary plans that have positive effects on the outcome of the disease. Moving forward, more studies should be done to find out dietary guidelines to help and improve the quality of life in IBD patients. Ultimately, this review emphasizes the importance of diet in the outcome of Inflammatory Bowel Disease.

We took up this study because the first line of management of IBD would be dietary modification and reducing consumption of FODMAP.

Conflicts of interest- The author(s) declared no potential conflicts of interest with respect to research, authorship or publication of this article.

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