

Inflammatory Bowel Disease at the Time of COVID-19: Beyond Nutritional Aspects

Sonia Morya¹, Jaysi Kumari¹ and Farid Mena^{2*}

¹*Department of Food Technology and Nutrition, School of Agriculture, Lovely Professional University, Punjab, India*

²*Department of Nanomedicine and Advanced Technologies, California Innovations Corporation, San Diego, CA, USA*

***Corresponding Author:** Farid Mena, Department of Nanomedicine and Advanced Technologies, California Innovations Corporation, San Diego, CA, USA.

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Abstract

Inflammatory Bowel Disease (IBD) is a group of inflammatory conditions of the colon and small intestine. Crohn's disease (CD) and ulcerative colitis (UC) are the principal types of IBD and are gaining interest due to their rising prevalence. CD and UC are chronic, recurrent inflammatory diseases of the digestive system that often manifest in adolescence and earlier adulthood. IBD is caused by an unbalance in intestinal microbiota and an unregulated inflammatory response mediated by the immune system. IBD is medically defined by stomach discomfort and cramping that may be accompanied by bloody diarrhoea. Extra intestinal symptoms of IBD include arthritis, sacroiliitis, and ankylosing spondylitis. A lower BMI is also common in these people. Histologic, laboratory, sonographic, endoscopic, and radiologic data are frequently used to confirm a clinical diagnosis of illness. Doctors who manage IBD individuals should pay close attention to extraintestinal symptoms to reduce the morbidity.

Malnutrition has been shown to affect 20% to 85% of IBD individuals. Malnutrition in IBD individuals is caused by several conditions, such as limited oral food consumption, malabsorption, chronic blood and protein loss, and gut bacterial invasion. Poor dietary intake, and selective malnutrition or sarcopenia, is linked to inadequate health results therapeutic responsiveness and consequently, life quality. Dietetic examination including analysis of overall calorie consumption, energy expenditures, radiographic examination, and functional capacity testing should be part of the nutritional analysis. Individuals suffering from IBD are at a comparable incidence of malnutrition. As a result, these individuals must commence appropriate nutritional treatment. If normal diets are inadequate to provide enough energy and protein, oral dietary supplementation, or artificial nutrition, such as tube feeding or parenteral nutrition, will be used to prevent or overcome malnutrition. The oral approach should be favoured over enteral or parenteral feeding. Pandemics provide a significant barrier to individual healthcare. Some phytochemicals and plant extracts could be of great help in the IBD management. Nevertheless, the effect of the coronavirus disease 2019 (COVID-19) pandemic on the healthcare of IBD disease has rarely been studied. For instance, it remains unclear if persons suffering from IBD are more (or less) susceptible to COVID-19 and what are the underlying mechanisms to such effects.

This concise review aimed at providing an update on IBD physiopathology, current and potential therapeutic strategies of IBD and its management in the pandemic context.

Keywords: IBD; CD; UC; Malnutrition; Enteral Nutrition; Malabsorption; Phytotherapy; COVID-19

Introduction

CD and UC are chronic, rebounding, digestive diseases that emerge in adolescence and earlier adulthood typically. The incidence of malnutrition observed in individuals with IBD ranges from 20 to 85%. In 70% to 80% Crohn's disease (CD) and 20% to 40% ulcerative colitis (UC) of ambulatory patients with IBD, numerous research studies have indicated the huge incidence of losing weight. For both UC and CD, malnutrition may develop, however, proteins and particular nutrient deficiency appear to have a greater frequency in CD than in UC, perhaps because this might impact any region of the gastrointestinal system and, beyond all else, small bowel. The basic reason for malnutrition includes a decrease in oral meal consumption, nutrient malabsorption, a decrease in entry nutritional needs, growing energy demand owing to systemic inflammation, and sometimes iatrogenic causes (drug- and surgery-related) [1]. The evaluation of nutrient intake and the requirement for complementary nutritional treatment is critical in the therapeutic management of individuals with IBD. Interestingly, several controllable protective variables for IBD, such as influenza vaccination, decreased smoking rates, vitamin D consumption, and increased attentiveness were discovered. Also, COVID-19 has been linked to a decreased risk of IBD in China, Italy, and Spain [2-4]. Approximately 12 of 1918 IBD individuals were identified with COVID-19 in a Spanish research, with a reduced adjusted prevalence rate of COVID-19 (OR 0.74) relative to the overall populace but a comparable death rate (OR 0.95) [4]. Furthermore, serious COVID-19 consequences may be less common in IBD individuals than in normal [5].

The purpose of this review article is to emphasize the importance of diet, innovation, and precision medicine in individuals with IBD.

Inflammatory bowel diseases (IBD) and nutritional therapy

IBD is a complicated interaction between genetic variations, intestinal microbiota, the host immune system, and environmental conditions (e.g. nutrition, medicines, lactation, and smoking) [6-8]. The interplay among the human immune system, the intestinal barriers, and the gut microbiota influences the link among vital nutrients and intestinal homeostasis [6]. Patients with IBD are at a significant danger of malnutrition which can arise because of decreased oral ingestion, elevated nutritional requirements, higher gastrointestinal nutrient deficiencies, and, in rare cases, drug-nutrient interaction [9,10]. Malnutrition is the leading factor of growth regression in paediatric individuals. Contrarily to UC, malnutrition is a major issue with CD since it can impact any section of the gastrointestinal system. As a result, even though the illness is dormant, the danger of malnutrition persists. Except in active illness, UC is generally limited to the colon and hence exhibits minimal malabsorptive issues. Because of the elevated danger, patients with IBD must be tested for malnutrition at the onset of the test and on a constant schedule [11]. Malnourished individuals should get proper nutritional treatment since failing to do so impair their prognosis and quality of life [11,12]. In recovery, the energy need of IBD individuals is usually not raised, nor is the protein demand. In active IBD, protein requirements are raised, hence protein consumption must be 1.2 - 1.5 g/kg body weight. Furthermore, individuals with IBD are at a significant risk of nutritional deficits owing to diarrheal losses and/or poor food consumption. Iron, calcium, selenium, zinc, and magnesium deficiency are the more frequent micronutrients deficits. Vitamin shortages affect all vitamins, especially vitamin B12, folic acid, and vitamins A, D and K. Depletions of selenium, zinc, and magnesium, for example, are induced by insufficient food consumption and continuous loss due to diarrhoea. Deficiency consequences included bone health deterioration, tiredness, slow wounds recovery and cartilage degradation. Cholestyramine, which can interact with the uptake of fat-soluble vitamins, iron, and vitamin B12, is one case of a medication's effects. Steatorrhea is the most common adverse effect caused by impaired fat absorption [13]. As a result, individuals' test readings must be evaluated on a frequent schedule and any deficiencies must be addressed as needed. Iron insufficiency and anaemia, that happen more commonly in CD must be treated with iron, are the primary common extra - intestinal manifestations of IBD. Anaemia is frequently linked by various significant problems such as fatigue sleeping difficulties, restless legs syndrome, or attention problems [13]. Patients with moderate anaemia can be given oral iron whether they are receptive of it and the condition is dormant. Intravenous iron should be explored in individuals with acute IBD, those who have previously been intolerant to oral iron, those with hemoglobin levels below 100 g/L and those who require erythropoiesis-stimulating medications. Extreme instances of anemia (less than

80 g/L) require blood transfusion. Individuals may also be deficient in calcium, vitamin D, folate, vitamin B12, and zinc. People should be given vitamin B12 if more than 20 cm of the distal ileum is removed. Inadequate calcium and vitamin D values are prevalent in IBD sufferers particularly those with duodenal and jejunal illness [7]. Calcium shortage is associated with vitamin D insufficiency, which is associated with insufficient regular consumption inflammatory state, diarrhoea, and glucocorticoid medication. The incidence amongst IBD patients ranges from approximately to 70% in CD individuals to 40% in UC individuals. However, it is unclear if vitamin D insufficiency is a factor or a result of IBD. Furthermore, there is some evidence that vitamin D insufficiency may have a role in the formation of IBD in genetically susceptible people. Nevertheless, pre-clinical researches, mostly in mice models have revealed that the active form of vitamin D regulates gut microbiota activity and promotes anti-inflammatory responses in IBD. Whenever orally nutritional consumption is inadequate throughout severe illness, oral nutritional supplements (ONS) are the first line of defence. Tube feeding is better to parenteral feeding if oral feeding is insufficient. Parenteral nutrition is demonstrated in IBD (i) when oral or tube feeding is insufficient, (2) whenever the bowel is obscured and there is no chance of placing a feeding tube beyond than the interruption or afterward this has unsuccessful, or (iii) when other problems including anastomotic spillage, or a high-output intestinal fistula happen [11]. Formulations or substrates, such as glutamine or omega-3 fatty acids, are not indicated throughout active illness, nor is the usage of probiotics. Probiotic treatment with *Escherichia coli* Nissle 1917 or VSL#3 may be investigated for the development of recovery in people with mild to intermediate UC [14]. Enteral only feeding has been widely utilized to induce revocation in paediatric CD, for which avoidance of steroids is crucial for children health. A few latest paediatric research studies have affirmed that enteral exclusive nourishment can stimulate revocation in 60 - 86% of young kids [15,16] and is related to relatively high revocation rates, better growth, and longer steroid-free periods [6]. Furthermore, the effect was eliminated when partial enteral feeding was combined with free diet availability. However, a new research found that partial enteral feeding, when combined with such a diet based on components expected to impact the microbiota or intestinal permeability, can be helpful for inducing revocation in children and adolescents. In revocation, ONS or artificial nutrition are only advised if dietary counselling is insufficient to correct malnutrition. Furthermore, specialized diets or supplements containing omega-3 fatty acids are not indicated for remission persistence. A thorough analysis found no evidence to substantiate the concept that omega-3 fatty acid supplement helps initiate and sustain revocation in IBD. Numerous investigations, though, have shown that various genotypes might be linked with a varied responsiveness to omega-3 fatty acid dietary therapy. Probiotic treatment can be explored for recovery retention in UC and not in CD [11]. Furthermore, scientific research indicates that curcumin administration may be useful for inducing and maintaining remission in UC individuals [17]. Curcumin inhibits NF-kB stimulation, which inhibits cytokine release by macrophages and intestinal epithelial cells [18] and so alleviates caused colitis in mice models. Table 1 provides an overview of dietary guidelines in IBD.

#	Key Recommendations
	Frequent screening for malnutrition and micronutrient deficiencies
	Energy and protein requirements are steady in treatment but rise in active diseases
	Iron supplements in the treatment of anaemia
	If oral feeding is not sufficient then tube feeding is superior to parenteral feeding
	Decrease the intake of red and processed meats
	Decrease the intake of myristic acid (palm oil, coconut oil, dairy fats).
	Consume more omega-3 fatty acids, DHA, and EPA.
	Marine fish is suggested, but supplements are not recommended
	Decrease the intake of saturated fats
	Consume high quantity of fruits and vegetables
	In symptomatic or important fibrostricturing CD (Crohn's disease), it is significant to restrict insoluble-fibre consumption
	Decrease consumption of emulsifiers and thickeners (carrageenan) and processed foods comprising titanium dioxide and sulfites
	Reduce the consumption of maltodextrin and artificial sweeteners
	Maltodextrin and artificial sweeteners may contribute to dysbiosis, inflammation and increased intestinal permeability
	Trans fats should be avoided
	Consumption of unpasteurized milk products should be prevented

Despite numerous research studies show reduced diseases activities and a longer duration to recurrence after adopting certain dietary routines, the effectiveness of most of these diet programs remains unknown. The low-residue diet (10 - 15g fiber per day) is a hallmark of dietary regimes in IBD individuals particularly those at danger of gastrointestinal obstructions [19]. Furthermore, there is little data to support the effectiveness of low-residue diets in IBD. An Italian survey of 70 sufferers with non-Crohn's disease (CD) who were randomized allocated to obey a low-residue diet (3 g/day of fiber) or an ordinary Italian diet (13 g/day of fiber) for a mean of 29 months found no variation in medical output which include side effects, required for hospital treatment, surgery, unique health problems, nutritional therapy, or postoperative viability. Many forms of fiber have been postulated to get a significant impact on the gut microbiota and hence perhaps on the maintaining of cure in IBD sufferers. A large prospectively group analysis of individuals in treatment with CD (n = 1130) and UC (n = 489) analysed the relationship among fiber intake and the likelihood of illness recurrence [20]. CD individuals who consumed more fiber were 40% fewer prone to suffer a flare after 6 months than those who consumed lesser fiber. Fiber consumption, on either side, had no effect on UC individuals. Many excluding diet strategies are currently acquiring popularity for IBD therapy. A low-FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) diet has been recommended to help individuals with managed IBD (those who do not have acute inflammation) [21]. A low-FODMAP diet was shown to lessen the severity of complaints (e.g. stomach, belching, bloating, flatulence, delayed expulsion, nausea, and heartburn) in 78 percent of IBD individuals. The carbohydrate diet is an innovative diet method that restricts intricate carbs and processed sugar. The logic behind this diet is that sugars and intricate carbohydrates are malabsorbed and may promote changes in the microbiota configuration, leading to IBD-related intestinal inflammation. The effects of the carbohydrate diet on the medical phase of IBD, on the other hand, have yet to be verified. As a result, no oral diet in IBD can be widely suggested to encourage concern in IBD individuals with severe diseases at this time.

A new approach for inflammatory bowel disease therapy

IBD reduces standard of living, particularly in adolescents and young adults who have more serious signs such as diarrhea, abdominal discomfort, bloody stools, fever, exhaustion, decreased appetite, and weight loss [22]. IBD is characterized by impaired intestinal epithelial barrier activity and enhanced permeability. Gut luminal components, pathogenic bacteria, and benign microbiota are improperly transferred into the intestinal lamina propria in the absence of adequate barriers, resulting in inflammation. Treatments to repair the intestinal barrier that are specific and non-toxic are desperately required [23]. Graham., *et al.* [24] reported the development of a small drug that operates via myosin light chain kinase 1 (MLCK1) to re-establish barrier functionality of a damaged intestinal epithelium [24]. In rodent models of IBD, this novel medicine reduces inflammation and disease asperity, and it has hope for humans with IBD and other disorders related with epithelial barrier malfunction, including celiac disease and graft-versus-host disease. A monolayer of diverse kinds of columnar epithelial cells, comprising cell types particular to the small or large intestine, maintains intestinal barrier stability. These epithelial cells work together to build strong biological barriers. Structural proteins bind these cells sideways to each other, allowing the physical barrier that regulates the transit of solutes and water through the intestinal epithelium to remain intact [23]. The claudins and occludins make a flexible closure called as a tight junction, which forms the paracellular boundary among epithelial cells [23,25]. Myosin light-chain kinase (MLCK) is a well-known controller of tight junction permeability, and its failure to operate effectively whether owing to mutation or increased expression, can result in disease conditions not just in the gut but also in other organs including the lungs and the heart [25]. The perijunctional acto myosin ring (PAMR) is a cytoskeletal actin and myosin II ring that surrounds each intestinal epithelial cell and is related with tight junction proteins. Phosphorylation of the myosin light chain (MLC), a tiny polypeptide component of myosin, by MLCK compresses this ring, causing strain on tight junction proteins to release and increasing barriers permeability. TNF- α , a highly inflammatory cell signalling molecule found in IBD individuals' intestinal tissues, promotes MLC phosphorylation in the PAMR via MLCK1. Tight connections are loosened, allowing food antigens, macromolecules and microbial constituents to enter the sterilized lamina propria beneath, as illustrated in figure 1.

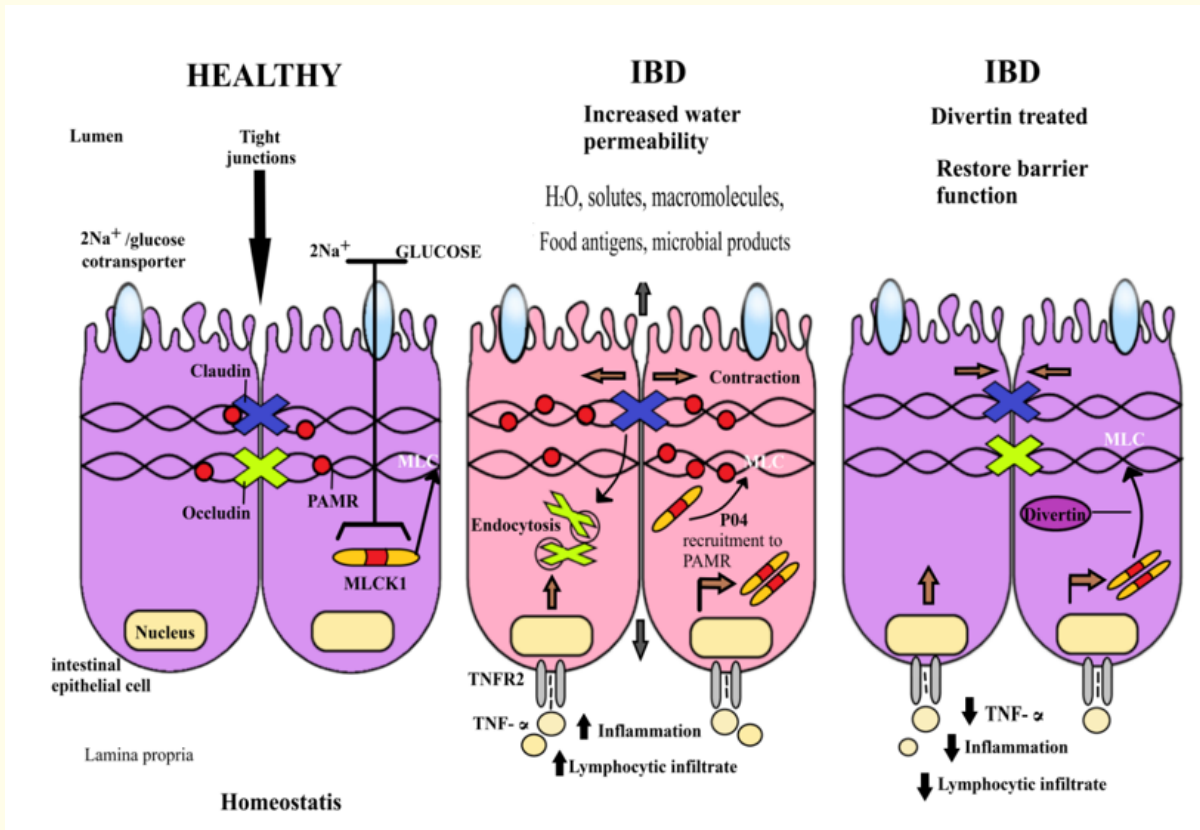


Figure 1: Divertin can restore fixed junction function in IBD models.

Other current and emerging concepts in inflammatory bowel disease management

Biochemical markers (e.g. calprotectin, lactoferrin) have now become more universally accessible enabling for more objective surveillance of intestinal inflammation [26]. Even though the methods indicated above are routinely used in varying configurations for illness prediction, they merely scratch the surface of prognostic potential (Figure 2). Doctors are eagerly awaiting the actual verification and useful correlation of newer ‘omics’ non-invasive techniques. Undoubtedly, all these innovative mechanisms will enable us to dive into the uncharted seas on the tip of the iceberg known as “deep remission.” Therefore, the definition of this comparatively recent phrase is unknown. To mention just some, concepts focus on keywords like ‘molecular,’ ‘epigenetic,’ ‘microbial,’ or ‘metabolomic mucosal healing.’ The expanding area of microbiota study brings up new options for the creation of novel biomarkers in CD. Furthermore, recent studies may be able to meet this unfulfilled requirement in CD treatment. Microbiota-based biomarkers may be beneficial in the differentiated diagnosis surveillance, and prognosis of CD. Furthermore, the area is currently in its infancy and requires further growth from a medical perspective [27].

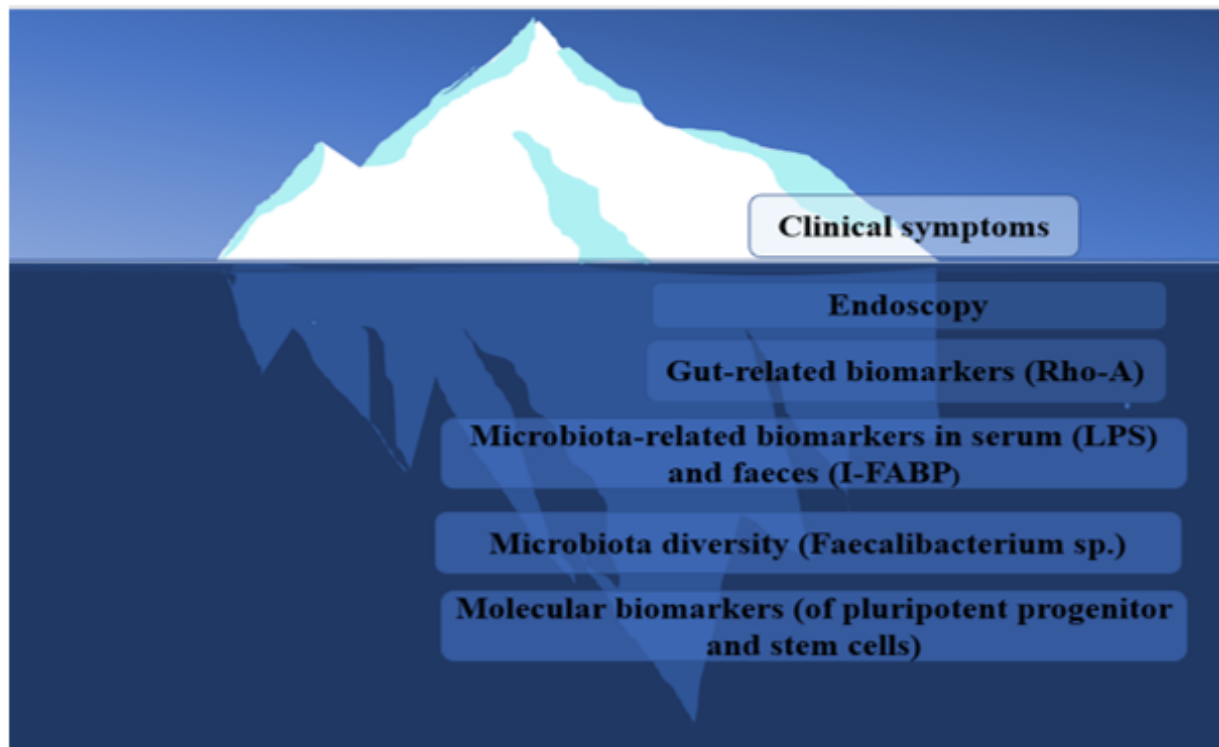


Figure 2: Iceberg representation of recent and emergent concepts in inflammatory bowel disease management.

The primary objective of medical treatment should be to create and maintain a state with steroid-free revocation [28]. New types of medications for IBD therapy are being tested in clinical trials include janus kinase inhibitors, anti SMAD7 oligonucleotides, anti-tumour necrosis factor (TNF), peroxisome proliferator activated receptor ligand, anti-integrins-IV, probiotics, and cell-based treatments. However, conventional IBD medicines are ineffective for many individuals. Other therapy for induction and management of remission are in high desired.

Phytotherapy in the management of IBD

Interest for complementary and alternative medications, especially herbal treatments, has been shown to be greater amongst IBD patients (21 - 60%), owing to their presumed natural benefits [29]. Although not every regularly utilized phytomedicines are secure, most herbal treatments on the market are rather safe when compared to conventional pharmaceuticals. Because of growing interest in research on medicinal plants, and the high demand for herbal therapy, very efficient medications derived from plants such as opiate anaesthetics, aspirin, and Taxol have been discovered. For centuries, several medicinal herbs have been used to treat or prevent severe diarrhoea. Herbal therapy for the establishment and management of IBD resolution in both UC and CD patients shall be deeply investigated.

COVID-19 hazards in individuals with inflammatory bowel diseases

The new coronavirus (SARS CoV-2) was initially detected in Wuhan in December 2019 and swiftly spread to the rest of the world [30-32]. Around February 2020, the pandemic quickly expanded throughout Europe, with Italy being the most afflicted country and Lombardy

being the more impacted region [33]. People with IBD were instructed to isolate and follow regular safeguards towards COVID-19, as per suggested by World Health Organization (WHO), but should maintain their treatments, particularly the immunosuppressive or biologic ones [34-36]. It is unclear if IBD individuals are even more sensitive to COVID-19 or even more likely to develop major diseases. As a result, there has been widespread concern between IBD sufferers and physicians about the possibility of enhanced vulnerability. This is connected to IBD treatment, which includes immunosuppression, which may put individuals at danger of opportunistic infections and respiratory disorders [37]. Therefore, it is still unknown if immunomodulators and biologics enhance the chance of disease or the development of serious cases of COVID-19 [38]. According to preliminary data from China, the prevalence of serious illness among IBD sufferers may be less than in the overall population [2]. Moreover, investigations on the efficacy of IBD medication have found no link among treating with biologics and/or immunomodulators [39]. A current study of 525 IBD/COVID-19 patients from the SECURE-IBD registry found no elevated severity with TNF antagonists, but significant association with corticosteroids and the conventional risk variables of higher age and comorbidity [40]. These first findings are encouraging and imply that IBD individuals may be at lower risk of COVID-19. Furthermore, given the lack of substantial case-control investigations, the processes behind this result remain unknown. To examine the incidence of COVID-19 signs, official diagnosis, and hospitalization for COVID-19 in IBD individuals versus general gastroenterology controls, more clinical research projects shall be carried out.

Enteral versus parenteral treatments in the management of IBD: Pros and cons

Enteral nutrition (EN) treatment, which uses oral nutrition supplementation or tube feeding, is used to restore, and sustain the nutritional condition of those who have a low oral consumption. In normal procedure, EN should be prescribed in the following situations: serious malnutrition, modest malnutrition with food consumption anticipated to be inadequate for more than five days, normal nutrient intake with inadequate food consumption for more than ten days, or severe hypercatabolism. EN is commonly acknowledged to be better to parenteral nutrition (PN) since it is linked with fewer problems and cheaper costs. Furthermore, luminal nutrients are now thought to be a basic trophic component for the intestinal mucosa, inhibiting bacterial translocation and maintaining gastrointestinal functionality. Numerous investigations have shown that EN is effective in active CD sufferers while the methods of activity are uncertain [1]. This has been hypothesized that nutrition can alter commensal microbiota and the gut immune responses by lowering antigen contact. As a result, EN appears to have an anti-inflammatory impact on the intestinal mucosa by decreasing Interleukin-6 (IL-6) synthesis and raising insulin-like growth factor (IGF)-1 secretion. EN has been demonstrated to be beneficial in treating the early stage of CD, with remit frequencies varying from 20% to 84.2 percent, irrespective of disease site. Furthermore, it needs to be shown when EN is a hugely successful treatment for Crohn's disease (CD). Along with its effectiveness in inducing remit positive benefits on growth, and low harmful impacts continuous, EN may be regarded a first-line treatment in children. Short bowel disorder with significant loss of nutrition and/or fluid that cannot be treated with enteral feeding is among the most important reasons for PN in IBD sufferers. PN is also used in individuals with obstructed diseases when a feeding tube cannot be placed well above blockage section and when this treatment has unsuccessful. Nutritional assistance must be administered earlier in the preoperative phase since, regardless of mode of delivery, it reduces the incidence of surgical problems. The effective use of PN necessitates adequate individual screening and understanding of its consequences, including metabolic changes necessitating frequent nutritional management or issues due to the catheterization itself [1].

Conclusion

Nutritional factors in IBD are especially important since they can alter disease severity degree. According to the existing evidence, a poor nutritional status, as well as selective malnutrition or sarcopenia, is related with bad health outcome responsiveness to treatments, and, hence, standard of living. Malnutrition in IBD patients is caused by several reasons. Dietetic examination including regular calorie consumption and energy expenditures radiographic examination, and functioning capability testing should all be part of the dietary recommendations. EN may be regarded a first-line treatment in kids due to its effectiveness in inducing remission favourable impacts on growth and lack of negative effects. Novel findings in the areas of microbial and stem-cell-based biomarkers may lead to emerging

approaches to the management of IBD individuals. Herbal therapeutics may also be useful, including as adjuvants since the majority of IBD individuals respond well to standard treatments. Issues with herbal medications in IBD are related to (i) the fact that refractory and complex patients are virtually usually omitted from herbal therapy studies, (ii) a shortage of repeatability, licensing restrictions and a lack of scientific understanding of indications for medicinal plant products. Interestingly, IBD patients did not elicit a greater risk of catching COVID-19 when compared to controls, but it is still unknown if IBD could be affected in a more deleterious way.

Eventually, a multidisciplinary examination of IBD patients is generally recommended, and dietary programs should generally be individualized to everyone.

Conflicts of Interests

The authors declare no conflicts of interests.

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Contributions

All the authors contributed substantially to this article with research, writing and review of first and final draft. FM managed the project and submitted the manuscript. All the authors read and agreed with the content. All the authors declare that the manuscript has not been submitted nor is under consideration elsewhere.

Bibliography

1. Balestrieri P, *et al.* "Nutritional aspects in inflammatory bowel diseases". *Nutrients* 12.2 (2020): 372.
2. An P, *et al.* "Protection of 318 inflammatory bowel disease patients from the outbreak and rapid spread of COVID-19 infection in Wuhan, China (2020).
3. Norsa L, *et al.* "Uneventful course in IBD patients during SARS-CoV-2 outbreak in northern Italy". *Gastroenterology* 159.1 (2020): 371-372.
4. Taxonera C, *et al.* "2019 novel coronavirus disease (COVID-19) in patients with inflammatory bowel diseases". *Alimentary Pharmacology and Therapeutics* 52.2 (2020): 276-283.
5. Lukin DJ, *et al.* "Baseline disease activity and steroid therapy stratify risk of COVID-19 in patients with inflammatory bowel disease". *Gastroenterology* 159.4 (2020): 1541-1544.
6. Sáez-González E, *et al.* "Bases for the adequate development of nutritional recommendations for patients with inflammatory bowel disease". *Nutrients* 11.5 (2019): 1062.
7. Fletcher J, *et al.* "The role of vitamin D in inflammatory bowel disease: mechanism to management". *Nutrients* 11.5 (2019): 1019.
8. De Souza HS and Fiocchi C. "Immunopathogenesis of IBD: current state of the art". *Nature Reviews Gastroenterology and Hepatology* 13.1 (2016): 13.
9. Hanauer SB. "Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities". *Inflammatory Bowel Diseases* 12.1 (2006): S3-S9.

10. Goh J and O'morain CA. "Nutrition and adult inflammatory bowel disease". *Alimentary Pharmacology and therapeutics* 17.3 (2003): 307-320.
11. Forbes A., et al. "ESPEN guideline: Clinical nutrition in inflammatory bowel disease". *Clinical Nutrition* 36.2 (2017): 321-347.
12. Gajendran M., et al. "Analysis of hospital-based emergency department visits for inflammatory bowel disease in the USA". *Digestive Diseases and Sciences* 61.2 (2016): 389-399.
13. Scaldaferri F., et al. "Nutrition and IBD: malnutrition and/or sarcopenia? A practical guide". *Gastroenterology Research and Practice* (2017).
14. Fujiya M., et al. "Probiotic treatments for induction and maintenance of remission in inflammatory bowel diseases: a meta-analysis of randomized controlled trials". *Clinical Journal of Gastroenterology* 7.1 (2014): 1-13.
15. Cohen-Dolev N., et al. "Differences in outcomes over time with exclusive enteral nutrition compared with steroids in children with mild to moderate crohn's disease: results from the GROWTH CD Study". *Journal of Crohn's and Colitis* 12.3 (2018): 306-312.
16. Connors J., et al. "Exclusive enteral nutrition therapy in paediatric Crohn's disease results in long-term avoidance of corticosteroids: results of a propensity-score matched cohort analysis". *Journal of Crohn's and Colitis* 11.9 (2017): 1063-1070.
17. Lang A., et al. "Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial". *Clinical Gastroenterology and Hepatology* 13.8 (2015): 1444-1449.
18. Wang J., et al. "Curcumin improves intestinal barrier function: modulation of intracellular signaling, and organization of tight junctions". *American Journal of Physiology-Cell Physiology* 312.4 (2017): C438-C445.
19. Hwang C., et al. "Popular exclusionary diets for inflammatory bowel disease: the search for a dietary culprit". *Inflammatory Bowel Diseases* 20.4 (2014): 732-741.
20. Brotherton CS., et al. "Avoidance of fiber is associated with greater risk of Crohn's disease flare in a 6-month period". *Clinical Gastroenterology and Hepatology* 14.8 (2016): 1130-1136.
21. Kumari J and Morya S. "Celiac disease: An epidemiological condition: Insight on gluten free diet, significance and regulatory recommendations". *The Pharma Innovation* 10.5 (2021): 641-654.
22. Ng SC., et al. "Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies". *The Lancet* 390.10114 (2017): 2769-2778.
23. Farkas AE and Nusrat A. "Pharmacological Targeting of the Inflamed Intestinal Barrier". *Current Pharmaceutical Design* 22.35 (2016): 5400-5414.
24. Graham WV., et al. "Intracellular MLCK1 diversion reverses barrier loss to restore mucosal homeostasis". *Nature Medicine* 25.4 (2019): 690-700.
25. Buckley A and Turner JR. "Cell biology of tight junction barrier regulation and mucosal disease". *Cold Spring Harbor Perspectives in Biology* 10.1 (2018): a029314.
26. Moniuszko A., et al. "Rapid fecalcalprotectin test for prediction of mucosal inflammation in ulcerative colitis and Crohn disease: a prospective cohort study". *Polish Archives of Internal Medicine* 127.5 (2017): 312-318.
27. Marlicz W., et al. "Emerging concepts in non-invasive monitoring of Crohn's disease". *Therapeutic Advances in Gastroenterology* 11 (2018): 1756284818769076.

28. Atreya R., *et al.* "Update: Chronic inflammatory bowel disease". *Deutsche Medizinische Wochenschrift* 140.23 (2015): 1762-1772.
29. Hung A., *et al.* "Complementary and alternative medicine use is prevalent among patients with gastrointestinal diseases". *Digestive Diseases and Sciences* 60.7 (2015): 1883-1888.
30. Ashour HM., *et al.* "Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks". *Pathogens* 9.3 (2020): 186.
31. Han Q., *et al.* "Recent insights into 2019-nCoV: a brief but comprehensive review". *The Journal of Infection* (2020).
32. Guan WJ., *et al.* "Clinical characteristics of coronavirus disease 2019 in China". *New England Journal of Medicine* 382.18 (2020): 1708-1720.
33. Odone A., *et al.* "COVID-19 deaths in Lombardy, Italy: data in context". *The Lancet Public Health* 5.6 (2020): e310.
34. Ferreira-Silva J., *et al.* "Implications of COVID-19 for the busy gastroenterologist". *European Journal of Gastroenterology and Hepatology* (2021).
35. Sarzi-Puttini P., *et al.* "How to handle patients with autoimmune rheumatic and inflammatory bowel diseases in the COVID-19 era: An expert opinion". *Autoimmunity Reviews* 19.7 (2020): 102574.
36. WHO (2019) - Coronavirus disease (COVID-19) advice for the public (2019).
37. Kirchgerner J., *et al.* "Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases". *Gastroenterology* 155.2 (2018): 337-346.
38. Macaluso FS and Orlando A. "Could patients with inflammatory bowel disease treated with immunomodulators or biologics be at lower risk for severe forms of COVID-19?" *Gastroenterology* (2020).
39. Bezzio, C., *et al.* "Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study". *Gut* 69.7 (2020): 1213-1217.
40. Brenner EJ., *et al.* "Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry". *Gastroenterology* 159.2 (2): 481-491.

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