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EDITORIAL

Interaction between diet and genetics in patients with inflammatory bowel disease

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Abstract

In this editorial, we comment on the article by Marangoni *et al*, published in the recent issue of the *World Journal of Gastroenterology* 2023; 29: 5618-5629, about "Diet as an epigenetic factor in inflammatory bowel disease". The authors emphasized the role of diet, especially the interaction with genetics, in promoting the inflammatory process in inflammatory bowel disease (IBD) patients, focusing on DNA methylation, histone modifications, and the influence of microRNAs. In this editorial, we explore the interaction between genetics, gut microbiota, and diet, in an only way. Furthermore, we provided dietary recommendations for patients with IBD. The Western diet, characterized by a low fiber content and deficiency the micronutrients, impacts short-chain fatty acids production and may be related to the pathogenesis of IBD. On the other hand, the consumption of the Mediterranean diet and dietary fibers are associated with reduced risk of IBD flares, particularly in Crohn's disease (CD) patients. According to the dietary guidance from the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), the regular consumption of fruits and vegetables while reducing the consumption of saturated, trans, dairy fat, additives, processed foods rich in maltodextrins, and artificial sweeteners containing sucralose or saccharine is recommended to CD patients. For patients with ulcerative colitis, the IOIBD recommends the increased intake of natural sources of omega-3 fatty acids and follows the same restrictive recommendations aimed at CD patients, with the possible inclusion of red meats. In conclusion, IBD is a complex and heterogeneous disease, and future studies are needed to elucidate the influence of

epigenetics on diet and microbiota in IBD patients.

Key Words: Diet; Genetics; MicroRNAs; Gastrointestinal microbiome; Inflammatory bowel diseases; Crohn's disease

Core Tip: Diet-related issues are one of the main concerns that inflammatory bowel disease (IBD) patients bring to their clinicians and dietitians and are known to place a substantial burden on patients' quality of life. In this article, we discuss the interaction between diet and genetic factors such as microRNAs and the importance of diet in IBD patients. Furthermore, we provide dietary recommendations for patients during IBD flare as well as healthy nutritional guidelines to be followed during disease remission based on unprocessed or minimally processed foods.

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INTRODUCTION

In this editorial, we comment on the article by Marangoni *et al*[1], published in the recent issue of the *World Journal of Gastroenterology* about "Diet as an epigenetic factor in inflammatory bowel disease". In this review, the authors discuss the role of epigenetics in the pathogenesis of inflammatory bowel disease (IBD) and its modifications through diet as a mechanism for modulating the intestinal microbiota and attenuating the inflammatory process.

The term epigenetic was studied in the middle of the 19th century by biologist British Conrad Hall Waddington[2], to describe the interaction between genes and environment that allows the emergence of phenotypes. The first publication about epigenetics and IBD was in 1996[3]. In patients with IBD, the most studied modifications have been DNA-methylation and noncoding RNA that may be induced by smoking and diet[4,5]. Interestingly, this DNA-methylation is a process that is dependent on cofactors dietary such as substrates and nutrients (folate, vitamins B12, D, and others)[2] and is associated with inflammation, microbiota composition, and microRNAs (miRNAs) which can affect IBD by interfering with T cells differentiation[6]. Marangoni *et al*[1] provided an elegant review of the role of DNA methylation in IBD and its consequences to the inflammatory process.

In the recent review, Natasha and Zilbauer[2] claim that genetic changes may account for modest percentages of IBD, while epigenetic factors could potentially have contributed to the increase in the incidence of disease in recent decades and could be a key role of environmental factors in IBD pathogenesis.

It is worth highlighting that factors determining the degree of cellular epigenetic changes include the type of environmental factors and duration[2]. Some authors consider three critical periods during which the environment may favor the onset of the IBD: In utero, or the early postnatal phase (during gut microbiota colonization), and just before the disease onset[2,7]. Some data suggest that epigenomic reprogramming happens in response to maternal diet modifications, an excess of prenatal micronutrient supplementation (folate, methionine, betaine, and vitamin B12), maternal infection during prenatal, that increase interleukin-6 cytokine and induce epigenetic changes in fetal intestinal, and maternal smoking[7]. These factors could impact the development of IBD in infants.

Therefore, several nutrients present in the diet influence epigenetic modifications. In this way, phenotypic characteristics could be altered through changes in lifestyle and the environment in which the individual lives[3]. The Western diet, characterized by a low fiber content and deficiency of the micronutrients[5], impacts the short-chain fatty acids (SCFAs) levels and can induce epigenetic changes related to IBD, with the decrease in miR-143/145a, miR-148a, and miR-152 in colonocytes[7].

The inhibition of SCFA production (acetate, butyrate, and propionate) due to the low-fiber diet appears to play a critical role in the epigenetic control of the inflammation[5]. SCFA are essential for epithelial cell homeostasis and can epigenetically regulate the immune response and induce intracellular signaling pathways through the activation of G-protein coupled receptors[8].

The high-fat diet or diet rich in n-6 linoleic acid, particularly arachidonic acid, or high sugar diet have a proinflammatory activity that can change the miRNA profile of the visceral adipose exosomes or DNA methylation respectively, resulting in gut microbiota dysbiosis, dysregulating gut immune homeostasis, and increasing the risk of inflammation[5,7]. In the same way, the chronic alcohol consumption increases miR-122 and miR155 expression in the intestine and decreases occludin expression, leading to increased intestinal permeability[7].

Of note, the microbiome may induce epigenetic changes both in the intestinal epithelium and in immune cells[7]. Species bacteria such as *Faecalibacterium Prausnitzii, Roseburia* (Phylum Firmicutes), and Bacteroides genera, have anti-inflammatory action and are reduced in IBD while Proteobacteria (*Enterobacteriaceae and Bilophila*) are increased[8]. The bacteria commensal concerns the bioavailability of methyl groups through their production of folate and affects the host DNA methylation[7]. Many studies support that diet may change genome expression and induce host epigenetic

modification stably changing DNA structure[3].

Notably, lipopolysaccharides, a major component of bacteria Gram-negative[9], also play an important role in the epigenetics of IBD, as it has pro-inflammatory activity, increasing inflammatory cytokines[7] and the intestinal permeability[8].

Furthermore, the interaction between miRNA and gut microbiota in IBD patients has been emphasized by recent studies[10,11]. However, the exact mechanisms through which miRNAs are involved in IBD or dysbiosis are still unexplored. It is hypothesized that miRNAs could act as physiological regulators of the inflammatory process more than it participate in the inflammatory pathogenesis[12]. Intestinal miRNAs can interact with host microbiota and alter the growth and composition of bacterial gene expression[12]. On the other hand, gut microbiota can conversely regulate the expression of miRNA[13], altering the host status and predisposing to diseases. Some examples are the influence of gut microbiota on fecal miRNAs let-7, and miR-148, which target Enterobacteriaceae and Proteobacteria, respectively, and miR-21, which increases the abundance of IBD-related Bacteroidetes phylum and reduces the abundance of protective Firmicutes and Clostridia phylum[13]. In conclusion, the dysregulation of miRNAs could cause microbiota changes, leading to intestinal epithelial dysfunction, and immune hyperactivation[14]. Despite the recent findings, the complex relationship between intestinal microbiota and miRNAs in IBD deserves more attention.

In addition to miRNA, the role of circular RNA (circRNAs) in IBD has also been studied. CircRNAs are noncoding RNAs with covalently closed loop structures[15]. CircRNAs are involved in various diseases such as metabolic disorders [16], cardiovascular diseases[17], cancer[18] and IBD[19], showing their potential role as biomarkers for diagnosis, prognosis, or even as therapeutic targets for IBD. CircRNAs act together with miRNA in various inflammatory process, acting as miRNA sponges and altering their expression, and interacting with proteins[19]. Changes in the expression of circRNAs can impair the intestinal epithelial barrier and intestinal epithelium homeostasis[19], as demonstrated that depletion of circPan3 in human inhibited the renewal of intestinal stem cells, leading to the inhibition of epithelium regeneration[20]. A list of circRNAs has been associated with IBC, both Crohn's disease (CD) or ulcerative colitis (UC), all related to the intestinal epithelium and inflammatory process, and some are overexpressed (Circ_0001187; CircRNA_103765; CircRNA_102610; CircRNA_103516; CircRNA_102685; CircAtp9b; CircRNA_004662; CircSMAD4; CircKcnt2; CircZbtb20) while others are under expressed (CircHECTD1; CircHIPK3; CircGMCL1; Circ_CCND1; CircCDKN2BAS1; Circ_0007919; Circ_0001021)[19]. Despite this, circRNAs are not well characterized, and more in-depth studies are necessary to elucidate its role and applications in clinical practice for IBD patients.

Despite the need for greater elucidation on the role of the interaction between genetics and microbiota in the inflammatory activity of patients with IBD, it is worth highlighting that nutritional therapy is a safe and non-invasive treatment for IBD, by altering the gut microbiota and increases the production of SCFA, which appears to play a critical role in the epigenetic control of the inflammatory response[5].

DIETARY TIPS FOR PATIENTS WITH IBD

Diet-related issues are one of the main concerns that IBD patients bring to their clinicians and are known to place a substantial burden on patients' quality of life.

Every clinician who focuses their practice on IBD patient management is faced with situations where the patient with IBD requests recommendations on what types of foods he/she should avoid or consume since it is not uncommon for the patient to believe and report that certain foods seem to exacerbate his disease. It is important to emphasize that dietary manipulations must be tempered in these settings since there are some risks of restrictive diets in this nutritionally challenged population. Indeed, malnutrition in the IBD population already is high. In addition, many of these patients already have wrong beliefs about diet and adopt a series of food or food group restrictions such as a gluten-free diet, and paleo and vegan diets, which increases the risk of malnutrition. Thus, it's always important to work with a dietitian skilled in IBD management.

While it is well accepted that diet is one of the main modulators of the gut microbiota, thought to play a crucial and causative role in IBD, currently, there are no widely accepted evidence-based dietary approaches for managing patients with IBD[21-23]. In certain clinical contexts, some dietary tips are beneficial and important to emphasize. For example, a Mediterranean diet rich in a variety of fresh fruits and vegetables, monounsaturated fats, complex carbohydrates, and lean proteins, and low in ultra processed foods, added sugar, and salt[23] is recommended for all patients with IBD, a low-residue or fiber diet (avoiding, especially leafy green vegetables, nuts, seeds, beans, and kernels) for CD patients with symptomatic strictures to avoid bowel obstruction, a low FODMAP diet for patients with functional gut symptoms in association with quiescent IBD, or a low-fat diet for bile acid diarrhea after ileocecal resection, and an increased intake of fluids and calcium and reduced intake of oxalate-rich foods for those patients with kidney stones[22,23].

In the meantime, what dietary recommendations could a clinician caring for patients with IBD offer to their patients in daily clinical practice?

Despite the time-honored axiom "you are what you eat", no specific diet or nutritional intervention has been shown to prevent or treat IBD, except for the use of exclusive enteral nutrition as induction therapy for pediatric CD and the Crohn disease exclusion diet (CDED) for adults CD[5,24]. Regardless of this fact, some diet strategies help control symptoms. Based on experience in clinical practice in IBD, some dietary strategies for managing symptoms during flares can be recommended (Table 1).

Conversely, a wide range of recent studies have evaluated the relationship between ultra-processed food consumption (UPF) and IBD pathogenesis and have systematically shown a strong association between higher levels of consumption of UPFs and an increased risk of being newly diagnosed with CD[25,26]. UPF components, such as emulsifiers, thickeners,

Table 1 Tips for dietary adjustments during flares of inflammatory bowel disease[5,9,22,25-27,29]

No.	Tips
1	Avoid foods that may exacerbate diarrhea such as raw vegetables, fresh fruits with peel, prunes, spicy foods, fried or greasy foods, concentrated sweets, and caffeinated beverages
2	Avoid ultra-processed food
3	Prefer smaller, more frequent meals that are better tolerated and can increase calories and nutrient intake
4	Try to incorporate into your feed that constitutes the nutritional basis of the Mediterranean diet
5	Follow a lactose-free diet because it is not uncommon to develop transient lactose deficiency during flares
6	Avoid alcoholic drinks
7	Consider using nutritional supplements if solid foods are not well tolerated during the flare or your appetite is much reduced
8	Consider the use of EEN or CDED (PEN + modified oral diet) for Crohn disease according to the patient's tolerances

CDED: Crohn's disease exclusion diet; PEN: Partial enteral nutrition; EEN: Exclusive enteral nutrition.

salt, artificial sweeteners, phosphate, and food colorants (titanium dioxide, Azo dyes) can negatively affect the intestinal barrier, inducing dysbiosis, affecting the mucus layer, increasing the permeability of the intestinal epithelium, or directly interacting with the immune system[25,27].

Additionally, cumulative evidence suggests that a Mediterranean diet and a specific carbohydrate diet may help induce clinical remission in patients with CD, although this issue is still debated[23,28,29]. Indeed, in a recent randomized trial, researchers compared the consumption of a Mediterranean-style diet to the consumption of the specific carbohydrate diet for 12 wk in adult patients with CD who presented mild to moderate activity[30]. After 6 wk of following these 2 different diets, researchers found similar rates of symptomatic remission (46.5% *vs* 43.5% for the specific carbohydrate diet and Mediterranean diet, respectively; $P = 0.77$). Similarly, a reduction in fecal calprotectin levels was achieved in 34.8% with the specific carbohydrate diet and in 30.8% with the Mediterranean diet ($P = 0.83$). While the specific carbohydrate diet has some evidence that it can be beneficial for patients with CD, this trial was not able to show that it was better than the Mediterranean diet. For the practicing clinician, this finding has fundamental importance: The Mediterranean-style diet is less complex for patients to adopt in their busy lives compared to the specific carbohydrate diet. Moreover, this diet has the potential to bring several health benefits, including cardiovascular health outside of its favorable effects on CD patients[31].

Notably, maintenance dietary strategies in IBD lack evidence, except for the Mediterranean diet and consumption of dietary fibers which are associated with reduced risk of IBD flares, particularly CD[32]. Interestingly, some preclinical data suggest that a Westernized diet rich in saturated fat, refined carbohydrates, proteins from meat, processed foods and food additives influence the abundance, colonization, and phenotypic behavior of *Escherichia coli* in the gut, which may in turn initiate or contribute to gut inflammation. Conversely, the Mediterranean diet and specific dietary fibers may decrease *Escherichia coli* colonization and protect from invasion and adherence and consequently intestinal inflammation [33]. Moreover, from an epidemiological point of view, a Westernized diet that includes low consumption of fiber, fruit, and vegetables, has been shown to have pro-inflammatory effects and has been associated with a wide range of immune-mediated conditions, including a higher prevalence of IBD[34]. Regrettably, the Mediterranean diet has an important limiting factor, that is, its high cost, which can make access difficult in low-income countries.

Hopefully, future studies will be able to better determine the putative interrelationship between the consumption of specific food products, or their constituents, intestinal microbiome, and epigenetic mechanisms in IBD to target these factors in managing IBD. While we await the results of these studies, at present, some dietary tips that can be easily adopted by IBD patients in their busy daily lives can be appropriate, including consuming a well-balanced diet consisting mainly of fresh ingredients such as fruits, vegetables, legumes, whole grains, lean protein, olive oil, fish, limited red meat, and low-fat and nonfat dairy products, while avoiding processed meats, UPFs, food additives and emulsifiers[35-37]. Endorsing these dietary tips recent dietary guidance from the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) based on the best available evidence to date recommends that CD patients engage in regular consumption of fruits and vegetables while reducing the consumption of saturated, trans, dairy fat, additives, processed dairy or foods rich in maltodextrins, artificial sweeteners containing sucralose or saccharine, and processed food containing nanoparticles[37]. For patients with UC, the IOIBD recommends the increased intake of natural sources of omega-3 fatty acids (for instance, from oil olive, wild salmon, and other natural sources, not from supplements). Likewise, the types of food that patients with UC should avoid are similar to CD with the possible inclusion of red meats [37]. Ultimately, well-designed randomized controlled clinical trials are required before evidence-based dietary recommendations for IBD management can be made. It is also plausible that in the future personalized dietary strategies for each patient could be implemented based on better knowledge of the interaction between nutrients, gut microbiome and metabolome, and individual genetics.

ADVANTAGES AND LIMITATIONS OF EPIGENOME STUDIES

Epigenome-wide association studies brought advantages such as (1) finding novel methylation sites associated with disease; (2) evaluating the environmental impact of genetic regulation; and (3) explaining part of the heritability missed out by genome-wide association analysis. On the other hand, there are still gaps such as (1) expansion of sample size and ethnic diversity; (2) existence of the heterogeneity of sample material; and (3) causal inference of the identified epigenetic is challenging[6].

The complexity and heterogeneity of IBD make it a challenge because it is an evolving disease, and one treatment will not suit all patients. It is believed that precision medicine is the future for the treatment of IBD and among the studies and databases, epigenetics is included. Future perspectives are needed to elucidate the influence of epigenetics on diet and microbiota in IBD patients.

CONCLUSION

Diet is thought to play a role in the pathogenesis of IBD and may contribute to triggering IBD flares. In particular, some dietary components may interact with gut microbiota and genetics to trigger or perpetuate intestinal inflammation. Patients with IBD often requests recommendations on what types of foods he/she should avoid or consume, since it is not uncommon for the patient to associate their diet with symptoms. Briefly, cumulative evidence strongly suggests that higher levels of consumption of UPFs increase the risk of CD. A diet low in UPFs could encourage induced remission or control of symptoms in patients with IBD. Conversely, a healthier or Mediterranean-style diet is likely to be protective for CD development. From a therapeutic point of view, the specific carbohydrate diet, CDED, or a Mediterranean-style diet may be beneficial for the treatment of patients with CD who have mild to moderate symptoms. A diet low in red and processed meat may reduce the risk of flares in UC. In addition, a low FODMAP diet is beneficial for patients with functional gut symptoms in association with quiescent IBD. For patients with IBD in remission, the consumption of the Mediterranean diet and dietary fibers as adjunctive therapies may be recommended to reduce the risk of IBD flares, particularly in CD patients. For patients with UC, the increased intake of natural sources of omega-3 fatty acids and the following of restrictive recommendations aimed at CD patients may be useful in reducing UC flare-ups. All patients with IBD should be monitored for malnutrition, vitamin D, and iron deficiency and, in some situations, for vitamin B12 deficiency.

FOOTNOTES

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