Review

Intestinal Microbiome, Small Intestinal Bacterial Overgrowth and Inflammatory Bowel Diseases - What are the Connections?

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ABSTRACT: IBD (inflammatory bowel diseases) represent chronic idiopathic inflammatory diseases, prone to relapse in the digestive tract; it is estimated that they result from the interaction of the intestinal microbiome with the intestinal immune system. The inflammatory microbiome exerts multiple beneficial roles. Perhaps the central element to developing IBD is dysbiosis; there is still an incompletely established association between intestinal microbiome changes in patients with IBD and SIBO (small intestinal bacterial overgrowth). Influencing the intestinal microbiome may play an adjuvant therapeutic role in the treatment of IBD. We present a synthesis of the connections between the entities mentioned above.

KEYWORDS: *inflammatory bowel disease, small intestinal bacterial overgrowth, intestinal microbiota*

Intestinal Microbiome

The small intestine is, from a microbiological point of view, a transitional area between the stomach (under 10^3 colony forming units/ ml) and colon (approximately 10^{12} microorganisms per gram of colonic content), which comprises more than 1000 different species of microorganisms.

The number of microbial species present in the human gastrointestinal tract is estimated to range between 1000-1150; at the same time, there are at least 160 species coexisting in every individual [1,2].

The intestinal microbiome presents multiple roles - summarized in Table 1.

Table 1. Beneficial roles of the intestinal microbiome

• removal of undigested food elements
• removal of xenobiotics
• synthesis of vitamins/micronutrients (vitamin K, folic acid, biotin)
• signalling mechanisms for restoring the mucosal barrier
• secretion of antimicrobial substances (bacteriocins and lactic acid)
• to decrease the risk of colonization with pathogenic bacteria
• determination of physiological statuses [2,3,4]
• biological transformation of bile salts [5]
• adjuvant in the metabolism of certain drugs (sulfasalazine, digoxin) [5]

There is some data in the literature on differences between the microbiome of obese individuals and individuals with normal body weight, which could lead to differences in caloric extraction from ingested food [5,6,7].

The most important species are Firmicutes and Bacteroidetes, Proteibacteria and Actinobacteria, Veruccomicrobia and Fusobacteria [2,8]. Some of these species are considered to exert anti-inflammatory and anti-tumorigenic roles, as well as inhibition of pathogens: bacteria producing butyrate (Faecalibacterium prausnitzii, Roseburia spp) and those producing lactic acid (Lactobacillus and Bifidobacterium) [2,9].

SIBO (small intestinal bacterial overgrowth)

SIBO is characterized by bacterial overpopulation of the small bowel [10] or by alterations in the type and ratio of these microorganisms [11]. The classic definition is represented by the presence of at least 10^5 CFU/ml of intestinal aspirate.

The spectrum of clinical manifestations is very variable; from nonspecific signs and symptoms (bloating, unorganized abdominal pain syndrome, excessive flatulence, nausea, abdominal cramps) to severe consequences due to diarrhoea and malabsorption (hypoalbuminemia and underweight / weight loss) [12,13], fat soluble vitamin deficiencies: osteomalacia and hypocalcaemia secondary to

vitamin D deficiency [14,15], megaloblastic anaemia secondary to vitamin B12 deficiency [14,16], iron deficiency anaemia (by an incompletely established mechanism). The clinical significance of the symptoms described by patients (especially forms that do not present a significant biological impact) is difficult to determine, as many of the manifestations reported overlap those of irritable bowel syndrome; some reports or studies indicate the presence of a single symptom, while others describe up to 10-20 symptoms [14].

Regarding the diagnosis of SIBO, a recent systematic review [17] concluded that there is no gold-standard diagnostic test. The following diagnostic modalities are the ones available:

- Some authors consider that the best diagnostic modality is represented by intestinal fluid aspirate from the proximal jejunum, quantitative cell counting and culture [18]. Presence of over 10^5 CFU/ ml Gram negative coliform bacteria or strictly anaerobic bacteria is considered a defining criterion of SIBO [19]. However, this technique has several limitations, reducing its practical application: invasive, low availability, time-consuming, expensive, difficult transport and handling, risk of oral bacteria contamination of the duodenal aspirate, possibility of overlooking a SIBO with distal site [14].
- Empirical antibiotic treatment followed by secondary follow-up of symptom resolution [11]. There is no standardized approach in terms of the type of antibiotic used, of the doses administered or period of administration.
- Respiratory tests. They are based on the ability of the intestinal bacterial flora to metabolize an exogenous substrate (glucose, lactulose, D-xylose), producing gases such as CO_2, methane or hydrogen.

More commonly used is the hydrogen glucose breath test (HGBT). Anaerobic bacteria preferentially metabolize carbohydrate molecules. Secondary to this fermentation, result: (a) *short-chain fatty acids - SCFA* (water is retained in the intestines by a phenomenon of osmotic gradient, which causes diarrhoea); (b) *hydrogen* crossing the intestinal wall reaches the general circulation, and is removed as part of the breath volume; (c) *carbon dioxide*. The hydrogen expired is measured in ppm (parts per million) from exhaled air using precise and reliable mobile devices [20]. The positive diagnostic criteria for HGBT is represented by an increase of over 12 ppm compared to the base value after administration of 50 g glucose during the test, which lasts 2 hours [11]. Compared with aspirate and microbiological culture methods, HGBT has a sensitivity of 62% and specificity of about 82% [21].

The breath test also has several limitations: it requires a low-fibre diet for at least 24 hours before the procedure, smoking and exercise can affect its accuracy, antibiotics and laxatives should be avoided, differences in luminal pH can affect carbohydrate metabolism, rapid transit or delay in gastric emptying may generate false results [14].

Intestinal Microbiome and IBD

IBD (ulcerative colitis-UC and Crohn's Disease-CD) are chronic idiopathic diseases, prone to relapse in the digestive tract, and considered at the moment to be a result of the interaction between intestinal microbiome and intestinal immune system [22,23]. The composition of the intestinal microbiome influences susceptibility to develop IBD [24].

There is important evidence on the involvement of the intestinal microbiome in the pathogenesis of IBD; experimental findings that mice lacking intestinal germs do not develop severe colitis come to support this hypothesis [25].

Dysbiosis (altering the intestinal microbiome ratio) is probably central to developing IBD [26]. In IBD, microbiome diversity is limited.

Intestinal microbiome changes in IBD and some consequences are represented in Table 2.

Pathogenic microorganisms associated with IBD are:

Mycobacterium avium paratuberculosis (MAP)-can be isolated from water, milk and meat and is resistant to pasteurization. It seems that the incidence of positive samples of MAP is no higher in CD than in the control population if we refer to faeces tests, but is significantly increased when the comparison is made by biopsy of the distal ileum or colon [2,37,38]. However, the role of MAP in the aetiology of inflammatory diseases remains uncertain.

Helicobacter seems to be negatively associated with IBD [26]. Hepaticus, bilis, trogontum and rodentium species apparently induce an immune response against commensal bacteria, and secondary immune-mediated intestinal inflammation [26,39].

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Table 2. The special features of the intestinal microbiome in IBD

• Decrease of species of Firmicutes (Clostridium cluster IX and IV)
▪ Associated with reducing the amount of SCFA (of which butyrate has the ability to inhibit pro-inflammatory cytokines)
▪ Decrease of Faecalibacterium prausnitzii was recently found in Crohn's disease (CD); administration of this strain has anti-inflammatory effects (27,28)
• Decrease in species of Bacteroides (27,28,29)
▪ Including "spatial reorganization" of its species
▪ Increased bacterial adhesion occurs (30)
• Decrease in species of Bifidobacterium adolescentis, Dialister invisus, and increase in frequency of Ruminococcus gnavus (27, 31)
• Decrease in species of Roseburia hominis, Lactobacillus, Bifidobacterium si Akkermansia (2, 32, 33)
• Overgrowth of sulphate-reducing bacterial species (Desulfovibrio spp.), especially in patients with ulcerative colitis (UC) and pouchitis (27, 34)
• Increase in number of bacteria belonging to phylum Bacteroidetes (26, 35)
• Initiating role of chronic inflammation in overpopulation with species of Proteobacteria (26)
• Increase of pathogenic E.coli concentration, especially in ileal Crohn's Disease (26, 36)

Adherent invasive Escherichia coli (AIEC)- adhere and invade the epithelial cells. Prevalence of AIEC in ileal biopsies of patients with Crohn's disease is significantly higher than in control patients (36.4% vs. 6.2%) [40].

Clostridium difficile is incriminated in inflammatory disease flares, with rates varying widely between 5-60% [41]. Administration of immunosuppressive drugs increases the risk by 2-3 times. Currently, it is unclear whether C. difficile contributes to the intestinal inflammation characteristic of IBD or patients with such diseases are susceptible to infection with C. difficile [2].

Campylobacter-with its species, ureolitycus and concisus, alongside jejuni, can alter the intestinal barrier by translocation of commensal bacteria [2,42,43]. In a survey from 2011 [44] a several times increase in the risk of developing Crohn's disease was demonstrated in the first year, as well as the next 10 years, after acute infection with C. jejuni.

Salmonella. In a 2011 study [44] it was shown that infection with non-typhoid strains of Salmonella increases the risk of both ulcerative colitis and Crohn's disease in the first year after infection (5.4 times higher risk in the first year and 1.6 times in the next 10 years).

Other microorganisms. Epstein Barr virus can promote inflammation and increase multiplication in B lymphocytes [2,45]. Recently, the presence of Fusobacterium varium in significantly higher titre has been demonstrated in patients with UC [46]. Anti-K. pneumoniae antibodies are more common in patients with IBD (the severity of colonic inflammation increases in experimental models, the expression of IL-1β, IL-6 and TNF-α increases) [26,47]. Other possibly involved microorganisms: CMV, Candida albicans - the exact role has not yet been established.

SIBO and IBD

Causes of SIBO development in patients with IBD are multiple: postoperative absence of the ileo-cecal valve, presence of entero-colonic fistulas, motility disorders, intestinal strictures, alterations in the intestinal microbiome.

In current clinical practice, the use of respiratory H_2 tests presents high diagnostic accuracy, which is why it is commonly employed for highlighting SIBO.

In a 2009 study, Klaus et al [48] identified a prevalence of 25.3% of SIBO in patients with diagnosis of Crohn's disease, who reported an increase in the daily number of stools or flatulence. SIBO patients presented on average more stools/day (5.9 vs.3.7) and a lower body weight (63kg vs. 70kg). The association of SIBO was positive in patients with intestinal resection or mixt intestinal and colonic impairment, but no positive association with Crohn's disease activity index was found.

Changes in the treatment of IBD in recent years have led to the assumption that biological or immunosuppressive medication may increase the risk of infections. Regarding the risk of intestinal bacterial overgrowth, the assumption has recently been refuted; overall prevalence of SIBO in patients in remission was 16.8%, with no noticeable differences between patients under immunosuppressive, biological or mixed treatment [49].

When using H_2 glucose and lactulose breath tests to highlight SIBO and oro-cecal transit time, one can observe that the oro-cecal transit time was significantly higher in patients with CD compared to those with UC, and the prevalence of SIBO is higher in patients with CD (45.2%) compared to those with UC (17.8%) [50].

Similar data have been reported in a very recent study [51]: when using HGBT, prevalence of SIBO in patients with IBD is 20.6%, higher in CD versus UC (30.2% vs. 14.1%).

Influencing the Intestinal Microbiome as a Treatment Modality in IBD

The role of probiotics

There are few data in the Cochrane database regarding probiotic efficiency in CD [27]; Lactobacillus GG seems ineffective as an adjunct to standard medication in maintaining clinical remission in CD [52]. It appears that Saccharomyces boulardii could have a positive improvement effect on maintaining the permeability of the intestinal barrier [28,53].

In the case of UC, a mix of probiotics called VSL # 3 (Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus, Streptococcus thermophilus) proved effective as adjuvant therapy in maintaining remission, as well as in prevention of pouchitis [27,54]. Similar results were obtained for E. coli Nissle 1917 [55].

The role of prebiotics

Administration of fructo-oligosaccharide in patients with CD apparently has no clinical benefits [56], but was associated with a significant reduction in Harvey Bradshaw index and an increase in faecal bifidobacteria concentration [57].

As for UC, different prebiotics proved a certain degree of efficiency: Germinated barley foodstuff and Ispaghula husk are effective in inducing remission in patients with moderate to severe UC [27,58,59]; oligofructose combination with inulin seems to reduce the degree of inflammation [60]; inulin reduces inflammation in pouchitis [61].

The role of antibiotics

There are numerous data in the literature concerning the effectiveness of metronidazole and ciprofloxacin in the treatment of pouchitis and CD, as well as in UC.

Rifaximin (an antimicrobial agent active in the intestinal lumen) appears to be effective in inducing remission in patients with moderately active CD (remission rates of up to 62% in week 12) [62].

Helminth therapy

Colonization with live strains or extracts of Schistosoma mansoni or Hymenolepis diminuta appear to exert effects against chronic colitis [2, 63], while Trichuris suis and Necator americanus could have therapeutic potential in IBD [2,64,65].

Faecal microbiota transplantation

It is a relatively safe treatment modality in diseases like C. difficile infection (efficiency up to 92%) and IBD (there are reports in the literature of efficiency from 0% to 76%) (2,66). It is not however recommended in cases with important intestinal inflammation [2].

Conclusions

Involvement of the intestinal microbiome in the aetiology of IBD is an area of great interest, likely to be elucidated in the coming years. Presence of SIBO to a quite important extent creates the possibility of using H_2 breath tests to identify the patients who could benefit from influencing the intestinal microbiome.

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