Probiotic Use in IBD Patients

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Probiotics demonstrated to be effective in the treatment of inflammatory bowel disease (IBD). However, the safety profile of probiotics is still insufficiently explored.

Crohn disease ulcerative colitis inflammatory bowel disease probiotics prebiotics synbiotics

1. Introduction

Inflammatory bowel disease (IBD) includes two major disorders: Crohn's disease (CD) and ulcerative colitis (UC). With respect to the pathogenesis of IBD, the scientific literature suggests a fundamental role of the microbiota residing in the intestinal lumen and an inappropriate immune response to microbial factors [1][2]. The intestinal microbiota is acquired at birth—primarily influenced by delivery mode, changing rapidly during the first year of life according to nutritional factors such as breast feeding or artificial nutrition [3][4]. It is unique for each individual, although environmental factors including diet, drugs—especially anesthetics and antibiotics—stress and diseases may cause significant fluctuations [5]. Modifications of the quality and quantity of microbial communities may in turn contribute to intestinal inflammation, promoting IBD in genetically predisposed individuals [6]. On the other hand, intestinal microbiota can be modulated using probiotics, with attenuation of intestinal mucosal inflammation [7][8]. For example, in patients with UC, *Escherichia coli* 1917 Nissle was as effective as 5-acetyl salicylic acid in preventing relapse, and *Lactobacillus* GG was even more effective than mesalamine in prolonging relapse-free time [9][10]. The probiotic combination of VSL#3 was able to induce and maintain remission and reduce UC activity [11][12]. Moreover, *Lactobacillus reuteri* ATCC 55,730 showed to reduce clinical and endoscopic disease activity in children with UC [13]. In contrast, based on randomized controlled trials (RCTs) the efficacy of probiotics in CD is limited [14], although the addition of a prebiotic to *Bifidobacterium longum* showed a modest benefit in a small study [15]. Moreover, Kazemi et al. in patients with IBD detected a large decrease in C reactive protein and TNF-alpha cytokine following a treatment with probiotics [16]. In a recent study, we observed a reduction in the occurrence of major adverse outcomes related to IBD—requirement of treatment with systemic steroids, hospitalization, and surgery—in patients exposed to probiotic supplementation for 25–74% of the disease duration [17]. Although the US Food and Drug Administration recognized as safe some probiotics when added to food [18], the World Health Organization and the Food and Agriculture Organization of the United Nations in 2002 [19], reported that, theoretically, probiotics may be responsible for: Systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, gene transfer and minor gastrointestinal symptoms [20]. Hempel et al. reviewed 622 probiotics intervention studies in human for adverse effects; among them, 387 studies reported the

presence or absence of specific adverse events including fungemia and bacteremia potentially associated with probiotic exposure [21]. Overall, in RCTs, the relative risk (RR) for gastrointestinal infections or other adverse events, was not significantly increased (RR 1.06; 95%CI: 0.97–1.16; p = 0.201) in patients exposed to probiotic compared with controls [21]. The authors conclude that "[…] despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence". For example, several studies and meta-analyses have assessed the efficacy of probiotics in IBDs. However, although data regarding side effects caused by probiotic have been reported by some authors [14], those related to meta-analyses are absent.

2. Current Insights on Probiotic Use in IBD Patients

The results of our meta-analysis of RCTs show that patients with IBD exposed to probiotics experience side effects more frequently than those exposed to placebo.

There exists a robust body of literature on probiotics in patients with IBD; however, the majority of available studies are clinical trials designed to evaluate the efficacy of probiotics and prebiotics versus placebo, or other conventional therapies, for the achievement or maintenance of remission in patients with CD or UC [22]. In spite of that, the safety profile of probiotics and prebiotics in patients with IBD remains less explored, probably because they have been consumed as food for hundreds of years, especially in dairy products such as yogurt (the most famous are the Sardinian one: gioddu, the Caucasian: chefir; the Russian: kumis and the Egyptian: leben and for this reason perceived as safe. Described since ancient time in the Bible as a precious food, the acid milk regained popularity with the Nobel prize I.I. Mechnikov, who suggested its consumption against senility, up to nowadays with several probiotic strains, alone or combined, commercially available in hundreds of different products. Although the widespread use of probiotics, prebiotics and synbiotics, studies usually miss to report adequately adverse events related to their use, despite in some subgroups of patients their use was associated with severe side effects [20][21].

Our meta-analysis attempted, for the first time, to investigate the occurrence of side-effects in IBD patients undergoing treatment with probiotic/synbiotics and contrary to expectations, in a total of nine randomized placebo-controlled trials, we found that the risk of total side effects was higher in patients exposed to probiotics (RR 1.35) and the effect persisted (RR 1.33) when the analysis was restricted to double-blind RCTs. Interestingly, we observed a rising trend in the risk when the analysis focused on gastrointestinal symptoms (RR 1.78), or more specifically on abdominal pain (RR 2.59). These results are consistent with a previous meta-analysis addressing the benefit of probiotic in patients with UC and CD. Derwa et al. reported as a secondary endpoint of their meta-analysis a RR of 1.21 (95% CI = 0.64–2.27) to develop adverse events from six controlled RCTs in UC patients exposed to probiotics compared with placebo. The occurrence of adverse events reported by only one RCT did not reach a significant difference between CD patients treated with probiotics or placebo [14]. Similarly, in a systematic review and meta-analysis on the efficacy of probiotics, prebiotics, synbiotics and antibiotics in irritable bowel syndrome (IBS)among 36 trials with a total of 4183 patients Ford et al. found that patients treated with probiotics experienced adverse events more often as compared with those treated with placebo (19.4% versus 17.0%)

although the RR was not significantly higher. Moreover, the authors detected significant heterogeneity among studies [23].

These findings are difficult to explain, since they are in contrast with the intrinsic meaning of probiotic “pro bios” in favor of life. For example, in a recent study conducted in a series of 200 IBD patients including both CD and UC, we observed a 93% reduction in the need for systemic steroids, hospitalization, and surgery related to the disease in CD patients, and a 100% reduction in UC patients taking probiotics for more than 75% of disease duration [17]. Similarly, in a study including 170 IBD patients exposed to probiotics use, we noticed a reduction in the occurrence of skin lesions [24]; however, this reduction was dependent on the amount of probiotics taken [17][24]. Probably, the duration of treatment with probiotics may influence outcomes. In the two previous studies probiotics were taken for years, whereas in the RCTs included in our meta-analysis they were taken for a maximum of one year [25][26]. In general, it is an increasingly accepted concept that probiotic benefits may be dose-dependent, only manifesting themselves upon achievement of a threshold dosage [27]. Probiotic amounts in currently used formulations show a wide variability, ranging from 10^7 to 10^{11} CFU/g, which likely implies a high variability in the number of viable cells included in the products. It has been ascertained that the percentage of live cells capable of driving an effective change in fecal microbiota can vary from 1% to 92% [27]. We can assume that only formulations with a high bacterial load may exert a positive effect, while those with a low bacterial content have no effect or are even contrary to expectation. For example, daily doses of Lactobacilli equal to or greater than 10^{10} CFU induced a significant reduction in the duration of diarrhea in children. For lower doses of probiotics, an increase in the duration of diarrhea was paradoxically observed [28]. In addition to the duration and dose, the probiotic strain may play a central role in health and disease. For instance, in a double-blind placebo-controlled trial, Mangalat et al. observed a prominent proinflammatory triggering following the administration of *L. reuteri* in healthy adults as revealed by increased fecal calprotectin [29]. Moreover, some individuals taking probiotic may temporarily experience an increase in gas production and swelling, in addition to constipation, which in most cases disappears in a few weeks [30][31]. Several lactic bacteria produce bioactive substances such as histamine, tyramine, and phenylethylamine, which may induce headaches and other complaints [32]. These bioactive molecules are normally inactivated by mono-amino oxidases (MAO) in the intestinal wall and liver [33]. Minderhoud reported an alteration in neuroendocrine cells in IBD patients with IBS-like symptoms associated with lower MAO activity and an increase in biogenic amines [34]. A number of additional biogenic amines have also been isolated from bacterial strains commonly used in probiotic preparations [35]. These observations may provide a partial explanation for the occurrence of gastrointestinal side effects in patients exposed to probiotics including abdominal cramping, nausea, soft stools, flatulence, and taste disturbance, occurring in subjects receiving probiotics [20]. The gut microbiota resides almost completely in the colon and, to a lesser extent, in the small bowel. For this reason, it is plausible that probiotics affects especially colon microorganism communities. For the same reason treatment of IBD patients with probiotics is more effective in UC than in CD. In a review addressing the quantitative risk–benefit analysis of probiotic use in IBS and IBD, Bennet reported gastrointestinal symptoms as the most frequent side effects [36], although it is difficult to find a clear cut between gastrointestinal symptoms generated by the natural course of IBD and those generated by probiotic exposure. Another critical point is that in RCTs comparing probiotics with placebo in IBD patients, the conventional treatment was not similar in both arms, and in some series, the difference was

statistically significant [15][26][37][38]. Lack of uniformity in the concomitant medications in each of these studies may be one limitation of this systematic review and meta-analysis. In addition, the majority of RCTs lacked standardized methods for the assessment of side effects (for instance, a validated questionnaire), or their graduation. Moreover, the strain, amount, schedule, and duration of probiotics/synbiotic treatment used in RCTs were extremely variable. Finally, but no less important, we were unable to relate a specific strain to side effect occurrence, due to the paucity of data.

3. Conclusions

In conclusion, at present, the small number of RCTs, the heterogeneity of the design and probiotic schedule across studies do not allow a satisfactory explanation of the apparent negative effect of probiotics in causing side effects in IBD patients. Future studies are required to identify the most appropriate species, strains or mixture thereof, and amounts of probiotics that are effective for IBD, while limiting potential side effects. To achieve this goal is fundamental that researchers measure and carefully report safety profile of probiotic/prebiotic/synbiotic in order to provide physicians guidelines to manage their patients with this treatment.

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