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Review Article

Gut microbiota, dysbiosis and colon lavage

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ABSTRACT

Gut microbial dysbiosis is considered an alteration of diversity and abundance of intestinal microbes, which contributes to the onset of many disorders. Several factors cause dysbiosis, depending on lifestyle (nutrition, stress, environment, smoking, physical activity) or particular diseases (inflammatory, autoimmune, chronic diseases). Drugs (i.e. antibiotics, anticancer drugs), as well as medical and surgical procedures, can often cause dysbiosis. Mechanical bowel preparations (MBP) and the so called bowel cleansing have an immediate impact on intestinal microbial composition. Whether these acute changes may lead to any clinical consequences is still unknown. It is tempting to speculate that such dysbiosis fostering events, at least in patients already presenting abdominal complaints, such as irritable bowel syndrome (IBS), or inflammatory bowel disease (IBD) patients, may drive additional or more severe symptoms. Recently, the possibility of using probiotic supplementation has been addressed in the literature, with the purpose to counteract intestinal dysfunctional changes observed in relation to a dysbiotic state. Whereas probiotics are recognized to be effective and safe in restoring gut microbiota dysbiosis, preliminary evidence suggest that this approach may prove helpful even in case of transient dysbiotic states related to colonoscopy bowel preparation.

1. Introduction

Surprisingly, our body is composed of microorganisms (bacteria, protozoa, fungi, viruses, and archaea) to a greater extent than human (*H. sapiens sapiens*) eukaryotic cells [1], therefore it is presently considered a super-organism (or holobiont). Intestinal microbiota (IM) is the most important among the various microbial consortia inhabiting our body, because of its complex relationship with health and disease. Researchers have started to examine its architecture in depth only recently, thanks to the introduction of culture-independent methods, which have overcome standard classical microbiology tools, unsuited to investigate most of the microbial species harboured in the gut [2,3]: such "omics" techniques (meta-genomics, meta-transcriptomics, meta-proteomics etc.) have broadened our horizon, generating huge data sets, that can be proficiently mined for new information about composition and functional properties of the vast microbial communities we host in the gut, as well as in other body sites (see, for instance, the Human Microbiome Project) [4]. All microbiota, among which IM, are consortia of microorganisms living in symbiosis with the host, generally with reciprocal benefit [5–7]. IM can be considered a meta-stable system, i.e. a system in continuous dynamic balance with its host [8]. Such balance is mostly preserved (microbiota resilience) even in face of sudden changes in IM, as observed after antibiotic treatments or acute intestinal infections, diet modifications or other external factors, which impact composition, evenness and relative species abundance, and thus reshape the IM itself [9]. Resilience is a very important property of a healthy microbiota: it is a factor protecting us from some dysbiotic state associated diseases, like IBD, IBS, or metabolic disorders (diabetes, obesity) [3]. On the other hand, a dysbiotic shift of the microbiota may have implications for human health, and even lead to chronic disease [10]. When microbial homeostasis is altered, expansion of an opportunistic or pathobiont flora could occur within the gut microbiota [11]. In normal conditions, symbionts (bacteria generally useful for human health) restrain the growth of these bacteria: examples are various *Lactobacilli* and *Bifidobacteria* strains, *Faecalibacterium prausnitzii* (*Firmicutes* phylum), *Bacteroides thetaiotamicron* (*Bacteroidetes* phylum), which are usually considered "anti-inflammatory species" [11]. In case of dysbiotic changes, opportunistic infections may develop (for instance by means of *Enterobacteriaceae* or *Streptococcaceae* overgrowth), followed by mucosal low-grade inflammation, increased intestinal permeability and eventually by the so called "leaky gut" [3,12]. A

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vicious cycle can ensue, since leaky gut worsens inflammation and dysbiotic alteration, ultimately leading to systemic inflammation and related diseases [13]. The long list of chronic illnesses potentially related to a dysbiotic condition includes nutritional disorders (type 2 diabetes, obesity, metabolic syndrome), chronic intestinal inflammatory diseases (IBD), functional disorders, like IBS, hepatic disorders, such as NASH and NAFLD, chronic cardiovascular diseases, atopy and allergies, colorectal cancer, chronic neuropsychiatric disorders (autism, depression), and finally arthritis [3]. A high fat diet has been demonstrated to increase pro-inflammatory gut molecules, and augment intestinal permeability, thus creating the inflammatory conditions for a potential chronic disease [14]. While this causal relationship between leaky-gut and chronic disease is clear, we still lack a universally accepted definition of dysbiosis [15]. In particular, the complex mechanisms leading to a state of disease from the perturbation of microbial homeostasis have not been fully elucidated, as well as the mechanisms able to counterbalance this alteration. The outline is probably better understood for some diseases, such as IBD and Crohn's disease, in which loss of richness of particular species has been observed [16,17], less so for others, such as many neuro-psychiatric diseases, including autism and depression [18], in which perturbation of the so-called microbiota-brain-gut axis has been assumed. The most severe gut dysbiosis is observes during *Clostridium difficile* infection [19], the paradigm of a formidable expansion or blooming of a single "keystone pathogen", *C. difficile* [12], possibly followed by the development of a potentially lethal inflammatory bowel disease, i.e. pseudomembranous colitis [17].

Reduction of beneficial microbes, expansion of pathobionts, and decrease of microbial diversity are indeed the main determinants of gut dysbiosis [15]. A recent hypothesis postulates that a change in human ancestral microbiota can alter the context in which immunological, metabolic and cognitive development occur in early life, thus predisposing to an increase of chronic diseases [20]. The different manifestations of dysbiosis share some common biological and microbiological features: (a) reduction of short-chain fatty acids (SCFAs) producing bacteria, especially butyrate (specifically *Faecalibacterium*, *Roseburia*, *Lachnospiraceae*, *Eubacterium*); (b) a higher degradation of mucous layer, with displacement of *Akkermansia muciniphila*, a useful symbiont with anti-inflamatory properties; (c) reduction of hydrogen and methane production in the intestine, and simultaneous increase of hydrogen sulphide (H_2S), which is noxious to the epithelium; (d) rise in relative abundance of Gram-negative bacteria (especially *Proteobacteria*) expressing lypopolisaccaride (LPS) in the outer membrane, also known as endotoxin, the accumulation of which determines and stimulates the inflammatory process; (e) increase of oxidative stress in the mucosa, which implies bacterial proliferation where oxygen is more available [21,22].

Persistence of these mechanisms is able to maintain and enhance a state of dysbiosis. In particular, since SCFAs play a significant role in many metabolic and immunological activities, their reduced production is pivotal in introducing disturbances in the aforementioned, acting as "triggerfor several diseases, including cardio-metabolic related ones [23].

Recently, the acute microbial change induced by bowel lavage for colonoscopy procedures, and its related clinical consequences, has gained attention. Preparing for colonoscopy requires bowel cleansing regimens that combine fasting and laxatives (mainly in the form of drinks). While such preparations are able to alter the rich microbes array hosted in the gut, research suggests that the primal microbiota shape is restored within two to four weeks. Actually, whether this microbial populations shift has any clinical counterpart, or any (metabolic) long-term sequelae, is not clear yet, neither so if early probiotics supplementation show any preventive effect.

In this review we focus on: (a) the main causes of dysbiosis; (b) bowel preparations induced dysbiosis; and (c) the most recent clinical evidence of probiotics supplementation to prevent this disorder.

2. The eukariote-microbiota super-organism concept and intestinal dysbiosis

From an evolutionary point of view, the already mentioned symbiotic relationship between the two ecosystems of human body and microbiota is ordinarily conserved, because of their natural mutual advantage. The three most relevant functions exerted by IM in the intestinal tract are: (a) competition with pathobionts for colonization; (b) polysaccharides digestion with production of SCFAs; (c) cooperation with the immune system [3]. Moreover, IM is able to undergo rapid variation in response to extreme environmental changes (shortage of food and water, changing in climate and habitat, diseases with a high mortality rate), conferring optimal adaptability to the host too, eluding the need to wait for evolution to act on the genetic pool in a much longer lapse of time [8]. In short words, human super-organism adaptability strongly depends on epigenetic influences exerted by the IM.

Therefore, dysbiosis represents the either temporary or permanent failure of homeostatic equilibrium of IM [15]. As already said, alterations within the beneficial microorganisms population, expansion of pathobionts, and reduction of biodiversity are considered the microbial drivers that lead to dysbiosis. This is the case of IBD, in which the inherent specific changes of gut microbiota have recently been revealed [17], whereas in IBS a significant reduction of *Bifidobacteria* and *Prevotella* has been observed [24].

Small intestinal bacterial overgrowth (SIBO) syndrome is another representative example of pathobionts expansion, generally due to an increase of *Proteobacteria*, and in particular, inside the *Enterobacteriaceae* family, of *Salmonella*, *Shigella*, and *Escherichia* genera: it causes a variety of functionalgastrointestinal symptoms, in the absence of maldigestion or malabsorption [25]. On the other hand, vaginal or intestinal *Candida albicans* overgrowth that follows large-spectrum antibiotic treatments is prototypical of fungal (mycobiota) expansion [26,27]. Exploration of mycobiota is still at an early stage, likewise comprehension of its role in gastrointestinal diseases, such as IBD.

A reduction of microbial diversity is common in type 2 diabetes, and in obesity, as well as in the elderly, in which a particular form of senescence-related dysbiosis causes severe immunological disturbances. Genetics and environmental factors come into play in old age: a reduced intake of prebiotics, vegetables and fruit is especially important in maintaining this serious condition. Elderly people also show reduced abundance of SCFAs (in particular butyrate) producing bacteria, including *F. prausnitzii*, and other species displaying anti-inflammatory properties [28]. As a matter of fact, significant differences have been observed between the microbiota of healthy old subjects, which is similar to the IM of healthy adults, and the one hosted in the frail, high-risk, elderly home residents [29]. In such cases, a strong correlation has been observed between a drastic contraction in biodiversity and the simultaneous deterioration of autonomy, nutritional status, depression and anxiety-related parameters.

Overall, these qualitative and quantitative variations end up in a deterioration of IM, a phenomenon today conclusively linked to immunosenescence [30]: it is characterized by a less biodiverse IM, a dysbiotic condition whose stigmata are a high level of pro-inflammatory compounds (so-called "inflammaging"), and a substantial curtailment of microbial saccharolytic metabolism with consequent boost of the proteolytic one.

3. Dysbiotic consequences of colonoscopy preparation

Although efficacy and safety of various, mainly polyethylene glycol (PEG) based, intestinal preparations have been extensively studied, their effect on IM composition has rarely been questioned. In 2006, a first study was published on possible IM disorder subsequent to bowel cleansing for colonoscopy [31], followed by other six, where different methodologies, populations studied and duration of investigation were chosen [32–37]. Table 1 summarizes the seven studies published so far.

In general, preparations for colonoscopy can display multiple negative effects on the IM: PEG-based ones rather efficiently remove intestinal mucus, aside from flushing-outëndoluminal bacteria, consequently altering microbiota balance. Further on, bowel preparations convey oxygen into the lumen, thus negatively affecting anaerobes populations; in addition, they can reduce availability of nutrients (especially fibres) used for bacterial metabolism, and also accelerate intestinal transit time. All these putative factors can rapidly modify IM composition and its homeostasis, inducing a transient dysbiosis due to variation in relative abundance of both mucosa-adhering and luminal bacteria. However, despite the majority of studies conducted so far have demonstrated the efficacy of bowel preparations to induce compositional distortion and reduction of microbial diversity, comparable to that observed with antibiotics administration [38], no unique general pattern of microbial modification has emerged; likewise, no information on the duration of this effect has come out yet. Some studies report a short effect on microbial composition, while others report changes lasting at least 2 weeks, and in some cases up to 4 weeks after colonoscopy. Overall, studies suggest that microbiota variations seem more sustained in patients suffering from diseases per se associated to intestinal dysbiosis, such IBS or IBD. Moreover, some reversible changes affect composition of the mucus layer, even if these phenomena have not been easily demonstrated in the present studies.

Increase of *Proteobacteria* and *Enterobacteriaceae* combined with a reduction of *Lactobacilli*, as well as a drastic change in Gram-positive to Gram-negative ratio, has been commonly observed, similarly to those previously highlighted in subjects with infectious diarrhea [39].

A recent study [37] evaluated IM composition in ten subjects undergoing colonoscopy for colorectal cancer screening, with normal endoscopic findings. Faecal samples were collected before, immediately after and one month after the intake of a 4-liters PEG preparation, and were examined via 16S rDNA Ion Torrent profiling, to evaluate changes eventually occurred in gut microbiota composition (Fig.1). At phylum level (Fig. 1a) results indicate reduction of the *Firmicutes* relative abundance, and increase of *Proteobacteria*, both restored one month later. At class level (Fig. 1b) increase of *γ-Proteobacteria* and *Coriobacteria*, and significant reduction of Clostridia were observed after colonoscopy. After one month, *γ-Proteobacteria* still showed a 2.5-fold reduction, compared to baseline. Finally, at family level (Fig. 1c) strong reduction of *Lactobacilli* and raise of *Enterobacteriaceae* were recognized; these modifications still persisted one month after colonoscopy. In addition, *Streptococcaceae* showed a 4-fold increase after 30 days. As mentioned before, these quantitative and qualitative alterations (in particular the increase of *Proteobacteria*) are very similar to those observed in moderate-severe diarrhea episodes occurring in children in developing countries [39]. Interestingly, as reported in the literature, significant increase of *Streptococcaceae* can also be related to faecal protease contents and the simultaneous increase of intestinal permeability, which often take place in many intestinal and extra-intestinal diseases [40–42].

The majority of the above cited studies mainly addressed IM modifications linked to bowel cleansing immediately after colonoscopy, or the next the day. Very few data have been reported concerning potential side-effects related to change of IM composition after a longer period. The only exception is a survey by Zubarik et al. [43], who reported persistence of abdominal pain in 5.4% of subjects 30 days after colonoscopy. Similar data (5.3% of subjects complaining post-colonoscopy abdominal pain) were also reported by Bini et al. [44]. Another study, conducted by Ko et al., reports a significant reduction of patient satisfaction and increased social costs related to colonoscopy [45]. According to the authors, 11% of patients complain about abdominal discomfort on the 7th and 30th day post-colonoscopy, and 94% of the subjects take 1–2 days off work, due to a minor and not well specified symptomatology.

Analysis of the mentioned literature shows that bowel preparation is definitively able to induce a short-lasting perturbation, and possibly a more prolonged one, of IM composition, with loss of bacterial diversity.

A practical question arises, that is, whether supplementation with probiotics might prevent such dysbiosis and/or reduce duration or severity of symptoms occurring *de novo* after colonoscopy. In addition, at least theoretically, reduction of microbial diversity induced by bowel cleansing might have some attractive features, that we will pinpoint below.

A randomized double-blind controlled study has been recently performed to evaluate the role of probiotics after colonoscopy [46]. The study enrolled 259 patients, supplemented daily after colonoscopy with a mixture of oral probiotics, containing *Lactobacillus acidophilus NCFM* and *Bifidobacterium lactis Bi-07* (2.5×1010 capsule CFU), or placebo. Patients were instructed to self-report intestinal symptoms on day 1, 2, 4, 7 and 14. Primary end-points of the study were assessment of the time necessary to reach resolution of abdominal pain or distension following colonoscopy, and bowel movement pattern change. The results of the study showed that patients receiving probiotics experienced a reduced duration of abdominal pain (1.99 vs 2.78 days, $p < 0.033$), while no differences were observed between the two groups as far as abdominal distension and bowel movement pattern were concerned. Interestingly, a subgroup analysis revealed that patients who already suffered from abdominal pain before colonoscopy reported symptomatic improvement (i.e. less days with abdominal pain) if treated with probiotics (2.16 vs 4.08 days, $p < 0.0498$).

The same group has recently replicated the study using carbon dioxide insufflation during colonoscopy [47]. This system allows quick reabsorption of CO2 at tissue level, thus improving abdominal distension. Two hundred and forty subjects undergoing colonoscopy were randomized to receive either the same probiotics mixture or placebo: no significant difference in post-procedural discomfort, bloating or time to restore normal bowel function was proven between the two groups. However, a subgroup analysis of the patients with pre-existing IBS-like symptoms showed a reduced incidence of bloating after probiotics intake.

These preliminary studies seem to indicate an effective role of selected probiotics in ameliorating minor symptoms arising after colonoscopy, such as abdominal pain and distension, particularly in patients already exhibiting IBS-like symptoms before the examination.

Finally, it appears somehow paradoxical that a transient reduction of microbial diversity may have positive implications too. For example, one factor, identified as bad outcome predictor following faecal microbiota transplantation (FMT) in the treatment of patients with recurrent C. difficile infection, is poor bowel preparation at the time of procedure [48].

Table 1
Mechanical bowel preparations and intestinal microbiota changes: a summary of main characteristics and results of published studies.

Author (ref)	Year	No. patients	Bowel cleansing	Sample	Study type	Collection timing	Dysbiosis
Mai [29]	2006	5	Not reported	Faecal	Open	Before colonoscopy, During Colonoscopy, after 6-8 weeks	Yes
Harrell [30]	2012	12 healthy donors	PEG 4 l	Mucosa	Open, 3 groups	Before colonoscopy, after 1 week	Yes, reduction of microbial diversity
Gorkiewicz[31]	2013	4 healthy donors	PEG 150 g/ for 3 days	Faecal + mucosa	Open	Before colonoscopy, after 4 days after 2 weeks	Yes, IDB-like
O'Brien [32]	2013	20 pazients	PEG 2 l + bisacodyl	Faecal	Open	Before colonoscopy, after 1 week after 4 weeks after 12-24 weeks	No
Jalanka [33]	2015	23 healthy donors	PEG 1 l × 2 vs 2 l	Faecal	RCT	Before colonoscopy, During colonoscopy, after 2 weeks, after 4 weeks	Yes, short duration, ridotta reduction of microbial diversity
Shobar [34]	2016	10 IBD pazients and 8 healthy donors	Not reported	Faecal + mucosa	Open	Before colonoscopy, During Colonoscopy	Yes, reduction of microbial diversity in IBD and healthy subjects
Drago [35]	2016	20 healthy donors	PEG 4 l	Faecal	Open	Before colonoscopy, During colonoscopy, after 4 weeks	Yes, prolonged duration

RCT = Randomized Clinical Trial.

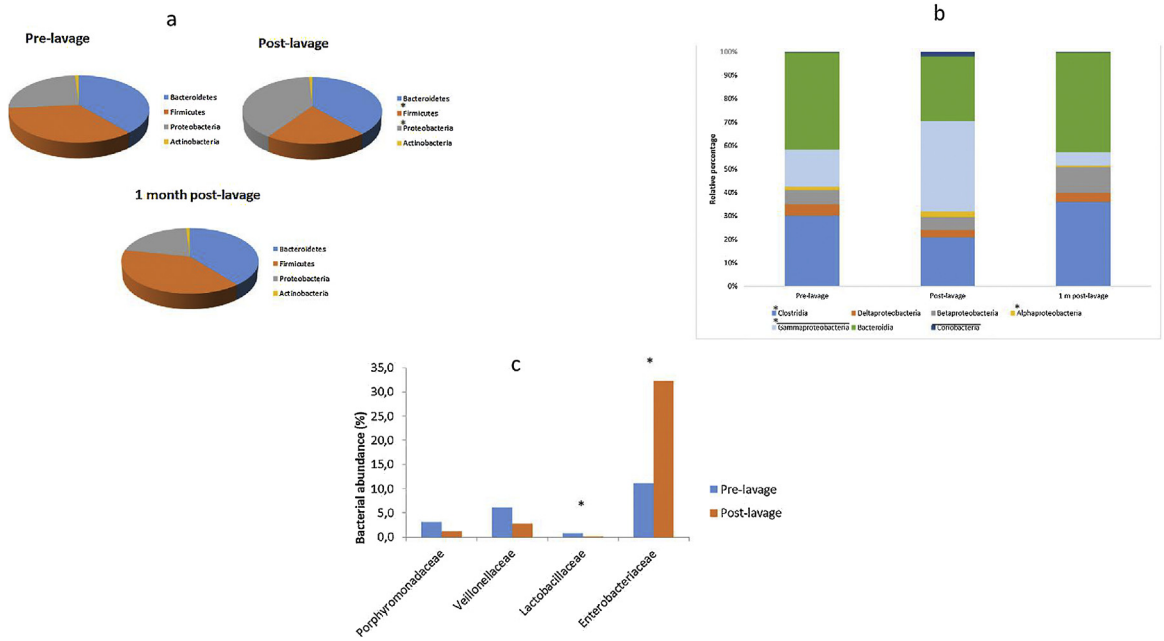

Fig. 1. Bacterial abundances after mechanical bowel preparations (Ref. [37]). *Statistically significant ($p < 0.05$).

4. Conclusions

Maintaining a healthy gut microbiota is now recognized as one of the most critical factors regarding overall health. Whenever damaged or disrupted, steps should be taken to re-establish a healthy microbiota as soon as possible. Colonoscopy is universally recognized as the most accurate test for colorectal cancer detection, and early diagnosis saves lives. It is considered safe when performed by doctors experienced in the procedure. Nevertheless, these acknowledged benefits may be at least marginally/transiently obscured by the recognition that the associated bowel cleansing, essential to a successful exploration of the colon, may induce both a dysbiotic state and some abdominal symptoms resembling those experienced by IBS patients. Despite the limited scientific evidences regarding clinical impact, relevance and time-frame of this phenomenon, it is very likely that early probiotic supplementation may reduce or prevent it. It is not clear yet whether all the subjects, or more likely only those already exhibiting abdominal symptoms should be treated. In this respect, posology, type of strains to be supplemented and optimal duration of prophylaxis remains to be clarified. Finally, some recent data may indicate that the transient reduction of microbiota diversity associated with bowel preparation may also prove to be beneficial, at least in the frame of FMT [49,50].

Conflicts of interest

None declared.

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