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Dysbiosis of the Intestinal Microbiota in IBS

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1. Introduction

The human gastrointestinal (GI) microbiota is a rich and dynamic community inhabited by approximately 10^{14} bacteria, most of which have not yet been cultivated in the laboratory (Zoetendal *et al*, 2006). The GI microbiota has been suggested as one of the etiological factors in irritable bowel syndrome (IBS), with a putative role in the development and maintenance of IBS symptoms (for a review, see Bolino & Bercik, 2010). The worldwide prevalence of IBS is 10-20% among adults and adolescents, depending on the diagnostic criteria applied (Longstreth *et al*, 2006). Abdominal pain or discomfort, irregular bowel movements and constipation or diarrhoea are common symptoms of IBS. Symptoms outside the GI tract, such as fatigue, anxiety and depression, are also often encountered. At its worst, IBS can cause significant effects on patients' well-being, but it is not known to predispose to any severe illnesses. Patients can be grouped into three subtypes according to bowel habits: diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C) or mixed-subtype (IBS-M). However, the symptom subtype of each patient may vary over time (Longstreth *et al*, 2006).

Compared to non-IBS controls, subjects with IBS have been associated with a greater temporal instability of the GI microbiota and quantitative changes have been detected within several distinct bacterial groups or species-like phylotypes, which are defined based solely on sequence data (see Table 1 for references). In analyses covering the overall microbial community, IBS subjects have shown a tendency to cluster apart from the healthy control subjects (Ponnusamy *et al*, 2011; Rajilić-Stojanović, 2007). Moreover, the IBS symptom-subgroups IBS have been proposed to differ from each other according to the GI microbiota of subjects within these groups (Lyra *et al*, 2009; Malinen *et al*, 2005; Rajilic-Stojanovic, 2007). The most distinctive symptom sub-type is IBS-D, which could also be a result of the impact of the diarrhoea on the microbial environment in the gut. In addition, comparatively low quantities of bifidobacteria, which are generally considered beneficial to health, have been detected in several IBS studies (Balsari *et al*, 1982; Enck *et al*, 2009; Kerckhoffs *et al*, 2009; Krogius-Kurikka *et al*, 2009; Si *et al*, 2004). This finding, though still preliminary, encourages development of probiotic and prebiotic therapies for IBS. On the other hand, elevated numbers of Proteobacteria and Firmicutes, including *Ruminococcus* – like phylotypes, *Lactobacillus* sp. and *Veillonella* sp., have been reported.

Quantitative and qualitative microbial alterations in the GI tract of IBS subjects may have a functional role in the syndrome aetiology or merely reflect the status of the gut, but still have diagnostic or prognostic value in clinical practise and research (Kassinen, 2009;

Salonen *et al*, 2010). In the following chapter, these IBS-related alterations within the human GI microbiota are reviewed.

2. Intestinal microbiota

The intestinal microbiota is individual-specific and relatively stable through time (Zoetendal *et al*, 1998). From a microbial point of view, a tremendous variety of physiologically connected environments exists in the human GI tract. The mouth and stomach harbour their distinct microbiotas (Bik *et al*, 2006; Zaura *et al*, 2009). In the small intestine, the bacterial load and diversity rise from 10^4 to 10^8 cells per millilitre of intestinal content towards the distal ileum. *Veillonella, Streptococcus, Clostridium* cluster I and *Enterococcus* form the core genera of the small intestinal lumen (Booijink *et al*, 2010). Reaching the colon, the transit slows down and the bacterial density rises from 10^8 in the caecum and ascending colon to an average of 10^{11} to 10^{12} cells of bacteria per gram in faeces. The proportion of obligate anaerobic bacteria expands to 99%. The phyla Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia are present in the colon (Andersson *et al*, 2008; Kurokawa *et al*, 2007). In the small and large intestines, the mucosal and luminal microbiotas are distinct from each other (Booijink *et al*, 2007; Zoetendal *et al*, 2002). Recently it has been shown that the human GI microbiota roughly groups into three entorotypes, with either *Bacteroides, Prevotella* or *Ruminococcus* predominating (Arumugam *et al*, 2011).
The GI microbiota has a dynamic mutualistic relationship with its host affecting host nutrition and metabolism, immunocompetence and tolerance, GI tract surface maturation and function and even behaviour, thus possessing a potentially tremendous impact on host well-being (for review see Sekirov *et al*, 2010). Multiple theories linking IBS aetiology with the intestinal microbiota have been proposed, which, together with the discovered IBS-associated GI microbiota alterations, imply that bacteria may well play a role in IBS aetiology.

3. Gut microbiota in IBS

Alterations in the GI microbiota related to IBS have been investigated since the early 1980s' by conventional culture-based methods and an array of molecular methods (Table 1). Several of the published studies are based on the same Finnish sample panel originating from a probiotic intervention and additional healthy control subjects. For clarity, these studies are represented under a separate sub-heading in Table 1. Besides differing from control subjects, IBS also differs from IBD including Crohn's disease and ulcerative colitis (Enck *et al*, 2009; Ponnusamy *et al*, 2011).

Study	**Samples**	**Method**	**Outcome for IBS[1] subjects**
Balsari *et al*, 1982	20 IBS, 20 Controls	Culturing	Less coliforms, lactobacilli and bifidobacteria
Si *et al*, 2004	25 IBS, 25 Controls	Culturing	Less bifidobacteia More *Enterobacteriaceae*
Rajilić-Stojanović, 2007	20 IBS, 20 Controls	HITChip	Distinctive clustering; Subtype-specific alterations; Higher inter-individual variation

Kerckhoffs *et al*, 2009	41 IBS 26 Controls	FISH, qPCR; Fecal and mucosal brush samples	Bifidobacteria in feces and *Bifidobacterium catenulatum* on the mucosa decreased
Enck *et al*, 2009	7765 IBS, 198 CD, 515 UC, 10478 Other GI diag.	Culturing	Less bifidobacteria than in samples of subjects with other GI complaints
Malinen *et al*, 2010	44 IBS	qPCR, Questionnaires	Previously IBS associated phylotype now associated with sensation of symptoms
Codling *et al*, 2010	47 IBS, 33 Controls	DGGE; Fecal and mucosal samples	Lower inter-individual variation
Tana *et al*, 2010	26 IBS, 26 Controls	qPCR, culturing, SCFA, questionnaires, X-ray	*Veillonella* and lactobacilli elevated; Acetic, propionic and total SCFA elevated and correlated with symptoms
Noor *et al*, 2010	11 IBS, 13 UC, 22 Controls	DGGE	Less diversity among *Bacteroides*
Carroll *et al*, 2010	10 IBS-D, 10 Controls	Culturing, qPCR; Fecal and mucosal biopsy samples	Less aerobes and more lactobacilli in feces
Carroll *et al*, 2011	16 IBS-D, 21 Controls	T-RFLP; Fecal and mucosal biopsy samples	The microbial profiles grouped according to origin (mucosal or luminal) rather than health status. Microbial composition at both mucosa and lumen altered in IBS-D.
Ponnusamy *et al*, 2011	11 IBS, 8 non-IBS patients	DGGE, qPCR	Higher diversity of total bacteria, *Bacteroides* and *Lactobacillus;* Elevated amino acids and phenolic compounds
Saulnier *et al*, 2011	22 Pediatric IBS, 22 Control children	Pyrosequencing, PhyloChip	Gammaproteobacteria including *Haemophilus influenzae* elevated; *Ruminococcus* –like phylotype associated with IBS; *Allistipes* correlated with pain

Studies on a Finnish sample set[2]

Study / Method	**Healthy controls**	**IBS subjects on placebo**	**IBS subjects on probiotic[3]**
Kajander *et al*., 2005; Intervention	NA	Analysed as control	Total symptom score reduced (borborygmi)
Malinen *et al*., 2005; qPCR 300 gut species	Analyzed as control	High *Lactobacillus* sp. in IBS-D Low *Veillonella* sp. in IBS-C	NA
Mättö *et al*., 2005; Culturing, DGGE	Analysed as control	More coliforms; Higher aerobe:anaerobe ratio	NA

Maukonen *et al*., 2006; DGGE, TRAC,	Analysed as control	Less *Clostridium coccoides-Eubacterium rectale* in IBS-C (RNA); Less stable microbiota (RNA)	NA
Kajander *et al*., 2007; qPCR 300 gut species	NA	Analyzed as control	No alteration
Kassinen *et al*., 2007; G+C%, sequencing, qPCR	Analyzed as control	Altered community structure; 3 altering phylotypes	NA
Lyra *et al*., 2009; qPCR 14 phylotypes	Two associated phylotypes	IBS-D and IBS-C associated phylotypes; IBS-D distinguishable	NA
Krogius-Kurikka *et al*., 2009; G+C%, sequencing	Actinobacteria abundant	NA	NA
Krogius-Kurikka *et al*., 2009; G+C%, sequencing, qPCR	More Actinobacteria and Bacteroidetes	IBS-D enriched with Proteobacteria and Firmicutes, especially Lachnospiraceae	NA
Lyra *et al*., 2010; qPCR 8 phylotypes	NA	Analyzed as control	Quantities shifted towards healthy like levels
Rinttilä *et al*., 2011; qPCR 12 pathogens	Analyzed as control	*Staphylococcus aureus* more prevalent in IBS	NA

[1]The abbreviations in order of appearance stand for IBS, irritable bowel syndrome; HITCip, Human Intestinal Tract Chip; FISH, fluorescent *in situ* hybridization; qPCR, real-time quantitative PCR; CD, Crohn's disease; UC, ulcerative colitis; GI, gastrointestinal; DGGE, denaturing gradient gel electrophoresis; SCFA, short chain fatty acids; IBS-D, diarrhea-predominant IBS; T-RFLP, terminal-restriction fragment length polymorphism; NA, not analyzed; and IBS-C, constipation-predominant IBS.
[2]The sample set consisted of probiotic intervention samples from the intervnetion by Kajander *et al*., (2005) and additional control samples from subjects devoid of gastrointestinal symptoms. The detected alterations are given under the sample group they apply to.
[3]The probiotic supplement was a combination of *L. rhamnosus* GG and Lc705, *B. breve* Bb99 and *P. freudenreichii* ssp. *shermanii* JS administered for 6 months at a daily dose of 8–9 x 10^9 CFU with equal amounts of each strain (Kajander *et al*, 2005).

Table 1. Studies on irritable bowel syndrome (IBS) related intestinal microbiota.

3.1 Culture-based analyses

Using culture-based techniques, the GI microbiota of IBS patients was characterized as having less coliforms, lactobacilli and bifidobacteria in a study with 20 IBS patients and 20

controls (Balsari *et al*, 1982). Likewise, in a later study (Si *et al*, 2004) with 25 IBS patients fulfilling the Rome II criteria and 25 controls, lower levels of bifidobacteria were detected in IBS patients, but the level of bacteria belonging to the family *Enterobacteriaceae* was higher in IBS patients. Contrary to Balsari *et al*. (1982), Mättö *et al*. (2005) detected more coliforms in IBS subjects' and no difference in the bifidobacterial counts using culture-based methods, whereas the number of coliforms and aerobe:anaerobe ratio were elevated (26 IBS and 25 control subjects). In 2009, Enck and colleagues conducted an impressive culturing study by analysing the intestinal microbiota of a total of 34 313 subjects of varying conditions (Enck *et al*, 2009). Routine analyses were applied to *Clostridium difficile, Bifidobacterium* spp., *Bacteroides* spp., *Escherichia coli, Enterococcus* spp. and *Lactobacillus* spp. A total of 7 765 IBS subjects were included in the final data analysis revealing a significantly lower abundance of *Bifidobaterium* spp. In the latest study based on culturing, aerobes were elevated in the faecal samples of IBS-D patients compared with control subjects, whereas anaerobes, *Clostridium* spp., *Bacteroides* spp., *Lactobacillus* spp., *Bifidobacterium* spp., and *Escherichia coli* were not altered in IBS-D (Carroll *et al*, 2010).

Taken together, evidence for increased numbers of aerobes and comparably low counts of bifidobacteria exist from culture based analyses with the latter giving good grounds for prebiotic and probiotic therapy research. The results on coliforms are contradictory between different studies.

3.2 Community structure with molecular methods

The overall microbial community from faecal samples of IBS subjects has been analysed applying denaturing gradient gel electrophoresis (DGGE), microarray (HITCip and PhyloChip), and sequencing (conventional Sanger sequencing and 2nd generation 454 pyrosequencing). All of these methods are capable of detecting the unculturable species in the microbiota, although they bear restrictions due to primer and probe dependency and technical biases. The main advantage is the possibility to gain a non-restricted overview and with sequencing, to able to design targeted primers and probes for applications based on PCR or hybridization.

Greater temporal instability of the intestinal microbiota of IBS patients compared with that of healthy controls has been detected with RNA-based DGGE (Maukonen *et al*, 2006). Applying DNA-based DGGE on the same sample set did not show IBS related temporal variation (Maukonen *et al*, 2006), but variation due to antibiotic therapy was observed (Mättö *et al*, 2005). The inter-individual variability has been assessed in two studies with contradictory results. With the HITChip microarray analysis IBS subjects showed significantly more inter-individual variation compared with the controls (Rajilić-Stojanović, 2007), whereas with DGGE more variation was seen amongst control subjects (Codling *et al*, 2010). This discrepancy is likely due to methodological differences as the probe or primer based bacterial targets differ.

Moreover, the biodiversity, an expression of species richness and abundance, is decreased in IBS (Noor *et al*, 2010). Loss of species richness was especially evident among *Bacteroides* species, which was speculated to suggest their putative protective role in the GI tract (Noor *et al*, 2010). Krogius-Kurikka *et al*. (2009) also found IBS-D related GI microbiota to lack diversity in a sequencing analysis, but the number of samples pooled prior to analysis was lower in the IBS-D sample possibly affecting the result (Krogius-Kurikka *et al*, 2009). On the other hand, Saulnier and colleagues (2011) analysed multiple samples from 22 pediatric IBS patients and 22

control subjects with 454 pyrosequencing (54 287 reads per sample) and a portion of the samples further with the PhyloChip which targets revealing no significant difference in bacterial bacterial quantities or richness, although qualitative changes were detected between the two subject groups and in relation to perception of pain (Saulnier *et al*, 2011).
Thus, at least for adult IBS subjects, the diversity and species richness in the GI microbiota are diminished, which would together with the alternating symptoms explain a higher temporal and inter-individual variation in the gut microbiota. A less stable microbiota is potentially more vulnerable to external interference (infection, antibiotics, stress), possibly leading to a recurrent aberration in gut function.

3.3 From community to phylotype level

In addition to the overall community structure and stability in the GI tract, the thousands of bacterial species therein, referred to as phylotypes when based only on molecular data, are important. Aspects such as their absolute and relative abundance, prevalence and association to symptoms sub-types and perception have been studied.
The sample set studied by Mättö *et al.* (2005) and Maukonen *et al.* (2006) was further studied using 20 quantitative real-time PCR (qPCR) assays covering approximately 300 bacterial species (27 IBS patients and 22 controls gave faecal samples at the first time-point; 21 IBS patients and 15 controls gave faecal samples at three time-points at three-month intervals) (Malinen *et al*, 2005). The first time-point was analysed with IBS subjects divided into symptom subgroups; IBS-D, IBS-C and IBS-M. Statistically significant differences were observed with real-time PCR assays targeting *Lactobacillus* spp. (less abundant in IBS-D than in IBS-C), *Veillonella* spp. (less abundant in controls than in IBS-C) and *Bifidobacterium* spp. (less abundant in IBS-D than in all other groups). The *Clostridium coccoides* and *Bifidobacterium catenulatum* group assays detected more target bacteria in controls than in IBS patients when the results from the three different time-points were averaged and the IBS subjects analysed as a single group.
Thereafter, the samples were analysed with percent guanine plus cytosine (%G+C) profiling (Kassinen *et al*, 2007): The pooled symptom subtype profiles diverged with the %G+C profiling and the three most diverging fractions were subsequently studied using 16S rDNA Sanger sequencing. Real-time PCR assays targeting specifically the alterations between the sequesnce libraries of IBS and control subjects were designed and applied in several studies highlighting a ruminococcal phylotype in relation to IBS-D and a taxonomically unclassifiable phylotype with the control subjects and IBS subjects under probiotic theraphy (Lyra *et al*, 2010; Lyra *et al*, 2009; Malinen *et al*, 2010).
Ruminococcal bacteria have also been associated with Crohn's disease and pediatric IBS (Frank *et al*, 2007; Martinez-Medina *et al*, 2006; Saulnier *et al*, 2011). Ruminococci include mucolytic bacteria with a possible competitive advantage in a disturbed gut with excessive mucus secretion. Novel uncultured bacterial phylotypes discovered in relation to IBS and health may also perform well as diagnostic microbiome signatures (Kassinen *et al*, 2007; Lyra *et al*, 2009; Saulnier *et al*, 2011) although their possible relation to the syndrome is mere speculation at this stage. The genera *Bifidobacterium, Coriobacterium* and *Collinsella* within the phylum Actinobacteria have been less abundant in IBS patients (Enck *et al*, 2009; Kassinen *et al*, 2007; Kerckhoffs *et al*, 2009; Lyra *et al*, 2009). Correspondingly, redused levels of Actinobacteria including bifidobacteria have been associated with Crohn's disease patients

(Fyderek *et al*, 2009; Manichanh *et al*, 2006; Sokol *et al*, 2009), and *Collinsella aerofaciens* has been associated with a low risk of colon cancer (Moore & Moore, 1995).
These more specific changes, once well established in relation to both healthy and non-IBS GI patient controls, have potential in diagnostics and tailor-made therapeutic approaches. The possibility of finding a causative agent for IBS, for instance among the ruminococcal phylotypes, is intriguing though still a future challenge.

3.4 Microarray analyses

Two 16S rRNA gene sequence based microarrays with a wide array of target phylotypes have been applied to IBS samples. The advantage of microarrays is their semi-quantitative nature, high-throughput capability and more straightforward applicability to diagnostic and therapeutic applications.
The first microarray analysis focusing on IBS-associated GI microbiota applying a microarray (The Human Intestinal Tract Chip, HITChip) was published in 2007 (Rajilic-Stojanovic, 2007). The HITChip is a 16S rRNA gene-based phylogenetic microarray specifically designed to target the human intestinal microbiota (Rajilic-Stojanovic *et al*, 2009). It is unable to quantify phylotypes directly, but relative changes in hybridization signals can be detected between 0.1% and 3% subpopulations in an artificial mixture of 30 phylotypes (Rajilic-Stojanovic, 2007). The HITChip study on IBS encompassed 20 IBS patients sub-grouped according to symptom subtype and 20 healthy controls. With a hierarchical cluster analysis, the phylogenetic fingerprints of the faecal microbiota of IBS patients and controls grouped into two distinctive groups, with one dominated by IBS patients' samples (14 IBS patients and 4 controls) and the other by healthy controls' samples (16 controls and 6 IBS patients). The clustering did not correlate with the IBS symptom subtype. Stronger variation in the composition of the microbiota was seen among the IBS patients' profiles.
Within the phylotypes targeted by the HITChip, the IBS-C group of IBS patients had lower levels of *Bacteroides* species (*Bacteroides ovatus, Bacteroides uniformis, Bacteroides vulgatus*) and *Clostridium stercorarium*-like bacteria and higher levels of *Bacillus* spp.; the IBS-D patients were characterized by higher levels of *Aneuribacillus* spp., *Streptococcus mitis* and *Streptococcus intermedius*-like bacterial phylotypes from the order *Bacilli*. Various IBS-subgroup dependent differences were detected within *Clostridium* cluster XIVa (*C. coccoides* group). For instance, *Roseburia intestinalis* was more abundant in IBS-D and Ruminococcus gnavus in alternating-type IBS than in healthy controls. Several phylotypes within the *Clostridium* cluster IV (the *Clostridium leptum* –group) were more prominent in IBS-C than in IBS-D. (Rajilic-Stojanovic, 2007)
The other microarray analysis was done on pediatric IBS subjects applying the PhyloChip (Saulnier *et al*, 2011). PhyloChip targets a wider array of microbes not specifically restricted to the expected human intestinal tract inhabitants (Brodie *et al*, 2006) although it is well applicable also to analysing intestinal microbiota (Nelson *et al*, 2011; Saulnier *et al*, 2011). Saulnier and colleagues (2011) discovered that Proteobacteria, especially Gammaproteobacteria, are abundant in pediatric IBS subjects. Within these Gammaproteobacteria the species *Haemophilus parainfluenzae* was commonly encountered. Similarly the pyrosequencing analysis revealed elevated numbers of Protebacteria and unclassified ruminococcal phylotypes in association to pediatric IBS and (Saulnier *et al*, 2011). In the PhyloChip analysis, several *Bacteroides* phylotypes, including a *Bacteroides vulgatus* –like phylotype, were elevated in healthy children (Saulnier *et al*, 2011), as has

previously been noted in the case of adult subjects with ulcerative colitis (UC) or IBS (Noor *et al*, 2010).

These efficient high-throughput methods have potential for analyzing large enough sample sets to identify common alterations in the heterogeneous IBS subject population. So far too few studies have been published for making a consensus on the results. In addition, it would be beneficial if the sampling schema would include several samples linked to thorough symptom data from each subject as both the microbiota and the symptoms in IBS are prone to alter over time.

3.5 The mucosal microbiota

The mucosal microbiota is of special interest in health related studies as it is in an intimate contact with the host. In a healthy intestine, the mucosal microbiota resides on the mucosal lining of the epithelium, whereas in a damaged intestine straight contact with the host epithelium is plausible. Fluorescent in situ hybridization (FISH) applied on mucosal samples of patients with IBD, IBS or no GI symptoms revealed that mucosal bacteria were more abundant in IBS patients than in healthy controls, although the difference was less evident than with the IBD patients (Swidsinski *et al*, 2005). The proportional amounts of the different bacterial groups targeted in the FISH analysis (*Bacteroides-Prevotella, Bacteroides fragilis, Eubacterium rectale-Clostridium coccoides, Faecalibacterium prausnitzii* and *Enterococcus faecalis*), however, were similar between IBS patients and controls (Swidsinski *et al*, 2005). Likewise, Carroll and colleagues (2010) found no significant difference between the abundances of cultured bacteria (aerobic, anaerobes, *Clostridium* spp., *Bacteroides* spp., *Lactobacillus* spp., *Bifidobacterium* spp., and *Escherichia coli*). With qPCR, elevated levels of *Pseudomonas aeruginosa*, a gram-negative opportunistic pathogen, have been detected in duodenal brush samples of IBS patients. Nevertheless, a recent terminal-restriction fragment length polymorphism (T-RFLP) analysis was able to differentiate between the composition of IBS-D patients' and control subjects' mucosal microbiota, although the overall microbial profiles clustered according to site of sampling (mucosal or luminal) rather than health status (IBS-D or healthy control) (Carroll *et al*, 2011).

Taken together, no drastic alteration in the mucosal microbiota of IBS subjects has been defined. The mucosal and luminal microbiotas differ in IBS subjects as they do in healthy controls, underlying the importance of research on this specific niche. One reason for the small number of mucosal IBS studies is the invasive nature of mucosal sampling as colonoscopy is not a regular procedure in IBS diagnostics or treatment.

4. Microbial metabolites and enzymes

4.1 Short Chain Fatty Acids (SCFAs)

The principal products of microbial carbohydrate metabolism in the human GI tract are short-chain fatty acids (SCFAs), which can be absorbed by the human host. The SCFAs produced throughout the GI tract are mainly acetate, butyrate and propionate, but in the colon acetate predominates (Cummings *et al*, 1987). The colonic epithelial cells prefers butyrate over other SCFAs as an energy source, and butyrate has been shown to have a positive effect on health (Pryde *et al*, 2002). The most abundant intestinal butyrate-producing bacteria are Firmicutes from Clostridial clusters XIVa and IV (*Clostridium, Eubacterium, Fusobacterium*) (Pryde *et al*, 2002). Starch fermentation by starch-degrading

bacteria results in comparatively high amounts of butyrate (Chassard *et al*, 2008). Starch-degrading bacteria, including *Ruminococcus bromii* (Clostridium cluster IV), *Eubacterium rectale* (Clostridium cluster XIVa) and bifidobacteria (Leitch *et al*, 2007), comprise approximately 10% of culturable bacteria in faecal samples (Chassard *et al*, 2008).

Reduced amounts of total SCFAs due to lower levels of acetate and propionate have been measured in association with IBS-D, while an elevated concentration of n-butyrate seemed to be characteristic of IBS-D (Treem *et al*, 1996). Tana and colleagues (2010) analysed the microbiota and SCFAs from faecal samples donated by 26 IBS and 26 control subjects. Contrary to Treem *et al.* (1996), the IBS subjects had elevated numbers of *Veillonella* spp. and *Lactobacillus* spp. together with higher concentrations of total organic acids and acetic and propionic acid. The increase in acidic metabolites was more pronounced in the group of IBS subjects with worse GI symptoms, quality of life and emotional status according to subjective evaluation (Tana *et al*, 2010).

Colonic gas production (H_2 and CH_4) has been shown to be greater in patients with IBS (Rome II criteria) compared with controls using a standardized diet, which might be associated with alterations in the activity of hydrogen-consuming bacteria (King *et al*, 1998). An exclusion diet, mainly devoid of dairy products and cereals other than rice, reduced IBS symptoms and lowered the maximum gas excretion (King *et al*, 1998). Furthermore, functional constipation and IBS-C have been associated with methane production according to breath testing in a recent meta-analysis (Kunkel *et al*, 2011).

Thus, although the results on microbial metabolites in the colon are still scarce and to some extent contradictory, they have been linked to symptom severity and defecation habit sub-type. The elevated amount of butyrate among IBS-D subjects in one study is surprising, as butyrate is considered to have a positive effect on health.

4.2 Luminal proteases

Certain studies have suggested an association between luminal proteases and IBS. An elevated faecal serine protease activity has been associated with IBS-D (Roka *et al*, 2007). The faecal supernatants from IBS-D patients caused increased colonic paracellular permeability when administered to the mucosal side of a mouse colon strip and increased visceral hypersensitivity in mice (Gecse *et al*, 2008). Gecse *et al*. (2008) also showed that the effect on mucosal permeability is mediated by serine protease through protease-activated receptor two (PAR-2). Pre-incubation with serine protease inhibitors decreased the effect of the faecal supernatant from the IBS-D patients on the colonic paracellular permeability of mouse colon strips. Furthermore, the use of colonic strips derived from PAR-2-deficient mice completely removed the increase in colonic paracellular permeability. The elevated serine protease activity in IBS-D patients was suggested to be of microbial origin (Gecse *et al*, 2008). The PAR-2 mediated increase in visceral hypersensitivity appears to be specifically related to IBS-D in comparison to inflammatory bowel diseases (IBD) (Annahazi *et al*, 2009).

The evidence for the role of luminal proteases in IBS symptoms is at its early stage, but intriguing. It links the GI microbiota with the host's IBS symptoms through increased gut permeability and visceral hypersensitivity.

5. Post-infectious IBS

In a large cohort study (over 500 000 patients), gastroenteritis was concluded to increase the risk of developing IBS by a factor of ten (Rodriguez & Ruigomez, 1999). Post-infectious IBS

(PI-IBS) has been reported after *Campylobacter*, *Shigella* and *Salmonella* infections (Ji *et al*, 2005; Mearin *et al*, 2005; Spiller *et al*, 2000) and *Staphylococcus aureus* has been detected in a comparatively high prevalence in IBS subjects (Rinttilä *et al*, 2011). Nevertheless, PI-IBS appears to be a non-specific response (Spiller, 2007). Typically PI-IBS is characterized by loose stools, less depression and anxiety and increased enterochromaffin cells in mucosal biopsies compared with non-PI-IBS (Dunlop *et al*, 2003; Neal *et al*, 2002). Detecting an infectious agent from random IBS subjects is unlikely (Rinttilä *et al*, 2011), but this still does not rule out the possibility of an earlier infectious event having etiological importance.

Since the initial gastroenteritis triggering PI-IBS is a coincidental event, and among PI-IBS patients the symptoms are relatively homogeneous and psychological abnormalities are less common than in other IBS patients, PI-IBS presents a clearer model for studying the possible mechanisms underlying IBS (Spiller, 2007). On the other hand, PI-IBS may be etiologically too distinct to represent the whole of IBS subtype variety.

In addition to acute gastroenteritis triggering IBS symptomology, low-grade inflammation with focus on mast cells and monocytes has been suggested to have a pivotal role in IBS aetiology (for review see Ohman & Simren, 2010). Low-grade mucosal inflammation (Barbara *et al*, 2007; Chadwick *et al*, 2002; Dunlop *et al*, 2003; Ohman *et al*, 2005) and stable alterations in mucosal gene expression (Aerssens *et al*, 2008) of IBS patients of all symptom subtypes have been detected. Furthermore, the basal and *E. coli* lipopolysaccharide induced release of pro-inflammatory cytokines from peripheral blood mononuclear cells has been shown to be elevated in IBS-D patients compared to healthy controls (Liebregts *et al*, 2007). Additionally, antibodies against certain bacterial flagellin have been detected in IBS patients, particularly in PI-IBS patients, with a higher frequency than in healthy controls (Schoepfer *et al*, 2008).

Taken together, PI-IBS is a widely accepted sub-type of IBS which can reside from a variety of causative agents. Minimizing risk, severity and length of acute gastroenteritis would likely lower the risk of recurrent functional GI disturbances such as IBS.

6. Probiotics for balancing the GI microbiota in IBS

Being a syndrome diagnosed based on subjective assessment of GI function, the most important outcome in IBS intervention studies is the patients' sensation of symptom relief. This is usually assessed by applying GI symptom questionnaires. According to a recent meta-analysis, the separate IBS symptoms (abdominal pain, bloating and flatulence) and their composite sum have all been significantly improved with probiotics (Hoveyda *et al*. 2009).

From the microbiological point of view, it is of interest to see whether the symptom improvement during the intervention is linked to alteration within the GI microbiota – putatively to a state that better resembles that of healthy-like control subjects. If no change in the microbiota is seen in a specific study, this doesn't necessarily mean there hasn't been one as the methodology used may have missed the targets of interest. This has been the case for a multispecies supplement intervention trial with *L. rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99 and *P. freudenreichii* ssp. *shermanii* JS (Kajander *et al*, 2005), first assessed by qPCR assays targeting known GI bacteria (Kajander *et al*, 2007) and thereafter by targeting IBS associated phylotypes (Lyra *et al*, 2010). The analyses of 300 known GI bacteria showed no alterations due to the intervention (Kajander *et al*, 2007), but a vast number of phylotypes may have been missed with analyses restricted by primer target selection, whereas in the

latter study, when the same samples were screened with qPCR assays targeting specifically IBS associated phylotypes (Lyra *et al*, 2010), alterations towards levels previously measured in controls devoid of GI symptoms (Lyra *et al*, 2009) were measured.
Nobaek and co-workers (2000) have analysed abundances of *Enterobacteriacea*, sulphate-reducing bacteria and *Enterococci* in IBS subjects consuming a rose-hip drink with *Lactobacillus plantarum* (DSM 9843). No alterations were detected in the probiotic group, but the probiotic strain was detected in faecal and rectal mucosal samples (Nobaek *et al*, 2000). Here again, the analysis method covered only a minor portion of the entire microbiota.
In addition to affecting the bacterial levels and the stability of the GI microbiota, the relief of bloating and distention with probiotics may be linked to an effect on microbial metabolism (Schmulson & Chang, 2011).

7. Conclusion

Dysbiosis of the intestinal microbiota in IBS has been detected on several levels: the overall community appears to be less diverse with more variation between individuals and over time. These phenomena may reduce the resilience of the microbiota to external stressors, and both trigger and sustain functional aberrations in the gut. In addition to overall dysbiosis, specific bacterial groups are either elevated (*Lactobacillus, Veillonella, Ruminococcus, Enterobacteria,* aerobes as a group, *S. aureus*) or reduced (*Bifidobactrium, B. catenulatum, Bacteroides*) in IBS, but with the exception of bifidobacteria, the available data is not yet conclusive. Ruminococcal phylotypes have been associated specifically with IBS and also with inflammatory states in the intestinal tract in several studies and certainly deserve more attention. The analytical methodologies available for studying the GI microbiota have developed immensely in the past decade and the discovery of efficient microbial signature based diagnostic and therapeutic methods even for such a heterogeneous and subjectively defined patient group as IBS can be expected in the near future.

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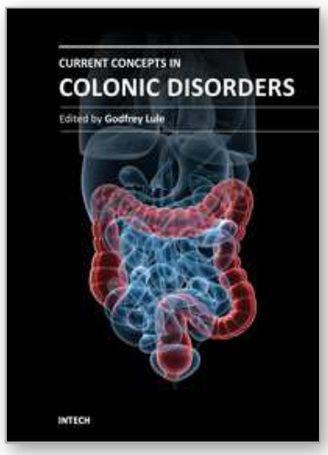

Current Concepts in Colonic Disorders
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The 21st Century has seen a resurgence of research of the gastrointestinal tract, especially since it was established that it plays a central role as an immune system organ and consequentially has a huge impact on causation, impact and transmission of most human ailments. New diseases such as the Acquired Immunodeficiency Syndrome, hepatitis and tumours of the gastrointestinal tract have emerged and they are currently subjects of intensive research and topics of scientific papers published worldwide. Old diseases like diarrhea have become extremely complex to diagnose with new and old pathogens, drugs, tumours and malabsorptive disorders accounting for the confusion. This book has set out algorithms on how to approach such conditions in a systematic way both to reach a diagnosis and to make patient management cheaper and more efficient. "Current Concepts in Colonic Disorders" attempts to put all the new information into proper perspective with emphasis on aetiopathogenesis and providing rational approach to management of various old and new diseases. As the book editor, I have found this first edition extremely interesting and easy to understand. Comments on how to improve the content and manner of presentation for future editions are extremely welcome.

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