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THE GUT MICROBIOTA AND GUT HEALTH: A PROBIOTIC PERSPECTIVE

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Over the last few years, new molecular techniques have accumulated a wealth of data about the commensal microbes in the gut.[1,2] This has resulted in the publication of several high level papers, attracting general interest: in 2012 the human microbiome was the subject of an article in The Economist. (www.economist.com/node/21560523).

Disturbances in the gut microbiota (dysbiosis) could be an early warning sign for certain diseases: e.g. low species diversity has been shown in inflammatory bowel disease (IBD), obesity, type-1 and type-2 diabetes, coeliac disease, allergy, asthma, autism, *Clostridium difficile* infection, cystic fibrosis and colorectal cancer (CRC).[3-8]

The 'chicken or egg' question is: does dysbiosis cause disease or, instead, is it a consequence of disease? We do not fully know the answer to this, and it may depend on the actual disease. Certainly some species have been linked to disease development or reduced disease risk but more research is needed. Probiotic trials could help provide further insight.

PROBIOTIC RESEARCH

Probiotics can have multiple mechanisms of activity: modulation of the intestinal microbiota, support of gut barrier function, modulation of the immune response (both mucosal and systemic), reducing harmful substances in the gut, etc. This range of mechanisms helps explain the broad range of research with probiotics. This article will review probiotic studies relating to gut health and function (and not infectious disease).

Irritable bowel syndrome (IBS) and constipation

Several lines of evidence point to the gut microbiota involvement in IBS pathogenesis: e.g. patients may have an aberrant gut microbiota,[9,10] and risk of developing IBS increases after infectious gastroenteritis.[11] Apart from the mechanisms already mentioned, probiotics may also be able to ameliorate disruptions in the gut-brain axis, which have been linked to IBS. Gut motility might also be influenced by increases in bacterial cell mass (and thus stool weight) and levels of short chain fatty acids (such as butyrate and acetate) in the colon.[12-14]

Any effect on IBS and constipation symptoms can be perceived by patients, thus current BDA guidance advises that patients monitor symptoms for at least four weeks.[15] There are also numerous

clinical trials but these vary considerably: e.g. in the strain(s) investigated, trial design and endpoints measured. This research is difficult, however, due to the heterogeneous nature of the patients and high placebo effect.

Several systematic reviews have examined probiotic evidence with IBS, and research remains active in this area.[16,17] Healthcare professionals should refer to the trials conducted with any individual probiotic, and choose a strain or product shown to have a positive effect on the symptom(s) that most concerns the patient.

There is now also a body of evidence for some probiotics and constipation (a gut function disorder not necessarily linked to IBS.)[18,19] For example, a recent review concluded that short supplementation with probiotics (particularly certain strains) decreases intestinal transit time in constipated or older adults.[20]

Inflammatory bowel disease (IBD)

The rationale for using probiotics in IBD is prompted by indications that the gut microbiota may drive inflammation in the gut.[21] Furthermore, an abnormal intestinal microbial profile has been observed, including reports of reduced species diversity,[22] and reduced levels of *Faecalibacterium prausnitzii* (an anti-inflammatory butyrate-producing species). An important probiotic mechanism could be downregulation of inflammation.

Although there are many mechanistic studies with probiotics, there are not as many randomised trials. Different strains of *Lactobacillus* or *Bifidobacterium* (including the mixture VSL#3), *Escherichia coli* Nissle 1917 and the yeast *Saccharomyces boulardii* have been investigated. Promising results are emerging for certain strains in inducing and maintaining remission in mild to moderately severe ulcerative colitis, as well as preventing primary pouchitis and its recurrence.[16,22-25] There is very poor evidence for Crohn's disease, and BDA guidelines do not support probiotic use for this condition.[26]

Colorectal cancer (CRC)

Mechanistic and human studies show that changes in the gut microbiota are associated with CRC progression and development, suggesting a potential for probiotics with CRC.[27] Several probiotic mechanisms in the gut might help: microbiota modulation, inactivation of carcinogenic compounds, reduced formation of carcinogenic metabolites, enhanced production of compounds (e.g. butyrate, which is important for colonic cells) involved in regulation of apoptosis and cell differentiation, inhibition of tyrosine kinase signalling pathways. Several lactobacilli probiotics have also been associated with improved activity of natural killer (NK) cells. These innate immune cells act against tumour development;[28] low levels of NK cell activity have been linked to increased risk of cancer.[29]

Trials investigating actual cancer development and progression need to be long term; one trial with *Lactobacillus casei* Shirota in patients at high risk of CRC lasted four years. The probiotic was associated with a reduced rate of tumours that were of moderate or higher atypia.[30] For faster results, biomarkers of CRC risk have been used, as was done in an EU-funded study investigating a synbiotic combination of *Lactobacillus* and *Bifidobacterium* strains, with oligofructose-enriched inulin prebiotic.[31,32]

The biological rationale of disease development and probiotic activity together with a few promising trials, indicate the need to conduct further research in this area.

Necrotising colitis (NEC)

The aetiology of NEC (which has a 30% mortality rate) is not fully understood but the gut microbiota may be involved: preterm babies' gut microbiota differs from those who are term; the microbiota of babies with NEC differs from that of other babies of low birth weight,[33,34] and antibiotic use is a risk factor. The extent of probiotic research has now reached the level of systematic reviews and meta-analyses,[35-37] which conclude that pro-

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biotic supplementation reduces risk of NEC in preterm infants, and may even reduce mortality. The most recent review found a reduction of incidence of NEC, overall death and neonatal sepsis in preterm neonates. Probiotic intervention was also associated with faster reintroduction of food, and less time in hospital (both $p < 0.001$).[38] As with other conditions however, it is advisable to check which strains have been studied and which have been shown to be effective.

CONCLUSIONS

New insights into the commensal microbes in the gut have further underlined the impact of this microbial community on the health and function of the gut, and indicated the potential for probiotic benefit. There are varied levels of evidence with regard to probiotic benefit for IBS, constipation, IBD, CRC and NEC, and research remains very active.

It is important to bear in mind that evidence is considered strain-specific; therefore dietitians are advised to check the supporting research for any probiotic they are considering using or recommending. A general guide to probiotics, including advice on safety and quality criteria, has recently been published by the *British Journal of Nursing*.[39]

References

1 Li K, Bihan M, Méthé BA (2013) Analyses of the stability and core taxonomic memberships of the human microbiome. PLoS ONE 8: e63139.
2 Arumugam M, Raes J, Pelletier E *et al* (2011) Enterotypes of the human gut microbiome. *Nature* 473: 174-180. [Erratum in *Nature* 474: 666].
3 Abrahamsson TR, Jakobsson HE, Andersson AF et al (2014) Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exper Allergy* 44(6):842-850.
4 Ahn J, Sinha R, Pei Z *et al* (2013) Human gut microbiome and risk of colorectal cancer. *J Natl Cancer Inst*. 105(24):1907-11.
5 Le Chatelier E, Nielsen T, Qin J *et al* 2013 Richness of human gut microbiome correlates with metabolic markers. Nature 500(7464):541-6.
6 Cotillard A, Kennedy SP, Kong LC *et al* (2013) Dietary intervention impact on gut microbial gene richness. *Nature* 500: 585-588.
7 Sokol H, Pigneur B, Watterlot L *et al* (2008) *Faecalibacterium prausnitzii* is an antinflammatory commensal bacterium identified by gut microbiota analysis of Crohn's disease patients. *PNAS* 105:16731-16736.
8 Spor A, Koren O, Ley R (2011) Unravelling the effects of the environment and host genotype on the gut microbiome. *Nat Rev Microbiol* 9: 279-289.
9 Simrén M, Barbara G, Flint HJ *et al* (2013) Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut* 62: 159-176.
10 Parkes GC, Rayment NB, Hudspith BN *et al* (2012) Distinct microbial populations exist in the mucosa-associated microbiota in IBS sub-groups of irritable bowel syndrome. *Neurogastroenterol Motil* 24:31-39.
11 Porter CK, Gormley R, Tribble Dr *et al* 2011 The incidence and gastrointestinal risk of functional gastrointestinal disorders in a healthy US adult population. *Am J Gastroenterol* 106:130-138.
12 Hemarajata P, Versalovic J. 2012. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Ther Adv Gastroenterol* 6(1):39-51.
13 Benton, D, Williams, C and Brown, A (2007) Impact of consuming a milk drink containing a probiotic on mood and cognition. *Eur J Clin Nutr* 61: 355–361.
14 Rao AV, Bested AC, Beaulne TM *et al* (2009). A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathogens* 1:6 doi:10.1186/1757-4749-1-6
15 McKenzie YA, Alder A, Anderson W *et al* (2012) British Dietetic Association evidence-based guidelines for the dietary management of irritable bowel syndrome in adults. *J Hum Nutr Diet* 25(3):260-274.
16 Whelan K, Quigley EMM (2013) Probiotics in the management of irritable bowel syndrome and inflammatory bowel disease. *Cur Opin Gastroenterol* 29(2):184-189.
17 Hungin AP, Mulligan C, Pot B *et al* (2013) Systematic review: probiotics in the management of lower gastrointestinal symptoms in clinical practice – an evidence-based international guide. *Aliment Pharmacol Ther* 38(8): 864-886
18 Miller LE, Ouwehand AC (2013) Probiotic supplementation decreases intestinal transit time: Meta-analysis of randomized controlled trials. *World J Gastroenterol* 19(29):4718-4725.
19 Chmielewska A, Szajewska H (2010) Systematic review of randomised controlled trials: probiotics for functional constipation. *World J Gastroenterol* 16(1):69-75.
20 Quigley EM. 2011. The enteric microbiota in the pathogenesis and management of constipation. *Best Pract Res Clin Gastroenterol*. 25(1):119-26.
21 Major G, Spiller R (2014) Irritable bowel syndrome, inflammatory bowel disease and the microbiome. *Curr Opin Endocrinol Diabetes Obes* 21:15-21.
22 Hold GL, Smith M, Grange C *et al* (2014) Role of the gut microbiota in inflammatory bowel disease pathogenesis: what have we learnt in the past 10 years? *World J Gastroenterol* 20(5):1192-210.
23 Jonkers D, Penders J, Masclee A *et al* (2012) Probiotics in the management of inflammatory bowel disease: a systematic review of intervention studies in adult patients. *Drugs* 72:803-823.
24 Guarner F, Khan AG, Garisch J *et al* (2012) World Gastroenterology Organisation global Guidelines. Probiotics and Prebiotics. October 2011. *J Clin Gastroenterol* 46(6):468-81.
25 Sanders ME, Guarner F, Guerrant R *et al* (2013) An update on the use and investigation of probiotics in health and disease. *Gut* 62:787-796.
26 Lee J, Allen R, Ashley S *et al* (2013) British Dietetic Assocaition evidence-based guidelines for the dietary management of Crohn's disease in adults. *J Hum Nutr Diet* Dec 6 [Epub ahead of print]
27 Candela M, Turroni S, Biagi E *et al* (2014) Inflammation and colorectal cancer, when microbiota-host mutualism breaks. *World J Gastroenterol* 20(4):908-922.
28 Hardy H, Harris J, Lyon E *et al* (2013) Probotics, prebiotics and immunomodulation of gut mucosal defences: Homeostasis and immunopathology. *Nutrients* 5:1869-1912.
29 Imai K, Matsuyama S, Miyake S *et al* (2000) Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. *Lancet* 356: 1795-1799.
30 Ishikawa H, Akedo I, Otani T *et al* (2005) Randomized trial of dietary fiber and Lactobacillus casei administration for prevention of colorectal tumours. *Int J Cancer* 116:762-767.
31 Rafter J, Bennett M, Caderni G *et al* (2007) Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients. *Am J Clin Nutr* 85(2):488-496.
32 Garcia-Inglesias T, Del Toro-Arreola A, Albarran-Somoza B *et al* (2009) Low NKp30, NKp46 and NKG2D expression and reduced cytotoxic activity on NK cells in cervical cancer and precursor lesions. *BMC Cancer* 9:186.
33 Neu J, Walker A. (2011). Necrotizing enterocolitis. *N Engl J Med* 364:255-264.
34 Morowitz MJ, Poroko V, Caplan M *et al*. (2010). Redefining the role of intestinal microbes in the pathogenesis of necrotizing enterocolitis. *Pediatrics* 125:777-785.
35 Deshpande G, Rao S, Patole S *et al* (2010) Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. *Pediatrics* 125:921-930.
36 Downard CD, Renaud E, St Peter SD *et al* (2012) Treatment of necrotizing enterocolitis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. *J Pediatr Surg* 47(112):2111-2122.
37 Alfaleh K, Anabrees J, Bassler D *et al* (2011) Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev March 16 (3):CD005496
38 Bernardo WM, Aires FT, Carneiro RM *et al* (2013) Effectiveness of probiotics in the prophylaxis of necrotizing enterocolitis in preterm neonates: a systematic review and meta-analysis. *J Pediatr (Rio J)* 89:18-24.
39 Thomas LV, Whelan K (2013) Your Guide to Probiotics. Published by British Journal of Nursing and Gastrointestinal Nursing. [Reprints available from science@yakult.co.uk]

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Questions relating to: *The gut microbiota and gut health: a probiotic perspective*
Type your answers below and then **print for your records** or print and complete answers by hand.

Q.1	What is dysbiosis?
A	
Q.2	State at least three diseases that have been associated with disturbance of the gut microbiota.
A	
Q.3	Describe at least three beneficial mechanisms of probiotic activity in the gut.
A	
Q.4	How can probiotics positively affect the symptoms of IBS?
A	
Q.5	What is the benefit of providing short supplementation of probiotics for constipation?
A	
Q.6	Describe how probiotics might help with IBD symptom relief.
A	
Q.7	Describe the probiotic gut mechanisms that could affect colorectal cancer.
A	
Q.8	What is the evidence to suggest that probiotics can reduce the risk of necrotising colitis in preterm infants?
A	
Q.9	Explain why it is important to consider choice of strain when using or recommending a probiotic.
A	
Q.10	What reference might you use to check advice on safety and quality criteria of probiotics?
A	

Please type additional notes here . . .