Forum GLUTEN-FREE
JOURNAL FOR HEALTH CARE PROFESSIONALS I EDITION 01/2015

Dr Schär Institute

The Intestinal Microbiome: Exploring a New World

The whole of the bacteria hosted in our intestine, or the microbiome, forms a vital critical mass that interacts with our body – "for better or worse" – starting from birth. As recent studies have shown, the intestinal microbiome appears to have significant connections to gluten-related disorders.

The articles published in this issue of the DSI Forum explore different perspectives on the relationships between the microbial flora populating our intestine – known as the intestinal microbiome – and gluten-related disorders, first among them coeliac disease: two apparently distant "worlds" that are actually surprisingly linked.

A glance at PubMed, the most complete medical-scientific database worldwide, shows that there has been an exponential growth in the number of publications on the intestinal microbiome since the early 2000s, jumping from 35 articles in 2004 to 1,656 in 2014! In 2014 alone, no fewer than 21 articles dealt with the relationships between the "bacterial world" of the intestine and coeliac disease. Such an increase is primarily due to the development of new technologies in molecular genetics that enable us to analyse the intestinal bacterial flora quickly, easily and accurately. Regarding coeliac disease, one of the most relevant topics today is the impressive increase in the frequency of this illness over recent decades, a phenomenon that cannot be ascribed to changes in genes, which require much more time to take place, but only to environmental changes. These include changes in diet, lifestyle, the spread of infections, and the bacterial population that has settled in our intestine.

As a paediatrician, I am particularly interested in the potential relationship between certain factors in early life, such as type of birth (natural or Caesarean), infant feeding, intestinal infections and the use of antibiotics, the intestinal microbiome and the risk of developing coeliac disease. The analysis of these aspects could help us to better understand the "recipe" for the genetic and environmental cocktail that leads to the development of gluten-dependent disorders – not just coeliac disease, but also non-coeliac gluten sensitivity. In terms of treatment, an understanding of persistent changes in the microbiome, known as dysbiosis, could foster the implementation of new treatments aimed at improving quality of life in people suffering from gluten-related disorders.

PROFESSOR CARLO CATASSI
Professor for pediatrician at the Marche Poltechnic University (Italy). President of the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition, years 2013-2016. Coordinator of the Dr. Schär Advisory Board

Gut Microbiota in Health and Disease

BRIDGETTE WILSON
BSC, MSC, PGDIP, RD.

Research Dietitian, King's College London. Bridgette is a Doctoral Student at King's College London and a registered Dietitian. Bridgette Completed a Bachelor of Biological Sciences and a Masters in Molecular Biology before training as a Dietitian. Following on from working in the NHS Bridgette returned to a research role to focus on the area of Gastroenterology. Bridgette currently works under the team of Professor Kevin Whelan and Dr Miranda Lomer at King's College London and is undertaking research into dietary interventions for irritable bowel syndrome.

As new evidence and better analytical techniques emerge, more information is becoming available about our gut bacteria. It is becoming clear that the type and relative amount of bacteria present in our gut plays an important role in both health and disease. Biotech companies are investing more in technologies to target this 'microbiome' as a potential moderator of our gut health and our innate immune system. The increase in incidence of immune mediated diseases and neurological disorders cannot be explained by shifts in human genetics.[1] Dysbiosis and loss of diversity is something that is now being commonly traced

> Most people have around 160 species from a possible 1000.

to these diseases as we look to our 'other genome' for clues. What has become abundantly clear from the work thus far conducted in metagenomics is that greater bacterial diversity or 'gene richness' is strongly associated with better health.

INFO

Key definitions

Microbiome: the collective name for the gut microorganisms.

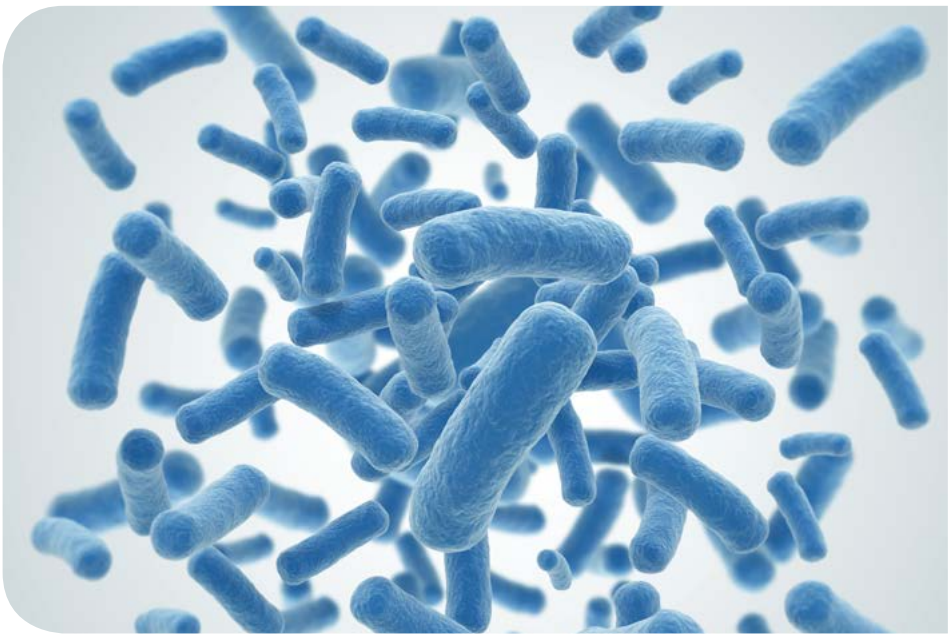
Dysbiosis : one or more potentially harmful microbial organisms predominating the gut microbial population.[3]

Metagenomics: the field of study which compares entire genomes.

Phyla: a taxonomic term for dividing organisms into groups with others of similar properties.

Enterotype: a term to divide humans into groups based on the gut bacteria present.

Transcriptome: the genes which have been expressed as proteins i.e the active part of the genome.

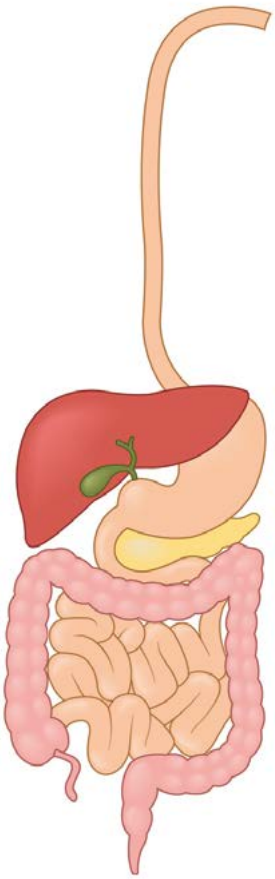


What species makes up the Microbiome?

Although great inter-individual variation exists at species level – most people have around 160 species from a possible 1000 – the phyla represented in the microbiome are quite narrow. Qin et al (2010) have identified a core set of bacteria present within all people. Three main enterotypes have been configured for the human microbiome.[2] The marker genera for which microbiome a subject belongs to are the Bacteroides, Prevotella and Ruminococcus (the latter group is further associated with the prescence of the Methanobrevibacter).[1]

Function

The functions of the gut microbiota are still being fully elucidated but some key aspects are: immune signalling and modulation; production of nervous system messengers; production of essential vitamins; regulation of fat metabolism; production of short chain fatty acids (SCFA) specifically butyrate, and branched chain fatty acids. Depending on the substrate fermented, other products of the microbiome include hydrogen, carbon-dioxide and methane gasses, ammonia, amines and phenolic compounds.[3]



The symbiosis between humans and the gut microbiota is becoming ever more apparent. The term 'superorganism' has been coined as the human body starts to be considered more a conglomerate organism of our own transcriptome plus the plastic and far greater transcriptome of the gut microbiota. The genes encoded by our gut bacteria outstrip our own by greater than 100-fold.[4] It is therefore not surprising that much focus of disease cause, prevention and cure is now being placed on this 'other genome'.

The enteric nervous system (ENS) is sometimes referred to in literature as the 'second brain'. This is due to it consisting of over 200 million neurons.[5] The ENS sends signals from the gut to the brain via endocrine, neuronal and immune afferent signalling.[5] In addition, the gut associated lymphoid tissue (GALT), which regularly samples and responds to signals from within the intestinal lumen, is considered the bodies major defensive organ against infection.[5]

The combination of interactions between the ENS the microbiome and the GALT has great potential to effect changes to physical, immunological and emotional wellbeing.

The symbiosis between humans and the gut microbiota is becoming ever more apparent.

What shapes the Microbiome?

The microbiome develops from birth. Route of delivery and early feeding affects the initial development of the microbiome. Weaning and childhood environment (rural or urban) likely has an impact on the development of the mature microbiome. Studies of isolated population groups in Africa show divergent and unique bacterial colonisation from that of a Western cohort indicating that environment is a strong driving force for colonisation.[6] Twin studies have also revealed that at least with some taxa there is a definite genetic influence on species abundance.[7] The spouses of identical twins also showed positive correlations which adds to the concept that both nature and nurture can affect gene richness of the gut microbiota.[8]

In the elderly the microbiome changes again, although it is not clear why this occurs. A reduction in butyrate producing bacteria is seen within the elderly population and a reduction in gene richness of the microbiome. Elderly living within the community maintain greater gene richness, thought to be an artefact of a more varied diet, than elderly in long term care.[9]

How do changes affect us?

Dysbiosis is associated with several disease states.[3] A recent review was published of the particular diseases and the associated alterations in bacterial populations.[4] New technologies have allowed a type of bacterial fingerprint to be developed for certain diseases which may provide both a powerful and non-invasive diagnostic tool and a potential target for therapy in treating these conditions.

In obesity studies, subjects with reduced gene richness showed greater overall adiposity, insulin resistance and dyslipidaemia and a more pronounced inflammatory phenotype.[10] Those with lower gene richness also gained more weight over time. Goodrich et al (2014) provide insight into the heritability of an obesogenic microbiome and the potential influence of methanogens and Christensenella spp. on metabolic disorders.

Both nature and nutrition can affect our microbiome

Studies in infants with genetic disposition to coeliac disease (CoD) show a reduction in Actinobacteria (which includes Bifidobacteria) and an increase in Firmicutes and Proteobacteria spp.[11] This said, a definitive link between microbial alterations and development of CoD disease has not been shown.[12] Dysbiosis has been identified in microbiome sequencing in irritable bowel syndrome (IBS).[13] Further studies have identified distinct differences in gut bacteria in different IBS subtypes in both luminal and mucosal populations.[14-16] A recent pilot study in paediatrics has identified that the microbiome may be indicative of the likelihood of the low FODMAP diet being effective in symptom alleviation.[17] Qin et al (2012) identified antagonistic behaviour between beneficial and harmful bacteria in type 2 diabetes. A decline in butyrate producing bacteria may be an indicator of increased risk of developing obesity related co-morbidities.[18]

How can we improve the Microbiome?

Dietary studies have shown the power of dietary manipulation in altering the microbiome[19] and this is one area with great potential. Feeding the host and feeding the microbiota is the obvious way in which manipulation of the microbiota may come about. A high fat-high protein diet has been linked to the Bacteroides enterotype, a carbohydrate rich diet corresponds to the Prevotella enterotype.[20] Short term dietary changes (~10 days) were shown to change the composition of the microbiome but not significantly affect the identity of the enterotype. Faecalibaterium prausnitzii, Bifidobacterium and Clostridium cluster XIVa have all been shown to be elevated by high fibre dietary supplements and these are three groups which are generally associated with better health.[1,21]

Other studies have definitively shown that prebiotics and probiotics to varying degrees are useful tools in promoting beneficial bifidobacteria and lactobacilli. Several studies have shown mechanisms by which different species of Lactobacilli and Bifidobacteria not only confer beneficial effects on the host but also inhibit attachment and activity of invading enteropathogens (Reviewed in;).[4] It may be that in the future more strains of bacteria (e.g. Akkermansia mucinophila and Christensenella minuta) will be targeted by both prebiotic and probiotic supplementation.[4] Faecal microbiota transplantation is another

technique for rapid correction of a disordered microbiome. Trials for intractable C.diff infected patients have shown promising results thus far. Lean donor faecal microbiota transplantation showed an improvement in insulin resistance in patients with metabolic syndrome[22] – lending support to the growing concept that dysbiosis plays an important role in the development of obesity related disorders. Antimicrobial strategies for modulation of the microbiome may have therapeutic potential in the future however current knowledge of the efficacy in this area is based on mice models and therefore not presently a recommended strategy.[4] A varied diet balancing all food groups should be utilised to provide alternating substrate and reduce the likelihood of unfavourable species becoming dominant within the gut. For perturbations in the microbiome brought on by antibiotics or a bout of gastroenteritis the use of prebiotics and probiotics are likely to be useful and are considered to be safe for general use. Stool diagnostics capable of detecting a decrease in diversity may be a useful tool for early disease prediction and preventative measures.

REFERENCES

1 Blottiere, H.M., et al., Human intestinal metagenomics: state of the art and future. Curr Opin Microbiol, 2013. 16(3): p. 232-9.

2 Qin, J., et al., A human gut microbial gene catalogue established by metagenomic sequencing. Nature, 2010. 464(7285): p. 59-65.

3 Roberfroid, M., et al., Prebiotic effects: metabolic and health benefits. British Journal of Nutrition, 2010. 104(S2): p. S1-S63.

4 Walsh, C.J., et al., Beneficial modulation of the gut microbiota. FEBS letters, 2014. 588(22): p. 4120-4130.

5 Al Omran, Y. and Q. Aziz, The brain-gut axis in health and disease, in Microbial Endocrinology: The Microbiota-Gut-Brain Axis in Health and Disease. 2014, Springer. p. 135-153.

6 De Filippo, C., et al., Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proceedings of the National Academy of Sciences, 2010. 107(33): p. 14691-14696.

7 Goodrich, J.K., et al., Human genetics shape the gut microbiome. Cell, 2014. 159(4): p. 789-799.

8 Nelson, K.E., et al., Metagenomics of the human body. 2011: Springer.

9 Claesson, M.J., et al., Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proceedings of the National Academy of Sciences, 2011. 108(Supplement 1): p. 4586-4591.

10 Le Chatelier, E., et al., Richness of human gut microbiome correlates with metabolic markers. Nature, 2013. 500(7464): p. 541-546.

11 Olivares, M., et al., The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. Gut, 2014: p. gutjnl-2014-306931.

12 McLean, M.H., et al., Does the microbiota play a role in the pathogenesis of autoimmune diseases? Gut, 2014: p. gutjnl-2014-308514.

13 Rajilic-Stojanovic, M., et al., Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. Gastroenterology, 2011. 141(5): p. 1792-801.

14 Saulnier, D.M., et al., The intestinal microbiome, probiotics and prebiotics in neurogastroenterology. Gut Microbes, 2013. 4(1): p. 17-27.

15 Parkes, G.C., et al., Distinct microbial populations exist in the mucosa-associated microbiota of subgroups of irritable bowel syndrome. Neurogastroenterology & Motility, 2012. 24(1): p. 31-39.

16 Sundin, J., et al., Altered faecal and mucosal microbial composition in post-infectious irritable bowel syndrome patients correlates with mucosal lymphocyte phenotypes and psychological distress. Aliment Pharmacol Ther, 2015. 41(4): p. 342-51.

17 Chumpitazi, B.P., et al., Gut microbiota influences low fermentable substrate diet efficacy in children with irritable bowel syndrome. Gut microbes, 2014. 5(2): p. 165-175.

18 Qin, J., et al., A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature, 2012. 490(7418): p. 55-60.

19 Cotillard, A., et al., Dietary intervention impact on gut microbial gene richness. Nature, 2013. 500(7464): p. 585-8.

20 Wu, G.D., et al., Linking long-term dietary patterns with gut microbial enterotypes. Science, 2011. 334(6052): p. 105-108.

21 Shen, Q., L. Zhao, and K.M. Tuohy, High-level dietary fibre up-regulates colonic fermentation and relative abundance of saccharolytic bacteria within the human faecal microbiota in vitro. European journal of nutrition, 2012. 51(6): p. 693-705.

22 Vrieze, A., et al., Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology, 2012. 143(4): p. 913-6.e7.

The Influence of the Microbiome on Gluten-Related Disorders

This short article provides an overview of the differences in microbiota which exist in gluten-related disorders, with a particular focus on coeliac disease. It goes on to outline a planned controlled prospective study which examines changes in intestinal microflora in patients with wheat sensitivity.

PROF. DR. MED. YURDAGÜL ZOPF

Medical Clinic 1,
University of Erlangen, Germany

PRIV. DOZ. DR. RER. NAT. WALBURGA DIETERICH

Scientific employee
Medical Clinic 1
University Erlangen, Germany

The increasing prevalence of food intolerances, especially in relation to certain carbohydrates, represents a global health problem.[1] Moreover, intolerance of gluten and gluten-bound substances, e.g. amylase-trypsin inhibitor (ATI) is blamed[2] for intestinal (e.g. meteorism, pain, constipation, diarrhoea) and extraintestinal symptoms (e.g. fatigue, headaches, joint pain, skin irritation) in affected patients.[3] The pathogenesis of food intolerances is blamed on factors such as changes in the composition of the intestinal flora and its influence on mucous membrane immune tolerance.[4]

The intestinal barrier is important to maintain homoeostasis in the intestine. If intestinal imbalance occurs, the intestinal barrier can be attacked and become permeable as part of leaky gut syndrome. It has been shown that there is an association between leaky gut syndrome and the development of gastrointestinal disease and possibly food intolerances.[5]

The microbiome of the human digestive tract therefore also appears to play an important role in influencing wheat/gluten-associated disease.[4]

It is common knowledge that the intestinal microflora is dependent on many factors. The microbial composition in the small intestine is primarily determined by the competition between micro-organisms and the host to ensure rapid absorption and utilisation of carbohydrates. The micro-organisms in the colon, on the other hand, are affected by both the complex utilisation of carbohydrates and competition among themselves.[6]

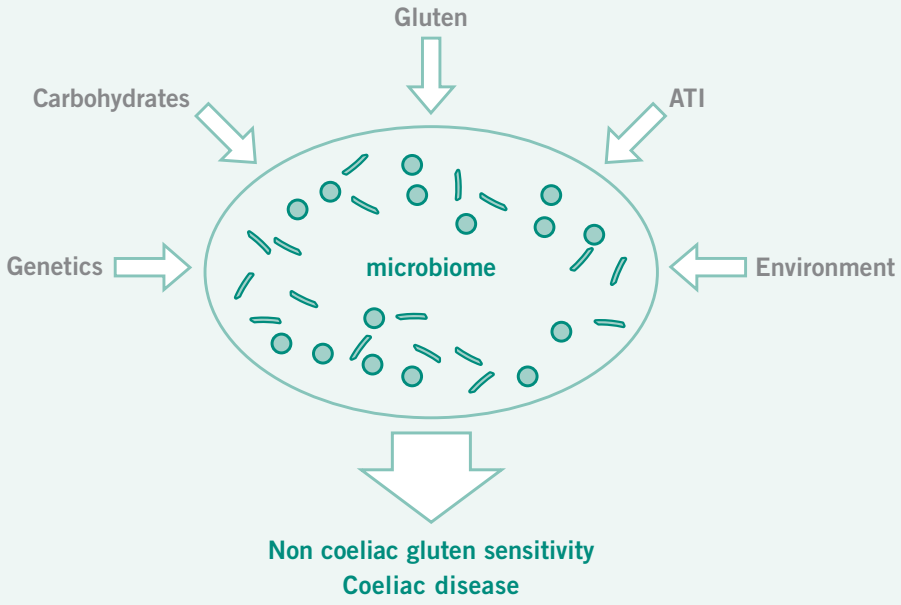
Nutrition plays an important role in this case. Mouse studies have already demonstrated that diet can rapidly alter the intestinal microbial composition.[7]

Numerous publications demonstrate the presence of streptococcus sp., E.coli, clostridium sp., GC-rich organisms, bacteroides uniformis, blautia glucerasea and bifidobacteria in the small and large intestine, which prefer different substrates.[8] It is interesting in this context that B. uniformis primarily utilises inulin, whereas other species primarily metabolise fructo-oligosaccharides or monosaccharides.[9]

An indication of the importance of microbial composition in coeliac disease is provided by the fact that there is a different bacterial population in these patients compared to healthy individuals. **A significantly higher proportion of bifidobacterium bifidum and increased numbers of lactobacillus sp. were found in coeliac patients, but their diversity decreased significantly after maintaining a gluten-free diet.**[10]

Coeliac disease patients have a different bacterial population when compared to healthy individuals.

Influences on the microbiome:



Furthermore, it was demonstrated in-vitro that certain bifidobacterium strains reduced the inflammatory immune response triggered by gliadin peptides, thus exerting a protective effect.[11,12]

In 2013, Wacklin et al. reported a possible link between the manifestation of coeliac disease in the form of gastrointestinal or extraintestinal symptoms and the microbiome.[13]

In another study, the duodenal microbiome of coeliac disease patients with persistent symptoms despite long-term GFD and normalised small-intestinal mucosa was studied in comparison with coeliac disease patients without symptoms. It was determined that there were differences in bacterial colonisation of the small intestine between patients without symptoms and patients with persistent symptoms. They had a significantly increased amount of proteobacteria, whereas the number of bacteroidetes and firmicutes was reduced. **Overall, the coeliac disease patients with persistent symptoms exhibited reduced microbial diversity.** In some subgroups of coeliac disease there is thus evidence of a dysbiosis as a possible cause of recurrent symptoms, in which case new treatment approaches, e.g. in the form of pro- or prebiotics, would be possible.[14]

In addition, Smecuol et al. have already investigated the effect of the probiotic bifidobacterium infantis Natren Life Start Strain Super Strain on the clinical progress of untreated coeliac patients. Of the 22 patients, 12 were given 2 B. infantes capsules and 10 were given 2 placebo capsules with meals. While taking the probiotic had no effect on intestinal permeability, symptoms of dyspepsia, constipation and gastro-oesophageal reflux improved significantly in the B. infantis group. There was also a significant increase in MIP-1ß (macrophage inflammatory protein-1ß) in the probiotics group. Although this study thus indicates a possible mitigating effect of probiotics on some coeliac disease symptoms, it requires confirmation by further studies.[15]

A study in patients with a high genetic risk of coeliac disease has shown an altered microbial composition even in infancy and childhood.

A recent study by Olivares et al. in patients with a high genetic risk of coeliac disease revealed an altered microbial composition even in infancy and early childhood, which is an indication that the change in the microbiome might take place at a very early stage. Compared to infants without increased coeliac risk, a significantly higher number of firmicutes and proteobacteria, and a smaller number of act-

inobacteria, were found in HLA-DQ2-positive carriers. The number of bifidobacteria species was also reduced. A genetic predisposition in the form of HLA-DQ2 thus appears to have an impact on the microbiome and could as such also contribute to the pathogenesis. This finding could be useful in determining the risk of coeliac disease.[16]

Generally, this data indicates that a link exists between the pathogenesis and the symptoms of gluten-related diseases and the human microbiome. However, the extent to which certain bacterial species are involved in the pathogenesis of coeliac disease or non-coeliac gluten sensitivity (NCGS), and the extent to which damaged mucosa provide preferential living conditions for these bacterial species, is still unclear and requires further investigation.

The initial data from Biesiekierski et al. (2013) allows us to speculate that fermentable carbohydrates are also the cause or at least an influencing factor in patients with wheat sensitivity. Therefore, we consider that it would be of particular interest to determine the differences in microbial colonisation between patients and healthy controls. In the context of a controlled prospective study, we are therefore examining changes in intestinal microflora in patients with documented wheat sensitivity with a mixed diet, gluten-free diet and low-FODMAP diet to determine the influence of carbohydrate chains on bacterial growth and differentiation thereof. The comparison with a healthy control group and a control population with proven coeliac disease is used for better differentiation between the bacterial strains that are responsible for the pathogenesis of wheat sensitivity.

The detection of the specific composition of flora in patients with wheat sensitivity could represent an innovative approach for targeted probiotic treatment with few side effects.

REFERENCES

1 Zopf Y. et al., The differential diagnosis of food intolerance. Dtsch Arztebl Int. 2009 May;106(21):359-69;

2 Junker Y. et al., Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J Exp Med. 2012 Dec 17;209(13):2395-408.

3 Volta U. et al., Non-celiac gluten sensitivity: questions still to be answered despite increasing awareness. Cell Mol Immunol. 2013 Sep;10(5):383-92.

4 Galipeau HJ, Verdu EF. Gut microbes and adverse food reactions: Focus on gluten related disorders. Gut Microbes. 2014;5(5):594-605.

5 Barbara G. et al., Mucosal permeability and immune activation as potential therapeutic targets of probiotics in irritable bowel syndrome. J Clin Gastroenterol. 2012 Oct;46 Suppl:S52-5.

6 Zoetendal, E.G. and W.M. de Vos, Effect of diet on the intestinal microbiota and its activity. Curr Opin Gastroenterol, 2014.

7 Ooi, J.H., et al., Dominant effects of the diet on the microbiome and the local and systemic immune response in mice. PLoS One, 2014. 9(1): p. e86366.

8 Zoetendal, E.G., et al., The human small intestinal microbiota is driven by rapid uptake and conversion of simple carbohydrates. ISME J, 2012. 6(7): p. 1415-26.

9 Tannock, G.W., et al., RNA-stable isotope probing (RNA-SIP) shows carbon utilization from inulin by specific bacterial populations in the large bowel of rats. Appl Environ Microbiol, 2014.

10 Nistal, E., et al., Differences in faecal bacteria populations and faecal bacteria metabolism in healthy adults and celiac disease patients. Biochimie, 2012. 94(8): p. 1724-9.

11 Medina, M., et al., Bifidobacterium strains suppress in vitro the pro-inflammatory milieu triggered by the large intestinal microbiota of coeliac patients. J Inflamm (Lond), 2008. 5: p. 19.

12 Laparra, J.M. and Y. Sanz, Bifidobacteria inhibit the inflammatory response induced by gliadins in intestinal epithelial cells via modifications of toxic peptide generation during digestion. J Cell Biochem, 2010. 109(4): p. 801-7.

13 Wacklin, P., et al., The duodenal microbiota composition of adult celiac disease patients is associated with the clinical manifestation of the disease. Inflamm Bowel Dis, 2013. 19(5): p. 934-41.

14 Wacklin, P., et al., Altered duodenal microbiota composition in celiac disease patients suffering from persistent symptoms on a long-term gluten-free diet. Am J Gastroenterol, 2014. 109(12): p. 1933-41.

15 Smecuol E, H.H., Sugai E, Corso L, Cherñavsky AC, Bellavite FP, González A, Vodánovich F, Moreno ML, Vázquez H, Lozano G, Niveloni S, Mazure R, Meddings J, Mauriño E, Bai JC., Exploratory, randomized, double-blind, placebo-controlled study on the effects of Bifidobacterium infantis natren life start strain super strain in active celiac disease. J Clin Gastroenterol, 2013. 47: p. 139-147.

16 Olivares, M., et al., The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. Gut, 2015. 64(3): p. 406-17.

The importance of the microbiota in the pathogenesis and treatment of coeliac disease

The importance of intestinal microbiota and role of probiotics is well documented in some clinical scenarios and conditions, for example, antibiotic-associated diarrhoea, irritable bowel syndrome. However, there are currently few studies on the relationship between coeliac disease and microbiota. This article looks to address and summarise the current knowledge base within this specific area.

DIPL. OEC. TROPH. UTE KÖRNER

is a qualified Nutritionist specialising in Allergology. Since completing her qualification in Nutritional Science, she has worked as a nutritionist, lecturer, journalist and writer, mainly in the field of Allergology and Gastroenterology. She writes books and speaks at lectures, training seminars and further education courses for doctors on the subject of food allergies and intolerances.

DR. MAIKE GROENEVELD

is a qualified nutritionist and home economist, and has worked as a freelance nutritionist, lecturer and writer for over 20 years. She advises both patients and companies on nutritional issues, and as a professional writer publishes books, brochures, specialist publications and internet articles.

Man is not a single living being; he lives in a community with trillions of bacteria and other micro-organisms. The gastrointestinal tract is densely populated: it has an estimated 100 trillion (10^{14}) micro-organisms, which are referred to as intestinal microbiota (formerly intestinal flora). The number of microbial cells in the intestine is ten times greater than the number of human somatic cells; they have about 150 times more genes than the human body which means they have an enormous metabolic activity [Le Chatelier et al. 2013]. Their metabolic products and neurotransmitters have a close interdependency with the somatic cells both inside and outside of the gastrointestinal tract. They support the digestive functions, help ward off pathogenic micro-organisms and contribute to the development and maintenance of the immune system and the intestinal barrier. The intestinal barrier is a complex system that separates the intestinal lumen from the inside of the body and is composed of the following elements [Bischoff et al. 2014]:

Mechanical: Epithelial cells with tight junctions, mucus

Humoral: Defensins, immunoglobulins, cytokines

Immune cells: Specific and non-specific immune cells

Muscle cells

Nerve cells

The intestinal microbiota are involved in metabolic processes and can modulate the barrier function [Viggiano et al. 2015]. In addition to a balanced microbiota, another important protection mechanism for a functioning intestinal barrier is the regulation of paracellular passage through tight junctions.

In recent years, scientists have achieved great progress in the study of microbiota thanks to the application of methods of analysis from molecular biology. The thousands of different types of bacteria that occur in the intestine can be divided into a total of six different subgroups. Up to 90 % of the intestinal bacteria belong to the groups of firmicutes and bacteroidetes, followed by proteobacteria, actinobacteria, verrucomicrobia and fusobacteria [Blaut 2015].

INFO Defensins are antimicrobial peptides of innate immunity.

The majority of micro-organisms are found in every human intestine. These are referred to as the core microbiome [Doré et al. 2013]. Every person also has a variable part. This makes up the individual microbiota. The composition and activity of the microbiota are influenced by several factors, including type of birth (vaginal or C-section), genes, age and lifestyle. Medicines (e.g. antibiotics) and diet play an important role: factors such as quantity and type of fibre and fermented foods are important.

> The composition and activity of the microbiota are influenced by several factors, including type of birth, genes, age and lifestyle, medicines (antibiotics) and diet.

According to recent studies, the composition of the microbiota plays an important role in the maintenance of health, because the different species of bacteria can have both protective and harmful effects [Doré et al. 2013]. Certain pathogenic bacteria can, for example, cause local inflammation, weaken the intestinal barrier and increase permeation of substances including gluten [Moraes L. F. de Sousa, Grzeskowiak L.M. et al 2014, Viggiano et al 2015].

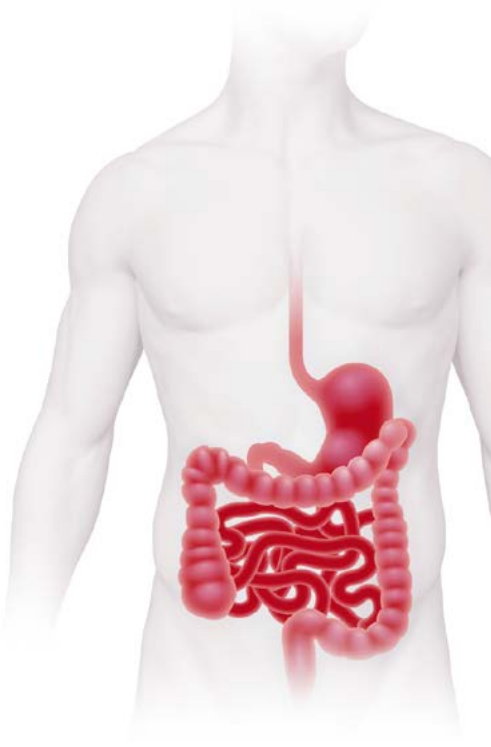
Coeliac disease and microbiota

It is known that missing peptidases in the human intestine mean that gluten is incompletely digested and that gluten peptides are absorbed via the small intestinal mucosa. Furthermore, there is growing evidence that a change in **intestinal permeability** due to increased permeability of tight junctions (TJ) is a major factor in the pathogenesis of coeliac disease. This makes it simpler for the remaining oligopeptides to be absorbed into the lamina propria and trigger the inflammation typical of coeliac disease.

It is still unclear whether disorders of the intestinal barrier are the primary cause or the consequence of coeliac disease [Sapone et al. 2012, Moraes L. F. de Sousa et al. 2014]. However, it has been possible to demonstrate that in the case of persons suffering from coeliac disease, gliadin is a strong stimulus for the release of zonulin. This protein increases intestinal permeability by facilitating the absorption of macromolecules via TJs [Drago et al. 2006].

> Comparative studies between children with coeliac disease and healthy control groups detected a lower number of lactobacilli and bifidobacteria in the former.

On the other hand, there is evidence that **changes in the intestinal microbiota** can lead to increased intestinal permeability and therefore may be involved in the pathogenesis of coeliac disease and allergic diseases. There are, however, only a few studies on the role of the microbiota in the pathophysiology of coeliac disease. It is believed that in the case of genetically susceptible patients, gram-negative bacteria are involved in the loss of gluten tolerance. Comparative studies between children with coeliac disease and healthy control groups detected a lower number of lactobacilli and bifidobacteria in the former. However, it is unclear whether a change in the microbiota of persons with coeliac disease is the primary cause or the consequence of coeliac disease. In biopsy specimens of the duodenum of untreated children with coeliac disease, more gram-negative bacterial strains were detected compared to treated children and healthy control groups, which suggests a change in the microbiota as a result of this disease [Moraes L. F. de Sousa et al. 2014].



Coeliac disease and probiotics

Currently, the only therapy there is for coeliac disease patients is a strict lifelong gluten-free diet (GFD), which includes avoiding traces of gluten. In the long term, this is difficult for many of those affected, especially without concomitant dietary advice. Despite complaints and the risk of complications and long-term consequences (e.g. malignancies, refractory coeliac disease) 30 % to 50 % of patients do not maintain a strict gluten-free diet [Körner, Schareina 2015]. Given the knowledge of changes in the intestinal microbiota in persons with coeliac disease, the following studies have demonstrated that the **use of probiotics** may constitute a promising approach to concurrent therapy in the case of coeliac disease:

In 2006, De Angelis et al. examined **combination preparation** VSL#3, which contains 8 different probiotic strains (e.g. bifidobacteria and lactobacilli). They demonstrated that compared with isolated strains and other commercially available products that were tested, the combination of these probiotic strains can split gliadin peptides more effectively, i.e. gliadin peptides are easier to digest with the aid of this probiotic combination preparation.

In the case of PBMCs*, De Palma's research group (2010) was able to reduce the secretion of interleukin-12 and IFN-gamma (pro-inflammatory cytokines) under the influence of gluten in-vitro, using specific **bifidobacteria**. This observation suggests an anti-inflammatory effect of the investigated bifidobacteria.

Lindfors et al. (2008) demonstrated that the **bacterial strain b. lactis** can prevent the toxic effect of wheat gliadin on epithelial cell cultures at doses of 106 and 107 CFU** per ml, but not at 105 CFU per ml.

In a mouse model by D`Arienzo et al. (2011), a milk product with the **l. casei ATCC 9595** strain (Actimel) enhanced the intestinal barrier function and prevented the intake of gliadin in the lamina propria.

* PBMC: peripheral blood mononuclear cell
** CFU: colony-forming units

NCGS and probiotics

As yet there is no practical study on the influence of the microbiota on the pathogenesis of this new disease in the specific case of gluten/wheat sensitivity. Unlike coeliac disease, an innate immune response is suspected in the case of NCGS. This is activated by gluten or wheat, but does not alter the intestinal mucosa or its permeability. However, there are indications of increased intestinal permeability in patients with neurological symptoms such as schizophrenia or autism and suspected NCGS.

INFO

Non-coeliac gluten sensitivity (NCGS)

is a reaction to gluten or wheat in the absence of coeliac disease or a wheat allergy. [Felber et al. 2014 (S2k-Leitlinie Zöliakie), Sapone et al. 2012, Catassi et al. 2013]

The aforementioned studies demonstrate that certain strains of bacteria aid the digestion of gliadin peptides. This may mean that patients with NCGS can as in the case of coeliac disease benefit from a concomitant course of probiotics. Further studies are required for specific recommendations.

In the case of some diseases (e.g., antibiotic-associated diarrhoea, irritable bowel syndrome, ulcerative colitis, pouchitis) there are studies that demonstrate clinically relevant efficacy of probiotics [Bischoff u. Köchling 2012]. However, the underlying mechanisms are still unclear. There are currently few studies on the relationship between coeliac disease and microbiota and the use of probiotics in the managementof coeliac disease. Since many effects of probiotic micro-organisms are strain-specific, evidence that has been obtained with a specific bacterial strain or preparation/product for coeliac disease cannot necessarily be transferred to other strains. Further investigation of the underlying mechanisms of action is necessary. Due to the positive effects reported and relative lack of known side effects, the trial use of probiotics can be considered.

There are currently few studies on the relationship between coeliac disease and microbiota and the use of probiotics in the management of coeliac disease.

INFO

Probiotics

are live micro-organisms that offer the host a health benefit if they are taken in sufficient quantities (FAO/WHO 2002; Hill et al. 2014). These are special types of non-pathogenic bacteria (in particular lactobacilli and bifidobacteria) that are especially resistant to acids and therefore to a large extent survive the passage through the stomach and small intestine. Probiotics are available in the form of medicines, food supplements and foodstuffs. Commercially available foodstuffs with live cultures include yoghurt, drinking yoghurt and mixed milk products. In freeze-dried form, probiotic bacteria can be found in products including cereals and baby food. Although the Health Claims Regulation (Regulation EU No. 432/2012 of the Commission of 16 May 2012) states that these foods may not use the term “probiotic” or claim a health effect, this does not rule out efficacy. Probiotic bacteria temporarily settle in the intestine and produce organic acids (e.g. butyrate). This reduces the pH, which repels pathogenic bacteria. Some probiotic bacteria strengthen the intestinal barrier, e.g. by inducing the formation of defensins from mucosal cells. An intact intestinal barrier ensures that nutrients can cross the intestinal wall, but that pathogenic bacteria and toxins are repelled.

Points to consider in the selection and use of probiotics – Make the correct choice!

Benefits are strain-specific

Sufficiently high bacterial count of 10^8 and 10^9 CFU per day

Favour products that also contain bifidobacteria

At the beginning of therapy: Take with meals and refrain from products with prebiotics such as inulin and oligofructose; in the case of simultaneous malabsorption of lactose or fructose, also avoid probiotic products with these ingredients where possible.

Slowly increase dosage (start with ½ the amount)

INFO

Useful websites

Research on microbiota and health:
www.gutmicrobiotaforhealth.com/

Human microbiome project:
www.hmpdacc.org/

REFERENCES

Binns N: Probiotics, prebiotics and the gut microbiota. ILSI Europe Concise Monograph Series 2013.

Bischoff, SC (Hrsg.): Probiotika, Präbiotika und Synbiotika. Georg Thieme Verlag, Stuttgart, 2009.

Bischoff SC, Köchling C: Pro- und Präbiotika. Akt Ernährungsmed 37, 287-306, 2012.

Bischoff SC, Barbara G et al.: Intestinal permeability – a new target for disease prevention and therapy. BMC Gastroenterology 14: 189, 2014. doi: 10.1186/s12876-014-0189-7.

Blaut M: Interaktion von Ballaststoffen und Mikrobiota. Aktuel Ernahrungsmed 40, 43–49, 2015.

Catassi C, Bai JC, Bonaz B et al.: Non-celiac gluten sensitivity: The new frontier of gluten related disorders. Nutrients. 2013, 5, 3839-3853; doi:10.3390/nu5103839.

Catassi C, Elli L .... : How the diagnosis of non celiac gluten sensitivity .... In Vorbereitung 2015.

Charisius H, Friebe R: Bund fürs Leben. Warum Bakterien unsere Freunde sind. Carl Hanser Verlag München, 2014.

De Angelis, M, Rizzelo C. G., Fassano A et al: VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for celiac sprue. Biochim. Biophys. Acta. 2006; 1762: 80-93.

Drago S, El Asmar R, Di Pierro M et al.: Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines. Scan J Gastroenterol. 2006; 41: 408–419.

Fasano A: Physiological, pathological, and therapeutic implications of zonulin-mediated intestinal barrier modulation: living life on the edge of the wall. Am J Pathol. 2008: 137: 1243–1252.

FAO/WHO: Probiotics in food. Health and nutritional properties and guidelines for evaluation. FAO Food and nutrition paper 85, 2002.

Felber J, Aust D, Baas S et al.: S2k-Leitlinie Zöliakie. 2014. URL: www.awmf.org/leitlinien.

Körner U, Schareina A: Nahrungsmittelallergien und -unverträglichkeiten in Diagnostik, Therapie und Beratung. 2. überarb. u. erw. Auflage. 2015 (in Vorbereitung).

Meddings J: The significance oft the gut barrier disease. Gut. 2008: 57: 438–440.

Moraes L. F. de Sousa, Grzeskowiak L.M. et al: Intestinal Microbiota and Probiotics in Celiac Disease. Clinical Microbiology Reviews 2014; 27: 482-489.

Sapone A, Lammers KM, Casolaro V et al.: Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. BMC Medicine. 2011, 9:23 (9 March 2011).

Sapone A, Bai J, Ciacci C: Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Medicine. 2012, 10:13 (7 February 2012).

Schuppan D, Zimmer KP: Diagnostik und Therapie der Zöliakie. Deutsches Ärzteblatt 2013; 110: 835-846.

Looking for information and support in Coeliac Disease and Non Coeliac Gluten Sensitivity? Trust in the Dr. Schär Institute.

The most respected professional resource for gluten free.

- Broad competence in coeliac disease and non coeliac gluten sensitivity
- 30 years experience and professional know how in research and development for gluten free food products and services
- A range of more than 350 gluten-free products
- Close collaboration with an International scientific committee

The Dr. Schär Institute is a part of the service of Dr. Schär, the international market leader in Europe for products and services in gluten free.

Visit **www.drschaer-institute.com** to access a number of resources for Coeliac Disease and Gluten Sensitivity.

Dr Schär Institute

Dr. Schär AG/SpA, Winkelau 9, I–39014 Burgstall, Tel. +39 0473 293300, professional@drschaer.com

Forum
JOURNAL FOR HEALTH CARE PROFESSIONALS
GLUTEN-FREE | EDITION 01/2015

News

Glutafin launches it's 'Group Session Tool Kit' for newly diagnosed coeliac patients

In recognition of the increasing interest in providing dietetic advice to newly diagnosed coeliac patients within a group setting, the Glutafin professional team have produced a **Group Session Tool Kit** for dietitians currently running or interested in running their own group sessions. The Tool has been reviewed by a panel of experienced independent dietitians and current group facilitators, and includes:

This resource is now available to download from the Dr Schär Institute website, a limited number of printed tool kits will also be available to order on a first come, first served basis. Visit **www.drschaer-institute.com/en/resources/** to download or order your tool kit today!

- A fully editable, unbranded group presentation that can be adapted to suit local policy and the individual style of the presenter
- A labelling activity to support patients in understanding which foods are suitable for a gluten free diet
- A sample request card to allow dietitians to order Glutafin products for demonstration/ sampling purposes during their group sessions.

Europe's No.1 in Gluten-Free to launch in UK

From **September 2015**, Schär, Europe's number one gluten-free brand, will be available to purchase in leading retailers throughout the UK. **The new Schär range will replace Dr Schär's existing DS-gluten free brand** and will offer a wide selection of tasty and high-quality ambient and frozen products. With decades of experience and a team of expert food technologists and health professionals, Dr Schär provides excellent gluten-free products as well as information and support to those following a gluten-free diet. To request information on the new range of Schär gluten-free products, please email: **professionals@drschaer.com**

Dr Schär

EDITOR
Dr Schär Institute
Dr Schär UK, Station Court, 442 Stockport Road, Thelwall, WA4 2GW
Helpline: 0800 988 8470, Email: professionals@drschaer.com
www.drschaer-institute.com

Text: zweiblick, Dr. Schär Professionals
Translation: NTL Traduzioni
Druck: Athesia

SEN1915_1