Yakult

Science for Health

EXPLORING THE LATEST RESEARCH INTO THE ROLE OF THE GUT MICROBIOME IN CLINICAL PRACTICE

YAKULT STUDY DAY
15TH JUNE 2021

INTRODUCTION FROM DR LOUISE DURRANT RD, SCIENCE MANAGER, YAKULT

In our second study day of 2021, we turn to the role of the gut microbiota in therapeutic areas examining, in turn, mental development and anxiety, gastrointestinal disorders, chronic kidney disease, and infection such as Covid-19. A theme running through all of these is the crosstalk between the gut microbiome and different parts in the body – the brain, the immune system and renal system. This emphasises the dynamic role that gut health and the microbiome play in overall health and wellness. I do hope you enjoy reading the summaries from our speakers' presentations. Remember you can listen to the talks by visiting the Yakult website.

THE ROLE OF THE MICROBIOME-GUT-BRAIN AXIS IN BRAIN DEVELOPMENT AND MENTAL HEALTH

The day kicked off with a presentation from Dr Kathrin Cohen Kadosh, University of Surrey, who covered the following points:

- **There is a window of opportunity to influence brain development from early infancy and childhood into the third decade of life;**
- **During this time, several dietary factors can have an important impact;**
- **The microbiome-gut-brain axis is the route via which the microbiome can influence brain development and function;**
- **Animal models and observational studies suggest that certain species of bacteria are associated with behaviours and clinical outcomes. This is being strengthened by intervention trials in humans.**

DIETARY DETERMINANTS OF BRAIN DEVELOPMENT

Mental health represents an important capital in our society – something that has become more obvious during the Covid-19 pandemic. Research has helped us to understand which dietary and lifestyle factors can have positive or negative effects on brain development. One of these factors is the gut microbiota.

Normal brain development, which encompasses both physical changes and the formation and reinforcement of neurological connections, occurs during childhood and continues until early adulthood. The brain starts to develop in utero but there is rapid change to the growth, migration and differentiation of brain cells until the age of 2-3 years. Most of the pre-frontal cortex development – the area of the brain responsible for complex processing tasks and attention – takes place from birth to early teens but maturation continues into a person's twenties. A failure to optimize brain development in this window of opportunity can have negative long-term consequences in terms of education, work potential, and mental health.

NUTRIENTS FOR BRAIN DEVELOPMENT & FUNCTION

Nutrient Group	Examples	Role in brain
Lipids	Linoleic acid	Fatty acid component of the brain, locomotor activity, cognitive function
	Alpha-linolenic acid	Language, executive function
	Docosahexaenoic acid	Structural role in brain, visual acuity, processing, attention, impulse control, IQ
Minerals	Iron	Hippocampal development, dopamine production, cognitive & motor function; Stronger evidence for maternal supplementation
	Zinc	Brain growth, creation of neurones & synapses, memory, learning, IQ, mood, executive functions
	Iodine	Prenatal brain neural differentiation, glial cell production, IQ, language
Vitamins	Vitamin A	Relational memory, cognitive function
	B complex (B12, folate)	Cell division, myelination, hippocampal development, creation of synapses & neurotransmitters, visuospatial abilities, social perception
	Vitamin D	Development of lateral ventricle & cortex, IQ, maternal deficiency linked to risk of ADHD & schizophrenia
Amino acids	Tyrosine	Neurotransmission, spatial recognition, mood
	Tryptophan	Neuroprotection, mood, cognitive function, linked to circadian rhythm and infant sleep
Psychobiotics	Probiotics	Specific strains of bacteria that release neuroactive substances, GABA linked to bifidobacteria, serotonin linked to entero- and streptococcus and lactobacillus
	Prebiotics e.g., fructans, oligosaccharides, fibre, unsaturated fatty acids	Act by selectively stimulating probiotic bacteria

INTRODUCING THE GUT-BRAIN AXIS

The microbiome-gut-brain axis is the route by which these nutrients influence brain development and function. Humans are colonised by over 30 trillion microorganisms and our body has developed and adapted its organs in symbiosis with these microorganisms. Therefore, modulating the gut microbiome – the combined genetic material of our microbiota – has the potential to impact the brain as summarised below:

Neurotransmitters, such as GABA and serotonin, are essential for normal mood and mental health. As studies suggest the gut microbiota can help regulate these substances, this presents exciting therapeutic opportunities for reducing risk of mood/mental disorders and managing symptoms. Gut dysbiosis – a significant reduction in bacteria diversity – has been found in people with anxiety, depression and autism.

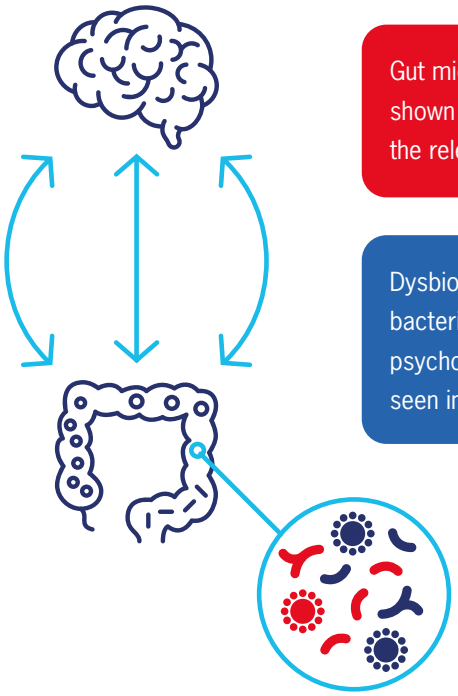
The gut-brain axis has been demonstrated in animal models as well as human studies. An observational study in babies and toddlers found associations between bifidobacteria and streptococcus, and positive emotionality and regulation, while infants with reduced microbiome diversity showed higher negative and fear reactivity[2]. Another study found links between microbial composition in 1-year-old infants and cognitive outcomes a year later, with Bacteroides associated with higher performance and Faecalibacterium associated with lower performance[3].

In the only longitudinal study to date, infants who had participated in a supplementation trial with L. rhamnosus for prevention of colic were followed up 13 years later[4]. The incidence of ADHD and Asperger's syndrome was significantly lower in children who received the probiotic. In addition, faecal samples taken during the first 6 months of life showed a lower level of bifidobacteria amongst those affected by ADHD and Asperger's syndrome.

THE EVIDENCE FOR A MICROBIOTA: BRAIN RELATIONSHIP

Gut-brain axis is defined as: *bidirectional communication via neural, endocrine and immune pathways*

Gut microbiota influences initial brain development but also brain responsiveness and function across the life-span



Gut microbial composition has been shown to regulate gene expression and the release of metabolites in the brain

Dysbiosis, a significant reduction in bacterial diversity, may lead to psychological abnormalities commonly seen in mental illness

THERAPEUTIC POTENTIAL

Two thirds of mental health problems begin before a person reaches 18 years of age[5,6]. Hence there are three critical periods of brain development – in infanthood, early childhood and adolescence – where there is sufficient brain plasticity to make a difference, for example using dietary interventions to improve the gut microbiome.

A recent randomised controlled trial (RCT) of prebiotics (galactooligosaccharides (GOS)) versus a placebo was carried out in 64 female adolescents with anxiety[7]. This is one of the first studies to test the complete trajectory of the microbiome-gut-brain axis by combining data from the gut microbiota, psychological status and brain neurotransmitters (visualised using brain scans). After four weeks of intervention, statistically significant changes were seen as follows:

- Increased bifidobacterial abundance in stool samples after GOS supplementation, especially in women categorised as 'high anxious';
- Decreased self-reported anxiety levels in the 'high anxious' group receiving GOS, but not the 'low anxious' or placebo groups;

There are critical periods of brain development - in infanthood, early childhood and adolescence - where there is sufficient brain plasticity to make a difference using dietary interventions to improve the microbiome.

This type of research can be developed further using a multidisciplinary approach, considering cultural use of psychobiotic-rich foods and ensuring other factors which influence the brain are taken into account, e.g., diet, sleep and exercise. The lived experience of stakeholders is also vital. A systematic review and stakeholder consultation[8] found that anxious youth were engaged with the concept of psychobiotics and dietary interventions but wanted advice from experts to consider their life situations.

In conclusion, the microbiome-gut-brain axis is a novel target for influencing neurodevelopment in children and young people. Supplementation with psychobiotics, such as probiotics and prebiotics, can be used to affect gut-brain axis dynamics and promote cognitive, emotional and brain development.

UNDERSTANDING THE ROLE OF THE GUT MICROBIOTA IN GASTROINTESTINAL HEALTH AND INFLAMMATORY BOWEL DISEASE

From the brain, we move onto the health of the gastrointestinal tract itself. The topic was discussed by Prof. Tariq Iqbal, University Hospitals Birmingham, who covered the following areas:

- **We have a good idea of what characterises a normal gut microbiota but still need to learn more;**
- **The role of the microbiota in gut infection, inflammatory bowel disease and irritable bowel syndrome;**
- **Faecal microbiota transplants – what, how and why;**
- **Current and future applications for modulating the gut microbiome.**

THE NORMAL GUT MICROBIOTA

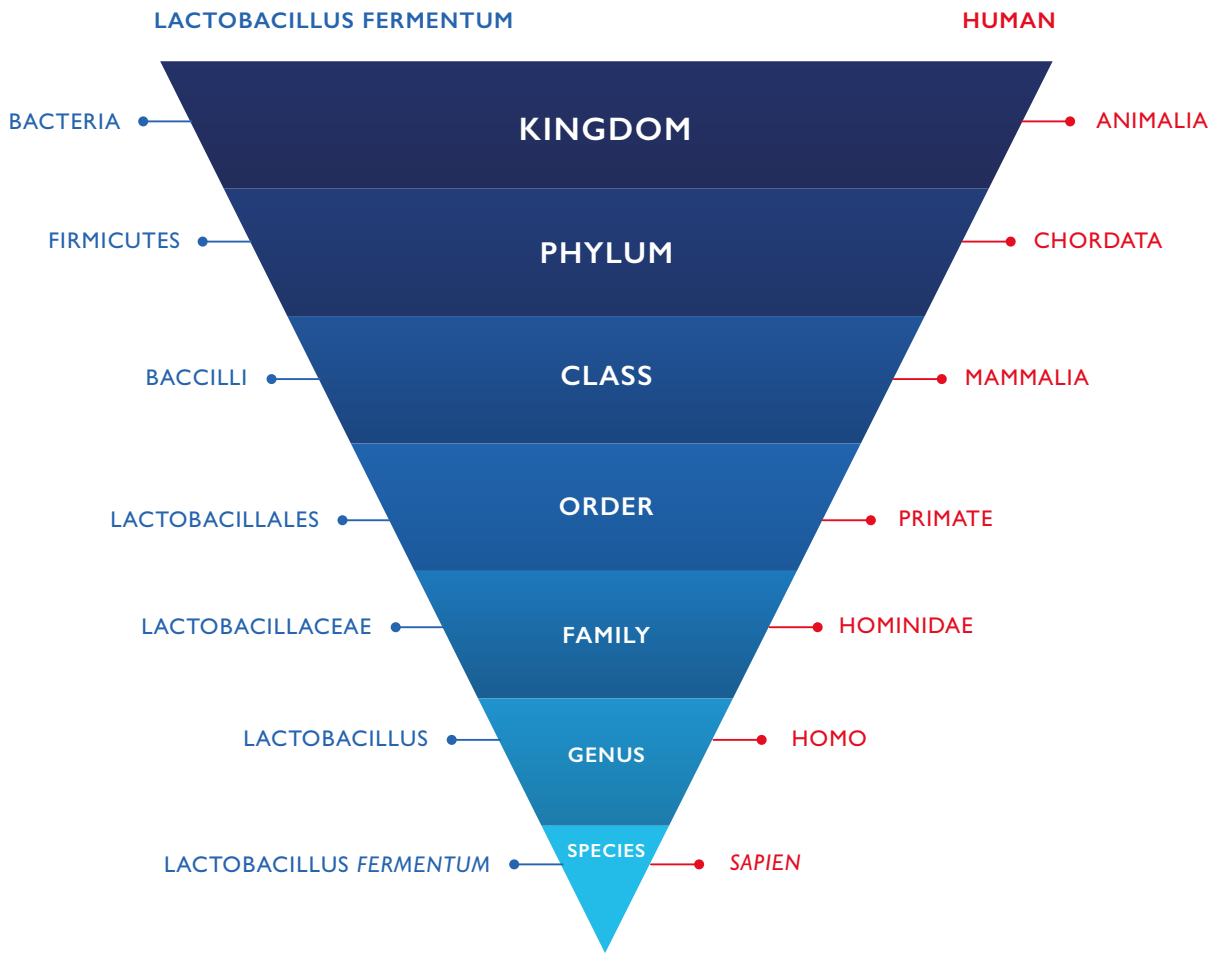
We now know that the gut microbiome has a profound impact on nutrient digestion, short-chain fatty acid (SCFA) production, vitamin synthesis, and epithelial homeostasis, as well as the development and normal maintenance of the mucosal and systemic immune systems - all of which are important in inflammatory bowel disease (IBD).

In the normal, healthy gut, around 90% of the microbiota is represented by the gram-negative Bacteroidetes and Firmicutes which break down complex sugars and proteins into SCFA and extract nutrients. In conditions of inflammation, such as in IBD, the microaerophilic Proteobacteria can thrive since there is more oxygen around. These tend to be pathogenic bacteria and can include Salmonella and Escherichia spp.

The gut microbiome remains dynamic throughout life from infanthood, where it is unstable and dominated by Firmicutes, to adolescence and beyond where the microbiome becomes more settled and increasingly dominated by Bacteroidetes.

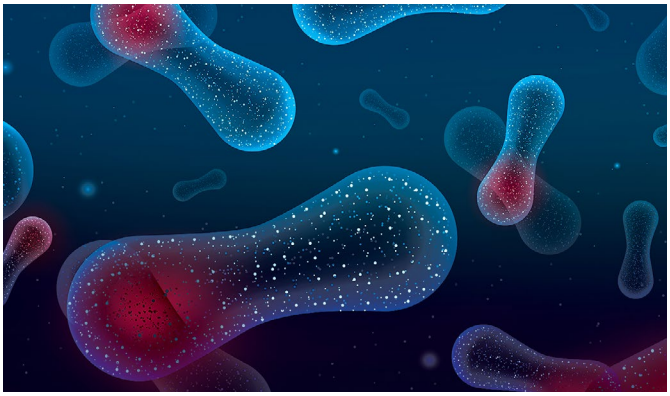
Many factors influence the gut microbiome, such as age, diet, health status, gut transit time, and medication, but you can change your bacterial diversity in 24-hours, for example by switching from an animal- to a plant-based diet. Improved methods, such as gene sequencing, help us to determine the exact identity of species and also provide information on functionality which is more important when trying to understand the role of the gut microbiota in health.

TAXONOMY EXPLAINED



CLOSTRIDIOIDES DIFFICILE (C. DIFFICILE) INFECTION

The first line treatment for C. difficile infection is administration of broad-spectrum antibiotics, but this has the unfortunate consequence of wiping out much of the gut microbiota, creating a barren environment which can be exploited by other pathogens. Gut dysbiosis occurs in a significant proportion of C. difficile patients – also commonly seen in IBD – which is characterised by reduced bacterial diversity, increases in pathogenic species, and loss of beneficial components, such as SCFA. Correcting this requires a whole microbiome approach, since individual probiotics provide an insufficiently powerful intervention.



FAECAL MICROBIOTA TRANSPLANT (FMT)

FMT are donor faecal samples used therapeutically in specific groups of patients. The sharing of gut microbiota is not new. As early as the 4th century, the historical record describes the use of 'yellow soup' in Chinese medicine to treat diarrhoeal disease. In modern times, the first case report from the 1950s described the successful use of FMT to treat colitis. Today, FMT are delivered via nasoduodenal tube or enema instead of orally, and donors are health screened. While FMT are used across Europe, the vast majority of the procedures are performed in the UK.

A meta-analysis of 37 clinical trials and case studies confirmed that 92% of patients with C. difficile infection responded favourably to FMT, both from clinical resolution and correction of dysbiosis[9]. FMT has been shown, through gene sequencing, to correlate with increased bile salt hydrolysis which may partly explain the efficacy of FMT since C. difficile uses bile salts for germination and proliferation[10].

FMT is a safe treatment as confirmed by a major review of adverse events reported by 129 RCTs[11]. Adverse effects were minor and self-limiting e.g., nausea or diarrhoea, with only a small number of serious effects, such as aspiration or infection, seen more often in patients with underlying gut barrier dysfunction.

INFLAMMATORY BOWEL DISEASE (IBD)

Crohn's disease and ulcerative colitis are common in Western countries but are being seen increasingly in the developing world. IBD is still largely incurable and a third of patients will lose their colon, while others have an increased bowel cancer risk. Hence, there is a need to understand the primary causes and develop more effective treatments.

The ultimate objective is to find the 'off switch' for IBD rather than simply treating the symptoms. FMT can be used as a treatment for these conditions, but can also help determine the makeup of a healthy gut microbiota.

Animal experiments suggest that the aetiology of IBD involves an interaction between genes and the gut microbiome. Germ-free animals do not develop colitis, even when predisposed by having IL-10 knock-out genes. Transferring faecal material from IBD patients to germ-free animals triggers colitis.

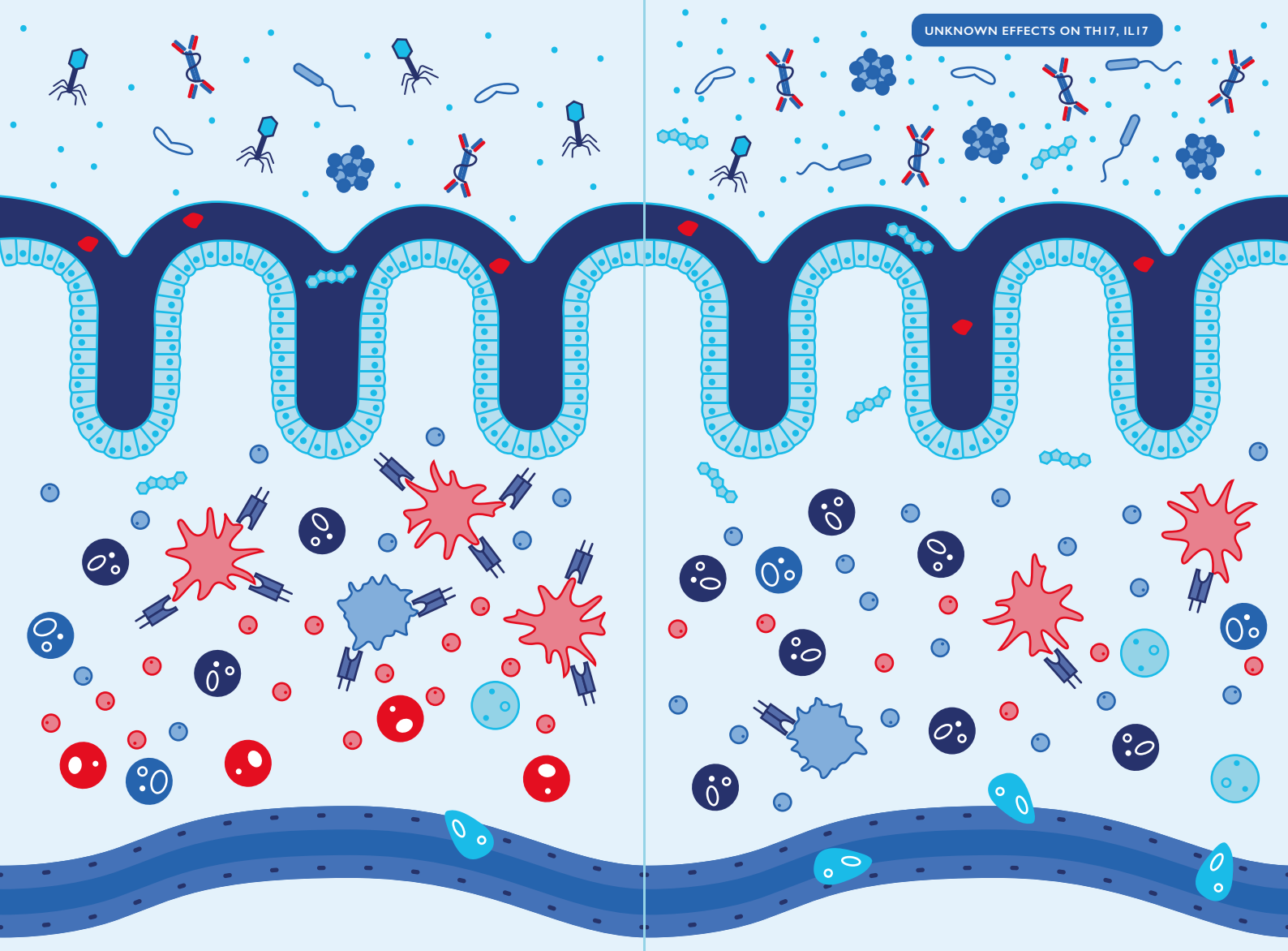
Research has improved our understanding of how the gut-microbiome relationship may promote the development of IBD. A normal gut barrier exists in symbiosis with the microbiota, and there is a clear separation of lumen bacteria and the systemic circulation. In IBD, however, the gut barrier is thin and unstable which permits bacteria to translocate and for adaptive immune cells to mount a response. As the figure below shows[12] in the microbiota in IBD is characterised by lower diversity and a greater ratio of Proteobacteria compared to Firmicutes[13,14].

IBD

INCREASE	DECREASE
TNFα, IFNγ, IL1ß	SCFA
APCS	AHR LIGANDS
MHCII EXPRESSION	SECRETORY LGA
	ANTIMICROBIAL PEPTIDES
	IL10, TGFß
	TREGS

IBD + FMT

INCREASE	DECREASE
SCFA	SCFA
AHR LIGANDS	AHR LIGANDS
SECRETORY LGA	SECRETORY LGA
ANTIMICROBIAL PEPTIDES	ANTIMICROBIAL PEPTIDES
IL10, TGFß	IL10, TGFß
TREGS	TREGS
RECRUITMENT OF GUT HOMING CD4 CELLS	



BACTERIOPHAGES (CLAUDIOVIRALES)

BACTERIA (CLOSTRIDIUM CLUSTERS)

SCFA (BUTYRATE)

SECRETORY IMMUNOGLOBIN A

ANTIMICROBIAL PEPTIDES

AHR LIGANDS

IL10, TGFß

TNFα, IFNγ, IL1ß

MHCII / HLA-DR

DENDRITIC CELLS

MACROPHAGES

NK CELLS

CD4 T CELL

GUT HOMING CD4 T CELL

TH17

TREG

Adapted from Quraishi MN et al. (2019) Clin & Experimental Immunol 119(1); 24-38

While antibiotics and probiotics have shown disappointing results in IBD, there is a clear role for FMT. From the first successful case report in the 1980s[15], evidence has accumulated from RCTs showing that 28% patients with ulcerative colitis achieved remission after FMT compared with 9% in the control groups[16].

The STOP-colitis trial, currently underway, is an open label, RCT of nasogastric versus colonic FMT delivery in patients with ulcerative colitis. The early results in the open label pilot suggest a 75% response to FMT, with only one adverse event, and a good correlation between conventional inflammatory biomarkers and immune response. The results will be published shortly.

FUTURE APPLICATIONS

The FMT concept is being advanced further by isolating the spores of promising species and delivering these to patients in tablet form. Early trials[17] have focussed on safety, but efficacy appears to be high with around 40% of patients achieving clinical remission of colitis.

The gut microbiome also appears to be implicated in irritable bowel syndrome (IBS), with differences in individual bacteria species seen in IBS patients, although these conclusions are from studies which failed to adequately control for confounders[18]. On the basis of five heterogenous RCTs there is no clear advantage to using FMT for IBS[19], but no safety concerns either so it is worth researching further.

FMT could have a role in treating gut-related side effects in patients receiving anticancer drugs, called immune checkpoint inhibitors, which give the body's T cells free reign to kill cancer cells. Early case studies suggest that FMT can successfully treat immunotherapy-related colitis.

In conclusion, the ultimate objective is to find the 'off switch' for IBD and related inflammatory bowel conditions rather than simply treating the symptoms. FMT can be used as a treatment for these conditions, but can also be a method of discovery to determine the makeup of a healthy gut microbiota.

MODULATING GUT MICROBIOME FOR CARDIOVASCULAR BENEFITS IN INDIVIDUALS RECEIVING DIALYSIS

The presentation by Prof. James Burton, University of Leicester, examined the role of the microbiome in managing cardiovascular risk in patients with chronic kidney disease (CKD). Key points were:

- **There is a window of opportunity to influence brain development from early infancy and childhood into the third decade of life;**
- **During this time, several dietary factors can have an important impact;**
- **The microbiome-gut-brain axis is the route via which the microbiome can influence brain development and function;**
- **Animal models and observational studies suggest that certain species of bacteria are associated with behaviours and clinical outcomes. This is being strengthened by intervention trials in humans.**

CKD AND CARDIOVASCULAR RISK

Defined as a progressive loss of renal function lasting more than 3 months, CKD is on the rise worldwide (prevalence of 10-12%) and now affects more people than type 2 diabetes. Indeed, the two conditions are interlinked, as poorly controlled type 2 diabetes (T2DM) and hypertension are major causes of CKD. Recently, CKD has been recognised as a systemic, rather than an organ-specific, condition with links to the gut and immune function[20].

Surprisingly, people with CKD are more likely to die, particularly of cardiovascular disease (CVD), before they reach the point in their disease when dialysis is required[21]. Hypertension, muscle wasting and reduced ability to walk, are increasingly seen as kidney function declines. One study[22] found that the 10-year mortality rate was 13 times greater when patients had T2DM plus CKD compared with age-matched controls.

CHARACTERISTICS OF DIALYSIS PATIENTS

As the prevalence of CKD rises, so does the number of patients receiving kidney replacement therapy, with the main option being hospital-based haemodialysis. The average dialysis patient nowadays is older, tends to have T2DM and will be unlikely to ever receive a kidney transplant. Therefore, reducing morbidity and improving quality of life is an important clinical goal.

The poor health outlook for patients receiving dialysis is underlined by a study showing that the annual mortality rate from CVD was higher in dialysis patients aged 25-34 years than in 70–80-year-olds from the general population[23]. In fact, medium-term survival is only lower in patients diagnosed with lung or pancreatic carcinoma[24].

One reason for this could be the bi-directional relationship between the gut microbiome and the kidneys which means that dysfunction in one organ transfers to the other, leading to poorer health. Another is the negative impact of dialysis which induces brief periods of ischaemia followed by restoration of blood flow – a condition called myocardial stunning which can increase the risk of heart failure with repeated dialysis[25].

THE KIDNEY-GUT AXIS – WHAT'S GOING ON?

The human gut is host to >100 trillion bacteria with the capability of producing >1 g of endotoxins a day. This is the name given to fragments of bacterial cell walls – made from lipopolysaccharides (LPS) – which litter the colon. Endotoxins normally don't access the systemic circulation in significant amounts thanks to the action of tight junctions in the gut barrier. However, a combination of gut dysbiosis and leaky gut – perhaps due to underlying disease – facilitates their entry. Once in the circulation, endotoxins are associated with pro-inflammatory cytokines, CVD and insulin resistance[26].

Gut dybiosis can impact on the kidneys and CKD and certain aspects of it's management, expecially dialysis, can create conditions for gut dysbiosis, leading to an inflammatory response and increased risk of CVD. Probiotics could be one way to break the cycle.

Leaky gut – as a consequence of gut dysbiosis – also allows the passage of potential pathogens into the body, leading to increased risk of infection. It's plausible that pathogens and increased inflammation could have direct toxic effects on the kidney but what about the other way around – could CKD influence the gut microbiome and gastrointestinal health?

Early research suggests that it does. CKD increases levels of uraemic toxins in the blood and gastrointestinal tract – substances which the sick kidney is unable to filter out and excrete in urine, e.g., urea, uric acid and oxalate. Aspects of CKD management including regular antiobiotic use, low fibre diets, phosphate binders and other medications, as well as complications such as metabolic acidosis, can all have a negative impact on the intergrity of the gut-blood barrier.

Dialysis could also have an effect through reduced blood flow to the gut and increased gut oedema which both enable translocation of endotoxins. This was illustrated by a study which measured levels of endotoxin in 249 patients with and without CKD[27]. The results revealed that endotoxemia was most evident in patients with the highest CVD burden, particularly those receiving haemodialysis.

POTENTIAL ROLE FOR PROBIOTICS AND EXERCISE IN CKD

Given that a healthy gut microbiota sustains and augments the gut-blood barrier, could interventions that are known to support gut health make a difference?

A meta-analysis[28] evaluated the use of probiotics and synbiotics in CKD, finding a limited number of low-quality RCTs. The analysis showed that supplementation reduced toxic metabolites associated with CVD and mortality in dialysis patients, and lowered the risk of gastrointestinal symptoms. A recent RCT[29] found no effect of regular cycling on endotoxin levels in haemodialysis patients but did see significantly lower levels of endotoxin and inflammatory markers in patients with the highest levels of overall physical activity and fitness. A new 6-month double-blind RCT is underway to test if consumption of *Lacticaseibacillus paracasei* Shirota (2x65 ml daily containing $6.5x10^9$ CFU) can modulate gut permeability and reduce endotoxin levels in haemodialysis patients.

In conclusion, gut dysbiosis can impact on the kidneys and CKD and certain aspects of its management, especially dialysis, can create conditions for gut dysbiosis, leading to an inflammatory response and increased risk of CVD. Use of probiotics could be one way to break the cycle and this is currently under investigation.

RELEVANCE OF THE GUT MICROBIOME IN CRITICAL CARE AND COVID-19

The final presentation, by Dr Ben Mullish, Imperial College London, brought clinical care right up to date with an exploration of potential interactions between the gut and Covid-19. The following areas were addressed:

- **This new field of discovery builds on previous models of the gut microbiome in infection and inflammation, including those relating to respiratory diseases;**
- **Gut dysbiosis could potentially influence the risk of, and severity of, Covid-19 infection by enabling translocation of viruses or endotoxins into the body;**
- **Covid-19 infection has long lasting negative effects on gut diversity, even weeks after recovery;**
- **Emerging work on probiotics shows a reduction in risk of, and recovery from, upper respiratory tract infections, and better recovery from Covid-19. FMT may also be a useful intervention.**

POTENTIAL GUT INTERFACE WITH COVID-19

It is already known that the gut microbiome can impact on respiratory health via the bi-directional gut-lung axis which modulates immune response and susceptibility to infection. New data on almost 4000 Covid-19 patients[30] have shown that genetic material from SARS CoV 2 can be detected not only in respiratory secretions and serum – as would be expected – but also in stool samples. In fact, there was more prolonged viral shedding from stools compared with other biofluids (22 vs. 19 days on average).

The entry point of SARS CoV 2 is via ACE 2 receptors on cells. While these are found in the lungs, they also exist in abundance in the gut suggesting a secondary viral route into the body via the gastrointestinal tract[31]. This may explain some of the reported secondary symptoms of Covid-19 which include nausea, vomiting, diarrhoea and anorexia.

Further evidence for a gut microbiome interaction comes from the experience of dealing with Covid-19 in patients. Clinicians are familiar with the lymphopenia (low white blood cells) seen at presentation, and the cytokine storm – a highly dangerous inflammatory response – seen in cases of severe disease. Both of these are linked to the immune response which is strongly influenced by the health of the gut barrier, and the gut microbiome. Underpinning this profile of risk are genetic factors but, more often, pre-existing clinical risk factors – such as type 2 diabetes, glucose dysregulation and 'inflammaging', an age-related chronic inflammatory state[32].

COULD THE MICROBIOME INFLUENCE COVID-19 SEVERITY?

An early study[33] which considered this question profiled the stool bacteria (using shotgun metagenomics) of 15 Chinese patients diagnosed with Covid-19 and compared the results with samples from healthy controls and patients with pneumonia. The results showed differences in microbiome composition of the Covid-19 patients, especially those with more severe disease, with a loss of Faecalibacterium prauznitzii and an excess of potential pathogens. In addition, lower levels of Bacteroides species were linked with a higher viral load.

Another study[34] tracked changes in the gut microbiome of 100 Covid-19 patients, finding that microbiome differences persisted even 30 days after viral clearance. When compared with controls, the stool samples of post-Covid-19 patients had significantly lower levels of 'anti-inflammatory' bacteria, such as F. prauznitzii and Bifidobacteria. There was also a close correlation between the gut microbiome, disease severity and immune response (indicated by levels of cytokines). This study shows that Covid produces long-term changes to the gut microbiota, even after patients recover.

Further evidence comes from a prospective analysis of Covid-19 patients' stool samples which found a reduction in microbiome diversity during active disease that failed to return to normal even after 6 months[35]. Worrying associations were noted between lower diversity and higher level of CRP and illness severity during the acute phase of the illness. This suggests correlations between inflammatory response and gut dysbiosis in Covid-19 patients, which could have implications for long Covid risk. One piece of the puzzle missing is the state of the gut microbiome in patients before they contracted SARS CoV 2.

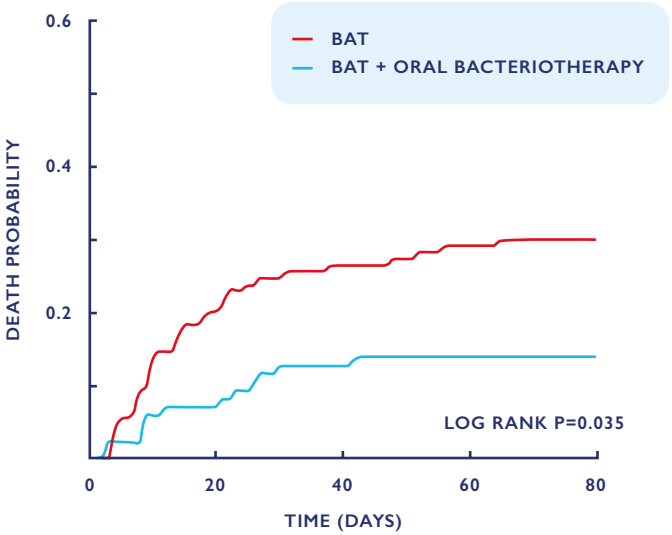
Possible mechanisms could relate to reduced gut barrier function, and this has been demonstrated in a recent study which found evidence of leaky gut in Covid-19 patients. More severe symptoms were associated with greater gut permeability and microbial translocation, increased gut metabolites in the blood, and disruptions to metabolic pathways linked to normal immune response[36]. Hence, the role of the gut in Covid-19 could relate not just to the risk of SARS CoV 2 crossing a weak gut-blood barrier, but the translocation of endotoxins and pathogens into the systemic circulation, leading to increased inflammation and a weakened immune response.

THERAPEUTIC OPTIONS INVOLVING GUT MODULATION

The big question is whether 'beneficial' gut microbial metabolites, such as SCFA, could mitigate the negative impact of Covid-19. While research is at an early stage, there are promising signals. Firstly, in a rat model[37], exposure to SCFA protected gut ACE-2 receptors against viral binding. Other animal models show that prebiotic supplementation (inulin/fructooligosaccharides) reduces pro-inflammatory cytokine expression[38].

In humans, a meta-analysis of RCTs found a positive effect of probiotics on non-Covid-19 upper respiratory tract infection (URTI) but no change in diarrhoea, mortality or length of hospital stay[39]. However, the studies were highly variable in terms of probiotic formulation and duration of treatment.

In a retrospective observational study of 200 patients with Covid-19[40], outcomes were compared in those receiving the best available treatment (BAT) or BAT plus a commercial probiotic supplement containing several Bifidobacteria and lactobacilli species. The results showed a significant reduction in risk of death in the BAT + oral bacteriotherapy group (11%) versus the BAT only group (30%) (see figure below).



Adapted from Ceccarelli et al. (2021) Front Nutr 7: 613928

Probiotics have also been investigated as a novel way to prevent URTI. A secondary analysis of a RCT which used probiotics as a weight loss tool found that the group receiving probiotics experienced a 27% reduction in URTI symptoms versus control, with effects seen within two weeks of probiotic use[41].

Other gut modulation options for Covid-19 may include FMT and, indeed, this has been investigated in a limited number of case reports which found improved clinical outcomes and reduced shedding[42]. Controlled trials are now required. The gut microbiome is also worth considering during mass Covid-19 vaccination as trials on influenza vaccines suggest that gut dysbiosis, as a consequence of antibiotic use, may reduce their effectiveness[43].

In conclusion, there is early evidence of a gut microbiome interaction with Covid-19 infection but detangling the strands of the story is hard due to the lack of direct studies. What is clear is that gut dysbiosis makes it easier for pathogens and endotoxins to access the systemic circulation, making it harder for the body to fight infection. Covid-19 itself may adversely alter the gut microbiome and have long-lasting effects on both gut barrier integrity and inflammation. Restoration of a healthy gut microbiota, for example via probiotics, could help to mitigate some of the effects of Covid-19 but this requires further investigation in controlled trials.

CONCLUSION

The overall conclusions of the Yakult study day are:

- **There are several bi-directional axis points where the gut microbiome interacts with key organs or functions of the body – namely the brain, kidneys, vascular system and immune response.**
- **Having a healthy gut microbiome, with good diversity and sufficient beneficial species to produce useful metabolites such as SCFA, is key for ensuring that these body systems/organs work effectively.**
- **There is a window of opportunity for optimal brain development, highlighting the importance of establishing an optimal gut microbiome in early life.**
- **Evidence suggests a role for gut modulators, such as prebiotics, FMT and probiotics, in disease risk reduction, immune response and quality of life.**

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