Yakult

Science for Health

YAKULT SCIENCE WEBINAR: SPORTS NUTRITION, GUT MICROBIOME & ATHLETIC HEALTH

YAKULT SCIENCE WEBINAR
24TH NOVEMBER 2021
12:00 - 1:45PM
UK TIME - 13:00

FREE WEBINAR
VIRTUAL EVENT

This report was prepared by **Lyndon Gee, Food & Health Writer,** based on the presentations given on Wednesday 24th November, 2021.

EXECUTIVE SUMMARY

INTRODUCTION

Yakult science presented a leading-edge international Science Webinar. Dr. Kate Synnott, welcomed delegates from 10 countries to the live and interactive webinar *'Sports nutrition, gut microbiome, and athletic health'*.

As Yakult communication specialist in science, Dr Synnott has an honors degree from Ulster University UK in human nutrition, and a PhD from University College Cork in Ireland.

Four experts provided some very interesting talks and insights. With presentations from Prof Paul Cotter, head of food bio-sciences and a senior principal research officer in Teagasc Food Research Centre in Ireland; Prof Vaisberg in Brazil, a medical doctor with a PhD in sports medicine, and a researcher into exercise immunology; and Dr. Claudia Osterkamp-Baerens, sports nutritionist in the Bavarian Olympic training center in Germany.

Presentations were followed by an expert discussion chaired by Prof Mike Gleeson, Emeritus Professor from Loughborough University who has 40 years research experience and a particular interest in exercise immunology.

SUMMARY

From the experts came strong evidence-based research that showed a clear correlation between the gut microbiome and health, for athletes and for non-athletes.

Prof Cotter summarized exciting developments in microbiology and outlined his extensive research into the influence of exercise, training status and diet on the gut microbiome. Prof Cotter's findings show that the athlete microbiome tends to have greater alpha diversity, likely mediated by both diet and exercise.

Prof Cotter's evidence demonstrates that in the short-term, the beneficial effects of exercise on the microbiome are subtle, but more substantial changes may be observed in the long-term.

He concludes that the gut microbiota contributes significantly to health and disease and there is potential to use the combination of diet and exercise to improve the microbiota for both athletes and the general population.

Prof Vaisberg shared insights into his recent paper, studying the daily intake of fermented milk and its effect on the immune and respiratory responses in runners training for and participating in a marathon race.

Looking in detail at the common mucosal system and the early defense mechanism against foreign organisms, Prof Vaisberg's results showed that the daily ingestion of fermented milk containing 40 billion of *Lacticaseibacillus paracasei* Shirota (LcS) for 30 days prior to a marathon was able to modulate both immunological and inflammatory responses in amateur runners after the marathon, presenting a protective anti-inflammatory effect.

Dr Osterkamp-Baerens outlined the importance of carbohydrate for athletic performance and in relation to exercise-induced gastrointestinal symptoms, amongst recreational and elite-level athletes.

She explained how gastrointestinal symptoms differ, with upper gastrointestinal symptoms more common amongst cyclists, and lower gastrointestinal issues more commonly affecting runners.

Detailing the case study of a female triathlete, Dr Osterkamp-Baerens outlined how, by adjusting the glucose:fructose ratio of the athlete's carbohydrate intake during the race and lowering the concentrations of carbohydrate in the drink, gastrointestinal symptoms were alleviated.

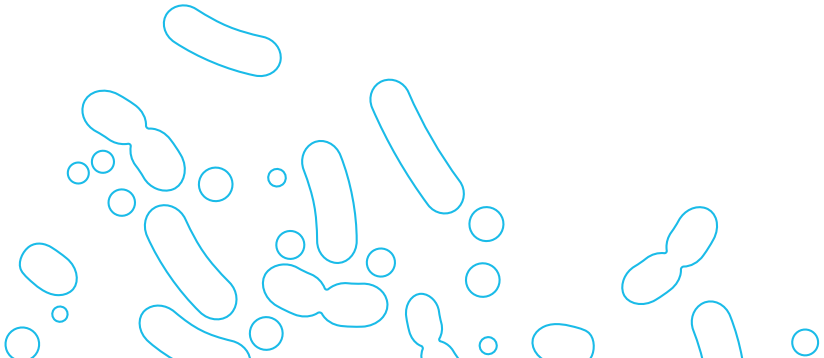
Dr Osterkamp advised that the absorptive capacity of the intestinal epithelium can be enhanced by 'training the gut'. She described the steps to implementing such protocols, including the adjustment of quantity and composition of carbohydrate intake during training sessions.

Prof Gleeson led an interactive conversation with the panelists, highlighting and expanding on the issues raised by each speaker and adding his own expert insights.

The discussion ranged from intervention impacts on the colonic microbiota, the challenges of measuring diversity and what is actually happening in the gut, to foods for optimizing the gut microbiota and the pros and cons of multi-strain probiotics.

The discussion also covered the effects of exercise and pollution, building on Prof Vaisberg's findings that pollution was inflaming the upper respiratory tract of athletes in his study and that by using *Lacticaseibacillus paracasei* Shirota he was able to reduce this inflammation.

The importance of a diverse, balanced, healthy diet was stressed by all. A diet that keeps the microbial diversity high has the potential to have a beneficial impact so it is advisable to enrich the diet with fermented foods, which themselves will have a rich source of microbes.



EXPERT PRESENTATIONS

THE POTENTIAL ROLE OF GUT MICROBIOTA IN ATHLETE HEALTH AND PERFORMANCE PRESENTED BY PROFESSOR PAUL COTTER

Prof Cotter firstly outlined how microbiology has changed in recent years. Historically, microbes were grown in the laboratory on Agar plates. This, however, yields only the tip of the iceberg because just a small percentage of microbes will grow this way. Now 'high throughput' DNA sequencing is increasingly used. This means we have the ability to look at entire microbial populations. The term metagenomics refers to the analysis of all the DNA from a microbial community. It can give an insight into what is happening in the gut and help understand how the gut is responding to diet and exercise.

NEXT GENERATION DNA SEQUENCING

The technology has developed rapidly in the last 15-20 years. The first devices allowed analyzing 1 million bits of DNA, now much bigger chunks, 130 – 400 million 'bits of the jigsaw' are decoded. Prof Cotter explained we can also now use much bigger individual bits of the jigsaw, effectively longer stretches of DNA. Further, some recent devices can be handheld and can be used in clinics, or for example at factories looking at food safety.

CRUNCHING THE DATA

As he says, this means scientists extract a huge amount of data and the challenge is how to translate it in a way that can be used by athletes and nutritionists.

The microbiome field has evolved dramatically in recent years, and we now have greater understanding of the role of the gut microbiome in health.

GUT MICROBIOME FUNCTIONS INCLUDE:

- Vitamin synthesis
- Digestion and absorption
- Immune stimulation
- Control pathogens
- Influencing the efficacy of energy harvest from ingested food
- Intestinal epithelial cell proliferation & differentiation, pH
- Signaling from the periphery to the brain

Prof Cotter investigates the microbiome by extracting DNA from fecal samples, then subjecting it to one of two different types of analysis. These are:

COMPOSITIONAL SEQUENCING

This gives an insight into particular types of microbes in the gut by focusing on one barcode gene. It was the state-of-the-art approach 4-5 years ago and is still used extensively.

Prof Cotter used the example of bacteria, explaining that using a PCR (Polymerase Chain Reaction) approach one can amplify bacterial sequences such as the 16S ribosomal DNA sequences that have conserved and variable regions and when registered, can be compared against large databases to determine the identity of the bacteria present in the sample.

The analysis gives a picture of the composition of the microbiome and their percentages, from the phylum to the genus level.

SHOTGUN SEQUENCING

This is the latest innovation, where, rather than focusing on just one gene, all the genes present in the community are sequenced in a random fashion; hence the term 'shotgun' sequencing.

This technology enables the capture of information about potential functional outcomes, for example the genes associated with virulence and antibiotic resistance (undesirable genes) and also how many genes are associated with health promotion, such as production of short-chain fatty acids, bacteriocins, or other probiotic traits.

It also gives a far more detailed picture of the composition of the microbiome because it is not just at a genus level, it also determines the species, whether it be *Lactiplantibacillus plantarum* or *Lactobacillus acidophilus*[1].

Prof Cotter explained, you can also put these genes back together into an entire genome and look at individual genomes within the metagenome. Shotgun sequencing also gives insight into the fungi, viruses, and phages (bacteriophages) present in the sample.

[1] NAME CHANGE INFORMATION: In 2020 the majority of Lactobacillus species have been renamed at the genus level; in that process *Lactobacillus casei* became *Lacticaseibacillus casei, Lactobacillus plantarum* became *Lactiplantibacillus plantarum*.

WHAT MODULATES THE BIOME?

Using both *in vitro* and *ex vivo* studies, as well as human and animal trials, Prof Cotter looks at what affects the human microbiome, not just from the gastrointestinal tract but also from the skin, lungs, throat and vagina. Alongside his team, Prof Cotter has studied the impact of antimicrobials, antibiotics, bacteriocins, probiotics, prebiotics and diet on the human microbiome, with a particular focus on fermented foods.

THE EFFECT OF EXERCISE

Working with the 2011 Irish national world cup rugby team, Prof Cotter's team analyzed the microbiome of 40 elite athletes against two different control groups; one with lower BMI (Body Mass Index; <25 kg/m^2) and one with higher BMI (>28 kg/m^2). This was to reflect the different BMI of the rugby players - bigger forwards, and leaner, faster backs.

Prof Cotter explained it was difficult to assess the activity and exercise levels of the various groups, because elite athletes have very different lifestyles. So, instead of the usual questionnaires, the researchers analyzed serum Creatine Kinase (CK) levels.

NEED TO KNOW: CREATINE KINASE LEVELS

CK is an enzyme which is found within the muscle. Elevation of CK is an indication of damage to muscle. When exercising intensely, micro-tears form in the muscle, CK is released into the blood and can be measured to give a marker of the amount of exercise an individual is taking.

DIET

The research also looked at macronutrient intake and found that the athletes had greater macronutrient and overall energy intake. Most notably, the athletes consumed a greater proportion of their energy from protein, compared to the control group.

MICROBIOME DIVERSITY

Prof Cotter explained that alpha diversity looks at the variation within an individual, while beta diversity describes the diversity within a group (e.g., athletes versus controls).

This directly compares the two environments side by side, looking at how related and unrelated are the two populations' diversity.

High microbiome diversity is generally regarded as good. Highly diverse microbial communities can cope better with different stressors, such as antibiotics, and will bounce back faster, and so are considered to be more resilient.

Prof Cotter discovered the athletes had a consistently higher alpha diversity in their microbiome than the control groups.

The study also found a correlation between higher microbiome diversity and higher protein intake, as well as higher levels of CK.

Prof Cotter believes that the benefits of exercise may come in the longer term and that it is not just exercise alone but the greater level of overall fitness one eventually achieves. More work is needed to substantiate this finding.

While it is virtually impossible to directly compare metagenomic sequences, it is possible to use data reduction techniques to visualize similarities between metagenomes. In these representations, each dot represents an entire microbial community, (an individual) with thousands of DNA sequences condensed into a single data point.

If two dots are close to each other it means their microbial community is very similar, if they are far apart, they are dissimilar.

When applied on the selected athletes, one can see that athletes are more heterogeneous and aggregate away from the control groups.

As, however, there was one athlete found in the middle of the control group, Prof Cotter looked at the diet of that individual and found this athlete was eating a lot of junk food and takeaways and not following the advice of the team's nutritionist.

MICROBIOTA DIVERSITY PATHWAYS

Prof Cotter also looked at the different genes and pathways that were encoded in the different samples. He found not only higher diversity of species, but also more diversity in the metabolic pathways, encoded in the athletes' microbiome. Working with Imperial College London, who undertook a metabolic analysis of urine and fecal samples, he found a clear distinction between the athletes and the control groups, e.g., in terms of Short-Chain Fatty Acids (SCFAs). Such a distinct difference between two healthy groups has not been seen previously. SFCAs are considered to be beneficial for health and it is known that their production in the gut is correlated to both microbial diversity and diet.

NEED TO KNOW: SHORT-CHAIN FATTY ACIDS

SCFAs are produced by specific microbes and have been shown to alter chemotaxis and phagocytosis, induce reactive oxygen species (ROS), change cell proliferation and function, have anti-inflammatory, anti-tumorigenic and antimicrobial effects, alter gut integrity and improve gut permeability and barrier function.

INVESTIGATING THE ROLE OF DIET AND EXERCISE IN GUT MICROBE-HOST CO-METABOLISM

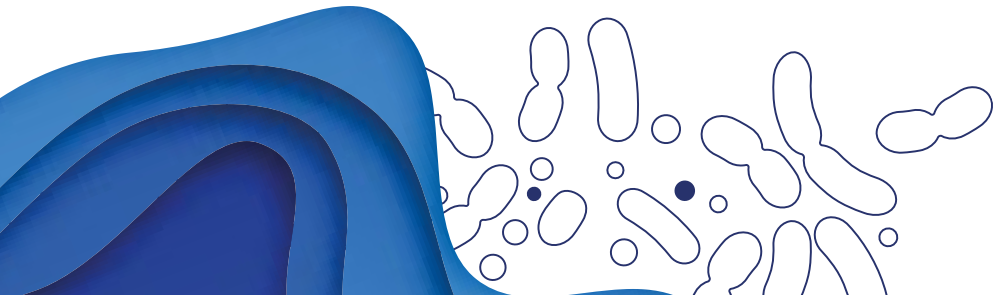
Prof Cotter outlined further research from Penny et al. 2020, to which he contributed. The research did a deeper dive into the role of diet and exercise for athletes and controls. They focused on the co-metabolism shared between the host and the gut microbiome. The study divided both groups (athletes and controls) according to a dietary assessment score, calculated from their 1H-NMR urinary profiles and illustrating adherence to healthy dietary habits according to WHO guidelines.

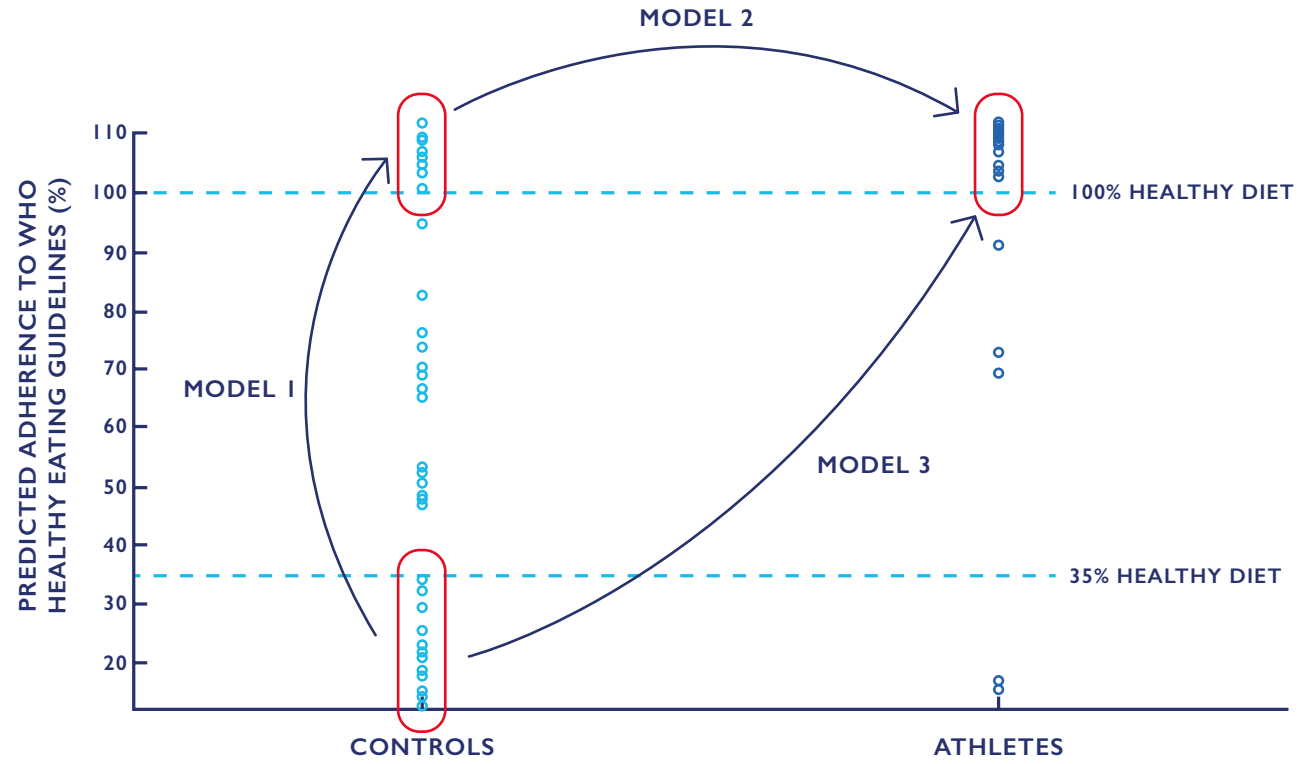
Models were then generated to compare the extremes of dietary habits (model 1), of exercise (model 2), and of the combined effect from both (model 3).

Prof Cotter says: 'when we evaluate all three models, we see some very intriguing insights.'

A first level of separation is on the basis of diet alone, obvious from minor shifts in urinary and fecal metabolites, some SCFAs and microbial diversity.

We see greater changes when looking at the exercise effect, of elite athletes versus the control group, with more pronounced changes in metabolites, including significant changes in the SCFAs acetate, propionate and butyrate, but no significant differences yet in the microbial diversity. When looking at the combined effects of diet and exercise though, unhealthy diet controls versus trained healthy diet athletes, we see significant differences in terms of metabolites, 4 out of 6 SCFAs as well as microbiome diversity.





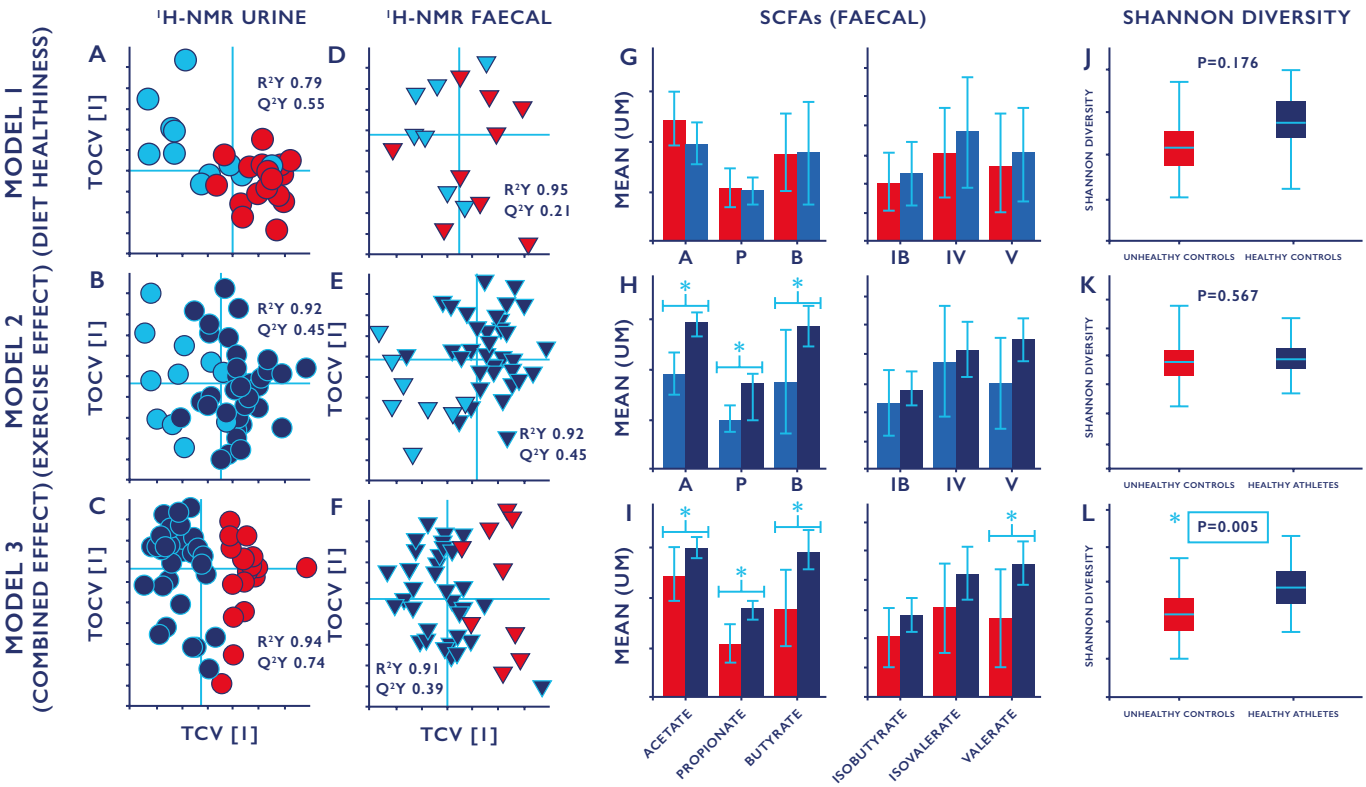


Image 1 & 2: Penney et al 2020 mSystems 5:e00677-20

CAN WE CHANGE GUT MICROBIOME IN 8 WEEKS?

Prof Cotter conducted a trial on 74 sedentary adults who were, by their own admission, 'couch potatoes'.

Split into 3 groups, one group was put through a regimen of exercise, another group exercise and whey protein intake, and the last group consumed whey protein but remained sedentary. Their microbiome was then studied for an 8-week period.

There were some subtle alterations and signs that individuals were beginning to see some changes in their microbiome composition, especially in group 2 with exercise and whey intake. However, since these were minor changes, the research team concluded that there is not a short-term fix for an "unhealthy" microbiome.

TRAINING FOR MARATHON & TRIATHLON

In a case study, two self-reported sedentary individuals undertook training over several weeks; one to compete in a marathon and the other in a triathlon.

As expected, the training improved their body composition and cardiorespiratory fitness. Their alpha diversity was also monitored, fluctuating over time with big dips around extreme training sessions, such as a 20-mile run. The marathon runner's alpha diversity was at its highest just before and immediately after running the marathon, but soon dropped dramatically after becoming ill with pharyngitis and diarrhea.

Some people experience symptoms of respiratory illness after running a marathon, because of reduced immunity. This triggers some interesting questions about the relation between the microbiota status and the immune system, and clearly more research needs to be done on a bigger scale to better understand that relation.

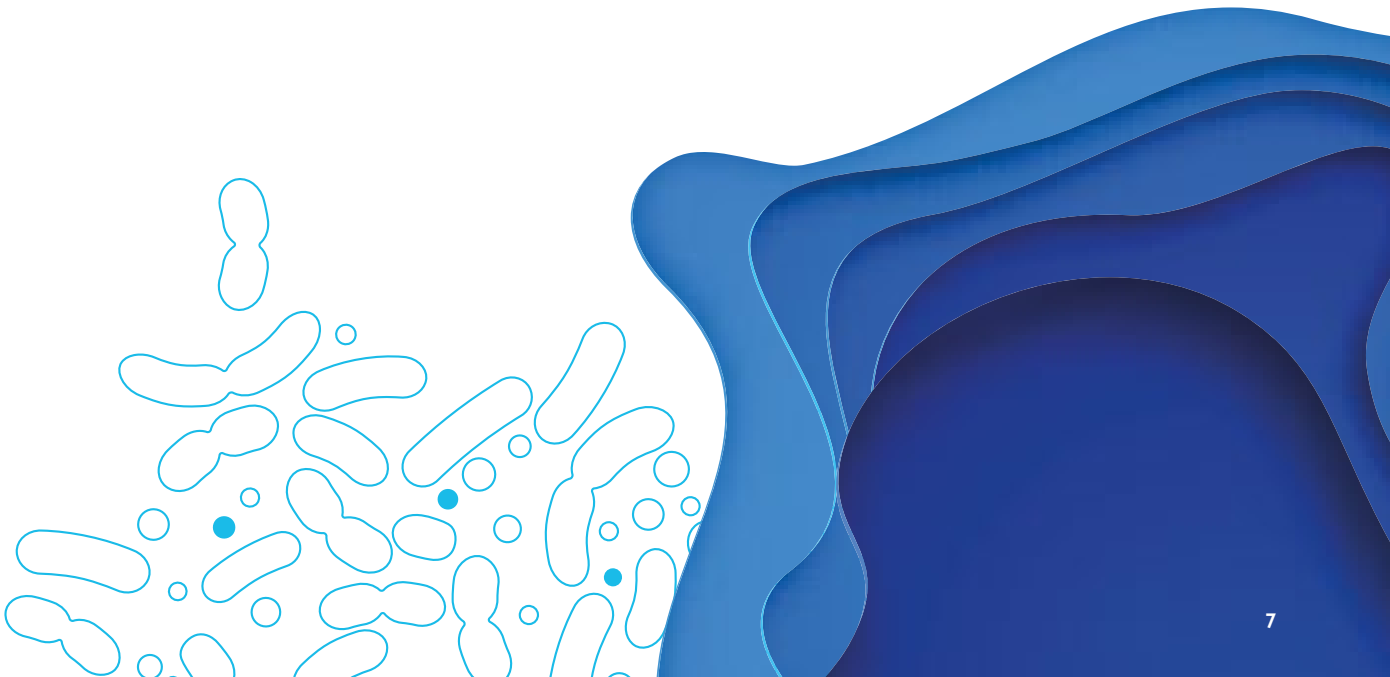
OTHER RESEARCH

Prof Cotter has been involved in a number of other studies, including with the Irish cricket team looking at the effect on the microbiome of travelling around the world, being exposed to different diets and risks of gastrointestinal infections.

Moreover, Prof Cotter and his team worked with Irish Olympians that travelled to Rio de Janeiro, to examine the difference between the microbiome of athletes competing in different types of events. Findings showed distinct differences between endurance sports and sports involving more muscle power.

IN CONCLUSION

- Gut microbiota contributes significantly to health and disease
- Diet and, now, exercise appear to be modulators of the gut microbiota; impact is most apparent when combined
- There is potential to use diet and exercise to improve the microbiota in non-athletes (and athletes)
- Future research directions include further characterization of the microbiome in different athletic populations, and examining the influence of the microbiome in athletic performance



DAILY INTAKE OF FERMENTED MILK CONTAINING *LACTICASEIBACILLUS PARACASEI* SHIROTA (LCS) MODULATES SYSTEMIC AND UPPER AIRWAYS IMMUNE/INFLAMMATORY RESPONSES IN MARATHON RUNNERS

PRESENTED BY PROFESSOR MAURO VAISBERG M.D., PH.D

Through social media Prof Vaisberg contacted marathon runners, seeking those who had suffered upper respiratory problems after a race. Securing 56 volunteers they were divided into two groups. Both groups were similar in terms of age, body composition and performance in marathons. For 30 days one group was given fermented milk with *Lacticaseibacillus paracasei* Shirota (LcS), the other group received a placebo, a non-fermented milk drink with identical taste, smell and color but no LcS.

The researchers collected samples of blood, saliva and nasal mucosa 30 days before the race and before any fermented milk was given. After 30 days with either fermented milk or a placebo. Volunteers were tested again at the end of the intake, 24 hours before running a marathon. They were further tested immediately after the race, 72 hours after, and once more 14 days later.

RESULTS

The tests looked at salivary immune-globulin A (SIgA). IgA is a secretory antibody protein that's part of the mucosal immune system. Immediately after the race the placebo group had a drop in SIgA levels. Prof Vaisberg found no such drop in the LcS group.

Looking also at salivary concentration of antimicrobial peptide defensin-α1 and lysozyme, there was a significant drop in defensin-α1 in the placebo group immediately after the race, although not anymore 72 hours after the race. No such drop was seen in the LcS group.

OTHER IMMUNE RESPONSES: MEASUREMENT OF CYTOKINES IN THE UPPER AIRWAYS

Prof Vaisberg measured cytokines in the upper airways (nasal mucosa), and found no difference between the two groups for the cytokines IL-4 and IL-12.

In the placebo group, however, an increase in some other pro-inflammatory cytokines was observed, including IL-5, IL-6 and IL-13, which are associated with chronic allergic inflammation of lungs. They saw no such change in the group taking the LcS probiotic.

In the placebo group there was also an increase in an important pro-inflammatory cytokine TNF-α (Tumor Necrosis Factor alpha), but this increase was not found in the LcS group.

Probably the most important finding though was the very significant increase of IL-10, an anti-inflammatory, regulatory cytokine, in the LcS group as compared to the placebo group where no changes were seen. Interestingly the gradual increase of the IL-10 levels match the intake period and were also going down after the intake of the probiotic had stopped, suggesting a link between the consumption of the probiotic drink and the levels of IL-10.

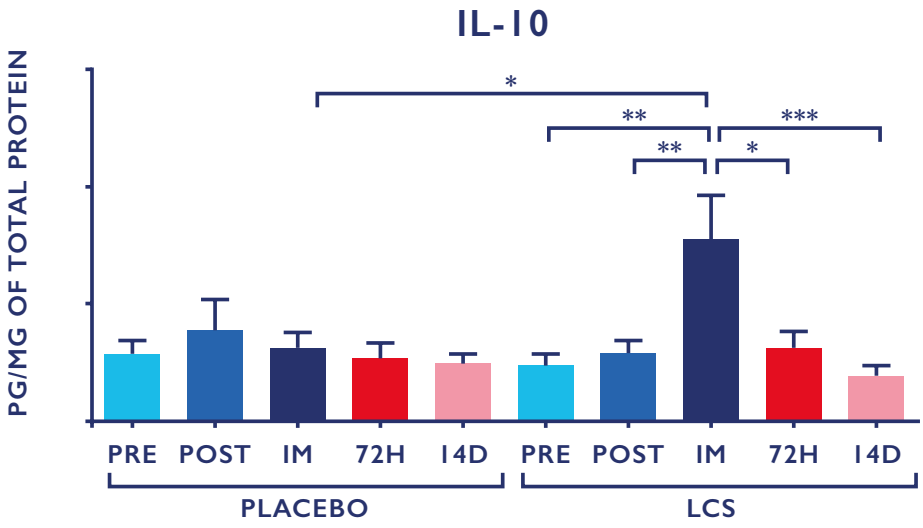


Image 3: LcS increase anti-inflammatory response on the upper airways. Concentration (pg/mg of total protein) of IL-10 in nasal mucosal lavage of the volunteers in the placebo and LcS groups at five different occasions: before (Pre) and 30 days after the ingestion of the fermented milk containing or not containing LcS (Post-ingestion); immediately (IM); 72 hours (72 h) and 14 days (14 d) after the marathon ends. Values are presented in median with the respective quartiles. * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$.

IN THE SERUM

For IL-1β, IL-4, IL-5 and IL-13 there were no changes in either group, although IL-5 levels seemed increased in the placebo group at the time of the marathon.

For IL-1ra, IL-6, IL-10 and IL-12, Prof Vaisberg measured significant increases in both groups towards the marathon, leveling out again after the marathon, but no differences were observed between the groups. For the pro-inflammatory cytokine TNF-α, the authors found an increase in the placebo group immediately after the marathon, which wasn't seen in the probiotic group; the difference between both treatment groups was statistically significant.

It was also interesting to note the differences between the results of cytokine measurements performed on serum versus mucosal lavages from the nose. The probiotic treatment was able to positively influence levels of IL-1β, IL-6 and IL-10 in the mucosal lavages, but not in the serum. Serum levels, but not nasal levels of IL-12 increased towards the marathon.

IL-10:IL-12 ratios have long been used to judge the anti-inflammatory / regulatory potential of probiotic candidate strains. When Prof Vaisberg calculated this ratio at the different sampling points (Table 1) significant differences between the probiotic and placebo groups were found for nasal mucosal lavages at the time of the marathon, thus showing that the probiotic is able to prevent inflammation on the upper airways. In an attempt to explain this observation, the neutrophil infiltration of the nasal mucosa was studied.

Results (Table 2) show that in the placebo group, neutrophil levels were significantly higher after ingestion as compared to the LcS group, an effect lasting till at least 72 hours after the intake period.

Variable/Occasion	IL-10/IL-12p70 ratio				
Group/Sample	**Pre**	**Post**	**IM**	**72 h**	**14 d**
Placebo/Serum	1.05 ± 0.10	1.12 ± 0.16	1.63 ± 0.43	1.28 ± 0.19	1.16 ± 0.11
LcS/Serum	1.09 ± 0.11	1.07 ± 0.13	1.40 ± 0.15	1.30 ± 0.13	1.11 ± 0.09
Placebo/Nasal mucosa lavage	1.20 ± 0.47	0.83 ± 0.10	1.12 ± 0.13	0.84 ± 0.11	1.00 ± 0.11
LcS/Nasal mucosa lavage	0.81 ± 0.10	0.94 ± 0.13	5.84 ± 2.74*,#	0.95 ± 0.12	0.76 ± 0.10
* Differences between placebo and LcS group for the same occasion ($p < 0.001$); # differences between IM (immediately post-marathon) and the other occasions in the LcS group ($p < 0.001$)					

Table 1: IL10/IL12 ratio differences between the LcS and placebo groups at different times around the marathon.]

Variable	Volunteers (n = 42)					P Value
	Placebo (n = 22)					
	Pre	**Post**	**IM**	**72 h**	**14 d**	
Neutrophil (%)	50 ± 3	43 ± 6 *	38 ± 3 *,#	53 ± 4[8]	53 ± 3	<0.05
	LcS (n = 20)					
	45 ± 4[ᵒ]	21 ± 3	28 ± 2	29 ± 3	48 ± 6[ᵒ]	<0.05
Differences between placebo and LcS group for the same occasion; # differences between IM and Pre, 72 h and 14 d in placebo group; ᵒ differences between Pre or 14 d and Post, and IM and 72 h in LcS group.						

Table 2: Neutrophil levels in the LcS and placebo group at different times around the marathon

In order to better understand how an orally taken probiotic could influence the immune system of the upper respiratory tract, Prof Vaisberg explained the complex links between the different mucosal immune systems in our body and the difference between its inductive- and effector arms.

NEED TO KNOW: THE MUCOSAL IMMUNE SYSTEM

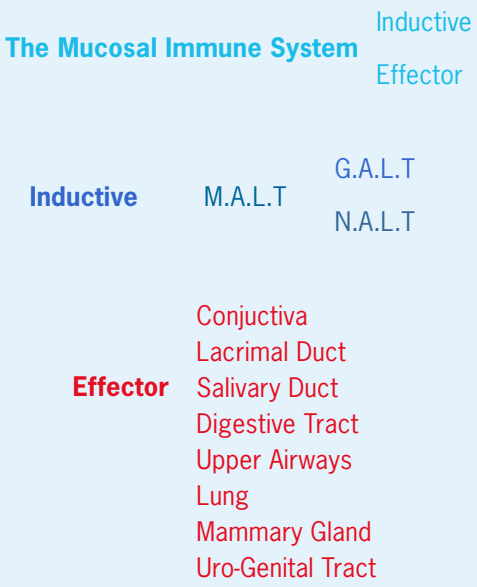
Every day we have contact with a great number of foreign antigens that we inhale or ingest when breathing or eating, respectively. So, the inductive arm of the mucosal immune system has to differentiate between the pathogenic antigens and the non-pathogenic antigens. Respectively, the system has to mount a pro-inflammatory response to pathogenic agents, or a response of tolerance (anti-inflammation) to non-pathogenic antigens.

Most responses are tolerogenic, if not, we would be inflamed all the time. The inductive arm of the mucosal immune system is represented by the so-called mucosal associated lymphoid tissue (MALT). For a long time the most important location of the inductive arm was considered the gut associated lymphoid tissue (GALT), but in recent years the nasopharynx associated lymphoid tissue (NALT) has gained more importance.

The GALT is in contact with the NALT through a wide range of effector molecules and regulatory mechanisms which could explain why an orally consumed probiotic may have an immune impact in the lungs.

IMAGE 4

COMMON MUCOSAL IMMUNE SYSTEM



NEED TO KNOW: TOLL-LIKE RECEPTORS (TLRS)

Prof Vaisberg explained the important role of Toll-like receptors (TLRs) in the development of tolerance. There are 11 TLRs in humans, transmembrane receptors, co-responsible for early defense mechanisms against foreign organisms. These receptors can recognize pathogenic species (antigens) but will also recognize commensal or probiotic bacteria and, depending on the TLR triggered, will initiate a proper innate and adaptive immune response.

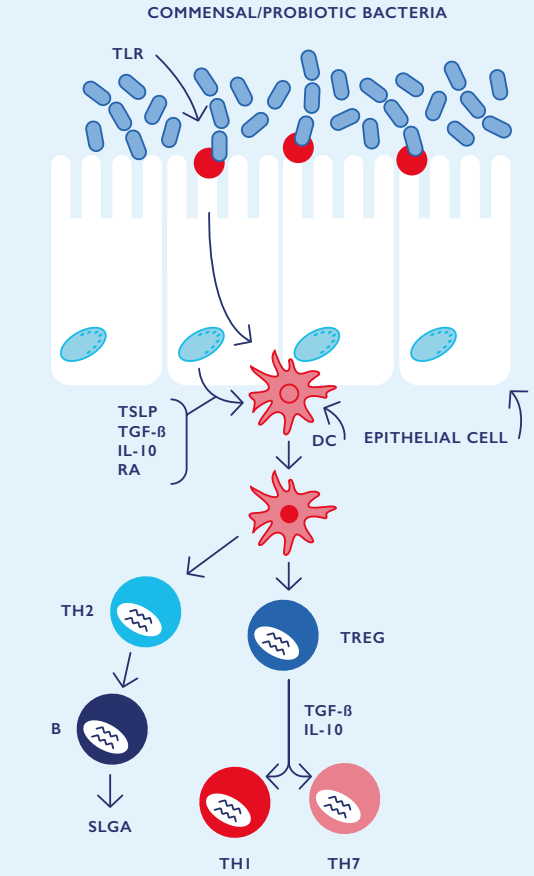
IN CONCLUSION

Prof Vaisberg's results showed that daily ingestion of a fermented milk containing 40 billion of *Lacticaseibacillus paracasei* Shirota bacteria for 30 days prior to a marathon race for amateur runners, was able to positively modulate both immunological and inflammatory responses in the blood and the upper airways mucosa. Higher pro-inflammatory cytokine levels in serum and nasal mucosa, as well as lower salivary levels of IgA and antimicrobial peptides, found immediately post-marathon in the placebo group, were significantly suppressed in the LcS group.

Taken together, Prof Vaisberg's study showed that the daily ingestion of fermented milk containing 40 billion LcS during 30 days before a marathon competition was able to:

- Maintain the salivary levels of both SIgA and antimicrobial peptides.
- Increase the nasal IL-10 levels, a classical anti-inflammatory cytokine, which led to the higher nasal IL-10/IL-12p70 ratio in LcS group immediately post-marathon.
- Reduce the nasal levels of proinflammatory cytokines, such as IL-1, IL-5, IL-6, IL-13, and TNF.
- Decrease the nasal mucosal neutrophil infiltration, demonstrating an anti-inflammatory effect induced by LcS in the upper airways

IMAGE 5



Modified from Gómez-Llorente, C., Munoz, S., & Gil, A. (2010). Proceedings of the Nutrition Society, 69(3), 381-389.

GUT ISSUES AND ENDURANCE SPORTS
PRESENTED BY DOCTOR CLAUDIA OSTERKAMP-BAERENS

Dr Osterkamp-Baerens began by stating that gut issues are very common in endurance sports. Quoting US Olympian and former marathon record holder Bill Rodgers, "More marathons are won or lost in the porta-toilets than at the dinner table."

She went on to say that competitive, recreational athletes are just as affected as elite athletes, with 20-30% of marathon runners reporting to have suffered severe gastrointestinal symptoms.

RESULTS

The tests looked at salivary immune-globulin A (SIgA). IgA is a secretory antibody protein that's part of the mucosal immune system. Immediately after the race the placebo group had a drop in SIgA levels. Prof Vaisberg found no such drop in the LcS group.

Looking also at salivary concentration of antimicrobial peptide defensin-α1 and lysozyme, there was a significant drop in defensin-α1 in the placebo group immediately after the race, although not anymore 72 hours after the race. No such drop was seen in the LcS group.

CHANGES TO GUT FUNCTION DUE TO EXERCISE

Due to the aerodynamic position cyclists adopt, creating a strong kink in the bowel area, cyclists are more likely to suffer from upper gastrointestinal symptoms than runners, who are more likely to suffer lower gastrointestinal symptoms. It is thought that the repetitive bouncing of the bowel and intestines whilst running may be a contributing factor. Changes to blood flow and sympathetic drive may also contribute to carbohydrate malabsorption and gastrointestinal symptoms. Studies have shown that intensive exercise can lower the tension of the lower esophageal sphincter and contraction of the esophagus itself is reduced. This can result in acid reflux and heartburn.

Dr Osterkamp-Baerens explained that reduced gastric emptying is also seen, meaning that food consumed just before or during exercise will stay in the stomach longer. This can trigger stomach cramps, pain and vomiting. Exercise may also lead to reduced small bowel motility (accumulation of residues causing cramps and diarrhea) and an increase of large bowel motility (urgency).

Most of these changes in gut function are only seen with high intensity exercise. Ordinary physical activities like walking, hiking and recreational running are unlikely to affect gastrointestinal function.

Lower gastrointestinal symptoms:

- Bloating
- Abdominal cramps
- Diarrhea
- Flatulence
- Stitch
- Urge to defecate

Upper gastrointestinal symptoms:

- Reflux/Heartburn
- Belching/Burping
- Stomach pain/cramps
- Nausea
- Vomiting

EXERCISE AND CARBOHYDRATE

There is strong evidence to show that carbohydrate intake during endurance exercise improves performance. Athletes will benefit from a higher carbohydrate intake during exercise, particularly longer endurance exercise (>2 hours). Therefore, it is very unfortunate that the gut functionality during exercises of higher intensity is a kind of reduced.

CASE STUDY

A 29-year-old, 157 cm, 48 kg female middle-distance triathlete was suffering from lower gastrointestinal symptoms during races, but not during training sessions and wanted to know why. She was consuming a self-made power drink consisting of an isotonic drink powder, 400ml orange juice and 3 hydrogels topped up with water to make 750ml, equivalent to 23g carbohydrate per 100ml (23%.) It is accepted there are higher risks of gastrointestinal distress related to drinks containing more than 12% carbohydrate, as is consuming a total carbohydrate amount of more than 60 g per hour with a high glucose share (she had a glucose:fructose ratio of 4.4 : 1).

Having analyzed the composition and adjusting the glucose/fructose ratio of her drink, the carbohydrate concentration was reduced from 23% to 16% and glucose : fructose ratio reduced to 1.6 : 1.

GLUCOSE/FRUCTOSE RATIO

Exogenous carbohydrate malabsorption is not only a major contributing factor to gastrointestinal distress but can also be a limiting factor to performance. Therefore, it is important that athletes implement mid-race nutritional strategies to maximize carbohydrate absorption and meet their energy requirements.

Glucose and fructose are absorbed by separate transporters in the small intestinal lumen; glucose by the sodium dependent glucose transporter-1 (SGLT-1) and fructose by sodium independent transporter glucose-transporter 5 (GLUT-5). The SGLT-1 transporter has an absorptive capacity of ~60g/h.

Co-ingestion of glucose and fructose, especially when requirements are approaching or exceed 60g/h, can maximize absorption of exogenous carbohydrate. Research has shown that the optimum ratio of glucose:fructose is 2 : 1 (or even less). However, if gastrointestinal distress is not caused by limited absorptive capacity, this strategy may not help to relieve symptoms.

TRAINING THE GUT

For events lasting >2 h, athletes will require exogenous carbohydrate intake to optimize performance. Many athletes realize this, but make the mistake of only consuming the large amount of carbohydrates during the event itself and not during training. Dr Osterkamp-Baerens also ascertained that the triathlete was not always consuming all her power drink during training sessions, but was drinking it all during races, too.

The increase in sympathetic drive and reduction in splanchnic perfusion can limit the absorptive capacity of the gut during exercise, compared to at rest. This may result in carbohydrate malabsorption and consequently gastrointestinal symptoms including pain, cramping and diarrhea.

The gut needs to be trained to absorb higher amounts of carbohydrate. To reach the point where athletes can absorb up to 90g carbohydrate per hour takes time and needs to be done gradually over weeks of training, so the gut becomes accustomed to absorbing such large amounts.

Dr Osterkamp-Baerens advises to have in mind, that carbohydrate consumption habits during training are often less than what athletes tell you, and therefore likely less than what athletes drink during a race!

Image 6: Osterkamp-Baerens, C. Neue Dimensionen in der Rennverpflegung. 2020 OSP Report 04 20
Modified from glut4science.com/publicaciones/entrenamiento-nutricional/training-the-gut-phases-from-0-to-120-g-h-carbohydrate/93

CASE STUDY OUTCOME

By adjusting the athlete's carbohydrate intake and the glucose : fructose ratio, and training of the gut, Dr Osterkamp-Baerens was able to help her overcome gastrointestinal issues.

IN CONCLUSION

- When dealing with a patient's gut issues during exercise, detailed anamnesis is crucial.
- Take a close look at any products they are using and do a detailed calculation of the carbohydrate intake per hour.
- Examine the combined grams of carbohydrate and glucose:fructose ratio of drinks and foods consumed during training and racing and optimize the composition.
- Aim for a glucose:fructose ratio of 2:1 (or less) for a carbohydrate intake per hour of >60 g per hour.
- Have in mind, that there are other reasons too, like gut illnesses or food allergies, which have to be excluded, if gut issues are persisting.

INTERACTIVE EXPERT DISCUSSION
CHAIRED BY PROFESSOR MIKE GLEESON

Q&A WITH PROF GLEESON AND PROF COTTER

Q: How do we know that measuring the microbial content and diversity in samples of feces in humans gives us a good representation of what's actually present and happening in the large intestine and the colon?

A: This is a challenge because what is collected in the feces isn't representative of what's happening right across the gut. We know it's representative of what happens in the large colon because of the collection of biopsies from surgeons that allows us to collect samples and compare and contrast.

But whilst it is quite similar to that of the large colon, it is quite dissimilar to that in the small intestine. We know this from biopsy samples as well, samples collected from ileostomy patients.

Fecal samples enable us to see how a particular intervention impacts on the colonic microbiota or the fecal microbiota, but there may be other changes that are happening elsewhere that we are overlooking. There is a big emphasis on finding a solution to this. As well as collecting biopsies and samples from the ileostomy bags, alternatives include animal studies, typically in pigs, as they are more reflective of the human anatomy.

A few research organisations are developing new smart boluses, or smart capsules that also healthy people can swallow. These will collect fecal / intestinal material as they travel through the gut. This will make research even better in the future.

Q: We know that endurance athletes and games players, like rugby players, generally have a higher energy, carbohydrate, protein, and usually micronutrient intake than the non-athletes. On a more practical note for athletes, is there any general advice you could give for them to be able to make their gut microbiota the best it can be?

Is it just about ensuring a diverse, balanced, and healthy diet or can we be a bit more specific, like recommending more high fibre, prebiotic foods or fermented foods or possibly even probiotic supplements?

A: Yes, a diverse, balanced, healthy diet as you suggest but some diets are better suited to particular types of sport.

With respect to the gut microbiome, I think anything that keeps the microbial diversity high, has the potential to have a beneficial impact.

So, include fermented foods, which themselves will have a rich source of microbes. Sometimes those microbes can themselves impact on the host, or they may make changes or produce metabolites that will impact on the host microbiome.

Probiotic supplements, especially natural strains that have been subjected to intensive investigation, can bring beneficial effects. I would encourage people to look at the evidence relating to particular probiotics. For example, the study presented by Prof Vaisberg, was fantastic and related specifically to the *Lacticaseibacillus paracasei* Shirota strain.

Consumers need to look to see what evidence is underpinning a particular probiotic. And similarly for a prebiotic, which are nutrients that encourage the growth of specific microbes in the gut, or even post-biotics, which include metabolites or dead microorganisms, can also all bring about beneficial effects. These are good in any diet, including an athlete's diet, but the specific requirements for each individual athlete type will vary depending on their sporting discipline.

Q: Health food shops sell multi-strain version of probiotics that claim to contain between three and ten different strains of probiotics. Is there any evidence that these things are actually more effective than a single strain that has some evidence backing it up?

A: Intuitively you would think yes. But it is a case of 'buyer beware' in that there are lots of cocktails of so-called probiotics out there for which there haven't been any human studies carried out.

Only if those strains are put together in a scientifically logical manner and there is science underpinning it, then that might be the case.

The definition of a probiotic requires that there be clinical evidence of a health benefit. So it's really down to the source of the probiotic and what research has been done. And whether there's evidence that it brings about a benefit or change in health or not.

Similarly with fermented foods, for example milk kefir can be beneficial but we know from our studies that maybe 20% of kefirs are quite good at producing cholesterol. Some kefirs may not contain the right microorganisms; so, unless you've done a bit of digging into the background, you may not be getting the specific benefits that you need.

Q&A WITH PROF GLEESON AND PROF VAISBERG

Q: Is the main conclusion from your study that taking the *Lacticaseibacillus paracasei* Shirota strain as a probiotic is having its effects by inducing an overall anti-inflammatory effect and dampening the pro-inflammatory effect?

A Large cities are very polluted, and we have been studying the effects of exercise and pollution. We found pollution was inflaming the upper respiratory tract of our athletes. By using *Lacticaseibacillus paracasei* Shirota we were able to reduce this inflammation.

Q: Your results show that there is some small, although very statistically significant differences in the IgA and the anti-microbial peptide response between the two groups running the marathon. Your main finding, however, is that you have a pro-inflammatory response in the placebo group with pro-inflammatory cytokines produced in the nasal mucosa, whereas you're not seeing that in the probiotic group. In fact, you see an increase in the anti-inflammatory cytokine IL-10.

My interpretation would be that probiotic intake might not necessarily affect infection incidence, but it may reduce symptoms and severity of infection should they occur, and might also help against airway inflammation caused by running in the cold or in a polluted air. Is that a fair interpretation?

A: Yes, the effect of the probiotic *Lacticaseibacillus paracasei* Shirota in the athletes seems to create an equilibrium, giving a balance in the relationship between pro and anti-inflammatory cytokines.

Q&A WITH PROF GLEESON AND DOCTOR OSTERKAMP-BAERENS

Q: Most athletes and game players are advised to consume their meal about three hours before the start of an event so it can be digested. We know it is important to have enough carbohydrate to restore the liver glycogen, which would have been depleted overnight. So what breakfast should an athlete have before they participate in an event assuming the event is at midday. Are there any particular recommendations you could give on the composition of the meal or to avoid certain things like fibre and fat, which might slow down digestion?

A: It's one of the main questions I get asked in consultations. Indeed it is tricky to get enough carbohydrates before intensive exercise such as competitions, especially if your race starts early in the morning.

It is very important that whatever you eat is easily digestible; porridge is ideal. It provides far more carbohydrates than toast or bread, and it contains a lot of water so it's easy to chew. It's also warming and soothing for the stomach.

I like yoghurt and fermented foods because of the live microbes, but be very careful just before an event or race because they can be a little acidic. And be careful with fruit too. A banana is okay, or some grapes, but be careful to avoid having too much fresh fruit, because many athletes feel that it does not offer that good gut feeling afterwards.

Q: Would the same apply to fruit juices, like 100% fruit juices, which are about 10% carbohydrate?

A: Fruit juices are fine, and most athletes digest them well. Some level of fructose in the breakfast is fine too, as it helps the absorption of the glucose.

Actually, fructose helps to boost glycogen levels in the liver in a much better way than glucose will. So, it's a good idea to consume some carbohydrates with fruit juice.

Q: Many endurance athletes take dietary ergogenic aids such as caffeine supplements, beetroot juice (or other nitrate containing compounds) a few hours before they participate in competitive events. Have you come across people having issues with those as a cause of gut complaints?

A: Yes, many athletes have got complaints with caffeine and red-beet shots, for example. As with all supplements athletes should be very cautious and test them in training. Especially athletes who are struggling with gut complaints during exercise and during races. They will benefit more from getting their carbohydrate intake right than from taking nitrate or caffeine supplements.

Q: Food intolerance is often discussed amongst athletes and some use IgG tests to determine which foods or range of foods they might be intolerant to. Would you recommend the use of such tests?

A: Food intolerance is a big issue for athletes struggling with gut complaints, but IgG tests are a waste of money. They show what foods you have eaten but do not show any evidence of intolerance or allergy. Athletes can also have a clinical malabsorption of fructose, or lactose intolerance, and we do have reliable tests for those issues.

Q: In relation to gut training for a runner: If we recommend to increase carbohydrate ingestion during training, could that potentially also increase intestinal permeability and actually provoke a problem?

A: As far I know, there are no indications that the carbohydrate intake during exercise does something bad to the intestinal permeability. It's more the redistribution of the blood. That is a big problem. Especially in these longer duration exercises, most of the blood flow goes to the muscle and the skin, and the gut doesn't get that much blood. That may cause the changes in permeability.

Heat seems to be another trigger. Perhaps because body temperature gets higher and heat also increases the risk of dehydration. Dehydration lowers the blood volume and is an additional factor blunting splanchnic perfusion.

The bouncing effect while running puts physical strain on the gut barrier which could be another point for disturbed permeability.

In contrast, I never found that training the gut with carbohydrates does any harm to the gut barrier.

THE EXPERTS

WELCOME AND INTRODUCTION: DOCTOR KATE SYNNOTT

Dr Synnott is the Communications Specialist Science at Yakult Europe. Previously she worked for Danone businesses including dairy and specialized nutrition, and Philips Healthcare in various healthcare and communication positions. Dr Synnott has an honors degree from Ulster University UK in Human Nutrition with diploma in Industrial studies and a PhD in Food Business, from University College Cork, Ireland in which she looked particularly at parental attitudes towards infant feeding practices across Europe.

PROFESSOR PAUL COTTER

Prof Cotter is the Head of Food Biosciences and a Senior Principal Research Officer, Teagasc Food Research Centre, Ireland. He is also a principal investigator in many Irish research centers including the APC Microbiome in Ireland, Vistamilk and Food for Health Ireland. A molecular microbiologist with a particular focus on the microbiology of foods, the food chain as well as probiotics and postbiotics. Author of >350 peer-reviewed publications and included in the Clarivate list of highly cited researchers for the past four years

PROFESSOR MAURO VAISBERG

Prof Mauro Vaisberg is a medical doctor with a PhD and is an expert in Sports Medicine. Although he is retired from the Federal University of Sao Paulo, he is still doing research in exercise immunology. His field of interest is currently the immune response to exercise, in particular the immune response of the athlete's airway mucosa and the exercise performed in a polluted environment.

DOCTOR CLAUDIA OSTERKAMP-BAERENS

Dr Claudia Osterkamp-Baerens is a sports nutritionist in the Bavarian Olympic Training Center in Germany. Dr. Osterkamp-Baerens qualified from Munich University with a degree in Nutrition and Food Science. Her special fields include the care of elite athletes at the Olympic Training Center of Bavaria as well as amateur athletes in her office in Munich.

DISCUSSION CHAIRMAN: PROFESSOR MIKE GLEESON

Prof Mike Gleeson is an Emeritus Professor, Loughborough University, UK. Prof Gleeson is retired since 2016 after 40 years of research and teaching mostly related to the diet, metabolism, health and performance of athletes. He has a particular interest in exercise immunology. He is still an active science writer and has recently published several books on sport nutrition and healthy lifestyle behaviors.

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