Gut microbe composition and metabolic syndrome

The interactions between gut microbial communities, obesity, and human health are complex, and researchers have only begun to thoroughly describe and disentangle them, experts tell The Lancet Diabetes & Endocrinology. The evidence base for therapeutic strategies based on manipulation of the microbiome is still largely descriptive and preclinical, they caution. But a new clinical study offers reason for cautious optimism that manipulating the microbiome’s composition in bifidobacteria’s favour just might help reduce physiological risk factors for metabolic syndrome in overweight adults.

The role of microbial fermentation of polysaccharides in facilitating the gut’s energy harvest is widely appreciated, as is the fact that gut mucosa represents the primary site for microbial interactions with the human immune system, which can trigger local and systemic inflammation, and possibly islet destruction. Mounting preclinical evidence also implicates the microbiome in the release of hormones in the gut, insulin resistance, lipid metabolism, and adiposity—and even satiety and mood.

Some beneficial gut bacteria do seem to be protective. Bifidobacteria, for example, seem to provide a barrier to mucosal absorption and circulation of antigens from other bacteria—antigens believed to underlie obesity-associated metabolic endotoxaemia. “The gut microbiota population is altered towards a less beneficial composition in overweight adults and this change can be accompanied by inflammation”, notes lead author Jelena Vulevic (University of Reading, Reading, UK).

“Bifidobacteria are an exclusively beneficial group of gut bacteria; all bifidobacterial species possess beneficial properties”, Vulevic notes. “However, for some species, these beneficial effects have been better characterised than for the others. For example, Bifidobacterium bifidum is known to be one of the main species present in healthy breast-fed infants and is absent in infants suffering from allergies.”

“The study is significant since it is one of the first studies of human prebiotic supplementation that has examined the effect of such a potential therapeutic on the gastrointestinal microbiome, which is increasingly being recognised as a key component in defining metabolic and immune status in humans”, says Susan Lynch, Director of the Colitis and Crohn’s Disease Microbiome Research Core at University of California San Francisco, San Francisco, CA, USA.

In Vulevic’s double-blind study of 45 overweight adults with three or more risk factors for metabolic syndrome, participants were randomly assigned to receive either maltodextrin placebo or a mixture of trans-galactooligosaccharides (B-GOS, a prebiotic designed and developed using enzymes from gut-dwelling B bifidum), during a 12-week intervention. B-GOS supplementation was associated at 12 weeks (but not at 6 weeks) with increased numbers of bifidobacteria in participants’ faecal samples, increased secretory IgA, and decreased faecal calprotectin, and plasma levels of C-reactive protein, insulin, triglyceride, and total cholesterol (TC), and TC-to-HDL cholesterol ratios.

“Administration of B-GOS to overweight adults resulted in positive effects on the composition of the gut microbiota, the immune response, and insulin, TC, and triglyceride concentrations”, Vulevic’s team reports. “B-GOS may be a useful candidate for the enhancement of gastrointestinal health, immune function, and the reduction of metabolic syndrome risk factors.”

“This is an important study in a human population, demonstrating the utility of non-digestible prebiotics as a means to modulate gastrointestinal microbiome composition and significantly improve clinical outcomes in obese subjects, even over a relatively short-term intervention period”, says Lynch, who was not involved in the study. “The study suggests that supplementation with a mixture of trans-galactooligosaccharides, perhaps in combination with other lifestyle changes, may represent an attractive and relatively inexpensive therapeutic strategy for management of obesity-associated metabolic syndrome.” The study also bolsters the case that bifidobacteria has “a pivotal role in clinical improvements”, Lynch notes.

Vulevic was surprised that the effects of B-GOS supplementation were not evident before 6 weeks, and suspects the stability of participants’ microbiota is “related to food habits, large calorie intake, and overeating among the volunteers”. “As a
Bifidobacteria colonise the gut

consequence, I think any dietary intervention intended to alter gut microbiota will be in part lost due to these dietary habits and the bioavailability of the substrates”, Vulevic cautions, adding that such interventions might fare better if “introduced at earlier stages of metabolic syndrome”.

However, studies of other dietary interventions, such as supplementation with lactobacillus, have yielded mixed results in human and animal studies. In a newly-reported pilot study of 30 human patients with metabolic syndrome, Lactobacillus casei Shirota did not affect insulin sensitivity, β-cell function, or biomarkers of inflammation and gut endothelial dysfunction over a 12-week intervention.

Another suspected risk factor for metabolic syndrome is chronic stress—and this, too, may interact importantly with the microbiome. “Evidence is emerging that cortisol levels are affected by the microbiota”, Vulevic notes. Mark Lyte (Texas Tech University Health Sciences Center, Abilene, TX, USA) proposes that gut bacteria secrete neuroendocrine hormones to communicate with the enteric nervous system and CNS, and that an intersection exists between neuroendocrinology and microbiology, which he has termed microbrial endocrinology. “The bacteria in the intestinal tract are communicating with our brains”, says Lyte. “That’s a real game changer.”

Anna Tagliabue from the Human Nutrition and Eating Disorders Research Centre (University of Pavia, Pavia, Italy) cautions that although the study is promising, it is “premature to speak of a diet or supplement” that can influence metabolic syndrome.

“It’s still early days for gut microbiome research”, Vulevic and others agree. The species composition of the human gut microbiome is not well understood, which is not surprising since the gut is a profoundly complex ecosystem, comprised of trillions of bacteria.

Early-life exposures to antibiotics probably disrupt normal development of gut microbiota in lasting ways. Marie-France de La Cochetière (INSERM Institute, Nantes, France), who specialises in molecular analysis of the intestinal microbiota, says that although antenatal antibiotics cannot be totally avoided, each course in early life “is like an elephant in a porcelain store”.

Which bacteria may be “proinflammatory or conversely anti-inflammatory” in type 1 diabetes is not yet known, notes Danny Zipris, (University of Colorado, Denver, CO, USA). “We are in the process of analysing the intestinal microbiota of children at risk for type 1 diabetes and hope to identify bacterial strains associated with the disease.”

Until recently, the composition of the adult gut microbiome was believed to be stable, a steady-state ecosystem. But some suspect that this vision might have been an artifact of simple and relatively insensitive sampling methods. Most gut bacteria cannot be cultured—a problem now being remedied with sophisticated next-generation genome sequencing.

Sampling techniques remain a challenge. Vulevic’s team, like most researchers, used faecal sampling, which avoids invasive colonoscopy and the alterations to the gut microbiome that can follow fasting and bowel preparation before colonoscopic procedures. But faecal sampling is far from ideal because the microbes in direct contact with human tissues are not as well represented in faeces as are the lumen-dwelling species associated with food wastes.

Establishing causality remains the central conceptual challenge for the field and effectively deciphering microbiome interactions with human immune and endocrine systems and their influence on health will be an interdisciplinary endeavour, Lyte and de La Cochetière agree.

Already, however, the field is fostering a reconceptualisation of the human body: “To me, the most important advances are in the concept of human as supraorganism: the microbiome ecosystem within the human one”, says de La Cochetière.

Vulevic’s team is now studying the effects of B-GOS in diabetic and overweight adults, and its effects on the gut-brain axis and modulation by beneficial gut microbes of cortisol levels, anxiety, and cognition.

“I think we are currently right in the middle of very exciting times in which human gut microbiota is becoming better understood and implicated in various conditions”, Vulevic said. “However, we have very little understanding of the mechanisms that underpin some of the observed effects of the human gut microbiota. This is perhaps not surprising, given the diversity and size of the human microbiome.”

“Lots and lots of work has still to be done”, agrees de La Cochetière. “And each step reveals a new world.”

Bryant Furlow