Translational Science

Targeting gut microbiota with a complex mix of dietary fibers improves metabolic diseases

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Long considered a bystander in the human gastrointestinal tract, the hundred trillion microbes residing in our gut, known as the gut microbiota, are now considered critical for human health (1). These microbial cells outnumber our own cells; hence the gut microbiota harbors at least 100-fold more genes than the human genome (2). This vast catalogue of genes encodes for diverse metabolic activities, allowing the gut microbes to adapt to their environment and to the energy sources available. This complex ecosystem has developed metabolic capacities that we are unable to perform on our own.

Intriguingly, the human body is very efficient at digesting and absorbing dietary fats, simple sugars, and proteins; however, humans are unable to fully metabolize many of the complex carbohydrates that are present in diets rich in cereals, fruits, and vegetables. Therefore, several carbohydrates that escape digestion in the upper gastrointestinal tract, including dietary fibers and prebiotics, are fermented by gut microbiota into multiple metabolites including short chain fatty acids (SCFAs) such as acetate, butyrate, and propionate (Figure 1). These microbial metabolites are involved in numerous physiological processes in the human host, ranging from energy, glucose, and lipid metabolism to immunity, inflammation, and cancer (3). In a recent issue of *Science*, Zhao et al. report the results of a small clinical trial of dietary manipulation of the gut microbiota in patients with diabetes (4).

The authors conducted an open-label, randomized clinical study in patients with type 2 diabetes, comparing isoenergetic diets that differed in the content of whole grains, traditional Chinese medicinal foods, and prebiotics. All participants were treated with Acarbose, which inhibits host amylases thereby reducing the digestibility of edible starches so that they reach the colon where they are fermented by gut bacteria. The control group (n=16) was counseled to follow dietary recommendations from the Chinese diabetes society, whereas the experimental group (n=27) received a specialized diet enriched in dietary fiber, traditional medicinal foods, and prebiotics (Box 1) for 84 days. Both groups exhibited a significant reduction in hemoglobin A1c (HbA1c); however, the reduction was greater in the experimental group. Overall, 89% of the experimental group achieved the target HbA1c <7%, compared to only 50% of the control group. At the end of the study, the improvement in fasting blood glucose levels was similar between the two groups. In addition, the experimental group

exhibited a greater reduction in body weight and an improved blood lipid profile. The authors concluded that increasing the quantity of non-digestible carbohydrates that reach the gut may be sufficient to improve the metabolic parameters of patients with type 2 diabetes (Figure 1).

The authors further explored whether the modulation of the gut microbiota observed with the experimental diet were causally linked to the observed metabolic improvements. Gut microbiota from trial participants pre- and post-intervention were transplanted into germ-free mice. Strikingly, mice colonized with the gut microbiota harvested post-intervention from either the control or experimental group displayed improved metabolic parameters as compared to mice colonized with the gut microbiota collected before the intervention. However, mice colonized with the gut microbiota from participants randomized to the experimental diet had a lower fasting blood glucose and post-prandial glucose than mice colonized with gut microbiota from participants on the control diet.

The metabolic improvements observed in study participants were correlated with changes in the composition of the gut microbiota at both the taxonomic and genetic level, including a significantly higher number of genes involved in carbohydrate utilization and butyrate synthesis. Consistent with this finding, the fecal levels of butyrate where significantly increased after 28 days of treatment and remained higher until the end of the study.

These results are consistent with previous human studies demonstrating that prebiotic feeding changes the composition of the gut microbiota and the production of microbial metabolites, and correlates with an improvement in metabolic parameters including blood glucose, lipid levels, and fat mass (5-7). Mechanistically, prebiotic feeding has been shown to increase the secretion of gut peptides including glucagon-like peptide-1 (GLP-1) and Peptide YY (PYY) in humans (5-7). These two hormones are involved in the regulation of appetite and glucose metabolism. In rodents, these gut hormones have been implicated as the key molecular factors linking the fermentation of prebiotic dietary fibers, the gut microbiota, SCFAs, and metabolic parameters (8). In their study, Zhao et al. also observed increased blood levels of GLP-1 and PYY. The relative contribution of these gut hormones to the observed results is unknown as the authors only explored two other metabolites, indole and hydrogen sulfide. Other studies have shown that prebiotic feeding profoundly changes the profile of numerous metabolites (7).

Overall, the results of this study are convincing and support the benefits of increasing both the amount and the variety of dietary fibers ingested. Nevertheless, we can anticipate barriers to implementation of similar nutritional modifications using conventional food items, even in Asian countries. Translational to practical applications in other settings, in particular Western countries, is likely to be even more challenging. Importantly, these findings may not be generalizable to all types of dietary fibers and/ or prebiotics. Despite these limitations, this interesting area of research may help to design future dietary interventions to modulate the composition of the gut microbiota to improve human health.

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Declaration of interests

PDC is inventor on patent applications dealing with the use of *A.muciniphila* and its components in the treatment of obesity and related disorders. PDC is co-founder of A-Mansia biotech SA.

BOX

Prebiotic (definition): a substrate that is selectively utilized by host microorganisms conferring health benefits (9).

Composition of the experimental diet described in Zhao et al.

The experimental diet consists of a mixture of several components rich in dietary fibers and traditional Chinese medicinal food plants, including extracts from whole grains including buckwheat, Job's tears (*Coix lachrymal-jobi L.*), oat, white bean, yellow corn, red bean, yam, peanut, lotus seed, bitter melon, kudzu starch, inulin, and resistant dextrin. The diet contains diverse type of fibers including β-glucans, arabinoxylans, cellulose, hemicellulose, resistant starches, gums, and oligosaccharides.

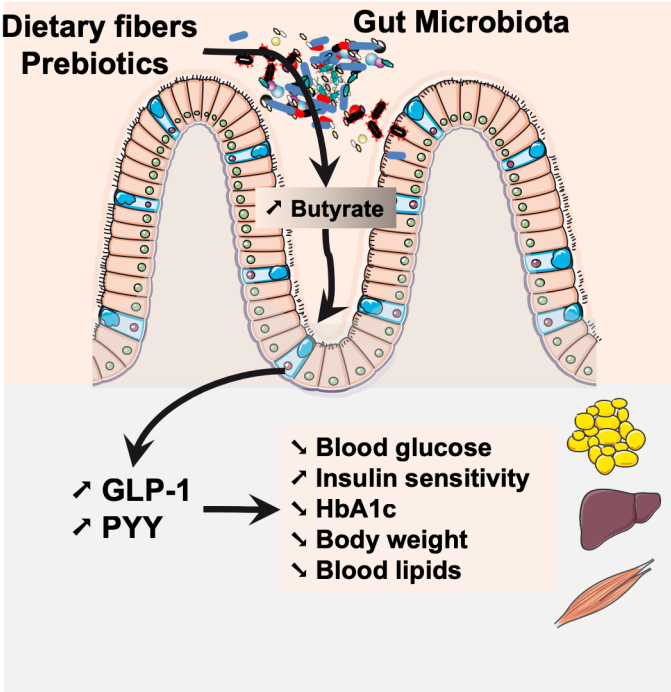

Figure 1: Targeted modulation of the gut microbiota improves metabolism

Dietary fibers and prebiotics are fermented by the gut microbiota into short chain fatty acids (SCFAs) such as butyrate. SCFAs are able to stimulate the secretion of both glucagon-like peptide-1 (GLP-1) and Peptide YY (PYY) by the enteroendocrine L-cells. GLP-1 increases glucose utilization and insulin sensitivity and ultimately contributes to reductions in hemoglobin A1c (HbA1c). In addition, PYY and GLP-1 promote weight

loss and reduce plasma lipids. Altogether, these mechanisms partially explain the beneficial effects observed with increased intake of dietary fibers and prebiotics.

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