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Whole Grains, Gut Microbiota, and Health—Time to Get Personal?

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In recent years there has been an increasing interest in investigating the link between diet, gut microbiota, and health (1, 2). The context has often been to evaluate the influence of diet on gut microbiota composition or whether microbiota can modify the effect of dietary interventions and their potential link to health outcomes (3–8). Many studies conducted are based on small post hoc analyses, and there is generally a lack of studies providing causal links between gut microbiota, diet, and health.

In this issue of the *Journal of Nutrition*, van Trijp et al. (9) conducted a post hoc analysis of a 12-wk parallel intervention study where the effect of an intervention diet rich in whole grain wheat compared with refined wheat on markers of nonalcoholic fatty liver disease (NAFLD) was studied. The main study was one of the first dietary intervention trials to investigate the effect of a high whole grain compared with refined grain intake on hepatic health and markers of NAFLD. The study found increased intrahepatic triglyceride in the refined wheat group compared with the whole-grain wheat group after 12 wk of intervention, as well as a tendency toward lower C-reactive protein concentrations in the whole-grain wheat group, but contrarily also higher postprandial triglyceride in the whole-grain wheat group (10). The current post hoc analysis aimed to investigate the changes in gut microbiota induced by the intervention diet and their correlations with the main outcomes of the study. The investigators found minor effects on the gut microbiota composition when comparing the diet groups after 12 wk (9). The effects were primarily an increased abundance of certain fiber-degrading bacteria in the whole-grain wheat group, which to some extent correlated with the positive effects of the dietary intervention on liver health (10).

The study is well designed and has several strengths, including the relatively long duration, the inclusion of a run-in period, and a dose significantly larger than the amount of whole grain in the habitual diet, while still remaining within the frame of what would be realistic to implement in a habitual diet. In addition, the intervention foods were well-characterized whole-grain products, with great similarity to products that are already available to consumers, which adds to the immediate relevance and applicability of the results. In addition, the researchers used objective biomarkers to assess compliance, addressing a critical issue in dietary intervention trials (11).

There are also limitations, including the small sample size, which may have made it difficult to detect actual effects of the intervention diet. Furthermore, the characterization of the gut microbiota was purely based on a compositional level (16sRNA). It would have been interesting to investigate the effect on different metabolites, such as SCFAs, bile acids, indole propionic acids, and others in order to gain insight into the functionality of the gut microbiota and its relevance for clinical outcomes (12). Furthermore, whole-grain wheat contains primarily insoluble fibers, with a comparably low potential for fermentation, and it might have been even more interesting to investigate the effects of rye or oats, which have greater potential for gut fermentation, as well as for reduction of blood lipids due to the greater content of soluble, viscous forming fibers (13, 14).

Van Trijp et al. only found minor alterations in gut microbiota composition following a whole-grain intervention, despite a high dose of whole grain and a long intervention period. This is in line with the results of several other whole-grain interventions (15–17) and calls for careful dissection of the reasons and for more effective strategies, such as personalized interventions, to be considered before new studies are conducted. One potential explanation for the modest effects could be the large within-individual variation in gut microbiota, making it difficult to detect general intervention effects when the sample size is small. The gut microbiota composition may also be resilient to long-term dietary modifications with whole-grain foods (15). While whole-grain food–based dietary interventions have shown limited ability to alter gut microbiota, interventions using specific food ingredients, such as different isolates of resistant starch and other dietary fiber fractions in relatively large doses, have been successful in inducing a response in gut microbiota composition (4, 18). This suggests that important components of whole-grain foods (dietary fiber) can affect the composition of the gut microbiota and provide valuable knowledge on a mechanistic level, but the translation of these findings into general dietary guidelines is less apparent, especially considering the transition into food-based dietary guidelines that has emerged in many parts of the world over the past decades (19). However, interventions based on specific food ingredients or supplements might prove to be beneficial when targeted towards specific groups within the population.

Another important aspect, which paves the way for both improved understanding of mechanisms and for new personalized strategies for improved diet-mediated prevention, is the fact

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that the response to dietary interventions might differ greatly between individuals in a way that calls for a distinction between responders and nonresponders to specific dietary interventions (20). Our recently published trial, testing the effect of whole-grain wheat compared with whole-grain rye in middle-aged men with signs of metabolic syndrome, found small but significant effects of the intervention on blood lipids overall. However, when assessing effects across participants with different enterotypes (based on their baseline gut microbiota composition) we found a differential response in LDL cholesterol when participants consumed whole-grain rye (15). Similar differential responses across enterotypes have been shown for high-fiber diets, weight loss (3, 6, 21), and blood glucose (22–24). Perhaps a mixture of responders and nonresponders were included in the current study, which clouded a difference in response between the 2 intervention diets when evaluating the entire group of participants?

The current evidence from whole-grain intervention studies, including the results from the present study, suggest that further large-scale whole-grain interventions on a general population will give us limited new knowledge about the role of diet, gut microbiota, and their interactions in relation to health outcomes. Rather, we need to design studies that can disentangle how different microbiota compositions can influence the response to a dietary intervention and how such effects mediate differential health responses. Furthermore, emphasis needs to be put on assessing the functionality of gut microbiota in addition to its composition, including fermentation capacity, substrate utilization, and the production of metabolites, such as SCFA, bile acids, and as yet unknown compounds. This can provide more detailed information about underlying mechanisms but also provide new tools and predictive biomarkers of responders/nonresponders that can guide optimization of the whole-grain diet for consumers with differential health responses. A substantial amount of work remains to be done to increase our understanding of the interaction between diet and gut microbiota and possibly its predictive power of the individual's response to dietary interventions. A deeper understanding based on such work will pave the way for dietary advice on a more individualized level with potential to increase the overall health of the population.

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