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Diet and long-term weight loss: what can we learn from our gut microbes?

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Sustained treatment of obesity remains a persistent challenge, with only 1 in 6 overweight or obese US adults reporting having maintained weight loss of 10% over 1 y (1). The interindividual variability in sustained weight-loss success has raised questions about the role of our highly personalized gut microbiota and whether measuring and/or manipulating our gut microbes might ultimately help in obesity prevention and control (2, 3).

The gut microbiota—the assemblage of intestinal microbial communities—is associated with obesity and, unlike the genome, it is highly malleable, making it an attractive therapeutic target for facilitating weight management. In the short term, the gut microbiota is impacted by changes in diet, as seen when shifting to an animal-based or plant-based diet (4) or when consuming diets with different fiber and macronutrient composition (5). Intervention studies have also found that weight loss through caloric reduction, regardless of diet composition, is associated with changes in the composition of gut microbiota (6–9), but these studies have been limited by lack of control groups, small sample size, or brief follow-up. Furthermore, in murine models, the gut microbiota has been shown to modify the energy harvested from diet and weight gain (10) and to predict weight regain (11). Yet, whether the gut microbial communities predict weight dynamics in humans has been sparsely studied (12).

In this issue of the *Journal*, Fragiadakis et al. (13) addressed 2 questions: *1*) can gut microbiota predict weight loss and *2*) does the gut microbiota change over 1 y with healthful low-fat or low-carbohydrate weight-loss diets. This study was embedded within the DIETFITS (Diet Intervention Examining the Factors Interacting with Treatment Success) randomized trial, which was conducted in nondiabetic overweight or obese adults who received a healthy low-carbohydrate or low-fat diet (14). The analysis of the 609 individuals who completed the trial showed that both diets were equally effective for weight loss at 12 mo (−6.0 kg for the low-carbohydrate diet and −5.3 kg for the low-fat diet) (14). In this current study, Fragiadakis et al. collected stool samples at baseline and the 3, 6, 9, and 12-mo visits from a subset of 49 participants and conducted 16S ribosomal RNA (rRNA) gene sequencing to profile microbiota. Contrary to the authors' primary hypothesis, microbiota composition at baseline or at 3 mo did not predict participants' total weight loss at 12 mo. Each of the 2 diets resulted in changes to the gut microbiota composition at 3 mo (increased relative abundance of the Proteobacteria, Bacteroidetes, and Firmicutes phyla in the low-carbohydrate arm and decreased relative abundance in the Actinobacteria and Firmicutes phyla in the low-fat arm at 3 mo). However, from 6 to 12 mo, these changes regressed toward baseline levels. The authors interpreted this pattern of regression as indication of microbial resilience to perturbation of the microbiota's baseline profile.

The authors' finding that baseline microbiome did not predict weight loss at 12 mo contrasts with previous small trials of shorter duration. In a single-arm trial of 26 overweight or obese US adults participating in a lifestyle weight-loss program, the 9 participants who lost >5% weight at 3 mo had higher relative abundance of *Phascolarctobacterium* and lower relative abundance of *Dialister* and microbial genes encoding carbohydrate-active enzymes at baseline (15). Another trial randomly assigned 62 Danish adults with high waist circumference to receive an ad libitum New Nordic Diet (high in fiber) or an average Danish diet for 26 wk. They found that there was a significantly greater weight-loss effect of the high-fiber New Nordic Diet (vs the average Danish diet) among individuals with a high *Prevotella*-to-*Bacteroides* ratio, measured by quantitative PCR analysis (16). Like the current study, both trials were limited by small sample sizes. These previous studies also used more traditional ordinary least-squares estimates, whereas Fragiadakis et al. used elastic net regularization, a machine-learning approach that can improve the bias-variance trade-off in small datasets.

To our knowledge, the study by Fragiadakis et al. is the first to provide insights into how weight loss with either a healthy low-fat or low-carbohydrate dietary pattern is associated with gut microbiota composition over a year-long period. However, since the diets in both arms were not directly observed and correlated with changes in weight, it is hardly possible to discern whether the within-group changes (or lack thereof) in microbiota composition were due to changes in diet composition or due to

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weight loss through energetic balance, which may have opposing effects. Moreover, it is worth noting that the weight-loss diets were not designed to impact the gut microbiota. For example, neither diet increased dietary fiber, one of the strongest drivers of beneficial gut microbes and microbially produced SCFAs (16, 17).

One of the most noteworthy findings of the current study was the reversal of within-group changes in microbiota composition at 6 through 12 mo after initial shifts at 3 mo, which the authors conclude may demonstrate resilience of microbiota composition despite maintenance of dietary patterns and body weight. If this finding is true, the resilience of microbiota could plausibly underlie the phenomenon of weight regain after initial weight loss, which may be regulated by feedback control processes instead of a simple calories in–calories out process (18). This hypothesis is consistent with evidence from murine models indicating that changes to the gut microbiota contribute to weight rebound after dieting (11). Fragiadakis et al. could have provided additional insights on this theory by *1*) examining whether the gut microbiota at 6 mo predicts weight regain from 6 mo to 12 mo and *2*) examining the changes in the gut microbiota function at 3 mo, as the capacity of the gut microbiota to harvest energy from food could be potentially increased by the changes in gut microbiota composition after the initial dynamic phase of weight loss. Certainly, this represents a ripe area for future investigation given the high rates of obesity and the intractable challenge of achieving sustained weight loss (1).

Several features of the study design and methods should be considered when interpreting the results. First, due to the small sample size ($n = 49$ across both arms and $n = 18$–22 for between-group comparisons) and a lack of statistical power, false-negative results cannot be ruled out. Second, the DIETFITS trial was not a controlled-feeding study. Instead, participants were instructed by dietitians to reduce intake of fat or carbohydrate, and actual dietary intake was self-reported. Third, the restriction to 20 g/d of total fat or digestible carbohydrate was limited to the first 8 wk of the study only. After that, participants were allowed to add fat or carbohydrate back to their diets, which resulted in mean intakes of fat and carbohydrate higher than the initial target. This feature casts some doubt on whether the regression of the microbial composition after 3 mo was actually due to regression of the diet toward the baseline macronutrient composition rather than the resilience of the microbiota. Fourth, both arms were "healthy diets" in that they were calorically restricted and emphasized high-quality foods such as maximal vegetable and minimal added sugar or refined grains (19). Because there was not a nonintervention control group, the trial could not compare the diet interventions with the natural shift of the microbiota abundance that would have occurred if these participants maintained their typical diet pattern and did not lose weight. Fifth, the use of 16S rRNA gene sequencing limited taxonomic precision and statistical power, and precluded insights into functional changes in the microbiota that could be obtained through shotgun metagenomic sequencing. Finally, whereas in the DIETFITS trial nearly 60% of the participants were white, this proportion increased to nearly 80% in this substudy, which may limit the generalizability of the findings.

In summary, Fragiadakis et al. provide new evidence that tempers previous enthusiasm about leveraging gut microbiota to predict dietary weight loss in a real-world setting, and furthermore suggests that gut microbiota may be resilient to initial weight-loss perturbations. Still, for the reasons noted above, the study size and design preclude strong interferences. Key questions remain. How is microbiota diversity, composition, and function affected by *1*) long-term isocaloric changes in diet composition or *2*) diet-induced weight loss versus no weight loss? Do microbiota composition and function predict individual metabolic responses to a given dietary pattern (e.g., high-fiber diets)? Do changes in gut microbiota help predict weight rebound after the initial dynamic phase of weight loss? There is need to move from small uncontrolled studies to randomized trials designed to answer these outstanding questions. Moreover, we need innovative trials that target the gut microbiota. These may include isocaloric feeding studies contrasting in *1*) microbiota-accessible carbohydrates (20), *2*) chemical compounds and other nonnutritive components of food (such as food additives) that are hypothesized to affect the gut microbiota (21), or *3*) dietary patterns rich in fermented versus nonfermented foods. A better understanding of the role of the microbiota in the pathogenesis of excess weight may lead to translatable microbiota-targeted therapies to alleviate the enormous global burden of obesity.

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References

1. Kraschnewski JL, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK, Sciamanna CN. Long-term weight loss maintenance in the United States. Int J Obes 2010;34(11):1644–54.
2. de Toro-Martin J, Arsenault BJ, Despres JP, Vohl MC. Precision nutrition: a review of personalized nutritional approaches for the prevention and management of metabolic syndrome. Nutrients 2017;9(8). doi:10.3390/nu9080913.
3. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015;372(9):793–5.
4. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505(7484):559–63.
5. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen Y-Y, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science 2011;334(6052):105–8.
6. Remely M, Tesar I, Hippe B, Gnauer S, Rust P, Haslberger AG. Gut microbiota composition correlates with changes in body fat content due to weight loss. Benef Microbes 2015;6(4):431–9.
7. Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, Almeida M, Quinquis B, Levenez F, Galleron N, et al. Dietary intervention impact on gut microbial gene richness. Nature 2013;500(7464):585–8.
8. Louis S, Tappu RM, Damms-Machado A, Huson DH, Bischoff SC. Characterization of the gut microbial community of obese patients following a weight-loss intervention using whole metagenome shotgun sequencing. PLoS One 2016;11(2):e0149564.
9. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature 2006;444(7122):1022–3.
10. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006;444(7122):1027–31.
11. Thaiss CA, Itav S, Rothschild D, Meijer MT, Levy M, Moresi C, Dohnalová L, Braverman S, Rozin S, Malitsky S, et al. Persistent microbiome alterations modulate the rate of post-dieting weight regain. Nature 2016;540(7634):544–51.
12. Christensen L, Roager HM, Astrup A, Hjorth MF. Microbial enterotypes in personalized nutrition and obesity management. Am J Clin Nutr 2018;108(4):645–51.

13. Fragiadakis GK, Wastyk HC, Robinson JL, Sonnenburg ED, Sonnenburg JL, Gardner CD. Long-term dietary intervention reveals resilience of the gut microbiota despite changes in diet and weight. Am J Clin Nutr 2020;111(6):1127–36.
14. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, Desai M, King AC. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. JAMA 2018;319(7):667–79.
15. Muñiz Pedrogo DA, Jensen MD, Van Dyke CT, Murray JA, Woods JA, Chen J, Kashyap PC, Nehra V. Gut microbial carbohydrate metabolism hinders weight loss in overweight adults undergoing lifestyle intervention with a volumetric diet. Mayo Clin Proc 2018;93(8):1104–10.
16. Hjorth MF, Roager HM, Larsen TM, Poulsen SK, Licht TR, Bahl MI, Zohar Y, Astrup A. Pre-treatment microbial Prevotella-to-Bacteroides ratio, determines body fat loss success during a 6-month randomized controlled diet intervention. Int J Obes (Lond) 2018;42(2):284.
17. Mueller NT, Zhang M, Juraschek SP, Miller ER 3rd, Appel LJ. Effects of high-fiber diets enriched with carbohydrate, protein, or unsaturated fat on circulating short chain fatty acids: results from the OmniHeart randomized trial. Am J Clin Nutr 2020;111(3):545–54.
18. Hall KD, Guo J. Obesity energetics: body weight regulation and the effects of diet composition. Gastroenterology 2017;152(7):1718–27.e3.
19. Stanton MV, Robinson JL, Kirkpatrick SM, Farzinkhou S, Avery EC, Rigdon J, Offringa LC, Trepanowski JF, Hauser ME, Hartle JC, et al. DIETFITS study (diet intervention examining the factors interacting with treatment success)—study design and methods. Contemp Clin Trials 2017;53:151–61.
20. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. Nature 2016;529(7585):212–5.
21. Johnson AJ, Vangay P, Al-Ghalith GA, Hillmann BM, Ward TL, Shields-Cutler RR, Kim AD, Shmagel AK, Syed AN, Walter J, et al. Daily sampling reveals personalized diet-microbiome associations in humans. Cell Host Microbe 2019;25(6):789–802, e5.