Effects of Diet-Modulated Autologous Fecal Microbiota Transplantation on Weight Regain

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Introduction: We evaluated the efficacy and safety of diet-modulated autologous fecal microbiota transplantation (aFMT) for weight regain attenuation after the weight loss phase.

Methods: In the DIRECT-PLUS trial, abdominally obese or dyslipidemic participants were randomly assigned to (1)healthy dietary guidelines, (2)Mediterranean diet, and (3)green-Mediterranean diet weight-loss groups. All groups received free gym membership and physical activity guidelines. Both iso-caloric Mediterranean groups consumed 28g/day walnuts (+440mg/d polyphenols provided). The green-Mediterranean dieters further consumed green tea (3-4 cups/day) and a *Wolffia-globosa* (Mankai strain;100g/day) green shake (+800mg/day polyphenols provided). After 6 months, 90 eligible participants (mean age, 52 years; mean weight loss, 8.3 kg) provided a fecal sample that was processed into aFMT by frozen, opaque and odorless capsules. The participants were then randomly assigned to groups that received 100 capsules containing their own fecal microbiota or placebo until month 14. The primary outcome was regain of the lost weight over the expected weight regain phase (months 6–14). Secondary outcomes were gastrointestinal symptoms, waist-circumference, glycemic status and changes in the gut microbiome, as measured by metagenomic sequencing and 16s-rRNA. We validated the results in a parallel in-vivo study of mice specifically fed with Mankai, as compared to control chow diet.

Results: Of the 90 participants in the aFMT trial, 96% ingested at least 80 of 100 oral aFMT or placebo frozen capsules over the transplantation period. No aFMT-related adverse events or

symptoms were observed. For the primary outcome, aFMT significantly attenuated weight regain in the green-Mediterranean group (aFMT, 17.1%, vs placebo, 50%; *P*=.02), but not in the dietary guidelines (*P*=.57) or Mediterranean diet (*P*=.64) groups (*P* for the interaction=.03). Accordingly, aFMT attenuated waist circumference and insulin rebound in the green Mediterranean group but not in the dietary guidelines or Mediterranean diet (P for the interaction=.04 and .03, respectively). The green-Mediterranean diet was the only intervention to induce a significant change in microbiome composition during the weight loss phase, and to prompt preservation of weight loss-associated specific bacteria and microbial metabolic pathways (mainly microbial sugar transport) following the aFMT. In mice, Mankai-modulated aFMT in the weight loss phase, compared with control diet aFMT, significantly prevented weight regain, and resulted in better glucose tolerance, during a high-fat-diet induced regain phase (*P*<.05 for all).

Conclusions: Autologous FMT, collected during the weight loss phase and administrated in the regain phase, might preserve weight loss and glycemic control and is associated with specific microbiome signatures. High-polyphenols, green plant-based or Mankai diet better optimizes the microbiome for an aFMT procedure.

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