Transmitting Diet-Related Microbial Benefit through Fecal Microbiota Transplant in NASH: Can Microbiota Cut Through the Fat?

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The interaction between dietary changes and gut microbiota can potentially affect host physiology and pathophysiology.[1] These are attractive targets for manipulation in obesity, nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH). However, most current studies are either relatively short in duration compared with the natural history of NAFLD or have not yielded significant results focused on fibrosis, which is the major determinant of liver-related mortality.[2] Diets such as carbohydrate-restricted, low-fat, Mediterranean, and plant-based/vegan create their unique signature on the microbiome.[1] These changes in the microbiome could, in addition, modulate their impact on host health. However, these diets in the real world are not often followed regularly, can be expensive in resource-strapped subjects, and require intensive monitoring.

In animal models, tissues from a donor following a healthy lifestyle, be it lean status or better brain function, can promote the similar phenotype in the recipient.[3,4] A pilot study has shown benefit in alcohol-related behavior after fecal microbiota transplant (FMT) in humans.[5] It is tempting to speculate that a similar result could be achieved in humans through a *magic FMT pill* that encapsulates all of the potential benefits of the lean habitus and vegan dietary practice without the effort of becoming lean or vegan (Fig. 1).

In this issue of Hepatology Communications, Witjes et al. transplanted stool from lean healthy vegan donors via esophagogastroduodenoscopy and a duodenal enteral feeding tube, performed 3 times over 8 weeks in patients with NASH free of comorbid conditions such as diabetes.(REF) Most patients in the study did not have significant liver fibrosis. The study showed a trend toward improvement in necro-inflammatory scores noted on pre-intervention and postintervention liver biopsies. This intensive study missed the primary endpoint, because the study recruitment was incomplete. More relevant from the viewpoint of microbiota, there were changes in the intervention group with related gene and metabolomic changes showing that there was engraftment of the FMT with a translational impact on metabolism. The team is to be greatly commended for conceptualizing and putting into practice this intense series of investigations. There are several important points to be learned from this incredible effort. First, study designs

Abbreviations: FMT, fecal microbiota transplant; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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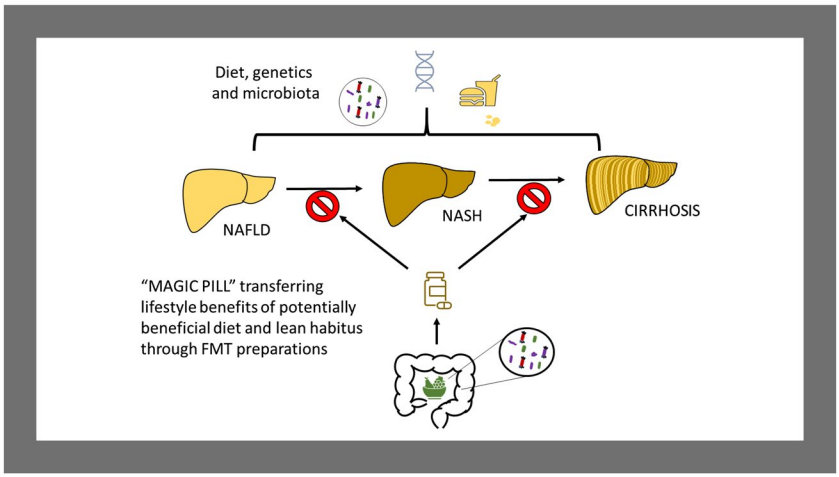

FIG. 1. Conceptualization of a potential magic pill developed from gut microbiota to transmit the phenotype of a beneficial lifestyle to recipients with NAFLD.

should ensure that *perfect is not the enemy of the good,* so we can minimize interventions while maximizing generalizability and acceptability of the study. Second, there is a glimmer of hope that multiple FMTs from donors with a healthier lifestyle could benefit from liver health without subjecting the recipients to the same rigors. Finally, specific microbial taxa rather than entire FMT preparations could further refine these in the future. The study has shed light on the importance of the role of dietary practices of the FMT donors on a vegan diet and on the FMT-related logistics that could be used as a future guide.

These results build on previous studies in metabolic syndrome and NAFLD/NASH that have not yielded major liver-related results with FMT.[6] However, there are hints toward improvement in insulin resistance and intestinal permeability in some of these studies. All of these studies raise important questions about whether FMT is a viable therapeutic alternative for NASH or whether it is a modality that needs more refinement. First, the stages of simple steatosis, versus NASH/NASH with fibrosis, all present unique challenges based on prevalence, recruitment, and endpoints.[7] These need to be balanced with expectations of clinical outcomes and acceptability of outcomes to regulatory agencies.[8] Second, one needs to consider the target to treat. Most studies have recognized fibrosis as the marker of prognosis; therefore, fibrosis-related outcomes, which are currently used in pharmaceutical trials, may be necessary.[8] Third, the broader cardiovascular context of NAFLD/NASH needs to be considered, as the results need to be generalizable.[9] Type 2 diabetes independently affects the microbiome regardless of liver disease, and especially if uncontrolled and insulin is being used.[9] Fourth, dietary changes themselves can induce NAFLD through *Gammaproteobacteria*, as Spencer et al. showed.[10] Therefore, controlling for the diet remains critical, which becomes challenging as the trials become longer. Finally, the role of genetic predisposition to NAFLD/NASH should also be considered.[2]

Microbiota resulting from beneficial lifestyles that can be reliably transmitted to affect lasting change in recipients remain a holy grail in translational human research. Major questions remain pertaining to delivery, duration, quantity, and follow-up of such interventions in patients with NAFLD and NASH, and further studies building on these current data are needed.

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