

Spotlight

Fecal microbiota transplantation and fiber supplementation, better together?

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SUMMARY

Fecal microbiota transplantation (FMT) is emerging as a tool to study the microbiome and as a potential treatment for several non-infectious diseases. Recently, Mocanu et al. showed that supplementing low fermentable fiber after FMT may improve insulin sensitivity in severely obese individuals.¹

Recently, Mocanu and colleagues published a clinical study titled “Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial” in *Nature Medicine*.¹ In a 2 × 2 factorial design, the authors compared high and low fermentable fiber with and without prior fecal microbial transplantation (FMT) from a lean donor. They reported that 6 weeks after low fermentable fiber supplementation and oral FMT, the homeostatic model assessment (HOMA2-IR), as a marker of insulin resistance, significantly improved (Figure 1).

This paper strengthens the core principle that the microbiome is in constant dialog with its environment as well as with its host. Although the FMT has a millennium-long history,² its mechanisms of action remain poorly understood. Since the majority of the FMT encompasses non-living particles,² this study provides evidence that the living microbial fraction and its engraftment in the FMT-recipient may drive at least in part the beneficial effects of FMT on insulin resistance in severe obesity.

As this is in our view a paper with major implications for the field, we would like to briefly discuss the caveats of this study, as the authors already largely acknowledge in the original publication. First, this was a proof-of-principle study with limited statistical power; and the main conclusions from this paper are derived from within-group comparisons, which in the setting of randomized trials should be interpreted with great caution.³ In addition,

only four healthy FMT donors were used and therefore were unable to be fully balanced across the four treatment arms. Although this is a well-known issue for FMT studies, as suitable donors can be hard to come by, it might convey a source of bias.⁴ Despite the fact that encapsulated (and not fresh) donor feces were used, these data are in line with our previous papers showing that healthy donor FMT can (temporarily) improve insulin sensitivity in obese treatment naive subjects, thus underscoring that donor FMT characteristics are a major predictor for clinical response.⁵ Moreover, we found that levels of baseline fecal microbial diversity and composition of the FMT recipient were major determinants in the improvement of insulin sensitivity after donor FMT.⁶ Thus, the current findings are exciting and should urgently be replicated, using not only a larger sample of recipients but also a greater pool of healthy donors.

From a methodological viewpoint, this paper also underscores that greater emphasis on standardization, or at least detailed monitoring, of the dietary intake and its (fiber) contents in donor FMT studies is needed. This likely applies to both the study participants as well as the donors to improve the reproducibility of these studies. Alterations in dietary composition are known to have profound and rapid effects on the composition of the gut microbiome, and one study even used autologous FMT to prolong the beneficial effect of a modified Mediterranean diet on weight regain.⁷ Interestingly, although their study was not designed to

investigate this issue in detail, Mocanu and colleagues did not find an obvious carry-over effect of low fermentable fiber on insulin sensitivity by week 12, while body weight was in fact lower.¹

It will be of major interest to address whether the potential improvement of donor bacterial strain engraftment by low fermentable fiber also holds true for other diseases for which donor FMT may be beneficial. This is especially the case in the management of cancers such as esophageal cancer⁸ or melanoma⁹ or graft-versus-host disease after stem cell transplantation,¹⁰ where healthy donor FMT seems to favorably improve the outcomes of these diseases. Although Mocanu and colleagues provide evidence that low fermentable fiber may improve the metabolic profile of the host in unison with FMT, it remains to be investigated whether repetitive treatment with donor FMT has more profound and long-term effects than single treatments by duodenal or rectal infusion.² We thus foresee that future studies will investigate whether it is possible to forego this cumbersome pretreatment and to develop a more feasible FMT protocol for repeated administration using ingestible capsules.

The optimization of FMT is of considerable interest, as several companies are already working on the standardization of FMT preparation, formulation, and mode of delivery to optimize its use in clinical practice,² extending FMT beyond its current use for recurrent *Clostridium difficile*. The findings by Mocanu and colleagues¹ provide a tantalizing perspective where co-supplementation



of low-fermentable fiber may further increase the potency of FMT. For direct clinical applications of the findings by Mocanu and colleagues in the setting of obesity, it is of interest that a large part of the metabolic benefits seemed to be mediated by an increase in incretin hormones. Given the current revolution in ever more potent incretin-based therapies, we believe that a focus on incretin-independent benefits from microbiome-directed interventions will be important for the justification of microbial interventions in the management of insulin resistance and subsequent type 2 diabetes.

In conclusion, Mocanu and colleagues¹ made yet another important contribution to the understanding of the role of the gut microbiome in cardiometabolic diseases, and the authors provided proof-of-principle for another way forward to improve the potential clinical benefit of microbial interventions. Replication of these findings, in the setting of obesity as well as a range of other conditions, may advance the field of medicine by optimizing the effect from microbiome directed therapies.

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DECLARATION OF INTERESTS

M.N. is a founder, holds stock in, and is a member of the Scientific Advisory Board of Caelus Health, the Netherlands. M.N. is on the Scientific Advisory Board of Kaleido Biosciences, USA. N.M.J.H. has received an honorarium from Boehringer Ingelheim. However, none of these conflicts of interest are relevant to this publication.

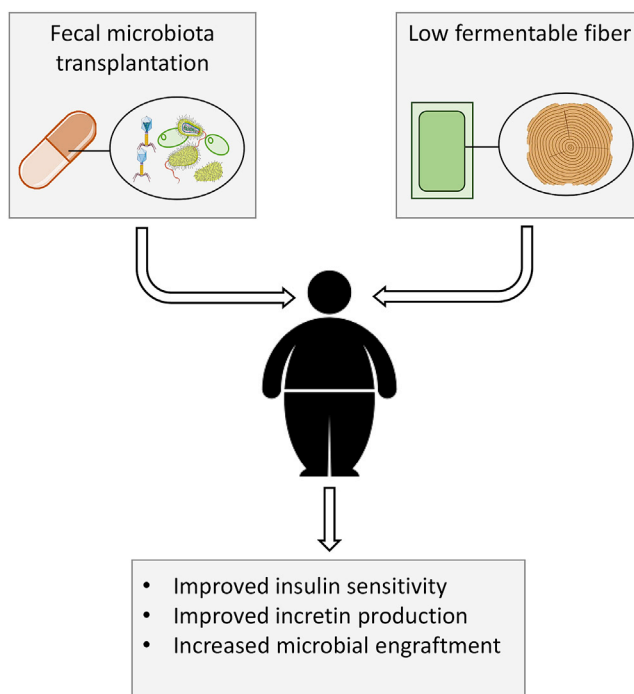


Figure 1. Main findings of Mocanu and colleagues

In a 2 × 2 factorial design, the authors compared high and low fermentable fiber with and without prior fecal microbial transplantation (FMT) from a lean donor.¹ They reported that 6 weeks after low fermentable fiber supplementation after oral FMT, the homeostatic model assessment (HOMA2-IR), as a marker of insulin resistance, significantly improved. They also reported improved engraftment of the microbiota and incretin production in the group that received low fermentable fiber after donor FMT.

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