Fecal Microbiota Transplantation: a Future Therapeutic Option for Obesity/Diabetes?

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Abstract:

Purpose of review: The aim of this review is to summarize the current data available on the metabolic effects of fecal microbiota transplantation (FMT) including obesity and glucose metabolism in humans.

Recent findings: Gut microbiota dysbiosis is a frequent characteristics observed in obesity and related-metabolic diseases. Pieces of evidences mostly generated in mouse models suggest that rescuing this dysbiosis associates with improved metabolism. In humans, dietary or bariatric surgery interventions are often accompanied by complete or partial restoration of this dysbiosis together with weight reduction and metabolic amelioration. Fecal microbiota transfer (FMT) is an interesting option to modify gut microbiota and has been associated with improved clinical outcomes, albeit only used in routine care for *clostridium difficile* infection. However, there are only limited data on using FMT in the metabolic context.

Summary: FMT from lean donors significantly improves insulin sensitivity in obese subjects with metabolic syndrome. However, there is a wide range of clinical responses. Interestingly in subjects with high microbial gene richness at baseline and when FMT donors that are metabolically compromised are used, no metabolic improvement is seen. Moreover, more studies evaluating the effect of FMT in overt type 2 diabetes patients are warranted. Furthermore, interventions (in the receiver prior to FMT) aiming to enhance FMT response also need evaluation.

Introduction

The intestinal microbiota is increasingly recognized to play major roles in human physiology and health. Indeed, amongst its numerous functions, it modulates and shapes host immunity, is able to digest some otherwise indigestible dietary derived nutrients (1) leading to the production of important metabolites for the host (2), including short chain fatty acids (SCFA) and is involved in biliary acid dehydroxylation and synthesis of several vitamins (1). Flourishing literature shows that many chronic diseases are associated with gut microbiota dysbiosis which include drastic change in microbiota composition, function and bacterial derived metabolite production. This is particularly described for obesity and Type 2 diabetes (T2D) (3–6).

Among reported features, in both mice (7) and humans (8), obesity is characterized by a decrease in bacterial diversity and low microbial gene richness (MGR: gene count number) in some (5,6). In overweight to severe obesity low MGR is associated with increased body mass index (BMI) as well as metabolic derangements including low grade inflammation and insulin resistance (5,6). The proportion of low MGR concerns 23 to 40% of individuals with overweight or moderate obesity (5,6) and increases up to 75% in severe obesity (9). Furthermore, low MGR-associated gut microbiota profile shows a switch towards increased bacterial strains with pro-inflammatory properties as well as a decrease in those with anti-inflammatory roles (5,6). Likewise, both mice and human studies demonstrated that T2D was also characterized by a modification of gut microbiota composition and function, when compared to healthy controls (10) or to individuals with impaired glucose tolerance (3,11). Nevertheless, causality or consequence of altered gut microbiota in metabolic diseases remains a source of discussion (12)

Several types of interventions are able to induce both beneficial metabolic outcomes and partial or complete correction of gut microbiota dysbiosis. For example, a moderately restrictive, fiber-enriched diet proposed to overweight or moderately obese individuals induced a significant increase of MGR especially in patients with baseline low MGR and, associations were found between changes in some bacterial groups and weight loss-improved metabolism (6). Likewise, bariatric surgery reserved for the most severe forms of obesity enables to significantly increase MGR and modify some bacterial species concomitantly with improvement in metabolic alteration and major weight loss (9). Although being based on associations, these studies suggest that the modulation of gut microbiota *per se* could at least be partly involved in those metabolic improvements. The role of gut microbiota modulation after bariatric surgery in the improvement of T2D has recently been reviewed in (13). Ingestion of dietary prebiotics have also demonstrated potential to induce weight loss and improvement of insulin resistance and overall metabolic health in rodent models (14). Nevertheless, when translating these interventions in humans, while prebiotics were indeed able to modify gut microbiota composition, their effects on metabolic health and weight was either very moderate with merely a slight decrease in post-prandial glycemia and no effect on weight loss (15) or completely absent (16). Similar observations can be made regarding the use of probiotics (17). Overall these studies suggest that interventions modifying gut microbiota could be considered for therapeutic innovation in the field of T2D and obesity, especially when taking baseline microbiota composition and diversity into account. This concept is further reinforced by fecal transfer experiments in rodents, highlighting the contribution of gut microbiota in weight reduction at least in mice.

For example, transferring feces from mice (18) or humans (19) who have undergone a bariatric procedure, into germ-free recipients, induces *per se* a weight reduction in the receivers. While the importance of weight loss is much lower than that induced by bariatric surgery, these studies highlight the important role of gut microbiota in weight reduction at least in mice, through fecal microbiota transfer (FMT). However whereas fecal microbiota transfer (FMT) is now a recommended procedure in the treatment of *Clostridium difficile* infection, as described below, it remains to be demonstrated whether FMT could also be considered in the standard care of common disorders including metabolic diseases or obesity.

In this review, we will first review how FMT is being more broadly used due to its clinical successes and its technological innovation. We will then focus on whether using gut microbiota modulation via FMT has demonstrated any beneficial therapeutic effects on obesity and/or T2D. Finally, we will discuss potential factors impacting and modulating FMT success.

Fecal microbiota transfer in humans

A success story in *Clostridium difficile* infection

The main routine care indication for FMT lays in the treatment of *Clostridium difficile* (CD) infection, reserved for cases resistant to antibiotherapy (20–23). This disease originates from the major gut microbiota dysbiosis induced by the use of several lines of antibiotic regimens. FMT enables to improve gut microbiota diversity resulting in an improved clinical response or even the cure of this disease in 80 to 90% of the cases (24) with 60% of complete remission one month after FMT (25). One of the first randomized clinical trial performed by our group was stopped prematurely since it showed, before the end of the trial, that FMT was efficient and

safe compared to antibiotics (26), and these results have now been confirmed in several other randomized control trials (22,27–29) as well as in a recent meta-analysis (30). Also, FMT has now been included in guidelines that recommend FMT in the context of recurrent CD infection to be used in standard of care (31–33). Most importantly, a consensus expert panel defined key recommendations for FMT use in CD infections (34) as well as the guidelines of technicality, regulatory, administrative and laboratory requirements for optimal FMT usage (35). FMT is now being tested in clinical trials in other diseases such as IBD (36,37) and Crohn's disease (38), which are also associated with a marked dysbiosis.

Novelty in administration route of FMT

FMT was, and is still in most research studies, performed either using nasojejunal tube, colonoscopy or enema, sometimes requiring several administrations to be efficient in some diseases (37). Most studies have observed good treatment tolerance both at the short and longer-term and very rarely adverse events are seen, which mostly seem to be originating from the initial disease severity rather than FMT itself (39,40). Importantly, careful selection of the FMT donors (34) ensures part of this treatment safety (37,39,41). Nevertheless, the risks originate mainly from the administration route. If no adverse event was deplored using enema, studies using nasogastric tube administration have reported few cases of intestinal bleeding and peritonitis (41). In a large meta-analysis including over 1000 patients, colonoscopy administration was also associated with adverse events leading to hospitalization in 0.97% of patients receiving FMT. One death directly due to FMT was reported and the patient died from aspiration during sedation, while undergoing FMT through colonoscopy administration for a chronic CD infection (39). Another death was reported due to pneumonia potentially caused by regurgitation during FMT

using a nasoduodenal tube (42). Although the most frequent adverse events are not serious and gathers intestinal symptoms such as bloating, flatulence, belching and abdominal cramps, abdominal discomfort, irregularity of bowel movements and vomiting (43,44), FMT procedure appears overall safe and a national FMT registry has been initiated to study potential long term side effects (45).

Based on the efficacy and (short term) safety of FMT in *CD* infection, technologic development have been made to enhance and facilitate FMT in routine clinical care and decrease adverse events linked to administration route by developing oral capsulized frozen FMT (46) and using frozen FMT stooling treated with glycerol as a cryoprotective procedure (47). Concerning the efficacy of encapsulated FMT, a recent randomized control trial demonstrated that oral administration was as efficient as classic administration routes to obtain beneficial health outcomes mainly in CD infection (48). Most importantly, no adverse event was observed post-FMT using this oral capsulized technique. Similar results have recently been reproduced in a study with 15 patients that were treated by 30 frozen capsules taken within two days (around 20g of feces) enabled 86.6% remission rate after one FMT and 100% remission rate after the second administration with excellent tolerance to this new administration route (49). The only adverse events observed were linked to the severity of the initial disease (49). Overall encapsulated FMT or “poop pills” as they are termed, seem to be a relevant and safe alternative to more invasive FMT administration route and will probably increase the feasibility and acceptability of this treatment.

Fecal microbiota transfer in metabolic diseases and obesity

Improved metabolic health in humans?

FMT used as a treatment option in obesity and other metabolic diseases has recently emerged. The reasons why gut microbiota modulation could beneficially affect glucose control has been extensively discussed herein (50) and include its actions on short chain fatty acid (SCFA) production, altered bile acids composition and adipose tissue inflammation (51). Our first pilot FMT study in metabolic syndrome included nine overweight/moderately obese individuals submitted to donor FMT originating from lean healthy controls that displayed a significant improvement in peripheral insulin sensitivity assessed by the gold standard, which is a stable isotope based euglycemic-hyperinsulinemic clamp (52). This beneficial effect was confirmed in a three times larger follow-up study which also observed a minor yet significant reduction in Hba1c at 6 weeks. Importantly, this study also showed that a reduced baseline microbial gene richness before lean donor FMT was associated with a better outcome (53). Despite the use of gastroduodenoscopy and nasoduodenal tube for donor FMT administration, no adverse events were reported. Importantly however, response to donor FMT showed a major inter-individual variability among receivers in both studies, with some patients displaying major improvements while others remained stable (52,53). Lean donor FMT induced differential microbiota modifications in good and poor responders (53). For example, after FMT, good responders displayed an increase in *Akkermansia muciniphila* which has been previously associated with metabolic health improvement in mice (54,55) but also in humans (56). Another critical question is the long term effect in FMT. The metabolic syndrome intervention showed that at 18 weeks, there was no remaining effect on insulin sensitivity and gut microbiota composition switched back to baseline

composition (53). This underscores the temporary nature of this FMT intervention. Nevertheless, these pioneering studies in treatment naive pre-diabetes (metabolic syndrome) male subjects demonstrate that FMT could be of therapeutic use to improve insulin resistance and decrease Hba1c (**Figure 1**), yet with a transient effect suggesting that multiple cures of FMT would probably be necessary.

Moreover as T2D is a chronic disease where patients need to take multiple glucose-lowering drugs several times every day it remains to be studied if FMT has any effect patient with severe insulin resistance and eventually decreased insulin secretion. Nevertheless, as our study data have shown, metabolic syndrome subjects with the most severe insulin resistance do not show any beneficial effect from lean donor FMT on insulin sensitivity. In line with our previously mentioned studies in obesity (52,53), it might thus be that gut microbiota play a role in the early stage of insulin resistance and T2D whereas its role could be less critical in glycemic control of patient with advanced stages of T2D. Nevertheless since FMT administrated by oral capsule appears safe, it provides an actionable tool to explore the relevance and differential effect of FMT in patients at different stages of glucose homeostasis alteration, paving the way to personalized approaches.

FMT and weight modulation

The rational to use FMT to induce weight loss originates from two reasons. Firstly, gut microbiota from obese individuals was found to be able to increase energy harvest as compared to lean individuals upon the same caloric intake (57), even if these results have been questioned since. Secondly, since FMT from obese mice or human into germ-free recipients is able to partly transfer weight gain (58–60), it is tempting to speculate that by contrast, using FMT from lean donors into overweight obese individuals could impact the receivers' corpulence, thus providing potential

innovative approach in the control of weight. This unproven concept is currently debated. Indeed, a recent study observed that FMT from mice upon chow diet into mice submitted to a high-fat diet (HFD) induced significantly greater weight gain than that obtained by HFD only (61). Turning to humans, some pieces of evidence accumulates suggesting that FMT could induce weight gain in specific cases. Indeed, FMT from a normal weight individual (BMI=25) to a patient suffering from anorexia nervosa led the receiver to increase (thus normalize) and stabilize her weight for 36 weeks post-FMT (62). Furthermore, a brief report observed that a patient suffering from *Clostridium difficile* infection gained weight and further became obese after receiving FMT from her overweight daughter (63), although she followed strict diet and physical activity. Noteworthy, weight gain in these cited examples could merely reflect that FMT in malnourished patients enables to restore a healthy situation with an eubiotic gut microbiota and induce energy storage in patients with previously chronic condition of under-nutrition, which thus might be more efficacious than in overweight subjects.

Nevertheless, the effects of FMT from lean donors have also been tested in overweight/obese patients in terms of weight modulation and no effect on weight was seen upon lean donor FMT (52,53). Thus, there is to date no significant proof that FMT, even those originating from lean donors is sufficient to induce weight loss. Most importantly, these first sets of data obtained in humans merely stimulates the need to carefully choose the donors both to avoid the transmission of communicable diseases but also to prevent weight gain. In this regard and in line with a study that showed that FMT from both mice (18) or humans (19) that underwent a bariatric procedure into germ-free recipients resulted in weight loss, De groot et al recently studied the effects of post-bariatric donor FMT compared to allogenic metabolic

syndrome donor FMT in obese insulin resistant males (De groot et al: gutjnl-2019-318320.R2 epub ahead of print). Despite the fact that post-bariatric donor FMT affects intestinal transit time in obese humans, in line with previous animal study (13), we did not observe any effect of post-bariatric surgery donor FMT on either insulin sensitivity or weight modification. Yet and surprisingly, allogenic metabolic syndrome donor FMT worsened insulin sensitivity in all FMT-treated subjects (De groot et al: gutjnl-2019-318320.R2 epub ahead of print). More insight is now needed to link the correct FMT donor to the recipient in order to gain maximum therapeutic efficacy.

Factors potentially modulating FMT response

Microbiota engraftment upon donor FMT

First, studies have demonstrated that donor FMT induced gut microbiota composition modification in the receiver as short as 1 week after intervention, switching the receiver's microbiota composition towards that of the healthy donor (64). Second, MGR increases post-FMT (52) and can even be restored (65) suggesting that FMT may act via normalizing microbiota dysbiosis, although this observation has not always been reproduced (53). Third, with time gut microbiota composition continues to change after FMT. Using SNV analyses it was observed that whereas it still resembles that of the donor one month post-FMT, the dominant bacterial strains in the receiver were not always similar to those of the donor (65). This result was further confirmed three months post-FMT (66). Importantly, FMT studies have sometimes used antibiotic prior to FMT, potentially inducing confounding effects on the engraftment of the donor's microbiota into the receiver. Interestingly, a recent study longitudinally analyzed the microbiota engraftment in different receivers without prior antibiotic use and showed a major inter-individual variability in FMT engraftment (67). FMT as compared to placebo induced a

significant modification of the receiver's microbiota that lasted at least 3 months, however, with time, the receiver's composition lost similarity with their donors. Furthermore, donor's specific species only moderately increased post-FMT in all receivers yet were specific to donor-receivers pairs and higher than those observed after placebo FMT (67). Finally, FMT induced a durable coexistence of bacterial strains present in the receivers and those transferred from the donor as well as a major strain replacement in the receiver yet variable from one receiver to the other (67) which could partially explain FMT variable responses (52,53). Overall, these results suggest that FMT induces the colonization of a new microbiota that can interact with that of the receiver and differs from that of the donor despite an observed beneficial clinical effect of FMT. Furthermore, it suggests that in the future, interventions aiming at improving FMT engraftment according to the receiver or the donor's microbiota should be undertaken in order to improve and maximize the clinical effect by increased donor bacterial engraftment (i.e. via dietary or antibiotic treatment before donor FMT).

Donor's microbiota composition and donor FMT success

Studies evaluating the donor's characteristic able to induce an optimal response are currently undergone. The notion of super-donor has emerged in inflammatory bowel diseases (IBD) field. Indeed, seven out nine patients who entered remission of their ulcerative colitis received their FMT from one single donor (68). Likewise, an FMT study in IBD patients using pooled feces from multiple donors finally evidenced that patients who entered remission had beneficiated from FMT containing the feces of one single donor thus suggested to be a super-donor (69). Importantly, all subjects who received the FMT were on TNFα blockers, which might have also affected FMT outcome. Whether the notion of a super donor is also valid in

the metabolic field still warrants further investigations. The donor's microbiota high diversity has been associated with good response in IBD remission (70). Nevertheless, whether a donor is considered a good donor for every disease type remains an open question. It might well be that to induce a good response in a specific disease, the donor's microbiota needs to be enriched in specific strains that are lowered or even absent in that specific disease. Further investigations are thus warranted.

Effects of concomitant drug use and donor FMT effect

Concomitant presence of drug and more specifically glucose-lowering drugs taken by the receiver is critical to be examined when using FMT to treat T2D. Metformin, the first line of anti-diabetic treatment, induces a change in the composition of gut microbiota with an increase in both beneficial bacterial strains (*Akkermansia muciniphila*) and known pro-inflammatory strains like *E. coli* (71,72). Forslund et al. observed a shift in microbiota composition in T2D patients with or without metformin with an increase in *E. coli* and a decrease in butyrate producing bacteria, while not impacting MGR (73). Importantly, Bäckhed's group identified a strong metformin related microbiota signature that in itself reproduced some of the beneficial effects of the molecule after FMT experiments in germ-free mice (74). These data suggest that evaluating the effect of FMT from healthy donors into T2D patients might be tricky since T2D patients receive one or associations of glucose-lowering drugs which impact differently the gut microbiota composition as this might interfere with the colonization or engraftment of the donor's gut microbiota after donor FMT.

Effects of concomitant dietary intervention and donor FMT effect

Gut microbiota profile is severely impacted by both short (75) and longer-term food intake habits specifically for the later, at the level of both enterotypes (76), microbial composition and gene richness (77). Nevertheless, acute modification of dietary intake also induces at least partial changes in gut microbiota composition (75,78). Dietary intake from receivers might most probably impact the clinical effects of FMT as discussed in (79) and demonstrated in rodent FMT experiments. Indeed, FMT from obese or lean twins into germ-free mice induced differential metabolic and corpulence improvement according to the diet administrated to mouse receivers (59). However, to date there is no standard recommendation regarding the optimal diet that would maximize the FMT beneficial therapeutic effect and bacterial strain engraftment. Moreover the donor's diet might also impact FMT clinical success. A recent study used FMT from vegan lean donors enabling a switch in gut microbiota composition in the receiver towards the vegan profile of the donor (80), but with some individual variability in receivers. Importantly, this switch was not accompanied by functional modification as seen with the measured production of trimethylamine. Potentially, the absence of functional effects might originate from inter-individual variability in microbiota composition within the receivers but also by the diet consumed by the receiver, which remained similar before and after FMT (80). It is tempting to investigate in the future whether modifying the diet after FMT could enhance FMT response yet.

Conclusion & Perspectives

The current literature suggests that FMT could improve metabolic state in particular insulin sensitivity yet the impact of FMT on weight loss in obese subjects needs further demonstration. Moreover, to make relevant progress in metabolic

disorders, several steps must be completed such as i) investigating FMT impact in patients with various degree of insulin-resistance toward overt T2D since evidences to date have been gathered in male subjects with metabolic syndrome, ii) evaluating gender effect, iii) deciphering the optimal mode of donor selection based on clinical information, administration procedure, cost issues and identify those able to induce a good response, and then iv) deciphering which patient profile might benefit the most from FMT. Nevertheless, while donor FMT has undergone technological innovation to simplify and improve its feasibility, it remains a complex and costly procedure, due to the donor's selection which includes a broad infectious analysis as well as complex preparation and administration technics. Furthermore, while FMT has demonstrated it cost-effectiveness in different severe diseases including *clostridium difficile* infection (81) and IBD (82), it remains to be proven whether this approach can be extended toT2D and particularly the most severe patients for whom glucose control remains above the target despite intensive medical therapy. A survey on a small study group of obese individuals recently demonstrated that a large number of them would be willing to undergo FMT if the donor was carefully selected (83), thus suggesting that this treatment could be proposed in standard of care for other indications than clostridium infection. If FMT successfully improve or treat T2D, this could lead to better physiopathology understanding and also pave the way towards other microbiota-related therapy developments. Indeed, the development of third generation probiotics based on newly identified beneficial bacterial strains associated with improved metabolism in humans is also and an emerging field that calls for future intensive research.

Figure legend

Figure 1: Effects of FMT in obese patients with metabolic alterations.

Obesity which represents a low-grade inflammatory disease with increased intestinal inflammation, and Type 2 Diabetes (T2D) are associated with gut microbiota dysbiosis. Literature has shown that fecal microbiota transfer from lean donors enables the engraftment of bacterial strains from the donor and thus induces improvement in insulin resistance, for a short period of time. In the future, oral capsulized FMT will have to be tested in T2D patients to evaluate whether it also improve intestinal inflammation, gut microbota dysbiosis and glycemic control.

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Conflicts of interest

M.N. is on the Scientific Advisory Board of Caelus Pharmaceuticals, the Netherlands.

K.C. is on the Scientific Advisory Board of LNC-Therapeutics

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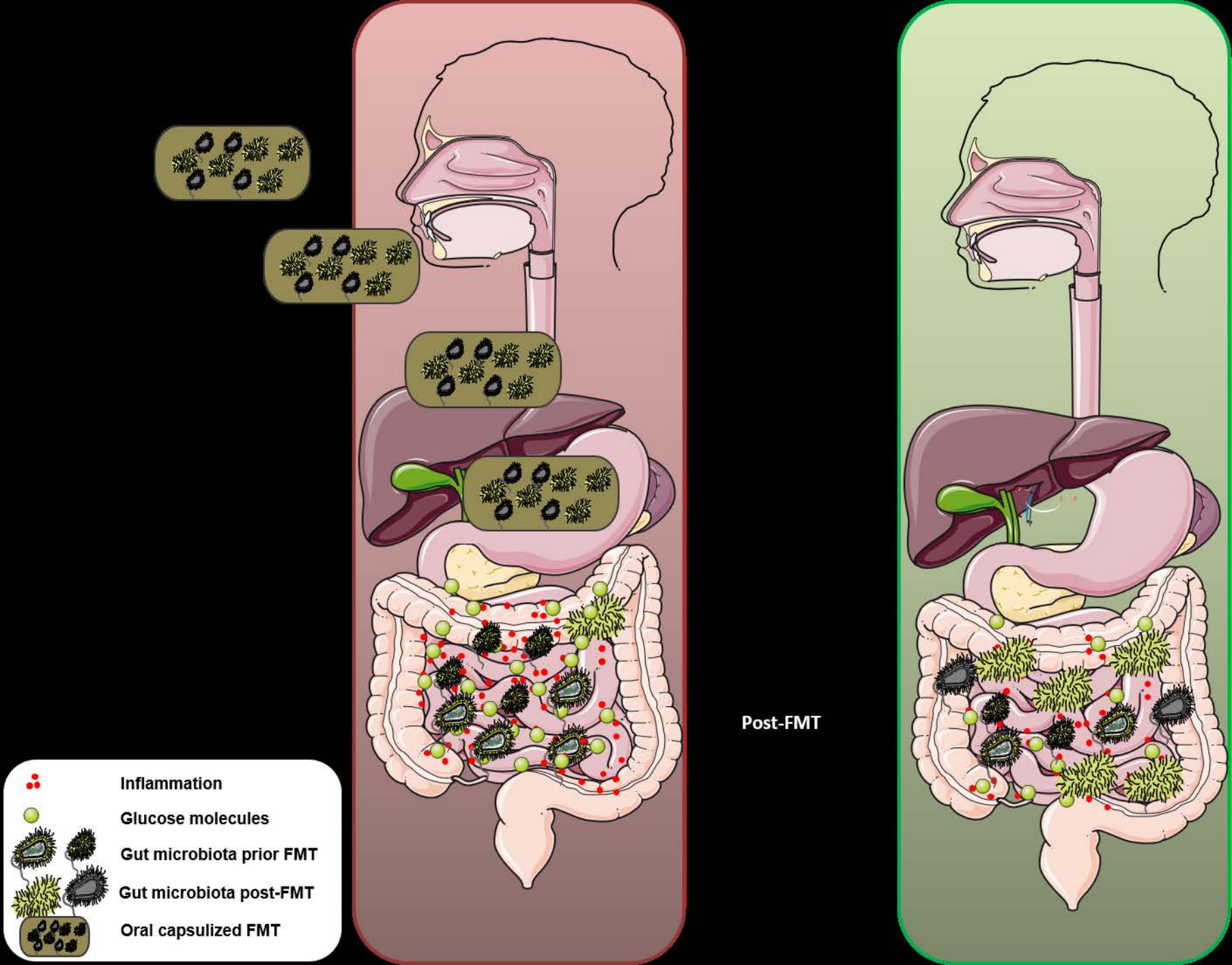
Inflammation
Glucose molecules
Gut microbiota prior FMT
Gut microbiota post-FMT
Oral capsulized FMT
Post-FMT