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ABSTRACT

The composition and function of gut microbiota play a role in obesity and metabolic disease, yet the mechanisms have not been fully described. As new discoveries and advances in the field have occurred, the relevance of gut microbiota in clinical care has become more substantial. There is promising potential for manipulation of the gut microbiota as treatment of obesity and associated health complications, both as a standalone therapy and as part of interventions such as weight loss. In this review we have compiled knowledge and concepts that are important in the consideration of gut microbiota for clinical care.

1. Introduction

Even though there have been notable scientific advances in the study of gut microbiota and obesity, a causal relationship between the two remains undefined [1]. Although promising mechanistic links have been uncovered in rodents, the myriad factors underlying human obesity and related-metabolic dysfunction (including genetics/epigenetics and lifestyle) make it difficult to demonstrate an independent role for gut dysbiosis. Studies have measured composition, functional potential, metabolomics, and ecologic dynamics of the gut microbiota, but we still do not know their relative contribution to complex disease pathophysiology and their concrete applicability to clinical care.

We, here summarize key discoveries made thus far that could have relevance in the management of obesity and its co-morbidities (Fig. 1).

2. Cross-talk between microbiota and host in metabolic disorders

Composition and function of the microbiota differ between healthy lean and obese subjects [2]. Gut microbiota is modified in obesity per se and related-comorbidities, including type 2 diabetes (T2D) [3–7], non-alcoholic steatohepatitis [8], and cardiovascular diseases [9]. The mechanisms believed to link the gut microbiota with obesity, at least in animals, include energy extraction capacity from food, influence on the integrity of the gut barrier, modulation of chronic inflammation and the immune system, and production of specific metabolites that, besides having a local effect on the gut-associated immune system and intestinal barrier, also signal to other tissues and organs including the brain, liver and adipose tissue.

2.1. Factors influencing gut microbiota and metabolic diseases

Metabolic diseases stem from a combination of factors, including host intrinsic characteristics, lifestyle and environment, genetic/epigenetic factors and gut microbiota composition and function. Diet has been widely studied in connection with the gut microbiota in obesity. For example, microbiota enterotypes, which have been used to group people according to their dominant phyla, are associated with long-term dietary habits [10]. Fermented foods and fiber consumption are associated with a healthier and more diverse microbiota [11]. As shall be described below, people living in more industrialized environments tend to have lower microbial diversity than people living in a more traditional manner.

Exchange of microbiota between individuals is another factor that shapes the microbial ecosystem. Adults consuming Western or restricted diets had distinct gut microbiota compositions, and lower richness was found in Western diet consumers. The microbes from these individuals were transplanted onto mice. Upon co-housing and enabling the transfer of gut microbiota (i.e. mice are coprophagic) recipients of the Western diet microbiota acquired traits of the restricted diet [12]. Similar results were seen in Ridaura et al. [13], showing the phenotypic transmissibility of some microbiota properties from humans to mice.

Pharmacology has an important effect on gut microbiota composition. Antibiotic treatment leads to profound and long-lasting modifications in the gut ecosystem [14]. Metformin, a key antidiabetic agent, has been identified as a confounder of microbiota observations in diabetes studies. These studies have suggested that the effect of metformin on the host may be partially induced through the gut microbiota

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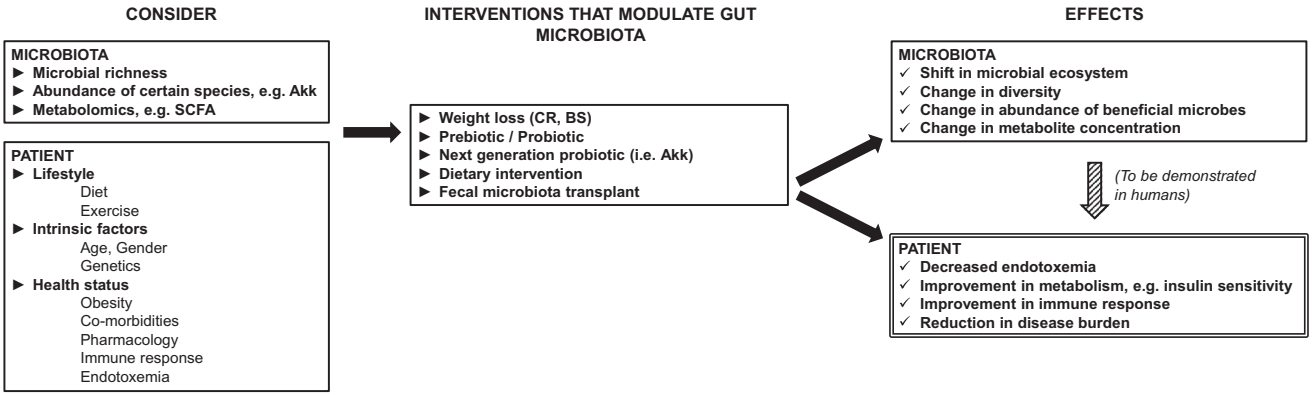

Fig. 1. Potential of gut microbiota in clinical care. Several aspects of gut microbiota composition and function have been implicated in metabolic diseases. Taking into consideration intrinsic patient characteristics, health status and environmental factors, manipulation of the gut microbiota could eventually be used in a wide array of treatments for metabolic disease, such as calorie restriction, bariatric surgery, prebiotic/probiotic intake and fecal microbiota transplantation. These treatments have shown changes in gut microbiota, which have been in turn associated with positive health outcomes, although causation remains to be demonstrated in humans. CR = calorie restriction, BS = bariatric surgery, Akk = *Akkermansia muciniphila*.

[15–17]. It is not excluded, however, that microbial composition may modify the pharmacology of drug compounds frequently used in metabolic disease leading in some circumstances to differential clinical effect as it was shown for example for digoxin, a well-known antiarrhythmic agent [18].

2.2. The gut microbiota influences host intestinal barrier and immune response

There is an association between gut dysbiosis and disruption of the intestinal barrier's integrity, specifically mucus production and layer thickness, tight junctions, insulin sensitivity, and inflammation. Disruption of the intestinal architecture may lead to leaking of gut-derived compounds that would otherwise stay in the gut lumen. Cani et al. termed the detection of lipopolysaccharide (LPS) in circulation 'metabolic endotoxemia,' and found it to be associated with chronic inflammation and disruption of metabolic homeostasis, particularly insulin sensitivity, in mice. LPS acts by activating Toll-like receptor 4 (TLR4) and inducing an inflammatory cascade. LPS from certain bacterial groups is more inflammatory than others, and it may be translocated in chylomicrons or by leaking through a permeable gut. High fat diets are associated with endotoxemia [19,20].

There is a complex interplay between microbiota, intestinal epithelium and the gastrointestinal immune system, with many metabolites and microbial components having a direct influence on the host's immunity. The production of metabolites from nutrients or modification of host-produced metabolites has a direct effect on immune cells and on both the integrity and permeability of the intestinal epithelium. The enteric immune system is constantly assessing and responding to the gut microbiota. A healthy gut ecosystem is needed in the development of immune tolerance, for example by promoting regulatory T cell (T_{reg}) differentiation and expansion [21], and prevention of autoimmune disease or chronic inflammation.

The most studied metabolites in connection with microbiota and host are short chain fatty acids (SCFA). They are synthesized from fiber metabolism by certain bacterial groups. SCFA act on the host in different ways. They serve as a source of energy for colonocytes, they have a critical influence on glucose homeostasis by inducing gluconeogenesis on colonocytes, as histone deacetylase (HDAC) inhibitors they impact epigenetic modifications, and they influence incretin secretion, specifically glucagon-like peptide 1 (GLP-1), through activation of G protein-coupled receptors GPR41 and GPR43 [22,23]. SCFA are elevated in obesity [24,25], where it is believed microbiota is more efficient at extracting energy from otherwise indigestible fibers, although this has not been fully demonstrated. Acetate may also have a role in central signaling of hunger and satiety [26,27]. SCFA have an anti-inflammatory effect through different pathways via both innate and adaptive immunity; they may inhibit pro-inflammatory cytokine production and promote T_{reg} expansion. They also maintain the integrity of the intestinal epithelial barrier [21]. Since differences were found in immune cells of the jejunum layer in severe obesity [28], it would be of major importance to examine the interaction between obesity-related immune dysfunction, the intestinal tract and gut microbiota. One example pertains to lymphocyte subtypes known to be modified in obese condition [29]. Mucosal-associated invariant T (MAIT) cells are innate-like T cells that recognize bacterial ligands. They are present in blood and enriched in mucosal and inflamed tissues [30]. We showed a depletion of circulating MAIT cells in obese and diabetic subjects [108]. MAIT cells in metabolic disorders have an exacerbated pro-inflammatory phenotype (increased IL-17). Furthermore, MAIT cell activation is directly influenced by metabolites synthesized from vitamin B2 and B9 by gut bacteria [30].

There are various other examples of microbiota metabolites and co-metabolites that have been implicated in metabolic disease. For example, trimethylamine (TMA) is generated from dietary choline and carnitine by certain bacterial taxa, and converted in the liver to trimethylamine N-oxide (TMAO). This compound has been consistently associated with increased risk of cardiovascular disease and mortality in humans and found to promote atherosclerosis in mice [31–33], though the mechanism remains unknown. Importantly, certain microbiomes (e.g. vegans and vegetarians) are unable to produce TMA. Another example is the production of branched chain amino acids (BCAA) by microbiota. A microbiome with a higher potential to produce BCAA has been associated with obesity [13], and insulin resistance [34]. This is relevant because high circulating concentrations of BCAA may disrupt glucose homeostasis and have been associated with T2D and obesity [35]. These findings call for detailed studies not only of microbiota composition but also of functional potential and metabolomics.

2.3. Gut microbiota diversity is decreased in metabolic diseases

A lower microbial diversity has been shown in populations where the burden of obesity and metabolic disease is greater [36–39]. When comparing fecal microbiota between groups from urban areas in the United States, rural areas in Malawi, and Amerindians from the Venezuelan Amazon it was found that subjects from the United States had the least diverse microbiota and the Amerindians had the highest diversity [36], suggesting a link between urbanization, low fiber content of Western diets, microbiota and metabolic diseases.

In a French group of overweight and obese adults (MICRO-Obes study) a lower microbial diversity, quantified using metagenomic sequencing, was associated with higher inflammation, dyslipidemia, adiposity and insulin resistance [41]. Individuals with higher diversity had a healthier dietary pattern [11]. Similarly, in a Danish group of lean and obese adults diversity was inversely associated with corpulence, and individuals with lower diversity had lower abundance of butyrate-producing bacteria such as *Faecalobacterium prausnitzii*. Moreover, these subjects had a lower *Akkermansia muciniphila* to *Ruminoccocus gnavus* ratio potentially resulting in higher mucus degradation, and a microbial functional potential less capable of handling oxidative stress [4]. As diversity appears to be an important phenotype, it remains to be determined whether lower microbial diversity is a consequence or one of the causes for the deterioration of metabolic health in obese individuals. One possible mechanism could be that a greater microbial diversity may lead to a complete and complex functional repertoire that is able to metabolize complex carbohydrates and other substrates more readily [22].

Analysis using 16S rRNA sequencing has yielded consistent results with metagenomics [42,43]. In a subset from the TwinsUK cohort lower diversity was associated with greater abdominal adiposity [42]. There were associations between host genetic variants and adiposity-associated OTUs, corroborating the existence of a link between host genetics and gut microbiota. In the same cohort lower diversity was associated with greater weight gain over 9 years of follow up [44]. Although similar observations have been obtained with different methodologies, metagenomics provides greater insight to both the composition and functional potential of the gut microbiome. A recent meta-analysis compared studies that had reported richness and Bacteroidetes-to-Firmicutes ratio using 16S rRNA sequencing [45]. There was consistent yet narrowly lower richness in obesity. This was partly attributed to low statistical power and large inter-individual differences in microbiota composition. Human microbiota studies usually lack statistical power to detect the mild effect sizes of the microbiota. Future studies should be carefully designed and presented in a way that allows harmonization with previous reports in an effort to find consistencies in the field.

2.4. Gut bacteria species and host health: the example of *A. muciniphila*

Akkermansia muciniphila (*A. muciniphila*) is one of most widely studied gut bacterial species in relation to obesity and glucose homeostasis [46]. *A. muciniphila* is a gram negative bacterium that can use mucin glycans of the intestinal mucus layer as its sole source of energy. In overweight adults we showed that *A. muciniphila* was associated with insulin sensitivity, smaller adipocyte size, and in general better metabolic health [47]. The mechanistic link between *A. muciniphila* and human health remains unknown. There is, however, compelling evidence in mice on how *A. muciniphila* may impact the host. Everard et al. showed that *A. muciniphila* abundance was lower in obese mice, and that increasing its intestinal abundance either with oligofructose or live culture gavage led to decreased endotoxemia, body fat, improved insulin sensitivity, and protected integrity of the gut barrier [48]. More recently, an outer membrane protein of *A. muciniphila*, Amuc_1100, has been identified. It is involved in pilus formation and stimulates the Toll-like receptor 2 (TLR2) system thereby possibly participating in cross-talk with the host and maintaining epithelial layer integrity. When given to mice, this protein had similar beneficial effects on the host than live *A. muciniphila* with respect to body composition, insulin sensitivity and protection of intestinal barrier integrity [49]. However, the mechanisms of action of Amuc_1100 and *A. muciniphila* may only partially overlap. This study also showed that *A. muciniphila* could be grown in synthetic medium and that Amuc_1100 remains active after pasteurization, making it an attractive therapeutic target. In fact, protocols for its preparation and preservation for therapeutic applications have already been developed [50]. Currently Dr. Cani's group is conducting a clinical trial of *A. muciniphila* supplementation in overweight and obese adults, hypothesizing that it will improve metabolic health (NCT02637115).

A. muciniphila abundance may increase through dietary changes. In mice, diets enriched with oligofructose [48], fruit-derived polyphenols [51,52], fish oil [53], or a fiber-free diet [54] have all led to increased abundance in gut *A. muciniphila*. However, we did not find an association between food or nutrient intake, or diet quality and *A. muciniphila* abundance in humans [47]. The modulation of *A. muciniphila* through prebiotic intake requires further investigation.

While the potential of *A. muciniphila* as an individual species in clinical applications is clear, the effect of its microbial ecosystem and intestinal environment must be considered. For example, we showed that the best clinical status was seen in individuals with both higher abundance of *A. muciniphila* and microbial diversity [47]. *A. muciniphila* is a producer of acetate and propionate [55], which may be used as sources of energy by other bacterial species. Future research should study the impact of increasing *A. muciniphila* abundance on gut ecology, functional potential, and metabolite output.

A. muciniphila combines a series of unique qualities. As a mucin degrader it resides in close proximity to the epithelial barrier; it has been shown to interact with human epithelial cell lines in vitro [56]. This bacterium has an attenuating and wide-ranging effect on the immune system [57,58]: animal studies show that it mediates the negative effects of interferon gamma (IFNɣ) on glucose homeostasis [59], has lower capacity to stimulate interleukin 8 (IL-8) production and TLR4 response than certain pro-inflammatory species [56], and induces the TLR2 pathway [49] which may have a protective effect on the epithelial layer. Therefore, it may be through strengthening of the epithelial barrier, reduction of gut permeability and endotoxemia, attenuation of the immune system, and improvement of glucose homeostasis that *A. muciniphila* impacts the host. Furthermore, as a SCFA producer an effect on the gut-brain axis is expected.

3. Approaches to modulate gut microbiota and improve metabolic disease

3.1. Weight loss, prebiotic and probiotic interventions

Dietary interventions lead to compositional and functional modifications in the gut microbiota (reviewed in [60]) that have been correlated with improvements in various health outcomes. The field is currently trying to go beyond correlations and discern the role that microbiota plays in outcomes from these interventions (Fig. 1).

3.1.1. Calorie restriction and dietary interventions

To gain a better understanding of how gut microbiota could impact the host, one approach would be to study the traits that have been consistently associated with better health and determine how they change with a dietary intervention, and their relationship with clinical outcomes. In the MICRO-Obes study, mentioned above, 49 overweight and obese adults underwent CR for 6 weeks followed by a weight maintenance regime for 6 additional weeks. The individuals that had low gene richness at baseline experienced a significant increase after CR [41]. Conversely, richness did not change for those with higher baseline levels. This suggests that there may be a diversity ceiling in each individual that, once reached, cannot be overcome by a dietary intervention alone [22]. The reversibility of microbial diversity was studied in mice consuming high or low amounts of microbiota-associated carbohydrates. For the mice whose diversity was lowered due to low consumption of the carbohydrates, it took supplementation of both the carbohydrates and replacement of lost microbial groups to restore diversity [61]. This study has implications in the consequences of Western-style diets on gut microbiota and health.

Additional findings from the MICRO-Obes study showed that *A. muciniphila* actually decreased over the weight loss period in subjects that had the highest baseline abundance, and only moderately

increased for subjects with low baseline abundance [47]. Throughout the intervention, subjects with higher baseline *A. muciniphila* retained an abundance 100-fold greater than those with low baseline levels.

Clinical outcomes and microbial compositional shifts in response to dietary interventions are variable among individuals (i.e. as responders and non-responders) [62]. This raises the question of whether personalized interventions are the next step in unveiling how the microbiota influences health outcomes, and how response to interventions can be optimized. Using metadata from 800 healthy or prediabetic individuals, which included microbiota, lifestyle and clinical parameters, together with machine learning, researchers recently were able to device an algorithm that predicts a person's glycemic response to a given meal [63]. They demonstrated in both the main and validation cohorts that these personalized interventions led to improved postprandial glycemic responses. Another approach has been developed by Shoaie et al. whereby studying the complex interactions between host, diet and microbiota composition, a dietary intervention that would in theory increase microbial richness was designed [64]. Future research should determine whether a beneficial outcome could be induced in non-responders through the use of personalized interventions.

While even short term dietary interventions lead to compositional changes in the gut microbiota [65], it is becoming increasingly clear that long term dietary habits and microbiota composition prior to a dietary or CR intervention impact the individual's response [10,41,47]. For example, a 10-day dietary intervention induced a change in microbiota composition as early as 24-h after baseline, but not enough for individuals to change their enterotype [10]. Associations between enterotypes and diet were also stronger when studying habitual diet through FFQ than recent dietary intake through 24-h recall. Deeper understanding of the complex interaction between dietary profiles and gut microbiota is mandatory.

3.1.2. Bariatric surgery

Bariatric surgery (BS) is increasingly being used and an effective treatment for T2D [66]. T2D remission occurs in an overwhelming number of patients shortly after surgery. The reconfiguration of the gut architecture and change in gut microbiota are believed to play a role in metabolic ameliorations (reviewed in [60,67,68]). Studies of gut microbiota after BS in humans have had for the most part small sample sizes. Some consistencies between human and animal studies have been found. For example, abundance of *A. muciniphila* and *Proteobacteria* increased after BS [69–73]. Richness has been found to increase 3 months after Roux-en-Y gastric bypass (RYGB) [73,74] but to decrease 6 months after bilio-intestinal bypass, as measured with 16S rRNA sequencing [75]. Changes in *F. prausnitzii* abundance have been inconsistent, with increases being reported in some instances [76,77], and decreases in others [71,73].

The functional potential of the microbiome warrants further study in bariatric interventions. Interestingly, the microbial functional potential of 13 patients undergoing RYGB changed to a greater extent than the abundance of individual species [73], highlighting the importance of not only studying compositional changes but also function and even metabolomics output. In this study, the functional potential reflected a reaction by the gut microbiota to the changes in oxygen levels and nutrient availability in the gut after the surgery.

Strong evidence for involvement of microbiota in clinical outcomes long term after surgery has been shown [72]. Varying degrees of overweight were replicated in germ free mice receiving microbiota from obese women or women that had undergone RYGB, or vertical banded gastroplasty. Differences in microbiota composition, function, and metabolomic output were seen between the different groups. The type of BS certainly has an effect on compositional modifications of the gut microbiota because the intestinal architecture, pH, incretin and metabolite secretion, changes in bile production [67,78], and even post-intervention diet [79] differ across surgeries. In fact, findings in humans generally differ across the different types of BS and follow-up time [80–82].

Microbiota may mediate changes in the host after BS in various ways. Secondary bile acids generated by microbes may play a role in the beneficial effects after BS. Higher levels of both primary and secondary bile acids have been observed after RYGB in humans [80,83–85] and in mice [86]. In humans, although not directly linked with clinical outcomes, an early postoperative rise in total bile acids was attributed to a surge in bacterially-derived secondary bile acids. Mouse studies have unveiled the potential mechanisms linking secondary bile acids and shifts in gut microbial communities to metabolic outcomes after BS, suggesting pathways through the activation of farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor (TGR5) [40,87].

Patient characteristics prior to an intervention have an impact on gut microbiota changes and clinical response to the surgery. In the future one could envision a system whereby clinical background, lifestyle and gut microbiota analysis of the patient prior to surgery are systematically analyzed and taken into account in the prediction and optimization of their response [60].

3.1.3. Do prebiotics and probiotics aid in weight loss interventions?

There is compelling evidence that pre and probiotics may have a positive impact on metabolic health in animal models and in humans (reviewed in [60,88–90]). Here we focus on human studies that have added pre or probiotic supplementation to weight loss interventions to determine if they synergize with the treatment and improve response.

Few weight loss studies with pro or prebiotic supplementation have been conducted. There has been a tendency towards greater weight loss and metabolic improvement when probiotics are taken in combination with CR [91–93]. Among these, an RCT compared outcomes after 12 weeks of CR in overweight and obese women that were given either a probiotic yogurt or a low-fat yogurt. Although there was no difference in weight loss, the group taking the probiotic yogurt experienced an improvement in blood lipid profile and glucose homeostasis [93]. Few strains and doses have been tested and the gut microbiota has not been characterized in most of these studies. Future studies should include these elements, probably combining different bacterial strains.

There have also been few BS interventions measuring the impact of probiotics supplementation post-surgery. One study found that RYGB patients taking 2.4 billion *Lactobacillus* daily for 6 months after surgery experienced lower bacterial overgrowth, greater short term weight loss, and improved vitamin B12 status over patients not taking the probiotic [94]. However, two other studies with different design found no added benefit of probiotic supplementation over placebo in measured outcomes [95,96]. Similarly to CR interventions, more studies testing varying doses and strains of bacteria are needed to clarify whether there is an added benefit of probiotic supplementation after BS.

3.2. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) not only offers great potential for the treatment of a wide array of diseases, but is also a good model to study causality in the relationship between gut microbiota and human metabolic disorders. Animal microbiota transplantation studies have demonstrated that gut microbiota may modulate obesity and related disruptions in host metabolism such as insulin resistance [24,97,98]. Ridaura et al. showed that higher weight gain could be transferred through gut microbiota by fecal transplants from human twins discordant for obesity to germ free mice [13]. When co-housed lean and obese recipient mice received a low fat high fiber diet, microbiota from the lean mice colonized the obese recipient mice thereby transferring the phenotype. Even though it is uncertain whether FMT would be an effective therapy against metabolic syndrome, it is a good proof of concept approach to study the causal relationship between microbiota and obesity.

FMT is an effective therapy to treat enteric infections, particularly *Clostridium difficile*, and perhaps also intestinal chronic inflammatory

diseases [99,100]. The prospect of using FMT for the treatment of metabolic diseases has also been contemplated but results have not been as definitive as in previous applications. This question has been best explored in a study where obese men with metabolic syndrome received either autologous or allogenic fecal microbiota from lean healthy donors [101]. Fecal microbiota transplants were done by duodenal tube into the small intestine. Median insulin sensitivity, as measured by glucose disappearance rate during euglycemic hyperinsulinemic clamps, tended to improve in the allogenic group after 6 weeks of transplantation. This effect however was variable between individuals, with some responders and non-responders. While microbial diversity was lower in the overweight group, it increased after allogenic transplantation. The abundance of butyrate producing bacteria increased in both fecal and small intestine microbiota samples.

These patients were further followed for a total of 3 months post FMT to study the resilience of the microbiota. New species were found to coexist with pre-existing ones in the recipients especially if they were phylogenetically related [102]. In fact, strain replacement was more marked than uptake of donor species, calling for future studies to examine microbial composition at the strain level. There were different degrees of engraftment and resistance to donor colonization. The microbiota of one of the healthy donors stood out as having greater ability to invade several recipients. Resilience of certain strains was detected up to at least 3 months after transplantation, but the changes in microbiota were not associated with clinical outcomes. The lack of a more marked effect of FMT on insulin sensitivity may be partly explained by the selection and characterization of recipients. Insulin resistance as a complication of metabolic disruption may manifest similarly across patients, but some of these pathologies may be more dependent on the gut microbiota than others.

For FMT to be used in a clinical setting in the treatment of metabolic disorders future studies should consider: analysis of gut microbiota composition at the strain level, background intra-individual variation of the gut microbiota so that it is not confused with treatment-specific changes, and immune response of the recipient [102–104]. To go beyond FMT, perhaps sets of strains identified as beneficial should be tested as supplements. This would circumvent identification of compatible donors and the risks associated with transplantation of fecal matter. There is also the question of resilience. Even though microbiota composition may be transplantable, using this as a treatment would require repeated inoculations to the patient. Studying what changes in lifestyle factors are required in order to better maintain donor microbiota composition is warranted.

There has been a lack of standardization in the procedures of FMT, which makes comparisons across studies difficult. Standardization should include guidelines in donor selection, route of delivery, pretreatment preparation of recipient, and collection and processing of the fecal sample [103]. The impact of host microbiota composition and genetics on the effectiveness of FMT to treat obesity-associated morbidities also needs to be studied.

A better understanding of what is being transferred is also needed. As explained by Bojanova and Bordenstein, not only bacteria but also colonocytes, metabolites, and other microorganisms such as viruses, phages, fungi, archaea, and protists are also transferred [105]. Focus has usually been given to bacteria but the other components are likely also having a biologically significant impact.

4. Conclusions

We have summarized current knowledge on gut microbiota in relation to obesity and clinical care. In order to broaden our understanding in this field and move onto established clinical applications, which may include personalized interventions, careful consideration should be given to study design, statistical power and method selection. Various confounders of gut microbiota observations, such as stool consistency and pharmacology [106] should be routinely measured. Furthermore, elements from both host and environment that influence gut microbiota composition and function should be studied through data integration analytical methods. This kind of approach is being applied in the METACARDIS study, where extensive phenotyping is being gathered from individuals representing the different stages of metabolic disease (NCT02059538). Finally, investigation of gut microbes in relation to metabolic disorders needs to include bacterial differences at the strain level, as well as other members of the microbial community, such as the enteric virome [107]. The gut microbiota is an important player in metabolic health and even though the mechanisms are not fully understood, further advances will be made through methodologic harmonization, deep phenotyping, and integration of knowledge.

Conflicts of interest

None.

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