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The Gut Microbiome and Obesity

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Abstract The gut microbiome consists of trillions of bacteria which play an important role in human metabolism. Animal and human studies have implicated distortion of the normal microbial balance in obesity and metabolic syndrome. Bacteria causing weight gain are thought to induce the expression of genes related to lipid and carbohydrate metabolism thereby leading to greater energy harvest from the diet. There is a large body of evidence demonstrating that alteration in the proportion of *Bacteroidetes* and *Firmicutes* leads to the development of obesity, but this has been recently challenged. It is likely that the influence of gut microbiome on obesity is much more complex than simply an imbalance in the proportion of these phyla of bacteria. Modulation of the gut microbiome through diet, pre- and probiotics, antibiotics, surgery, and fecal transplantation has the potential to majorly impact the obesity epidemic.

Keywords Microbiome · Obesity · Microbiota · Diet · Prebiotic · Probiotic · Microbial balance · *Bacteroidetes* · *Firmicutes*

Introduction

The human microbiome encompasses several trillion microbes residing in the gut and the genes that are encoded by them [1, 2]. The majority of these microbes reside in the colon, where they are present in a concentration of 10^9–10^{12} CFU/mL [3]. There is clear evidence from animal and human studies that the gut microbiome plays a crucial role in the functioning of the digestive tract and in harvesting energy from the diet [4, 5].

The microbiome maintains the integrity of the intestinal epithelial barrier thereby offering protection from pathogenic bacterial colonization [6, 7]. In addition, the microbiome is essential for metabolizing indigestible polysaccharides and in the absorption of short-chain fatty acids produced by bacterial fermentation [8]. It also plays a key role in the regulation of intestinal transit, thereby affecting the amount of energy absorbed from the diet [9]. These and other key functions elucidate the crucial role of the microbiome in weight gain and metabolism and are reviewed in more detail [10, 11].

Current data estimates that approximately 600 million people around the world are obese, with an additional 1.9 billion people being overweight [12]. One of the most cited microbiome related factors differentiating obese and healthy individuals has been the shift in the proportion of bacterial flora belonging to the *Firmicutes* and *Bacteroidetes* phyla which together comprise about 90 % of the microbiota of the adult gut [13]. The *Firmicutes* phylum comprises gram positive organisms from greater than 200 different genera including *Catenibacterium*, *Clostridium*, *Eubacterium*, *Dorea*, *Faecalibacterium*, *Lactobacillus*, *Roseburia*, *Ruminococcus*, and *Veillonella* while the *Bacteroidetes* phylum consists of gram negative bacteria from approximately 20 genera including *Bacteroides*, *Odoribacter*, *Prevotella*, and *Tannerella* [14]. Studies using 16S rRNA gene sequencing of the distal gut microbiota of *ob/ob* mice show that there is significant reduction in the abundance of *Bacteroidetes* and a similar increase in the *Firmicutes* phyla in obese mice [8]. However, subsequent studies have shown discrepancies in the proportion of *Bacteroidetes/Firmicutes* and its relation to obesity and it is

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likely that the influence of the gut microbiome on obesity is much more complex than simply an imbalance in the proportion and or interaction of these phyla.

Obesity as a Risk Factor for Cancer

Recent studies suggest that obesity is a risk factor for developing cancers of the endometrium, breast, cervix, ovary, colon and rectum, esophagus, kidney, pancreas, prostate as well as several hematological malignancies [15]. Obesity is also associated with increased mortality and worse outcomes in cancer patients [16]. This makes obesity a major preventable risk factor in the development of cancer. However, most weight reduction strategies are often unsuccessful in the long term and there is an increased focus on weight loss maintenance strategies [17]. With its close interaction with energy balance and metabolism, the gut microbiome is likely to be a major component in future weight loss and cancer prevention strategies. In this paper, the key findings from animal and human studies as well as the role of diet and modulation of the microbiome are discussed.

Experimental Evidence for the Link Between Microbiome and Obesity

Studies in animals have demonstrated that the association between the microbiome and fat deposition and resultant development of metabolic syndrome may begin as early as the prenatal period [18•]. Bacteria from pregnant mice gut have been demonstrated in mesenteric lymph nodes and are thought to possibly be transferred through the placenta into the fetus, where bacteria have been demonstrated in meconium, which is the first stool passed by the fetus and thought to be sterile except for the bacterial flora ingested during the process of birth [19]. The mode of delivery determines the initial bacterial composition of the gut with vaginally born piglets showing higher numbers of *Bacteroides*, *Prevotella*, and *Clostridium* species compared to piglets born by C-section [20].

Germ free mice have been shown to remain lean despite a high-fat, sugar rich diet [21]. This is thought to be secondary to two mechanisms: elevated levels of fasting-induced adipose factor (*Fiaf*), a circulating lipoprotein lipase inhibitor, and increased activity of phosphorylated AMP-activated protein kinase (AMPK) [21]. Bacteria in the gut suppresses the expression of *Fiaf* and of AMPK in the liver and skeletal muscle, leading to weight gain from a carbohydrate and fat rich diet [21]. One of the landmark animal studies demonstrating the role of gut microbiota in obesity demonstrated that the introduction of normal cecal microbiota from conventional mice led to a 60 % increase in body fat and insulin resistance within 2 weeks in adult germ free mice despite reduced food intake [4]. This was thought to be secondary to the role of bacteria in the absorption of monosaccharides from the gut with downstream induction of triglyceride production in the liver and insulin resistance [4].

Animal models have also been key to understanding the role of microbiota in energy harvest from the diet. Using distal gut bacterial 16S rRNA sequencing, Turnbaugh et al. demonstrated that *ob/ob* mice have a 50 % reduction in *Bacteroidetes* and an proportional increase in *Firmicutes* and *Archaea* resulting in increased fermentation of dietary polysaccharides and lesser energy remaining in feces as measured by bomb calorimetry [8]. This trait was also thought to be transmissible, with the introduction of *ob/ob* mice microbiota in germ free mice resulting in a 20 % greater increase in total body fat than introduction of lean mice microbiota [8].

The findings of microbial alteration in obesity demonstrated in animal studies have been largely mirrored in human studies [22]. Ley et al. demonstrated that obese participants on a calorie-restricted diet had an increase in the proportion of *Bacteroidetes* using 16S rRNA sequencing over the period of 12 months which correlated with weight loss [23]. Reduced levels of *Bacteroidetes* and microbial diversity have been demonstrated in monozygotic and dizygotic obese twins compared to their lean twins with the metagenomes of the obese group being higher in energy harvesting genes related to lipid and carbohydrate metabolism [24]. However, there is conflicting data regarding *Bacteroidetes*, with other studies showing none or positive association with weight gain and obesity [25–27]. Key studies on the role of the gut microbiome on development of obesity in humans from literature and their findings are summarized in Table 1.

Dietary Influences on Microbiome and Obesity

Being the substrate for microbial metabolism, diet has a major role to play in shaping the individual microbiome [38•]. The mode of delivery has a large role in the initial composition of microbiota in newborns, with infants with vaginal births having gut flora dominated by *Lactobacillus*, *Prevotella*, or *Sneathia* whereas cesarean birth babies had predominance of skin flora such as *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* [39]. Postnatally, breast fed babies have been demonstrated to have a predominance of *Bacteroidetes*, while formula fed infants have higher *Firmicutes* and *Verrucomicrobia* [40]. The effect of diet is clearly demonstrated by the changes seen in infant gut microbiome with introduction of different foods. This was elegantly demonstrated in a study by Koenig et al. where successive fecal samples were collected from one infant along with a diary of diet and health over a period of 2.5 years to study the development of the infant microbiome and study the effect of diet and health status on bacterial composition [41]. Using 16S rRNA gene sequencing,

Table 1 Studies in humans showing association of gut microbiome with obesity

Study	Subjects	Methods	Toward obese status	Toward lean status
Armougom et al. 2009 [28]	20 obese, 9 anorexic patients, 20 normal BMI	16s rRNA PCR	↑ *Firmicutes* ↓ *Bacteroidetes*	
Balamurugan et al. 2010 [29]	15 obese 7 normal BMI	16s rRNA PCR	↑ *Faecalibacterium prausnitzii*	↓ *Firmicutes*
Collado et al. 2008 [26]	18 overweight, 36 lean	FISH/flow cytometry and qPCR	↑ *Bacteroidetes* ↑ *S. aureus*	
Damms-Machado et al. 2015 [30][a]	5 obese post-sleeve gastrectomy, 5 obese on very low calorie diet	16S rRNA gene sequencing		↑/↓ *Bacteroidetes* ↓/↑ *Firmicutes*
Duncan et al. 2008 [27]	33 obese, 14 lean	FISH		↓ *Roseburia* ↓ *Eubacterium* ↑ *Clostridium*
Furet et al. 2010 [31]	30 obese, 13 lean	qPCR	↓ *Bacteroides* ↓ *Prevotella*	
Kalliomaki et al. 2008 [32]	25 obese or overweight, 24 lean	qRT-PCR and FISH/ flow cytometry		↑ *Bifidobacteria* ↓ *S. aureus*
Ley et al. 2005 [23]	12 obese, 2 lean	16S rRNA sequencing		↑ *Bacteroidetes*
Nadal et al. 2009 [33]	39 overweight or obese subjects	qPCR	↓ *Clostridium histolytica* ↓ *Coccoides* ↓ *E. recta*	↑ *Bacteroidetes* ↑ *Provotella*
Santacruz et al. 2009 [34]	36 overweight	qPCR		↑ *Bacteroidetes* ↑ *Lactobacillus*
Schwiertz et al. 2009 [25]	33 obese, 35 overweight, 30 lean	qPCR	↑ *Bacteroidetes*	↑ *Methanobrevibacter*
Sotos et al. 2008 [35]	8 overweight or obese	FISH	↓ *Roseburia* ↓ *Eubacterium*	↓ *Enterobacteriaceae* ↓ sulfate reducing bacteria
Turnbaugh et al. 2009 [24]	6 pairs of obese twins and 1 weight discordant pair	16S rRNA by Sanger and 454 pyrosequencing	↓ *Bacteroidetes* ↑ *Actinobacteria* ↑ *Firmicutes*	
Woodard et al. 2009 [36]	44 obese undergoing RnY gastric bypass	Prospective trial of probiotics post-RnY gastric bypass		↑ *Lactobacillus*
Zhang et al. 2009 [37]	3 post-gastric bypass, 3 obese, 3 lean	Sanger and 454 sequencing, qPCR	↑ *Archea*	↑ *Firmicutes*

[a] Study showed both sleeve gastrectomy and low calorie diet resulted in weight loss but with an inverse relationship between *Bacteroidetes/Firmicutes*

the authors demonstrated increasing bacterial diversity over time, with ingestion of solid foods causing a sustained increase in *Bacteroidetes* spp., fecal short-chain fatty acid levels, enrichment of genes associated with carbohydrate utilization, vitamin biosynthesis, and xenobiotic degradation [41].

The impact of different diets on the microbiome has been well demonstrated. In a study comparing the gut microbiota of children consuming a high fiber diet in Burkina Faso to a modern western high-fat/high-sugar diet in Europe, De Filippo et al. demonstrated that the gut flora in children from West Africa had a higher prevalence of *Bacteroidetes* and depletion in *Firmicutes* with some bacterial species being unique for fiber degradation such as *Prevotella* and *Xylanibacter* which were absent in the children from Europe [42]. In comparison, European children had higher *Firmicutes* and *Proteobacteria* [42]. Studies in animals have shown similar results, with introduction of a western high-fat high-sugar diet leading to restructuring of the gut microbiota with increase in the normally low abundance *Mollicute* lineage in the *Firmicutes* to flourish and causing suppression of *Bacteroidetes* [43]. Microbial transplantation of this *Mollicute* rich flora in to germ free mice led to higher adiposity than transplantation of flora from lean mice suggesting that the restructured flora may promote superior processing of sugars and fat [43]. Weight loss in obese humans with either a fat- or carbohydrate-restricted diet has been demonstrated to lead to a decrease in this *Mollicute* predominance with an associated increase in the abundance of *Bacteroidetes* [44]. However, the population shift in bacterial flora is not restricted only to changes in fat and sugars in diet.

With the obesity epidemic mirroring the increase in processing of food, there is also emerging data that the gut microbiome is adversely impacted by the use of preservatives and emulsifiers used in the packaging of food. Chassaing et al. demonstrated that the use of relatively low concentrations of two commonly used emulsifiers, namely carboxymethylcellulose and polysorbate-80, induced alterations in the gut flora with reduced *Bacteroidetes* and increase in *Ruminococcus*, *Verrucomicrobia*, and *Proteobacteria* [45••]. This change was associated with the development of colitis and onset of metabolic syndrome with increase in adiposity and weight and impaired glycemic control. This trait was also transmissible by fecal transplantation into germ free mice [45••]. Furthermore, environmental influences may also alter the composition and biodiversity of the gut microbiome which ultimately impacts the aforementioned pathways [46].

Modulation of the Microbiome Using Pre- and Probiotics

The significant impact of diet on the microbiome in the development of obesity and metabolic syndrome has led to renewed interest in modulation of the human gut microbiota, especially through the use of pre- and probiotics [47]. This effect can both be positive and negative on the development of obesity, as evidenced in animal husbandry where probiotics containing *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* species have long been used for inducing weight gain [48]. Prebiotics are nonviable food components that confer health benefit on the host associated with modulation of the gut microbiota such as inulin, fructo-oligosaccharides, and galacto-oligosaccharides, resistant starch, xylo-oligosaccharides, and arabinoxylan-oligosaccharides [47, 49, 50]. Prebiotics promote the growth of beneficial bacteria and could slow adiposity by inducing short-chain fatty acid (SCFA) production which modulates appetite regulating hormones and enzymes involved in lipogenesis [51]. Prebiotics such as inulin have also been thought to stimulate glucagon-like peptide 1 secretion which could improve glucose homeostasis [51–53]. Some of these positive effects of prebiotics have also been seen with increased use of dietary fibers, which also alter the gut microbiome and could work through similar mechanisms [54]. Probiotics are living microorganisms such as *Lactobacillus* and *Bifidobacteria* which, when ingested, provide health benefits, either directly or through interactions with the host or other microorganisms [55]. These bacteria compete for nutrients with existing microbiota thereby diminishing the numbers of bacteria with negative effects. In addition, probiotics could decrease adiposity by deconjugation of bile acids which are less efficient at lipid absorption from the diet [56]. There are abundant data in animals and limited data in humans that prebiotics mitigate lipogenesis, inflammation and insulin resistrance and promote weight loss [57]. A combination of pre-and probiotics has been termed synbiotics, and these could have a higher impact on the composition of the host microbiome by introducing bacteria while inducing an environment more favorable to the newly ingested bacteria. As we learn more about the gut microbiome and its impact on obesity, there is the potential to engineer a favorable metabolic environment for improved lipid and glucose metabolism through synbiotics.

Influence of Antibiotics on the Microbiome

Along with diet, pre- and probiotics, the use of antibiotics is the other major intervention which can significantly impact the development of obesity by altering the gut microbiota (Fig. 1 [48]). This is well established in the agricultural industry which widely uses antibiotics such as bambermycin, avilamycin, efrotomycin, and ionophore antibiotics (monensin, salinomycin, narasin, and lasalocid) exclusively for weight gain and increased growth [58]. In a study administering low dose penicillin, chlortetracycline, or vancomycin to young mice at weaning, Cho et al. demonstrated increased adiposity in young mice along with taxonomic changes in the

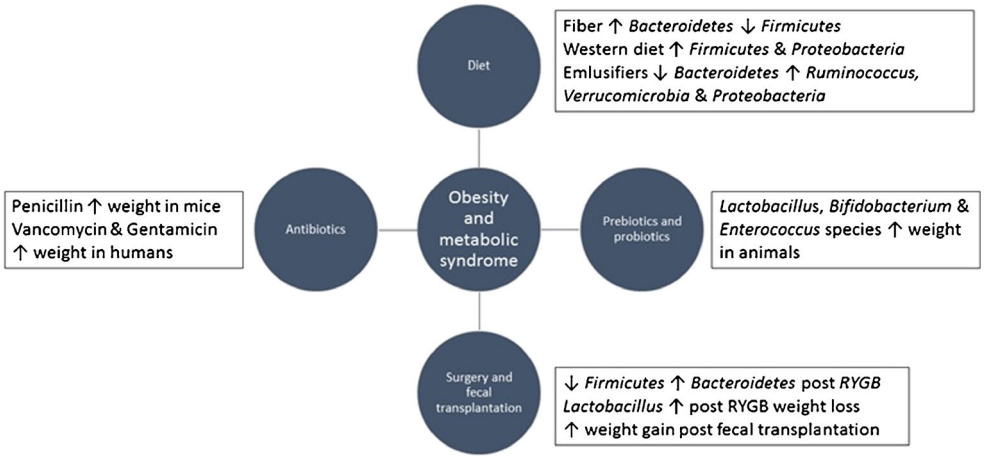

Fig. 1 Modulation of the microbiome influences development of obesity and metabolic syndrome

microbiome, changes in copies of key genes involved in the metabolism of carbohydrates to short-chain fatty acids, increases in colonic short-chain fatty acid levels, and alterations in the regulation of hepatic metabolism of lipids and cholesterol [59]. In a follow up study by the same group using low dose penicillin in weaning mice, Cox et al. demonstrated changes in ileal expression of genes involved in immunity as well as enhancement in the effect of diet-induced obesity by its effects of gene expression in the liver, metabolic hormone levels, and visceral adiposity [60••]. This trait was transferrable, with germ free mice transplanted with the microbiota of the treated mice showing similar effects showing that the altered microbiota and not the antibiotics per se cause promotion of adiposity [60••]. This effect of antibiotics inducing weight gain has also been demonstrated in humans with a study by Thuny et al. showing ≥10 % increase in BMI in adults older than 65 years after a 6-week course of vancomycin and gentamicin for infective endocarditis but not in controls or patients treated with other antibiotics [61]. The eradication of *Helicobacter pylori* with antibiotics has also been an area of interest, with the population decline in *H. pylori* mirroring the increase in obesity [62]. *H. pylori* eradication has been demonstrated to significantly increase post-prandial ghrelin and leptin levels, with previously *H. pylori* positive individuals having significantly greater increase in BMI over 18 months compared to negative individuals [63]. However, this effect could be mediated by the antibiotics used in treatment and not associated with *H. pylori*, since studies from developing countries show positive association of *H. pylori* infection with obesity [64, 65].

Iatrogenic Gut Microbiota Alteration

Though diet and the use of pre- and probiotics modulate the gut microbiome [66], their effect is relatively gradual compared to two widely used treatments with more drastic and lasting change in the microbiota, namely fecal transplantation and gastric bypass surgery. Fecal transplantation for recurrent *C. difficile* bacteremia has been shown to be very effective for cure with the rates of resolution of symptoms of diarrhea being much superior to antibiotics [67]. However, the long term effects of fecal transplant are still unknown with the FDA classifying fecal transplantation as an experimental treatment. Alang et al. reported a case of a 32-year-old woman with a 41-lb unintentional weight gain following fecal transplantation from a related, overweight donor [68•]. This is not surprising, given the large body of evidence from animal studies showing increased weight gain in germ free mice with fecal transplantation from obese mice [8]. With increasing number of fecal transplantations, studies focusing on the long term effects on weight gain and changes in the metabolic profiles of recipients will need to be done. Another area of emerging interest is the change in the gut microbiome induced by bariatric surgery [69•]. A study by Zhang et al. showed significant decrease in *Firmicutes* in post-gastric-bypass individuals compared to normal-weight and obese individuals [37]. These results were also mirrored by Furet et al. who demonstrated increased *Firmicutes* to *Bacteroidetes* at baseline in obese patients before Roux-en-Y gastric bypass (RYGB) surgery and a subsequent decrease in this ratio at 3 and 6 months post-surgery with accompanying weight loss, Table 1 [31]. The post-RYGB gut microbiome is also unique, given the lack of an acidic stomach which enables easier modulation of the gut flora with probiotics. A randomized trial using supplementation of *Lactobacillus* probiotics post-RYGB demonstrated 9 % greater weight loss in the treatment arm than in the placebo arm at 3 months [36].

Conclusion

There is strong evidence from animal and human studies supporting the role of the gut microbiome in the development of obesity. Modulation of the gut microbiota through diet, pre- and probiotics, antibiotics, and surgery provides the unique ability to influence weight and metabolic profile in either

direction. Future studies will be needed to further clarify the complex interactions between the various species of bacteria and to generate evidence toward interventions which will help slow down the escalating global epidemic of obesity.

Compliance with Ethical Standards

Conflict of Interest George Kunnackal John and Gerard E. Mullin declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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