Curr Infect Dis Rep (2013) 15:25–30
DOI 10.1007/s11908-012-0301-5

The Role of the Manipulation of the Gut Microbiota in Obesity

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Published online: 6 November 2012

Abstract The manipulation of the gut microbiota by diet, antibiotics, or probiotics could promote, prevent, or reverse the development of specific diseases, including obesity. A link has been proposed between obesity and the growth promoters (probiotics and antibiotics) that have been used in animals for more than 40 years to induce weight gain. Several species of the *Lactobacillus* genus that are frequently used as probiotics for human consumption merit particular attention because they are increased in the gut microbiota under high-fat diets, are more abundant in obese humans, and are selected by growth-promoter antibiotics; moreover, the administration of these bacteria in experimental models is linked to the development of obesity. However, other species or strains of the same genus are associated with an antiobesity effect. Newborns and infants are a particularly susceptible population in which the administration of antibiotics or probiotics could be related to the development of obesity in adulthood.

Keywords Gut microbiota · Manipulation · Obesity · Weight · Antibiotics · Probiotics · *Lactobacillus* · *Bifidobacterium* · Weight gain · Weight loss · Newborns · Bacteria · Diet · Meta-analysis · Enterotypes

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Introduction

One of the strangest phenomena that one of us (D.R.) has observed in his career, which has included the writing of over 1,500 scientific papers, is the lack of scientific communication between fields. Gut microbiota manipulation is an extreme example of this phenomenon [1, 2]: Despite the widespread manipulation of the gut microbiota in farm animals in all industrialized countries to induce weight gain in these animals (e.g., pigs, calves, and chickens) [3, 4], this practice has been neglected for a long time in the field of medicine [5]. The manipulation of the gut microbiota is achieved in farm animals not only through the use of low doses of antibiotics, but also through probiotics administration, including mainly *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* species.

During the course of our work on *Lactobacillus ingluviei* [6], we serendipitously discovered that this bacterium induced significant weight gain in chickens [7]. These findings were supported by similar studies of ducks and mice [8, 9]. We believe that this discovery provided the first indications to the scientific community of the existence of a possible link between growth promoters (probiotics and antibiotics) and the current epidemic of obesity [1, 5]. This work has led to vehement reactions from researchers who are funded by the food industry [10].

On the whole, work on probiotics is currently hampered by the fact that the vast majority of probiotics investigators are subsidized or have previously been sponsored by the food industry. In contrast to research in other sectors, such as the pharmaceutical industry, studies in the food industry never inform the public about the conflicts of interest that are associated with this type of financing. Most of the works

and symposia that promote the positive effect of probiotics are sponsored by the food industry [11].

The Observed Modifications of the Gut Microbiota in Obesity

This topic has recently been extensively reviewed [12••]. Ley and Gordon first observed that different digestive microbiota were present in obese subjects than in lean subjects at both the bacterial taxonomic [13] and gene functional [14] levels and determined that the microbiota of obese subjects displayed enhanced energy-harvesting abilities. Numerous subsequent studies have associated particular bacterial genera and species either with obesity (*Lactobacillus*, *Staphylococcus*, and *Faecalibacterium*) or with a lean phenotype (*Bacteroidetes*, *Methanobrevibacter*, and *Bifidobacterium*) (see Fig. 1; Table 1) [12••]. Notably, we linked *Bifidobacterium* with a lean phenotype in a meta-analysis that included five studies with consistent results from four countries (Finland, Germany, Spain, and China), demonstrating that this type of obesity-associated alteration transcends geographical diversity [12••].

Within the *Lactobacillus* genus, different species are associated with an obese profile (*Lactobacillus reuteri*) or a lean profile (*Lactobacillus gasseri* and *Lactobacillus plantarum*) such that the microbiota composition is related to body weight and obesity at the species level, which is extremely relevant for clinical studies and for the management of obesity. Similar to our pioneering work on *Lactobacillus* [15], other research groups have found correlations between the body mass index (BMI) and the *Lactobacillus* count by culture [16•], particularly for one bacterial species, *L. sakei*.

In pregnant women, the physiological increase in adiposity in the third quarter appears to be associated with a profound change in the digestive microbiota [17]. Santacruz et al. [18] reported that pregnant women with excessive weight gain had digestive microbiota that were enriched in *Staphylococcus*, Enterobacteriaceae, and *Escherichia coli* but depleted in *Akkermansia muciniphila* and *Bifidobacterium*. In this study, the *Bifidobacterium* genus was again associated with a statistically significant protective role against overweight and obese tendencies.

By contrast, Arumugam and the MetaHIT consortium [19] did not report any association between obesity and newly identified bacterial taxonomic enterotypes; however, their study was not designed to elucidate these types of correlations. Employing the same approach, Fraser et al. [20] identified three communities of interacting bacteria in the Old Order Amish sect that were similar to the three enterotypes that were described by Arumugam. Regression analyses for phenotype clusters found significantly different BMI among these enterotypes with a very significant *p*-value for network effect (Supplemental Table 2 of [20]).

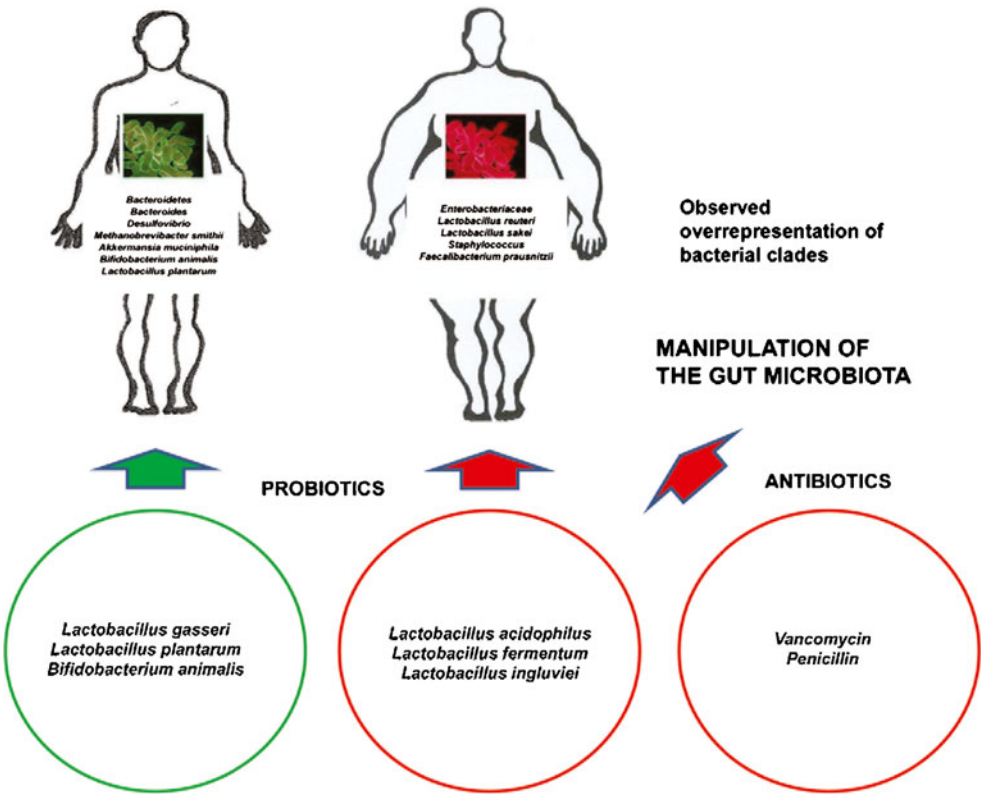

Fig. 1 The role of the manipulation of the gut microbiota in obesity. Specific bacterial clades in the human gut microbiota have been linked with obesity or lean status. Consistent data report that administration of such bacteria through oral probiotics administration could lead to weight change accordingly. Antibiotics have been linked with weight gain plausibly by the perturbation of the established gut microbiota increasing obesity-associated bacteria and decreasing lean-associated bacteria

The Effects of Diet

Diet drastically changes the diversity and composition of the digestive microbiota [21]. Ley et al. demonstrated that a low-calorie diet increased the proportion of *Bacteroidetes* in the gut microbiota of obese individuals to a level similar to the *Bacteroidetes* level of lean controls [13]. Recently, Murphy et al. [22•] found that a high-fat diet was associated with the opposite effect in mice, producing a decrease in *Bacteroidetes* and an increase in *Firmicutes*, and observed that this change corresponded more specifically to an increase in *Lactobacillus* and a decrease in *Bacteroides*. All of these results favor correlations between *Bacteroidetes* and lean status and between higher levels of particular *Lactobacillus* species and obese tendencies. The existence of apparently paradoxical significant results that indicate a correlation between a high-fat diet and decreased *Lactobacillus* levels [23, 24] does not contradict the role of *Lactobacillus* in the regulation of weight but stresses the importance of species-level analyses of the *Lactobacillus* in the microbiota [25, 26].

A structural resilience of the gut microbiota under high-fat dietary perturbations has been reported [27]; thus, it is unlikely that a diet that is devoid of probiotics or antibiotics can irreversibly alter the gut microbiota. However, many "natural" probiotics that are present in normal human food shape the digestive microbiota. In particular, lactobacilli are important in the production of foods that require lactic acid fermentation, such as dairy products (yogurt and cheese), fermented vegetables (olives, pickles, and sauerkraut), fermented meats (salami), and sourdough bread [28].

Gut Microbiota Transplantation

The most convincing evidence of causality between gut microbiota and obesity is the observation that obese phenotypes are transmissible by the transplantation of gut microbiota from obese donors; these transplantation experiments were first performed by Ley and Gordon [14, 17, 29]. More recently, Vijay-Kumar et al. [30••] found that the transplantation of the microbiota of obese TLR5-KO mice into axenic WT mice conferred many aspects of the donor phenotype, including hyperphagia, obesity, hyperglycemia, insulin resistance, colomegaly, and a high level of proinflammatory cytokines. This result suggests that the modification of the intestinal flora is a contributing factor in the development of obesity.

Antibiotics

Antibiotics have been used for decades as growth promoters [3, 4, 31] and are used in humans for the treatment of malnutrition [32]. In the 1950s, pioneering studies showed that administration of tetracyclines in premature infants [33] and young recruits of the U.S. Navy [34] was associated with weight gain. In patients with cystic fibrosis, long-term prescriptions of minocycline [35] or azithromycin [36–38] have been associated with weight gain. Other antibiotics have been associated with weight gain in humans, such as erythromycin [39], cotrimoxazole [40], or clarithromycin [41]; the last of these drugs is associated with acquired

Table 1 Scientific evidence suggesting that specific *Lactobacillus* species/strains may support infectious obesity

Evidence	References
Obese gut microbiota. Specific *Lactobacillus*[a] are found more frequently and abundantly in obese humans	Armougom, PlosOne, 2009 [15] Million, Int J Obes [London], 2012 [25] Stsepetova, Br J Nutr, 2011 [16•]
Diet. Specific *Lactobacillus*[b] are increased in the microbiota in mice with high-fat diet induced obesity	Murphy, Gut, 2012 [22•]
Antibiotics. Specific *Lactobacillus*[c] are selected by avoparcin and vancomycin, which are antibiotics that produce weight gain in animals and humans	Robinson, Gut Microbes, 2010 [53] Thuny, PlosOne, 2010 [44] Cho, Nature, 2012 [42]
Probiotics. The administration of specific *Lactobacillus*[d] in farm animals and experimental models is linked to acquired obesity.	Khan, Br Poult Sc, 2007 [7] Angelakis, Microb Pathog, 2012 [10]

[a] *L. reuteri* has been found more frequently and abundantly in the gut microbiota of obese individuals by qPCR. In the same study, *L. plantarum* and *Lactobacillus paracasei* were found more frequently in lean individuals by culture [25]. The *L. sakei* count in culture has also been correlated with BMI [16•]

[b] However, a seemingly paradoxical result reports a decrease in *Lactobacillus* under a high-fat diet [HFD] [23, 24], stressing the importance of analysis at the species level. One study reported a decrease in *L. gasseri* under an HFD [54]

[c] *Lactobacillus rhamnosus*, *L. paracasei*, *L. plantarum*, *L. fermentum*, *and L. reuteri* are resistant to glycopeptides, whereas *L. acidophilus*, *L. gasseri*, *Lactobacillus crispatus*, *Lactobacillus johnsonii*, *and Lactobacillus delbrueckii* are susceptible to vancomycin [55]

[d] In our recently published meta-analysis [26], *L. ingluviei*, *L. fermentum*, and *L. acidophilus* are associated with weight gain, whereas *L. plantarum* and *L. gasseri* exhibit the opposite trend

obesity in the context of eradicating *Helicobacter pylori*. Recently, Cho et al. [42] demonstrated that minor doses of antibiotics may produce the same type of growth-promoting phenomena in mice. Penicillin and vancomycin have both been tested in this context; these antibiotics cause mice to experience a change in their gut microbiota that is associated with weight and adiposity gains. Interestingly, the number of *Lactobacillaceae* sequences tripled in the group that received antibiotics. The same research group found that antibiotics-receiving infants are larger than controls [43••]. We reported that weight gain was observed in patients who were receiving vancomycin [44]; this molecule is similar to avoparcin, which is heavily used as a growth promoter in the farm industry. These data, in combination with the fact that the microbiota of obese individuals may be enriched in lactobacilli [15] (which are among the gram-positive bacteria that are resistant to vancomycin), strongly suggest that antibiotics may impact the metabolic phenotype through the pervasive perturbation of gut microbiota [45]; in particular, growth-promoter antibiotics appear to increase the prevalence of specific bacterial species that have been associated with obesity and to decrease bacterial species linked to a lean status.

Probiotics

A number of probiotics have been used for more than 40 years, with a European regulation on their use, to fatten animals, particularly young pigs. The existing literature regarding probiotics has recently been subjected to a meta-analysis that indicates that certain microbes are likely to cause weight gain in humans and animals, such as *Lactobacillus acidophilus*, *Lactobacillus fermentum*, *L. ingluviei*, and perhaps *L. reuteri* [25, 26]. In animals, studies have revealed that *L. reuteri* can increase weight gain in situations in which growth depression is caused by a lack of dietary protein and not by contagious disease [46]. This observation raises the possibility that *L. reuteri* improves the intestines' ability to absorb and process nutrients and increase food conversion. Moreover, Nahashon et al. [47] reported that feeding laying Leghorns with *Lactobacillus* significantly improved the retention of fat and produced increased cellularity of the Peyer's patches of the ileum. In an experimental model, we demonstrated that young mice fed with two doses of *L. ingluviei* experienced not only a weight gain, but also an increase in fat and the presentation of a metabolic syndrome profile [9]. In humans, bottle-fed infants receiving an *L. acidophilus* strain exhibited significant weight gain, as compared with controls [48].

By contrast, certain strains or species, such as *L. gasseri* and *L. plantarum*, appear to have a protective effect against obesity [26]. In a randomized controlled trial, Kadooka found that the oral administration of *L. gasseri* in adults with obese tendencies resulted in weight loss [49••], whereas in animal models involving a high-fat diet, *L. plantarum* resulted in weight loss through the secretion of conjugated linoleic acid [50].

It is notably difficult for allochthonous microbes introduced into a stable ecosystem to establish themselves, particularly if members of the same bacterial genus are previously established. This phenomenon is referred to as "competitive exclusion" and is the reason that a probiotic strain is frequently detectable in the gut only while the continued consumption of a probiotic product is occurring [28]. Conversely, Tannock reported that *L. reuteri* persist at constant population levels throughout life in the guts of formerly *Lactobacillus*-free mice that were inoculated by mouth with a pure culture on a single occasion [28]. In humans, Abrahamsson et al. [51•] demonstrated that the administration of *L. reuteri* to the mother and newborn during the first year of life was associated with a significant increase in the gut microbiota concentration of *L. reuteri* at 24 months, which was 1 year after the end of the administration period. Unfortunately, the weight of these subjects was not evaluated. These data support a dramatic and pervasive modification of the gut microbiota by probiotics administered in the first months of life. Long-term safety studies must certainly be conducted to assess whether *Lactobacillus* probiotics in newborns may favor obesity in adulthood.

Conclusion

Since 2006, when the first scientific studies on the metagenomic analysis of the human microbiota found a gut microbiota alteration that was associated with obesity [13, 14], a link has been proposed between the growth promoters that have been used for more than 40 years to induce weight gain in farm animals and the occurrence of continuous weight gain in humans. It appears necessary for the scientific community to analyze humans via prospective epidemiological studies. The role of products used in the food industry to fatten animals must be clarified to determine whether these products cause the same effects in humans. Several *Lactobacillus* species that are frequently used as probiotics for human consumption, typically in certain yogurts and juices [52], deserve special attention because they are increased in the gut microbiota of mice with high-fat-diet-induced obesity, they are found more frequently and abundantly in obese humans, they are selected by antibiotics inducing weight gain in animals and humans, and their administration in experimental models is linked to weight gain. These effects vary greatly for different species and strains of *Lactobacillus*, and the species- and strain-

dependent nature of these effects will be of importance in future studies (see Fig. 1; Table 1). Finally, newborns and infants appear to be a particularly susceptible population in which the manipulation of the developing gut microbiota by probiotics and antibiotics could plausibly be linked with acquired obesity.

Disclosure No potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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