Association of the Intestinal Microbiota and Obesity

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Obesity is a condition mainly caused by an alteration in energy intake, shifting towards positive energy balance, which can be influenced by genetic and environmental factors. The human gut is heavily populated with microbial organisms. Recent evidence suggests that obesity is influenced by specific bacterial phyla present in the human gut that have increased energy harvesting capabilities. The main objective of this review is to identify the microbial taxa that are related to obesity and weight loss. In this review, we also discuss the differences between the phylum ratio of the gut microbiota population of obese individuals and that of individuals who have healthy weight. It has been shown that obese individuals have a higher ratio of Firmicutes to Bacteroidetes than healthy weight individuals. The few studies to date have shown that weight-loss treatment may change microbial population of the gut, as there is a decrease in the ratio of Firmicutes to Bacteroidetes. Treating imbalances of the gut microbiota may offer new possibilities for treating obesity. [*P R Health Sci J 2015;34:60-64*]

Key words: Obesity, Intestinal microbiota, Weight-loss

One of the most important problems that public health is currently facing is the obesity epidemic, the causes of which include positive energy balance, genetics, and environment, among other factors. The gut microbiota outnumbers the host's tissue cells and metabolically regulates the ability of humans to digest and absorb nutrients from food. Recent studies have focused on the microbial environmental factor that pre-disposes humans to obesity.

The role that microbes have in energy homeostasis has driven research to study the association of intestinal microbiota and obesity. This study reviews the intestinal microbiota composition using animal models and human studies. Furthermore, the regulation of the human metabolism by the intestinal microbiota and microbiome is reviewed. Last but not least, the changes in the ratio of the gut microbial population with obesity and weight-loss treatments are discussed. A better understanding of this interaction could lead to the development of treatments that could metabolically correct this condition.

The obesity epidemic

Obesity is a condition characterized by an excess of body fat. It can be caused by genetic, behavioral, and/or environmental factors. In the US, 36% of the adult population is obese and another 27% are overweight, meaning that 63% of the adult population is overweight or obese (1,2). In Puerto Rico, a total of 66% of adults are overweight or obese (3). In addition, 32% of US children are overweight and another 17% are obese (4); in Puerto Rico, 32% and 16% of second graders were found to be overweight and obese, respectively (5). These statistics show that obesity has become an epidemic of major importance.

Excess body fat has negative physiological effects. Obesity is associated with conditions such as cancer, diabetes, heart disease, high cholesterol, high blood pressure, and stroke, among others (6). Because of this, health-related expenses associated with obesity are high; approximately $147 billion was spent for health care costs in the US during 2008 (1).

The impact of obesity on both financial and physiological health is such that studies examining the factors associated with the condition are urgently needed. Recently, researchers have directed their attentions to the microbial environmental factor that can be triggering obesity.

Intestinal microbiota composition

The microbiota present in the human gut outnumbers the host cells by a vast amount; bacterial cells exceed tissue cells by a factor of 10 to 20 (7). Such massive presence in the human body indicates that these microorganisms are important for the correct function of the host's metabolism and thus to that individual's health. Analyses of human feces have led to the study of the human intestinal microbiota. Suau et al. reported finding 271 billion bacterial cells per gram of feces (7). The predominant genera groups identified through comparative analysis of 16S rRNA sequences were Bacteroides, Clostridium, Eubacterium, and Fusobacterium. These groups accounted for

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24% of the known species, while 76% of the rRNA sequences did not correspond to any known microorganisms.

The major bacterial phyla present in the human gut are Firmicutes and Bacteroidetes, followed by Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia (8). By sequencing 16S rDNA from human feces, a total of 301 phylotypes were detected in the Firmicutes group and 65 phylotypes in the Bacteroidetes (8). These 2 groups compose 90% of the intestinal microbiota in healthy individuals (8); another study, found that Firmicutes accounted for 80% of the microbiota population in human feces (9). In agreement with these findings, a study of 124 European subjects with varying BMI values of normal weight, overweight, and obese individuals, reported that Bacteroidetes and Firmicutes were dominantly present in the gut (10). Other domains present in the gut are Archaeas, but they are represented only by the Methanobrevibacter smithii species (8).

Regulation of metabolism by intestinal microbiota

The gut microbiome, which is the genome of microorganisms residing in the gut, encodes for 150-fold more genes than the human genome (10). In a metagenomic sequencing study, Qin et al. reported a microbial gene catalogue of 3.3 million genes in the human gut (10). Because of this, it is important to study the role of commensal bacteria in the human gut and the functions of gut microbial genes. Among the microbiota's functions in the gut are the degradation of complex sugars such as pectin and cellulose and the synthesis of short-chain fatty acids such as acetate and butyrate (10). These microorganisms also supply the host with some vitamins, such as biotin, and amino acids (11,12). Therefore, the microbiota is needed for the metabolism of sugars, for the extraction of energy from compounds that the host cannot metabolize or absorb, and for the synthesis of amino acids and vitamins.

Intestinal microbiota also regulates fat storage. This was evidenced in a study in which germ-free mice were inoculated with normal gut microbial cells from conventionally raised mice, resulting in a 57% increase in body fat, even with a 27% reduction in food intake (13). Bacterial colonization also increased leptin levels, liver triglycerides (TG), and the storage of TG in the adipocytes of the inoculated mice. Therefore, intestinal microbiota regulates fat storage; this could also be the case in humans, but studies of this nature remain to be done.

Since Bacteroidetes and Firmicutes make up for the majority of the intestinal microbiota, researchers have studied their roles in metabolism. Hooper et al. specifically studied the Bacteroidetes phylum by inoculating germ-free mice with Bacteroides thetaiotaomicron, a Bacteroidetes species, and by profiling their gene expression using DNA microarray analysis (14). Results showed that Bacteroidetes increased nutrient processing through the upregulation of the glucose co-transporter SGLT-1 and that they also increased lipid absorption. In addition, bacteria of this phylum improved micronutrient absorption by upregulating the expression of cooper transporter CRT1, which shows that the microbiota can modify certain physiological functions. Not only colonization of Bacteroidetes regulates nutrient absorption, but it also fortifies the intestinal epithelial barrier through the upregulation of sprr2a, protecting the organs from bacterial colonization (14).

Studies with the other dominant phylum in the gut, Firmicutes, have proven its role in increasing epithelial lipid droplets. In a zebrafish model, researchers evaluated fatty acid absorption in the gut using fluorescently labeled fatty acids in germ-free fish exclusively colonized with Firmicutes microorganisms (15). They found that the zebrafish exclusively inoculated with Firmicutes had a significant increase in the amount of lipid droplets and a higher export of fatty acids to the liver compared to zebrafish inoculated with Proteobacteria and Bacteroidetes species. This suggests that microbial Firmicutes are responsible, in part, for lipid metabolism.

Interactions between these 2 phyla have also been studied (16). Using genome scale modeling and mathematical simulations of the interactions between the phyla, a recent study showed that Bacteroidetes are responsible for polysaccharide metabolism in the gut, while Firmicutes increase the metabolism of amino acids, such as glutamine (16). In fact, studies done on PPAR-α null mice, which delineate metabolic changes characteristic of metabolic syndrome and diabetes, have reported low levels of glutamine in tissues (17). This indicates that an unbalanced ratio of Firmicutes affects the metabolism.

Changes in microbial composition can also alter energy harvest. This was demonstrated in a study evaluating gut microbiota composition in 9 obese and 12 lean individuals after altering nutrient loads with 2 calorically different diets, a 2400 kcal or 3400 kcal diet consumed for 3 consecutive days, with a washout period between diets (18). It was observed that the higher calorie diet significantly increased the Firmicutes population and decreased the Bacteroidetes population in the gut. Although changes in energy harvest were not observed in obese subjects, a 20% increase of Firmicutes in lean individuals led to a significant loss in stool energy (approximately 150 kcal). Therefore, in humans, an alteration of nutrient load alters the intestinal microbiota, increasing energy harvest and decreasing energy in stools.

Role of intestinal microbiota in obesity

Gut microbial ecology can have an important function in energy homeostasis given the role of the microbiota in the host's metabolism. As discussed previously, bacterial colonization in germ-free mice leads to an increase in body fat (13). This finding links gut microbiota composition with obesity. Bacteria can have different gene composition and roles that regulate the human metabolism. Because of this, certain bacterial phyla might be linked to obesity.

Molecular studies in mice have helped in the discovery and understanding of the complex microbiota–obesity relationship. Genetically obese mice (ob/ob) that lack the leptin-coding gene have been widely used to study obesity. A

study in genetically obese and lean mice (ob/+, +/+) found that although Firmicutes was the dominant phylum in both mice strains, compared to lean mice, genetically obese mice had 50% less of the Bacteroidetes population and a higher Firmicutes population (19). Even though all mice strains were fed a polysaccharide-rich diet, obesity was significantly correlated with a change in phyla ($P<0.01$). This shows that obesity affects the gut microbial ecology of the 2 major phyla. Other genetic studies with ob/ob mice confirm that the Firmicutes to Bacteroidetes ratio is higher in obese mice compared to lean mice (20). The feces of the obese mice also have significantly less energy remaining when compared to the feces of their lean littermates, indicating that the ob/ob mice microbiota has better energy harvesting capabilities. This study also assayed the effect of the obese, or lean, microbiota on germ-free mice and found that the ob/ob microbiota recipient mice had a higher abundance of Firmicutes than the lean recipient mice did. Although food intake was the same, ob/ob microbiota recipients had greater percentage of body fat than the lean microbiota recipients. These results indicate that the intestinal microbiota is a major factor to consider when studying the development of obesity.

Animal studies that show enhanced energy harvest and nutrient absorption with intestinal microbiota are the basis for human studies. The first study that characterized the microbiota composition of obese and lean individuals showed that obese adult individuals have a higher ratio of Firmicutes to Bacteroidetes than lean adult individuals (21). This difference in the Firmicutes to Bacteroidetes ratio was also observed between male and female obese subjects awaiting Roux-en-Y gastric bypass surgery and lean control subjects (22). Furthermore, in a study with human monozygotic or dizygotic twins from European or African descent, it was reported that obese subjects had fewer Bacteroidetes and a less diverse microbiota than their lean counterparts (23). However, this study did not observe differences in the Firmicutes phylum.

Childhood obesity is an important aspect of the obesity epidemic since it is rapidly increasing. Studies in microbiota composition and obesity in children have confirmed the previously discussed findings. When compared to lean children, obese children also have a higher Firmicutes to Bacteroidetes ratio (24,25). Furthermore, a positive correlation between BMI and Firmicutes and a negative correlation between Bacteroidetes and weight has been reported in 5-year-old children (26). If the intestinal microbiota composition could predict a predisposition for overweight in children, it could help to understand the mirobiota-obesity relationship. This was studied by Kalliomaki et al. in 25 overweight or obese children and 24 heathy weight children from Finland (27). The analysis of fecal microbiota in the first year of the subjects' lives indicated that Staphylococcus aureus, a species from the Firmicutes phylum, were significantly in higher abundance in children who were becoming overweight than in healthy weight subjects. However, more studies are needed to confirm these results.

Association of intestinal microbiota and weight-loss

The association of changes in ratio of the microbial population with obesity raises the question as to whether there is a similar link between intestinal microbiota and weight-loss. The identification of the gut microbiota composition of obese subjects (BMI ≥30 kg/m^2) during diet treatment has helped to characterize the change in the Firmicutes-Bacteroidetes ratio at different stages (21). Ley et al. studied obese individuals before they were treated with a low-calorie diet and found a higher proportion of Firmicutes than Bacteroidetes in obese participants compared to lean subjects (BMI: 18.5–25 kg/m^2). After following a carbohydrate- or fat-restricted diet for 52 weeks, changes in Firmicutes and Bacteroidetes proportions in the gut were observed, making them more similar to those of lean subjects. In addition, the loss of body weight in these obese individuals was correlated with an increased presence of Bacteroidetes. These findings suggest that weight loss results in changes to the gut microbial ecology. Similarly, a study in 39 overweight and obese adolescents from Spain evaluated the effect of a program including nutritional counseling, calorie restriction, and physical activity for 10 weeks on the intestinal microbiota composition (28). Subjects that lost more than 4 kg in this period of time had a significant reduction of Firmicutes phylum and a significant increase of Bacteroidetes phylum. Contrarily, subjects that lost less than 2.5 kg did not experience these changes. However, more research is needed to confirm these results.

Future studies

A limitation of the current studies is that only a low percentage of microbial organisms are known (7). However, the recent availability of pyrosequencing 16S rRNA and analysis of community profiles through phylogenetic information has given light to new procedures for phylogenetic analyses to overcome this limitation (29). Knowing the microbiota composition of an individual may help to determine whether that individual is at risk for overweight or obesity. Because differences in the microbiota have been detected at early stages of childhood (27), an individual's microbiota may be used for early diagnosis and to detect predisposition for obesity. This may help reduce the severity of the current obesity epidemic; however, more research is needed. Furthermore, identification of specific foods, dietary patterns, and amounts of energy intake that can change the Firmicutes to Bacteroidetes ratio in the gut may help in the formulation of dietary advice, which could in turn aid in the prevention of obesity. More clinical studies are needed to further understand of the microbiota's composition in the gut in relation to different dietary patterns. In addition, studies in which the diet is manipulated and controlled to detect changes in the ratio of Firmicutes to Bacteroidetes are crucial to elucidate this association.

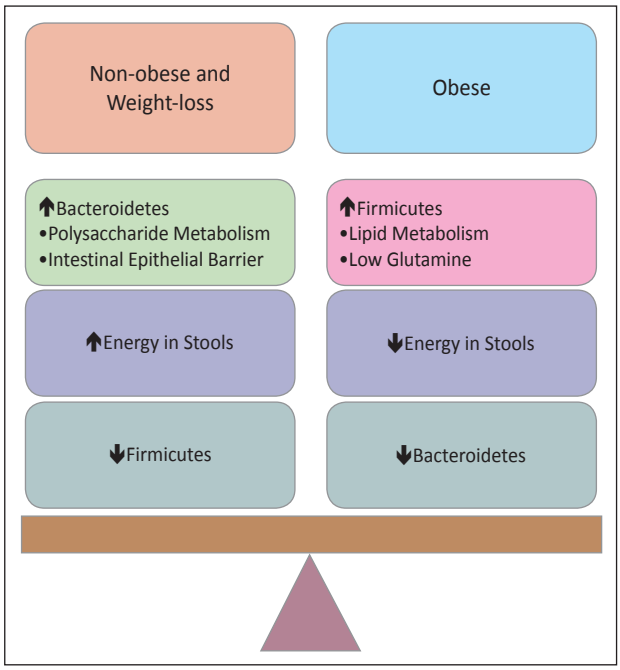

Figure 1. Microbial and metabolic differences in obese and non-obese/weight loss models. Obese individuals have different microbial composition compared to lean individuals; Firmicutes are higher and Bacteroidetes are lower in obese individuals. With weight-loss, the percentage of microbial population abundance changes; although Firmicutes are still the dominant phylum in the gut, the Firmicutes to Bacteroidetes ratio is decreased. Moreover, the microbiota has greater energy harvesting capacity and less amount of energy in stools in obese models while there is more energy in stools in non-obese models. These differences may be related to the different metabolic roles of such groups; Firmicutes increase lipid metabolism and lower blood levels of glutamine while Bacteroidetes increase polysaccharide metabolism and fortify the intestinal epithelial barrier.

Conclusion

According to the studies reviewed (Figure 1), obese individuals have a higher Firmicutes to Bacteroidetes ratio than lean individuals. With weight-loss, the Firmicutes to Bacteroidetes ratio decreases becoming more similar to the ratio in lean subjects. In addition, the microbiota has greater energy harvesting capacity with less amount of energy in stools in obese models while there is more energy in stools in non-obese models. These differences and changes with weight loss may be due, in part, to the metabolic role of the different groups.

Resumen

La obesidad es una condición causada mayormente por una alteración en la ingesta de energía, desplazándose hacia un balance energético positivo, que puede estar influenciada por factores genéticos y ambientales. El intestino humano está altamente poblado de organismos microbianos. Estudios recientes indican que la obesidad está influenciada por ciertos filos microbianos presentes en el intestino humano. El objetivo principal de esta revisión es identificar los taxones de la microbiota que están relacionados con la obesidad y la pérdida de peso. Esta revisión también describe la diferencia en la proporción de filos de la microbiota intestinal en individuos obesos y de peso saludable. Se ha demostrado que individuos obesos tienen una mayor proporción de Firmicutes a Bacteroidetes en comparación con individuos de peso saludable. Los pocos estudios realizados hasta la fecha han mostrado que los tratamientos de pérdida de peso pueden cambiar la microbiota intestinal, ya que hay una disminución en la proporción de Firmicutes a Bacteroidetes. El tratar los desbalances de la microbiota intestinal puede ofrecer nuevas posibilidades para el tratamiento de la obesidad.

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