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Mini Review

New Ways for Anti-Obesity: Gut Microbiota

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Abstract

Obesity and its associated disorders are major public health concerns. The formative causes are complicated in obesity patients, such as genetics, unhealthy diet style, less exercise behavior, drugs and so on. A number of ways have been put forward to improve the current status of the population of obesity, but making little achievements. Recently, numerous studies in rodents imply that the gut microbiota communities can influence directly or indirectly on energy homeostatic systems affecting the host in energy balance (weight gain or loss). Accumulating evidence has shown that the "obese microbiota" may be the vital factor causing the obesity and metabolic symptom. In this review, we have summarized several feasible ways to settle the obesity problem, and among that, the fecal microbiota transplant (FMT) would be the most promising therapeutic method.

Keywords: *Obesity; Gut Microbiota; Fecal Microbiota Transplant (FMT)*

Introduction

Obesity/overweight, which is characterized with BMI (body mass index) more than 30, has been a worldwide public health concern. It is a complex process depending on dietary and lifestyle, such as increased consumption of high energy diets and reduced physical activity, simultaneously with contributions from host in genetics, physiological status and so on [1-6].

Western diet was characterized by a high consumption of red and processed meats, refined grains, high-fat dairy products, and high-sugar drinks and desserts, and relatively low intakes of fruit, vegetables, whole-grain foods and white meat [7]. This dietary style specifically make people on the risk of obesity, type 2 diabetes, metabolic syndrome as well as cardiovascular diseases. The serious situation has been known that overweight and obesity were estimated to afflict nearly 1.5 billion adults worldwide in 2008. Moreover, the prevalent of obesity threatens both the industrialized and the developing countries at the same time [8,9]. In addition, based on the new data, the professional predicts that there are 2.16 billion adults will be overweight, and 1.12 billion will be obese in 2030 worldwide. So, new ways coming out to settle the obesity problems have no time to delay. A numbers of intervention methods have been implemented to solve this problem, but so much effort is being expended with so little apparent result.

Recently, researchers have focused on the gut microbiota trying to establish new method to cure people's plenty of diseases including obesity. The human gut microbiota consists of trillions of microorganisms, 10 times more than the number of cells constituting the human body [10]. To some extent, we share our body with the gut microbiome communities. The gut microbiota has multiple functions, for example, it is essential for processing dietary polysaccharides that cannot be digested by humans, such as resistant starch, oligosaccharides, which are cleaved into smaller molecules by specific enzymes produced by intestinal bacteria [11]. Till now, it is well known that the microbiota communities can protect host against pathogens and influence host nutrition uptake and utilization, immune functions, and even brain behaviors [10,12], and recent studies have suggested gut microbiota to be a vital environmental factor involved in the con-

trol of body weight and energy homeostasis [13-19]. Numerous experimental models using transgenic, knockout, and gnotobiotic even germ-free animals, like *Drosophila* or rodent animals, as well as human studies, provide evidence of a crucial role for intestinal microbiota in energy harvest and consequently obesity, and a tight association between obesity and alterations in the gut microbiota(dysbiosis) has been established [1]. All of these bacteria, estimated to be over 35,000 species belong to 4 major phyla, as using 16s rDNA sequence-based methods, among which *Proteobacteria* and *Actinobacteria* are the dominant phyla until weaning, while *Bacteroidetes* and *Firmicutes* are the dominant phyla in adult life [20-23]. Particularly, the obese compared to the lean people have fewer *Bacteroidetes* and more *Firmicutes* at baseline, as time going, the relative abundance of *Bacteroidetes* increased, and that of *Firmicutes* decreased, irrespective of their diet [4]. Thus, that makes it possible by way of changing the gut microbiome communities to cure obesity.

One vital reason of obesity: the disorder of gut microbiota communities

As we know, after birth, the infant gut progresses from sterility to extremely dense colonization in 1 - 3 year [24], ending with a mixture of microbes that is broadly very similar to the adult intestine till about three years old. The content of the gut microbiota varies with the diet, interestingly in early life the microbiota of a formula-fed baby differs from that of a breast-fed baby [25]. Moreover, changes also happen in the gut microbiota occurring with changes in exercise, antibiotics, prebiotics or probiotics changes the gut bacteria of the host, too [26]. Two groups used germ-free mice model found that germ-free animals were protected against both obesity and insulin resistance after high fat diet, which suggests that gut microbiota clearly influence the effects of diet on the host [27,28], on laboratory mice have demonstrated that host genetics can influence the gut microbial community structure, but that diet can overwhelm these genetic effects.

It is now well established that a healthy gut flora is largely responsible for the overall health, while a disorder in gut microbiota can make the host susceptible to diseases including obesity [20]. Several studies have demonstrated the changes in the composition of the gut microbiota in obesity [29-32], and obesity is associated with phylum-level changes in the microbiota [33]. For instance, studies in mice genetically predisposed to obesity reported a decrease of the *Bacteroidetes/Firmicutes* ratio [3], taxonomic analyses of the obese gut microbiota showed a depletion of the anti-inflammatory bacteria *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, and an increase of short chain fatty acids (SCFAs, such as butyrate, propionate, acetate) producers *Eubacterium* and *Roseburia*. Usually, intestinal epithelia obtain 60 - 70% of their energy supply from SCFAs, particularly butyrate. Studies show increased SCFAs level in obese people compared with control. Human studies also show the same phenomenon as a lower proportion of *Bacteroidetes* and a higher proportion of *Actinobacteria* in obese compared with lean individuals, and both the diversity of the microbiota and the *Bacteroidetes/Firmicutes* ratio are decreased in obese individuals [33].

The obese people may have their own “obese microbiota” formed with age. The *Firmicutes* that are increased in obese mice and humans have been shown to be more adopting at breaking down indigestible carbohydrates and converting them into absorbable products, such as. Westernized diets shift the gut microbiota populations toward a *Firmicutes*-friendly environment, leading to an overall increase in *Clostridia* populations. The increased *Clostridia* populations, which are more efficient in carbohydrate metabolism, extract greater energy from food, allowing for higher energy utilization, finally promote fat deposition.

Through these findings, it is not hard to see that the “obese microbiota” of the host increases dietary energy harvest, fatty acid metabolism and microbiota-associated inflammation as a result it favors weight gain and fat deposition [20], in turn, the obesity problem can be settled by the changing of the “obese microbiota”. If thus, it would seem likely that microbiota composition shift between lean and obese individuals would affect the efficiency of energy harvest in the gastrointestinal tract and may either facilitate or inhibit progression toward obesity.

New ways to alleviate the prevalent of obesity

The experimental evidences have increasingly proved the functional link between gut microbiota and obesity, and the manipulation of gut microenvironment could be the new method to prevent obesity. It is easy to imagine, antibiotics, probiotics, prebiotics and fecal

microbiota transplantation (FMT) can all impact on gut microbiota composition efficiently; thus, they represent tools with attractive therapeutic potential to control the "obese microbiota" [20]. Below we will review their current progresses in experimental and clinical trials in a systemic view, and come out with the powerful cure potentials of gut microbiota in anti-obesity.

First of all, antibiotics are the most convenient way to influence gut microbiota composition. Fast and efficient must be the advantages of antibiotics. However, we have to envisage several major concerns before proposing antibiotics as "anti-obesity drugs". Obviously, it is nearly impossible to identify correct target microorganisms from thousands of different species in the gut leaving aside the course of determining. Then, another situation should be addressed, due to the broad-spectrum activity and the fast speed, antibiotics target both "pathogenic" and "non-pathogenic" microbial populations efficiently, thereby potentially disrupting important interactions with the host [34]. At present, the antimicrobial drugs have been central to combat disease in modern medicine, which are liable to cause the disorder of the gut microbiota composition, leading to the increase of weight on the contrary. Finally, it should be taken into account that the response to pharmacological treatment deeply varies among individuals, particularly in obese subjects, in whom altered metabolism, protein binding and clearance of drugs potentially can affect the pharmacokinetics of antimicrobial agents [35,36]. For example, the post-therapy excretion of pharmacological agents, like the elimination of drug residues in the milk of lactating mammals [37], even the concentration is very low, will impact the gut microbiota of their offspring. These consequences couldn't be ignored. Thus, all these limitations would probably slow progress in this field and explain why interventional data on humans are still unavailable.

Probiotics are defined as live microorganisms conferred a health effect to the host, according to the WHO [38]. The genera *Lactobacillus* and *Bifidobacterium* have been reported to exert multiple beneficial effects on metabolic syndrome, such as weight loss, reduced body fat, and improved glucose tolerance in most animal studies and in some clinical trials [39]. Although these studies suggested a potentially beneficial effect of probiotics on the changes of body weight and adiposity, the results are far from conclusive [40]. However, some studies have reported that probiotics do not exert beneficial effects, especially to weight loss. It makes the real effect of probiotics complicated and confusing. Among the recently published meta-analysis papers, only selecting out 4 high-quality randomized controlled studies comparing the therapeutic efficacy of probiotics with placebo, in addition using body weight loss as the main end-point [41-44]. Unfortunately, as the pooled data failed to demonstrate significant differences in body weight, BMI and mean body fat mass between the probiotic group and controls, therefore it suggests that probiotics are ineffective on body weight modulation [40]. Further systematic review or meta-analysis that could provide critical evidence regarding the potential benefits of probiotics in weight loss is urgently needed. So, products should be picked up in the market carefully if we want to lose weight only by eating something. Of course, that is not to say, the probiotics are useless to our health absolutely, but it needs quite a long time to find out the efficient probiotics in weight lose exactly.

Prebiotics are known to be the non-digestible food ingredients that beneficially influence the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already colonized in the gut, and thus improve the host health [45]. Compared to antibiotics' broad-spectrum inhibitory functions to the whole microbial populations, the growth-promoting function to the beneficial gut bacteria by prebiotics, thus to alter the composition of the good gut microbiota appropriately make it a promising choice for anti-obesity.

For instance, two kinds of prebiotics, inulin-type fructans (inulin, oligofructose and fructooligosaccharides) and galactans (galacto-oligosaccharides), have been demonstrated to be able to enhance the growth of beneficial *Bifidobacteria* and *Lactobacilli*, as well as to reduce body weight, body fat mass and adiposity [46]. Certainly, the prebiotics also play some roles in the specific nutrition harvest, and the beneficial effects of prebiotics on metabolic parameters, that is, glycemia and insulinemia, have been confirmed, however, the impact on body weight still remains a matter of debate [47].

Fecal microbiota transplant (FMT) consists of infusion of fecal suspension from a healthy individual into the gastrointestinal tract of another person to cure a specific disease [20]. Strikingly, in animal experiments, the colonization of germ-free mice with the microbiota from the obese mice resulted in a significantly higher percentage of total body fat than that resulting from colonization with a microbiota

from lean mice. Inoculation of germ-free mice with fecal microbiome from human twins pairs discordant for obesity, led to the acquisition of an obese phenotype in rodents receiving microbes from the obese but not from the lean twin, despite no significant differences in daily chow consumption between the groups [48]. Based on the evidence in animal models that metabolic phenotypes can be transmitted via gut microbiota transplant, a first pilot study demonstrated that infusing intestinal microbiota from lean donors to male recipients with metabolic syndrome increased insulin sensitivity, although the body weight and adiposity were not modified [49]. We can come out some conclusions from these experiments that the FMT from health to the unhealthy person could recover their gut microbiota composition, and then solve the diseases in host causing by the disorder of gut bacteria, which indicates that FMT would represent a possible "biological therapy" to treat metabolic diseases, maybe just some capsules with the health gut microbiota community. Moreover, some studies also focus on the modification of gut microbiota composition and function after bariatric surgery, which represents a successful treatment choice for severe obesity. However, it should be acknowledged that the wide variability among the studies in respect to type and dosage of probiotics, treatment duration and absence of information on food behaviors or dietary patterns of the participants could, at least partially, affect the conclusion of the meta-analysis. Beyond that, future large-scale studies are needed to determine the efficacy, safety, and long-term effects of the FMT as a new intervention to solve the obesity crisis in the future.

Prospective

The research of gut microbiota is so prevalent now. Of course, it participates in a large amount of physiologic functions like intestinal development [50], CNS functional development [51,52], neuronal activity [53] and even the behavior of host [12,54-56]. Simultaneously, the disorder of gut microbiota has relationship with numerous diseases, such as obesity, type 2 diabete, colonic cancer, cerebrovascular disease, even some neurodegeneration diseases [57] (such as Parkinson disease [58]). The analysis of mice and human gut microbiota in correlation to body weight has supported the idea that intestinal bacteria are key players in the regulation of host energy homoeostasis and in the pathogenesis of obesity [20]. We could say that "stay with a fat, you'll be a fat" cannot be just a joke. Above all, to some extent, healthy life comes from healthy gut.

Conflict of Interest

No.

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