REVIEW

POTENTIAL PHARMACEUTICAL USES OF PROBIOTICS AND PREBIOTICS IN OBESITY MANAGEMENT

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Abstract

Although the pathophysiology of obesity is multifactorial, many recent studies have suggested that it implies an alteration of gut microbiota. The mechanisms by which dysbiosis contributes to obesity are numerous and include an increased energy harvest, alteration of intestinal barrier, systemic inflammation and hormonal imbalance. The therapeutic interventions for the improvement of intestinal microflora may promote weight loss and prevent weight gain. Probiotics and prebiotics have been proposed as practical and affordable solutions for reaching this goal. This paper, by reviewing the scientific literature, intends to clarify whether and in what conditions these agents can be used in the management of obesity.

Rezumat

Deşi fiziopatologia obezităţii este multifactorială, studii recente sugerează implicarea unor modificări ale florei intestinale. Mecanismul prin care disbiozele contribuie la instalarea obezităţii sunt numeroase şi includ o extracţie crescută de energie din bolul alimentar, alterarea barierei intestinale, inducerea unei inflamaţii sistemice şi a unui dezechilibru hormonal. În acest context, intervenţiile terapeutice destinate reechilibrării microbiomului intestinal pot reprezenta o soluţie pentru scăderea în greutate şi prevenirea obezităţii. Probioticele si prebioticele au fost propuse ca agenţi capabili de a realiza acest deziderat. În această lucrare ne-am propus ca, prin analiza literaturii de specialitate, să clarificăm dacă şi în ce condiţii probioticele pot fi utilizate în managementul obezităţii.

Keywords: obesity, probiotics, prebiotics, gut microbiota

Introduction

The incidence of obesity has reached epidemic proportions. It is therefore important to find a viable approach for this condition. Even if the most frequent cause which leads to the obesity development is a dis-balance between energy intake and energy expenditure, the pathophysiology of obesity is multifactorial, and includes genetic [2, 12] and epigenetic factors, like diet and sedentary lifestyles [38].

Because intestinal microflora is environmentally acquired, it could represent the link between these factors, a metabolic gateway between the outer environment and the host [54]. Although the role of gut microbiota in human health has been long neglected [43, 83] it could represent a potential new target for therapeutic drugs or nutritional interventions [48]. Microflora composition seems to be a key factor affecting energy homeostasis [89], many recent studies showing an association between obesity and an imbalance in the normal gut microbiota composition. In this paper, by thoroughly reviewing the specialty literature, we intend to systematize the current knowledge about the manipulation of the intestinal microbiota by probiotics and find out whether this method is or is not a viable solution for the management of obesity.

The role of intestinal microflora in the host metabolism

The human intestine harbours an extremely diverse ecosystem of bacterial flora, which includes 1014 bacterial species [109] and presents great individual variations [32]. The endogenous intestinal microflora is considered an essential "organ", being involved in many physiological processes like body nutrition, immune system regulation, angiogenesis, epithelial intestinal cell protection, although its role is not completely elucidated [32, 113]. In this paper, we are particularly interested on the involvement of the intestinal microflora in the host nutrition, metabolism and energy storage [8, 80].

The initial link between gut microbial ecology and obesity was determined by a series of pioneering studies led by Ley and Turnbaugh, carried out between 2005 -

2006 [62, 63, 112]. The first of these studies showed that there is a difference between the microbiome of fat and lean mice, with a greater representation of *Firmicutes* and fewer *Bacteroidetes* in the obese host microbiota [62]. This microbiota has greater energy extraction efficiency, with less energy leftovers in faeces and greater levels of short-chain fatty acids (SCFAs) in the cecum. Turnbaugh reported that, when the luminal contents from the ceca of obese or lean mice were transferred to lean germ-free recipients, the mice receiving the microbes from the obese donors gained more weight over a 2-week period compared to the recipients of microbes from lean donors, despite an equivalent food intake [112]. These observations were extended to humans by Ley [63] and later by Ferrer [39] which confirmed these findings comparing the intestinal microbiota in lean and obese adolescents. Other authors also showed the involvement of intestinal flora in the pathogenesis of obesity and type 2 diabetes [34, 68, 78].

There have been described more types of microbiota associated with obesity: a decrease in the *Bacteroidetes*/ *Firmicutes* ratio [8, 9, 34, 63, 108, 112, 110], a decrease in the *Archaea Methanobrevibacter smithii* [73, 108] or an increase in some bacterial groups like *Lactobacillus* [5], *Staphylococcus aureus* [25, 52], *Escherichia coli* [105] and *Faecalibacterium prausnitzii* [11].

Even though the most studies indicate that an increase in the ratio *Firmicutes/Bacteroidetes* is associated with obesity, not all studies have concluded this [31, 92]. A possible explanation is the use of stool culture to analyse the intestinal microbiota, a method which is not considered reliable enough, because the faecal biome may be different that the intestinal one, which varies significantly across different anatomical segments [32, 124].

It seems that obesity can be associated not only with a dysbiosis of the microbiota from the lower intestinal tract, but also from the small intestine, where bacterial overgrowth has been shown to be more common in morbidly obese patients than in healthy weight individuals [101]. Even the oral flora is modified in obese persons: salivary bacteria *Prevotellas* (a group within the *Bacteroidetes phylum*) were in greater abundance in the overweight persons, while *Selenomonas* was present only in the over-weight individuals [42]. These studies indicate that obesity may be associated with a dysbiosis of the normal microbiota throughout the body.

The relationship between obesity and dysbiosis

As already mentioned, Turnbaugh, Ley, Bäckhed and the other authors considered that modifications of intestinal microbiome influence energy homeostasis, since the energy extraction and storage is more efficiently, for the same diet, in an obese person compared to a lean one, which implies that dysbiosis can initiate obesity [8, 62, 111, 112]. Kalliomaki *et al*. [52] showed in a prospective study concerning the microbiota and weight gain in children, that those who became overweight by age 7 had lower levels of *Bifidobacteria* and higher levels of *Staphylococcus aureus* in infancy compared with those that kept a healthy weight. Also, in overweight adolescents, the response to a diet and exercise weight-loss program was dependent on the initial microbiota prior to the treatment [104]. Other authors also agree that the efficiency of energy extraction from diet depends on the community composition [61]. On the other hand, Murphy *et al*. didn't find any relationship between the compositional changes of the major phyla *Firmicutes*, *Bacteroidetes* and *Actinobacteria* and the markers of energy harvest [76].

Cani *et al.* have proposed as a possible mechanism by which a microbiome with a reduced number of *Bifidobacteria* can interfere the energy balance, increasing the intestinal permeability, which allows more lipopolysaccharide (LPS) to translocate to the serum, while greater levels of *Bifidobacteria* have been associated with reduced gut leakiness [20].

In fact, the structure of intestinal flora generates complex effects upon host metabolism, which are not limited to an increase in energy extraction capacity and influencing the gut permeability. As early as 1994, Uribe *et al.* claimed that intestinal microflora modulates the endocrine cells in the gastrointestinal mucosa of the rat [114]. Other researchers detailed the complex mode in which microbial flora is involved in the secretion of hormones that coordinate the energy intake and expenditure [19, 21, 29, 87, 102, 115, 119]. In 2010, Matsumura signalled the inhibitory effect of certain *Lactobacillus* strains upon pancreatic lipase activity [70], his finding being supported later on by the 2013 study of Zhou *et al*. [123]. As a matter of fact, the direct inhibitors of pancreatic lipase are already used as pharmaceutical agents in the management of obesity [46].

Therefore, the mechanisms by which dysbiosis contributes to obesity are numerous, including an increase in energy harvest, alteration of intestinal barrier, systemic inflammation, hormonal imbalance etc. [15, 20, 30, 112]. In spite of these, our basic understanding of gut microbiota ecosystem remains incomplete and many other mechanisms may be involved [10, 47, 65].

These studies suggest that therapeutic interventions aimed at reshaping the gut microbiota may be beneficial for weight loss as well as preventive against weight gain.

How are dysbiosis produced?

The genetic factors can influence the structure of intestinal microbiome, the members of a family

presenting certain common characteristics of the intestinal flora [112]. It is possible to exist a genetic determinant of the intestinal bacterial population, as have been described in some previous papers, which recorded that genetically 'identical' monozygotic (MZ) twin pairs [17] gain weight in response to overfeeding in a more reproducible way than do unrelated individuals [16] and are more concordant for body mass index (BMI) than dizygotes (DZ) twin pairs [67]. Other direct evidence for the existence of a transmissible obesity microbiota is the study of Ridaura *et al.* [99].

On the other hand, the environmental factors also significantly influence the structure of the intestinal microbiome. Diet-related microbiome associations have been more extensively studied [107, 116]. Intestinal microorganisms are specifically stimulated by a certain diet, their multiplication being induced by certain components of it [27].

In a paper published in 2014, Albenberg and Wu extensively discussed the fact that mutual relationship between the intestinal microbiota and its mammalian host is influenced by diet. Diet affects the structure and metabolome of the human intestinal microbiome and may contribute to health or the pathogenesis of some disorders such as coronary vascular disease and inflammatory bowel diseases [1].

A meta-analysis of the studies concerning the impact of host's geographic location and behavioural factors (diet and physical activity) on microbial community structure and obesity, concluded that the environmental factors influences the human gut microbiota in the development of the obese phenotype [57]. The study of microbiome in cloned pigs has demonstrated that association between the diet-induced obesity and increase in the relative abundance of *Firmicutes* that occurs even when the genetic variable was eliminated [93].

Bell considers that the excess production of bile acids induced by the high-fat and calorie diets and utilization of the artificial sweeteners in modern diet cause an acidic intestinal environment which promotes the development of intestinal bacteria associated with obesity [13]. However, certain diet components, such as the dietary resistant starch, appear to result in greater changes in gut microbiota compared to other dietary manipulations, both in the short-term dietary interventions and in the response to habitual long-term dietary intake [40, 118].

It seems that other characteristics of the diet, except its composition, can influence the intestinal microbiome structure. Thus, a study in humans showed that the proportion of *Bacteroidetes* bacteria increased after restricted diets over time, mirroring reductions in host weight, regardless of whether the hypocaloric diets followed were of carbohydrate-restricted or fat-restricted type [63]. Another factor that may influence gut microbiota is how the food is ingested throughout the day and how long the fasting periods last. Thus, the fasted mice have been shown to harbour a greater proportion of *Bacteroidetes* in their ceca compared to unfasted mice with equivalent body fat [26].

Other local environmental factors, such as physical activity behaviours may also influence gut microbiota composition [24, 36, 69, 94, 95]. Physical activity training has beneficial effects on the gut microbiota diversity and improves the ratio between certain bacterial genera [14, 24, 95].

The previous mentioned studies provide support for associations between the gut microbiota and the development of obesity through many levels of causation or determinants (e.g. dietary habits, daily physical activity, genetic factors etc.).

In conclusion, there are scientifically arguments in the specialty literature for the presence of a feedback between the intestinal microbiome and host's energy balance. Ley *et al.* consider that obesity affects intestinal microbial flora, but also suggests the opposite relationship, in which the manipulation of this structural community can be useful for adjusting the energy balance in obese patients [62].

The probiotic potential in treating obesity-associated dysbiosis

The studies depicted above are a powerful argument for manipulating the intestinal microbiome as a key to fight obesity. Although the microbiome transfer from lean to obese persons is a therapeutically procedure that has started to be studied [117], the administration of probiotics is a much simple solution, proved to be also effective.

The probiotics are defined by the Food and Agriculture Organization of the United Nations and the WHO (FAO/WHO) as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [45]. The diversity of the gut microbiota and its composition may be altered after the probiotic treatment [88] directly by modulating its bacterial content, and indirectly through bacteriocins produced by the probiotic bacteria [72]. The studies have demonstrated the beneficent effect of probiotic administration on the health of the digestive tract and in the management of some chronic diseases such as atherogenesis, allergy, inflammatory bowel disease [79, 96, 100].

The probiotics that can manipulate the gut microbiota may be interesting agents not only for the risk factors underlying the development of metabolic syndrome including dyslipidaemia, elevated fasting glucose levels and insulin resistance [56], but also for targeting obesity management [28, 77]. Administration of probiotics can induce the modulation of the structure and/or activity of the gut microbiota, with positive effects in the management of obesity [28]. Multiple

in vivo studies provide evidence that some probiotics can reduce diet-induced obesity in rodents [3, 6, 23, 53, 55, 62, 63, 66].

However, the intestinal flora is extremely complex, in the intestinal lumen exists a real ecosystem, characterized by diverse interactions and inter-dependencies and therefore the exact understanding of its controlling mechanisms requires intense studies, unfortunately only recently started. Possible due to this reason, the administration of probiotics has not always produced a consistent modification of the intestinal microbiome so it can generate a significant weight loss [7, 33, 90, 97]. A critical review of the specialty literature regarding the possibility of treating obesity by modifying the proportion of intestinal *Firmicutes* and *Bacteroidetes*, published in 2015, contends that the transfer of an obese microbiota to germ free and lean animals results in obesity, and the introduction of a lean microbiota will result in weight loss in obese animals; in humans the manipulation of microbiome only by utilizing probiotics has not been shown to result in weight loss [13]. Moreover, there are reports of probiotics that actually cause weight-gain in rodents [120] and some probiotics has been used for growth promotion in farm animals for at least 30 years [41] the most used being various strains of *Lactobacillus*: *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus fermentum*, *Lactobacillus reuteri* [4].

One of the most probable causes for these contradictory results can be considered the use of different probiotic strains. But, different probiotic species can exert variable effects on lipid accumulation and obesity [120]. In fact, even for the same genus of intestinal bacteria, certain strain can have paradoxical effects upon nutritional status. A very interesting meta-analysis, of clinical studies and experimental models, has been performed and published in 2012 [74]; and intended to assess the effects of *Lactobacillus* species on weight change. This analysis included 17 randomized controlled trials, 51 studies on farm animals and 14 experimental models. The conclusions of this research were that *Lactobacillus acidophilus* administration resulted in significant weight gain in humans and in animals, *Lactobacillus fermentum* and *Lactobacillus ingluviei* were associated with weight gain in animals, *Lactobacillus plantarum* was corroborated with weight loss in animals and *Lactobacillus gasseri* was associated with weight loss both in obese humans and in animals. This meta-analysis showed that the effect of *Lactobacillus* species on body weight in humans and animals is species-dependent and host-specific. The authors, at the end of their paper, warned about the potential effects of commonly marketed *Lactobacillus* – containing probiotics on weight gain [74].

Consequently, if many probiotic strains have varying metabolic effects [71], a major challenge for scientists is to discover the probiotic strains, which may help protect against obesity [71, 121].

Among the bacteria that were studied in relation to their role in body weight regulation, the *Lactobacillus gasseri* has shown the most promising effects on weight loss, both in mice and rats [44, 49, 75, 106] and also in obesity-predisposed humans [50]. In one of these studies, the administration of *Lactobacillus gasseri* produced in mice a significant reduction in average adipocyte size in mesenteric white adipose tissue ($p = 0.004$) and a decreased serum leptin concentrations to 32% compared with the control group [106].

A possible mechanism of this action, capable of explaining the anti-adiposity effects of *Lactobacillus gasseri* (LG2055) is that it may inhibit the absorption of dietary fat, increasing the amount of fat excreted with faeces [44, 70, 84] due to an action upon the fat emulsion size, leading to suppression of lipase-mediated hydrolysis [84]. Other Japanese authors consider that the possible mechanism underlying the anti-obesity effect of LG2055 is the improvement in the inflammatory state of the adipose tissue [75].

But constant consumption might be needed to maintain the effect. A randomized controlled trial [84] using 210 healthy Japanese adults with large visceral fat areas showed that consumption of LG2055 at doses as low as the order of 10(8) cfu/d for 12 weeks, exhibited a significant lowering effect on abdominal adiposity (-8.2% - 8.5%), waist and hip circumferences and body mass index (BMI). But, even for the same strain of LG2055, the 7 day-study or 4 weeks-study did not record a significant reduction in the percentage of adipose tissue in the studied group compared to control [49, 50, 51, 84].

Other strains of *Lactobacillus* have also been proposed and studied for their anti-obesity effects: *Lactobacillus fermentum* or *Lactobacillus amylovorus* [85], *Lactobacillus rhamnosus* [59, 103], *Lactobacillus sakei* [64], *Lactobacillus paracasei* [6], *Lactobacillus plantarum* [60]. The multi-strain probiotics, like combination of *Lactobacillus plantarum* and *Lactobacillus curvatus* [89, 121] or a probiotic formula like *VSL#3* [86, 119] showed synergistic effect on metabolic alterations in diet-induced obesity.

Association of prebiotics

The contradictory results regarding microbiota changes in response to probiotics in some studies may be partly due to an inter-individual variability in microbiota composition, caused by the environmental factors like diet and genetic background [37, 64]. Since the intestinal microbiota is shaped by diet [40], the association of certain prebiotics is a logical solution to promote the development of target bacterial strains

in the effort to obtain and maintain the desired microbiome.

Some recent studies have revealed that some nutrients which are capable to reverse host metabolic alterations in obese individuals, target the gut microbiota dysbiosis. The therapeutic potential of certain prebiotics, such as inulin and oligofructose, in obesity seems to be due not only to the effects upon gut satiety hormones, energy expenditure, gastric emptying, but also an increased proportion of *Bacteroidetes* and a decreased proportion of *Firmicutes*. The mechanisms involved are regulated in a dose-dependent manner [91]. Cani *et al*. also, have obtained in obese mice an increased proportion of *Bifidobacterium* after the oral administration of inulin-type fructans [18]. Non-digestible carbohydrates (NDC) derived from wheat may constitute functional cereal food products in the management of obesity and diabetes, notably through modulation of gut microbiota [81, 82]. Rastmanesh [98] considered that the reason are the polyphenols, found in certain fruits like grapefruit, apples or green tea, that can reduce the body weight in the obese people, and is precisely related to a modification in the relative proportion of *Bacteroidetes* and *Firmicutes*; the authors proposed the supplementation with polyphenols as a therapeutic solution for the obese individuals with higher *Firmicutes/Bacteroidetes* community ratio phenotype.

The analysis of mice intestinal content after the administration of berberine, a major pharmacological component of the Chinese herb *Coptis chinensis*, which was originally used to treat bacterial diarrhoea, revealed a marked shift of the gut microbiota structure and has been demonstrated to be clinically effective in alleviating type 2-diabetes [122].

Administration of trans-resverastrol and quercetin could counteract gut microbiota dysbiosis, produced by high-fat and sucrose diet, attenuating *Firmicutes/ Bacteroidetes* ratio and inhibiting the growth of bacterial species previously associated to diet-induced obesity (*Erysipelotrichaceae*, *Bacillus*, *Eubacterium cylindroides*) [35].

Summarizing the presented studies, it seems that the anti-obesity effect, characteristic to certain prebiotics, results exactly from their influence on the structure of the intestinal microbial flora. For this perspective, it is logical to assume that the therapies which are pursuing this goal will associate the probiotics and prebiotics, to take advantage of the synergistic effect.

Association of antibiotics

Attention has recently been drawn to the association between antibiotic use and weight gain in children and adults [72]. The possible mechanism is represented by a decrease in the diversity of intestinal flora, induced by antibiotics, because individuals with metabolic syndrome were also associated with a lower microbial diversity compared to the lean healthy subjects [117]. The richness of human gut microbiome has been linked to metabolic markers [58] and for this reason, a microbiota aggression like the antibiotic use may be a contributing factor to the increased incidence of obesity [22]. Actually, administration of antibiotics has been used for a long time as a growth promoter in animals. But, the effect on the intestinal microbial population may be different, depending on the used antibiotic. Thus, the administration of vancomycin in mice subjected to a high-fat diet has shown a smaller weight gain than in other mice, which followed a similar diet, with the same caloric content. The analysis of the intestinal microbiome has shown that vancomycin generated a change in the microbiome composition in the sense of a significant decrease in the proportion of *Firmicutes* and *Bacteroidetes*, but a dramatic increase of *Proteobacteria*, while maintaining the proportion of *Actinobacteria* at a level similar to the initial one. Other significant parameters of energy metabolism have also shown modifications after the treatment with vancomycin: lower fasting blood glucose, plasma TNFα and triglyceride levels compared with diet-induced obese controls. An increase in the proportion of *Bacteroidetes* and *Proteobacteria,* without a decrease in the proportion of *Firmicutes*, obtained by the administration of bacteriocin-producing probiotic, had no significant impact upon the metabolic profiles of the obese mice. The authors' conclusion was that the utilization of a specific antibiotic may be critical in the modification of intestinal microbiome as a therapeutic solution for improving the metabolic abnormalities associated with obesity [77].

Conclusions

Probiotics present a great therapeutically potential, still insufficiently explored, in the management and prevention of obesity. The studies previously depicted can be considered a strong argument for the necessity of conceiving a specific probiotic, able to induce the development of an intestinal ecosystem, which will promote a decrease in the host weight. Ideally, this should include strains that proved positive effects upon metabolism (e.g. *Lactobacillus gasseri*, *Lactobacillus rhamnosus*, *Lactobacillus curvatus*, *Lactobacillus plantarum* etc.) and should not contain strains that promote energy harvest (e.g. *Lactobacillus acidophilus* etc.). The administration of these probiotics should be carried out over a period of time long enough to produce sustainable modifications of the intestinal microbial flora, which will determine significant effects upon body weight (at least 12 weeks).

However, the modification of intestinal flora *via* this type of therapeutic agents is complex and should take into account both the type of the selected

strains and the necessity to create an environment which promotes survival and development. For this reason, an efficient therapy should also include therapeutic agents such as prebiotics (e.g. inulin, polyphenols, trans-resveratrol, quercetin etc.) and moreover, even an antibiotic (e.g. vancomycin) in order to reset a compromised microbial flora. Also, the modification of the environmental factors that generated the dysbiosis, such as the diet and sedentary lifestyles, is an important premise for the success of this therapy in the long term obesity management and prevention.

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