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The Effects of Probiotics on Body Weight and Biomarkers of Animal

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Abstract: Obesity is associated with the alteration of the gut microbiota. In order to determine the effects of probiotics on body weight management and its related biomarkers we performed a systematic review using clinical trial, interventional and experimental studies. We performed a broad search with no date restriction. Primary outcomes were included the parameters related to body weight management. Secondary outcomes were inflammatory markers, lipid profile, blood glucose and insulin level. A total of 12 animal studies were identified. Among these, six studies reported the significant changes in body weight and all the studies had documented significant improvements in at least one body weight related parameter. However, inflammatory markers and lipid profile were significantly improved in the animal model; changes in body weight and energy intake that could be due to probiotics supplementation were controversial. Different strains of gut microbiota have different effects on weight changes. Further studies are needed to identify the role of gut microbiota on weight regulation of human.

Key words: Probiotic, gut microbiota, weight regulation

INTRODUCTION

Obesity, is characterized by abnormal or excessive fat accumulation in the body (Mathur *et al*., 2011) which is now considered as an epidemic health problem worldwide. Several common diseases, such as Cardiovascular Disease (CVD), stroke, type 2 diabetes, arthritis, as well as several types of cancer are linked to obesity (Schmid *et al*., 2006). Prevalence of obesity had an upward trend in the world over the past decade which cannot be solely attributed to changes in the human genome, nutritional habits, or reduction of physical activity in our daily lives. Recently, some studies suggested a potential causality between some specific strains of bacteria or gene functions with obesity. On the other hand, previous studies (Bäckhed *et al*., 2007) indicated an association between obesity with structural alterations in the gut microbiota in animals and humans. Animal studies revealed that the related underlying mechanisms of the gut microbiota on obesity is due to adiposity and nutrient digestion and absorption (Semova *et al*., 2012). There are two possible explanation for the effect of gut microbiota on the obesity; Firstly, the ability of the host to extract energy from the diet will be improve through mediating the breakdown of indigestible polysaccharides (McNeil, 1984). Secondly some metabolic products such as propionate may attribute to beneficial roles of the gut microbiota (Al-Lahham *et al*., 2011). Energy balance also can be affected by conventional microbiota or specific commensals, modifying the expression of genes involved in macronutrient metabolic pathways and production of neuroendocrine factors in the gut and beyond (Samuel *et al*., 2008). In more recent studies, it has been reported that diet is a primary factor which can influence the microbiota structure initially related to an obese phenotype in animals (Fleissner *et al*., 2010; Murphy *et al*., 2010) and in humans (Jumpertz *et al*., 2011), suggesting that, the secondary factor is the role of microbes in energy balance. Microbiota composition alteration with diet is via the regulation of energy balance, including lipid absorption and energy harvest (Jumpertz *et al*., 2011). The interest of investigating the role of gut microbiota in obesity is also due to their consumption as probiotics such as *Lactobacillus* spp. and *Bifido bacterium longum*. Arguments supporting the role of probiotics in human obesity are based on their use in farm animals, as an alternative to antibiotics, to promote growth, as well as the analysis of mixed data from both animal and human interventions (Million *et al*., 2012) which have been the subject of opposing interpretations. Herein, evidence about the relationships between the gut microbiota composition and obesity, as

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well as the role played by probiotics in this disorder are reviewed in the light of data from intervention trials conducted in animals models.

MATERIALS AND METHODS

Data sources: Literature search was conducted according to the PubMed, Google scholar, Medline, ISI Web of knowledge, Cochrane Central Register of Controlled Trials (www.cochrane.org) and a recent evidence report/technology assessment restricted by language with no date restriction. The search terms were included: probiotics, obesity, weight management, weight loss, weight gain, *Lactobacillus* and *Bifidobacterium*.

Study selection and data extraction: The full text of studies including *Lactobacillus* or *Bifidobacterium* containing probiotics in the English language was used. We looked for weight management as a primary outcome. Inclusion criteria was the interventional, experimental and clinical trial studies in animal models. Exclusion criteria included human studies, synbiotics, prebiotics, systematic reviews, as well as study protocols.

Although, there are a large number of animal studies but meta-analysis could not be applied due to the variability in the duration of intervention, species of animals being studied and the strains of probiotics supplemented.

RESULTS

Thirty two studies were yielded through the search of which 20 were excluded due to not being constant with inclusion criteria (interventional, experimental and clinical trials studies in animal models). Finally, a total of 12 studies were selected for this review.

Since animal studies were not being blinded to the researchers, they had the same quality and only three of them mentioned about random allocation (An *et al*., 2011; Andersson *et al*., 2010; Naito *et al*., 2011). In order to determine the changes in body weight and fat mass various species of rats and mice were used (Table 1). The probiotic strains were either *Lactobacillus* or *Bifidobacterium*.

Changes in primary outcomes: Primary outcomes included changes in the body weight, food and energy intake, body fat mass and adipocyte size.

Although some previous studies reported that the probiotic supplementation, either *Lactobacillus strain* or *Bifidobacterium*, will attenuate the body weight gain (Matsuzaki *et al*., 1997), some others indicated that there is not a significant differences in the weight changes of control group with diet supplemented by probiotics group Chen *et al*. (2011); Hamad *et al*. (2009); Ma *et al*. (2008); Sato *et al*. (2008). Among the 12 studies which evaluate the effect of different types of bacterial strain on the body weight changes as well as body fat mass, six of them reported a significant reduction in weight gain.

Changes in adipose tissue weight and adipocyte size were controversial. Some previous studies (Chen *et al*., 2011; Sato *et al*., 2008) indicated that probiotic administration does not make changes in adipose tissue weight. However, Kang *et al*. (2013, 2010) reported that fat mass in white adipose tissues (mesenteric, subcutaneous, epididymal and perirenal) of diet supplemented probiotic group will be suppressed as compared to the control group. Moreover, probiotic containing diet affects the average adipocyte size. Sato *et al*. (2008) reported a significant reduction in average adipocyte size in mesenteric white adipose tissue ($p = 0.004$) of rats which were fed by *Lactobacillus gasseri SBT2055* (LGSP). They observed that, the numbers of small adipocytes from retroperitoneal and mesenteric of the rats fed the LGSP diet was significantly higher than those on the control group. Changes in the weight of adipose tissue and adipocyte size were accompanied by changes in daily energy and food intake. In a subsequent study by the same researchers on the obese Zucker rats, the average of food intake and consequently body-weight gain was higher in the Zucker obese rats in comparison with the lean rats ($p<0.001$). There was not a significant difference in the food intake per day of the rats fed with LGSP with standard fed groups (SD) (Lee *et al*., 2006).

Changes in secondary outcomes: Secondary outcome detected in these studies included inflammatory markers, lipid profiles, liver profiles, leptin and adiponectin hormones concentrations, blood glucose and insulin level.

Among 12 studies that examined inflammatory markers, eleven reported significant improvement in at least one marker.

There are controversial results regarding the effects of probiotics on interleukin (IL). Although Zarfeshani *et al*. (2011) indicated a significant reduction in the level of the IL-6 was using *Lactobacillus Casei*, Anderson *et al*. (2010) showed no changes in the levels of IL-6 in the case and control groups. The effect of probiotic on other inflammatory markers such as C-Reactive Protein (CRP) is also inconsistent (Zarfeshani *et al*., 2011). Beneficial effect of oral administration of *Lactobacillus casei* strain *Shirota* on insulin resistance in diet-induced (Naito *et al*., 2011) obesity mice as endotoxaemia markers were significantly decreased with probiotics supplementation. Furthermore, Chen *et al*. (2012) reported there is a significant inhibition of inflammatory parameters (IL 1b, myeloperoxidase and histological inflammatory activity index) using *bifidobacterium*. However, probiotics did not affect the serum amiloid A (an acute-phase protein that has been correlated with obesity and insulin resistance) (Andersson *et al*., 2010).

Table 1: Characteristics and Results of the animal reviewed studies

Probiotic strain	Animal model	Type of diet	Duration	Primary outcomes	Secondary outcomes	Reference
L. paracasei ST12 (NCC2461)	8 male wistar rat	High fat diet	12 weeks	↓ weight gain, ↓abdominal fat/S	↑ plasma FFA level /S	Tnida et al. (2008)
B. longum SPM 1204, SPM 1205, SPM 1207	36 male Sprague-Dawley (SD) rats	High fat diet	7 weeks	↓ weight gain, /S food intake, weight of spleen, kidney, heart, liver/NS	↓ TC, HDL-c, LDL-c, Tg, glucose, leptin, AST, ALT and lipase levels.a-Amylase levels/S	An *et al*. (2012)
B. longum BL1	21 male Sprague-Dawle (SD) rats	AIN93M+14% protein	3 weeks	↑body weigh/NS	↓TC, LDL-c, Tg, S/ HDL-c, phospholipid, ↑bile acid excretion in fecal NS	Xiao *et al*. (2003)
Bifidobacterium spp.	32 Male C57bl6/J mice	High fat diet (49.5%)	14 weeks	↓weight gain, body fat mass, energy intake/S	improved fasting plasma insulin levels and restored glucose-induced insulin secretion, ↓IL-1α, IL-1βand IL6, TNF-α /S	Cani *et al*. (2007)
L. gasseri SBT2055	Male Sprague-Dawley rats	Skim milk (34.7% pr)	4 weeks	↓adipocyte size in mesenteric white adipose tissue, ↑No. of small adipocytes in mesenteric and retroperitoneal adipose tissue/S, Body weight gain, adipose tissue, liver weight/NS	↓liver TAG, leptin /S, ↓serum lipid, glucose level, adiponectin /NS	Sato *et al*. (2008)
L. acidophilus aTCC 4356 and 43121supernatants.	38 male Sprague-Dawley (SD) rats	Na	1 injection in CNS	↓body weight/S	↑Leptin expression in brain and retroperitoneal adipose tissue/S	Fukuchi *et al*. (2007) Ma *et al*. (2009)
Bifidobacteria+Lactobacilliands +Streptococcus thermophilus	Wild-type male C57BL6 mice	High fat diet (60%)	4 weeks	↓weight gain/NS	↑Hepatic NKT cell numbers, ↓Inflammatory signaling improving steatosis and insulin resistance	
L. gasseri SBT2055 (LGSP)	Zucker rats	Skim milk	4 weeks	Body weight gain, food intake/NS	↑liver weight, ↓total, mesenteric and subcutaneous adipose tissue masses, ↓LPL activity, TC, HDL-c, hepatic phospholipid, /S, liver TAG/ NS	Hamad *et al*. (2008)
L. Cassei shirota	male C57BL/6J DIO (DIO) mice,	High fat diet	5 weeks	Body weight gain, energy intake/NS	↑insulin sensitivity, ↓blood glucose/S	Naito *et al*. (2012)
L. gasseri BNR17	Male C57BL/6J mice	High sucrose diet	10 weeks	↓body weight gain, fat mass in white adipocyte tissue, average adipocyte size in mesenteric, subcutaneous, epididymal and perirenal adipose tissues/S Daily food intake/NS	↓insulin, leptin/S, ↓TC, LDL-c, glucose/NS	Kang *et al*. (2013)
L. gasseri BNR17	male sprague-dawley (SD) rats	High carbohydrate diet	12 weeks	↓body weight gain, weight of MFPs, PFPs, EFPs/S	↓TC, LDL-c, Tg, HDL-c, total-pr/NS	Kang *et al*. (2010)
B. longum	Male wistar rats	High fat diet	12 weeks	↓weight gain, fat mass/NS	↓TG, IL-1β, MPO, HAI, FBS, LBP/S	Chen *et al*. (2012)

S: Significant, NS: Non-Significant, TC: Total Cholesterol, TG: Triglycerides, LDL-C: Low Density Lipoprotein, VLDL-C: Very Low Density Lipoprotein, FFA: Free Fatty Acid, HDL-C: High Density Lipoprotein, TAG: Triacylglycerol, NEFA: non-esterified fatty acids, IL-6: Interleukin 6, CRP: C Reactive Protein, IL-1β: Interleukin 1β, FBS: Fasting Blood Sugar, MPO: Myeloperoxidase, HAI: Histological Inflammatory Activity Index, LBP: Lipopolysaccharide-Binding Protein, MFPs: Mesenteric fat pads, PFPs: Perirenal fat pads, EFPs: Epididymal fat pads

Although, there was a significant improvement in lipid profiles (TC, HDL-c, LDL-c, Tg) of studies which used *Bifidobacterium longum* (An *et al*., 2011; Chen *et al*., 2011; Xiao *et al*., 2003), *Lactobacillus gasseri SBT 2055* (Hamad *et al*., 2009) and *lactobacillus acidophilus* (Yadav *et al*., 2007) but those which used *lactobacillus gasseri BNR17* did not show any changes (Kang *et al*., 2010, 2013).

An *et al*. (2011) showed that as compared with the High Fat Diet (HFD) group, the HFD-*Lactobacillus* (LAB) group had slightly decreased alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, leptin and lipase levels. They also reported that the level of α-amylase levels were not different between trial and control groups.

The effects of different kind of bacteria strains on the gastrointestinal hormones involved in body weight managements such as leptin was investigated in this review. Unlike some studies which showed that the level of leptin decreased using probiotic supplementation (An *et al*., 2011; Kang *et al*., 2013), Sousa *et al*. (2008) (Sousa *et al*., 2008) by immunoblotting of protein extracts from intestines and from retroperitoneal adipose tissue showed a mild increase in the level of leptin and leptin receptors.

DISCUSSION

We aimed to determine the effects of probiotic supplementation on obesity, weight management and related metabolic disorders in animal models. Based on the findings, probiotic supplementation will probably improve weight reduction as well as related metabolic disorders in obesity in animals.

Probiotic, body weight and fat mass: Six out of 12 animal studies did not show a significant reduction of body weight and fat mass between the supplemented groups with bacteria compared to the control group (Hosono, 1999; Kang *et al*., 2010, 2013; Lee *et al*., 2006; Matsuzaki *et al*., 1997). The possible reason for not achieving the desired result can be short duration of the intervention. Mechanisms by which probiotics might regulate body weight have not been clearly understood. One of the possible pathways of the effects of probiotic on the host is through reducing the leptin level, an anti-obesity hormone. Leptin is a 16 KDa secreted protein which is produced by the ob gene. Body weight managements will be regulated through controlling energy expenditure and food intake by leptin (Friedman, 2002; Jéquier, 2002). Leptin is produced by the adipose tissue and is released into the blood-stream. In parallel to fat deposits growth; the levels of blood leptin tend to increase. Therefore, there is a relation between level of leptin in blood with the percentage of body fat; markedly obese individuals have higher serum level of leptin as compared with non-obese individuals (Considine *et al*., 1996). In contrast, underweight individuals has markedly lower level of leptin compared with normal weight individuals (Ferron *et al*., 1997).

Furthermore, the specific mechanism (s) by which the diet supplemented by microbiota strain reduces the size of adipose tissue remains unknown. The suppression of the adipocyte hypertrophy is a possible mechanism of adipocyte size regulation by the *Lactobacillus gasseri SBT 2055* (LGSP) diet. Reduction in the energy input (intestinal absorption of lipids) may be resulted in the suppression of adipocyte hypertrophy by the LGSP diet. Hamad *et al*. (2009) reported that the maximum lymphatic absorption of phospholipids, triacylglycerol (TAG) and cholesterol in Sprague-Dawley rats will be decreased using LGSP diet. In addition, they reported that the LGSP diet will attenuate the absorption of dietary fat which can be supported by the elevation of the fecal Non-Esterified Fatty Acids (NEFA) excretion levels. This effect of the LGSP diet might be due to its ability to bind intestinal lipids. It was found that *L. gasseri SBT2055* has the ability to bind intestinal cholesterol (Hosono, 1999). In addition, lymphatic lipids absorption decreased by using the LGSP diet via the binding of lipids and consequently decreased the energy input which affected adipose tissue hypertrophy. This point requires further research in order to elucidate the mechanism involved.

Probiotic and lipid profile: There are controversial results regarding the effect of probiotic on lipid profile. However, Kang *et al*. (2013) did not show any significant changes in the lipid profile of the rats supplemented by *Lactobacillus gasseri BNR17*, the hypocholesterolemic effects of the some bacteria strains, including *Lactobacillus acidophilus* (Park *et al*., 2008) and *Bifidobacterium longum* (Xiao *et al*., 2003), has been established in previous studies. In addition, An *et al*. (2012) found that levels of triglyceride (TG), aspartate aminotransferase (AST), alanine amino transferase (ALT) and glucose in serum were reduced in HFD-LAB group as compared to the control group. Similar results have been observed with some specific probiotics strains (Lee *et al*., 2006; Yin *et al*., 2010). The mechanisms involved may be as follows (Rao *et al*., 2006; Suzuki *et al*., 1991):

1. the bacteria will bind with cholesterol which result in inhibiting the absorption of cholesterol back into the body
2. cholesterol elimination in feces will be facilitated by bacteria
3. cholesterol synthesis enzymes will be inhibited via fermentation products of lactic acid bacteria therefore, cholesterol production will be decreased
4. interference of the bacteria in the recycling of bile salt (a metabolic product of cholesterol) and facilitate its elimination which raises the demand for bile salt

made from cholesterol and thus results in body cholesterol consumption
5. the assimilation of lactic acid.

Probiotic and lipoprotein lipase (LPL): Among 12 reviewed studies, only two studies (An *et al*., 2011; Hamad *et al*., 2009) examined the effect of probiotic supplementation on LPL activity. According to their results LPL activity of will be decreased in the rats supplemented with probiotic compared to the control group. Hamed *et al*. (2008, 2009) indicated that, the LGSP diet consumption in obese rats make an increment in number of smaller adipocytes in the subcutaneous adipose tissue. Although the reason for this finding is unknown, they found a significant genotype and diet interaction on the LPL activity in sub-cutaneous adipose tissue of Zucker rats. Therefore, increase in the tendency towards reduced LPL activity in the obese rats might be due to the increased number of smaller adipocytes. The exact mechanism of probiotic on LPL activity is not clear yet. So, further researches are required to make this finding clearer.

Probiotic and inflammatory factors: Plasma concentrations of IL-6, IL-1β and IL-1α are increased in relation to high fat diet consumption. However, probiotic supplementation can prevent this increment. It seems that there is a linkage between bifidobacteria and endotoxaemia with metabolic disorders such as obesity. According to the previous studies, obese and diabetic mice (ob/ob and db/db) had higher plasma endotoxin levels which is correlated to higher plasma inflammatory markers (Brun *et al*., 2007; Cani *et al*., 2007). Indeed, there is an association between bifidobacterial supplementation with lower endotoxaemia and bacterial translocation which may result in a decrease of the inflammatory cascade activation in several models of gut bacteria translocation (Griffiths *et al*., 2004; Thomson, 1999; Wang *et al*., 2004).

Probiotic, blood glucose level and insulin: Two out of six studies (Kang *et al*., 2013; Sato *et al*., 2008) which determined the effect of probiotic on blood glucose and insulin, did not show significant differences in blood glucose and insulin level between the probiotics supplemented groups with control group. One of these studies used *Lactobacillus gasseri BNR17* (Kang *et al*., 2013) and the other used *Lactobacillus gasseri SBT2055 (LGSP)* (Sato *et al*., 2008). These results hardly reflect the effect of using different strains of probiotics. Fukuchi *et al*. (2004) indicated that blood glucose and insulin level in rats with high sucrose diet may be change but these metabolic abnormalities are time- or tissue-dependent (Fukuchi *et al*., 2004).

Conclusion: Beneficial effects of probiotic supplementation on the weight management have been indicated by most of the reviewed articles. Therefore, probiotic supplementation can be used to either prevent or manage the body weight gain. Hence, the effectiveness of the bacteria strains separately and in combination (*Lactobacillus*, *Bifidobacterium*) on the human weight management are still unclear. This question deserves further studies.

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