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Effects of Gut Microbiota and Probiotics on Obesity

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Abstract

Intestinal microbiota having important effects on energy homeostasis is associated with obesity and many metabolic diseases. The presence of "dysbiosis" seen with the imbalance of the ratio between the dominant bacterial phyla making up the microbiota plays a role in the pathogenesis of obesity. In the case of dysbiosis, the permeability of the intestinal barrier increases and the synthesis of short-chain fatty acids with significant metabolic effects decreases. Glucose and lipid metabolism is disrupted in the host organism, the susceptibility to inflammation increases and the metabolic endotoxemia results in obesity with these physiological changes in dysbiosis. Therefore, the use of probiotics has come to the forefront in recent years to protect the functional integrity of the intestinal microbiota and to prevent dysbiosis. As the result of various experimental and clinical studies conducted in probiotic applications, the mechanisms that can have an effect on energy metabolism and obesity development have been revealed. Accordingly, it has been reported that *Bifidobacterium* and *Lactobacillus* spp. strains, which are the main components of probiotics and nutritional supplements, have beneficial effects on obesity or metabolic complications (abnormal lipid profile and high glucose level) in animal studies. The effect of probiotics on weight control is not only a direct effect but also an indirect effect against harmful bacteria in the gut. The general limitations of all these studies are stated as small sample sizes and not having longer follow-ups.

1. Introduction

Obesity is considered to be an outbreak triggering the development of metabolic diseases such as type-2 diabetes, cardiovascular diseases, osteoarthritis, and some cancer types (Jiang, Lu, Zong, Ruan and Liu, 2016). While the obesity prevalence has been rapidly increasing, the recent data show that there are 600 million cases of obesity in the world (Cao et al., 2019). Obesity is mainly associated with the difference among disrupted energy balance, energy intake and energy consumption. However, changes in energy balance are not sufficient to explain the increase in obesity incidence (Kayser and Verges, 2013).

Although the therapeutic methods such as diet therapy, exercise, bariatric surgery and pharmacotherapy applied in the treatment of obesity, it is seen that the prevalence of obesity is on the rise all over the world (Cao ve ark. 2019 & Kazemipoor et al., 2015).

In recent years, obesity has been associated with structural changes in animal and human gut microbiota (Wardle, Griffith, Johnson and Rapoport, 2000). Accordingly, imbalanced gut microbiome (dysbiosis) and the decrease in microbiological diversity trigger the development of obesity (Turnbaugh et al., 2009 & Nieuwdorp, Gilijamse, Pai and Kaplan, 2014). In addition, it has been stated that gut microbiota is a potential indicator in obesity by contributing to food digestion, absorption, and adiposity (DiBaise, Frank and Mathur, 2012).

Therefore, the effects of gut microbiota on obesity has become the focus of research in recent years and a potential efficient target in obesity treatment. The aim of the present study is to investigate the relationship between gut microbiota and obesity and to examine the effects of probiotic responses affecting the composition of gut microbiota on obesity.

2. Gut Microbiota

Human gut microbiota, which is more in number than the total size of eukaryotic cells in the human body and host many bacterial phyla such as *Bacteroidetes*, *Firmicutes* is estimated to have 1014 bacteria types ((Azad, Kalam, Sarker, Li and Yin, 2018). According to recent studies, it has been found that the phyla that are the most in number in human microbiota are *Bacteroidetes* (*Porphyromonas*, *Prevotella*, *Bacteroides*), *Firmicutes* (*Ruminococcus*, *Clostridium*, *Lactobacillus and Eubacteria*), and *Actinobacteria* (*Bifidobacteria*) bacterial communities (Aagaard et al., 2014).

It is considered that a fetus is almost deprived of any bacterial communities or sterile during the intrauterine period. It has been reported that primitive microbiota is formed by a transfer from the mother to fetus's intestine during the labor (Koenig et al., 2011). Although the composition of gut microbiota is affected the most by the host genotype, the type of food and medication used, and changes in gut physiology in the early years, these factors may vary remarkably with age and dietary type (Franzosa et al., 2015 & Natividad and Verdu, 2013).

Microbiota has important physiological functions for the host. Among these are protecting the integrity of intestinal barrier (Den Besten et al., 2013), having a role in energy homeostasis (Bäumler and Sperandio,

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2016), protecting intestines against pathogenic bacteria (Gensollen, Iyer, Kasper and Blumberg, 2016) and regulating the immune system (Anastasiou, Karfopoulou ve Yannakoulia, 2015).

3. Gut Microbiota and Obesity

A hypothesis indicating that the composition of gut microbiota in healthy adults has an impact on the development of obesity and several metabolic diseases has been put forward with the human microbiome project (Arslan, 2014).

Gut bacteria are used in several and different mechanisms such as obtaining energy from food, lipopolysaccharide-induced chronic inflammation, regulating the storage of fatty acids in tissues, and peptide secretion in the gut (Thursby and Juge, 2017).

Imbalances caused by the disruption in the composition of gut microbiome, also known as 'dysbiosis' lead to a disruption in physiological functions of the microbiota (Clemente, Ursell, Parfrey and Knight, 2012) and obesity (Dreyer and Liebl, 2018). Obesity or increased body weight is associated with the ratio of the two dominant phyla in the gut microbiota, *Firmicutes* and *Bacteriodetes* (F: B) (Mathur and Barlow, 2015). Differences in the composition of gut microbiota in healthy and obese individuals have been shown to play a critical role in the pathophysiology of metabolic diseases and obesity (DiBaise et al., 2012). In obese individuals, this ratio has been found out to be higher compared to thin individuals (Sweeney and Morton, 2013 & Le Chatelier et al., 2013). In obese individuals with a dysbiotic gut flora, it has been reported that the bacterial diversity and richness of gut microbiota is less (Bakker, Zhao, Herrema and Nieuwdorp, 2015).

It has been reported that there are various evidence regarding the mechanisms of gut microbiota, having an effect on the host's energy metabolism and the development of obesity (Gérard, 2016 & Al-Assal, Martinez, Torrinhas, Cardinelli and Waitzberg, 2018). One of these mechanisms is conducted by short-chain fatty acids functioning in energy regulation (Schwiertz. 2010). The fermentation of undigested carbohydrates (dietary fiber) results in the formation of short-chain fatty acids (SCFA) such as propionate and butyrate in the gut. SCFA synthesized in gut flora provides approximately 10% daily energy need and is responsible for almost 75% of energy metabolism in colonic epithelium. In a study conducted with obese individuals, SCFA rate in gut has been found to be 20% more compared to thin individuals and the study has revealed the importance of microbiota in obesity etiology (Chakraborti, 2015). Accordingly, it has been underlined that SCFA rate may affect the host's metabolism rate and determine the direction of energy balance (Carvalho and Abdalla Saad, 2013).

In addition, these newly-formed short-chain fatty acids activate two receptors on G-protein in the cell wall (GPR41 and GPR43) (Chaudhri, Salem, Murphy and Bloom, 2008) and triggers peptide YY expression, which is an anorexigenic hormone slowing down the intestinal pathway and decreasing food intake (Lin et al., 2012 & Koliwad et al., 2009).

Another mechanism is lipoprotein lipase-induced. Accordingly, the expression factor called 'fasting-induced adipose factor (Fiaf)' and secreted in the gut flora inhibit the lipoprotein lipase enzyme and

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increases the level of a protein called 'angiopoietin-like 4', regulating lipolyze (Mandard et al., 2004). Some gut bacteria suppress the production of intestinal Fiaf; thereby causing the storage of fat as energy with the increase in lipoprotein lipase activity (Jansen, 2010). It is also known that gut microbiota deconjugates and dehydrolyzes bile acids taking a role in fat metabolism (Sayin et al., 2013). Therefore, it has been reported that microbiota, with the modulation of bile acid, can suppress diet-induced obesity via increased energy consumption (Gøbel, Larsen, Jakobsen, Mølgaard and Michaelsen, 2012).

In addition, gut microbiota may lead to obesity and metabolic disorders by triggering systemic inflammation. In the intestinal barrier which has been induced due to dysbiosis in the gut, chronic low-grade inflammation is thought to be an important trigger for the development of obesity (Cani et al., 2007). Gram negative bacteria attach to lipopolysaccharides (LPS) and Toll-like receptors in the cell wall due to the imbalance in gut microbiota and causes an inflammatory cytokine response (Schwiertz, 2010 & Bäckhed et al., 2004). In addition, it triggers obesity by attaching to peroxisome proliferator-activated receptor functioning in the LPS beta-oxidation process (Bäckhed, Manchester, Semenkovich and Gordon, 2007).

4. Probiotics and Obesity

Probiotics are defined as "live microorganisms having a beneficial effect on the host when administered in adequate amounts" by The Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO, 2002).

Probiotics have the ability to compete against gastrointestinal pathogens through the productions of antimicrobial components such as short-chain fatty acids, nitric oxide, bacteriocin or hydrogen peroxide and to reinstate the gut microbiota balance (Dahiya et al., 2017).

In addition, it has been underlined that microbiota has a huge impact on the onset or development of obesity (Mazloom, Siddiqi and Covasna, 2019). Therefore, it has come to the forefront that gut microbiota can be manipulated through diet or other means in order to provide functional integrity of the gut microbiota and to eliminate dysbiosis. Accordingly, probiotics which have been investigated extensively in order to positively manipulate the composition of gut microbiota, have been the center of interest in studies related to obesity (Yadav, Lee, Lloyd, Walter and Rane, 2013).

In animal and human studies conducted with probiotic administrations, *Lactobacillus* and *Bifidobacterium* spp. strains have been investigated on obesity mainly and that these strains could have "anti-obesity" effects (Park et al., 2013 & Kim, Jeong and Kim, 2015 & Ivey et al., 2014).

5. The Use of Probiotics in Obesity Treatment

A hypothesis suggesting that the composition of gut microbiota or metabolic functions could be an alternative in terms of supporting probiotics with natural and safe components, preventing obesity and related diseases, and their treatment (Chang et al., 2011). Several clinical and experimental studies have been conducted on this subject-matter (Chang et al., 2011 & Rajkumar et al., 2014 & Alcock, Maley and Aktipis, 2014).

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In line with the hypothesis indicating that gut diversity could be increased with adding probiotics into diets, it has also been suggested that excessive eating could be controlled, and food intake could be decreased (Million et al., 2012). It has been reported that probiotics are effective in reducing body weight by providing conjugated linoleic acid production from linoleic acid (Lee et al., 2007), suppressing leptin (Karlsson et al., 2011), increasing fasting induced appetite factor expression ((Bäckhed, Manchester, Semenkovich and Gordon, 2007). and insulin sensitivity (Naito et al., 2011) and reducing oxidative stress (Awney, 2011). Changes in the gut microbiota induced by the addition of probiotics have been associated with changes in body weight both in animals and humans ((Kadooka et al., 2010 & Kootte et al., 2012).

In studies conducted on animal models, many *Lactobacillus* and *Bifidobacterium* spp strains, the main components of probiotic supplements have been reported to have beneficial effects on obesity and metabolic complications (abnormal lipide profile and high glucose level) (Kondo et al., 2010 & Yoo et al., 2013).

One of these studies has reported that the probiotic supplement called *Lactobacillus plantarum KY1032*, simultaneously administered with *Lactobacillus Curvatus* HY7601 or *Lactobacillus curvatus* HY7601 to the rats fed with a high-fat and high-cholesterol diet, for 9 weeks, has suppressed the increase of body weight and fat tissue (Yoo et al., 2013). In another 6-week study where probiotic supplement composed of same lactic acid bacteria (*Lactobacillus Curvatus* HY7601 and *Lactobacillus curvatus* HY7601*)* administered orally to the rats, it has been found that there was a significant decrease in body weight and blood leptin level (Jeung and et al, 2019). In a very recent study, it has been found out that *Lactobacillus paracasei* CNCM I-4270, *Lactobacillus* rhamnosus I-3690 or *Bifidobacterium animalis subsp. lactis* I-2494 strains have remarkably decreased weight gain as a result of the use of probiotic supplements in rats fed with a high-fat diet for 12 weeks without any dietary response ((Wang et al., 2020).

Similarly, it has been underlined that *Lactobacillus plantarum* No. 14 (LP14) strain might be beneficial in preventing obesity by suppressing lipogenic gene expression and reducing the cell size of white fat in rats fed with a high-fat diet (Takemura, Okubo and Sonoyama, 2010). In another study conducted on rats for 24 weeks, rats have been administered *Lactobacillus gasseri* SBT2055 (LG2055) strain with a diet containing 10% fat. In conclusion, a significant decrease in triglyceride level and body weight has been observed (Takemura, Okubo, Sonoyama and Kadooka, 2014) Parallel to the results of these studies, in some other experimental studies carried out with *Lactobacillus gasseri* SBT2055, the decreasing effect on the body weight has been observed. (Den Besten et al., 2013 & Kootte et al., 2012).

In a study conducted by Roselli et al. with *L. rhamnosus (LGG)* and L. *acidophilus* LA1 / K8 strains of *Lactobasillius* for 8 weeks, it has been seen that the regular use of probiotics as a mix of *L. rhamnosus* (LGG) and *L. acidophilus* LA1 / K8 (La) has reduced body weight gain (Roselli et al., 2019),

In a study conducted with rats in order to demonstrate the effect of several strains of bifidobacteria on body weight, it has been observed

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that the response of *Bifidobacterium pseudocatenulatum* SPM 1204, *Bifidobacterium longum* SPM 1205 and *B. longum* SPM 1207 strains has reduced body weight gain in rats fed with a high-fat diet (An et al., 2011).

In a rat study conducted by Yin et al. (Yin et al., 2010) for 6 weeks, the effects of 4 different bifidobacterial strains (*Bifidobacteria L66-5, L75-4, M13-4 and FS31-12*) on some biochemical parameters associated with obesity have been investigated. It has been concluded that *Bifidobacterium L66-5* strain has caused a significant increase in body weight. The other two remaining *Bifidobacterium* strains (*L75-4 and FS31-12*) have been found to have no significant effect on body weight. In addition, it has been thought that the intentional manipulation of gut microbiota could be a helpful strategy in obesity treatment given that fact that all strains have significantly reduced liver and serum lipide levels. It has been reported that the response involving a probiotic supplement of *Bifidobacterium animalis subsp. lactis* BB-12 strain alongside with fructooligosaccharides has significantly reduced energy intake, body fat mass, and body weight in obese rats (Bomhof et al., 2014).

Despite being limited, in meta-analysis studied obtained from clinical studies conducted on humans, it has been reported that there have been significant changes in BMI after probiotic responses administered as food or food supplement (Zhang, Wu and Fei, 2016). Details demonstrate that weight gain has been associated with *Lactobacillus reuteri, Lactobacillus sakei, Lactobacillus acidophilus* and *Lactobasillius casei* responses whereas weight loos has been associated with *Lactobacillus gasseri, Lactobacillus amylovorus* and *Lactobasillus plantarum* strains in human studies (Agustina et al., 2013 & Štšepetova et al., 2011 & Vendt et al., 2006).

A 24-week clinical study conducted on obese female and male individuals with the combination of probiotic supplement (*Lactobacillus rhamnosus* CGMCC1.3724 (LPR)) and hypocaloric diet has demonstrated that probiotic supplement in the treatment process has caused a significant decrease in body weight and body weight only in women. Therefore, it has been stated that long-term LPR probiotic supplement supports obesity treatment since it has caused an increase in satiety, improvement in appetite control, and positive behaviors in obesity management in women (Sanchez et al., 2014). In a 10-year follow-up study conducted by Luito. (Luoto, Kalliomäki, Laitinen and Isolauri, 2010), it has been observed that the use of probiotics containing *Lactobacillus rhamnosus* GG, ATCC 53103 strain, administered in the prenatal period and in the first 6 months after birth to the mother, might cause changes in the baby's gut microbiota; thereby having the chance to decrease weight gain in the early years of childhood.

In clinical studies conducted with *Bifidobacterium* strains, it has been reported that these strains are associated with body weight loss (Sanchis-Chordà et al., 2019 & Minami et al.,2018 & Pedret et al., 2019) A study conducted by Sanchis-Chorda et al. (Sanchis-Chordà et al., 2019) in order to analyze the effect of *B. pseudocatenulatum* CECT 7765 has demonstrated that the use of *B. pseudocatenulatum* CECT 7765 could improve BMI z-scores in obese children with insulin resistance. In a double-blind randomized study conducted on overweight adults, it has been observed that the use of *B. breve* B-3 has caused a decrease in body fat mass and fat

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percentage in a way that would support these results (Minami et al.,2018). *B. animalis subsp. lactis* CECT 8145 has caused a decrease in BMI, waist-to-height ratio, and insulin resistance in abdominal obese individuals (Pedret et al., 2019).

In several different studies, probiotics have been administered as fermented milk, yoghurt, or cheese which do not provide a chance to evaluate the number of live bacteria properly. In this case, probiotics also contain probiotic bacteria or prebiotic components fermented by the host microbiota. The administration of yoghurt containing *L. acidophilus* La5, *B. lactis* Bb12 *ve L. casei* DN001 to patients with high BMI has been found to be associated with a decrease in body weight, BMI, body fat percentage, and leptin level in addition to a decrease in serum levels of inflammatory parameters (Zarrati et al., 2013).

In a double-blind randomized controlled study effects of the consumption of functional yoghurt product with adding several probiotic types (*Streptococcus thermophilus, Lactobacillus acidophilus, Bifidobacterium infantis and Bifidobacterium breve (CBG-C2), Enterococcus faecalis FK-23)* on parameters related to metabolic syndrome have been analyzed. It has been concluded that there has been a decrease in body weight and body mass index after a response containing a fermented product supplemented with some bacteria strains. However, in contrast to other research results, the presence of other parameters affecting body weight and its relation to bacterial strains could not be found (Chang ve diğerleri, 2011).

Unlike *Lactobacillius* and *bifidobacteria*, the high prevalence of gram positive *Faecalibacterium prausnitzii* found commensally in the gut has been associated with obesity. If beneficial interactions of probiotic supplements used today could be explained better in a way based on scientific evidence, the modulation of gut microbiota with probiotic supplements could be a preventive approach in order to limit obesity and metabolic results in the future (Balamurugan et al., 2010).

3. Conclusion

Studies conducted on gut microbiota and obesity have been remarkably increasing and the effects of microbiota on energy metabolism have gained importance. It is considered that manipulating the gut microbiota with probiotic responses to eliminate dysbiosis could be a supportive approach in obesity treatment. Probiotics are safe since they are tolerated well, suitable to long-term use, and have no notified adverse reaction.

Although it has been reported that the use of probiotics has an effect on body weight, carbohydrate and fat metabolism by supporting the gut microbiota, it increases insulin sensitivity while decreasing the susceptibility to inflammation. Longer follow-ups and more clinical studies are required in order to analyze the effects of its use in obesity.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

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