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MINIREVIEW

Intestinal Microbiota, Obesity and Prebiotics

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Abstract

Over the past few decades there has been a significant increase in the prevalence of obesity in both children and adults. Obesity is a disease that has reached epidemic levels on a global scale. The development of obesity is associated with both environmental and genetic factors. Recent studies indicate that intestinal microorganisms play an important function in maintaining normal body weight. One of the objectives in the gut microbiota research is to determine the role it plays and can it be a reliable biomarker of disease risk, including the predisposition to obesity. This article discusses (1) the role of prebiotics and gut microbiota in maintaining a healthy body weight and (2) potential influence on the gut microbiota in the prevention and treatment of obesity.

Key words: microbiota, obesity, prebiotics, SCFA

Gut microbiota

The colonization of the human gastrointestinal tract begins within a few hours after birth but is not identical in all infants. The initial impact on the microbiota of the digestive system of children is determined by the impact of labor, hospital environment, food, mother/child diseases and drug use (Salminen and Isolauri, 2006). In the early years of life the gastrointestinal tract is colonized by bacteria belonging to the genus *Lactobacillus*, *Staphylococcus*, *Enterococcus*, *Escherichia*, *Enterobacter*, *Bifidobacterium*, *Bacteroides*, *Eubacterium* and *Clostridium* (Moore *et al.*, 2011; Libudzisz *et al.*, 2012). An intensive phase of colonization of bacteria in the human gastrointestinal tract usually lasts until two years of age, after which the child gut microbiota begins to resemble that of adults (Nowak and Libudzisz, 2008). Another change in the composition and quantity of microorganisms is in the elderly. There is a significant reduction in the quantity of bacteria of the genus *Bacteroides* and *Bifidobacterium*, where *Clostridium*, *Eubacterium*, and *Fusobacterium* begin to dominate. This change is related to the increase in the pH of the intestinal tract to approximately 7.0–7.5, which can cause gastrointestinal diseases in the elderly. Although the composition of the intestinal microbial changes during the human life span, in the healthy person it remains quite stable and has a "character of climax" (Nowak and Libudzisz, 2008). Strains of *Firmicutes* and *Bacteroidetes* account for more than 90% of the total population of the intestinal microbiota. At dominate genus level types are obligate anaerobes: *Bacteroides*, *Eubacterium*, *Clostridium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, *Bifidobacterium* and *Fusobacterium*, as well as facultative anaerobes: *Escherichia*, *Enterobacter*, *Enterococcus*, *Klebsiella*, *Proteus*, *Lactobacillus* (Shen *et al.*, 2013).

The gut microbiota have many beneficial functions, among them are: help in digestion; effect on immunity; stimulates the development of microvilli; fermentation of dietary fiber and prebiotics that are very beneficial to the human body short-chain fatty acids (SCFA) (butyric, propionic and acetic acids) as well lactic acid. Microbiota may play a beneficial role in the metabolism of potentially harmful substances such as cholesterol, nitrosamines, heterocyclic amines and bile acids (Neish,

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2002; Stewart *et al.*, 2004; Alan *et al.*, 2013). Microbiota may also be a source of antigens and harmful compounds, and even pathogens. The most preferred state for a human is a state of natural balance of microbiota (Everard and Cani, 2013; Walker and Lawley, 2013). Adverse changes to human health caused by the composition of microbiota are referred to as "dysbiosis" (Tamboli *et al.*, 2004; Feng *et al.*, 2010; DuPont and DuPont, 2011). The consequence of dysbiosis may be a leakage of the intestinal barrier and the reduction of the total quantity of SCFA (Clausen *et al.*, 1991). Dysbiosis may precede the clinical manifestations of intestinal diseases and is tied to the occurrence of colorectal cancer and inflammatory bowel diseases. Dysbiosis can also lead to serious systemic disorders (Tamboli *et al.*, 2004; Feng *et al.*, 2010; DuPont and DuPont, 2011).

Influence of diet on correct development of the gut microbiota

Ridaura (Ridaura *et al.*, 2013) found that the intestinal microbiota of lean and obese people induces a similar phenotype in mice, namely, that the microbiota transplanted from a lean individual (donor) causes the decrease of fat in obese mice (recipient) where mice were fed a reduced fat diet (4 wt%) and a high content of plant polysaccharides. In addition, research was done on four pairs of adult female twins, both lean and obese, from which the microbiota was transferred to germ-free mice. In animals that received microbiota from obese people, obesity developed; whereas mice containing intestinal microorganisms from a lean person had normal body weight (Ridaura *et al.*, 2013). Research was also performed to check whether isolates from stool specimens from a slim twin would colonize the intestine of germ-free mice colonized already inhabited by microbiota derived from an obese twin. It turned out that the isolates from the slim twin prevented the development of obesity in germ-free mice with the microbiota from the obese twin. Analysis of the microbiota of these mice showed increased participation of strains of *Bacteroides* in germ-free mice colonized with samples from the slim twin. This indicates that strains of *Bacteroides* and their quantity may have a significant impact on reducing the development of obesity, but it should be noted that it is important to determine not only the genus type but also the species of a given strain. Increased abundance of *Bacteroides* has been correlated with low fat diet that contained higher levels of fruit and vegetables; however, this correlation disappeared when diet proportions of ingredients were reversed (Ridaura *et al.*, 2013; Walker and Parkhill, 2013). It has been shown that bacterial strains derived from slim persons transferred to germ-free obese mice can prevent the formation of obesity when the mice diets consist of fiber, increased amounts of polysaccharides and small amounts of fat (Ridaura *et al.*, 2013). This indicates that the composition of the intestinal microbiota, and its effect on reducing the development of obesity is closely correlated with the consumed diet (Ridaura *et al.*, 2013).

Based on the dominance of certain types of bacteria, Arumugam (Arumugam *et al.*, 2011) has isolated three bacterial enterotypes: *Bacteroides*, *Prevotella* and *Ruminococcus*. The presence of a specific enterotype is not dependent on age, gender, or ethnicity. Wu (Wu *et al.*, 2011) demonstrated that enterotype is dependent on the type of diet. Consuming large amounts of saturated fats and proteins determine the development of enterotype *Bacteroides*, while enterotype *Prevotella* reveals itself in people whose diet consists of high amounts of saccharides and fiber and is low in fats and animal proteins. The type and proportions of the microorganisms present in the gut, *i.e.*, enterotype determines the metabolic products which have important consequences for the host. These metabolites can be either beneficial or harmful. For example, short-chain fatty acids (SCFA) are formed by the fermentation of indigestible polysaccharides in the large intestine by specific groups of bacteria (Archer *et al.*, 2004; Cani *et al.*, 2004; Delzenne *et al.*, 2005; Tarini and Wolever, 2010). SCFA have numerous positive functions and these include: butyric acid that stimulates intestinal epithelial tissue, nourishes the intestinal cells and affects their proper maturation and differentiation; propionic acid has a positive effect on the growth of hepatocytes; acetic acid has a positive effect on the development of peripheral tissues. SCFA regulate glucose and lipid metabolism, stimulate the proliferation and differentiation of intestinal enterocytes, lower pH effect on the intestinal contents, and thus help out in the absorption of minerals by increasing their solubility (Blaut and Clavel, 2007; Lin *et al.*, 2012). It has been shown that in spite of SCFA as a source of energy, it contribute toward reducing the formation of obesity by inhibiting fat accumulation in adipose tissue, increased energy expenditure and increasing production increase of hormones associated with the feeling of satiety (Keenan *et al.*, 2006; Gao *et al.*, 2009; Kimura *et al.*, 2013). Influence of butyric acid on regulation of energy homeostasis of the organism may be associated with stimulation of leptin synthesis in adipocytes, induction of GLP-1 secretion by L cells of intestine and increased fatty acid oxidation (Gao *et al.*, 2009; Nicholson *et al.*, 2012). In examining the influence of metabolites of the gut microbiota on the human body, it has been confirmed that the additional source of energy to the host (human) may be propionic acid used in the synthesis of glucose and lipids (Bates *et al.*, 2007; Cani *et al.*, 2008).

The role of the intestinal microbiota in maintaining normal body weight

In 1998, the World Health Organization (WHO) classified obesity an epidemic on a global scale (WHO Report 2008, WHO Report 2009). In terms of frequency, obesity precedes the occurrence of AIDS and malnutrition. An alarming phenomenon is the growth of this obesity epidemic in children. Until just recently, adipose tissue was considered only as a reservoir of body energy substrate. Today it is known that it is an important part of the endocrine system (Fichna and Skowrońska, 2006). Pathologically increased amounts of fat in the body can result in numerous disorders in the proper functioning of the many different systems, organs and tissues. Particularly dangerous complications may occur in the cardiovascular, respiratory, endocrine, and psychosocial systems. It is estimated that 80% of the diseases in man are caused by problems associated with excessive body weight (Nowak *et al.*, 2010). Statistics predict continuous deterioration of this situation, which is a challenge for the public health sector in many countries of the world (WHO Report 2008; WHO Report 2009). The problem of obesity relates to people of all ages, and the causes have very complex character, from bad habits to environmental impact (to stress and genetic factors). A major problem is the obesity transfer from childhood to adulthood (Fichna and Skowrońska, 2006; WHO Report 2008; WHO Report 2009). Many studies have shown that obesity is also associated with significant changes in the composition and function in metabolism of the intestinal microbiota. It is recognized that a particularly important fact is to keep a correct proportion of *Bacteroidetes* and *Firmicutes* strains in the intestine (Ley *et al.*, 2006; Sanz and Santacruz, 2008). Research teams Bäckhed, Gordon and De Filippo have also indicated that obesity in humans is likely to be related to the composition of the gut microbiota (Bäckhed *et al.*, 2004; Ley *et al.*, 2006; De Filippo *et al.*, 2010). Bäckhed and colleagues determined the share of *Firmicutes* and *Bacteroidetes* in obese mice and mice with normal body weight and found that the proportion of *Bacteroidetes* is significantly lower in obese mice (20%), while in mice with normal weight the bacteria was at a larger amount – up to 40 % (Bäckhed *et al.*, 2004; Bäckhed *et al.*, 2007). In turn, Flessner demonstrated that supplying mice with high animal fat and low fiber diet results in a quantity reduction of *Bacteroidetes* strains, but conversely the growth of *Firmicutes* (Flessner *et al.*, 2010). Studies were carried out on a group of twelve obese humans, who had an increased presence of *Firmicutes* and reduced presence of *Bacteroidetes* from 1 to 5%. After supplying one group's diet with reduced fat content and for others group a diet with decreased portions of saccharides, the proportions of the major groups of microorganisms changed. In both groups' there was a gradual decline in quantity of *Firmicutes* and *Bacteroidetes* increased up to 20% (Ley *et al.*, 2006). In order to determine the relationship between the microbiota and the amount of energy, Jumpertz (Jumpertz *et al.*, 2011) conducted research on a group of 21 volunteers where an interchangeable diet of 2400 and 3400 kcal/day was administered. Fecal microbiota composition was monitored. It showed a 20% growth of *Firmicutes* strains was accompanied by a 20% reduction in the quantity of *Bacteroidetes*, and changes in the proportions of these strains were directly related to gain in body weight. It seems that an important role of gut microbiota is bifidobacteria. It showed that in overweight people and sick people with type 2 diabetes the amount of *Bifidobacterium* was significantly lower (Schwiertz *et al.*, 2010; Wu *et al.*, 2010).

De Filippo (De Filippo *et al.*, 2010) compared the composition of intestinal microbiota in children ages 1 to 6, living in extremely different conditions. The first group of children came from rural areas of Africa (Burkina Faso); and the second group consisted of children from Italy (Florence). The intention of the study was to determine the correlation between the applied diet, and the composition of the intestinal microorganisms. The diet of children living in Africa was low in meat, but contained significant amounts of vegetables, starch and dietary fiber (about 672.2 kcal toddler ages 1–2 years old and 996 kcal children ages 2–6 years old), while nourishment to children from Europe consisted mainly of meat, and their diet contained a lot of animal fats, sugars, but poor in vegetables and fiber (about 1,068.7 kcal children ages 1–2 years old and 1,512.7 kcal children aged 2–6 years old). Regardless of the diet used in the gastrointestinal tract, this study showed that the dominant bacteria types present were *Actinobacteria*, *Bacteroidetes* and *Firmicutes*, but their percentage was different and dependent on diet. In children coming from rural areas of Africa, *Actinobacteria* and *Bacteroidetes* dominated, respectively 10.1% and 73%; while bacteria from the phylum *Firmicutes* accounted for 10%. Within the *phylum Bacteroidetes* the dominant bacteria were *Prevotella* (53%), which indicates the microbiota of these children was mainly enterotype *Prevotella*. In the case of children coming from Florence, increased body weight was found and intestinal microbial system was different than in the case of children from Africa. The dominant bacteria of the phylum *Firmicutes* (51%), and *Actinobacteria* and *Bacteroidetes* were 6.7% and 27% respectively. A high concentration of SCFA, which has been demonstrated in children from Burkina Faso, is an additional source of energy for the host. Despite the low calorie intake, normal development was observed in these children (De Filippo *et al.*, 2010) (Fig. 1).

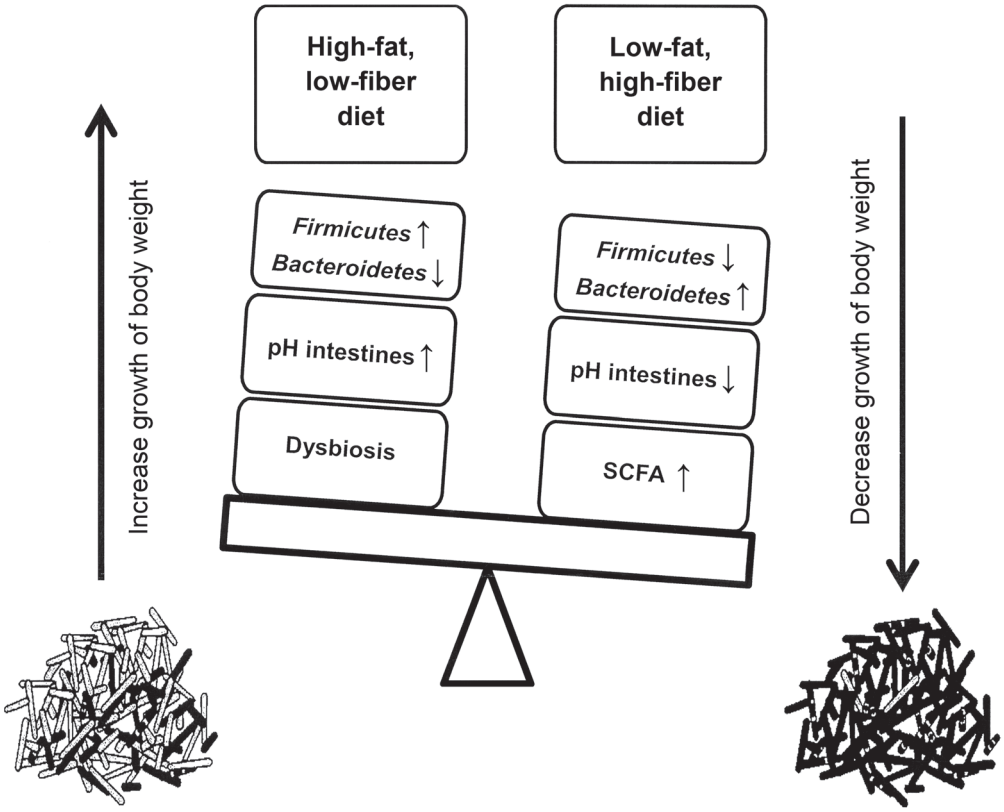

Fig. 1. Effect of diet on the development of gut microbiota and normal body weight (own layout on the basis of Archer *et al.*, 2004; Cani *et al.*, 2004; Delzenne *et al.*, 2005; Tarini and Wolever, 2010).

The gut microbiota vs. obesity – the potential mechanisms

The impact of gut microbiota on the development or slowing down of obesity is not yet fully known. It is believed that obesity is associated with elevated serum levels of lipopolysaccharide (LPS), which is a component of the cell wall of Gram-negative bacteria (Amar *et al.*, 2011a; Amar *et al.*, 2011b). LPS, due to proinflammatory properties, may be involved in the development of inflammation, present in type 2 diabetes. Intravenous administration of lipopolysaccharide in mice resulted in the development of insulin resistance and weight gain. *In vivo* correlation was observed between the increase in plasma concentrations of LPS and the implementation of a high fat diet. Cani (Cani *et al.*, 2007) concluded that fat contained in food may be an important regulator of the concentration of LPS. The introduction of four weeks of high fat diets in mice resulted in a two or even three time increase in plasma levels of LPS (Cani *et al.*, 2007; Tilg *et al.*, 2009). This phenomenon was confirmed in people diagnosed with obesity and type 2 diabetes (Cani *et al.*, 2007; Amar *et al.*, 2011a; Geurts *et al.*, 2011). In the origin of obesity a vital role may be played by intestinal alkaline phosphatase (IAP), which is involved in the degradation of lipids derived from food, and also has an important role in the detoxification of LPS (dephosphorylation of lipid part of LPS). Furthermore, increased activity of the IAP is associated with reduced endotoxemia which is caused by metabolic dysfunctions (Everard *et al.*, 2011). It has been shown that the expression of IAP may be controlled by gut microbiota (Bates *et al.*, 2007). In obese people with type 2 diabetes changes in the intestinal barrier were detected, namely an increase of cellular permeability (Everard *et al.*, 2013). The increase in intestinal permeability was observed in obese mice and can be associated with a change in the expression, localization and distribution of proteins belonging to the tight-junctions of the small intestine (Brun *et al.*, 2007; Cani *et al.*, 2008; Cani *et al.*, 2009; Everard *et al.*, 2012). Another potential factor linking gut microbiota to obesity is blocking the expression of fasting-induced adipose factor (FIAF) by the microbiota. FIAF inhibits the activity of lipoprotein lipase (LPL), an enzyme responsible for the storage of energy in fat. The decreased expression of FIAF determines increased LPL activity and enhances the process of storing energy in the form of fat (Bäckhed *et al.*, 2004). Gut microbiota modulates the activity of the endocannabinoid system and thus has an effect on the function of the intestinal barrier. These studies revealed an important role of the intestinal barrier in the etiology of obesity and Type 2 diabetes (Everard *et al.*, 2013).

Prebiotics

Since gut microorganisms to some extent are responsible for the formation of obesity, modulation of microbiota is seen as a potential tool in the prevention and treatment of disease. It was shown that the growth of beneficial microbiota, and therefore sealing the intestinal barrier and changes in the metabolism of endotoxin in the blood can be modulated by the addition of prebiotics to the diet (Everard *et al.*, 2013).

FAO/WHO defines prebiotic as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already established in the colon, and thus improve the host's health" (FAO Technical Meeting on Prebiotics, Prebiotics, 2007). Prebiotics are not hydrolyzed and absorbed in the upper parts of the gastrointestinal tract and unchanged reach the large intestine where they are nutrients for beneficial bacteria (Kowalska-Duplaga, 2003). Examples of substances having prebiotic properties are fructooligosaccharides, gluco-oligosaccharides, isomaltooligosaccharides, maltooligosaccharides, lactulose, raffinose soy oligosaccharides, stachyose, xylooligosaccharides, and inulin resistant starch (Wang, 2009; Xu *et al.*, 2009). Recently research was conducted to confirm prebiotic properties of new substances such as resistant dextrins derived from potato starch (Jochym *et al.*, 2012). These formulations have a bifidogenic effect and stimulate the growth of gut microbiota, thus limiting the growth of *Clostridium* strains (Barczynska *et al.*, 2010; Barczynska *et al.*, 2012).

Studies conducted on rats and healthy persons confirmed that prebiotics reduce hunger and increase the feeling of satiety (Cani *et al.*, 2007; Parnell and Reimer, 2009). Positive effects of modulation of gut microbiota are: the production of SCFA, increased level of PYY (this peptide is synthesized and secreted by the L-cells of the ileum and colon, and has a stimulant effect on satiety center) and GLP-1, resulting in a reduced glycemic, reduction of insulin resistance, reduced fat cells, and the perception of satiety (Delzenne *et al.*, 2011; Alvarez-Castro *et al.*, 2012; Paranel *et al.*, 2012). Adding to diets a mixture of inulin and xylooligosaccharides resulted in lowering the LPS level in blood plasma (Lecerf *et al.*, 2012).

In a study examining the effects of diet containing large amounts of polysaccharides on the composition of microbiota showed that after four week there was a fundamental change in the composition of the microbiota and its metabolic functions (Duncan *et al.*, 2007; Brinkworth *et al.*, 2009; Russell *et al.*, 2011; Walker *et al.*, 2011; Karen *et al.*, 2013). Adding resistant starch to the diet caused the number of *Ruminococcus bromii* to double (Abell *et al.*, 2008). For 17 weeks 10 volunteers were treated with diets enriched with RS4 resistant starch, and their stool samples were studied by analyzing for the presence of *Bifidobacterium*. It turned out that after a diet consisting of RS4, the amount of these bacteria increased (Abell *et al.*, 2008). Also a reduced amount of *Firmicutes* bacteria was observed, thereby increasing *Bacteroidetes and Actinobacteria* (Martinez *et al.*, 2010). The addition of fructooligosaccharides and inulin mixture (10 g/d) to the diet stimulated of the growth of bifidobacteria, in particular *Bifidobacterium adolescentis* (Ramirez-Farias *et al.*, 2010). It is proposed that the lactate produced by the bifidobacteria can be converted to butyrate by *Eubacterium hallii* and *Anaerostipes caccae* (Duncan *et al.*, 2004; Belenguer *et al.*, 2006; Falony *et al.*, 2006).

Summary. The World Health Organization (WHO) predicts that by the year 2015 the number of obese people in the world (17 years old and over) will rise above 700 million. Obesity is associated with clearly excessive caloric intake compared to low energy outflow. However, the gut microbiota have a key role in the development of adipose tissue and disorders of energy homeostasis (Everard *et al.*, 2012). An important role in maintaining a healthy body weight is to keep the proper proportion of strains of bacteria belonging to the *Firmicutes and Bacteroidetes* phylum (Bäckhed *et al.*, 2004; Bäckhed *et al.*, 2007; Turnbaugh *et al.*, 2008; Hildebrandt *et al.*, 2009; De Filippo *et al.*, 2010; Murphy *et al.*, 2010; Geurts *et al.*, 2011). It is also important not to be limited only to diversify the phylum of bacteria but also take into account the genus of bacteria within the phylum and determine the amount of these bacteria to the appropriate enterotypes of *Bacteroides* and *Prevotella*. Research is being currently being conducted to find the relationship between gut microbiota and metabolic pathways. One of the proposed mechanisms that can be relied on is the ability of the gut microbiota to increase energy from diet. It was also observed that obesity is associated with elevated levels of lipopolysaccharide (LPS) in blood plasma (Amar *et al.*, 2011a; Amar *et al.*, 2011b), but not only elevated levels of LPS in blood plasma because in obesity there is a vital role played by alkaline phosphatase (IAP) (Bates *et al.*, 2007). IAP is involved in the degradation of lipids derived from food, and it also plays an important role in the detoxification of LPS. The next potential factor linking gut microbiota to obesity is caused by blocking the expression of microbiota fasting-induced adipose factor (FIAF) (Bäckhed *et al.*, 2004). Despite extensive research on the role of the gut microbiota in maintaining a healthy body weight, the mechanisms of intestinal microbiota's influence on the development or reduction of obesity is not fully known. It is necessary to carry out research

to determine the impact of intestinal microbiota on the functioning of metabolic pathways on both animal and obese people.

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