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Review

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Effect of Diet on the Gut Microbiota Associated with Obesity

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Obesity is abnormal or excessive fat accumulation that is associated with progression of metabolic diseases including type 2 diabetes mellitus, cardiovascular disease, nonalcoholic fatty liver disease, and cancer. Gut microbiota (GM) have received much attention as essential factors in development and progression of obesity. The diversity, composition, and metabolic activity of GM are closely associated with nutrient intake and dietary pattern. Scientific evidence supports the idea that dietary pattern directly changes the GM profile; therefore, diet is a crucial component related to interactions between GM and obesity progression. A literature review showed that dietary factors such as probiotics, prebiotics, fat, fatty acids, and fiber dramatically alter the GM profile related to obesity. Furthermore, different dietary patterns result in different GM composition and activity that can contribute to amelioration of obesity.

Key words: Diet, Prebiotics, Probiotics, Gastrointestinal microbiome, Obesity

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INTRODUCTION

Overweight and obesity have nearly tripled in the population since 1975. According to the World Health Organization (WHO), over 1.9 billion adults were considered overweight in 2014, representing 39% of the world's population. Over 340 million children and adolescents aged 5–19 years were also overweight or obese in 2016. Finkelstein et al.[1] estimated an increase of 3.3 billion people with a body mass index (BMI) ≥25.0 kg/m^2, corresponding to 57.8% of the adults worldwide by 2030. Obesity is described as an accumulation of excessive fat mass concomitant with low-grade chronic systemic inflammation.[2] Obesity has commonly been associated with development of other metabolic disorders such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and some types of cancer.[3,4]

The gastrointestinal tract contains at least 10^{14} bacteria, with the most abundant numbers in the large intestine.[5] The number of genes in the intestinal microbiome is 150- to 500-fold greater than in human DNA.[6] The collected gut microbiota (GM) are described as a "forgotten organ" that is sensitive to dietary, environmental, and host factors with function complicatedly intertwined with host metabolism.[7] Both endogenous and exogeneous factors such as autoimmune disease, chronic disease, medications, antibiotics, smoking, stress level, and diet affect the diversity and composition of GM. Each individual has a unique GM composition and profile that may affect nutrient metabolism. Recent evidence has suggested that GM is a contributing factor in the progression of obesity.[6,8,9] The GM is capable of modulating host metabolism through energy balance, chronic low-grade inflammation, and intestinal barrier function.[6] Furthermore, the composition and diversity of GM are different

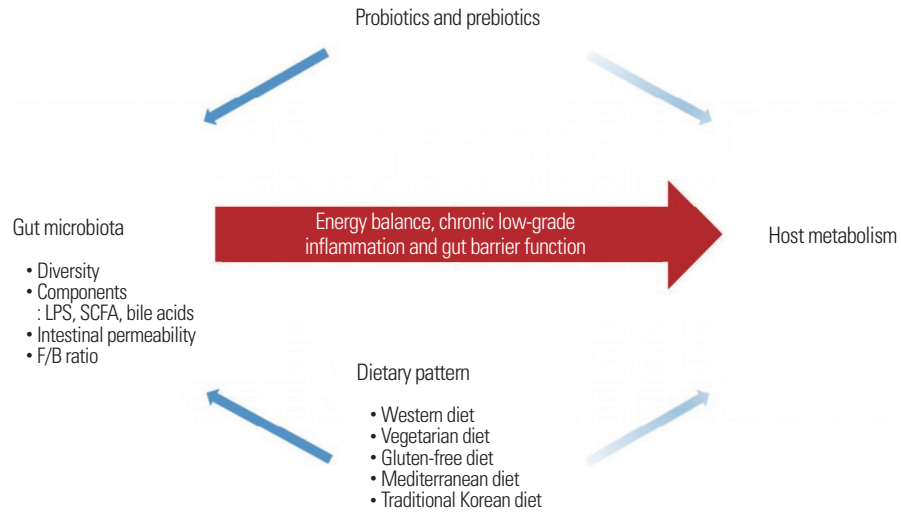

Figure 1. Effect of dietary factors on alteration of gut microbiota associated with host metabolism. LPS, lipopolysaccharide; SCFA, short chain fatty acid; F/B, *Firmicutes*/*Bacteroidetes*.

between healthy weight and obese individuals.[8] Therefore, the main objective of this review is to discuss whether GM altered by probiotics, prebiotics, and specific diet composition can contribute to amelioration of obesity (Fig. 1).

ASSOCIATION BETWEEN OBESITY AND GM

Obesity is a multifactorial, chronic disorder associated with other metabolic diseases. Recently, GM has received attention as a metabolic factor that affects the interactions between exogeneous factors and host metabolism. The GM is known to affect host metabolism by modulating energy balance, chronic-low grade inflammation, and gut barrier function.[10] Modulation of these factors is highly associated with obesity; therefore, the GM is considered an environmental regulator of obesity. Several mechanisms of obesity and GM interactions have been suggested. The GM is comprised of a dynamic population of microorganisms including bacteria, archaea, fungi, and viruses. The dominant bacterial species in human GM are *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Cyanobacteria*, and *Verrucomicrobia*.[11] The microbiota profile depends on the host, and changes in GM diversity can contribute to host metabolism. Compositional changes in GM may disturb the homeostasis between host metabolism and GM. Many studies have investigated the relationship between GM and obesity and found that the number of *Firmicutes* was increased while the number of *Bacteroidetes* decreased in obese animal and humans.[12-14] *Bacteroidetes* have fewer genes involved in carbohydrate and lipid metabolism than *Firmicutes*. The increased *Firmicutes*/*Bacteroidetes* (F/B) ratio plays a role in increasing energy storage in host adipose tissue by facilitating extraction of energy.[13,15] In addition, GM usually exhibit low bacterial diversity in obese subjects.[16] Therefore, the F/B ratio and resident bacteria of the intestine may contribute to development of obesity. Several human clinical trials have reported that a low level of *Bifidobacteria* is also involved in obesity.[17] In both children and pregnant women, *Staphylococcus aureus* was associated with overweight,[18] and *Enterobacteriaceae* were significantly increased with obesity.[19,20]

Development of obesity also has been linked to abnormal energy intake and expenditure.[21] Increasing evidence suggests that energy balance (energy intake and expenditure) is highly intertwined and modulated by GM.[22] GM can regulate energy intake and appetite by production of short-chain fatty acids (SCFAs) of nondigestible polysaccharides.[23] The SCFAs, such as acetate, butyrate, and propionate, produced by bacterial fermentation act as substrates of energy as well as modulators of satiety and food consumption when they combine with G-protein coupled receptor 41 (GPR41) and GPR43 in intestinal epithelial cells.[24,25] The SCFAs also stimulate secretion of peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), which can suppress intestinal mobility transit allowing higher uptake of nutrients.[23,25]

INTESTINAL PERMEABILITY

Many environmental factors such as diet, energy intake, and exercise can dramatically influence GM.[26,27] Specific foods and diets can influence the abundance of different bacteria in the GM, which can affect host health. Probiotics can increase GM diversity and SCFA production and reduce T2DM and CVD. Several suggested mechanisms linking microbiota to weight changes include an increased capacity of some bacteria to extract energy, improved transfer of calories from food to host, and changes in host absorption metabolism.

PREBIOTICS AND GM

Prebiotics have been defined by the Food and Agriculture Organization (FAO) of the United Nations and WHO 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 health."[28] As mentioned above, dietary prebiotics have typically been classified as nondigestible fiber that passes undigested through the upper gastrointestinal tract and stimulates and colonizes the growth of beneficial microorganisms.[29] Bindels et al.[30] reported that prebiotic ingredients include inulin, fructooligosaccharides (FOS), galactooligosaccharides, and human milk oligosaccharides. The prebiotics usually found in fruits and vegetables may lead to various health benefits in the host.[31] Among the advantages of prebiotics are promotion of ion and trace element absorption such as that of calcium, iron, and magnesium and immune system regulation by increasing Immunoglobulin A production and modulating cytokine production through mechanisms mediated by microbial metabolic products.[29] Prebiotics selectively stimulate the growth of *Bifidobacteria* and *Lactobacillus* species, which can produce greater microbial diversity within the microbiome. Through stimulation by beneficial microbiota and following fermentation, these prebiotic substrates manufacture SCFAs such as butyrate, propionate, and acetate, which are the primary energy sources of the intestine and have metabolic effects on the host. Prebiotic effects on regulation of satiety and food consumption are due to production of higher SCFA level, which improves GLP-1, PYY, and ghrelin production.[32] In addition, prebiotics also have anti-obesity effects involved in improvement of lipid metabolism by modulated GM composition.[33-35] Oligofructose-treated animals showed lower triglyceride level and adipose tissue mass.[36] Short-chain FOS treatment also ameliorates plasma lipid metabolism and hyperinsulinemia, which are associated with changes in GM composition in diet-induced obese mice.[36] Nihei et al.[37] also found that supplementation with α-cyclodextrins showed modulation of GM and SCFA production in diet-induced obese mice. These effects were associated with modulation in gene expression of lipid metabolism, including upregulation of peroxisome proliferator-activated receptor γ (PPAR-γ) and PPAR-α and downregulation of sterol regulatory element-binding protein-1c and fatty acid synthase.[37] Several clinical trials have shown a strong association between prebiotic-altered GM and obesity (Table 1).[38-43]

PROBIOTICS AND GM IN OBESITY

According to FAO/WHO, probiotics are "live microorganisms which confer a health benefit on the host when administered in adequate amounts."[22] Recent studies have shown that *Bifidobacterium* (*B. breve* B3, *B. infantis*, and *B. longum*) and *Lactobacillus* (*L. rhamnosus*, *L. casei* strain Shirota [LAB13], *L. gasseri*, and *L. plantarum*) species have been used as probiotic treatments in obese animal models due to a lack of pathogenicity and reduced antibiotic resistance.[33] In fact, many studies have reported that animals fed with the above-mentioned strains of *Lactobacillus* and *Bifidobacterium* showed suppression of weight gain, fat depots, and white adipose tissue compared to placebo-treated control animals. However, experimental studies clearly differ in both experimental duration and daily probiotic dose administration, which lead to different effects on body weight and/or fat mass. These probiotics showed antiobesity effects through beneficial changes in GM, lower insulin resistance, and higher satiety by modulation of the mechanism.

The effects of *Lactobacillus* and *Bifidobacterium* strains, alone or in combination, have also been well-described in obese adults, leading to reduced body weight, waist circumference, and fat depots.[44-50] Clinical studies have shown that the anti-obesogenic effects of probiotics are due to both the probiotic dose and experimental duration. *L. gasseri* (SBT2055 and BNR17) treatment showed reduced

Table 1. Clinical trials on the association between prebiotics and obesity

Study	Study design	Prebiotics intervention	Beneficial effect
Edrisi et al. (2018)[38]	Overweight and obese adults (n=105); randomized control trial (Intervention I and Intervention II)	Energy-restricted diet containing rice bran (intervention I), rice husk powder (intervention II), or a low-calorie diet for 12 weeks	Reduction of body weight, BMI, waist circumference, reduction in inflammatory markers
Genta et al. (2009)[39]	Obese and slightly dyslipidemic premenopausal women (n=35); double-blind, placebo-controlled study	Placebo syrup (tartaric acid 2.5%, carboxymethylcellulose 1.8%, saccharine 2.5%, and glycerine 10%)+healthy hypocaloric diet or yacon syrup (approximately 12.5 g FOS/day)+ healthy hypocaloric diet for 17 weeks	Reduction of body weight, BMI, waist circumference, fasting serum insulin, and HOMA-IR; increased satiety
Hume et al. (2017)[40]	Overweight and obese children aged 7–12 years (n=42); randomized, double-blind, placebo-controlled trial	8 g/day oligofructose-enriched inulin or equicaloric dose of a 3.3 g maltodextrin placebo/day for 16 weeks	Increased satiety, prospective food consumption, and ghrelin; decreased energy intake
Nicolucci et al. (2017)[41]	Overweight and obese children aged 7–12 years (n=42); single-center, double-blind, placebo-controlled trial	8 g/day oligofructose-enriched inulin or equicaloric dose of a 3.3 g maltodextrin placebo/day for 16 weeks	Decreased body weight z-score, percent body fat, and trunk fat; increased *Bifidobacterium* and decreased *Bacteroides*
Parnell and Reimer (2009)[42]	Overweight and obese adults (n=39); intervention study	21 g/day oligofructose-enriched diet or equicaloric dose of maltodextrin placebo/day for 12 weeks	Decreased body weight, fat mass, energy intake, postprandial insulin, and ghrelin
Reimer et al. (2017)[43]	Overweight and obese adults (n=39); single-center, placebo-controlled, double-blind, randomized controlled trial	Prebiotic bar (inulin-type fructan with 6 g oligofructose+2 g inulin from chicory root) or control isocaloric bar (100 kcal/bar) for 12 weeks	Decreased hunger; increased *Bifidobacterium*

BMI, body mass index; FOS, fructooligosaccharides; HOMA-IR, homeostasis model assessment of insulin resistance.

visceral adipose tissue and waist circumference in adults with obese tendencies or obesity.[46,47] Pedret et al.[48] reported that *Bifidobacterium animalis* subspecies. Lactis CECT 8145 intervention significantly reduced waist circumference, waist circumference/height ratio, and BMI. The therapy based on *L. rhamnosus* CGMCC1.3724 showed weight loss in obese women in comparison with obese men.[49] High- and low-doses of probiotic mixtures (different strains of *Lactobacillus* and *Bifidobacterium*) showed similar beneficial effects on weight, BMI, and body fat mass in obese postmenopausal women, but only the high-dose group showed improvement in lipid profile.[50] In these findings, the efficacy of probiotic treatment in human studies is still unclear due to small cohort studies and short-term follow-up. Thus, further studies are needed to identify selective probiotic strains that may produce effective changes in weight or body fat loss, either alone or in combination with other probiotic strains (Table 2).[44-50]

INFLUENCE OF DIET ON GM IN OBESITY

Diet is one of the critical factors in progression of obesity and is profoundly linked to GM composition.[51] Nutrient intake and eating habits directly influence the composition, diversity, and metabolism of GM.[51,52] Furthermore, the composition and functionality of GM respond quickly to changes in dietary composition. Several studies showed that, within 2 days after the start the dietary intervention, the GM responded and exerted changes in composition.[53] Interestingly, a healthy dietary pattern related to GM profiles exerted protective effects against development of diabetes in obese individuals.[54] Therefore, a balanced diet is required to maintain the composition and proper function of the GM. Many dietary patterns such as Western diet, vegetarian diet, gluten-free diet, and the Mediterranean diet have been shown to affect the distinct diversity of the GM that may affect host metabolism.[52]

The Western diet consists of high intake of saturated fats, refined grains, sugar, salt, and high fructose corn syrup and a low intake of fiber. It is highly associated with obesity and metabolic disease. The Western diet promotes inflammation and changes the profile of the GM from healthy to the obese pattern.[55] It also has been shown to decrease the total bacteria amount as well as the beneficial *Lactobacillus* species (sp.) and *Bifidobacterium* sp. in the gut.[15]

Vegetarian and vegan diets consist of plant-based foods and are rich in dietary fiber, in contrast with the Western diet. Abundant fiber in these diets promotes stable GM profile and increases the presence of lactic acid bacteria.[56] Both the vegetarian and vegan diet were shown to lower *Bacteroides* sp. and *Bifidobacterium* sp. The GM profile of the vegan diet exerted an increase in the abun-

Table 2. Clinical trials on the association between probiotics and obesity

Study	Study design	Probiotics intervention	Beneficial effect
Gomes et al. (2017)[44]	Obese women aged 20–59 years (n=43); randomized, double-blind, placebo-controlled intervention, clinical trials	*Lactobacillus acidophilus*, *Lactobacillus casei* *Lactococcus lactis*, *Bifidobacterium bifidum*, *Bifidobacterium lactis* (2×10^{10} CFU/day), or a placebo for 8 weeks	Reduction of waist circumference
Higashikawa et al. (2016)[45]	Overweight adults aged 20–70 years (n=62); randomized, double-blind, placebo-controlled clinical trial	10^{11} CFU/day of living or heat-killed *Pediococcus pentosaceus* with dietary intervention or a placebo for 12 weeks	Reduction of BMI after heat-killed LP28
Kadooka et al. (2010)[46]	Adults with overweight and obesity (BMI between 24.2 and 30.7 kg/m^2, n=87); multicenter, double-blind, randomized, placebo-controlled intervention trial	200 g/day of fermented milk containing *Lactobacillus gasseri* (5×10^{10} CFU/100 g fermented milk) or 200 g/day of fermented milk without probiotic for 12 weeks	Reduction of body weight, BMI, and fat areas including abdominal visceral and subcutaneous fat
Kim et al. (2018)[47]	Obese adults aged 20–75 years (n=90); randomized, double-blind, placebo-controlled trial-controlled trial	Low (10^9 CFU/day) and high (10^{10} CFU/twice a day) dose of *L. gasseri*+or placebo for 12 weeks	Decreased waist circumferences in low dose; decreased visceral adipose tissue in high dose
Pedret et al. (2019)[48]	Abdominally obese randomized, parallel, double-blind, placebo-controlled trial adults (n=126)	10^{10} CFU/cap/day of *Bifidobacterium animalis* subsp. Lactis CECT 8145 or its heat-killed form or placebo for 12 weeks	Reduction in BMI and the ratio of waist circumference/height
Sanchis-Chordà et al. (2019)[49]	Obese adults aged 18–55 years (n=125); randomized, double-blind, placebo-controlled trial	1.62×10^8 CFU/2 cap/day of *Lactobacillus rhamnosus* or 250 mg of maltodextrin+3 mg magnesium stearate for 12 weeks	Reduction in weight
Szulińska et al. (2018)[50]	Obese postmenopausal women aged 45–70 years (n=81); randomized-double-blind, placebo-controlled clinical trial	Probiotic mixture including different *Lactobacillus* and *Bifidobacterium* strains in low dose (2.5×10^9 CFU/day) and high dose (10^{10} CFU/day/two sachets per day) or placebo for 12 weeks	Reduction in body weight, BMI, and fat mass in both low dose and high dose groups; improvement of lipid profiles in the high dose group

CFU, colony-forming unit; BMI, body mass index; subsp., subspecies.

dance of protective microbiota.[57] Additionally, abundant polyphenol (e.g., from tea, coffee, berries, and vegetables such as artichokes, olives, and asparagus) content in these diets exerted increases in intestinal barrier protectors (*Bifidobacterium* and *Lactobacillus*), butyrate-producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia*), *Bacteroides vulgatus*, and *Akkermansia muciniphila*. It also decreased lipopolysaccharide producers (*Escherichia coli* and *Enterobacter cloacae*) that can induce inflammation.

The effects of a gluten-free diet on the GM is well known since gluten-related disease is closely associated with GM profile and metabolism.[58] The gluten-free diet lowered the abundance of *Bifidobacterium* sp., *Lactobacillus* sp.,[59] and *Ruminococcus bromii* and *Roseburia faecis*, whereas the *Victivallaceae* and *Clostridiaceae* were increased.[58,60] Poorly digested fermentable carbohydrates (fermentable oligo-, di-, mono-saccharides, and polyols [FODMAPs]) are known to increase digestive problems and cause irritable bowel syndrome; therefore, a low FODMAP diet is used clinically to reduce intestinal symptoms. The diversity and metabolism of GM significantly changed by the FODMAP diet. The low FODMAP diet reduced the total GM count as well as the number of bacteria involved in gas production. GM alteration by the low FODMAP diet exerted an increase in *Actinobacteria* and a decrease in *Bifidobacterium*.[61,62]

The Mediterranean diet consists of vegetables, olive oil, and fruits, a moderate intake of poultry, and a low intake of red meat and dairy products. It is well known as one of the healthiest dietary patterns. GM composition in the Mediterranean diet is high in *Lactobacillus*, *Bifidobacterium*, and *Prevotella* that is closely associated with the prevention of obesity and improvement of lipid and cholesterol profiles. Furthermore, the Mediterranean diet lowered *Clostridium* sp. that can induce inflammation.[63] The Mediterranean diet provides high dietary fiber and polyunsaturated fatty acid (PUFA) content. Dietary fatty acids can also affect GM composition. The consumption of n-3 PUFAs and conjugated linoleic acid exerted beneficial effects on the GM compared to that of n-6 PUFAs and saturated fatty acids. The GM profile in obesity changed, and was similar to that of normal individuals, by n-3 PUFA consumption.[64]

The prevalence of obesity dramatically increased to 40% according to the data from the 2015 Korea National Health and Nutrition Examination Survey for Korean adults.[65] Dietary pattern and lifestyle changed dramatically with the rapid industrialization in Korea

Table 3. The effect of diet on GM associated with obesity

Diet	Effect on GM associated obesity
Western diet: high intake of saturated fat, refined grains, sugars, salt, and high fructose corn syrup and low intake of fiber[15,55]	Promotes inflammation and changes the GM profile to the obese pattern Decrease in total GM amount Decrease in beneficial *Lactobacillus* sp. and *Bifidobacterium* sp.
Vegetarian and vegan diets: plant-based foods and rich in dietary fiber[56,57]	Increase in the abundance of protective microbiota Increase in intestinal barrier protectors (*Bifidobacteria* and *Lactobacillus*), increase in butyrate-producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia*) Decrease in inflammation-inducing lipopolysaccharide producers (*Escherichia coli* and *Enterobacter cloacae*) → prevents obesity
Gluten-free diet[58,59]	Decrease in *Bifidobacterium* sp., *Lactobacillus* sp., *Ruminococcus bromii*, and *Roseburia faecis* Increase in *Victivallaceae* and *Clostridiaceae*
Mediterranean diet: consists of vegetables, olive oil, fruits, a moderate intake of poultry, and a low intake of red meat and dairy products[63,64]	Increase in *Lactobacillus*, *Bifidobacterium*, and *Prevotella* → prevents obesity and improves lipid and cholesterol profiles Decrease in *Clostridium* that can induce inflammation.
Korean traditional diet: high consumption of vegetables and fermented foods, moderate intake of legumes and fish[65,66]	Increase in *Bacteroides* (*Bacteroidaceae*) and *Bifidobacterium* (*Bifidobacteriaceae-Actinobacteria*) Decrease in *Prevotella* (*Prevotellaceae*) → prevents obesity

GM, gut microbiota; sp., species.

over the last several decades. The consumption of Western food and less physical activity increased obesity and metabolic diseases. The traditional Korean dietary pattern is high in consumption of vegetables and fermented foods, with moderate intake of legumes and fish. Compared to the animal-based Western diet, this plant-based diet altered high levels of *Bacteroides* (*Bacteroidaceae*) and *Bifidobacterium* (*Bifidobacteriaceae-Actinobacteria*) and lower levels of *Prevotella* (*Prevotellaceae*). The decrease of *Bacteroides* (*Bacteroidaceae*) and increase of Prevotella (*Prevotellaceae*) showed a higher risk for obesity (Table 3).[15,55-59,63-66]

CONCLUSION

The diversity, composition, and metabolic activity of the GM are closely associated with nutrient intake and dietary pattern. Specific dietary factors and dietary patterns alter the GM profiles that can regulate or affect progression of obesity. More studies and longterm trials are needed to understand the effects of dietary pattern on alteration of the GM associated with obesity.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Review concept and design: JEY, BK; drafting of the manuscript: BK, HNC; critical revision of the manuscript: JEY.

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