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Diet, Bariatric Surgery and Gut Microbiota

Diyet, Bariatrik Cerrahi ve Bağırsak Mikrobiyotası

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Abstract/Öz

Gut microbiota that composed of microorganisms and defined as a complex ecosystem, functions as an organ is affected by several factors including mode of delivery, breastfeeding, antibiotics use, and host environment. Gut microbiota plays a substantial role in food digestion and regulates intestinal structure and functions. There is a strong interaction between food intake and gut microbiota. Recent studies have shown an association between gut microbiota and obesity. Different metabolic pathways underlying effects of microbiota alterations on the incidence of obesity have been suggested. Some of these include the production of short-chain fatty acids through increased dietary polysaccharide levels, gene regulation increasing adipose tissue storage, and inflammation. Studies of the association between obesity and microbiota have indicated that the Firmicutes/Bacteroidetes ratio is higher in obese individuals than in individuals with normal weight. Moreover, as the genetic diversity of gut microbiota decreases, adiposity, insulin resistance, and inflammation increase. Lifestyle (diet and physical activity) changes are among the important approaches to treat obesity; however, bariatric surgery can be performed in individuals with a body mass index of >40 kg/m^2 and/or those with comorbidities. Weight loss after bariatric surgery can increase gut microbial diversity. Soon after bariatric surgery (before weight loss), improvements in biomarkers related to type 2 diabetes have been observed. These findings indicate the presence of mechanisms underlying the success of bariatric surgery beyond weight loss. After bariatric surgery, decrease in Firmicutes and increase in Bacteroidetes in the gut have been reported.

Keywords: Microbiota, obesity, bariatric surgery

Mikroorganizmalardan oluşan ve bir organ gibi işlev gören kompleks bir ekosistem olarak tanımlanan bağırsak mikrobiyotası doğum şekli, anne sütü alımı, antibiyotik kullanımı ve yaşanılan çevre gibi pek çok faktörden etkilenmektedir. Bağırsak mikrobiyotasının intestinal yapı ve fonksiyonu düzenleyen işlevlerinin yanında besinlerin sindiriminde de önemli rolü bulunmaktadır. Besin alımı ve bağırsak mikrobiyotası arasında karşılıklı güçlü bir etkileşim vardır. Son yıllarda yapılan çalışmalar bağırsak mikrobiyotası ve obezite arasında da etkileşim olduğunu göstermektedir. Mikrobiyotadaki değişikliklerin obezite gelişimi üzerine etkileri ile ilgili farklı metabolik yollar bildirilmiştir. Bunlar: diyet polisakkaritlerinin işlenme kapasitesinin artması yoluyla kısa zincirli yağ asitlerinin oluşumu, adipoz doku depolarını artıran gen regülasyonları ve inflamasyon üzerine etkileridir. Obezite ve mikrobiyota ilişkisini araştıran çalışmaların büyük kısmında obez bireylerin bağırsaklarında Firmicutes/Bacteroidetes oranının normal ağırlıklı bireylerdekine göre daha yüksek olduğu bulunmuştur. Ayrıca, bağırsak mikrobiyotasındaki gen çeşitliliği azaldıkça adipozite, insülin direnci ve inflamasyonda artış görülmektedir. Obezitenin tedavi yöntemleri arasında yaşam tarzı değişiklikleri (diyet ve fiziksel aktivite) büyük yer kaplamakla birlikte beden kütle indeksi >40 kg/m^2 olan ve/veya komorbiditeleri olan bireylerde bariatrik cerrahi yöntemleri uygulanabilmektedir. Bariatrik cerrahi uygulamasının ardından yaşanan ağırlık kayıpları da bakteriyel çeşitliliği arttırmaktadır. Bariatrik cerrahiden sonraki birkaç gün içinde (vücut ağırlığında kayıp olmadan önce) tip 2 diyabet ile ilgili belirteçlerde iyileşmeler olduğu gözlenmiştir. Bu sonuçlar da bariatrik cerrahinin başarılı sonuçlarında ağırlık kaybından öte mekanizmaların etkili olabileceğini düşündürmektedir. Yapılan çalışmalarda bariatrik cerrahi sonrası bağırsak mikrobiyotasında Firmicutes oranında azalma, Bacteroidetes oranında ise artış olduğu görülmüştür.

Anahtar Kelimeler: Mikrobiyota, obezite, bariatrik cerrahi

Introduction

Gut microbiota (bacteria, fungi, viruses, etc.) is a complex ecosystem, which functions as an organ. The colonization in the intestine begins in the womb and the infants' rate of being exposed to bacteria rises within a first few days of life (1). Affected by a great number of factors, such as the mode of delivery, mother's microbiota, intake of breast milk, environmental exposure to bacteria, early use of antibiotics (2), microbiota becomes more stable after 2-3 years of age; however, it continues to develop during adulthood (3).

Microbiota has many important roles, such as helping the digestion of complex nutritional components, amino acid synthesis, and bile acid biotransformation, forming a barrier against pathogenic microorganisms. In addition, it is involved in regulating intestinal structure and histological functions (4). The number of bacteria in the gastrointestinal tract is higher than that in all cells found in the human body, and the bacterial genome is 100 times greater than the human genome (5). Therefore, a human that has both genomes is called "super organism" (6).

Microbiota varies throughout the gastrointestinal tract in terms of types and number of bacteria (7). The greatest diversity and number of bacteria are found in the colon. The colonic microbiota

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includes hundreds of bacterial types and thousands of subtypes (nearly 10^{11} cell/g). The pH is partly acidic in the proximal colon due to bacterial fermentation, and it tends to change toward neutral following secretion by the host and water absorption. Colonic physiology turns intestinal matter into appropriate bacterial habitats (8). Despite the diversity of types and numbers of bacteria, fecal microbiota is considered as the reflection of colon microbiota. Gut microbiota mainly constitutes seven different enterotypes: Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria, Verrucomicrobia, Acidobacteria, and Actinobacteria. The most dominant enterotypes include Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The existence of them and that of other groups differs depending on the factors such as age, diet and stress (9). Of the gut microbiota, 90% of them consists of gram-negative Bacteroidetes and gram-positive Firmicutes (10).

Diet and gut microbiota

It is known that there is a strong interaction between food intake and microbiota composition (11). Enterotypes are influenced by dietary habits. Each enterotype comprises dominant bacterial types, which have the ability to derive energy from different types of food. In a study in which mice were fed with a high-fat diet, the number of Bacteroidetes in mice gut microbiota was reported to increase regardless of changes in body weights (12). In a study carried out on humans by means of food consumption frequency survey, it was demostrated that Bacteroides (enterotype 1) was demonstrated to be related to the consumption of animal-based proteins and saturated fats in the long-term, whereas Prevotella (enterotype 2) was related to with carbohydrate-based diet. This study indicated that diet modifications might lead to changes in microbiota. And it shows that dietary habits and/or short-term nutrition limitations are needed to be considered as a significant parameter in the relationship between body-mass index (BMI) and microbiota composition (13).

In a study conducted by Walker et al. (14), a diet was applied to 14 mildly overweight/obese patients with metabolic syndrome and they were monitored for 10 weeks. In the first seven weeks of the study, the participants were given diets with stable energy according to their resting energy rate and during the last three weeks, they were divided into three groups where three diets were applied, one included high-resistance starch, second was high in non-starch polysaccharides (NSP) diet, and the other one was weight-reducing diet with high protein. Participants' microbiotas changed (regardless of weight loss) occurred in the during the study. These changes were seen in specific bacteria known to play a role in the digestion of carbonhydrates such as Roseburia and *Eubacterium rectale* not at a level of enterotype but taxa. Main bacterial groups of gut microbiota are presented in Figure 1 (15).

Obesity and gut M-microbiota

Obesity is characterized by excess fat mass in the body, which causes negative effects on the health. It is regarded as a risk factor for cardiovascular diseases, hypertension, type 2 diabetes, metabolic syndromes, non-alcoholic steatohepatitis (NASH), and certain cancer types, such as colon cancer (16). Having reached to alarming levels particularly in countries with western pattern diet and sedentary lifestyle, obesity prevelance has risen rapidly in the last two or three decades all over the world (17). Some of the causes that might lead to obesity include lifestyle habits, exposure to toxic substances, genetic/epigenetic factors, and hormones (18). Recent studies have indicated that gut microbiota plays role not only in the development of obesity but also in the pathophysiology of complications that cause obesity to be complex and chronic (19, 20).

In the studies on mice that showed the microbiota's role in weight control, germ-free mice, when compared to normal mice, was seen to have less adiposity despite the higher level of food consumption. These results remark the role of microbiota in energy stores (21, 22). Moreover, the fact that microbiota influences obesity development was associated with the role of gut microbiota in energy regulation and the increase in the capacity of processing indigestible diet polysaccharides (6, 21). This ensures the absorption of short-chain fatty acids from the intestine (23). Microbiota also has an impact on gene regulation in order to ensure the rise in adipose tissue stores (24).

High Firmicutes/Bacteroidetes ratio were found in the case of obesity regardless of food consumption in many studies investigating the association between obesity and microbiota (25, 26). In a study conducted with obese and normal-weight participants, 12 obese and 3 normal-weight participants' gut microbiotas were compared, and it was shown that obese participants had a distinctively low level of Bacteroidetes and high level of Firmicutes compared with lean participants (27). Even though the number of participants were limited in this study, similar results were found in two extensive studies carried out on both mice and humans (25, 26). However, in another study, no difference was found in regard to the level of Bacteroidetes between obese and nonobese individuals (28). Likewise, in a study by Jumpertz et al. (29), at different BMI levels, 3 dominant types (Bacteroidetes, Firmicutes ve Actinobacteria) were found at similar levels in the intestine. These contradictions between the studies indicate that microbiota can vary at the level of types between populations (30). Bacterial diversity can show a great difference between the people living in different countries. In the societies like the U.S. where obesity and obesity-driven diseases are common, the diversity and richness of gut microbiota are lower in comparison with Malawi and Amerindian societies (societies that live in Central and Southern America) (31). Similarly, children in the rural areas of Africa were found to have more microbiota diversity and richness in comparison with the children in eastern Europe (32). These findings are consistent with study results showing that obesity is related to the lower bacterial diversity in mice (22) and humans (26). Weight loss after bariatric surgery for the treatment of morbid obesity increases bacterial diversity (33).

Obesity is known to have a relation with the changes in gut microbiota, yet no definite explanation can be made as to how microbiota affects obesity pathology and whether the changes in microbiota are the cause or the result of obesity. Although there is no consensus on a specific gut microbiota pattern in obesity etiology, it is known that the microbiota changes in the intestine play a part in obesity and insulin resistance development. The contradictory results in this area make it difficult to find the most suitable bacteria as disease biomarkers. The most important mechanisms that explain the impacts of microbiota on obesity are the provision of additional energy acquire from digested foods and impacts on inflammation (34).

Humans do not have an enzyme to ferment cellulose or other complex carbohydrates. However, the gut microbiota has an ability to ferment these molecules in the gastrointestinal tract. Released

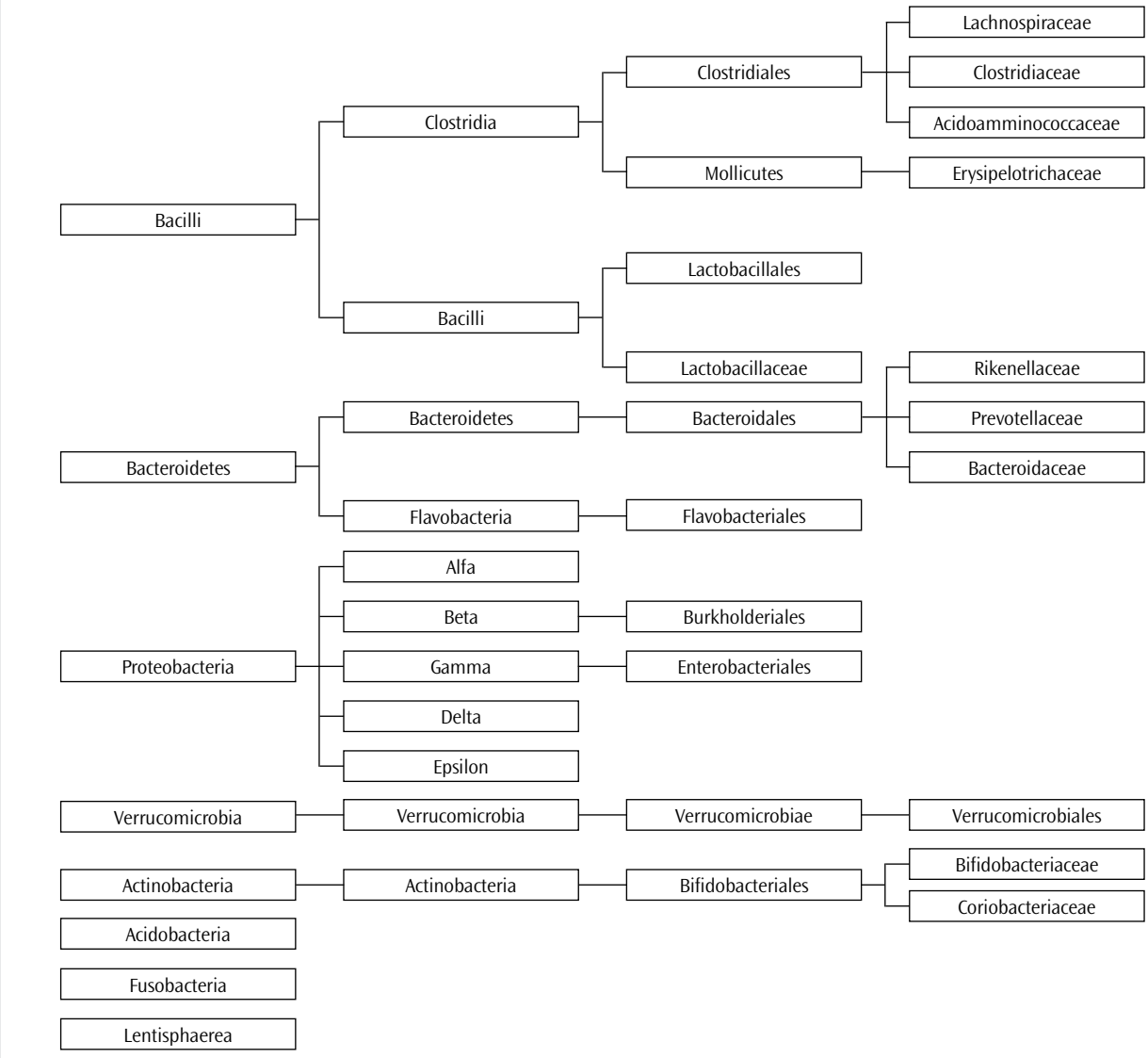

Figure 1. Bacterial groups of gut microbiota (15) (Tagliabue A, Elli M. The role of gut microbiota in human obesity: recent findings and future perspectives. Nutr Metab Cardiovasc Dis 2013; 23: 160-8.)

monosaccharides are either absorbed or metabolized into short-chain fatty acids, and these substances are transferred to the liver or transformed into triglycerides. These *de novo* synthesized lipids are then stored in adiposities through a pathway involving fasting-induced adipose factor (FIAF). The fasting-induced adipose factor is a lipoprotein lipase (LPL) inhibitor (35). Suppressing FIAF in intestinal epithelium leads to rise in LPL activity (24). Furthermore, absorption of released monosaccharides increases hepatic lipogenesis via carbohydrate-responsive element-binding protein (ChREBP) and sterol regulatory element-binding protein type-1 (SREBP-1) activation (24, 36).

Microbiota also plays an important part in spending the energy acquired from the diet. It is seen that the microbiota in obese individuals inhibits fatty acid oxidation with certain mechanisms. These mechanisms are as follows: (i) FIAF suppression induces peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1) and other genes in fatty acid oxidation and (ii) a decline in adenosine monophosphate activated protein kinase (AMPK) in muscle and kidney causes a decline in phosphorylation of Acetyl-CoA carboxylase (ACC) and an increase in malonyl-CoA generation leads to a decrease in Carnitine palmitoyltransferase 1 (CPT-1) inhibition and mitochondrial fatty acid oxidation (37).

Obesity is associated with chronic low inflammation. In the case of obesity, adipocytes and infiltrated macrophages in adipose tissue release inflammatory cytokines (38). This low-grade systemic inflammation causes the translocation of bacterial LPSs from the intestinal lumen into the circulation. Two- to three-fold increase in plasma LPS (metabolic endotoxemia) (39) is found in the pathology of many chronic diseases, such as obesity, insulin resistance, diabetes, and atherosclerosis. A high-fat diet may lead to metabolic endotoxemia or make this situation worse. Intestinal permeability may raise LPS translocation following changes in the composition of intestinal microbes that regulate local inflammation in intestinal wall or mucosal structure. Intestinal permeability is also related to the limited number of Bifidobacterium in the intestine (40).

Bariatric surgery and gut microbiota

Obesity is a worldwide concern owing to the rapid rise in its prevalence and its association with certain diseases that affect the qual-

ity of life and survival (41). Treatments, such as diet and physical activity, during the treatments of morbid obesity can be insufficient in the long-term (42) in terms of weight loss (43). Those whose BMI is over 40 kg/m^2 or those whose BMI is over 35 kg/m^2 and who also have comorbidities and patients who have tried to lose weight with non-surgical procedures, yet failed can make a decision of bariatric surgery in order to reach their weight goal. Bariatric surgery is a method that ensures a great amount of weight loss (41). Different surgical procedures can be named in two main categories: completely restrictive method (laparoscopic adjustable gastric banding (LAGB) and sleeve gastrectomy) and both restrictive and malabsorptive method (roux-en-Y gastric bypass (RYGB)) (44).

Roux-en-Y gastric bypass is a hybrid technic that includes both restrictive and malabsorptive mechanisms. The procedure aims to create a small gastric pouch (15-20 mL) and to bypass duodenum and proximal intestine. The gastric pouch is connected to jejunum via a narrow roux-en-Y gastrojejunal anastomosis. In order to ensure the continuity of the intestine, generally 75-100 cm anastomosis is performed on gastrojejunostomy between the biliopancreatic limb and alimentary limb. Sleeve gastrectomy is based on the 2-8 cm resection of the main part of the stomach's fundus and corpus (45).

In addition to ensuring weight loss, bariatric surgery ameliorates metabolic health. Thus, "metabolic surgery" has been considered a more appropriate term recently (46). There are numerous results showing that most gastrointestinal operations designed primarily for weight loss heal or eliminate type 2 diabetes (47). Bariatric/metabolic surgery has been found more efficient than traditional medical treatments in terms of healing type 2 diabetes in many randomized or non-randomized controlled study (48, 49). Within a few days after the surgery, long before the weight loss, rapid recoveries in the levels of blood glucose show that other mechanisms beyond weight loss cause these changes (50).

According to the relationship that is known between the microbiota and adiposity both in humans and mice (26), the microbial community is a factor that ensures the success in surgery-based weight loss. In order to determine the enteric microbes' roles in this procedure, researchers defined the intestinal microbiota in humans who went through bariatric surgery and in mouse and rat models subjected to the same procedure (51).

Patients with a history of bariatric surgery, the data related to gut microbiota composition is limited. However, certain studies paved the way for advanced researches on enteric microbes' impact on surgery-related weight loss. The first study that used molecular microbiology technics for the purpose of investigating the impact of bariatric surgery on gut microbiota was performed by Zhang et al. (52) in 2009. In this study, faecal samples were taken from three normal weight individuals, three morbid obese individuals and three individuals with bariatric surgery history, then the microbiota was studied. An average of 40 kg weight loss was seen in the group with bariatric surgery history. This study indicated that obesity and gastric bypass affected the gut microbiota composition for certain. When the microbiota compositions were summarized by taxonomic classification, Gammaproteobacteria rose while Clostridia declined in the group with bariatric surgery history. Additionally, Verrucomicrobia was found in great numbers in the group of obese and normal weight individuals while it was found rarely in the group with bariatric surgery history. Post-operative microbiota is richer than *Enterobacteriaceae, Fusobacteriaceae* and *Akkermansia.* Besides, it is seen that *Firmicutes* is dominant in normal weight and obese individuals and it declines after surgery. This study showed that gut microbiota was distinctly different between the normal weight, obese and post-operative groups. One of the most notable results of this study is that Archea bacteria which use H_2 are only seen in obese individuals, not in lean or post-operative group. Archea bacteria generate energy from indigested polisaccharides.

In another study, Firmicutes and Bacteroidetes were found in smaller amount after surgery (53). As for the study performed by Furet et al. (54), the gut microbiota of 13 normal weight and 30 obese individuals (7 of them have type 2 DM) in the 3rd and 6th month both at the beginning and after the operation. In the beginning (pre-operation), Bacteroides and Prevotella bacteria were found distinctively less in obese individuals in comparision with thin individuals. In addition, *Faecaelibacterium prausnitzii* is lower in number in diabetic obese individuals when compared to lean controls and to obese patients without diabetes. After bariatric surgery, in all individuals, Bacteroides/Prevotella population approximated the level in lean individuals in the 3rd month and it was seen stable in the 6th month after surgery. It was also reported in the results of the same study that post-operative *Faecalibacterium prausnitzii* levels increased. *Escherichia coli* levels distinctively rose in the post-operative 3rd and 6th month when compared to the samples and lean controls in the beginning. Since it is a member of *E.coli*, Gammaproteobacteria class, this result is coherent with the observations of Zhang et al. (52). As for *Bifidobacterium* and *Lactobacillus* levels, they distinctively declined in the post-operative 3rd and 6th month in comparison with the beginning. *Faecalibacterium prausnitzii* levels in diabetic obese individuals increased in the post-operative 3rd and 6th month in comparison with these individuals' samples at the beginning. *Faecalibacterium prausnitzii* is negatively correlated with serum concentrations of inflammatory markers (e.g. hs-CRP and IL-6). This observation bears out the idea that *F. prausnitzii* plays an anti-inflammatory role in inflammatory intestinal diseases (55).

Despite the fact that 50% of the characteristics related to gut microbiota components and obesity depend on energy intake, certain bacteria types, such as *Faecalibacterium prausnitzii*, are directly related to certain diseases, such as low-grade inflammation, obesity, and type 2 diabetes, regardless of energy intake. This situation emphasizes that response to surgical intervention depends on preoperative characteristics and greatly varies among individuals (56).

Differences seen between the studies might be related to the number of patients in the study, metabolic phenotype (the degree of obesity an/or type 2 DM) and/or technology differences. Apart from that, it is not precisely known whether bacteria modifications are relevant to food intake and digestion or surgical procedure differences. It is known that changes in certain bacteria groups are highly affected from food intake, yet it needs to be explained if energy restriction or surgery-based modifications play a specific role in changes seen in gut microbiota after bariatric surgery based weight loss (54).

Gut microbiota can transform into metabolic phenotypes. Liou et al. (57) transferred gut microbiota from RYGB-operated mice into normal mice. It was observed that this transfer resulted in weight

loss and decrease in fat mass in receiving animals. This indicates that changes in postoperative gut microbiota led to weight loss. However, it was also shown that changes in gut microbial composition post RYGB had important impacts on metabolism. Decrease in the Firmicutes/Bacteroidetes ratio and increase in Proteobacteria (52, 53) were also reported. These changes can be partially explained by changes in diet (58). A complex relationship is also observed between gut microbiota and bile acids. High levels of free bile acid in the lower parts of the intestine create an environment that ensures the growth of Proteobacteria, which decrease in secondary bile acids, thereby increasing levels of serum primary bile acids (59). Taken together, these data indicate that changes in intestinal anatomy, gut microbiota, and bile acid levels have curative effects on systemic metabolism through complex mechanisms (60).

Discussion and Conclusion

An interaction is known to exist between gut microbiota and obesity which occurs a result of certain genetic, environmental, socioeconomic and dietary factors. In comparison with lean individuals, obese individuals have different intestinal microbiota. Particularly, Firmicutes bacteria group/Bacteroidetes group rate is higher in obese individuals. Although bariatric surgery, a method to treat morbid obesity, is known to both promote weight loss by affecting microbiota and have curative impacts on metabolic health, comprehensive studies are still needed in this field.

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