

Gut Microbiota as a Target in the Pathogenesis of Metabolic Disorders: A New Approach to Novel Therapeutic Agents

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Key words

- gut microbiota
- obesity
- diabetes
- osteoporosis

Abstract

As the prevalence of metabolic disorders increases dramatically, the importance of identifying environmental factors affecting metabolism control becomes greater accordingly. Gut microbiota, a complex ecosystem inhabiting the human gastrointestinal tract, is one of these potential factors. Recently, the evidence has shown the associations between alteration in gut microbiota composition and obesity, diabetes, and osteoporosis. However, the causality of gut microbiota on metabolic health has yet to be explored in interven-

tion studies and the underlying mechanisms need to be investigated more in depth. Gut microbiota plays critical roles in the control of immunity, food intake, lipid accumulation, production of short chain fatty acids, insulin signaling, and regulation of bone mass. The gut microbiota represents a novel potential therapeutic strategy for the treatment of metabolic disorders. In this review, we provide insights into the role of the gut microbiota in metabolic disorders and its modulating interventions such as prebiotics, probiotics, and fecal microbiota transplantation.

Introduction

The prevalence of metabolic disorders is increasing worldwide, leading to recognize them as public health concerns. The most prevalent metabolic disorders are diabetes mellitus, obesity, and osteoporosis. The involvement of both genetic and environmental factors makes the pathophysiologies of these disorders complicated. Gut microbiota is suggested as a potential contributor to the development of metabolic disorders in recent years [1,2].

Gut microbiota is defined as the microbial community inhabiting the intestine; and gut microbiome are its genomic contents, which are 100- to 150-fold more numerous than the human genome [3]. These microbes, as an endocrine organ, play important roles in human health and their imbalances are related to numerous diseases such as inflammatory bowel disease, cardiovascular diseases, allergies, and metabolic disorders. Recent evidence in mice and humans has shown that gut microbiota is linked with the development of metabolic disorders [1,4–6]. Although only limited species of gut microbiota could be cultured by conventional culture techniques [7], advances in next generation sequenc-

ing and its metagenomic applications allowed the study of the microbiota composition in metabolic disorders without cultivation [8]. Results of the human microbiome studies, which are part of the human genome projects could have possible clinical applications like personalized medicine in the future [8]. It is noteworthy that despite the inter-individual variations in gut microbiota, serial stool collections have shown that core gut microbiota composition of an individual remains stable over time. Therefore, susceptibility to the development of specific diseases was different among subjects. The composition of the gut microbiota is modulated by prenatal events, delivery methods, infant feeding, duration of lactation, complementary foods, geographical location, and environmental factors such as life style, antibiotic use, and dietary pattern [9]. It seems that these factors, effective in altering gut microbiota composition, can be used for therapeutic purposes.

In this review, the mechanisms by which the gut microbiota may affect host metabolism are considered, and the methods of gut microbiota modulation as novel therapeutic strategies in metabolic disorders including obesity, diabetes, and osteoporosis are provided, as well.

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Gut Microbiota and Obesity



Role of gut microbiota in obesity

Due to the epidemic spread of obesity all over the world and the complications related to weight gain in public health, gut microbiota have gained a growing interest as an environmental factor that may affect the possibility of obesity [10,11]. Increased energy intake and decreased physical activity are the main causes of obesity. In addition, various gene polymorphisms have been identified to have role in the pathogenesis of obesity [12,13]. Moreover, different factors such as specific proteins in human cells and many hormonal factors have effective roles in regulating metabolic homeostasis and weight balance [14–17]. Microbiota also has been taken into consideration as a possible reason for affecting energy homeostasis. It was suggested that gut microbiota with environmental predisposition can lead to obesity through stimulating the development of impairment in energy homeostasis [18]. Numerous explorations have turned to the intestinal microbiota's contribution to obesity followed by exploring the first evidence of the link between obesity and intestinal microbiota [19,20]. Animal studies have indicated that microbiota leads to changing the production or secretion of molecules that affect both energy balance and energy stores (fat mass) [21,22]. Bacteroidetes (Gram-negative) and Firmicutes (Gram-positive) are the main phyla of gut bacteria. Firmicutes with more than 200 genera has the highest proportion as the most important of which are: *Mycoplasma*, *Bacillus*, and *Clostridium*. Firmicutes (60–65%), Bacteroidetes (20–25%), Proteobacteria (5–10%), and Actinobacteria (3%) together comprise about 97% of the gut microbiota [23,24]. On the other hand, Arumugam et al. suggested that the microbiota of most individuals could be categorized into 3 dominant enterotypes characterized as *Bacteroides*, *Prevotella*, and *Ruminococcus*, which are independent of age, gender, ethnicity, or body mass index [23,25]. Bacteroidetes and Firmicutes are 2 main groups of gut microbiota, whose proportion is changed in obese mice [19]. Administration of “western diet” to mice resulted in increased abundance of bacteria of the phylum Firmicutes and decreased abundance of bacteria of the phylum Bacteroidetes [26,27]. Human studies have also evaluated the gut microbiota in obese individuals and have documented a reduction in Bacteroidetes accompanied by a rise in *Lactobacillus* species belonging to the Firmicutes phylum in obese subjects [28,29]. On the other hand, some human studies have found different patterns in these alterations, such as the increase in species of both Bacteroidetes and Firmicutes in overweight women [30] or a decrease in Bacteroidetes with no differences in Firmicutes phylum in obese individuals [31]. Finally some studies have shown no difference between Bacteroidetes (B) and Firmicutes (F) at the phylum level [32–35]. Therefore, the F/B ratio could not be used as an informative biomarker in distinguishing obese from nonobese individuals. The earlier studies in this field have focused on microbiota changes in phyla proportion. In recent years, novel next generation sequencing technology based on the analysis of the 16S rRNA bacterial gene allowed for the identification of the bacteria that colonize our gut in the species level. In a recent case-control study in obese and normal weight school-aged children, the relative abundance of bacterial and fungal gut microbes was evaluated. Obese children revealed a significantly lower abundance in *Akkermansia muciniphyla*, *Faecalibacterium prausnitzii*, *Bacteroides/Prevotella* group, *Candida spp.*, and *Saccharomyces spp.* compared to normal-weight children [36].

Recent studies reveal that *Lactobacillus spp.* and *bifidobacterium spp.*, which are the main bacterial population of the small intestine are not all the same and they may have different characteristics according to the species. For example, within the genus *Lactobacillus*, *L. plantarum* and *L. paracasei* are associated with leanness whereas *L. reuteri* is associated with obesity [37]. Drissi et al. have revealed that weight gain-associated *Lactobacillus spp.* appears to have limited ability in the catabolism of fructose or glucose and might reduce ileal brake effects. Whereas the weight protection-associated *Lactobacillus spp.* have developed defense mechanisms for enhanced glycolysis and defense against oxidative stress [38]. In a recent animal study, *Lactobacillus sakei* OK67 ameliorated high-fat diet-induced obesity in mice by inhibiting gut microbiota lipopolysaccharide production and nuclear factor- κ B activation and inducing colon tight junction protein expression [39].

Some studies have reported that *Akkermansia muciniphila* has been founded at a lower concentration in obese individuals. This kind of gut species has potentially protective effects against obesity, metabolic conditions, inflammation, and insulin resistance. So it is a good candidate for consideration as a probiotic [40].

Using the Shannon index, species diversity within the gut has been reported to be lower in obese subjects [41]. However, it should be noted that metagenomic studies nowadays often rely on matching bacterial DNA sequences to reference databases, and these existing sequence databases could accordingly miss important unrecognized bacteria.

Germ-free mice transplanted with the microbiome from obese donors gained significantly more weight compared to germ-free mice transplanted with the microbiome from lean donors, which implies a causal role for the microbiome in obesity and weight gain [19]. However, the contribution of gut microbiota to obesity in humans is unclear and more human studies are needed to evaluate the species level and their changes to reveal the gut microbiota composition and modulation as novel diagnostic or therapeutic strategies to treat obesity and related complications. Major issues while comparing the results of different human studies of intestinal microbiota are potential confounders and some existing technical differences including differences in taxonomy database, taxonomy assignment algorithm, DNA extraction protocols, and PCR primers [41]. Moreover, potential confounding effects of diet, previous use of antibiotics, age, gender, and smoking status on microbiota composition and function should be controlled in obesity-related microbiome studies [42].

Underlying mechanisms in obesity

The gut microbiota might affect energy balance in human through several mechanisms. Fermentation of indigestible dietary compounds serves as an energy source to the host and plays a critical role in releasing of satiety hormones [43,44]. The possible effect of gut microbiota is associated with producing short-chain fatty acids (SCFAs) through fermentation of dietary fiber [45]. The major microbiotic phyla affecting SCFA production in the gut are Firmicutes and Bacteroidetes, as well as the minor phyla Melainabacteria [45]. SCFAs, especially butyrate significantly increases plasma levels of gastric inhibitory peptide (GIP), glucagon-like peptide 1 (GLP-1), peptide YY (PYY), insulin, and amylin, which would have a net effect on slowing digestion and nutrient intestinal transit, promoting satiety, and increasing plasma insulin. Acetate is reported to increase leptin released by fat cells; propionate increases G-protein mediated secretion of

PYY and GLP-1 in the gut and controls the rates of lipolysis and lipogenesis in fat cells [46,47].

Gut microbiota can facilitate the extraction of calories from ingested dietary substances through increasing the absorption of monosaccharides from the gut [19]. Carbohydrate response element-binding protein (ChREBP) and liver sterol response element-binding protein type-1 (SREBP-1) were demonstrated to be involved in the absorption of monosaccharides in the intestine and hepatic lipogenesis induced by the gut microbiota [48]. The other mechanism is the central effect of gut microbiota on leptin signaling [49–51]. The mice with a mutation in the leptin gene (metabolically obese mice) have different microbiota compared with other mice without the mutation [20]. Germ-free mice have significantly increased antiobesity molecule GLP-1 and also reduced anorexigenic brain-derived neurotrophic factor (Bdnf), and leptin resistance associated suppressor of cytokine signaling 3 (Socs3) expressions in both the brainstem and hypothalamus, in comparison with conventionally raised mice. As a consequence, the suppression of any of these molecules by microbes leads to weight gain [49].

Considering the chronic low grade inflammation state in obesity, a new hypothesis has been proposed correlating intestinal flora and obesity. In high-fat diet animal models, the inflammation that leads to diabetes and obesity has been suggested to be triggered by the lipopolysaccharides (LPS) of gram-negative bacteria [52]. Increase in the uptake of LPS and the permeability of the intestine leads to a systemic inflammation [53]. Everard et al. have shown that microflora bacteria interacting with the mucus layer may have a critical effect on obesity [40]. Another mechanism involved in weight control by intestinal microbiota is regulation of fasting-induced adipose factor (FIAF) expression. FIAF is a protein produced by enterocyte, which has an inhibitory effect on lipoprotein lipase (LPL). Unbalanced gut microbiota can suppress FIAF expression and increase LPL activity and triglyceride accumulation in adipose tissue [54] (◉ Fig. 1).

Modulation of gut microbiota in obesity

Studies have indicated that the microbiota composition can be affected by external disturbances such as diet, disease, and environment [55,56]. Dietary changes could lead to 57% of the total structural variation in gut microbiota whereas changes in genetics explain no more than 12% [57]. Prebiotics and probiotics are examples of dietary manipulation of the gut microbiota. Probiotics are defined as 'live microorganisms that their administration in adequate amounts causes health benefits on the host' [58]. The most commonly used probiotic microorganisms have been the following genera: *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Enterococcus*, *Streptococcus*, *Pediococcus*, *Leuconostoc*, and *Bacillus*. However, as probiotic properties have been shown to be strain specific, identification of particular strains is very important. On the other hand, it is also demonstrated that probiotics are safe and beneficial for healthy individuals, caution in selecting of probiotics for immunocompromised patients or patients with a leaky gut is needed [59].

A prebiotic is an ingredient that its fermentation leads to beneficial changes in the gut microbiota [60]. There is evidence that rise in *Bifidobacterium* spp. produced by some prebiotics is accompanied by an increase in GLP1 and PYY secretion by the intestine. These 2 molecules have favorable effects on insulin resistance and the functionality of beta cells [61–63]. In addition, the modulation of gut microbiota with prebiotics increases GLP2 production in the colon, which is associated with higher

expression of zonula occludens-1 (ZO-1), tight junction protein, that decrease plasma LPS through improving the mucosal barrier function [63,64]. Various compounds including lactulose, lactitol, galacto-oligosaccharides, fructo-oligosaccharides, inulin, isomalto-oligosaccharides, polydextrose, resistant starch and gums can act as prebiotic [65]. Metagenomics studies could be helpful to assess the concept of prebiotic activity of different compounds. Studies on the prebiotic effect of various dietary fiber and polyphenols food sources are being conducted.

Fecal microbiota transplantation (FMT), a method that transfers intestinal bacteria from a healthy donor into a patient, is also considered as an important "physiologic" factor in the prevention and treatment of metabolic dysregulation. This method may be effective in improving the obesity, insulin resistance, and metabolic syndrome [66]. FMT from lean donors to individuals with metabolic syndrome significantly increased insulin sensitivity, fecal butyrate concentrations, microbial diversity, and the relative abundance of bacteria related to the butyrate-producing *Roseburia intestinalis* [67]. The effects of FMT on weight control, however, needs to be explored in future clinical trials and it should be noted that like all personalized medicines, some interventions may not only be ineffective in controlling an individual's obesity, they may even be an additional risk factor.

Gut Microbiota and Diabetes



Role of gut microbiota in diabetes

Changes in the gut microbiota were observed during the lifespan from infancy to elderly [68,69]. Different factors that influence these alterations can lead to metabolic disorders such as diabetes. For instance the gut microbiota of babies born vaginally is similar to their mothers, but those delivered by caesarean section have delayed microbial colonization by *Bacteroides*, *Bifidobacterium*, and *Lactobacillus*. Therefore, the incidence of type 1 diabetes mellitus (T1DM) has been noted to occur more frequently in them [70,71]. Studies in children with a high genetic risk for type 1 diabetes revealed significant differences in the gut microbiota between children who developed autoimmunity and those who remained healthy. In these children strong association between *Bacteroides dorei* and type 1 diabetes was discovered. Therefore, increase in *Bacteroides dorei* abundance may be useful for predicting T1D autoimmunity in genetically susceptible infants [72].

Alteration of gut microbiota composition has been also observed in type 2 diabetes mellitus (T2DM). Studies have indicated that there is a significant reduction of Firmicutes and *Clostridia*, while the relative proportion of Bacteroidetes and *Betaproteobacteria* increases in type 2 diabetic patients compared with the healthy persons [5]. Recent studies demonstrated that disrupted mucus-bacterial interactions might be contributing to gut dysbiosis and inflammation. Artificial sweeteners and 2 commonly used emulsifiers including carboxymethylcellulose and polysorbate-80, which were components of processed foods, induced adiposity and glucose intolerance/metabolic syndrome via altering gut microbiota composition [73,74].

Animal studies showed that transplantation of gut microbiota from conventionally raised obese mice to germ-free mice leads to a significant increase in body fat content and insulin resistance in recipient mice [19,75]. Some studies showed significantly higher levels of *Lactobacillus* species and lower levels of *Clostridium* species in the T2DM group [76,77]. Moreover, the

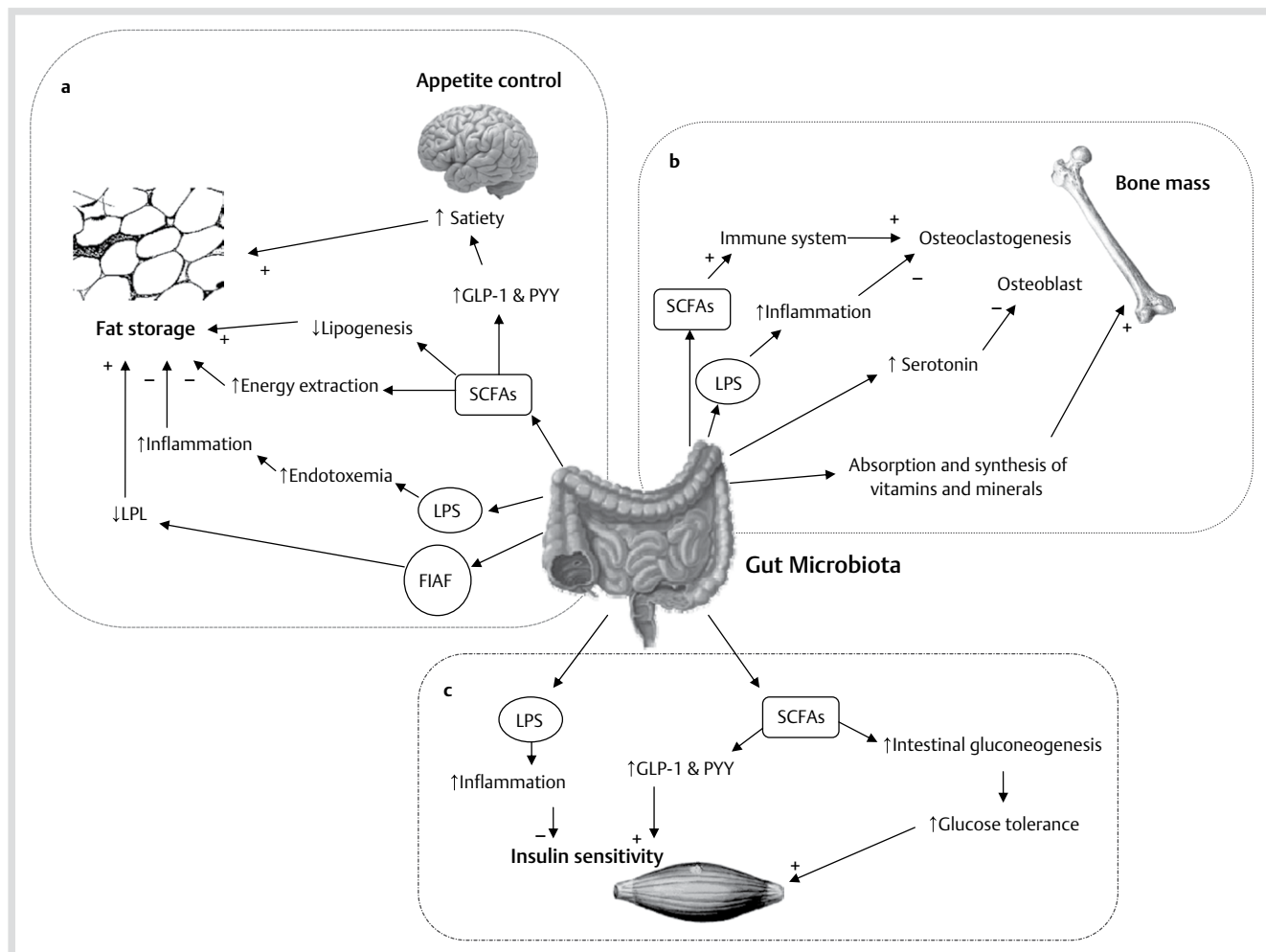


Fig. 1 The mechanisms underlying the effects of gut microbiota on metabolic disorders. **a, Obesity:** Short chain fatty acids (SCFAs) produced via fermentation of indigestible polysaccharides stimulate the release of gut hormones glucagon like peptide-1 (GLP-1) and Peptide YY (PYY). These hormones promote satiety, and regulate eating behaviors through central nervous system (CNS). SCFAs also regulate energy extraction and lipogenesis and decrease gut permeability. Improved gut barrier function decreases the uptake of lipopolysaccharides (LPS) and systemic inflammation, which results in body weight control. Gut microbiota also regulate expression of fasting-induced adipose factor (FIAF), which inhibits lipoprotein lipase (LPL) activity and fat storage. **b, Osteoporosis:**

The effects of gut microbiota on bone mass are mediated through immune system which regulates osteoclastogenesis. Moreover, other contributing mechanisms include absorption and synthesis of vitamins and minerals and regulation of gut-derived serotonin which has a suppressive effect on the osteoblasts. **c, Diabetes:** SCFAs stimulate intestinal gluconeogenesis, which improves glucose tolerance. Moreover, SCFAs could improve insulin sensitivity by increasing GLP-1 and PYY. Unbalanced gut microbiota triggers metabolic endotoxemia and inflammation by increasing LPS which affects insulin sensitivity. The positive and negative signs are indicative of beneficial and harmful effects, respectively.

abundance of *Bifidobacterium* decreases in obese individuals and T2DM patients [78]. Researchers have identified 47 metagenomic linkage groups in the T2DM-associated gene markers from the gut metagenome. They indicated that the abundance of butyrate-producing *Clostridiales* including *Roseburia* and *Faecalibacterium prausnitzii*, which have a protective role against T2DM, decreased significantly in patients with T2DM but the proportion of *Clostridiales* that do not produce butyrate increased [76]. Zhang et al. revealed that patients with T2DM have increased the proportion of Firmicutes and *Clostridia* in comparison with healthy individuals, and the level of *Betaproteobacteria* increased significantly in the prediabetes and T2DM [79]. Therefore, special gut bacterial strains may act as early diagnostic markers for identification of subjects at risk of T2DM.

Underlying mechanisms in diabetes

The possible mechanisms through which gut microbiota is associated with obesity may be related to diabetes as well. One of these mechanisms is the essential role of the gut microbiota in the fermentation of indigestible dietary polysaccharides into SCFAs that act as regulators of food or energy intake and inflammation [80, 81]. SCFAs, acetate, propionate, and butyrate, bind to G protein-coupled receptors (GPCRs) such as GPR41 and GPR43, in the enteroendocrine cells [82]. SCFAs-mediated activation of GPR43 in the adipose tissue prevented fat accumulation by suppressing insulin signaling [83]. Moreover, activated GPR43 in the intestine could increase insulin sensitivity by stimulating the secretion of GLP-1 [84]. Since insulin resistance and T2DM are associated with low-grade inflammation, the inflammatory effective factors such as change in gut microbiota can be a possible mechanism for them [85, 86]. Gut microbiota is full of molecules such as lipopolysaccharide

(LPS) and peptidoglycan, which can lead to inflammation and related metabolic disorders [52]. Alteration in gut microbiota triggers metabolic endotoxemia and inflammation by LPS- and CD14/toll-like receptor (TLR) 4-dependent mechanisms [61]. LPS, lipids, fatty acids and chemokines stimulate c-Jun N-terminal kinase (JNK) and I κ B kinase (IKK)- β pathways intracellularly. IKK β activates family of nuclear factor (NF)- κ B transcription factors and promotes the expression of many mediators of inflammation that can result in insulin resistance. JNK increases the phosphorylation of insulin receptor substrate (IRS)-1 at serine sites and decreases normal signal transduction by the insulin receptor/IRS-1 axis, therefore this leads to insulin resistance [87]. Furthermore, tight junction proteins such as zonula occludens (ZO)-1 and occludin in intestinal epithelial cells reduce gut permeability and inflammatory markers and improve insulin resistance accordingly [88].

Dietary soluble fibers stimulate intestinal gluconeogenesis (IGN), which exert an antidiabetic effect contrary to the general idea that gluconeogenesis impairs glucose tolerance [89]. The expression of IGN gene is stimulated by butyrate through a cAMP-dependent mechanism, but propionate activates IGN gene expression through a gut-brain axis [89]. The IGN released glucose signals the brain by the peripheral nervous system and exerts beneficial effects on dietary intake and glucose tolerance [90] (◉ Fig. 1).

Modulation of gut microbiota in diabetes

The modulation of gut microbiota is a novel therapeutic strategy for glycemic control performed by known components such as prebiotics, probiotics, and some drugs like metformin. Probiotics may have antidiabetic effects due to the compositional changes of the intestinal microbiota [5]. Studies indicated that probiotic consumption led to a healthier gut microbiota and has been identified as an effective supplementary treatment in insulin resistance and its related complications [91,92]. *Bifidobacteria* and *Lactobacilli* are commonly used strains of probiotics in functional foods and dietary supplements [93]. Studies have indicated that the consumption of *L. acidophilus*, *L. casei*, *L. lactis*, and *L. plantarum* DSM15313 decreases the glycemic curve, insulin resistance, and HbA1c [94,95]. Marques et al. showed that γ -aminobutyric acid (GABA)-producing *Lactobacillus brevis* attenuated hyperglycemia in streptozotocin-induced type 1 diabetes rat models [96]. Probiotics may exert antidiabetic properties via immune-modulatory effects [87,97,98]. Further research is warranted into dosage magnitude, and mechanism of probiotics' effects [98].

Prebiotics, which are fermentable polysaccharides, promote SCFA production, stimulate the growth of beneficial bacteria such as *Bifidobacterium*, and improve gut barrier function [99]. Therefore, prebiotics improve gut permeability, decrease metabolic endotoxemia, reduce inflammation, and improve glucose intolerance [51,64].

Metformin can also affect the gut microbiota. Shin et al. have demonstrated that metformin can increase the abundance of *Akkermansia muciniphila*, mucin-degrading bacteria, in the gut of mice fed a high fat diet. Therefore, metformin may exert its antidiabetic effects by modulation of the gut microbiota through increasing the *Akkermansia muciniphila* population [100]. Moreover, results of in vitro study investigated the effects of acarbose on ruminal fermentation characteristics and the composition of the microbiota revealed that the proportion of Firmicutes and Proteobacteria was decreased and the percentage of Bacteroidetes, Fibrobacteres, and Synergistetes was increased in acarbose group compared with the control group. This study documented that acarbose could be useful for preventing the accumulation of LPS in the rumen [101].

Recent articles indicated the fecal microbiota transplantation as a new potential therapeutic option in T2DM. Vrieze et al. reported that fecal microbiota transplantation from lean donors to obese subjects with metabolic syndrome increased butyrate-producing bacteria and improved insulin sensitivity [67]. In future, well-designed trials are needed to develop a new treatment for diabetes.

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Gut Microbiota and Osteoporosis

▼ Role of gut microbiota in osteoporosis

Osteoporosis, a major bone health concern, could result in a huge economic burden on health care systems. The bone health depends both on how much bone is acquired until peak bone mass is attained at 20–30 years of age and on the rate of the subsequent bone loss. Hereditary and environmental factors are major determinants of the variances in peak bone mass and age-related bone loss [102,103]. The potential of gut microbiota to affect bone health is a rather new area of investigation. Recent evidences have demonstrated gut microbiota as a regulator of bone mass mediated through effects on the immune system [6]. Unbalanced microbial composition of the gut microbiota has been suggested to be involved in different inflammatory diseases, within and outside the gastrointestinal tract, including inflammatory bowel diseases, rheumatoid arthritis, allergies, obesity, and metabolic syndrome [104,105]. Moreover, inflammatory and autoimmune conditions have been associated with low bone mass, suggesting the relationship between the immune system and bone metabolism [106].

Bone-forming osteoblasts and bone-resorbing osteoclasts are responsible for bone remodeling. The skeleton provides hematopoietic stem cells, which differentiate into osteoclasts or immune cells (T cells) depending on local microenvironment status [107]. Evidences indicate that low-grade inflammation affects bone turnover and subsequently bone mass [108]. Therefore, it was suggested that gut microbiota, which is correlated with immune system, could work as a regulator of bone mass and a new gut microbiota-bone research field, known as osteomicrobiology was proposed.

The germ-free mouse is a useful model to study the effects of gut microbiota on bone mass. Sjogren et al. demonstrated that the absence of gut microbiota in germ-free mice was associated with increased bone mass. It was found that bone marrows of germ-free mice have fewer CD4+ T cells and osteoclast precursors compared to conventionally raised mice. These fewer CD4+ T cells in bone marrows are caused by fewer CD4+ T cells circulating in the blood and secondary lymphoid tissue resulting in a decreased expression of inflammatory cytokines [6].

As human grows older, osteoporosis become more prevalent, in a way that one in 3 women and one in 5 men experience osteoporotic fracture after the age of 50 [109]. Although gut microbiota varies widely among individuals, there are significant changes in gut microbial composition of older adults. Gut microbiota shift from obligate anaerobes to facultative anaerobes in the elderly, leading to inflammation. Gut microbiota in older adults have higher amounts of pathogenic Proteobacteria and Bacilli and lower amounts of anti-inflammatory Lactobacilli

[110]. Evidence indicated that as elderly move from living in the community to long-term care facilities, large microbial changes occurred in their gut microbiota [111]. These changes alter bone and body composition and increase the risk of osteoporosis.

It seems that the analysis of the gut microbiota composition in osteoporotic subjects could evaluate the possible associations between bone mineral density and specific bacterial phyla, genera, and species. Moreover, the analysis of the gut microbiota composition in cohort studies can be used to determine the predictive role of the gut microbiota for low bone mass and osteoporotic fractures risk.

Underlying mechanisms in osteoporosis

It was proposed that the most probable mechanism by which gut microbiota affects bone mineral density involves the immune system, which in turn regulates osteoclastogenesis [108]. Moreover, SCFAs could regulate inflammation and possibly exerts their direct effects on bone [112]. Direct effect of butyrate on bone cells was the inhibition of osteoclast formation. Furthermore, it was found that SCFAs could regulate osteoclastogenesis indirectly through affecting on T cells in the colon [112]. In addition to osteoclastogenesis suppression, gut microbiota enhance absorption and synthesis of various vitamins and minerals including vitamins K and B12, calcium, and magnesium, which increase bone density and strength [109, 113]. The effects of prebiotic and probiotic supplementation on gut microbiota composition and mineral absorption needs to be further investigated. Although, it should be considered that how precise could the fecal microbiome composition reflect the microbiome of intestinal active site for mineral absorption.

Studies have shown that gut microbiota also can influence bone mass by the neurotransmitter serotonin. Several microbial species directly synthesize serotonin, some others, however, regulate the availability of tryptophan as a serotonin precursor. Serotonin has a suppressive effect on osteoblast and may control bone mass via this pathway [114–116] (◉ Fig. 1).

Modulation of gut microbiota in osteoporosis

The microbiota composition of osteoporotic subjects could be modulated by dietary manipulation like prebiotics and probiotics. Prebiotic supplementation in animal models altered gut microbiota in favor of *bifidobacteria* and increased short chain fatty acids, and improved mineral absorption and bone density as well [113, 117].

Studies have shown that different *Lactobacillus* strains, including *L. reuteri*, *L. paracasei*, and *L. plantarum* supplementation suppressed bone loss in ovariectomized mouse models [118, 119]. Therefore, it was proposed that the gut microbiota composition could be involved in the bone loss experienced by postmenopausal women who lose the immunosuppressive effects of estrogen. *Lactobacillus reuteri* also decreased intestinal inflammation and increased bone density in healthy male mice and type 1 diabetic mice [120, 121]. Moreover, yacon flour in combination with *B. longum*, as a synbiotic food, helped to increase the concentration of minerals in the bones of rats [122]. Taken together, as certain probiotic bacteria may benefit bone and others may harm bone by promoting inflammation, future randomized clinical trials are needed to assess the possible effects of probiotic and prebiotic supplementation on bone health.

Conclusion and Future Perspectives



From the grounds up, the development of new strategies for prevention and control purposes for the rapid spreading of metabolic disorders are critical. Recent studies implicate that metabolic phenotypes are associated with altered intestinal microbiota composition compared to healthy counterparts. However, most of the published human studies are associative and causality of gut microbiota in metabolic disorders should be investigated in further research in order to allow using gut microbiota modulation as a target for preventing or treating human metabolic disorders. Integration of gut metagenomics studies with other high-throughput techniques like metabonomics can expand our knowledge of the gut microbiota-host interactions and will discover underlying cellular and molecular mechanisms involved in metabolic health. Apprehending the role of gut microbiota in the modulation of host metabolism can provide novel therapeutic strategies. Future studies to identify specific bacterial species associated with metabolic phenotypes can help in providing therapeutic solutions by modulating the gut microbiota.

The ways through which the modulation of intestinal microbiota might be achieved include dietary intervention using prebiotics and probiotics or microbial transplantation from healthy donors. Administrations of prebiotics, as a dietary method of gut microbiota modulation, resulted in an increase in the lactobacillus and bifidobacterium species and also a dose-dependently increase in the satiety hormones levels including GLP-1 and PYY. Studies are ongoing to select the best type of prebiotics with beneficial effects on metabolic health. Furthermore, as many medicinal plants are used for the treatment of metabolic disorders throughout the world whose effects may be linked to the modulation of gut microbiota, prebiotic properties of these herbal medicines should be investigated [123–125].

Moreover, the selection of new probiotic strains including *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, and *Bacteroides uniformis*, which efficiently modulate the human gut microbiome in preclinical trials is a new strategy to improve metabolic disorders [126].

Fecal microbiota transplantation (FMT) has been demonstrated to alter the gut microbiota of the recipient. Ongoing placebo-controlled trials are being conducted in humans to examine if microbiota transplantation can improve metabolic health. Fecal transplantation studies might reveal the causality relationship between specific intestinal bacterial strains and metabolic health. However, critical issues including host immune response, determination of suitable donors, and preparation of donor samples before treatment should be considered in FMT.

Regarding the primary driving sources of metabolic disorders, investigating the gut microbiota composition in genetic variants of metabolic disorders could be effective in order to implement more personalized treatment. Although the association between gut microbiota and obesity-related metabolic abnormalities has been shown in recent studies, a proportion of obese individuals are free of metabolic abnormalities. The mechanisms underlying this protective profile of the metabolically healthy obese are not known. On the other hand, metabolically nonobese individuals are a subgroup of normal weight subjects with a variety of obesity-related co-morbidities. Future studies are needed to investigate the differences in microbiota composition between these different metabolic phenotypes. This knowledge can result in new therapeutic areas in the field of obesity and metabolic

disorders. Moreover, osteosarcopenic obesity, the concurrent appearance of obesity and low bone and muscle mass is a condition whose etiological studies are limited. Evaluating the gut microbiota composition in this condition could be useful for developing a new strategy to improve the health outcomes.

Conflict of Interest

There is no potential conflict of interest relevant to this article.

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