

REVIEW ARTICLE

GUT MICROBIOTA: FROM THE PERSPECTIVE OF CARDIOMETABOLIC DISEASES

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Abstract

Considering the prevalence of obesity, diabetes and cardiovascular diseases, significant interest has been focused on the gut microbiota-diabetes and cardiovascular system interaction, because the gut microbiota has been recognized as a modulator of human health. Dysbiosis, characterized by pathological changes in the gut microbiota, has been reported in cardiometabolic disorders, such as overweight and obesity, dyslipidaemia, atherosclerosis and hypertension. Furthermore, dysbiosis can disturb gut immunity, which increases the risk of acute cardiometabolic events. Therefore, the changes in the composition of the gut microbiota can affect host metabolism and immunity. The aim of this review is to look through the current knowledge over gut microbiota and expand the view on key roles of intestinal microflora during development of cardiometabolic diseases as T2DM, hypertension, dyslipidemia and atherosclerosis, also discuss the roles of microbiota regulating agents such as pre- and probiotics.

Keywords: Microbiota, obesity, diabetes, metabolic disease, cardiovascular.

Introduction

The term *microbiota* defines a population of microorganisms located in a specific environment. *Metagenome* is a term for all the genetic material present in an environmental sample, consisting of the genomes of many individual organisms. Humans host different metagenomes from multiple locations such as skin, lungs, vagina, mouth, but the intestines host the most. The human gastrointestinal tract contains in average 10¹⁴ microorganisms/ml of luminal content, and features over 5000 bacterial species, weighing in average 1.5 kg (1-3).

Metabolic disorders like overweight and obesity have spread worldwide, today reaching epidemic proportions, leading to more than almost 3 million people die each year. In addition, 44% of diabetes cases, 23% of ischemic heart disease cases and between 7% and 41% of certain cancer burdens are attributable to overweight and obesity (4-7). Hypertension and type 2 diabetes (T2DM) are closely related to each other in clinical setting, and hypertension by itself, is a complication of T2DM, a major risk factor for cardiovascular disease and a symptom of metabolic syndrome (8,9).

The aim of this review is to look through the current knowledge over gut microbiota and expand the view on key roles of intestinal microflora during development of cardiometabolic diseases as T2DM, hypertension, dyslipidemia and atherosclerosis.

Gut Microbiota

All mammals were born sterile, without any flora. Following the first a few hours or days, the mother's and the environmental flora colonized the overall body of the newborn in a specific order. The initial infant gut microbiota is simply structured mainly by *Bifidobacteria*, but even though the infant's gut is only colonized fully by maternal and environmental bacteria during birth; the way of labor might change almost everything (10). Whereas the vaginally delivered infant's intestinal microbiota resemble the mother's vaginal microbiota (*Lactobacillus*, *Prevotella* or *Sneathia* spp.), babies born by caesarean section harbour microbiota similar to those on maternal skin surface, *Staphylococcus*, *Corynebacterium* and *Propionibacterium* spp.

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Intestinal microbiota of the infant is associated and effected by not only mode of delivery, but also with gestational age at birth, diet composition and antibiotic use. It undergoes substantial changes in time with respect to feeding pattern. It is because of which is thought to be due to the breast milk containing -prebiotic- oligosaccharides; the composition of gut microbiota differs between breast-fed and formula-fed infants (11-13).

The adult intestinal microbiota has been shown to be relatively stable, majorly phyla of *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria* which are commensal anaerobic species. The core intestinal microbiota changes to become distinct in older people from that observed for younger adults, with a greater proportion of *Bacteriodes* spp and distinct abundance patterns of *Clostridium* groups (14).

Ecological progression and rules shape the microbial diversity through the life cycle, however, before reaching an ideal microbial ecology, the microbes have interactions with the host, which have not been fully elucidated yet. The exchanges between bacteria and host's epithelium may differ in different parts of intestines because of anatomical differences and the extent to which the secreted mucus layer covers the epithelium. Gut microbiota has so strong impact on the control of many major physiological functions that the bacterial to host interactions actually help to mature the intestinal epithelial layer, the mucosal innate immune system, the enteric nervous system, as well as the intestinal vascular system (15-17).

The microbiota functions in tandem with the host's defences and the immune system to protect against pathogen colonisation and invasion. It also performs an essential metabolic function, acting as a source of essential nutrients and vitamins and aiding in the extraction of energy and nutrients, such as short-chain fatty acids (SCFA) and amino acids, from food. Ultimately, the host depends on its intestinal microbiota for a number of vital functions and thus the intestinal microbiota may contribute to health. It is, however, difficult to describe the precise impact of the intestinal microbiota on human health and the involvement in human disease (18).

It has been also suggested that the intestinal microbiota composition is associated with conditions such as allergies, intestinal inflammatory diseases, certain types of cancer, cardiometabolic diseases like diabetes, dyslipidaemia and atherosclerosis-related conditions as hypertension and coronary heart disease. The alteration of intestinal microbiota was suggested to be responsible to increased intestinal permeability and mucosal immune response, contributing to the de-

velopment of metabolic diseases. It is also proposed that altered microbiota increases metabolic endotoxin secretion leading to chronic low-level inflammation, by modulating intestinal permeability (19-22).

Alteration Of Microbiota With Antibiotics, Pro-, Pre- and Synbiotics And Its Consequences

Once adult microbiota established, influencing factors such as antibiotics, prebiotics and probiotics could modulate its ecological architecture, but these effects are always reversible, suggesting that a tight host-microbiota relationship has been established during the neonatal life where the host shapes the microbiota and vice versa. There is huge potential for manipulating the microbiota to sustain, improve, or restore the microbiota in at risk or diseased individuals. Microbial *dysbiosis*, described as the decrease of useful bacteria and the increase of harmful bacteria, has been associated with diabetes, obesity, atherosclerosis and metabolic syndrome. In microbial dysbiosis, increase of harmful metabolites and changes to composition of bile acids occur via carbohydrate and protein fermentation, hence, as a result, insulin resistance pathways are activated (23-24).

Antibiotic treatment is a method for gut microbiota modulation. Antibiotics have been used for more than sixty years to treat various infections and recent studies have shown that antibiotics can promote weight gain in agricultural animals and have also been linked to obesity in humans who had been given antibiotics during early infancy. Treatment with norfloxacin and ampicillin (1g/L each) for 2 weeks, suppressed the numbers of cecal bacteria in mice. The treated animals displayed a significant improvement in fasting blood glucose and oral glucose tolerance. The enhanced insulin sensitivity was independent of food intake, weight loss or adiposity. When diet-induced obese and insulin resistant mice were treated with the non-absorbable antibiotics polymyxin B and neomycin, they had a gradual reduction in glycemia, associated with a modified cecal microbiota (25-27).

Probiotics are a class of live microorganisms which, when ingested in appropriate amounts, may confer health benefits to their host. Consumption of probiotics may be associated with immune system stimulation, decreased cholesterol blood levels, protection against respiratory and intestinal diseases, reduction of inflammatory responses and antitumorigenic effects. These claims stem from the ability of probiotics to secrete antimicrobial substances, competing with other pathogens, strengthening the intestinal barrier and modulating the immune system. As probiotics, *Bifidobacteria* and *Lactobacilli* are the most commonly used strains in functional foods and dietary

supplements. Intestinal microbiota modulation by probiotics also appears to offer beneficial outcomes to insulin-resistant individuals via mechanisms both related and unrelated to inflammation. In an animal study, researchers observed that a fermented milk product containing probiotic bacteria significantly delayed the onset of glucose intolerance, hyperglycemia and hyperinsulinemia in diabetic rats induced by high fructose concentration (28,29).

Prebiotics are best known as a type of dietary fiber called oligosaccharides which are a type of non-digestible fiber compound and just like other high-fiber foods. Prebiotics were first defined by Gibson and Roberfroid as non-digested food components that, through the stimulation of growth and/or activity of a single type or a limited amount of microorganisms residing in the gastrointestinal tract, improve the health condition of a host but, in 2007, WHO experts described prebiotics as a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota. Prebiotics may be used as an alternative to probiotics or as an additional support for them. However different prebiotics will stimulate the growth of different indigenous gut bacteria. Prebiotics have enormous potential for modifying the gut microbiota, but these modifications occur at the level of individual strains and species and are not easily predicted a priori. There are many reports on the beneficial effects of prebiotics on human health (30).

Symbiotics have both probiotic and prebiotic properties and were created in order to overcome some possible difficulties in the survival of probiotics in the gastrointestinal tract. Therefore, an appropriate combination of both components in a single product should ensure a superior effect, compared to the activity of the probiotic or prebiotic alone. In elderly T2DM patients who consumed a daily dose of 200 mL of a symbiotic drink containing 10^8 CFU/mL *Lactobacillus acidophilus*, 10^8 CFU/mL *Bifidobacterium bifidum* and 2 g oligofructose over 30 days, there was a significant increase in high-density lipoprotein cholesterol and a significant reduction in fasting glycemia (30-32).

The Role of Intestinal Microbiota on Body Weight, Diabetes and Cardiovascular Diseases

Humans do not have the enzymes necessary for digestion of many types of plant polysaccharide, such as cellulose, xylans, resistant starch and inulin. However, these indigestible carbohydrates can be fermented by intestinal microbes to yield energy and to produce SCFAs. Energy metabolism can be profoundly regulated by host gut microbiota, that, microbiota modulates energy balance (5,33,34).

As it is well known, energy balance results from an equilibrium between energy intake and energy expenditure. The related experiments suggested the hypothesis that obesity-associated gut microbiome has an increased capacity for energy harvest from the diet, the so called "storage effect" hypothesis, which is based on microbial fermentation of dietary polysaccharides that cannot be digested by the host, intestinal absorption of monosaccharides and lipid metabolism regulation by microbiota (33,35).

The role of the intestinal microbiota in the regulation of host body weight and energy homeostasis was revealed primarily in rodents. Germ-free mice transplanted with fecal microbiota from obese donors had a significantly greater increase in total body fat than those colonized with microbiota from lean donors (36).

Furthermore, both obesity and diabetes are characterized by a state of chronic low-grade inflammation with abnormal expression and production of multiple inflammatory mediators such as tumor necrosis factor and interleukins. Recent studies based on large-scale 16S rRNA gene sequencing and more limited techniques, based on quantitative real time PCR (qPCR) and fluorescent in situ hybridization (FISH) have shown a relationship between the composition of the intestinal microbiota and metabolic diseases like obesity and diabetes. As an example, *Bifidobacterium* levels significantly and positively correlated with improved glucose tolerance and low-grade inflammation in mice treated with prebiotics (37).

Actually several studies on mice and human subjects, provided evidence that increase in body weight was associated with a larger proportion of *Firmicutes* and relatively less *Bacteroides*. In another study, intestinal microbiota in T2DM were characterized that the proportions of phylum *Firmicutes* and class *Clostridia* were significantly reduced in the diabetic group compared to the control group (38,39).

Intestinal microbiota, which strongly influences fat storage in white adipose tissue, may as well tightly regulate lipid metabolism and its consequences on cardiovascular diseases. Microbiota, although present at low concentration in the duodenum and jejunum, where most of the lipids are absorbed, would be informing the intestinal cells with lipid metabolites. Plasma levels of cholesterol and a number of lipid species in the serum triglycerides and phosphatidylcholine were reduced by the microbiome whereas they were increased in the tissue such as the adipose tissue and the liver. This suggests that the clearance of lipids was increased by the microbiota (40).

The origin of the factors triggering inflammation before the onset of cardiometabolic diseases is not totally clear, but it is proposed that the lipopolysaccharides (LPS) which are highly inflammatory component of the cell wall of the gram-negative bacteria were causally involved in the onset of the low-grade inflammation in response to a fat-enriched diet. Mice fed a high-fat diet for a short period of 2 weeks were characterized by a moderate 2-3 fold increase in blood LPS defined as metabolic endotoxemia. Adipose tissue, liver and muscle inflammation developed on the basis of this steady high concentration of plasma LPS. Cardiovascular diseases have been linked to infection for several decades by augmenting pro-atherosclerotic changes in vascular cells. A microbiome has been found in atherosclerotic plaques since bacterial DNA can be identified in more than 50% of all plaques and its origin could be intestinal or oral. The vascular risk was really increased in population studies where the plasma concentration of LPS was increased. Therefore, microbiota from intestinal or oral origin is now certainly recognized as a risk and a causal factor of the cascade of events leading to atherosclerosis (41-43).

Moreover, one experimental finding supporting the hypothesis of blood pressure regulation by the gut microbiota was provided on propionate, one of the end-products derived from the gut microbiota. In response to propionate, the expression of renal olfactory receptor 78 increases and mediates the secretion of rennin. Consequently, the blood pressure, an important risk factor for cardiovascular diseases and metabolic syndrome, elevates. It has been reported that *Lactobacillus johnsonii* ingestion could not only maintain low blood glucose level in streptozotocin induced diabetic rats, but also prevent rats from elevated blood pressure by reducing the renal sympathetic nerve activity and enhancing the parasympathetic nerve activity through the sympathoadrenal axis (44,45).

Conclusion

There is strong evidence that the intestinal microbiota is a regulator of human health. The evidence from animal and human studies supports that gut microbiota is in correlation with many cardiometabolic diseases such as obesity, diabetes, dyslipidaemia and hypertension. Unappreciated complexity and considerable diversity of the bacterial microbiome have been gradually uncovered via culture-independent methods. However, the direct relationship between gut microbiota and cardiometabolic diseases remains obscure. In addition, the diversity of microbiome

enhanced the difficulty in identifying strains in correlation with disease state, which restricted therapeutic interventions for the exact target.

Even though the intestinal flora as a modulator of human health, look like a novel therapeutic target for preventing cardiometabolic diseases, larger randomized controlled studies of adequate sample size and duration and well-defined therapeutic schedules and endpoints are strongly advised.

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