Contribution of diet to gut microbiota and related host cardiometabolic health: diet-gut interaction in human health

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ABSTRACT

Obesity and cardiometabolic diseases in both developed and developing counties in a state of nutrition transition are often related to diet, which also play a major role in shaping human gut microbiota. The human gut harbors diverse microbes that play an essential role in the well-being of their host. Complex interactions between diet and microorganisms may lead to beneficial or detrimental outcomes to host cardiometabolic health. Despite numerous studies using rodent models indicated that high-fat diet may disrupt protective functions of the intestinal barrier and contribute to inflammatory processes, evidence from population-based study is still limited. In our recent study of a 6-month randomized controlled-feeding trial, we showed that high-fat, low-carbohydrate diet was associated with unfavorable changes in gut microbiota, fecal microbial metabolites, and plasma proinflammatory factors in healthy young adults. Here, we provide an overview and extended discussion of our key findings, and outline important future directions.

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Introduction

The human gut harbors trillions of microbes that perform multiple functions and exert effects on host cardiometabolic health. Among many factors that could influence gut microbiota, diet has received the most considerable attention because diet is the easiest to modify and presents the simplest approach for potentially preventive or therapeutic intervention. Diet can interact with microorganisms to directly promote or inhibit their growth and change the colonic luminal microenvironment, and indirectly affect host metabolism and immune system. The capability of gut microbiota to extract energy from specific dietary components such as non-digestible carbohydrates in turn confers a more competitive advantage to selected members of the gut microbial community at the expense of less-adept members. Dietary constituents might also disrupt protective functions of the intestinal barrier in ways that could affect the microbiome-host interface and prompt gut microbiota imbalance, contributing to inflammatory processes and conferring downstream implications on the host. Recent advances in sequencing techniques for characterizing the gut microbial communities have accelerated our ability to understand how diet modulates gut microbiota, and most importantly, its effect on human health. Rapid and substantial strides have been made in unraveling the composition and functionality of gut microbiota, despite a large variability exists in gut microbial community among individuals. This enables us to understand the contribution role of diet in shaping gut microbiota and host cardiometabolic health.

Contributing role of diet in shaping gut microbiota

Gut microbiota is involved in energy harvest and storage, as well as in a variety of cardiometabolic functions such as fermenting and absorbing undigested carbohydrates, a trait that has probably
acted as strong evolutionary force toward the establishment of bacteria as human symbionts. Variation in diet is one of the key contributing factors to the human gut microbiota diversity, which evolves in parallel with the diet of our evolutionary ancestors in which a symbiotic relation exists.

Many studies used animal models to explore and identify the mechanism of diet-gut-health axis, though the degree to which findings translate to humans is unknown. In humans, observational studies including cross-sectional and cohort studies can provide association between diet and gut microbes, while which are limited by the inability to reveal causal relations. Gut microbiota in the US individuals who consuming a modern western diet showed a less diversity than their rural counterparts whose diet is dominated by plant-based polysaccharides such as corn and cassava. Similarly, children living in a village of rural Africa following their traditional diet showed higher diversity in their gut microbiota than those from western Europe adhering to a typical Western diet. The traditional diet in rural African was primarily low in fat and animal protein, and rich in starch, fiber, and plant polysaccharides. On the contrary the diet of children from Western Europe was high in fat, animal protein, and sugar, but low in fiber. Other diets that have also been reported to be associated with changes in gut microbiota compositions include Mediterranean diet and vegetarian diet.

Evidence of the strongest level is obtained from randomized controlled trials. A ten-day clinical trial with nine participants reported that the composition and function of the gut microbiota were rapidly changed when carbohydrates were eliminated from the diet, even though exclusion of all carbohydrates is unsustainable and unlikely to be beneficial to human health. Other controlled-feeding studies using less extreme differences in diet with regard to macronutrient distribution suggested that diet can alter the gut microbiomes of obese individuals over timescales of week to years.

**Involvement of gut microbiota in cardiometabolic diseases**

Increasing attention has been paid to the modulation of gut microbiota in recent years, partly due to the observation that the microbiota plays a much more important role in human health than previously thought. Dysbiosis is a term referring to the changes in the composition of normal gut microbiota. Numerous studies have shown that microbiota dysbiosis is linked to the pathologies of obesity and cardiometabolic diseases, characterized by lower microbial diversity or abnormal microbiota composition.

Obesity has been long accepted to be correlated with a shift in the relative abundance of the Bacteroidetes and Firmicutes phyla, which collectively constitute more than 90% of all phylogenetic types of gut microbes. Studies using germ-free mice showed that the lean and obese phenotypic traits are transmissible by gut microbes transplantation. Though the exact mechanisms linking gut microbiota to obesity is far from being clearly understood, it's widely believed that gut microbiota can increase energy harvest from diet and contribute to low-grade inflammation, leading to the development of obesity. Key metabolites involved in these processes are short chain fatty acids (SCFAs), such as butyrate, propionate, and acetate. SCFAs are the major metabolites produced by bacterial fermentation of non-digestible carbohydrates, which play an important role in the maintenance of health and the development of disease. The effect of SCFAs on obesity is controversial. Some studies have found that SCFAs have an anti-obesity role via regulating the balance between fatty acid synthesis and oxidation (favoring the latter and inhibiting the former). While others supported a concept that people with obesity have a higher relative abundance of carbohydrates-fermenting bacteria than lean people. This leads to an increased SCFAs biosynthesis rate, which provides an extra energy source for the host. Nevertheless, SCFAs have been associated with reducing risk of other diseases including gastrointestinal disorders, cancer, and cardiometabolic diseases.

Trimethylamine-N-oxide (TMAO) is another main metabolite through which gut microbiota participate in the development of cardiometabolic diseases. Gut microbiota could metabolize trimethylamine-containing compounds such as carnitine, choline, and phosphatidylcholine to trimethylamine, which is further converted by hepatic flavin-containing monoxygenases to TMAO, a proatherogenic metabolite.
animal and human studies provide evidence to support the role of gut microbiota in TMAO biotransformation.\textsuperscript{27–29} TMAO was not detected in germ-free mice after a carnitine or choline challenge but was produced after microbial colonization of germ-free mice.\textsuperscript{27,28} A human intervention study elucidated the TMAO synthesis pathway, which was markedly disrupted upon antibiotic treatment, indicating that the pathway was gut microbiota dependent.\textsuperscript{30} Several large-scale cohorts observed the striking associations between circulating TMAO levels and cardiometabolic diseases.\textsuperscript{31} The mechanistic role for TMAO in cardiometabolic disease, mainly cardiovascular disease, is supported by numerous animal model studies showing that manipulation of TMAO levels modulates atherosclerosis and related processes.\textsuperscript{27,28} Collectively, these data suggested the possible involvement of gut microbiota in the pathogenesis of cardiometabolic disease via TMAO.

The impact of diets with different fat content on gut microbiota among population in a state of nutrition transition

Over the past few decades, China has been experiencing nutrition transition from the traditional low-fat, high-carbohydrate diet to a diet relatively high in fat and low in carbohydrates. This nutrition transition is in parallel with a dramatic increase in the risk of obesity, type 2 diabetes, and cardiovascular disease. Does the modern high-fat, low-carbohydrate diet in China have adverse effects on cardiometabolic health and is the gut microbiota engaged in these processes? Our recent randomized controlled-feeding trial answered these two questions.\textsuperscript{32,33}

In this trial, we designed three isocaloric diets with different dietary fat to carbohydrate ratios: a low-fat diet (fat 20% and carbohydrates 66% energy, corresponding to the macronutrient distribution 30 years ago during which obesity was rare in China), a moderate-fat diet (fat 30% and carbohydrates 56% energy, the upper limit of fat intake recommended by the Chinese Nutrition Society), and a high-fat diet (fat 40% and carbohydrates 46% energy, approximating the current consumption of Chinese residents in megacities) to represent macronutrients change in China. Rather than giving dietary instructions, we used controlled-feeding design and provided the participants in all three dietary groups with all foods and beverages throughout the 6-month intervention to avoid inaccurate calculation of the dietary intakes and minimize the dietary confounders. We found that the high-fat, low-carbohydrate diet appeared to be associated with a higher cardiometabolic risk profile than the low-fat, high-carbohydrate diet.

To assess if gut microbiota was affected by the dietary intervention and in turn influence the host metabolism, we further measured the gut microbiota composition and fecal metabolomics profile. Overall, the high-fat, low-carbohydrate diet was associated with unfavorable effects on gut microbiota and microbial metabolites. The relative abundances of Bacteroidetes phylum and Bacteroides and Alistipes genera were increased, while Firmicutes phylum and Faecalibacterium genus were decreased after high-fat, low-carbohydrate diet intervention. Meanwhile, the high-fat, low-carbohydrate diet increased fecal concentrations of palmitic acid, stearic acid, and arachidonic acid, but decreased butyric acid concentration. In addition, the high-fat, low-carbohydrate diet was associated with increased levels of plasma proinflammatory factors such as high sensitivity C-reactive protein and thromboxane B\textsubscript{2}, relative to the low-fat, high-carbohydrate diet.

Factors worthy of consideration in diets with different fat content

We used isocaloric design and protein intake was kept at the same level across all diets. The difference in dietary fat intake was achieved by replacing a proportion of energy derived from carbohydrates (white rice and wheat flour, the most widely consumed carbohydrate sources in China) with fats (soybean oil, the most widely used edible oil in China).

White rice and wheat flour contain a certain amount of resistant starch, 3% in the former and 2% in the latter. Resistant starch can escape digestion by human pancreatic amylase in the small intestine and thus, reach the colon.\textsuperscript{34} In the colon, resistant starch is fermented by gut microbiota and yields SCFAs, providing a source of energy for the bacteria in this anaerobic environment and potentially
altering the composition of the microbiota and its metabolic activities. In addition to resistant starch, wheat flour is a source of fermentable oligo-, di- and monosaccharides, and polyols (FODMAPs), with a level of around 1.6%. FODMAPs are poorly absorbed in the small intestine for a slow transport mechanism or an ineffective/reduced enzymatic activity and are rapidly fermented by the colonic microbiota. By virtue of the need to increase fat intake in the high-fat diet, the intake of carbohydrates (in the form of white rice and wheat flour) was decreased. Considering the ability of resistant starch and FODMAPs to change microbial structure and their metabolic products, one might argue that the difference in these non-digestible carbohydrates across three diets in our trial explained the difference in butyrate-producing genus, *Faecalibacterium*, as well as the difference in fecal butyric acid concentration since non-digestible carbohydrates are the main substrates for SCFAs. Admittedly, the unfavorable effects of the high-fat, low-carbohydrate diet could be, at least in part, due to the decreased amount of non-digestible carbohydrates. However, it should also be noted that the absolute difference in non-digestible carbohydrates across three diets is actually very small, because of their low content in white rice and wheat flour. The largest difference was between high-fat and low-fat diets, with a difference of 2.8 g resistant starch and 0.16 g FODMAPs, much less than the documented levels that was able to change gut microbial structure. Thus, the effects exerted by non-digestible carbohydrates in our trial might be limited.

The target gradient in dietary fat intake was achieved by adding different amounts of soybean oil to the diet. Soybean oil is rich in polyunsaturated fatty acids (PUFAs, 60.9% of the total fatty acids, Table 1), especially n-6 PUFAs (54.9% of the total fatty acids, Table 1). This led the high-fat, low-carbohydrate diet in our trial to be a high-PUFAs diet, with a level of 24% total energy, which is much higher than the recommended range for PUFAs by WHO (6–11% total energy). Compared to the low-fat, high-carbohydrate diet, the increased PUFAs in high-fat diet was mainly n-6 PUFAs. An increase in dietary n-6 PUFAs consumption could potentiate inflammatory process, via biosynthesis of proinflammatory arachidonic-acid-derived eicosanoids including prostaglandins, thromboxanes, and leukotrienes. This was observed in our trial that fecal concentration of arachidonic acid and plasma thromboxane B<sub>2</sub> level were increased after the high-fat, low-carbohydrate diet consumption.

Recent evidence from animal models suggested the involvement of the gut microbiota in the proinflammatory effect of n-6 PUFAs. Mice fed a diet rich in n-6 PUFAs exhibited higher levels of metabolic endotoxemia and systemic low-grade inflammation, while endotoxemic and inflammatory status were dramatically reduced in transgenic fat-1 mice, which could convert n-6 to n-3 fatty acids. Following treatment with broad spectrum antibodies, the differences observed between the wild type and fat-1 mice in markers of metabolic endotoxemia and inflammation were eliminated, suggesting the mediating role of the gut microbiota. Similarly, in another mice study, n-6 PUFAs-rich diet also caused intestinal microbial dysbiosis and inflammation. Consistent with these previous findings, we found the predicted microbial lipopolysaccharide biosynthesis and arachidonic acid metabolism pathways were increased in response to the high-fat, low-carbohydrate diet.

### Implication for future research

Our trial has shown the unfavorable effects of high-fat (mainly, high n-6 PUFAs), low-carbohydrate diet on gut microbiota, fecal metabolomic profiles, and

| Fatty acid        | % of the total fatty acids |
|-------------------|---------------------------|
| SFAs              | 14.8 (0.5)                |
| C16:0             | 10.4 (0.3)                |
| C18:0             | 3.7 (0.1)                 |
| C20:0             | 0.3 (0.01)                |
| C22:0             | 0.3 (0.02)                |
| C24:0             | 0.1 (0.01)                |
| MUFAs             | 24.0 (0.3)                |
| C18:1 n-9         | 24.0 (0.3)                |
| C20:1 n-9         | 0.2 (0.01)                |
| PUFAs             | 60.9 (0.8)                |
| n-3 PUFA          | 6.0 (0.2)                 |
| C18:3 n-3         | 6.0 (0.2)                 |
| n-6 PUFA          | 54.9 (0.6)                |
| C18:2 n-6         | 54.4 (0.6)                |
| C18:3 n-6         | 0.5 (0.01)                |
| n-6/n-3 PUFA      | 9.1 (0.2)                 |

Note. Fatty acids were measured by gas chromatography. Abbreviations: SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.
plasma proinflammatory factors. Although the two animal studies mentioned above and our trial indicated that n-6 PUFAs induces a proinflammatory response in the host, it must be reported that some other studies have also shown the opposite. For example, increased n-6 PUFAs consumption was found to be inversely associated with serum C-reactive protein concentrations in Japanese men and women.

One possible explanation for this inconsistency could be that the level of n-6 PUFAs intake in these studies are different. The high-fat diet in our trial and the animal study contained a much higher n-6 PUFAs than that in the Japanese studies (>20% total energy vs. <7% total energy). Evidence of the association between n-6 PUFAs and gut microbiota in humans is also limited. More research is warranted to confirm our findings.

In our trial, we only measured the gut microbiota using 16S rRNA gene sequencing at baseline and the end of the intervention. In the future, more complete time series analysis of gut microbial communities at higher resolution (by adopting metagenomic sequencing technique) is needed to assess variation that is associated with diet intervention. Detailed time series of gut microbiota data should provide better understanding of both how long it takes for the intervention diet to change the microbiota and what degree of the change in the microbiota can withstand before unfavorable cardiometabolic effect appears.

Another very interesting angle for future studies is the influence of host genome and especially its interaction with diet on gut microbiota. Although the environment (food composition and timing, antibiotic and other drug use, weather, hygiene, and so forth) is the main force driving variation in the microbiota across individuals, genetics and the associated physiological differences may still have a role in shaping the microbiome. Several recent studies have already identified the associations between specific genetic variants and the gut microbiome. Larger cohorts and more comprehensive data sets will need to be collected and analyzed across populations to draw more robust conclusions. By further studying the effect of gene-diet interaction on gut microbiota, we will be able to better predict the response of microbiome features to the diet and promote personalized nutrition to improve human health.

Disclosure of potential conflicts of interest

The authors declare no conflicts of interest.

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