Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU27675

Gut Microbiota as a Modifiable Factor in Metabolic and Cardiovascular Diseases

Zihan Qian

GUIXUE Education, Hangzhou, China
qianzihananan@gmail.com

Abstract. Chronic non-communicable diseases (NCDs) are one of the main causes of illness and death around the world. For many years, genes and lifestyle were seen as the main reasons for these diseases. But new studies show that the gut microbiome also plays an important role in these diseases. This review summarizes what we know about the role of gut bacteria in metabolic and cardiovascular diseases. It describes how an imbalance in gut bacteria drives the development of obesity and type 2 diabetes (T2DM). The main processes are increased energy extraction from food and chronic inflammation caused by the LPS/CD14 pathway. At the same time, this paper discussed intestinal microbial metabolites, especially the importance of trimethylamine oxide (TMAO) in CVD. It causes atherosclerosis by affecting cholesterol metabolism, platelet reactivity, and bile acid metabolism.Nowadays, there are many ways to prevent metabolic diseases and reduce the impact of TMAO, the most basic of which is to modify diet. These results can have a better understanding on the interaction between diet and disease. Also, it is possible to develop new diagnostic biomarkers and treatment strategies for intestinal microbiome. Future research should focus on solving existing problems and turning these findings into personalized clinical interventions, thus to reduce the burden of NCDs.

Keywords: Gut Microbiota Dysbiosis, Energy Harvesting Capacity, LPS/CD14 Pathway, Trimethylamine N-oxide (TMAO), Chronic Inflammation.

1. Introduction

Chronic non-communicable diseases (NCDs) now pose a formidable threat to global health systems. According to statistics from the World Health Organization, Noncommunicable diseases (NCDs) led to at least 43 million deaths in 2021, equivalent to 75% of non-pandemic-related deaths globally [1]. The traditional view holds that genetic factors and unhealthy lifestyles are the main causes of chronic diseases. However, recent studies have found that the human symbiotic microbiota (especially the gut microbiota) plays an indispensable role in the occurrence and development of chronic diseases.

The human microbiome consists of trillions of bacteria, fungi, and viruses, among which the gut microbiota is the most abundant, closely linked to the host's metabolism, immunity, and endocrine functions. More and more evidence indicates that dysbiosis may promote the occurrence of chronic diseases by influencing pathways such as inflammation and immune regulation. Therefore, deeper

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.AU27675

exploration of the association mechanism between the microbiome and chronic diseases is essential for the prevention and treatment of chronic diseases.

In recent years, significant progress has been made in the research of the microbiome and chronic diseases. In terms of metabolic diseases, Turnbaugh et al. found that the obese microbiome has an increased capacity to harvest energy from the diet [2]. Cani et al. conclude that the LPS/CD14 system, which will be explained later, sets the threshold for high-fat diet–induced metabolic disease occurs [3].

Wang et al. and Tang et al. focused on cardiovascular disease. Studies have shown that the intestinal microbiota metabolize dietary phosphatidylcholine to produce trimethylamine N-oxide (TMAO) [4,5]. The higher the concentration of TMAO in the blood, the greater the risk of major adverse cardiovascular events. This discovery provides opportunities for novel diagnostic modalities and therapeutic approaches for atherosclerotic CVD.

This review focuses on two representative areas: metabolic diseases and CVDs. It examines how gut microbiota dysbiosis contributes to the development of chronic diseases. Specifically, we investigate the way microbial composition influences energy harvest, inflammation, and barrier integrity in obesity and diabetes. The impact of microbiota-derived metabolites, such as TMAO, on the cardiovascular risk is also stated. By integrating mechanistic, experimental, and clinical evidence, this work emphasizes the microbiota as a modifiable factor in NCDs and outlines its potential for novel diagnostic and therapeutic strategies.

2. Intestinal flora and metabolic diseases

2.1. Gut microbiota and energy harvest

The relationship between intestinal flora and metabolic diseases has been one of the research hotspots in the past two decades. Among metabolic diseases, obesity and T2DM are very common all over the world, causing huge pressure on public health and social economy. The traditional view is that these diseases are mainly caused by the imbalance between calorie intake and consumption and genetic susceptibility. However, more and more evidence shows that intestinal flora plays an important role in metabolic pathways, energy homeostasis and inflammatory response, and thus plays a key role in the occurrence and development of metabolic diseases.

Turnbaugh et al. provided key evidence. They found that the composition and function of intestinal flora of obese individuals were significantly different from that of lean people. Specifically, the flora of obese people is better at extracting energy from food. Through the precise experiment of sterile mice, researchers found that after transplanting the intestinal flora of obese (ob/ob) mice into sterile lean mice, the body fat content of recipient mice increased significantly despite the same amount of food intake. This phenomenon is mainly related to the rich carbohydrate active enzymes (CAZy), especially glycoside hydrolases (CAZy families 13 and 77, which contain a-amylases and amylomaltases), can decompose complex dietary polysaccharides more efficiently. Metagenomic analysis showed that the genes involved in the synthesis of short chain fatty acids (SCFAs), especially butyric acid and acetic acid, were more abundant in the obese microbiome. The results of the bomb calorimeter test confirmed this finding: the fecal energy excretion of the recipient mice with obese flora was lower than that of the control group. Although short chain fatty acids such as acetic acid, propionic acid and butyric acid are generally beneficial to intestinal health. However, the over abundance of energy harvesting bacteria may lead to an increase of net heat availability, thus promoting fat accumulation. Thus, the intestinal flora can significantly affect the balance of nutrient absorption and storage [2].

DOI: 10.54254/2753-8818/2025.AU27675

2.2. Gut microbiota and systemic inflammation

In addition to energy acquisition, intestinal flora also plays a key role in the regulation of systemic inflammation, which is closely related to insulin resistance and T2DM. The research of Cani et al. provided important insights for this relationship. They found that LPS/CD14 signaling pathway is the key mediator of diet induced metabolic diseases. Opolysaccharide (LPS), which is one of the major components of the outer membrane of Gram-negative bacteria, can stimulate innate immune responses by binding to the CD14/Toll-like receptor 4 (TLR4) complex on immune cells. This LPS/CD14 signaling has been reported as a major mediator of the association between a high-fat diet, low grade inflammation, and insulin resistance related to metabolic disorders. Studies have shown that high-fat diet may result in "metabolic endotoxemia", which means higher levels of lipopolysaccharide (LPS) in the blood. Once the LPS entered the blood, it combined with CD14/TLR4 receptor complex on immune cells. The mRNA concentrations of TNF-α, IL-1, IL-6 and plasminogen activator inhibitor (PAI) -1 increased in different combinations in the liver, visceral and subcutaneous fat pools and muscles of mice fed with high-fat diet and LPS infusion, which activated the pro-inflammatory signaling pathway. This low-grade chronic inflammatory response will damage the insulin signal of peripheral tissues, leading to insulin resistance and glucose intolerance. Cani et al. Found that mice without LPS receptor (CD14 mutant) showed hypersensitivity to insulin, while under high-fat diet, their time of insulin resistance, obesity and diabetes was delayed. So they further pointed out that the LPS/CD14 system sets the threshold at which high-fat diet–induced metabolic disease occurs

2.3. Butyrate-producing bacteria and intestinal barrier function

Recent work shows that patients with T2DM often have fewer butyrate-producing bacteria, such as Faecalibacterium prausnitzii and Roseburia species [6]. Butyrate is one of the main SCFAs. It provides energy for colonocytes, while also enhancing epithelial barrier integrity and exerting anti-inflammatory effects [7]. When these bacteria are reduced, the protective effect weakens. As a result, microbial products like LPS can more easily cross the gut barrier and enter the blood, which drives systemic inflammation. SCFAs, including butyrate, also act on gut receptors to increase the release of GLP-1 (glucose like peptide-1) and PYY, two hormones that support blood sugar balance and help regulate appetite.

2.4. Evidence from animal and human studies

Animal experiments and human studies further support these mechanisms. Compared with the mice with the symbiosis of lean human flora, the sterile mice transplanted with the flora of obese people accumulated more fat even if they consumed the same amount of calories. Human studies have shown that the bacterial diversity of obese people has decreased, and the proportion of Firmicutes and Bacteroidetes has changed [2]. This shows that obesity and diabetes are not only caloric or genetic diseases, but also closely related to intestinal microbial composition and function.

2.5. Therapeutic implications: probiotics, prebiotics, and diet

Recognizing the role of intestinal flora in metabolic diseases also provides new ideas for treatment. Probiotics or prebiotics intervention can help regulate the balance of flora and improve metabolism. For example, supplementation of inulin fructans such as Oligofructose can promote the activity of intestinal probiotics, increase the secretion of GLP-1, improve liver insulin sensitivity, and reduce

DOI: 10.54254/2753-8818/2025.AU27675

liver inflammation, so as to improve glucose metabolism and body fat accumulation [8]. Dietary changes is a simple but efficient method.Eating more fermentable dietary fiber increases the number of beneficial bacteria, such as bifidobacteria. These bacteria help strengthen the gut barrier, lower plasma endotoxin levels, and reduce intestinal permeability. Glucose tolerance and insulin sensitivity may increase with less inflammation.This shows that changing the diet to improve gut flora can support better metabolic health [9]. Overall, the studies mentioned in this section show that gut microbiota imbalance contributes to metabolic diseases in several ways. It may increase energy harvest, drive chronic inflammation, and weaken the intestinal barrier.]. It should be noted that the mechanisms involving intestinal flora are not only associated with metabolic diseases, but also contribute significantly to CVDs and other chronic diseases.This insights provides a new perspective for us to understand the common pathogenesis of chronic diseases.

3. Intestinal flora and cardiovascular diseases

3.1. From traditional risk factors to new mechanisms

Besides metabolic diseases, the gut microbiota also plays a crucial role in cardiovascular diseases, such as atherosclerosis, myocardial infarction, and stroke. Most of the studies on CVD have focused on the conventional risk factors such as dyslipidemia, hypertension and smoking.They are regarded as the main pathogenic basis. However, breakthrough studies have revealed that intestinal microbial metabolites can directly affect cardiovascular risk, thus expanding the research framework of CVD pathogenesis [4].

3.2. Discovery and metabolic sources of TMAO

Research by Wang and his team found that TMAO is a pro atherosclerotic metabolite produced by intestinal microbial metabolism. Studies have shown that dietary phosphatidylcholine (widely found in eggs, red meat and dairy products) can be metabolized by intestinal flora to produce trimethylamine (TMA). TMA is absorbed into the blood and then enters the liver, where it is converted into TMAO under the action of flavin monooxygenase (FMO) [4]. The high level of TMAO in plasma is closely related to the significantly increased risk of major adverse cardiovascular events, including atherosclerosis, myocardial infarction and stroke [5].

3.3. Atherosclerosis promoting mechanism of TMAO

The mechanism study further reveals how TMAO promotes the occurrence of CVD. Studies have found that TMAO can promote macrophage foaming, inhibit cholesterol reverse transport, and enhance platelet high reactivity, which are key steps in the occurrence and development of atherosclerosis [4,6,7].

Animal experiments have shown that choline, carnitine, or TMAO can lead to the impairment of RCT function, which can be reversed by the use of antibiotics to inhibit the intestinal flora. Further mechanism studies found that TMAO downregulated the expression of key enzymes in bile acid synthesis (such as CYP7A1 and CYP27A1) and transporters in the liver, thus blocking the excretion of cholesterol through bile acid pathway [6].

TMAO, a metabolite of intestinal microorganisms, can significantly enhance the reactivity of platelets, thus promoting thrombosis. In vitro experiments showed that TMAO could enhance the response of platelets to various agonists, such as ADP, thrombin and collagen, and promote the release of intracellular calcium ions. In animal models, acute or chronic exposure to TMAO

DOI: 10.54254/2753-8818/2025.AU27675

significantly shortened the time of thrombosis. In addition, dietary supplementation of choline or TMAO can increase plasma TMAO levels and enhance platelet function, and this effect is eliminated in sterile mice or after the use of antibiotics to inhibit intestinal flora. Microbial transplantation experiment further confirmed that TMAO dependent platelet hyperreactivity was a transmissible phenotype [7].

In addition, TMAO also affects bile acid metabolism and cholesterol homeostasis, further aggravating cardiovascular risk. TMAO can activate farnesol X receptor (FXR) and small heterodimer chaperone (SHP) by changing bile acid spectrum (such as increasing the proportion of DCA and thdca in serum and reducing the proportion of Ca and TMCA), thereby inhibiting the expression of CYP7A1 and reducing bile acid synthesis. This process leads to the obstruction of cholesterol excretion, the increase of serum total cholesterol and low density lipoprotein levels, and finally aggravates the development of atherosclerosis [8].

These findings indicate that TMAO is not only a biomarker reflecting microbial activity, but also a bioactive molecule that has a direct impact on vascular health.

3.4. Possible therapeutic approaches

The present results suggest that cardiovascular risk is not only affected by host genes and lifestyle, but also regulated by metabolic activity of intestinal flora [4]. This understanding may stimulate new possibilities for diagnosis and treatment. Plasma TMAO level detection can potentially become a novel cardiovascular risk assessment biomarker which can supplement traditional indicators such as low-density lipoprotein cholesterol and C-reactive protein [5]. At the same time, a variety of interventions for TMAO are also under study, including reducing the intake of TMA precursors through diet, blocking TMA production by microorganisms with antibiotics or small molecule inhibitors, and reshaping the structure of intestinal flora with probiotic intervention [4].

3.5. Complexity and controversy

However, the association between TMAO and cardiovascular disease is not entirely consistent and appears to be influenced by multiple factors, including host genetics [9], dietary patterns [5], and gut microbiota composition [10]. Not all studies have consistently observed the association between TMAO and cardiovascular outcomes. Some researchers have even suggested that TMAO is more likely to be a marker of potential metabolic disorders than a direct pathogenic factor [11]. Nevertheless, the research of Wang et al. And Tang et al. Laid the foundation for the conceptual connection between intestinal flora and CVD, and promoted the development of the whole field of microbiome cardiovascular research.

3.6. Future research directions

Future research still needs to answer some key questions. For example, which specific microbiota play the most central role in TMA generation? Can we develop interventions that can effectively reduce TMAO levels without damaging the overall intestinal ecology? How does the genetic polymorphism of host FMO enzyme affect TMAO metabolism and disease susceptibility? The solution of these problems is very important for the transformation of basic scientific achievements into clinical applications.

DOI: 10.54254/2753-8818/2025.AU27675

4. Conclusion

This paper reviews a large number of evidences, and clearly points out that human intestinal flora is the key regulator of the risk of major chronic non communicable diseases, especially metabolic diseases and CVDs. Imbalance of intestinal flora promotes the development of disease through a variety of mechanisms. For example, it can enhance the efficiency of obtaining energy from the diet and promote fat accumulation. Metabolic endotoxemia caused by dysbacteriosis can lead to persistent low-grade systemic inflammation and insulin resistance. Some of its metabolites, such as TMAO, directly promote atherosclerosis. The understanding of disease risk now extends beyond genetics and lifestyle to include the gut microbiome as a key modifiable factor. It shows that diet, metabolism, and immunity are closely connected through the gut microbiota. Limiting the production of harmful metabolites through dietary intervention, prebiotics, probiotics or specific microbial enzyme inhibitors is a new way to prevent diseases and relieving health burdens in the world.

However, limitations in this area still exist. Human data are highly heterogeneous. Moreover, the role of some metabolites like TMAO remains controversial. Whether they are direct causal factors or merely biomarkers reflecting disease risk is still uncertain. This problem is more complex when considering the potential confounding factors such as renal function. Further studies should be conducted over a larger population and over a longer time span to determine a more reliable causal relationship and resolve current inconsistencies. Research should be focus on how to translate the mechanistic insights into clinical applications. This includes the development of individualized dietary recommendations and the development of safe and effective interventions based on microbiome . Only in this way can we better meet the challenges of chronic diseases

References

[1] World Health Organization. (2024). Noncommunicable diseases. Retrieved from https: //www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

[2] Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2007). An obesity-associated gut microbiome with increased capacity for energy harvest. Nature, 444, 1027–1031.

[3] Cani, P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A. M., Fava, F., Tuohy, K. M., Chabo, C., Waget, A., Delmée, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrières, J., Tanti, J. F., Gibson, G. R., Casteilla, L., ... Burcelin, R. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes, 56(7), 1761–1772.

[4] Wang, Z., Klipfell, E., Bennett, B. J., Koeth, R., Levison, B., Dugar, B., Feldstein, A., Britt, E., Fu, X., Chung, Y. M., Wu, Y., Schauer, P., Smith, J., Allayee, H., Tang, W., DiDonato, J., Lusis, A., & Hazen, S. (2011). Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature, 472, 57–63.

[5] Tang, W. H., Wang, Z., Levison, B. S., Koeth, R. A., Britt, E. B., Fu, X., Wu, Y., & Hazen, S. L. (2013). Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. New England Journal of Medicine, 368(17), 1575–1584.

[6] Liu, T. X., Niu, H. T., & Zhang, S. Y. (2015). Intestinal microbiota metabolism and atherosclerosis. Chinese Medical Journal, 128(20), 2805–2811.

[7] Zhu, W., Gregory, J. C., Org, E., Buffa, J. A., Gupta, N., Wang, Z., Li, L., Fu, X., Wu, Y., Mehrabian, M., Sartor, R. B., McIntyre, T. M., Silverstein, R. L., Tang, W. H. W., DiDonato, J. A., Brown, J. M., Lusis, A. J., & Hazen, S. L. (2016). Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. Cell, 165(1), 111–124.

[8] Ding, L., Chang, M., Guo, Y., et al. (2018). Trimethylamine-N-oxide (TMAO)-induced atherosclerosis is associated with bile acid metabolism. Lipids in Health and Disease, 17, 286.

[9] Hartiala, J., Bennett, B. J., Tang, W. H., Wang, Z., Stewart, A. F., Roberts, R., McPherson, R., Lusis, A. J., Hazen, S. L., Allayee, H., & CARDIoGRAM Consortium. (2014). Comparative genome-wide association studies in mice

DOI: 10.54254/2753-8818/2025.AU27675

and humans for trimethylamine N-oxide, a proatherogenic metabolite of choline and L-carnitine. Arteriosclerosis, Thrombosis, and Vascular Biology, 34(6), 1307–1313.

[10] Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J., Org, E., Sheehy, B. T., Britt, E., Fu, X., Wu, Y., Li, L., Smith, J., DiDonato, J., Chen, J., Li, H., Wu, G. D., Lewis, J. D., Warrier, M., Brown, J. M., Krauss, R., & Hazen, S. L. (2015). Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature Medicine, 19, 576–585.

[11] Canyelles, M., Borràs, C., Rotllan, N., Tondo, M., Escolà-Gil, J. C., & Blanco-Vaca, F. (2023). Gut microbiota-derived TMAO: A causal factor promoting atherosclerotic cardiovascular disease? International Journal of Molecular Sciences, 24(3), 1940.