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Gut Microbiota and Cardiovascular Diseases: Perspectives

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Abstract

Gut microbiota (GM) is a collection of bacteria, fungi, archaea, viruses and protozoa, that inhabit human gastrointestinal tract and play an essential role in human health and disease. These microflora act as a virtual endocrine organ that interact with many functions in the human host. Recent researches and clinical data indicated that the GM has a significant role on the occurrence and development of cardiovascular diseases (CVD). The aim of the present review is to discuss the recent data on the role of GM in the pathogenesis of CVD and its risk factors and the therapeutic implications of modifications of these GM and its products on management of CVD.

Keywords: *Gut Microbiota; Cardiovascular Disease; Atherosclerosis; Obesity; TMAO*

Glossary

- Microbiota is the collection of micro-organisms inhibiting the gut, urinary tract, respiratory tract and skin.
- Microbiome is the genome of microbiota.
- Probiotics is the use of certain bacterial strain to alter GM e.g. *Lactobacillus, Bifidobacterium* and *Lactococcus*, for the benefit of the human host.
- Prebiotics are substances that stimulate the growth/or activity of some beneficial bacteria for host benefit e.g. fruits vegetables and cereals.
- Symbiosis is the normal composition of GM in heathy subject.
- Dysbiosis is the alteration of the composition of GM with some diseases.

Normal gut microbiota

Normal human intestine harbour trillions of bacterial cells that play an important role in normal human physiology. Most of the known intestinal microbial community is composed of bacteria in the phyla *Bacteroidetes, Firmicutes* (especially *Clostridia* species), *Actinobacteria, Proteobacteria* and *Verrucomicrobia* [1]. The phyla *Firmicutes* and *Bacteroidetes* are the main dominant flora, accounting for more than 90% of the total population [2]. These patterns of GM are relatively stable over time within an individual and relatively consistent among family members while varying widely between unrelated individuals living in different households [3]. Also, GM are

involved in immune system functions by activating and differentiating a wide range of T and B lymphocytes, as well as modulating the mucosal production of immunoglobulins (especially immunoglobulin A) [1].

The use of non-culture dependent DNA sequencing and bioinformatics allow more study of the structure and functions of the intestinal microflora and possible signalling pathways that GM may be associated with the development of certain diseases [4] (Figure 1).

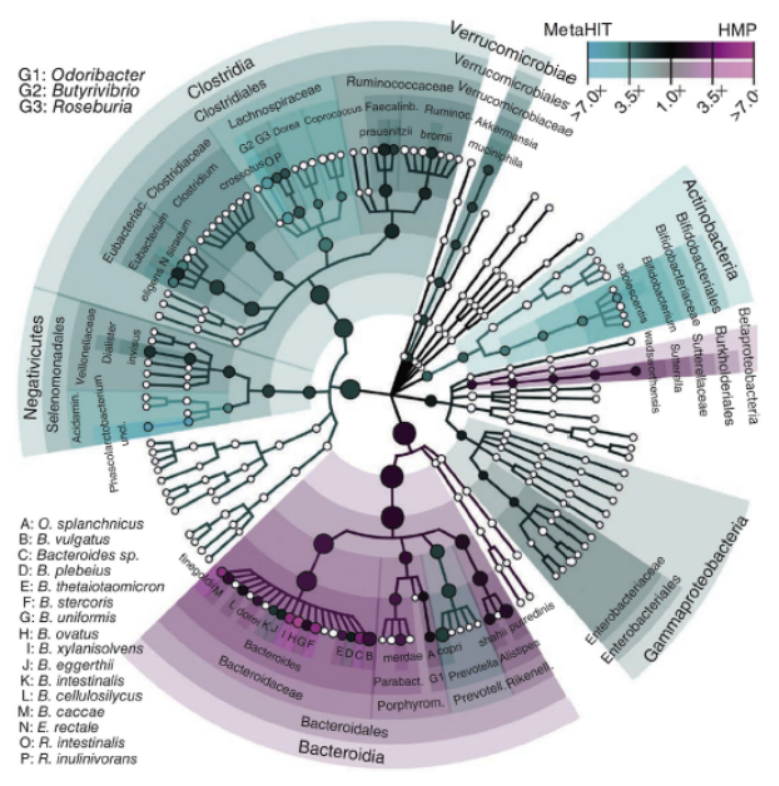

Figure 1: *Phylogenetic Tree Representing Human Gut Microbiota [6].*

The intestinal microflora is involved in the regulation of various human functions, such as providing metabolic nutrition to the host, participating in growth promotion and immune regulation, eliminating pathogenic microorganisms and maintaining the integrity of intestinal barriers and normal homeostasis [5].

The intestinal bacteria can be categorized into three categories [6]:

1. Physiological bacteria (symbiotic with the host), such as *Bifidobacterium, Lactobacillus*.
2. Conditional pathogens, such as *Enterobacteriaceae, Enterococcus*.
3. Pathogens, such as *Proteus, Staphylococcus aureus*.

Pathogenic role of GM in CVD (Figure 2)

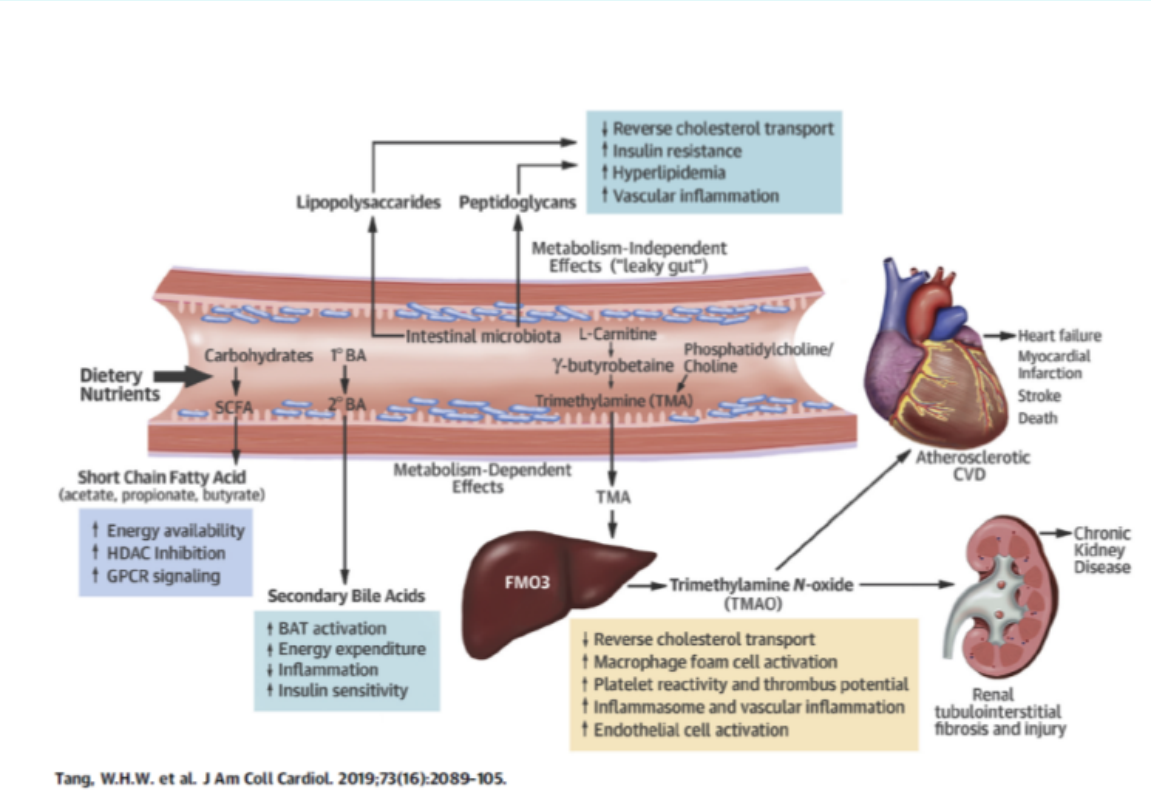

Figure 2: *The role GM in CVD.*

Coronary artery disease

The evidences of the role of GM in atherosclerotic coronary artery disease (CAD) are:

1. Some CV risk factors as aging, obesity, sedentary lifestyle and dietary patterns are associated with a change of composition and functions of GM [7].
2. The detection of DNA from various species of bacteria in atherosclerotic plaques [8].
3. The composition of GM differs in patients with CAD from those in healthy control [9].
4. Many experimental studies using mice and rat models that confirm the role of GM in experimental atherosclerosis [10].
5. Trimethylamine (TMA) is generated by gut bacteria by metabolizing choline, phosphatidyl choline an L carnitine and is absorbed through the portal circulation to the liver where it is oxidized by hepatic Flavin monooxygenase (FMO3) to trimethylamine oxide (TMAO) which proved to have a role in atherogenesis by
    a. Inhibition of reverse cholesterol transport [11].

b. Increase foam cell formation [10].

c. Decrease body cholesterol clearance by inhibition of bile acid synthesis [12].

6. Li., *et al*. revealed that TMAO level in acute coronary syndrome (ACS) was an independent predictor of short and long term outcome [13].

7. TMAO can also be used to assess the plaque burden of CAD.

Hypertension

The mechanisms of hypertension are complex and multifactorial:

1. Through its relation to some hypertension (HTN) risk factors as obesity, metabolic syndrome and diabetes [14,15].

2. With the use of hypertensive animal models many authors confirm the relation of GM alteration with the genesis of HTN [16].

3. Few human studies found a relation between HTN and pre HTN and GM alterations. These studies represent a further evidence that microorganisms could exert an important modulating function in the onset and maintenance of high BP [15,16].

4. Recent findings show that short chain fatty acids (SCFA) bind the G protein-coupled receptors GPR41 and GPR43 and olfactory receptors Olfa78 in the kidney, heart, sympathetic ganglia and blood vessels to modulate blood pressure [17].

5. Other researchers have found that TMAO can increase blood pressure and hydrogen sulphate can directly act on blood vessels to modulate blood pressure [18].

6. The *Firmicutes* and *Bacteroidetes* ratio (F/B) was recently reported being increased in spontaneously hypertensive rats and AngII-induced hypertension rats [19].

7. A large study to evaluate the role of GM in HTN is ongoing (ClinicalTrials.gov ID: NCT02188381).

Dyslipidaemia

A recent survey found that the GM composition can explain 6.0% of the variation in triglycerides and 4.0% of that in HDL-C and 4.5% of that in BMI, independent of age, sex and genetics at the human population level [20].

The GM metabolic product TMAO hand many effects that alter lipid metabolism and lead to atherosclerosis:

1. It inhibits host reverse cholesterol transport activity with increase HDL C and triglyceride level [13].

2. It increases oxidation of LDL C to oxidized LDL [21].

3. It increases foam cell formation [14].

4. It inhibits bile acid synthesis that decreases cholesterol excretion in bile [15].

Heart failure

- Many recent studies revealed that changes in intestinal microecology can directly damage cardiac muscle cells and cause cardiac dysfunction. In the mouse model of dietary intervention, it was found that elevated serum TMAO levels in mice resulted in cardiac injury and fibrosis and were prone to heart failure (HF) [22].
- Also, studies found that, higher the TMAO level in patients with HF, higher the mortality rate in 5 years and TMAO can better evaluate the prognostic value [23].
- Another study on 972 patients with acute HF, the investigators found that serum TMAO levels could predict adverse prognostic events, whereas TMAO+NT-proBNP could predict a higher prognostic value [24].
- Also, recent study showed that serum TMAO levels were elevated in patients with chronic HF, and TMAO levels were associated with cardiac function and survival [25].
- Pasini., *et al*. showed that patients with chronic heart failure (CHF) were colonized by more pathogenic bacteria than the control patients. *Candida, Campylobacter* and *Shigella* species were proven to be positively correlated with the severity of disease [24].
- With bowel wall edema during splanchnic congestion accompanying HF, intestinal barrier function is impaired, and structural components of microbiota may have enhanced interaction with host intestinal Mucosa. This lead to inflammatory and immune changes that play some role in HF pathogenesis [25].

Diabetes and cardiometabolic syndrome

1. Many experimental studies confirm the relation between GM alteration and development of obesity and metabolic syndrome [26].
2. An increase in *Firmicutes* to *Bacteroidetes* ratio F/B was demonstrated in experimental animal and human subjects with MS [26]. A recent study showed a marked dysbiosis characterized by an increased F/B ratio in obese people with MS compared with obese people without MS and non-obese people [27].
3. A state of low grade inflammation due GM alteration may play a role in development of obesity and MS [25].
4. Disturbance of SCFA production by GM was detected in patients with MS and DM and was considered as a factor in the low grade inflammation, insulin resistance, dysregulation in the production of incretins. These processes are involved in the regulation of the feeding and energy balance, presumably through SCFA as signal molecules [28].
5. SCFAs display beneficial effects on peripheral tissues, such as adipose tissue, liver and skeletal muscles, leading to an improvement of insulin sensitivity [29].
6. Transplantation of faeces from lean subjects to individuals with insulin resistance and metabolic syndrome has been shown to improve insulin sensitivity and increase the number of butyrate-producing bacteria [28].

7. Metformin was found to have many actions on GM and its diversity and metabolites that add to euglycemic actions of that drug [30].

Chronic kidney disease

1. Changes in GM composition produce excessive quantities of uremic toxins but less metabolites that have protective role in inflammation, oxidative stress, fibrosis and kidney diseases progression [31].

2. Poesen., *et al*. performed a stool metabolomic analysis of healthy subjects, patients with CKD on hemodialysis, and household contacts fed on the same diet to evaluate how much CKD and dietary factors can affect faecal metabolites composition. The results of the analysis showed a clear discrimination between healthy and the CKD group, while there was a strict similarity between CKD and household contacts group. Conversely, in the same study, they observed that CKD and non-CKD mice fed the same diet had a very different metabolomic profile of the stool [32].

3. Wikoff., *et al*. showed that the presence of several protein-bound uremic toxins, such as indoxyl sulfate (IS), are dependent on composition of GM and a fiber-poor diet leads to gut dysbiosis and development of large quantities of these uremic toxins (e.g. NH_3, amines, phenols, and indoles) [31].

4. In CKD there are histologic changes of the gut wall, breaking of epithelial tight junctions with increased permeability that contribute to endotoxemia and systemic inflammation [32].

5. Studies found that elevated TMAO concentration in patients with CKD were associated with an increased risk of mortality [31].

6. Reduction of SCFAs occurs in CKD and contribute to the abnormal immune and inflammatory response in these patients [33].

7. The relation of GM and CKD is bidirectional in which CKD alter GM composition and functions and this changes further aggravate the kidney injury [33].

Stroke

- The brain and gut are connected by a network of neurons, forming a complex microbiota-gut-brain axis that exhibits strong bi-directional interactions [34].

- Clinical and experimental studies have reported that the gut microbiota is associated with risk factors for stroke such as hypertension, diabetes, and obesity [33].

- Increased TMAO levels have been linked to increased risk of incident major adverse cardiovascular events (MACEs) independent of traditional cardiovascular risk factors [33] (Figure 3).

- A high rate of incident stroke was found in higher TMAO tertile in a Chinese study [34].

- Increased serum TMAO levels have been associated with increased carotid intima-media thickness (IMT) in subjects at risk for type 2 diabetes, independent of insulin resistance, visceral obesity, and fatty liver. This high TMAO level decrease with interventions that decrease carotid IMT.

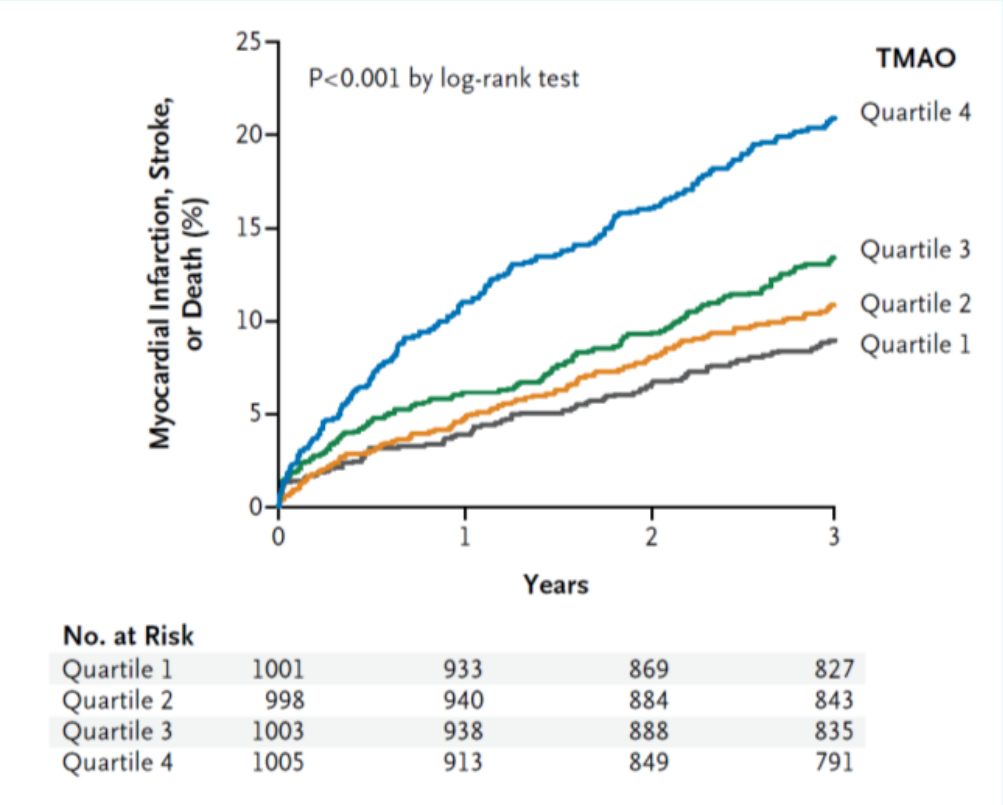

Figure 3: *TMAO quartile and CV outcome.*

Therapeutic interventions

A lot of experimental and clinical trials of different modalities of interventions that modify GM or its metabolomics as a therapeutic target in many CVD are done and many other clinical trials are in the pipelines. The most important aspects of these studies are discussed below.

Dietary interventions

- Mediterranean diet is especially popular in recent years and is confirmed to prevent CVD and reduce the mortality of CVD in men and women [35].
- Studies have shown that the level of TMAO in the urine of patients who did not adhere to the Mediterranean diet increased [35].
- High fibre diet and acetic acid (fibrous fermentation) can reduce the proportion of F/B, increase the number of bacteriobacterium, reduce myocardial fibrosis in hypertensive mice and prevent the progress of hypertension and HF.
- Dietary fibre intake is associated with reduced risks and improvement of a range of diseases from inflammation and infection to metabolic disorders as well as increased abundance of SCFA-producing bacteria.

- Other healthy foods have been shown to have beneficial effects on the gut microbiota e.g. fish oils [35].
- Shifts from animal-based to plant-based diets can modify regional and systemic productions of SCFAs, thereby potentially contributing to some of the proposed beneficial effects of these diets.

Exercise

- It is generally accepted that moderate exercise is beneficial to health and gut microbiota alterations modulated by exercise have been observed in mice and humans [36].

Probiotics

- These include lactic acid bacteria, bifidobacteria, actinomycetes, yeasts that can correct intestinal dysbiosis and are beneficial for host health.
- Probiotics can inhibit inflammation, protect and repair the intestinal mucosal barrier and improve intestinal function.
- Probiotics especially fermented milk produced significant BP reduction in hypertensive patients in many studies.
- Many clinical studies confirmed the beneficial effect of probiotics on LDL-C and CV risk.

Prebiotics

- Prebiotics are non-digestible organic substances that can selectively stimulate the growth or activity of one or more bacterial species to obtain beneficial effects on the host.
- Most prebiotics are carbohydrates that are present in natural products such as fruit, vegetables and cereals.
- Inulin and other oligosaccharides proved effective in reducing atherosclerosis in experimental animal.

Antibiotics

- Broad-spectrum antibiotics are commonly used in cardiovascular experiments targeting the gut microbiota.
- Antibiotics show benefit in BP reduction in experimental animals and reduction of LDL C and aortic atherosclerosis.
- However, results in human studies are controversial.

Faecal microbiota transplantation (FMT)

- Faecal microbiota transplantation (FMT) is capable of contributing nutrients, inhibiting the growth of pathogenic bacteria and regulating the immune system of the host through transplanting functional bacteria from healthy individuals into the gastrointestinal tract of patients, thereby helping patients reconstruct the normal functions of the gut microbiota.
- It can be performed via several routes including colonic, nasogastric or oral.
- The healthy stool is transplanted using nasogastric (NG) or nasojejunal tubes, oral capsules, enemas and endoscopic techniques including upper gastrointestinal (GI) endoscopy, sigmoidoscopy and colonoscopy.

- FMT proved to be effective in treating recurrent Clostridium difficile infection, inflammatory bowel disease and irritable bowel syndrome.
- However, the potential for treating CVD needs further investigation.
- FMT showed some efficacy in patients with metabolic syndrome and patients with obesity.

Others

- Choline analogue 3,3 di methyl butanol (DMB) can block choline metabolic pathway and decrease TMAO.
- Resveratrol stimulate the growth of beneficial bacteria and reduce TMAO formation.
- Fructose mono-oxygenase (FMO3) inhibitors also decrease TMAO synthesis.
- Meldonium that reduce L carnitine.
- Aspirin.

Conclusion

Over the last several years, accumulating data have suggested an important link between the intestinal microbiome and CVD. These link was found to have multifactorial mechanisms including effect on intestinal mucosal integrity, induction of systemic inflammatory and immune disturbance that have a role in many CVD. Also, the production of some metabolites as SCFA and bile acids may have a beneficial effect on atherosclerosis, hypertension and glucose homeostasis.

We now recognize that microbiome dependent metabolism may also lead to production of metabolites with potential adverse cardiovascular effects, such as TMAO, which may promote atherosclerosis and heightened thrombosis risks.

Many therapeutic strategies as dietary modification, use of probiotics and prebiotics and FMT were found to have a beneficial effect in CVD management but the establishment of these therapy need large well designed prospective clinical trials.

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