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REVIEW PAPER

Gut microbiota and cardiovascular diseases

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ABSTRACT

The gut microbiota, comprising trillions of bacteria, fungi, viruses, and protozoa, is a crucial component of a healthy physiological ecosystem in humans, playing a vital role in numerous essential functions. It is unique in every individual and exhibits variability throughout different stages of life, influenced by both external and internal factors. Gut dysbiosis refers to changes in the composition of gut microbiota and metabolites, which have been linked to the development of cardiovascular diseases. This could account for the development of cardiovascular diseases in humans even after controlling all modifiable risk factors. Targeting the gut microbiota may help reduce this residual risk. Although various interventions have been attempted to restore normal gut microbiota in gut dysbiosis, the majority of these have been tested in animal models and are still in early experimental stages.

Keywords: *Gut microbiota; gut dysbiosis; trimethylamine N-oxide.*

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INTRODUCTION

Gut microbiota (about 100 trillion in number) encompasses the communities of bacteria, fungi, viruses, and protozoa that are a component of a healthy physiological ecosystem in humans. It is involved in multiple functions, namely the maintenance of gut barrier integrity, the metabolism of dietary nutrients, and the regulation of host immune responses.[1] Hence, it is rightly referred to as a multifunctional organ or "superorgan." [1]

Numerous internal and external factors influence the gut microbiota throughout life. These include mode of delivery and feeding, environmental exposures, diet, smoking, medications, exercise, weight gain, pregnancy, and genetic influences.[2]

POSSIBILITY OF A GUT MICROBIOTA-HEART LINKAGE

The presence of bacterial DNA in atherosclerotic plaques initially raised the possibility of a linkage between gut microbiota and the heart. Bacteria from the phyla Firmicutes, Proteobacteria, and Actinobacteria, which are abundant in the gut and oral cavity, have been identified in atherosclerotic plaques, suggesting a host-microorganism interaction and the potential for the occurrence of cardiovascular diseases in humans.[3] Thus, the oral cavity and the gut might serve as reservoirs of these pathogenic microbes.

Few studies have established the association between periodontal disease

and CVD, as well as poor dental hygiene and acute myocardial infarction.[4,5] Poor dental hygiene has been associated with low-grade inflammation (elevated levels of C-reactive protein and fibrinogen) and increased rates of fatal and nonfatal CVD, like myocardial infarction, stroke, heart failure, and coronary revascularisation.[6] Another study demonstrated a higher abundance of Anaeroglobus in the oral cavity of subjects with symptomatic atherosclerosis (stroke or myocardial infarction) compared to healthy controls.[7] Similarly, few other studies have linked bacteria residing in the oral cavity (Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans) to atherosclerotic processes in animal models.[8-10] Although the mechanism by which these microbes contribute to the development of atherosclerotic lesions in the host is not fully understood, further studies need to be carried out to conclude whether the infections initiate or augment the process of atherosclerosis in the host.

GUT DYSBIOSIS AND CVD

The diversity of the gut microbiota changes as individuals age. Older individuals have a lower diversity of gut microbiota and a lower number of beneficial bacteria. A reduction in the Firmicutes: Bacteroides ratio, accompanied by a relative increase in pathogenic facultative anaerobes, has been demonstrated.[11] These changes have been linked to the development of CVDs in older people.[11] In addition, the decrease in the ability of the kidneys to eliminate proatherogenic microbial metabolites as the individual ages also plays a role.[12] Although hormone regulation and metabolism are different in both sexes, their direct link to the development of gut dysbiosis and CVDs has shown inconsistent results.[12]

Early-life gut microbiota development also contributes to the lifelong risk of cardiovascular disease. Maternal health status during pregnancy, including dietary habits, smoking, and the use of antibiotics, plays a crucial role in shaping the baby's gut microbiota.[13] Other factors, namely mode of delivery of the baby (vaginal vs caesarean section), hospital environment, mode of feeding of the baby (breast milk vs formula feeding) and administration of antibiotics, all play important roles in the development of gut microbiota in the baby.[13] Gut dysbiosis during early life can potentially increase your susceptibility to acquiring certain diseases later in life. Low gut microbial diversity and colonisation of the infant gut with Escherichia coli, Clostridium difficile, and Proteobacteria have been linked to the development of allergic diseases in later life, such as eczema, atopic dermatitis, and asthma.[13] Obesity has been linked to decreased populations of Bifidobacterium and a relative increase in Staphylococcus aureus in infants.[13] Increased levels of Proteobacteria in preterm babies have been linked to impaired nutrient absorption, gut barrier damage, and inflammation with a resultant increase in gut permeability.[13] Systemic translocation of bacteria and metabolites leads to systemic inflammation, which may heighten the subsequent risk of ASCVD. Babies delivered via caesarean section were found to be at a higher risk for type 1 diabetes mellitus, potentially mediated by an altered gut microbiota (reduced Firmicutes and butyrate-producing gut bacteria, with a relative abundance of Streptococcus, Ruminococcus, Blautia, and Rikenellaceae.[13] Thus, numerous factors appear to influence the early gut microbiome and the subsequent development of diseases in later life.

Gut dysbiosis refers to the changes in the composition of the gut microbiota and its metabolites, which can be transient or persistent, and may be a possible mechanism for the development of cardiovascular diseases (CVD).[11] Gut dysbiosis has been linked to atherosclerosis, coronary artery disease, hypertension, heart failure, and atrial fibrillation [11,12]

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Colonisation and overabundance of opportunistic pathogens and facultative anaerobes, accompanied by a relative decrease in the naturally occurring beneficial microbiota, have been demonstrated.[2,11] Weakened gut barrier function secondary to bowel hypoperfusion and ischaemia also facilitates the translocation of microbes and their metabolites.[2]

Short-chain fatty acids, bile acids, and indole-3-propionate, which are microbial metabolites, are beneficial to the host, as they possess anti-inflammatory and antimicrobial properties and also maintain gut barrier integrity.[2] The pathogenic microbial metabolites, namely trimethylamine N-oxide (TMAO), phenacetylglutamine, indoxyl sulphate, and lipopolysaccharide (LPS), are proinflammatory and pro-atherogenic.[2,12]

Of all the microbial metabolites mentioned above, TMAO, short-chain fatty acids, and bile acids have been studied the most extensively. TMAO precursors, namely choline, phosphatidylcholine, and L-carnitine, are abundant in commonly consumed food products like red meat, eggs, and dairy products. Gut bacterial enzymes, including choline TMA lyase (Cut C/D) and carnitine Rieske-type oxygenase/reductase systems (Cnt A/B and YeaW/X), metabolise these precursors into trimethylamine (TMA), which is absorbed into the portal circulation and is subsequently oxidised to TMAO by flavin-containing monooxygenase-3 (FMO3) in the liver.[14] TMAO has been linked to endothelial dysfunction, impaired reverse cholesterol transport, foam cell formation, increased platelet aggregation, and the development of atherosclerosis.[15,16] TMAO has been correlated with CVD risk, major adverse cardiovascular events (MACEs) and recurrent events. Studies have revealed that each 10 µmol/L increase in plasma TMAO level is associated with a 7.5% increase in MACE, including myocardial infarction and stroke.[14,17] Plasma TMAO levels have also been used to predict MACCE in established atherosclerotic cardiovascular diseases (ASCVD) and mortality in the absence of clinical ASCVD. [12,18,19] In patients with heart failure, TMAO levels correlated with functional class and diastolic dysfunction, as well as mortality [1,2]

The short-chain fatty acids (SCFAs), namely acetate, propionate, and butyrate, are generated from the fermentation of dietary fibre by gut microbiota. SCFAs play a crucial role in regulating blood pressure by activating G-protein-coupled receptors (GPR41 and GPR43) and inhibiting histone deacetylases.[20] In addition, SCFAs mitigate hypertensive damage by influencing regulatory T-cells and reducing proinflammatory cytokines (IL-17 & TNF-α).[21] By reducing the accumulation of triglycerides and enhancing HDL cholesterol synthesis, SCFAs reduce CVD risk.[22] Clinical and experimental studies have revealed that a fibre-rich diet enhances SCFA production, which in turn reduces blood pressure, decreases inflammation, and maintains endothelial integrity.[21,23] Conversely, gut dysbiosis and decreased SCFA production have been linked to increased blood pressure and systemic inflammation [24,25]

Secondary bile acids generated by gut microbiota play an important role in the regulation of dyslipidemia through interactions with TGR5 (Takeda G protein-coupled receptor) and X receptor FXR (farnesoid X receptor).[19,21] Gut dysbiosis alters the composition of bile acids, with a relative decrease in hydrophilic bile acids and an increase in hydrophobic bile acids. This alteration has been linked to vascular inflammation, endothelial dysfunction and atherosclerosis [22,26]

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Table 1 Microbial metabolites and associated cardiovascular outcomes

Microbial metabolites	Cardiovascular outcomes
TMAO	Atherosclerosis, MI, stroke, heart failure, mortality, recurrent CV events[12,20]
LPS	Atherosclerosis and heart failure increase gut permeability[12,20]
SCFAs	BP regulation, anti-inflammatory, lowers CV risk[12,20]
Secondary bile acids	Anti-inflammatory effects, lipid regulation[12,20]

***NB**: TMAO—Trimethylamine N-oxide, MI—Myocardial infarction, C—Cardiovascular, LP—Lipopolysaccharide, SCFAs—Short-chain fatty acids.*

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THERAPEUTIC INTERVENTIONS

Dietary modifications: A diet rich in fruits, vegetables, whole grains, fibre, and lean proteins has been shown to promote the growth of beneficial commensals and prevent the growth of opportunistic pathogens, thereby reducing the risk of developing CVDs.[12]

The Mediterranean diet (MedDiet) has been shown to promote the growth of beneficial bacteria (Faecalibacterium prausnitzii and Bacteroides uniformis), which results in the generation of SCFAs and the regulation of vascular tone and lipid metabolism with an overall decrease in systemic inflammation.[27,28] This has demonstrated a significant benefit in preventing CVDs. A marked reduction in markers of systemic inflammation (C-reactive protein), triglycerides, low-density cholesterol (LDL), systolic and diastolic blood pressure with an increase in high-density cholesterol (HDL) has been demonstrated, which mitigates CV risk.[27,28]

Microbiome-based: Probiotics (strains of live microorganisms), prebiotics (non-digestible fibres), and synbiotics (a combination of prebiotics and probiotics) have all been shown to promote the growth of beneficial gut bacteria. Probiotic strains (Lactobacillus acidophilus, Lactobacillus reuteri, and Bifidobacterium lactis) reduce cholesterol levels by deconjugating bile salts, stabilise the gut barrier, prevent gut translocation of LPS into the systemic circulation, and decrease the release of proinflammatory cytokines, leading to lowering of systemic inflammation.[29] Prebiotics stimulate the selective growth of beneficial gut bacteria (Bifidobacterium and Lactobacillus), which promotes SCFAs production and lowers systemic inflammation with improvement in lipid profile and gut barrier integrity.[29] Postbiotics (short-chain fatty acids) have also been shown to reduce blood pressure.[12]

Collectively, microbiome-based approaches have demonstrated significant cardiovascular benefits in numerous studies to date.

Pharmacologic: Antibiotics, antibiotic-like substances (e.g., garlic), and statin therapy have also been investigated in various animal models.[12]

Antibiotics can help reduce markers of systemic inflammation by selectively eliminating specific bacteria. However, as antibiotics are not a targeted approach, they can potentially lead to the elimination of both beneficial and harmful gut bacteria, thereby raising concerns regarding long-term consequences on overall gut health and systemic effects.[12] Clinical trials carried out in individuals with established CVD found no statistically significant reduction in MACE with antibiotics (azithromycin, clarithromycin, gatifloxacin). Studies do not

support the use of antibiotics to modulate gut microbiota.[30-33]

Statin use and gut microbiota have a complex relationship. Statins facilitate the growth of certain beneficial gut bacteria, namely Lactobacillus spp. (reduced gut cholesterol absorption) and butyrate-producing bacteria.[34] Statins also lower plasma TMAO levels and prevent translocation of LPS across the gut barrier.[34] Gut microbiota, in turn, have been linked to the lipid-lowering ability of statins.[34] Studies have revealed that a greater diversity of gut microbiota, with a relative abundance of Lactobacillus, Eubacterium, Faecalibacterium, and Bifidobacterium, and fewer Clostridia, is associated with a favourable response to statin therapy.[34] Bacteroides and Lactobacillus-enriched gut microbiota were found to be associated with stronger statin responses.[34] Clostridium sp. has been linked to statin-induced hyperglycemia.[34] Thus, modulating the gut microbiota may help in improving the lipid-lowering efficacy of statins in dyslipidemic patients.

Metformin, a commonly used oral anti-diabetic medication, has been found to favorably promote the growth of Bifidobacterium and other beneficial bacteria, which in turn have been suggested to enhance the anti-diabetic efficacy of metformin.[12,35] Studies have revealed that metformin facilitates the growth of SCFAs-producing bacteria, as well as A. muciniphila (maintains gut barrier integrity) and inhibits the growth of pathogenic bacteria.[35] An increased abundance of Lactobacillus spp. has also been demonstrated.[35]

Faecal microbiota transplantation is a promising tool for restoring the gut microbiota.[12] It works on the principle of transferring stool from healthy donors to recipients, thereby restoring gut microbial diversity and the Firmicutes: Bacteroidetes ratio in a dysbiotic gut.[12,29] This enhances the generation of SCFAs and bile acids and suppresses the production of TMAO, thereby reducing systemic inflammation with cardioprotective effects. A significant reduction in insulin resistance, coupled with an elevation in HDL cholesterol levels, has been demonstrated.[12,29]

Newer approaches: Newer targets include those that inhibit TMAO synthesis by targeting choline TMA lyase and carnitine Rieske-type monooxygenase to reduce TMAO levels.[29] Polyphenol-rich compounds (tomato extracts) have been shown to decrease the production of TMAO by modulating gut microbiota.[29] Trials are also investigating the safety and efficacy of small molecule inhibitors that selectively inhibit TMAO production.[29] Other microbial metabolites, namely bile acids, SCFAs, and aromatic amino acid-derived compounds, have also been selectively targeted.[29] Techniques like metagenomics and metabolomics to profile an individual's microbiome will further help in providing personalised targeted therapeutics in gut dysbiosis and reduce the cardiovascular risk. CRISPR-Cas-mediated editing of harmful microbial genes has been explored as an attractive option to manage gut dysbiosis [29]

CHALLENGES

The high interindividual variability of gut microbiota, as well as the variability within an individual at different stages of life in response to numerous internal and external influences, has prompted the need for **personalised** therapeutics for managing gut dysbiosis. The lack of standardised diagnostic tests for gut dysbiosis and validated cut-offs has further contributed to this challenge. Although most studies have been carried out in animal models, which fail to recapitulate the pathophysiologic heterogeneity in humans, large-scale studies on humans are needed to manage gut dysbiosis and associated CVD effectively. The genetic variability in humans, coupled with environmental influences, leads to numerous comorbidities, a phenomenon that is profound. Furthermore, a single animal

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model cannot fully capture the complex pathophysiology of CVDs occurring in humans.

FUTURE PERSPECTIVES

Multicentric randomised controlled trials with profiling of every participant's gut microbiota would help in the development of personalised therapeutics to address gut dysbiosis effectively. Using metagenomics and metabolomics to profile each individual's gut microbiota and selectively targeting microbial metabolites such as TMAO, SCFAs, bile acids, and aromatic amino acid-derived compounds will lead to the development of personalised therapeutics. CRISPR-Cas-mediated editing of harmful microbial genes is another attractive option to target pathogenic microbial pathways. All these techniques will help us reduce residual cardiovascular risk. However, the greatest challenge is developing accessible and cost-effective personalised therapeutics using the above-mentioned microbiome-based precision techniques.

CONCLUSION

Gut microbiota is a modifiable cardiovascular risk factor. It is unique in every individual and exhibits variability throughout different stages of life, influenced by both external and internal factors. Gut dysbiosis has been linked to the development of numerous cardiovascular diseases, which could account for the residual cardiovascular risk in some individuals.

Although numerous therapeutic options have been developed to manage gut dysbiosis, the uniqueness of gut microbiota in every individual has prompted the need for individualised microbiota-based treatment programs, which can provide personalised therapeutic options for cardiovascular diseases. Large-scale, multicentric, randomised trials may help address this issue, which will reduce the residual cardiovascular risk. TMAO and short-chain fatty acids can serve as valuable diagnostic and therapeutic options for CVDs. Although dietary modifications, prebiotics, and probiotics serve as therapeutic options for managing gut dysbiosis in current times, microbiome-based precision medicine and the development of microbiome-targeted therapies hold enormous promise. Faecal microbiota transplantation is another promising therapeutic approach. CRISPR-Cas systems can offer editing of the pathogenic gut microbiome to provide personalised therapy. Translating these newer techniques into cost-effective individualised therapies in the near future will redefine cardiovascular care in those with residual cardiovascular risk.

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