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Original Research Paper

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CAN YOUR GUT HEALTH AFFECT YOUR HEART?

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ABSTRACT A healthy gut can play a role in reducing the risk of heart disease. Good gut health is a great contributing factor in ensuring physical and mental health. Gut issues like constipation can contribute to heart problems due to inflammation and increased blood pressure. Food sensitivities, like lactose intolerance, may increase the risk of cardiovascular disease. The heart-gut cross-talk is an exciting field of study with implications for cardiovascular disease. Understanding the complex connection between the heart and the gastrointestinal tract may lead to the development of novel therapeutic targets and therapies for the prevention and management of cardiovascular diseases. Several metabolites produced by gut microorganisms from dietary metabolism have been linked to pathologies such as atherosclerosis, hypertension, heart failure, chronic kidney disease, obesity, and type 2 diabetes mellitus. In general, patients with CVD had decreased beneficial microbes but increased opportunistic pathogens in their intestines. More specifically, CVD patients had decreased SCFA-producing species and increased TMAO-producing microbiomes. SCFA, an anti-inflammatory metabolite, increases the expression of anti-inflammatory factors, improves intestinal barrier integrity, and inhibits pro-inflammatory cytokines. Meanwhile, TMAO, a pro-inflammatory and pro-atherosclerotic metabolite, is involved in foam cell formation, maturation, and secretion of inflammatory cytokines and adhesion molecules that result in vascular inflammation. Therefore, the imbalance of SCFA and TMAO contributes to inflammation, a characteristic risk factor for CVD.

KEYWORDS : Gut-microbiome, Type 2 diabetes (T2DM), Cardiovascular disease (CVD), Intestinal epithelial cells (IECs), Short-chain fatty acids (SCFAs), Mitochondrial reactive oxygen species (ROS), Trimethylamine-N-oxide (TMAO)

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death and disability in developed countries. CVD is responsible for approximately one of every three deaths in the United States and one of every four deaths in Europe (1)

Further, the steady increase of common risk factors for CVD, such as obesity, type 2 diabetes (T2DM), and the metabolic syndrome, compels the search for more effective strategies to prevent and modify the course of these cardiometabolic disorders (2)

Microbial sequencing analysis has provided a wealth of information about the presence of characteristic gut microbiota associated with CVD (3,4)

Also, a growing body of evidence shows that manipulation of the composition of gut microbiota affects host metabolism (5,6)

Recent studies suggest that gut microbiota produce numerous metabolites, some of which are absorbed into the systemic circulation and are biologically active, whereas host enzymes further metabolize others, and then serve as a mediator of microbial influence on the host (7,8)

Thus, the gut microbiome, functioning as a virtual endocrine system, communicates with distal organs through metabolism-dependent pathways (9)

In a recent metagenomic study involving 218 individuals diagnosed with atherosclerosis and 187 healthy controls, deviations from a healthy gut microbiome were noted, characterised by elevated levels of Enterobacteriaceae such as Klebsiella spp, Enterobacter aerogenes, and Escherichia coli, and some Streptococcus spp (10)

Butyrate-producing bacteria are linked to fatty acid metabolism, resulting in oxidative stress and deleterious cardiometabolic consequences (11)

The gut microbiota contributes to human health and diseases have expanded our insight into how microbial composition and function affect the human host(12)

The striking features of the Indian Cardiovascular Disease (CVD) scenario are its high prevalence among the young population, accelerated disease progression, and high mortality rate. (13)

Since gut dysbiosis may raise the risk of CVD by inducing inflammation, dyslipidaemia, and changes in the composition of the gut microbiota, it is crucial to consider its potential impacts (14)

The microbiome and its interactions with the human host are thought to be involved in many biological processes that control health and illness. A disruption in these regulatory pathways compromises barrier integrity and is associated with pathological disorders (15)

The breakdown of the intestinal barrier allows bacteria and chemicals produced by bacteria to enter the mucosa, triggering uncontrolled inflammatory signal cascades (16)

One of the main causes of insulin resistance and obesity is assumed to be metabolic endotoxemia, which results from the loss of barrier integrity (17)

Several researchers are exploring the approach of probiotic and prebiotic-derived metabolites administration to improve intestinal microbiota homeostasis, maintain gut barrier integrity, and modulate immune response (18,19)

Alterations in the gastrointestinal microbiome, gut epithelial permeability, and gastrointestinal disorders contribute to

heart failure progression through various pathways, including systemic inflammation, metabolic dysregulation, and modulation of cardiac function.(20)

Gut Microbiota

Microbiota in general refers to commensal, pathogenic, and symbiotic microbes that are found in multicellular organisms, which include not just bacteria but also other microbes such as protists, fungi, and viruses. (21)

The human gut consists of approximately 500–1000 bacterial species, and healthy gut flora is largely responsible for maintaining an individual's overall health status (22)

The gut microbiota stimulating regeneration of epithelium through the production of short-chain fatty acids (SCFAs) and some other metabolites, leading to the production of mucus, fermentation of non-digestible carbohydrates, and a lot more (23,24)

The human gut microbiome consists of trillions of bacterial cells, which are 10-fold more significant than human body cells (25).

The average human gut contains 1 kg of diverse groups of bacteria that mostly perform beneficial activities, often involved in metabolite production and transportation, and maintenance of gut homeostasis (26,27)

"The Conflict Of The Gut Microbiota"

The gut microbiota has been characterized as a vital organ, forming its multidirectional connecting axis with other organs. This gut microbiota axis is responsible for host-microbe interactions and works by communicating with the neural, endocrinal, humoral, immunological, and metabolic pathways. Microbiomes in the human gut not only help in the digestion of food but also control functions of other organs like the liver, according to a new study. Bifidobacteria, in the intestine, digest the healthy sugars in breast milk that are important for growth. Other bacteria digest fiber, producing short-chain fatty acids, which are important for gut health. The gut microbiome controls the immune system and infection. Recent research suggests that the gut microbiome affects the central nervous system and controls brain function. Gut bacteria produce certain vitamins, including vitamin K. Bifidobacteria and Lactobacilli, found in probiotics and yogurt, can help seal gaps between intestinal cells and prevent leaky gut syndrome.

Microbial–Myocardial Axis

Gut bacteria produce small molecules of metabolites. These metabolites act as communication signals between the gut and other parts of the body, like the heart, lungs and the brain.

Short-chain Fatty Acids (SCFAs)

These are fatty acids of two to six carbon atoms. (28)

These are derived from intestinal microbial fermentation of indigestible foods. SCFAs in the human gut are acetic, propionic, and butyric acids. They are the main energy source of colonocytes, making them crucial to gastrointestinal health. (29)

SCFAs all possess varying degrees of water solubility, which distinguishes them from longer-chain fatty acids that are insoluble.

Short-chain fatty acids (SCFAs) are emerging as important players in cardiovascular health, influencing the development and progression of heart diseases.

Gut bacteria produce these during the fermentation of dietary fiber. SCFAs like acetate, propionate, and butyrate can impact various aspects of cardiovascular function. Some SCFAs may contribute to heart disease, while others. SCFAs, produced by gut bacteria from dietary fiber, play a role in regulating blood pressure, improving vascular function, and potentially reducing the risk of heart diseases like atherosclerosis and heart failure. However, some SCFAs, like succinate, can worsen ischemic injury.

SCFAs are produced when dietary fiber is fermented in the colon (30)

Macronutrient composition (carbohydrate, protein, or fat of diets affects circulating SCFAs (31)

Acetate, propionate, and butyrate are the three most common SCFAs. Butyrate is particularly important for colon health because it is the primary energy source for colonocytes (the epithelial cells of the colon). The liver can use acetate for energy (32)

SCFAs and medium-chain fatty acids are primarily absorbed through the portal vein during lipid digestion, while long-chain fatty acids are packed into chylomicrons, enter lymphatic capillaries, and then transfer to the blood at the subclavian vein (33)

SCFAs have diverse physiological roles in body functions, affecting the production of lipids, energy, and vitamins. They may affect appetite and cardiometabolic health.

SCFAs induce vasodilation in blood vessels ex vivo and hypotension in vivo (34,35)

Acute administration of SCFAs lowers blood pressure, and this effect is mediated in part by G protein–coupled receptors such as olfactory receptor 78 and G protein–coupled receptor 41 (GPR41)(36)

Exogenous SCFA treatment has also been shown to have cardioprotective effects, as well as protective effects against acute kidney injury, inflammation, and hypertension (37,38)

Although the hypotensive effect of SCFAs has been studied for decades (39,40)

Acetate

A short-chain fatty acid acutely lowers heart rate (HR) as well as mean arterial pressure in vivo in radiotelemetry-implanted mice. Acetate acts in a sympatholytic manner on HR and exerts negative inotropic effects in vivo. Acetate is the most abundant SCFA present in the plasma, followed by propionate and butyrate (41,42)

Propionate

Propionate, a short-chain fatty acid produced by gut bacteria, has been shown to have protective effects on the heart, particularly in the context of heart disease and related conditions. It can improve heart function after myocardial infarction, reduce cardiac fibrosis, and mitigate cardiac hypertrophy and hypertension. Propionate also influences cardiac metabolism, potentially shifting the heart's fuel preference from fatty acids to glucose. However, disrupted propionate metabolism can also lead to negative consequences, including cardiac dysfunction.

Propionate improved Heart function after myocardial Infarction: Reduces Cardiac Fibrosis. Treatment can reduce fibrosis in the infarcted border area and non-infarcted areas after myocardial infarction.

Propionate can reduce cardiac hypertrophy, fibrosis, and

hypertension in animal models and reduce susceptibility to Arrhythmias.

Propionate treatment has been shown to reduce susceptibility to cardiac ventricular arrhythmias.

It can reduce systemic inflammation and local cardiac immune cell infiltration.

It can prevent atherosclerosis by influencing immune cells and potentially regulating lipoprotein levels.

Propionate can influence how the heart uses fuel, potentially favoring glucose oxidation over fatty acid oxidation, according to research.

Elevated levels of propionate can lead to histone propionylation and increased acetylation, impacting gene expression and potentially causing cardiac problems. Disrupted propionate metabolism can also lead to mitochondrial dysfunction and increased oxidative stress. Propionate can influence macrophages, shifting them towards an anti-inflammatory M2 phenotype and reducing pro-inflammatory cytokine production.

Propionate can modulate the activity of regulatory T cells and effector T cells, potentially contributing to its cardioprotective effects.

Propionate can affect the heart's fuel preference, favoring glucose oxidation and potentially impacting energy production.

Butyrate

It is a short-chain fatty acid produced by gut bacteria and has been shown to have beneficial effects on the heart and cardiovascular system. Butyrate can increase cardiac output. Improves blood flow. Butyrate can protect against heart damage from ischemia. Butyrate can relax blood vessels, reducing systemic vascular resistance and improving blood flow. Butyrate improves the contractile function of the heart, including the left ventricle. Butyrate can reduce heart damage caused by ischemia and reperfusion, which is a common complication of heart attacks. Butyrate may help protect against atherosclerosis, a condition where plaque builds up in the arteries. Butyrate's potential vasorelaxant and antihypertensive effects could help manage high blood pressure. Butyrate interacts with GPCRs, such as GPR41 and GPR43, on blood vessel smooth muscle and endothelial cells, which can affect blood pressure and blood vessel tone. Butyrate can reduce inflammation, which is a key factor in many cardiovascular diseasesButyrate can influence gene expression through epigenetic modifications, potentially contributing to its protective effects on heart cells.

Succinate

It can worsen ischemic injury. Succinate accumulation during ischemia plays a critical role, particularly in heart attacks and strokes. During ischemia, the lack of oxygen and nutrients leads to a buildup of succinate within cells. When blood flow is restored, this accumulated succinate is rapidly oxidized, causing a surge in reactive oxygen species (ROS) production. Ischaemia-reperfusion (IR) injury occurs when blood supply to an organ is disrupted and then restored, and underlies many disorders, notably heart attack and stroke. While reperfusion of ischaemic tissue is essential for survival, it also initiates oxidative damage, cell death, and aberrant immune responses through the generation of mitochondrial reactive oxygen species (ROS) (43,44)

TMAO (Trimethylamine N-oxide)

TMAO is a compound linked to heart health. It is produced by gut bacteria from certain nutrients like choline, carnitine, and betaine, and it's been associated with an increased risk of cardiovascular diseases. Elevated TMAO levels are linked to atherosclerosis, heart failure, and other heart-related issues. Trimethylamine-N-oxide (TMAO) is a metabolite produced from dietary nutrients by the gut microbiome, which was first discovered in 2011 and used to predict the risk of cardiovascular disease (45,46)

The precursors of TMAO, including phosphatidylcholine, choline, and L-carnitine, are commonly found in cheese, red meat, seafood, egg yolks, and other foods. (47,48)

To date, four different microbial enzyme systems have been identified that can convert precursor substances into trimethylamine (TMA), including choline-TMA lyase (cutC/D), carnitine monooxygenase (cntA/B), betaine reductase, and TMAO reductase (49)

Myocardial infarction (MI) remains the leading cause of death globally, imposing a significant burden on healthcare systems and patients. The gut–heart axis, a bidirectional network connecting gut health to cardiovascular outcomes, has recently emerged as a critical factor in MI pathophysiology. Disruptions in this axis, including gut dysbiosis and compromised intestinal barrier integrity, lead to systemic inflammation driven by gut-derived metabolites like lipopolysaccharides (LPSs) and trimethylamine N-oxide (TMAO), both of which exacerbate MI progression.(50)

Significance Of Microbes

Several studies have been carried out on the same, exploring the various genera involved, the association between them, and their importance in maintaining good health. The healthy human gut is colonised mainly by organisms belonging to two phyla, namely Bacteroidetes and Firmicutes. Mice have always been excellent models for pharmaceutical research. They have also been proven useful in studying the interaction between the host and intestinal microbes. Since human beings and mice occupy a common niche, there might be a significant association between their gut microbiota. According to earlier studies, mice gut microbiota shows considerable similarity to the human gut microbiome.(51)

How Do Gut Bacteria Reduce Heart Disease Risk?

Researchers have discovered that one of the good bacteria found in the human gut has the potential to reduce the risk of heart disease. The bacteria's activity in the intestines reduces the production of a chemical that has been linked to the development of clogged arteries, the study, published in the Journal of Biological Chemistry, said."The organism we studied affects health by preventing a problematic compound from becoming a worse one," said study researcher Joseph Krzycki from the Ohio State University in the US. For the findings, the research team traced the bacteria's behaviour to a family of proteins that they suspect could explain other ways that good gut organisms can contribute to human health. Previous research has already shown that the bacterium is "good" because it calms inflammation in the gut. The chemical linked to the clogged arteries that characterise atherosclerosis is called trimethylamine, or TMA. It is produced during metabolism when certain intestinal microbes, generally the bacteria considered unhelpful to humans, interact with specific nutrients from food. Among those nutrients is L-carnitine, a chemical compound found in meat and fish that is also used as a nutritional supplement to improve recovery after exercise. The research team discovered that E. limosum interacts with L-carnitine in a different way in the gut, and that interaction eliminates L-carnitine's role in the production of TMA (other nutrients also participate in TMA production in the gut). The researchers attribute the bacteria's beneficial behaviour to a protein called MtcB, an enzyme that cuts specific molecules of

compounds to help bacteria generate energy and survive. The process is called demethylation and involves the removal of one methyl group -- a carbon atom surrounded by three hydrogen atoms -- to change a compound's structure or function. "The bacterium does this for its benefit, but it has the downstream effect of reducing the toxicity of TMA," Krzycki said. (52)

Correlation Between Your Heart And Gut

Researchers have tried to find a link between our gut and heart health. While these two areas in the body are entirely different and have varying functions, research studies have provided several evidence suggesting that an unhealthy gut microbiome can contribute to cardiovascular diseases. That said, on this World Heart Day, we have Janvi Chitalia, Integrative Gut Microbiome Health Coach and Functional Medicine Nutritionist, who will tell us all about the correlation between your gut and heart.Over the past few decades, cardiovascular diseases (CVDs), including coronary artery disease (CAD), stroke, heart failure, and hypertension, have been recognized as a leading global cause of death with the highest morbidity and mortality rates all around the world.(53)

Warning Signs Of Poor Gut Health

The cardiologist wrote, "You've heard it before — 'Gut is the second brain'. But that's outdated. Today, your gut is the first brain. And your poor little brain up there? It's just trying to keep up. Watch out for these 5 warning signs your gut health might be disrupted — because when your gut goes off track, everything else follows." (54)

1. Frequent illnesses and weakened immunity
2. Skin issues like acne, eczema, and rashes
3. Frequent sugar cravings.
4. Unexplained fatigue and brain fog
5. Constant bloating and indigestion

CONCLUSION

Trust your gut. Follow your heart. One hundred trillion bacteria, from at least several hundred species, inhabit the gastrointestinal tract. Many of these microbes are good for you. They help you digest food, metabolize drugs, and protect you from infection by harmful invaders. When the balance of the gut microbiome goes away, the damage isn't limited to gut troubles and may also affect the heart. Propionate, a gut-derived metabolite, can have beneficial effects on heart health by reducing fibrosis, inflammation, and improving heart function. However, disruptions in propionate metabolism can also lead to cardiac dysfunction and other issues. Some SCFAs, produced by gut bacteria, may contribute to heart diseases. Dietary fiber plays a role in regulating blood pressure, improving vascular function, and potentially reducing the risk of heart diseases like atherosclerosis and heart failure. However, some SCFAs, like succinate, can worsen ischemic injury. Further research is needed to fully understand the complex role of propionate in cardiac health and disease.

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