openheart

The heart-gut axis: new target for atherosclerosis and congestive heart failure therapy

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To cite: Forkosh E, Ilan Y. The heart-gut axis: new target for atherosclerosis and congestive heart failure therapy. *Open Heart* 2019;**6**:e000993. doi:10.1136/openhrt-2018-000993

Received 12 December 2018
Revised 22 March 2019
Accepted 29 March 2019

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ABSTRACT

The human gut microbiota has been identified as a possible novel risk factor for cardiovascular disease. The intestinal microbiome plays a role in the pathogenesis of atherosclerosis and heart failure. Even though studies in rodents suggested that gut microbes may affect the risk of heart disease, this link has not been shown in humans. In the present study, we review several potential mechanisms by which the gut microbiome and bacterial translocation are associated with the development of cardiac disorders making them potential targets for novel therapeutic measures for these conditions. Modulation of the gut microbiota as a mechanism for altering the pathogenesis of disorders is an area of growing interest. Alteration in the gut microbiota is being explored as a method of reducing risk factors associated with cardiac diseases.

INTRODUCTION

The intestinal microbiome plays an important role in controlling whole-body metabolic homeostasis and organ physiology.[1] Cardiovascular diseases (CVD) including coronary heart disease (CHD) are leading causes of mortality in the Western world affecting about one-third of the population. Studies over the last decade suggested a potential role for the gut microbiome in the pathogenesis of atherosclerosis, CVD and heart failure. Even though studies in rodents suggested that gut microbes may affect the risk of heart disease, this link has not been shown in humans.[2] In the present study, we review several mechanisms for the potential role of the microbiome and bacterial translocation (BT) that may contribute to the pathogenesis of CVD and serve as targets for therapeutic approaches.

THE HEART-GUT AXIS: A ROLE FOR THE GUT MICROBIOME IN THE PATHOGENESIS OF HEART DISEASES

Endotoxaemia induces a chronic inflammatory state which contributes to atherosclerosis and CVD

A persistent low-grade inflammatory response underscores a metabolic syndrome and is also a risk factor for CVD.[3 4] Inflammatory markers are associated with obesity and the risk of obesity-associated CVD.[5] Perturbation of the intestinal microbiota and changes in gut permeability are triggers for the chronic inflammatory state.[5] 'Metabolic endotoxaemia' is a term used to describe a link among gut bacteria, endotoxins and their circulating levels, with inflammatory-induced obesity and metabolic diseases linking it to CVD.[6] The microbiome, with aberrant gut microbiota profiles, is important for the pathogenesis of inflammatory-induced obesity, type 2 diabetes mellitus and other disorders associated with a metabolic syndrome.[6 7] Gut microbiota signatures were identified using gut flora analyses in animal obesity, type 1 and type 2 diabetes and non-alcoholic fatty liver disease studies; however, their relevance in humans is yet to be determined.[6 8]

High serum lipopolysaccharide (LPS) activity is associated with cardiometabolic disorders, which supports the role of bacterial infections and immune responses in their aetiology.[9] The transfer of microbiota from obese animals induces metabolic disease and obesity in germ-free animals.[10] Conversely, transfer of pathogen-free microbiota from lean healthy human donors to patients with metabolic disease can increase insulin sensitivity.[11–13] In a recent study, 2452 patients were followed up for 10 years, and LPS activity was found to be associated with total energy and carbohydrate intake in lean, healthy subjects. High LPS was associated with obesity, metabolic syndrome, diabetes and CHD events, independent of other established risk factors.[9]

Role of the microbiome in the progression of atherosclerosis

The intestinal microbiota impacts lipid metabolism and may exert a protective effect on atherosclerosis development.[14 15] Using a low cholesterol diet in the Apoe$^{-/-}$ mouse model, a group raised in germ-free conditions showed a greater development of atherosclerotic plaques than controls did.[16]

Treatment of Apoe$^{-/-}$ mice with the gut bacteria *Akkermansia muciniphila*, reduced the size of atherosclerotic plaques, an effect that was attributed to its anti-inflammatory activity.[17]

The interplay between the microbiome and dietary-derived compounds is associated with CVD

Several dietary-related effects of the gut microbiota contribute to the pathogenesis of CVD. Acute or long-term high-fat diets lead to a rise in endotoxin levels.[6] Metabolites derived from the gut microbial metabolism of choline, phosphatidylcholine and L-carnitine directly contribute to CVD pathology, which underscores the increased risk of eating too much red meat.[8] These dietary nutrients have a trimethylamine (TMA) moiety, which participates in the development of atherosclerotic heart disease.[18] Hepatic production of trimethylamine-N-oxide (TMAO) from gut microbiota-derived TMA enhanced cardiovascular risk.[1] Levels of both gut microbiota-dependent TMA and hepatic flavin monooxygenase 3-dependent TMAO are predictors of atherosclerosis and CVD, further supporting a link between the gut microbiota and heart disease.[18–20] In mice, a strong association was noted between atherosclerotic plaque size and plasma TMAO levels.[21] A study of the relationship between fasting plasma choline and betaine levels and the risk of major adverse cardiac events (MACE), which includes death, myocardial infarction and stroke, in relation to TMAO was conducted with 3903 subjects undergoing coronary angiography over 3 years of follow-up. This study showed that higher plasma choline and betaine levels were associated with an increased risk of MACE.[19] Phosphatidylcholine, TMAO and betaine predicted CVD in an independent large clinical cohort.[22] TMAO levels correlated with the degree of severity of heart failure and with adverse outcomes.[20]

Gut microbial transplantation can transmit choline diet-induced TMAO production and atherosclerosis susceptibility.[21] Dietary supplementation of mice with choline and TMAO promoted macrophage scavenger receptors associated with atherosclerosis, while betaine supplementation only promoted macrophage scavenger receptors associated with atherosclerosis.[22] Suppression of intestinal microflora in atherosclerosis-prone mice inhibited dietary choline-enhanced atherosclerosis. Both phosphatidylcholine/choline and/or L-carnitine are found in large quantities in red meat and were suggested to increase the risk of CVD. Genetic variations controlling the expression of flavin monooxygenases, an enzymatic source of TMAO, segregated with atherosclerosis in hyperlipidaemic mice.[22] Other studies demonstrated beneficial properties for L-carnitine consumption against metabolic diseases including skeletal muscle insulin resistance and ischaemic heart disease (IHD). Fish is a significant source of TMAO, but dietary fish consumption exerts positive effects on cardiovascular health.[1]

The gut microbiota promotes energy harvest and storage from the diet and is beneficial during periods of nutrient deprivation.[23] Fasting produces a marked change in gut microbiota, with increased levels of short-chain fatty acids (SCFAs) generated from the microbial fermentation of glycans when compared with germ-free controls. During fasting, a microbiota-dependent, peroxisome proliferator-activated receptor-alpha-regulated increase in hepatic ketogenesis occurs, and myocardial metabolism is directed to ketone body utilisation.

Taken together, these data support a role for the interplay between the gut microbiome and dietary compounds in the pathogenesis of heart disease.[23]

Increased gut permeability as a risk factor for CVD

An impaired intestinal barrier function is followed by BT, and bacterial products trigger an inflammatory cascade. This has been associated with obesity and insulin resistance.[24] Moreover, patients with inflammatory bowel diseases (IBDs) who have high permeability of their intestinal barrier suffer from a higher risk of CHD despite a lower prevalence of other risk factors.[25] The increased long-term risk of IHD in these patients is related to the chronic inflammatory state, and interventions reducing the inflammatory burden may attenuate this risk.[26] During 1–13 years of follow-up after the diagnosis of IBD, the risk of IHD was high. This risk was lower among patients with IBD using 5-aminosalicylic acids, thiopurines and tumour necrosis factor (TNF) alpha antagonists, or among those treated surgically.

SCFAs are fermented from dietary fibres by the gut microbiota.[27] The most abundant SCFAs are acetate, propionate and butyrate, which are mostly metabolised in the colon and have numerous effects within the gastrointestinal tract, including maintaining the integrity of the large and small intestinal barrier. SCFAs that reach the systemic circulation were shown to have the ability to modulate CVD risk factors including the reduction of blood pressure and regulation of glucose and lipid homeostasis.[28]

BT is associated with the pathogenesis of heart failure

BT contributes to congestive heart failure (CHF) leading to a vicious cycle where impaired cardiac function impacts intestinal microcirculation leading to a barrier defect of the intestinal mucosa.[25] Small intestinal function is altered in decompensated CHF and translocation of LPS contributes to a state of chronic inflammation.[29] CHF is associated with a reduction of active and passive carrier-mediated intestinal transport and is more profound in oedematous patients. Active carrier-mediated intestinal transport was reduced in decompensated CHF, indicating epithelial dysfunction due to intestinal ischaemia. Oedematous patients had the highest blood concentrations of LPS, TNF and soluble tumour necrosis factor receptor R1 (sTNF-R1). CHF patients with higher LPS concentrations had the highest concentrations of TNF and sTNF-R1.[29]

Composition of gut microbiota in patients with CAD

Studies comparing the gut microbiota derived from faecal samples of three groups: patients with CAD, healthy volunteers and patients with coronary risk factors without CAD, revealed a significant increase in the order *Lactobacillales* in the CAD group. In addition, a higher percentage of lactobacilli were found in multivessel diseases than in single-vessel diseases.[30] A study including almost 12 000 participants showed a correlation between poor oral hygiene and CVD events, elevated C reactive protein and fibrinogen.[31] The bacteria found in the atherosclerotic plaques predominantly exist in the oral cavity and gut of the same person, suggesting a similar origin indicating the possible contribution of these bacteria to the development of atherosclerosis and CVD. In a study using pyrosequencing of 16S rRNA in atherosclerotic plaque, oral, and gut samples of 15 patients with atherosclerosis, a combination of *Veillonella* sp and *Streptococcus* sp in atherosclerotic plaques correlated with their abundance in the oral cavity. *Chryseomonas* sp was identified in all atherosclerotic plaque samples with *Veillonella* sp and *Streptococcus* sp identified in a majority of the samples.[32] Several species, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, were shown to cause an increase in plaque size in animal models following an oral or intravenous infection.[33–35]

An interplay between the gut microbiome with gut and systemic hormones affects CVD

Gut microbiome alterations are related to changes in gut hormones.[36] Decreased intestinal signalling for fats was described in mice lacking gut microbiota.[37] Plasma levels of the energy homeostasis hormones, ghrelin and PYY 3-36, are associated with left ventricular mass indices. These associations indicate a possible interaction between gut peptides and the cardiovascular system in hypertension and obesity.[38]

The gut microbiota affects different tissues, adipose deposits, hormonal, pharmacological, nutritional and life style factors, and can also affect adiponectin clearance and release from T-cadherin-associated tissue reservoirs.[39] Altered adiponectin levels are present in patients with heart failure. Inflammation downregulates adiponectin production and its levels are reduced in obesity and its associated comorbidities.[39] A positive association between inflammation and adiponectin has been reported in inflammatory disorders, in contrast with the negative correlation typical of metabolic diseases.

The interplay of the gut microbiome with bile acid metabolites affects the pathogenesis of heart disorders

Bile acids are associated with signalling. Gut microbial depletion affects the bile acid submetabolome of several organs including the heart in rats.[40] Unconjugated bile acids comprise the largest proportion of the total measured bile acid profile in the heart. In contrast, taurine-conjugated bile acids (taurocholic acid and tauro-beta-muricholic acid) dominate the cardiac bile acid profile in germ-free animals. These communication networks are affected by microbial activities noted by farnesoid X receptor-regulated pathway transcripts. The presence of specific microbial bile acid cometabolite patterns in the heart suggests a signalling role for these compounds and highlights the extent of gut microbiome effects on these pathways.[40]

TARGETING THE GUT MICROBIOME AS A TREATMENT FOR CVD

The intestinal microbiome represents a new potential therapeutic target for the treatment of cardiometabolic diseases.[41] Intervention studies in humans aiming to selectively alter the composition of the microbiota or to pharmacologically manipulate the microbiota to influence production of their metabolites are being explored. Several examples for such manipulations are described below.

Probiotics

Probiotics are live microorganisms which are beneficial to the host.[42] Human studies with probiotic strains show that ingestion of viable microorganisms with an ability to hydrolyse bile salts lowers blood cholesterol, alleviating a risk factor for CVD.[8] Certain probiotic bacterial strains reduce cholesterol and hypertension.[42–46]

Studies in animals suggested that probiotics can attenuate heart failure.[47] Oral probiotic *Lactobacillus rhamnosus* GR-1 administration altered the progression of postinfarction heart failure. Animals-administered GR-1 exhibited a significant attenuation of left ventricular hypertrophy, and improved systolic and diastolic left ventricular function. Metabolomic analysis showed differences in the preservation of myocardial taurine levels in treated mice. Beneficial effects were also evident after the cessation of therapy, suggesting the persistence of the GR-1 effect.[47]

Prebiotics

Increased consumption of whole-plant foods, including fruits, vegetables and whole-grain cereals, provides the rational for efficacious prebiotics. Prebiotics modulate the gut microbiota exerting an inverse correlation with the risk of cardiometabolic diseases.[48] Diets based on the high intake of fermentable fibres and plant polyphenols alter the microbial activities within the gut.[8] In a study by Marques *et al*, a high-fibre diet and acetate supplementation reduced blood pressures, cardiac fibroses and left ventricular hypertrophies.[49] Fibres and polyphenols are converted into biologically active compounds by the colonic microbiome thereby upregulating the colon-systemic metabolic axis.[50] Polyphenols derived from dietary plants exert a protective effect on vascular endothelial cells using antioxidants that prevent the oxidation of low-density lipoprotein.[51]

Cranberry *Vaccinium macrocarpon* Aiton extract (CE) reduced the high fat/high sucrose-induced weight gain, visceral obesity, liver weight and triglyceride accumulation in mice.[52] CE administration improved insulin sensitivity, lowered intestinal triglyceride content and

alleviated intestinal inflammation and oxidative stress. CE treatment increased the proportion of the mucin-degrading bacterium *Akkermansia* sp in the metagenomic samples.

A positive association between increased dietary intake of whole grains and a reduced risk of cardiometabolic disorders has been shown.[48] Wholegrain foods have been associated with lower blood glucose. In vitro, total bacterial populations increased significantly in cultures when cereal samples were supplemented with pH-controlled anaerobic cultures of human faecal microbiota. Proliferation of the genus *Bifidobacterium* and *Lactobacillus–Enterococcus* groups were noted.[48]

Dietary measures that alter the immune system of the gut

Selection of health promoting foods and the design of functional foods are being explored as a means of promoting a 'healthy' microbiome.[50] Circulating LPS arising from gastrointestinal tract microbiota is associated with both infection and inflammation, and may be affected by daily nutrition.[9] Strategies that modulate the gut microbiota or their metabolic activities by whole-plant foods, probiotics and prebiotics may be at the base of healthy eating pyramids advised by regulatory agencies and can decrease the risk for CVD.[8]

Consumption of a Western diet, which is low in dietary fibre and fermentable substrates and high in saturated and transfatty acids, is associated with the depletion of metabolic fuels, resulting in an alteration of the gut microbial profile and contributes to increased cholesterol levels.[53] End products of bacterial fermentation, particularly the SCFAs (propionate), may be associated with this increase. A shift towards a plant-based diet may confer protective effects against atherosclerotic CAD by increasing endothelial protective factors in the circulation while reducing factors that are injurious to endothelial cells.[51]

Targeting the bacterial LPS

In the Bruneck study, plasma levels of bacterial LPS constitute a strong risk factor for CVD. LPS levels were measured in a random population of 516 subjects aged 50–79 years. Subjects with elevated serum levels beyond the 90th percentile faced a threefold increased risk of incident atherosclerosis, which is more pronounced in subjects with chronic infections and in current and ex-smokers.[54–57]

Interventions that target 'leaky' mucosal membranes, endotoxin-coupled lipid absorption or removal of circulating endotoxins, can reduce the progression of inflammatory-induced metabolic diseases.[6] Bovine colostrums were shown to improve gut BT. In vitro, this reduced apoptosis is measured by active caspase-3 and caspase-9, baxalpha, Bcl-2, heat shock protein 70 expression and epithelial electrical resistance in colonic cell lines.[58] In both animals and humans, oral administration of bovine colostrum-derived anti-LPS compounds were associated with the alleviation of insulin resistance, hyperlipidaemia and liver damage associated with the metabolic syndrome.[59–61]

Lactoferrin (LF) is a natural immunomodulator that regulates immune responses including the control of inflammatory cytokine production during acute inflammation.[62] LF administered prior to LPS protected rats from LPS-induced hypotension. The effect was associated with a decrease in serum TNF-alpha and interleukin 6, and with histological protection of intestinal tissue post LPS administration.[62]

Bariatric surgery as a means for altering gut microbiome

Bariatric procedures such as the Roux-en-Y gastric bypass (RYGB) operation improve obesity-associated metabolic disorders in addition to their weight loss effects. In a rat model, plasma bile acids, phosphocholines, amino acids, energy-related metabolites, nucleoside and amine metabolites, cardiac glycogen and amino acids were altered following the RYGB procedure. These surgically induced metabolic shifts were associated with an alteration of the gut microbiota.[63] These changes reflected an enhancement of cardiac energy metabolism through tricarboxylic acid cycle intermediates, cardiorenal protective activities and biochemical caloric restrictions.

Physical activity as a means of altering the gut microbiome

Exercise can also alter the gut microbiota. Exercise increases faecal concentrations of SCFA in lean participants compared with obese ones.[64] In a mouse model, transplanting the gut microbiome from mice that received exercise to germ-free mice led to weight gain and to a significant elevation of the butyrate:acetate ratio.[64] This finding supports the assumption that gut production of SCFAs helps to enhance energy within a physically active mouse, thereby becoming a survival benefit during caloric deficient periods.[65]

The microbiome–drug interaction

The intestinal microbiome plays a role in drug bioavailability, activity and toxicity.[66] The high variability in the bioavailability of digoxin among individuals was suggested to be associated with alterations in the microbiome. Inactivation of digoxin was found when it was incubated in vitro with the gut bacterium *Eggerthella lenta*. Arginine supplements might be a potential intervention in increasing digoxin activity by inhibiting the expression of cardiac glycoside reductase gene operons that can inactivate digoxin.[66]

SUMMARY

The gut microbiome and BT are associated with the development of CVD. Modulation of the gut microbiota is an area of growing interest as a means of altering the pathogenesis and complications of cardiac disorders. Altering the gut microbiota may become an attractive method for reducing risk factors and minimising the severity and complications associated with these disorders.

Contributors Both authors wrote the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

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