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Gut microbiota and cardiovascular disease health

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Learning outcomes:

By the end of this article, you should understand:

1. The links between the gut microbiota and cardiovascular disease pathology
2. The factors that may influence this relationship, and needs for future research
3. The potential therapeutic targets of the gut microbiota which may influence cardiovascular health

Introduction to CVD

Cardiovascular disease (CVD) is a term used to describe diseases of the heart and circulatory systems, including peripheral vascular disease, coronary heart disease (CHD), pericardial disease, valvular heart disease, atrial fibrillation (AF), vascular dementia and stroke (1,2).

The British Heart Foundation estimates that 7.6million people are living with CVD in the UK (2). CVD is estimated to cause 27% of all deaths (2), cancer has overtaken CVD as the leading cause of death for women, but CVD remains the leading cause of death in men (3).

Risk factors for myocardial infarction (MI) include smoking, genetic predisposition, abnormal blood lipid profile, high blood pressure, diabetes mellitus, abdominal obesity, psychosocial factors (such as depression), low consumption of fruit and vegetables, alcohol consumption and low physical activity levels (4). A large proportion (80%) of people with CVD also have a comorbidity, with as many as a quarter having five comorbidities (5), such as depression, arthritis, asthma, anxiety, type 2 diabetes and obesity (5).

Introduction to the gut microbiota

Our gut microbiota (GM) is the collection of living organisms that reside in the entire gastrointestinal (GI) tract. The GM is predominantly bacterial, but also contains viruses, fungi and archaea. The GM has many roles, some of which are well defined including the development of the immune system, harvesting of energy from food, production of certain vitamins, maintaining barrier integrity and protecting against pathogens (6). The GM has also been associated with the development of many diseases, through the modification of multiple metabolic communication pathways. There is ongoing research looking at its role in non-gut diseases such as those of the brain, lung, skin and cardiovascular systems.

CVD and dysbiosis

Dysbiosis can be defined as **'any change to the composition of resident commensal communities relative to the community found in healthy individuals'** (7). This change in GM composition is linked with changed physiological function, (8) and is the focus of much research in many disease states.

Studies have found differences in the GM of people with CVD (9). One study which reviewed the GM of 218 people with atherosclerosis versus healthy controls found increased abundance of pathogenic strains of *Enterobacteriaceae* (including *Escherichia coli, Klebsiella species,* and *Enterobacter aerogenes*) and *Streptococcus species,* and a reduction in Bacteroides, which are thought to have a positive anti-inflammatory action (10). They proposed that the different microbial compositions may affect their metabolic products, increase inflammation and contribute to atherosclerosis.

Other studies have demonstrated different profiles of GM in people with hypertension, with increased ratio of Firmicutes to Bacteroides, which may lead to reduced Short Chain Fatty Acids (SCFA) action and increased inflammation. In animal models, a GM transplant from hypertensive rats significantly increased blood pressure in healthy rats, indicating GM involvement (11).

A number of small studies of patients with heart failure (HF) have found reduced GM diversity and low levels of core bacterial species (12,13). These changes are associated with reduced barrier integrity in the gut and inflammation, also people with HF are more likely to have pathogenic species in the gut and suffer from *Clostridium difficile* infection (13).

While altered GM composition has been found in those with CVD, at this stage (as with most diseases) it is unclear as to the directionality of the relationship. There are also many confounding factors as the risk factors and pharmaceutical treatment of CVD also impact the GM (10).

Potential messengers and pathways

The dysbiosis seen in CVD can impact the metabolism of various microbe-produced or modulated molecules, which may play a role in the pathogenesis of the disease. Research in this area relies mostly on epidemiology and pre-clinical trials which are not conclusive. However, some key messengers and pathways have been implicated (see Table 1) (9).

Table 1: Potential GM mediated messengers and pathways that influence CVD

Messenger/pathway	Detail
Trimethylamine-N-oxide	The GM metabolises nutrients choline and carnitine, such as L-carnitine (found in animal products red meat, fish and eggs) (14). This process produces trimethylamine which is converted into trimethylamine-N-oxide (TMAO). TMAO has a role in both lipid, sterol and glucose metabolism. TMAO also interacts with platelets and can increase clotting and be pro-thrombotic, which has been demonstrated in mice models and also some very small human trials (15). Other studies show atherogenic effect, mediated by the GM (16). This could explain the link between high red meat intakes and CVD risk (17). TMAO levels are positively correlated with risk of cardiovascular events such as MI, stroke and death (14), however, the directionality of this relationship (as with much epidemiological research) has not yet been proven. More human intervention studies are required.
Bile acids	Bile acids are essential for the emulsification and absorption of dietary fat. They are produced from cholesterol in the liver. The GM plays a role in the metabolism of bile acids, during their conversion to secondary bile acids, which is an important step in their lifecycle. Dysbiosis can reduce this process and therefore impair cholesterol metabolism, lead to increased LDL cholesterol levels and contribute to atherosclerosis (18). The composition and amount of bile acids, and their derivatives are significantly altered in those with HF (13). Receptors for bile acid derivatives have been found to be involved in many metabolic pathways including homeostasis of body weight, glucose and lipid metabolism, vascular health and blood pressure (18).
Short-chain fatty acids (SCFA)	SCFAs are a key metabolite of the GM, produced by the fermentation of dietary fibre. They include acetate, propionate and butyrate. SCFA are a key energy source for gut epithelial cells, act as anti-inflammatory immune system messengers and also help regulate certain metabolic pathways including lipid metabolism (9). One study has shown improvement in dysbiosis and an increase in SCFA-producing Bacteroides species upon fibre supplementation in hypertensive mice. These had positive improvements including lowering blood pressure, reducing cardiac fibrosis and left ventricular hypertrophy through downregulation of inflammatory cytokines and gene regulation (19). More human studies are required.
Other factors	Dysbiosis and alteration of the GM and the messengers outlined above may impact the overall barrier integrity in the gut of those with CVD and have an overall pro-inflammatory effect through other pathways (20).

Therapeutic interventions targeting the GM

Diet influences both GM and CVD risk, and diets that decrease risk of CVD often improve GM diversity. A direct, causal link has not been demonstrated, however, it is sensible to focus on dietary manipulations that target both areas in addition to standard medical treatments.

Fibre intake

Prebiotic fibre is the primary fuel of our GM, fermentation results in altered composition and activity of the GM, such as an increase in SCFA producing *bifidobacteria* (21). Alongside known benefits of SCFA (including healthy gut cell turnover and reduced risk of bowel cancer) they may also improve CVD metabolic outcomes (as discussed above). Epidemiological studies show that fibre intake is inversely correlated with CVD risk (22). In the UK, it is recommended to have 30g/fibre per day, however, most people do not meet this target, with the average adult consumption being only 18-19g/day (23).

Diverse plant-based eating

Low fruit and vegetable consumption has been shown to be a key risk factor for CVD (4). This may be due to its impact on fibre, polyphenol and overall energy intake (being low energy density). In addition, newer research is highlighting the importance of a varied plant based diet, showing that those who consume over 30 different plant foods per week have more diversity in their GM, which is considered to be a marker of a healthy GM (24).

Mediterranean-style diet

A Mediterranean style is high in vegetables, fruits, grains and legumes and low in red meat and processed carbohydrates. It has been found beneficial in both primary and secondary prevention of CVD (25). The exact mechanism of the diet isn't entirely understood, however, it includes benefits of antioxidants, fibre, low saturated and trans fatty acid content and low sodium. These factors may reduce oxidative stress, increase nitric oxide production (a vasodilator) and reduce inflammation (26), which may involve GM-mediated pathways.

Reduced red meat intake

Another potential benefit of increased plant consumption, is the natural reduction of red meat intake. TMOA intake is lower in vegetarian and vegans versus meat eaters; red meat has been shown to increase circulating and faecal TMOA levels (27). Despite the lack of certainty of the role of red meat in CVD, UK recommendations advise a maximum portion of 70g/day, (28) due to convincing evidence for the risk of bowel cancer.

Polyphenols

Polyphenols are organic compounds found in plant foods including fruit, cocoa, tea and coffee (29). Some of the highest sources of polyphenols are dark chocolate, flaxseed, berries (including blackcurrants, blackberries and strawberries), as well as olives, pecans, hazelnuts and soy (29). Most polyphenols enter the colon undigested, where they interact with the GM, being converted into phenolic acids, SCFA or affect the composition and activity of the GM (21). Specific polyphenols have been shown to have cardioprotective effects, for instance, improving vascular function and atherosclerosis through interaction with the GM (8).

Probiotics

Probiotics may beneficially impact the GM metabolites outlined in table 1, alongside improved barrier function in the GI tract (20).

A recent meta-analysis of 34 studies including 2,177 adults found statistically significant effects of probiotics in the reduction of systolic and diastolic blood pressure, total cholesterol, LDL-C, serum glucose, HbA1C and Body Mass Index (BMI); and elevation of HDL-C (30). This review combined the results of studies using capsule, powder and milk-based probiotics and did not identify particular strains or groups of people who would most benefit from probiotics. It is important to note that some studies have shown no benefit and there is no consensus recommendation on this yet due to the weak quality evidence base.

Individual clinical trials show that the strains *Lactobacillus reuteri NCIMB 30242* and *Lactobacillus plantarum* reduce LDL and total cholesterol levels (8,30). Additionally, one systematic review focused on the role of *Lactobacillus plantarum* in the lowering of blood pressure, and found clinically small, but statistically significant improvements for lowering systolic and diastolic blood pressure (31).

More large, high-quality trials are required to determine clear guidelines for use of probiotics in CVD. Currently they are not included in national treatment guidelines, however, they are considered safe to use in CVD (32).

Practice recommendations

- Encourage reduction of red meat intake, UK guidelines state a maximum intake of 70g/day. Swap red meat for lean meat such as chicken and turkey, oily fish and encourage regular intake of plant based alternatives, for example tofu, soy, edamame, beans and legumes.
- Encourage a diverse, plant-based Mediterranean-style diet, rich in wholegrains, fruit and vegetables and sources of Omega 3 fatty acids, such as oily fish and nuts and olive oil.
- Focus on fibre intake to increase SCFA production, aim for 30g/day.
- Encourage dietary diversity, aiming for 30 (or more) different plant foods per week.
- There is not currently strong evidence to recommend specific probiotic supplements for the treatment or prevention of CVD, however there is growing evidence of some benefit in the reduction of LDL and total cholesterol, and there is no risk of harm. This should be in conjunction with dietary and lifestyle changes.

Summary

- Dysbiosis is common in people with CVD.
- The GM is emerging as a modulator of the pathology of CVD through interactions with various metabolic pathways.
- Research is growing, but still limited in quality and more high-quality human trials are required.
- Diet can impact GM and CVD risk, so it is a potential therapeutic target.
- A high-fibre, Mediterranean-style diet, rich in varied plants and low in red meat is recommended to improve both the GM and reduce CVD risk.

Continuing Professional Development (CPD) Questions

1) Which of these are risk factors for CVD?

- a. Smoking
- b. Low fruit and vegetable intake
- c. Low physical activity levels
- d. All of the above

2) Which of these statements best describes the term 'Dysbiosis'?

- a. A change in microbial composition relative to that found in the healthy population
- b. Takeover of bad bacteria in the microbiome
- c. Unhealthy gut bacteria composition

3) The gut microbiota are thought to impact CVD risk

- a. Through direct communication with the heart muscle and blood vessels
- b. Through a complex network of intermediary messengers which impact metabolic processes
- c. Through both of the above

4) Trimethylamine-N-oxide (TMAO) is produced from nutrients found in which types of foods?

- a. Wholegrains
- b. Fruits and vegetables
- c. Red meat and animal products such as eggs

5) Which of the following foods is not high in polyphenols?

- a. Salmon
- b. Dark Chocolate
- c. Berries

6) Research shows that for a healthy diverse microbiome we should aim to eat how many different plant foods per week?

- a. 20
- b. 25
- c. 30

Answers on the last page

References

1. Piepoli MF, Abreu A, Albus C, Ambrosetti M, Brotons C, Catapano AL et al. Update on cardiovascular prevention in clinical practice: A position paper of the European Association of Preventive Cardiology of the European Society of Cardiology*. Eur J Prev Cardiol 2019; 27: 181–205.
2. British Heart Foundation. BHF CVD UK Statistics Factsheet. 2021.[Internet] 4 February 2021. Available from: https://www.bhf.org.uk/what-we-do/our-research/heart-statistics.
3. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE et al. European Society of Cardiology: Cardiovascular Disease Statistics 2019. Eur Heart J 2019; 41: 12–85.
4. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 937–952.
5. Tran J, Norton R, Conrad N, Rahimian F, Canoy D, Nazarzadeh M et al. Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: A population-based cohort study. Plos Med 2018; 15: e1002513.
6. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J 2017; 474: 1823–1836.
7. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. Cell Microbiol 2014; 16: 1024–1033.
8. Ahmad AF, Dwivedi G, O'Gara F, Caparros-Martin J, Ward NC. The gut microbiome and cardiovascular disease: current knowledge and clinical potential. Am J Physiol-heart C 2019; 317: H923–H938.
9. Ahmad AF, Ward NC, Dwivedi G. The gut microbiome and heart failure. Curr Opin Cardiol 2019; 34: 225–232.
10. Jie Z, Xia H, Zhong S-L, Feng Q, Li S, Liang S et al. The gut microbiome in atherosclerotic cardiovascular disease. Nat Commun 2017; 8: 845.
11. Adnan S, Nelson JW, Ajami NJ, Venna VR, Petrosino JF, Bryan RM et al. Alterations in the gut microbiota can elicit hypertension in rats. Physiol Genomics 2017; 49: 96–104.
12. Luedde M, Winkler T, Heinsen F, Rühlemann MC, Spehlmann ME, Bajrovic A et al. Heart failure is associated with depletion of core intestinal microbiota. Esc Hear Fail 2017; 4: 282–290.
13. Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. Nat Rev Cardiol 2019; 16: 137–154.
14. Zeisel SH, Warrier M. Trimethylamine N-Oxide, the Microbiome, and Heart and Kidney Disease. Annu Rev Nutr 2016; 37: 1–25.
15. Zhu W, Wang Z, Tang WHW, Hazen SL. Gut Microbe-Generated Trimethylamine N-Oxide From Dietary Choline Is Prothrombotic in Subjects. Circulation 2017; 135: 1671–1673.
16. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT et al. Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013; 19: 576–585.
17. Zhong VW, Horn LV, Greenland P, Carnethon MR, Ning H, Wilkins JT et al. Associations of Processed Meat, Unprocessed Red Meat, Poultry, or Fish Intake With Incident Cardiovascular Disease and All-Cause Mortality. Jama Intern Med 2020; 180: 503–512.
18. Ryan PM, Stanton C, Caplice NM. Bile acids at the cross-roads of gut microbiome–host cardiometabolic interactions. Diabetol Metab Syndr 2017; 9: 102.
19. Marques FZ, Nelson E, Chu P-Y, Horlock D, Fiedler A, Ziemann M et al. High-Fiber Diet and Acetate Supplementation Change the Gut Microbiota and Prevent the Development of Hypertension and Heart Failure in Hypertensive Mice. Circulation 2017; 135: 964–977.
20. Novakovic M, Rout A, Kingsley T, Kirchoff R, Singh A, Verma V et al. Role of gut microbiota in cardiovascular diseases. World J Cardiol 2020; 12: 110–122.
21. Tuohy KM, Conterno L, Gasperotti M, Viola R. Up-regulating the Human Intestinal Microbiome Using Whole Plant Foods, Polyphenols, and/or Fiber. J Agr Food Chem 2012; 60: 8776–8782.
22. Kim Y, Je Y. Dietary fibre intake and mortality from cardiovascular disease and all cancers: A meta-analysis of prospective cohort studies. Arch Cardiovasc Dis 2016; 109: 39–54.
23. National Diet and Nutrition Survey. Results from the National Diet and Nutrition Survey rolling programme for 2016 to 2017 and 2018 to 2019 for food consumption, nutrient intakes and nutritional status December 2020 Accessed February 2020: NDNS: results from years 9 to 11 (2016 to 2017 and 2018 to 2019) - GOV.UK (www.gov.uk)
24. McDonald D, Hyde E, Debelius JW, Morton JT, Gonzalez A, Ackermann G et al. American Gut: an Open Platform for Citizen Science Microbiome Research. Msystems 2018; 3: e00031-18.
25. Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E et al. Benefits of the Mediterranean Diet: Insights From the PREDIMED Study. Prog Cardiovasc Dis 2015; 58: 50–60.
26. Schwingshackl L, Morze J, Hoffmann G. Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. Brit J Pharmacol 2020; 177: 1241–1257.

27. Tang WHW, Bäckhed F, Landmesser U, Hazen SL. Intestinal Microbiota in Cardiovascular Health and Disease JACC State-of-the-Art Review. J Am Coll Cardiol 2019; 73: 2089–2105.

28. Scientific Advisory Committee on Nutrition. Iron and Health Report. TSO. London. 2010.

29. Pérez-Jiménez J, Neveu V, Vos F, Scalbert A. Identification of the 100 richest dietary sources of polyphenols: an application of the Phenol-Explorer database. Eur J Clin Nutr 2010; 64: S112–S120.

30. Dixon A, Robertson K, Yung A, Que M, Randall H, Wellalagodage D et al. Efficacy of Probiotics in Patients of Cardiovascular Disease Risk: a Systematic Review and Meta-analysis. Curr Hypertens Rep 2020; 22: 74.

31. Lewis-Mikhael A-M, Davoodvandi A, Jafarnejad S. Effect of Lactobacillusplantarum containing probiotics on blood pressure: A systematic review and meta-analysis. Pharmacol Res 2020; 153: 104663.

32. Olas B. Probiotics, Prebiotics and Synbiotics—A Promising Strategy in Prevention and Treatment of Cardiovascular Diseases? Int J Mol Sci 2020; 21: 9737.

Answers

1. d
2. a
3. b
4. c
5. a
6. c

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