Population health and the gut ecosystem: The role of cardiovascular therapeutics on the gut microbiota.

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Abstract

The gut microbiota ecosystem is gaining global traction due to its contribution to the development of Cardiovascular Disease (CVD) and its major role in the metabolism of drugs used in the treatment of patients with atherosclerosis, hypertension, dyslipidemia, and heart failure.

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Introduction

The gut microbiota ecosystem is gaining global traction due to its contribution to the development of Cardiovascular Disease (CVD) and its major role in the metabolism of drugs used in the treatment of patients with atherosclerosis, hypertension, dyslipidemia, and heart failure. In the recent paper titled "Cardiovascular Health and The Intestinal Microbial Ecosystem: The Impact of Cardiovascular Therapies on The Gut Microbiota", Alhajri et al. provided a practical description of how the intestinal microbiota are associated with these diseases and how it can alter the metabolism of medications used in the management of CVD which can modulate the pharmacokinetics and pharmacodynamics and result in production of toxic metabolites that could interfere with the drug response. The intestinal microbiota can modulate the response to statin, antihypertensive medications (i.e., Angiotensin Enzyme inhibitors (ACEi), and β-blockers), and platelets aggregation inhibitors.

As our understanding of the intestinal microbiota ecosystem grows, so does our realization of the critical role it plays in the development and treatment of chronic disease. In this mini review we highlight the interaction between the intestinal microbiota and most commonly used CVD therapeutics.

CVD and Role of Gut Microbiota

Cardiovascular Disease (CVD) is one of the most common diseases across the globe, and has been found to increase morbidity and mortality among people. CVD is a broad term that includes hypertension, stroke, heart failure, coronary artery disease, peripheral vascular disease, stroke, rheumatic heart disease, cardiomyopathies and congenital heart diseases [1].

Several studies have shown that the gut microbiota plays an important role in CVD, with imbalances between bacteroidetes to firmicutes ratios a strong indicator for dysbiosis, with links to atherosclerosis, heart failure and other diseases [2]. Imbalances in gut microbiota can occur due to lifestyle change, which mainly involves diet, environmental factors, intestinal infections and even certain medications. Dysbiosis increases the production of harmful metabolites, which likely underlies the pathological pathways of CVD.

Intestinal microbiota can metabolize choline, phosphatidylcholine, and L-carnitine into Trimethylamine (TMA), which is then further oxidized into Trimethylamine N-Oxide (TMNO) by hepatic Flavin Monooxygenases (FMO3). Animal dairy products such as milk, eggs and red meat have high levels of TMA, and are an important contributor to intestinal microbiota. TMNO is associated with an overall worse prognosis in heart failure patients, as it enhances atherosclerosis, thrombosis and ischemia. Higher risks of hypertension have also been associated with increased TMAO levels. TMAO can accumulate at the heart or kidney and trigger inflammation, foam cell synthesis, and platelet accumulation [3].

Short Chain Fatty Acids (SCFAs) are also fermented from dietary fibers by intestinal microbiota, and have been shown to have positive outcomes for patients with CVD. SCFAs are also a drug target for the management of hypertension [2]. Supplemental acetate and butyrate is linked to decreased blood pressure.

Bile acids that are produced by the liver are important for fat absorption in the small intestine. These bile acids are converted to lithocholic acid and deoxylithocholic acid that are known as secondary bile acids by the intestinal microbiota [4]. A mice study showed significant increase of Firmicutes (54% to 98%) while decrease in Bacteroidetes when cholic acid was given as a supplement [5].

Disruption of Gut Barrier Function

Gut barrier function disruption can occur due to microbial imbalance in the gut- microbial cellular components such as LPS and peptidoglycan can stimulate host immune responses, leading to inflammatory signals that worsen CVD outcome.

Many antibiotics, prebiotics, probiotics, dietary intervention and fecal microbial transplantation methods target intestinal microbiota and their metabolites for better CVD outcomes [2]. Antibiotics such as vancomycin, neomycin, and minocycline

can positively impact blood pressure by regulating gut microbiota. Ampicillin can decrease Low Density Lipid (LDL) and Very Low Density Lipid (VLDL) concentrations in the blood. Fecal microbial transplantation from a healthy individual to a diseased individual can restore normal gut microbiota by reducing inflammation, and can potentially be useful in treating patients with CVD [2]. Use of probiotics has gained much attention, as they increase the growth of intestinal microbiota, thereby reducing inflammation and producing favorable CVD outcomes. Changes in diet can delay or improve CVD-usage of high fiber diet and acetate can lead to improvement in patients with heart failure and hypertension [2].

CVD Drugs and Microbiota

Aspirin is one of the widely used medications to reduce CVD, and has been associated with changes in gut microbiota. ACE inhibitors and calcium channel blockers have also been seen to have a positive association with gut microbiota. Research shows that administering atorvastatin to patients with hypercholesterolemia had increased levels of anti-inflammatory bacterial species in their guts while those patients who did not receive atorvastatin had increased levels to inflammatory bacterial species.

The impact of the microbiota on the efficacy of drugs is an upcoming topic, with bacteria's interaction with chemotherapeutic drugs described under the TIMER model (Translocation, Immunomodulation, Metabolism, Enzymatic degradation, and Reduced diversity) [6,7]. The interaction of microbiota with cardiovascular drugs, on the other hand, is less elucidated. However, previous studies have shown a relation between the use of these drugs and the microbiome.

In the presence of fecal bacteria, antihypertensive drug amlodipine has been found to decrease in concentration, while its metabolite increases. When exposed to a post-ampicillin environment of suppressed gut microbiota metabolic activity, amlodipine was absorbed in a more enhanced manner. This indicates that in the case of antibiotics, or any change in the microbiota, there is an impact on blood pressure when controlled by hypertensive drugs [8].

The variation in statin response is generally quite known, as measured by varied LDL-C levels post-treatment. In one study, healthy subjects were given statins, and 46% got a reduction of >50% LDL-C levels, while 43% experienced 0%-50% reduction in LDL-C levels, with 11% experiencing no change or increased LDL-C [9]. The main statins generally prescribed all have evidence of being modulated by the gut microbiome, with the magnitude of simvastatin-induced LDL-C lowering potential indicated by baseline concentrations of three secondary bacterially-derived bile acids [10]. Gut-derived bile acids are thought to have a direct influence on drug pharmacokinetics, thus impacting drug responses. In addition, there is a possibility that statins alter the amount of some bacterial species, thus potentially impacting the bile acids that alter drug kinetics, though this is yet to be tested [10].

Rosuvastatin can drastically change the gut microbiome, with the level of certain bacterial groups directly correlated with the efficacy of the drug, as indicated by LDL-C lowering. For example, it was found that some bacteria such as *Firmicutes* have negative associations with LDL-C levels, while others such as *Cyanobacteria* are positively correlated. However, this study had no control group [11]. In one RCT with a placebo group, it was found that treatment with *Lactobacillus reuteri* , which contains increased bile salt hydrolase activity, led to greatly reduced LDL-C levels [12].

Atorvastatin is also related to a change in gut microbiota. Between untreated and atorvastatin-treated hypercholesterolemia patients, untreated patients had a bacterial collection with species that are associated inflammation, such as *Streptococcus* , while the treated patients has more anti-inflammatory species such as *Faecalibacterium prausnitzii* [13].

Digoxin has been found to interact with the species *Eggerthella lenta*, which deactivates the drug. Increased consumption of protein in the diet is associated with increased arginine, which would inhibit *E. lenta's* reduction of digoxin [14].

Patients with heart valve replacement are often given that the Vitamin K antagonists such as warfarin as an anticoagulant. The gut microbiota can influence the effects of warfarin and amongst the most important genera are *Enterococcus* and *Escherichia-shigella* . Increase in *Enterococcus* gut microbial population is associated with higher anticoagulation in patients with heart valve replacement. On the other hand, patients who had increased levels of *Escherichia-shigella* have reduced reaction to warfarin [15]. It has been suggested that the changes are observed due to production of metabolites by the gut microbiota in the presence of Vitamin K antagonists, bacteria producing Vitamin K in the gut and changes in structure of the drug by the gut microbiota [16].

Anti-platelet-A recent study with mice suggested that anti-thrombotic properties of aspirin are enhanced when given with an oral antibiotic such as ampicillin. Administration of ampicillin led to decrease in aspirin metabolism by gut microbiota and increase in the primary metabolite (M1) of aspirin. Analysis of the fecal samples from the rats treated with ampicillin revealed changes in the quantity and composition of gut microbiota. This suggests that administration of antibiotics with aspirin can lead to changes in gut microbiota causing decreased metabolism of aspirin and increasing its antithrombotic effects. However, more studies are needed to gain more evidence regarding this recent finding [17].

Other Therapies

Drugs that inhibit the formation of TMAO can reduce the incidence of atherosclerosis. Certain molecules produce TMA when fermented by bacteria, and are then metabolized to TMNO, which is further metabolized into FMO3 by hepatic enzymes. This pathway and its components have been associated with CVD. Furthermore, FMO3 is held accountable for the metabolism of some therapeutic molecules. It was further found that the molecules create a dysbiosis that impacts

the efficacy of some therapeutic drugs. With this information, therapies that target the molecules may be considered outside of those previously mentioned, which would lead up to the lowering of TMAO at multiple levels, impacting drug concentrations and metabolism. Such examples of the targeting of these various regulatory levels include a change in diet, which would reduce TMA and TMAO by remodeling the gut microbiota. Modulation can also occur at the stage of inhibiting FMO3 with drugs such as methimazole and indole.

Clinical Applications

There are various levels at which therapies can be used to achieve better cardiovascular health. The gut micro biome impacts drug metabolism and distribution, thus playing a large role in the efficacy of some therapies. Different microbial compositions in itself result in different variations in these drug metabolism and efficacy, indicating the clinical relevance of microbial composition. The difference in outcome based on micro biome composition is not insignificant, but in fact critical to the effects of the host system and health outcome. These outcomes may be positive or negative based on composition, indicating the need for a careful diet regimen for those who wish to take, for example, anti-hypertensive medication. In many cases, patients already have compromised gut micro biome compositions, and thus medication associated effects need to be monitored, for example, *via* fecal samples.

Conclusion

This further has implications on drug dosage and courses, as well as gives a larger understanding of the drug within the host system. Overall, the significance of the gut micro biome in patient treatment cannot be stressed enough. Balanced micro biome profiles have been linked to better lipid profiles, blood pressure, and BMI in those with metabolic syndromes. With an established role of importance, the role of gut micro biome health is crucial in the next steps for cardiovascular health outcomes.

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