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Review Article

Faecal Transplant Therapy: A Promising Treatment Modality for Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVD) are considered as "lifestyle" diseases and so far "No unified procedure" or medicines are effective in the management of this group of diseases. Researchers and clinicians have indicated that no safe therapeutic window is available in therapeutics at present. Recent research showed that gut microbiota are effective in managing lifestyle diseases therefore we introduced the influence of gut microbiota in the prognosis of the CVDs. Faecal transplant therapy(FMT) has been anticipated to treat many diseases similar to recurrent bacterial *Clostridioides difficile* infection which has been used worldwide. Recently, FMT was tried on an animal model to treat CVDs, and recent human trials that were tried to manage CVDs in humans by FMT showed encouraging results. The mechanism of action of transplanted bacteria to manage CVDs in the human population is also discussed. In-depth knowledge on the pros and cons of FMT will pave the way to standardize the procedure once the lacuna existing at present in treating CVDs, is paved, this technology will be useful for the masses.

More Information

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Introduction

Cardiovascular Diseases (CVDs), especially coronary atherosclerosis, arteriosclerosis, Hypertension (HTN), and Heart Failure (HF), are the main causes of death, accounting for a huge health and economic burden on the global population. Inflammation, diabetes, diet, nutritional status, and lifestyle are identified as causal factors for CVDs [1,2].

In arteriosclerosis thickening and stiffening of arteries take place, due to which flow of oxygen and nutrients are restricted [3], whereas in atherosclerosis plaque formation in the arteries takes place which results in high blood pressure, because of high blood pressure there is a possibility for the plaque to burst, resulting a blood clot formation". Hypertension (HTN) is the predominant and most common risk factor associated with stroke and Coronary Heart Disease (CHD). Pregnancy can also increase the risk of developing high blood pressure. Uncared prolonged high blood pressure increases the risk of developing a number of serious long-term health conditions such as damaging the blood vessels in the kidneys or eyes and coronary heart disease.

Decreased blood flow to the heart can cause angina. Heart attack, which happens when the lack of blood supply results in the death of the heart muscles without enough oxygen. Stroke can end up in serious disabilities in speech, movement, and other basic activities and may be fatal. It is well established that adults with diabetes, high blood pressure, or both have a higher risk of developing chronic kidney disease.

The highly diverse gut microbiota maintain the symbiotic relationship of the host and regulates the host immune system [4] The intestinal microbiota maintains epithelial barrier integrity and shapes the mucosal immune system, balancing host defense and oral tolerance with microbial metabolites, components, and attachment to host cells. To avoid aberrant immune responses, epithelial cells segregate the intestinal microbiota from immune cells by constructing chemical and physical barriers, leading to the establishment of host-commensal mutualism [5-6].

Relationship between gut microbiota and CVDs

The gut microbiota has emerged as a critical factor in human health and diseases. In the recent past, published information has provided enough evidence to confirm the relationship between gut microbiota and human Cardiovascular Diseases (CVDs). Widespread modern technological advancements in the scientific world such as metagenomic sequencing and metabolomics [3] provided a platform to collect scientific evidence for the functional significance in maintaining health as well as the involvement of gut microbiota in the prognosis of many human diseases [7-16]. In this review, we focussed

our attention on the relationship between gut microbiota and CVDs. It has also been revealed that intestinal microbiota-related metabolites, such as Trimethylamine-N-oxide (TMAO), Short-Chain Fatty Acids (SCFA), and Bile Acids (BAs), are also related to the development, prevention, treatment, and prognosis of CVDs. Animal models as well as human trials are in vogue to standardize the modality to utilize FMT as an alternative in therapeutics due to the serious side effects of the drugs currently used for the CVDs. The human gut is a huge microbial habitat with hundreds of species of bacteria. The role of biologically active metabolites produced by the gut microbiota in various aspects of host physiology is indispensable to the extent that gut microbiota is given the status of the ninth system of the human body [17]. They are responsible for maintaining the integrity of the intestinal epithelial barrier, regulating immune function [18;10], digesting nutrients, producing vitamins, and preventing the invasion of pathogenic bacteria, which is essential for human health [2]. The dysbiosis of the gut microbiota due to dietary habits, environmental factors, intestinal infections, and other factors leads to intestinal malnutrition, triggers inflammation, and abnormal metabolism a causal factor for the prognosis of CVDs [18].

Gut microbiota and coronary atherosclerosis The connection between gut microbiota and atherosclerosis was already described in 1999, when endotoxin levels, following bacterial translocation, were found to be independently correlated with carotid atherosclerosis measured by duplex ultrasound [19]. Traditional risk factors contribute to about half of the atherosclerotic burden in linear regression and genetics are believed to explain another 10 percent. Microbiota and their many metabolic products may largely account for the rest [20]. For example, DNA of oral microbiota *Veillonella* and *Streptococcus* were found in the plaques of individuals with atherosclerosis, and their abundance correlated with the increased number of these species in the oral cavity [20]. As for gut microbiota, Karlsson, et al. [21] found in 2012 that atherosclerosis is associated with a different gut metagenome [22]. Metagenomic sequencing technique gave evidence that gut microbiota in patients with atherosclerosis differed from healthy individuals, dominated by higher levels of *Streptococcus* and *Enterobacteriaceae* [20]. In addition, the *Roseburia*, *Ruminococcaceae*, and *Clostridium* may regulate the metabolic activity of Bile Acids (BAs) and aromatic compounds, which will further speed up the progression of coronary atherosclerosis [23]. The dysbiosis may aggrevate pro-atherosclerotic effects through metabolism-dependent pathways by altering the production of various metabolites, including TMAO, BAs, serum indoxylate, protocatechuic acid, and Lipopolysaccharide (LPS) [2].

One mechanism of microbiota-mediated atherosclerosis induction is through L-carnitine and phosphatidylcholine (from red meat, cheese, and eggs). These food components are first converted by the microbiota to trimethylamine (TMA), then by the liver into Trimethylamine-N-oxide (TMAO), which increases atherosclerotic burden [24] and promotes a prothrombotic phenotype [25]. Studies have given evidence for the role of TAMO in immune system regulation, cholesterol metabolism, oxidative stress, and inflammatory responses to a certain extent, thereby increasing the risk of coronary atherosclerosis [2]. Faecal transplantation (FMT) of TMAO-rich gut microbiota into germ-free mice was suggested to promote platelet function and arterial thrombosis giving a clue for the role of TMAO in the prognosis of arterial thrombosis [26]. Microbiota can also protect from atherosclerosis, as recently shown when *Akkermansia muniphila* reversed Western diet-induced atherosclerosis and endotoxemia in ApoE-knockout mice [27]. Another recent study in ApoEKO mice showed that the probiotic mixture VSL#3 can protect from atherosclerosis [28]

Gut microbiota and hypertension

Scientific evidence is available for the influence of gut microbiota on the regulation of blood pressure and abnormal bacterial populations may be one of the causal factors for the development of HTN. In fact, compared with healthy individuals, the abundance and diversity of gut microbes in hypertensive patients decreased, instead the genus Prevotella was significantly increased [29]. In addition, an FMT study confirmed that the faecal microbiota of patients with HTN can increase the blood pressure in germ-free mice, revealing a close link between gut microbiota and the regulation of blood pressure [30].

The excessive formation of gut microbiota metabolites is also considered to be a key factor in the occurrence of HTN more than their composition, for example, neurotransmitters produced within the autonomic nervous system by genera *Bifidobacterium*, *Lactobacillus*, *Streptococcus*, and *Escherichia coli* will alter vascular tone, leading to HTN [31]. Higher levels of circulating TMAO are positively associated with a high risk of blood pressure [31]. In turn Liu, et al. [32] found that the use of the *Lactobacillus rhamnosus* G strain can prevent HTN deterioration by reducing the levels of TMAO [31]. HTN is the most common risk factor associated with CVDs, and as the main risk factor for stroke and CHD morbidity and mortality, it has always been a hot topic. Recently, studies have shown that the gut microbiota is involved in blood pressure regulation and that abnormal bacterial populations are associated with HTN [31]. Hence, there exists a link between gut microbiota and HTN.

Gut microbiota and heart failure

Heart Failure (HF) is an irreversible end-stage disease with high mortality, characterized by edema and dyspnoea. Studies have found that patients with HF presented increased levels of pathogenic bacteria such as *Candida* and decreased levels of anti-inflammatory bacteria such as *Faecalibacterium*,

therefore contributing to the development of HF by participating in the regulation of the mucosal immune system [2]. This indicated that there exists a correlation between gut microbiota and HF. Gut microbiota metabolites such as SCFAs, TMAO, indoxyl sulfate, and LPS also play an important role in the development of HF as in atherosclerosis.

In a healthy mouse model, Savi, et al. [33-36] demonstrated that TMAO is responsible for elevated calcium release from cardiomyocytes, thereby disturbing their contractility [36]. The effect can be reversed by increasing the direct dietary TMAO supplementation to elevate systemic TMAO levels. By increasing myocardial fibrosis and inducing HF through NLRP3 inflammations-related signaling, suggesting that TMAO may be a potential target for the treatment of HF [34;35]. Wang, et al. [35] found that 3,3-dimethyl-1- butanol (DMB) ameliorated adverse cardiac structural remodeling in overload-induced HF mice by down-regulating TMAO levels [35]. Indoxyl sulfate exacerbates cardiac fibrosis, cardiomyocyte hypertrophy, and atrial fibrillation [2].

Microorganism-targeted therapies Studies on animal models as well as human trials suggest a strong influence of the gut microbiota on CVDs, the relationship between pathophysiology and gut microbiota is still unverified. A standardized alternative approach in therapeutic is wanting to escape from the side effects of antibiotics. Worldwide though there existed several microorganism-targeted therapies used in CVDs earlier, now the focus is to accumulate in-depth knowledge from human trials as well as animal models. FMT refers to the replacement of enteric pathogens by introducing the fecal contents of healthy subjects into the gastrointestinal tract of patients [35]. To elucidate the influence of the gut microbiota on atherosclerosis pathogenesis caused by genetic deficiency an atherosclerosis-prone mouse model (C1q/TNF-related protein 9-knockout (CTRP9-KO) mice) was generated. Kim, et al. [36] used mice model FMT to eliminate the increased Bacteroides/Firmicutes ratio ultimately reducing inflammation in cardiomyocytes and myocarditis [36;37]. In a previous study of oral and gut samples from patients with atherosclerosis, the abundance of *Veillonella* and *Streptococcus* in atherosclerotic plaques correlated with their abundance in the oral cavity, suggesting that the plaque microbiota may correlate with disease markers of atherosclerosis [18]. Furthermore, patients with symptomatic atherosclerosis had a higher relative abundance of Anaeroglobus in the oral microbiota than asymptomatic atherosclerosis controls [38]. In a previous study, Kim, et al. [37] found patients with asymptomatic atherosclerosis enriched with *Collinsella* genus but *Roseburia* and *Eubacterium* were more in healthy controls [38;39]. The probiotic bacterium *Akkermansia muciniphila* attenuates atherosclerotic lesions by improving metabolic endotoxemia-induced inflammation by restoring the gut barrier [25]. Two other dominant species of the genus *Bacteroides vulgatus* and *Bacteroides dorei*, have also been observed to be beneficial since they are capable of impairing the formation of atherosclerotic lesions in atherosclerosis-prone mice, markedly ameliorating endotoxemia, decreasing gut microbial lipopolysaccharide production, and effectively suppressing proinflammatory immune responses [40]

CTRP9-KO mice protected against the progression of atherosclerosis. In turn, the transplantation of CTRP9-KO microbiota into WT mice promoted the progression of atherosclerosis. Kim, et al. [37] proved in into CTRP9-KO mice CTRP9 gene deficiency is related to the distribution of the gut microbiota in subjects with atherosclerosis. Transplantation of WT microbiota into CTRP9-KO mice protected against the progression of atherosclerosis. Conversely, the transplantation of CTRP9-KO microbiota into WT mice promoted the progression of atherosclerosis. In other words, the effect is two-way since genetic variations that affect atherosclerosis alter the composition of the gut microbiota and altered gut microbial composition affects the progression of atherosclerosis, giving a clue to suggesting that fecal microbiota transplantation may help to prevent atherosclerosis. In this study, Kim, et al. [37] also showed that mutations in the genetic background can alter the composition of the gut microbiome and result in atherosclerosis. In such a situation, FMT from healthy donor stool can protect against this disease in CTRP9-deficient mice. These observations from experimental studies indicate the possibility of controlling gut microbial composition to treat arteriosclerosis caused by genetic deficiency. *Akkermansia muciniphila, B. vulgatus*, and *B. dorei* did not show any differences between KO and WT control mice in this study. This is probably due to differences in the relative abundances of the dominant gut microbiota in mice and humans. This result may also be due to a deficiency of the CTRP9 gene [37].

From clinical trials, promising results were observed for FMT to restore the gut microbiota of healthy people after the use of antibiotics quickly [41]. For the fear of transferring endotoxins or infectious agents resulting in the development of new gastrointestinal complications during FMT therapy, currently, this technique is not encouraged for treating CVDs [2]. Dietary intervention to regulate the treatment of CVDs has broad prospects since fibre-rich diets have been proven to improve the growth of beneficial symbiotic bacteria and inhibit the growth of opportunistic pathogens [42]. Xiao, et al. [43] suggested that whole grains and traditional Chinese medicine foods can reduce *Enterobacteriaceae* pathogenic bacteria and increase intestinal protective bacteria such as *Bifidobacterium* [42]. In addition, acetic acid-producing microbiota thrives well in high-fiber diets which in turn lowers blood pressure [44]. The fibre-rich diet gives an additive value to the enhancement of beneficial bacteria in the host gut [45]. It was found that *Bifidobacterium breve* and *Lactobacillus fermentum* may have antihypertensive effects by restoring gut microbiota balance and preventing endothelial dysfunction [46]. Lam et al. [47] were surprised to find that *Lactobacillus plantarum* improves ventricular function and reduces myocardial infarction size

[46]. In the myocardial ischemia rat model also similar results were obtained when treated with *Lactobacillus rhamnosus* GR-1 [48]. *Saccharomyces boulardii* reduces the level of inflammatory markers and serum creatinine, with promising results in patients with HF [49]. Furthermore, resveratrol from *Polygonum cuspidatum* can alleviate Trimethylamine-N-Oxide (TMAO) induced atherosclerosis by remodeling the microbiota and reducing TMAO levels [50]. Besides, exercise proves to be a booster from Firmicutes to Bacteroides, increasing the number of bacterial metabolites preventing myocardial infarction. However, the effects of exercise on the gut microbiome are transient and reversible [2].

Additionally, Berberine, Coptis chinensis, can modulate the gut microbiota, which in turn affects CVDs [51]. In summary, Microorganism-targeted therapy mainly regulates CVDs through FMT, dietary interventions, and probiotics.

Conclusion

The involvement of gut microbiota in the occurrence and development of CHD, HTN, and HF has been proved in a large number of studies. Gut microbiota influences CVDs through immune regulation, the inflammatory response, gut barrier integrity, and metabolic homeostasis. CVDs, in turn, also affect the structure and function of the gut microbiota. The two-way effect between Microbiota and CVDs, and the mechanism of action through metabolic pathways has been well studied. At present, most studies are based on animal experiments to correlate the involvement of gut microbiota in the prognosis of CVDs. In-depth studies based more on human trials and clinical studies alone will be helpful to standardize procedures like FMT on recurring *Clostridioides difficile* infection. Some approaches based on gut microbiota for the treatment of CVDs are still in clinical trials and have potential advantages as well as limitations. Therapeutic strategies to improve the gut microbiota are potential avenues for the treatment of CVDs.

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