Review

The gut microbiome and atherosclerosis

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Abstract

The importance of the microbiome in the pathogenesis of metabolic diseases such as diabetes, hypertension, dyslipidaemia, obesity and cardiovascular diseases are emerging. The gut microbiome, once thought to have a limited function of producing vitamins and in bile acid metabolism is now known to be important in regulation of the gut barrier function, development and regulation of the immune system, glucose and lipid metabolism, synthesis of neurotransmitters and even regulation of our circadian rhythms. The composition and relative abundance of different microbiota play a pivotal role in health and disease. Microbial dysbiosis, which is characterized by reduced diversity of the microbiome with overabundance of bacteria of the Proteobacteria phyla, is associated with development of metabolic disease, autoimmune diseases, neuropsychiatric diseases and allergies. Such dysbiosis leads to metabolic endotoxemia resulting in a chronic inflammatory state and also leads to altered lipid and glucose metabolism. Dysbiosis also leads to production of certain atherogenic substances such as trimethylamine *N*-oxide that lead to development of cardiovascular disease. Many factors such as diet, physical activity, antibiotics, sleep deprivation and the environment influence the composition and variability of our microbiome. The human microbiome project, which is currently underway is likely to shed more light on the importance of this largely neglected commensal flora.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in Sri Lanka in recent years resulting in 28.5 deaths/100,000 population in year 2016 [1]. Metabolic diseases such as diabetes, dyslipidaemia, hypertension and obesity along with physical inactivity are known to be the main risk factors of development of atherosclerosis. Atherosclerosis is a chronic inflammatory disease which is initiated by endothelial dysfunction and activation, leading to influx of monocytes, mast cells and T cells into the intima of medium and large arteries. In these sites these monocytes differentiate into lipid loaded macrophages subsequently resulting in atherosclerotic plaques [2]. Low grade endotoxaemia (presence of bacterial lipopolysaccharides) leading to a chronic inflammatory state, has shown to be an important mediator of atherosclerosis [3]. Certain types of gut microbiota have also shown to initiate and aggravate atherosclerosis by production of pro-atherogenic substances such as trimethylamine *N*-oxide (TMAO) [4]. The changes in the gut microbiome that lead to chronic low grade endotoxaemia and how the composition of the gut microbiome leads to development of atherosclerosis and associated metabolic diseases are described below.

The gut microbiome

More than trillions of microbes colonize our body at a given time and the collection of their genome is known as the human microbiome [5]. The gut microbes are the largest component of the microbiome, and the importance of the type and relative abundance of different microbial species in health and in causing disease is emerging [5, 6].

Many factors influence the composition of our gut microbiome such as the diet, genetic makeup, antibiotic usage, physical activity and our lifestyle such as occupation, sleep, stress and pets [5]. The gut microbiota establishes itself after birth and stabilizes around two to three years. It becomes most diverse by adult life with the predominant microbial genera being Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria [7]. The gut microbiome directly influences the development of our immune system and is responsible for at least 10% of the variability of the immune response [5]. They also play an important role in fermenting unabsorbed starch and dietary fiber to generate short chain fatty acids (SCFAs) that act as a source of energy, and are involved in many metabolic and biochemical processes in the host [6]. SCFAs such as butyrate produced by certain bacteria play a crucial role in maintaining gut barrier function and has many anti-inflammatory properties [7].

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A dysfunctional gut barrier results in certain microbial products such as LPS entering the circulation resulting in a chronic low grade endotoxemia and an altered immune response to gut microbiota resulting in allergy and autoimmunity [6].

Gut microbiota also synthesizes many vitamins such as vitamin K2 (menaquinone), vitamin B5 and vitamin B12. Vitamin K2 plays a vital role in reducing calcification of the vasculature and elevated HDL levels and reduces total cholesterol levels [6]. Vitamin B5 and B12 which are exclusively produced by the gut microbes act as a co-enzymes in many biochemical reactions in the host and are required for the normal function of the immune system [6]. Therefore, reduction in the bacterial populations that synthesize these vitamins and certain SCFAs have been implicated with conditions ranging from gastrointestinal discomfort and irritability, insomnia, haematological changes and neuropsychiatric disorders [8]. Due to the diverse functions of the gut microbiome, microbial dysbiosis has been implicated in metabolic diseases such as diabetes, hypertension, CVD, cancers such as colonic cancer, autoimmune diseases such as inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, atopic diseases and neurological diseases such as Alzheimer's disease, Parkinson's disease, autism spectrum disorders and depression [6, 9, 10]. A summary of the functions of the gut microbiome is shown in Figure 1.

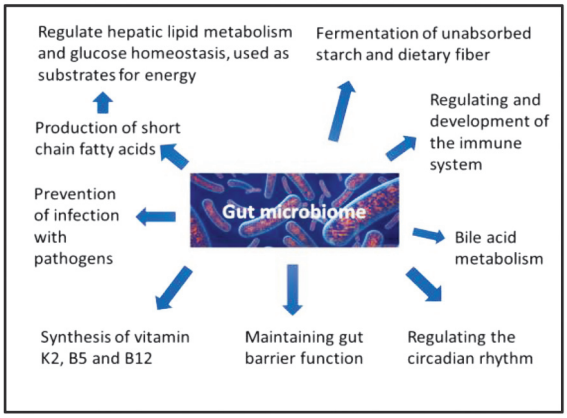

Figure 1: A summary of the functions of the gut microbiome. The gut microbiome has numerous functions including fermentation of complex carbohydrates and fiber generating energy, short chain fatty acids important in glucose and lipid metabolism, synthesis of vitamins, regulating the immune system, regulating circadian rhythms, synthesis of neurotransmitters, bile acid metabolism and prevention of infection with pathogens.

Gut microbiome and metabolic diseases

The diversity of the gut microbiome plays a crucial role in the development of metabolic diseases. The low diversity of gut microbiota has shown to associate with obesity, insulin resistance, dyslipidaemia and development of many inflammatory diseases [11]. Interestingly, the microbiome signature (the relative abundance of different genera of microbiota), is so vastly different between obese and lean individuals, that obese and lean individuals can be classified with >90% accuracy, based on their microbiome signature alone [12].

It is well established that metabolic diseases such as type 2 diabetes mellitus, insulin resistance and obesity occur as a result of low grade chronic inflammation due to the presence of lipopolysaccharide (LPS)[13]. These diseases are characterized by an increase in inflammatory cytokines and markers of acute phase reactive proteins such as C-reactive protein [13]. This low grade endotoxaemia (low levels of LPS in sera)[14], which is seen in individuals with metabolic diseases has shown to associate with the composition of the gut microbiome[15]. The LPS derived from the cell walls of many gram-negative bacteria enter the circulation due to the dysfunctional gut barrier. This LPS activates many types of cells in the immune system such as macrophages, monocytes, mast cells, activating them and inducing production of inflammatory mediators [15]. Diets rich in fat stimulate the growth of 'harmful' microbiota in the gut, while simultaneously reducing the microbiota which are important for maintaining the intestinal barrier [15]. Apart from their action on immune cells, LPS and possibly other metabolites from the gut microbes are thought to act on adipose tissue, influencing the type and quantity of adipokines produced by it [16]. For instance, gut microbes have shown to be important in mediating the action of leptin, which is an adipokine with a wide range of immune-metabolic functions [16].

Blood LPS has also shown to act on the kupffer cells in the liver and is known to play an important role in the development of non-alcoholic fatty liver diseases (NAFLD) [17]. LPS activates many inflammatory pathways in the kupffer cells and other types of hepatic macrophages, leading to production of many inflammatory mediators subsequently resulting in liver injury and fibrosis [17].

This dysbiosis that predisposes to many of the above metabolic diseases is associated with an increased abundance of the genera Proteobacteria, along with a reduction of Bacteriodetes and an overabundance of Firmicutes. Diets rich in fat, refined carbohydrates and poor in fibre have been shown to increase the population of Proteobacteria along with artificial sweeteners and emulsifiers[18]. Indeed, studies done by us in Sri Lankan individuals with type 2 diabetes show that despite the differences in dietary patterns and genetic composition, our patients too have an overabundance of Enterobacterciae (bacteria of Proteobacteria genera)[19]. Apart from metabolic diseases, an overgrowth of Proteobacteria is seen in many inflammatory diseases (inflammatory bowel diseases) and certain cancers [18]. A summary of the mechanisms by which microbial dysbiosis leads to metabolic diseases is shown in figure 2.

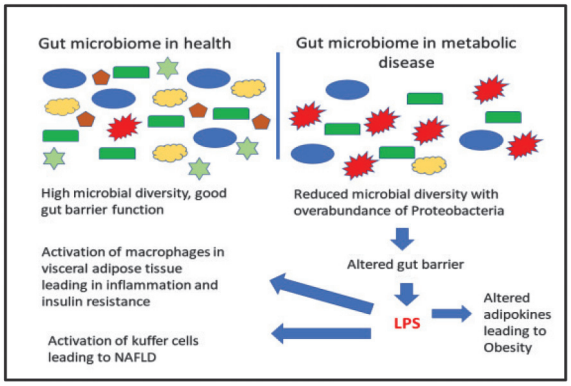

Figure 2: Microbial dysbiosis leading to metabolic diseases. Microbial dysbiosis is associated with a reduced diversity of the gut microbiome with an overabundance with bacteria of the Proteobacteria phyla. This results in gut barrier dysfunction and LPS entering the circulation. LPS stimulates immune cells in visceral adipose tissue and in many other sites in the body resulting in an increase in inflammatory mediators which cause insulin resistance, altered lipid metabolism and gluconeogenesis. Altered production of adipokines leads to changes in lipid metabolism and appetite causing obesity. LPS also acts on kuffer cells in the liver, thereby activating them and causing liver injury and fibrosis.

Gut microbiome and atherosclerosis

Elevated levels of Trimethylamine N-oxide (TMAO) has shown to associated with an increased risk of developing CVD [20,21]. Microbial dysbiosis has shown to contribute to atherosclerosis by production of proatherogenic metabolites such as TMAO, which are derived from the bacterial breakdown of meat-derived products, fish and food rich in phosphatidylcholine [4].

Bacteria are absolutely necessary for generation of TMAO from meat products and fish [22].

Increase in Enterobacteriaceae (Proteobacteria genera) and a decrease in the abundance of *Faecalibacterium prausnitzii* was significantly associated with higher levels of TMAO [4]. The increased abundance of pathogenic microbiota such as Enterobacteriaceae, Streptococcus, and Desulfovibrio are thought to further contribution to increased TMAO levels in serum by inducing the dysfunction of the intestinal barrier [4].

As seen with development of metabolic diseases, a reduction in the microbial diversity was shown to be an independent risk factor for development of CVD [23]. It was shown that species of the Prevotellaceae family, Lachnospiraceae family and Veillonellaceae and Erysipelotrichaceae families were associated with a several fold increase in the lifetime risk of development of CVD [23]. This data again shows that disturbance in the relative abundance of the main bacteria genera, with as overabundance of Proteobacteria was associated with CVD. Another prospective study, which examined the relative abundance of Proteobacteria in relation to other bacteria genera showed that an overabundance of Proteobacteria was associated with an increased risk of developing acute cardiovascular events [24]. Collectively, these data show that microbial dysbiosis is an independent risk factor for development of CVD and is an important risk factor for development of comorbidities associated with CVD such as diabetes mellitus, obesity and dyslipidaemia.

Effect of diet on the gut microbiome

The diet significantly influences the composition of the gut microbiome since birth. While an individual's genes are thought to be responsible approximately 12% of the changes in the composition of the gut microbiome, diet accounts for 57% of the changes seen [25]. The gut microbiome changes throughout life and is dependent on the method of delivery, whether the baby is breast fed or formula fed, and later in life the relative composition of the diet, i.e. whether the diet is predominantly plant based or animal based. For instance, while the predominant microbial genera in breastfed babies is Bifidobacteria, in those who were formula fed, Escherichia coli, Clostridium difficile, Bacteroides fragilis and Lactobaccili are the predominant genera [26].

Although after weaning the gut microbiome is relatively stable, the composition of the microbiome is largely affected by the diet [27].

The microbiome is vastly different in those who consume a predominantly animal-based diet, compared to those with a vegetable-based diet, [27]. Individuals who predominantly consume a Mediterranean diet, rich in grains, legumes, nuts, vegetable and fruits were found to have bacteria which produce high levels of short chain fatty acids (SFCAs), which are known to have a protective effect against metabolic diseases, inflammatory bowel disease and colonic cancer [28]. In contrast, those who consumed an animal-based diet had an increased abundance of bacteria resulting in intestinal inflammation and also higher urinary levels of TMAO associated with atherosclerosis [27, 28]. An increase in the content of dietary fiber correlates with production of SCFAs by certain bacteria and also associates with an increased bacterial diversity [11]. In fact, it has been shown that the gut microbiome of African children who consume very high fiber diets are enriched with certain bacterial species such as Prevotella and Xylanibacter, which are the main producers of SCFAs such as butyrate [29]. Most individuals living in Western countries who consume largely a diet very poor in fiber completely lack these type of beneficial bacteria [29]. SCFAs have potent anti-inflammatory roles by inhibiting transcription of inflammatory genes and reducing inflammatory cytokine production, which are known to associate with cardiometabolic diseases [29].

Lifestyle and gut microbiome

The beneficial effects of physical activity in reducing the incidence of metabolic diseases and reducing the risk of CVD and its complications are well established. Although the beneficial effects of exercise can be largely attributed to the reduction of insulin resistance, proportion of visceral fat, cardiac remodeling and improvements in aerobic capacity [30, 31] recent evidence shows that exercise has marked effects on the gut microbiome as well [32]. Professional athletes were shown to have a highly diverse gut microbiome that associates with good health when compared to age and gender matched controls who were mostly physically inactive [33].

However, as professional athletes are likely to be given very healthy diets rich in vegetables, fruits and high in protein and complex carbohydrates compared to their physically inactive peers, the effect of exercise alone on the gut microbiome needs further evaluation.

Reduction in the duration and quality of sleep is well known to be associated with many metabolic diseases such as diabetes, obesity and CVD [34]. Apart from metabolic diseases, sleep deprivation and altered circadian rhythms have shown to be risk factors for development of many functional and neuropsychiatric diseases [35]. Apart from humans, the gut microbiota too display circadian rhythms, and the function and the metabolites produced by the microbiota changes throughout the day based on this rhythm [35]. The circadian rhythms generated by the gut microbiota has shown to interact with the human genes governing circadian rhythms and thereby influences the transcription of these genes and also induces epigenetic modification in them [36]. Sleep deprivation and shift work has shown to have direct impacts on the gut microbiome, and its circadian rhythms, which in turn result in marked changes in human circadian gene transcription patterns [35].

Dogs have been ‘man’s best friend’ since Stone Age. It has been shown that those who live on farms and who own pets are less likely to develop asthma and other atopic diseases [37]. Studies have now shown that owning a pet, and especially dogs, is associated with the development of a more diverse, ‘healthy’ gut microbiome [37]. Young children who were exposed to pets during early infancy had a higher abundance of the species *Oscillospira and Ruminococcus,* both which have been associated with a reduced risk of asthma and occurrence of obesity [38].

Finally, the environment too influences the gut microbiome and those living in rural areas have shown to have markedly different gut microbiota compared to genetically similar, aged and gender matched individuals living in built up city areas [39]. Although the diet, changes in levels of physical activity, changes in sleep pattern etc. are all likely to account for these differences, the importance of the environment in influencing the composition of our gut flora is emerging [39].

In summary, the gut microbiome which comprises of trillions of cells, influence our metabolic health, our immune system and also our cognition and mood. Since the time early man evolved, the microbiome evolved with us and is likely to have had a significant impact on who we are today. The importance of this largely neglected commensal flora is emerging and the human microbiome project, which is currently underway is likely to shed more light on how these microbes influence us.

However, it is clear that recent changes in human behavior such as changes in diet, physical activity, sleep patterns and exposure to the environment appear to lead to dysbiosis of our microbiome leading to a vast array of diseases.

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