Environment, Gut Microbiota, and CAD

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Gut microbiota has been shown to affect the cardiovascular system through different mechanisms, representing a potentially modifiable risk factor for atherosclerosis. This opens new perspectives on therapeutic and preventive strategies for coronary artery disease (CAD). Gut microbiota strongly varies depending on several environmental and lifestyle factors, such as pollution and diet, and maintains a symbiotic relationship with the gut mucosa, with substantial metabolic, immunological, and gut protective functions in the healthy individual.

gut microbiota | coronary artery disease | trimethylamine-N-oxide | short-chain fatty acids | lipopolysaccharides | pollution | Western diet

1. Introduction

Coronary artery disease (CAD) is the leading cause of mortality in Western societies, affecting about one-third of the population before the age of seventy [1]. Over the past decades, several risk factors for CAD have been identified, including smoking, hypertension, hypercholesterolemia, diabetes, and obesity [2]. Despite the increasing ability to correct such factors, the incidence of heart diseases remains high and they still represent the major cause of mortality. Therefore, research has recently focused on finding new risk factors so as to identify alternative therapeutic strategies and prognostic indexes. Among these, the gut microbiota.

The hypothesis that microorganisms can influence coronary atherosclerosis was first proposed a long time ago, when, in 1978, Fabricant et al. demonstrated that Marek's herpes virus could cause atherosclerosis in chickens [3]. They subsequently observed that such an atherosclerotic effect could be prevented by vaccination, thus revealing the therapeutic potential of these experiments [4]. Since then, many microorganisms have been associated with coronary atherosclerosis, and some of them are also thought to act with a direct mechanism: the presence of bacterial deoxyribonucleic acid (DNA) in human atherosclerotic plaques has been demonstrated, especially of microorganisms from the oral cavity [5][6] or the respiratory tract [7]. In other cases, microorganisms such as HIV or Helicobacter Pylori can cause chronic inflammation that predisposes to the development of atherosclerosis [8][9].

2. Gut Microbiota Composition in CAD Patients

Although a close relationship between gut microbiota and atherosclerotic plaque formation has not yet been demonstrated, the latest evidence confirms that an abnormal microbiota predisposes to the development of CAD [10] and that gut bacterial composition differs in CAD patients compared with healthy patients; the results are,

however, not homogeneous in terms of specific differences. A study analyzed fecal metagenomes of 12 patients with symptomatic atherosclerotic plaques showing an increase in the abundance of *Collinsella* and a reduction in the abundance of *Eubacteria*, *Roseburia* and Bacteroides species compared with the control group [11]. Emoto et al. reported an increase in *Lactobacillales* and a reduction in the abundance of Bacteroidetes phylum (*Bacteroides* + *Prevotella*) in CAD patients [12].

3. TMAO, Microbiota, and CAD

One of the most studied mechanisms behind the association between gut microbiota and cardiovascular diseases involves TMAO. When large quantities of choline, carnitine, betaine, and other choline-containing compounds are ingested, intestinal bacteria degrade them into trimethylamine (TMA) which passes into the portal circulation and is then metabolized in TMAO by flavin-containing monooxygenase (FMO) enzyme in the liver [13]. Several studies have shown a direct correlation between TMAO levels and coronary atherosclerosis [14][15]. In fact, TMAO has a positive correlation with metabolic syndrome [16] and with age, BMI, total and LDL cholesterol, apolipoprotein B levels and tumor necrosis factor (TNF) alpha levels [17].

4. SCFAs, Microbiota, and CAD

Gut microbiota can also play a protective role against coronary atherosclerosis through the synthesis of SCFAs. SCFAs are the main products of intestinal fermentation of dietary fibers, and acetate, propionate, and butyrate are the most abundant [18]. These SCFAs can bind to a lot of G-protein coupled receptors (GPR) and may have an anti-inflammatory and immunomodulatory effect depending on this bond. Acetate is produced by many intestinal bacteria while only a few members of the families *Veillonellaceae* and *Lachnospiraceae* are propionic acid-producing bacteria, and butyrate is synthesized by *Coprococcus*, *Faecalibacterium*, *Eubacterium*, and *Roseburia* [19].

5. LPS, Microbiota, and CAD

Gut microbiota can trigger the immune system and atherosclerosis through Toll-like receptor (TLR) activation by LPS. LPS, also called endotoxin, is a Gram-negative bacteria membrane component and its correlation with the atherosclerotic process has been demonstrated long ago in experimental mice models [20], through induction of a low-grade inflammation [21]. A recent metagenomic analysis conducted by Zhou et al. has compared 100 STEMI patients with 49 healthy control and 50 stable CAD subjects, proving that the production of LPS increases in the first group and assuming that it may be due to a raise in intestinal permeability [22].

6. Pollution, Microbiota and, CAD

It is well known that one of the most important risk factors for cardiovascular disease is environmental pollution, meaning gas emission of chemical contaminants [23]. This is mainly because exposure to environmental pollutants

promotes a systemic vascular oxidative stress reaction and a rise of radical oxygen species which induce endothelial dysfunction, monocyte activation and changes in lipoproteins [24]. Recent studies are revealing how pollution not only directly affects the composition of gut microbiota but also regulates its interaction with the immunity system and production of metabolites involved in atherosclerosis [25].

Exposure to heavy metals is associated with a large number of toxic effects, even on the cardiovascular system [26]. Different studies observed that mice exposed to cadmium have significant changes in gut microbiota, an increase in LPS production and an alteration in bile acid formation [27][28]. Some pesticides that contaminate food, water and soil can induce a gut dysbiosis that promotes a pro-inflammatory state and metabolic disorders: exposure to carbendazim, a broad-spectrum benzimidazole fungicide, changes gut microbiota composition and reduces the level of serum lipoprotein lipase, altering lipid metabolism [29]. Particulate matter air pollution, a combination of elements, heavy metals, polycyclic aromatic hydrocarbons and inorganic ions [30], has been associated with a spectrum of disease which goes from lung cancer to hypertension [31][32] and can also affect the gut microbiota, leading, again, to an increase in inflammatory response as revealed in studies conducted on murine models [33][34].

7. Diet, Microbiota, and CAD

In more than 4000 patients undergoing coronary angiography, a strong association was found between fasting plasma levels of TMA and the incidence of adverse cardiovascular events [35]. As previously described, TMA, rapidly oxidized into TMAO, is a gut microbe-dependent metabolite mainly generated from dietary choline and L-carnitine. These dietary components are found in a high variety of foods. The richest sources are meat, fish, poultry, dairy, and eggs, representing predominant food groups of a Western diet. Moreover, elevated TMAO levels were observed over a 4-week interval in individuals consuming a high-fatty diet compared to individuals consuming a low fatty diet [36]. Thus, a Western diet may increase circulating TMAO levels leading to cardiac inflammation and fibrosis, contributing to cardiac dysfunction. Dietary L-carnitine chronic supplementation could accelerate CAD by altering the microbial composition [37].

On the other hand, the Mediterranean diet is well known to be an optimal dietary prevention of cardiovascular events [38][39]. Specifically, greater adherence to a Mediterranean diet showed a beneficial role on reducing TMAO levels [38]. Moreover, a high-fiber diet increased SCFA levels, including levels of acetate. Interestingly, dietary intake of fiber and supplementation with acetate could modulate cardiac molecular pathways beneficial for cardiovascular function, lowered blood pressure, decreased cardiac hypertrophy and fibrosis, and improved heart function in experimental hypertension [40].

8. Probiotics, Microbiota and CAD

As shown by several studies, probiotics exert a protective effect against CAD, mainly through a positive impact over all the main risk factors for atherosclerosis. Recent evidence, in fact, points out that regular consumption of

probiotics would provide beneficial effects in lowering low density lipoprotein (LDL) cholesterol, blood pressure, inflammatory mediators, blood glucose levels, and body mass index [41].

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