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REVIEW ARTICLE

From obesity through gut microbiota to cardiovascular diseases: a dangerous journey

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Abstract

The co-existence of humans and gut microbiota started millions of years ago. Until now, a balance gradually developed between gut bacteria and their hosts. It is now recognized that gut microbiota are key to form adequate immune and metabolic functions and, more in general, for the maintenance of good health. Gut microbiota are established before birth under the influence of maternal nutrition and metabolic status, which can impact the future metabolic risk of the offspring in terms of obesity, diabetes, and cardiometabolic disorders during the lifespan. Obesity and diabetes are prone to disrupt the gut microbiota and alter the gut barrier permeability, leading to metabolic endotoxaemia with its detrimental consequences on health. Specific bacterial sequences are now viewed as peculiar signatures of the metabolic syndrome across life stages in each individual, and are linked to pathogenesis of cardiovascular diseases (CVDs) via metabolic products (metabolites) and immune modulation. These mechanisms have been linked, in association with abnormalities in microbial richness and diversity, to an increased risk of developing arterial hypertension, systemic inflammation, nonalcoholic fatty liver disease, coronary artery disease, chronic kidney disease, and heart failure. Emerging strategies for the manipulation of intestinal microbiota represent a promising therapeutic option for the prevention and treatment of CVD especially in individuals prone to CV events.

Introduction

The World Health Organizations affirmed that cardiovascular diseases (CVDs) are responsible for the death of 17.9 million people per year, which corresponds to 31% of all deaths [1]. Of these, 85% are attributed to heart attack and stroke. The spectrum of noncommunicable disorders generally classified as CVDs includes arterial hypertension, coronary artery disease (CAD), and cardiomyopathies that promote heart failure (HF) and cerebrovascular diseases in later stages. Vasculature instabilities at the level of endothelial function and arterial stiffness can instigate the development of CVDs. Significant progress has accompanied our recent understanding of the relationship linking gut microbiota to metabolic disorders, particularly diabetes, and obesity, foretelling the onset and progression of CVDs. This review will explore the main findings supporting a functional role for gut microbiota in the pathophysiology and progression of CVDs and their metabolic correlates. Insights on therapeutic approaches aiding microbiota restoration in connection with CVD will also be discussed.

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Background, molecules and mechanisms of microbiota actions

The microbiota are a complex ecosystem composed of about 10^{14} microorganisms. They include bacteria, eukaryotes, viruses, and archaea, located in body regions that interact with the external world such as the skin and organs belonging to the respiratory, gastrointestinal, and urogenital systems. Up to 80% of microbiota is represented by *Firmicutes* and *Bacteroidetes* [2], with other phyla including *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, and *Fusobacteria*. The whole genetic heritage of the microbiota, the microbiome, approximately encloses 3.3 millions of genes. High-throughput sequencing technologies have dramatically improved our understanding of the complex relationship linking the microbiome to the host through the encoding of multiple active metabolites that are capable of bidirectional interactions, both at the molecular and cellular level. The human microbiota work as a dynamic entity competent for self-modulation (resilience and resistance phenomenon) in response to external stressors during conventional life events [3]. Exogenous factors occurring early in life like the type of birthing, the type of milk feeding, antibiotics, and dietary habits can influence intra- and interindividual qualitative and quantitative variability of microbiota. Intrinsic factors are also known to modulate microbial composition and abundance, such as pH, gut motility, mucus, and antimicrobial peptides. Arumugam et al. [4] proposed the division of the human microbiota into three main subgroups, termed enterotypes. These include *Bacteroides*, *Prevotella*, and *Ruminococcus*, which shape the individual *core microbiota* and tend to remain stable after temporary perturbations.

Locally, an adequate gut microbiota is key to maintain unaltered the integrity and permeability of the intestinal epithelial barrier. At the systemic level, gut microbiota contribute to promote the maturation of the enteric nervous system, develop innate and adaptive immunity, and maintain body homeostasis [5–8]. Metabolic phenotyping of microbiota enterotypes displays intrinsic functions that, depending on bacterial strain prevalence, are instrumental to (a) help the host to absorb fats and fat-soluble vitamins contained in the diet, (b) digest complex carbohydrates and plant polysaccharides via enzymes that are not expressed by the human genome, and (c) partake in bile acid-related metabolism. Intestinal processing through fermentation of different nondigestible food components present in the human diet by colonic microbes leads to the production of short-chain fatty acids (SCFAs; acetate, propionate, and butyrate), trimethylamine-N-oxide (TMAO), bile acids, incretin hormones, polyamines, polyphenols, and vitamins. In turn, SCFAs act as signaling molecules and source of energy for colonic epithelial cells [9, 10]. Other molecules can trigger genetic and epigenetic pathways so as to promote the reprogramming of the cell genome in response to environmental stimuli, or to shape the immune system during the weaning phase [11]. In physiological conditions, the activity of the gut microbiota and the stability of the gut barrier are preserved through the function of tight junction proteins, a normal endocannabinoid system tone and lipopolysaccharide (LPS) detoxification by intestinal alkaline phosphatase [12]. LPS is a microorganism-derived proinflammatory component that is continuously released into the colon upon the death of gram-negative bacteria. High-fat diet (HFD) is particularly effective in altering microbiota composition [13] and favor LPS absorption across the intestinal barrier through chylomicrons [14], thereby prompting a condition of systemic inflammation. A healthy lifestyle and an appropriate dietary intake are thus essential components for the balance between microbiota and host.

Quantitative and qualitative alterations of microbiota communities, a condition often referred to as dysbiosis, has been shown to be associated with several human disorders such as obesity, diabetes mellitus, CVDs, asthma, inflammatory bowel disease, as well as neurodegenerative and psychiatric disorders. A metagenome-wide association study (MGWAS) on people with type 2 diabetes showed a moderate degree of gut microbial dysbiosis, decreased butyrate-producing bacteria and increased opportunistic pathogens conventionally capable of inducing bacteraemic infections (*Bacteroides caccae, Cl. hathewayi, Cl. ramosum, Cl. symbiosum, Eggerthella lenta*, and *E. coli*), as well as an enrichment of other microbial functions conferring sulfate reduction and oxidative stress resistance [15].

The role of metabolic phenotypes

Obesity and diabetes are accepted emblems of metabolic impairment. However, obesity is per se a heterogeneous condition, as exemplified by different phenotypes that can be identified in association with metabolic and CVD risk. Recognizing the significance of this spectrum is key to understand the varying degree of metabolic impairment associated with nonobese and obese phenotypes. These include metabolically unhealthy obese (MUO), metabolically healthy obese (MHO), and normal weight obese subjects (NWO) [16]. MUO are generally characterized by a body mass index (BMI) > 30 kg/m^2, high visceral fat mass, increases in proinflammatory adipocytokines exacerbating adipose tissue (AT) dysfunction, proatherogenic state, and dyslipidemia. Hence, MUO individuals are particularly prone to develop type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), and atherosclerotic CVD [17–20]. Conversely, MHO individuals show a BMI > 30 kg/m^2 with a percentage of body fat (BF) mass > 30% and waist circumference > 90 cm, but they harbor normal lipid and BP

profiles, and show a rather healthy insulin sensitivity [21]. Patients with the MHO profile are thus less exposed to the risk of metabolic complications normally associated with obesity, possibly as the result of early-onset obesity (<20 years), which would allow implementation of adaptive mechanisms and preserve insulin sensitivity. Also relevant is the proportion of visceral fat and its related detrimental effects on insulin sensitivity, being relatively lower in MHO than in MUO. However, when endothelial parameters of MHO are plotted against those of lean subjects, an increase in intima media thickness and a reduced endothelial function can be documented in MHO subjects, in spite of their apparently normal metabolic profile [22]. Moreover, lifestyle and diet change have no effect on BMI modifications in these subjects [23].

As far as the NWO phenotype is regarded, this describes the profile of subjects with normal body weight and BMI (<25 kg/m^2) who harbor an increased total body fat mass percentage (>30% in female; >25% in male) [24, 25]. The NWO phenotype thus presents with normal weight and metabolically healthy AT excess, but is characterized by chronic low-grade inflammation and is thus at increased risk for CVDs. In addition to NWO, researchers have also conceptualized another metabolic phenotype represented by persons with metabolically obese normal weight (MONW), in whom premature cardiometabolic impairment hyperinsulinemia, dyslipidemia, and propensity to increased CVD risk may occur in spite of a normal BMI [26–28]. In particular, NWOs do not carry the overtly adipose body composition of MHOs, and are distinguished from MONWs owing to a relatively healthier metabolic profile that does not predispose them to the metabolic syndrome. However, NWO are exposed to the consequences of a chronic low-grade inflammatory state. Individuals with NWO show, in fact, increased circulating levels of interleukin (IL)-1α, IL-1β, IL-6, IL-8, and tumor necrosis factor-α, which are correlated with the increased fat mass percentage [29]. In addition, CV risk markers are borderline normal in NWO whereas some CVD risk indices, i.e., those linked to an atherogenic lipid profile and chronic proinflammatory state, are reminiscent of those documented in populations with overt obesity [30]. Moreover, glutathione, nitric oxide (NO) metabolites ($NO_{2\_}$/$NO_{3\_}$), and antioxidant nonprotein capacity levels are generally lower in NWO women than controls from the normal population. In contrast, lipid hydroperoxide levels are higher in NWO compared with normal weight subjects, highlighting that NWO women are also unprotected against oxidative stress related to metabolic abnormalities [31]. Further, the NWO syndrome can be associated with the presence of polymorphisms responsible for inflammation, CVD, and sarcopenia [32, 33]. Corroborating these findings, other studies reported that (a) NWO is independently associated with cardiometabolic deregulation and risk of CV mortality, (b) blood pressure (BP) values and prevalence of dyslipidaemia/hyperglycemia are higher in NWO than lean women and, (c) odd ratios for the presence of at least two nonadipose components of the metabolic syndrome increase with the severity of NWO and associate with an increased CVD risk independent of BMI [34, 35]. Lastly, NWO women manifest increased anxiety scores and attention to weight control, with an excessive body dissatisfaction and drive for thinness [36].

In NWO and obese women, modulation of the microbiota with selected probiotics (*Streptococcus thermophilus, Bifidobacterium animalis subsp lactis, Streptococcus thermophiles, Lactobacillus bulgaricus, Lactococcus lactis subsp lactis, Lactobacillus acidophilus, Lactobacillus Plantarum, Lactobacillus Reuteri*) [37] has been found to be associated with a change in body composition parameters, such as weight, waist girth, body water, and BF while improving the depression status, anxiety, body dissatisfaction, and eating behavior [38].

Hence, it is crucial to identify phenotypes at CV risk not only by assessing anthropometric parameters (e.g., BMI), but also by measuring the total amount of BF, regional fat distribution, visceral, and/or ectopic fat accumulation that is responsible for the secretion of adipokines and bioactive molecules both related to metabolic disorders and gut microbiota [39, 40].

Impact of nutriepigenetic and personalized nutrition on microbiota

Epigenetic factors suggested to mediate interactions between the environment and the genome [41] involve DNA methylation, histone modifications, and regulation of genes by small noncoding regulatory RNAs (miRNA), which are capable of posttranscriptionally repression of gene expression through interaction with the complementary sites in the 3′ untranslated regions of target genes. In this context, DNA methylation has received particular attention [42]. Among the nutrients that play a role in modulating DNA methylation are methionine, folic acid, choline, betaine and vitamins B2, B6, and B12 [43]. In addition, also polyphenols, including those contained in green tea, soy, and turmeric, such as epigallocatechin-3-gallate, genistein, and curcumin, show epigenetic effects, modulating gene expression, chromatin remodeling, and DNA methylation [44, 45]. In the last decade, the role of methylation has been thoroughly investigated in the attempt to correlate microbiota changes with the development of metabolic diseases [46]. Gut microbiota may alter host histone acetylation and methylation in human tissues. SCFAs production seems particularly relevant for epigenetic regulation of inflammatory reactions. In fact, a reduction in the consumption of fiber-rich foods resulted in

lower production of SCFAs by gut bacteria, with consequent alteration of chromatin [47, 48].

Despite the need for more accurate information on how diet can change epigenetics via microbiota, evidence exists that gut bacteria can communicate with the host through their metabolites, influencing gene transcription and potentially driving the development of noncommunicable diseases.

Microbiota and cardiovascular diseases

Obesity and the metabolic syndrome

Epidemiologic studies highlighted direct and indirect effects of obesity on several CV risk factors such as dyslipidaemia, hypertension, glucose intolerance and diabetes, CAD as well as several types of cancer [20, 49]. AT expansion and dysfunction modulate, in coordinated fashion with infiltrating macrophages and leukocytes, the secretory profile of adipocytokines that are capable of ensuing a proinflammatory state linked with the metabolic complications of obesity. Gut microbiota is postulated not to be an innocent bystander but, rather, one of the factors influencing the genesis of obesity and the different components of the metabolic syndrome (Fig. 1). Mechanisms proposed to explain this role include the regulation of energy extraction from nutrients and the ability of microorganism to ferment undigested dietary polysaccharides generating SCFAs [50]. Generally, an "obese microbiota" has been characterized to be able of extracting more energy from the diet [51]. SCFAs have been shown to induce lipogenesis, increase triglyceride levels, and favor transcription factor-1 binding, the sterol regulatory elements involved in lipogenesis [50]. Another mechanism resides in the ability of microbiota to decrease liver fatty acid oxidation by suppressing the adenosine monophosphate kinase (AMPK), a mediator of cellular energy expressed in the liver and muscle fibers [52]. It has also been demonstrated that fasting-induced adipose factor, a circulating lipoprotein lipase inhibitor, increased cellular uptake of fatty acids, and adipocyte triglyceride accumulation [53]. Interestingly, overgrowth of *Lactobacillus*, *E. coli*, and *Faecalibacterium* show increased ability for the extraction of calories from food and may contribute to the positive energy state associated with obesity [54]. Evidence has also accumulated linking the metabolic syndrome to dysbiosis and metabolic endotoxemia, with toll-like receptor-2 (TLR-2)-mediated inflammatory response being stimulated by LPS, which subsequently increases the secretion of proinflammatory cytokines [55].

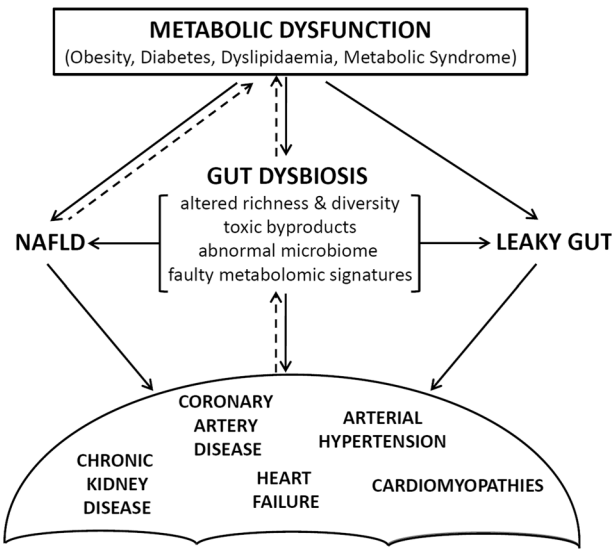

Fig. 1 Interplay between metabolic dysfunction, microbiota and cardiometabolic problems. Summary of the relationships between cardiovascular diseases and gut microbiota through chemical and mechanical microbial activities. NAFLD nonalcoholic fatty liver disease.

Bacterial populations of obese subjects show low levels of microbial diversity with respect to lean subjects [56, 57]. Under specific conditions, this form of dysbiosis can contribute to the development of the diseases [58]. The crosstalk between gut microbiota, diet, and immune system activates mediators and signaling pathways, which influence metabolism and disease related to BF accumulation. A reduction of *Bifidobacterium* and *Atopobium* was observed in obese compared with the nonobese rats in combination with higher abundance of *Clostridium cluster XIVa* and *Lactobacillus*. The specific role of diet as a factor contributing to the obese phenotype is corroborated by the finding that HFD induces a reduction in the *Clostridium cluster XIVa* (*Clostridium coccoides*) group, *Bifidobacterium*, and *Bacteroides* while increasing *Firmicutes* [59]. Angelakis et al. [54] reported a higher abundance of *Bacteroidetes phylum* in the gut microbiota of obese and overweight adults compared with lean individuals. However, the type of diet does not seem to change the balance between *Firmicutes* and *Bacteroidetes* in the obese state, where an increase in *Firmicutes* is generally observed [60, 61]. A similar profile of increased *Firmicutes*/*Bacteroidetes* ratio is observed in the fecal microbiota of obese humans [62, 63].

The open question, therefore, remains whether dysbiosis observed in obese subjects is a consequence of host genotype or another result of overnutrition. The simultaneous presence within the gastrointestinal tract of obese subjects of H2-producing *Prevotellaceae* and H2-utilizing methanogenic *Archaea*, like *Firmicutes*, is claimed to explain the accelerated fermentation, the increase in the production of SCFAs, and high energy uptake [64].

Intriguingly, the severity of obesity elicits an additional effect on microbiota diversity and expression. A reduced microbial gene richness has been documented in 75% of

patients with severe obesity versus 40% of those with moderate obesity [65, 66]. Significant differences exist in α diversity, β diversity, and species between patients with severe obesity and controls [67]. In extremely obese classes, however, low bacterial richness is only modestly influenced by bariatric surgery despite underlying metabolic improvements [65]. This suggests that weight loss and metabolic amelioration determined by bariatric surgery may not be directly related to changes in bacterial species and bacterial richness.

Diabetes mellitus and dyslipidemia

Evidence on the role of dysbiosis in glycaemia and lipid abnormalities provides a tool for understanding the pathophysiology and the treatment of diseases such as diabetes mellitus and dyslipidemias. Significant differences in microbiota composition exist between healthy and diabetic subjects, and the mechanisms proposed to explain the influence of microbiota on insulin resistance include metabolic endotoxemia, low-grade chronic inflammation, modifications in the secretion of the incretins and butyrate production [68, 69]. Metagenome studies in Chinese and Scandinavian diabetic cohorts identified a reduced abundance of butyrate-producing bacteria (*Roseburia intestinalis* and *Faecalibacterium prausnitzii*) and an increased expression of microbial genes involved in oxidative stress, LPS generation, and intestinal permeability, all representing proinflammatory signatures [15, 70]. People with obesity and diabetes have been repeatedly shown to host excessive proliferation of gram-negative bacteria, abnormal LPS release with consequent increased intestinal permeability and endotoxemia, which act on TLR and innate immunity to determine the release of proinflammatory cytokines and define a condition of systemic inflammation [15, 68, 71]. By contrast, human and animal studies provided evidence that some bacterial species, such as the mucin-degrading gram-negative *Akkermansia muciniphila*, can benefit metabolic homeostasis, glucose tolerance, and systemic inflammation. In fact, its abundance is inversely correlated with the presence of diabetes and obesity [72–74] and increases during metformin treatment [75].

With regards to lipid metabolism, intestinal microbes are involved in hepatic lipid and bile metabolism, reverse cholesterol transport, energy expenditure, and insulin sensitivity [76–79]. Of particular interest is bile acid metabolism, since intestinal microbiota are indispensable for the transformation of primary bile acids into secondary acids [79]. In turn, primary and secondary bile acids can act as ligands for specific liver receptors, such as the farnesoid X receptor, which regulates triglyceride turnover as well as the export of VLDL (very-low-density lipoprotein) and de novo lipogenesis, or the Takeda G protein-coupled receptor 5, which acts on glucose metabolism and insulin sensitivity [80–82]. Through still unclear mechanisms, the microbiota can act on lipid metabolism also through SCFAs and TMAO [82–85].

Studies in rodents investigating the relationship between intestinal microbiota and plasma lipids showed that cholesterol and triglyceride levels were reduced in plasma of conventionally raised mice compared with germ-free mice, whereas they were increased in the AT and liver [77]. A clinical study conducted on 893 subjects found 34 bacterial taxa associated with BMI and blood lipids, and revealed that microbiota explain 6% of the variance in triglycerides and 4% of that of high-density lipoproteins (HDL) independent of age, gender, and genetic risk factors [78]. These authors added evidence that the gut microbiome provides a small but significant contribution to the variation in TG (triglycerides) and HDL in part independently of BMI variations.

Arterial hypertension

Arterial hypertension is a multifactorial disorder relating to genetic and environmental factors. In addition to the recognized role of obesity, dietary factors, physical activity, and chronic stress, there is accumulating evidence of a role for microbiota in inducing and maintaining high levels of BP. The linking mechanisms include effects mediated by SCFAs, systemic inflammation, and a number of vasoactive metabolites, such as serotonin, dopamine, norepinephrine, p-cresol sulfate, indoxyl sulfate, and TMAO [86]. The effect of SCFAs acetate, propionate, and butyrate on BP seemingly depends on their binding to the G protein-coupled receptor GPR41 (e.g., free fatty acid receptor 3), GPR43, GPR109A, and GPCR olfactory receptor 51E2 (e.g., Olfr78 in mice and OR51E2 in humans) [87]. The consequence of receptor binding varies depending on the ligand. In the renal afferent arteriole, for example, Olfr78 stimulation causes renin release and activation of the renin–angiotensin system, while GPR41 stimulation promotes local vasodilation, as it happens for propionate [88, 89]. It has also been demonstrated that the absence of gut microbiota can protect mice from Angiotensin II-induced arterial hypertension, vascular dysfunction, and hypertension-induced end-organ damage [90]. Noticeably, these receptors are expressed in smooth muscle cells of small resistance vessels, and GPR41 stimulation determines an increase in energy expenditure through activation of the sympathetic nervous system, leading to an increase in BP [88, 91]. Studies in mice also suggested that dysfunctional gut-sympathetic communications can associate with increased gut permeability, dysbiosis, and systemic inflammation, all of which play a role in hypertension [92, 93]. In mice and in small human cohorts, it has also been shown that a salt-rich diet encourages a depletion in

Lactobacillus species, which associates with increased T_H17 cells and increased BP [94].

With regards to TMAO, its association with arterial hypertension is not currently clear, although animal data suggest a propensity of elevated TMAO levels to influence the susceptibility to elevated BP [95].

Interestingly, fecal transplant from hypertensive to normotensive mice promoted an increase in systolic BP of the recipient mice, while fecal transplant from normotensive to hypertensive rats was insufficient to reduce systolic BP or normalize dysbiosis [96, 97]. Transplant of pathological microbiota from obstructive sleep apnea-induced hypertensive rats to normotensive rats has been shown to induce hypertension and dysbiosis after only 1 week [98]. As suggested by Marques et al., the hypotensive effect of a diet high in fiber could depend on the change of the microbiota with an increase in some acetate-producing bacteria such as *Bacteroides acidifaciens* [99].

Although evidence of a link between microbiota and hypertension in humans is limited, there are studies showing a lower richness and diversity of intestinal microbiota in hypertensive patients compared with normotensive counterparts [95, 100, 101]. An MGWAS revealed 53,953 microbial genes differently distributed between hypertensive patients and controls: opportunistic pathogenic spp. were more frequently distributed in hypertensive gut microbiota, whereas SCFAs-producing spp. were higher in controls, showing a correlation between hypertension-associated spp. and the severity of disease [100]. Of note, microbiota alterations typical of hypertension can be already identified in prehypertensive subjects, suggesting that these changes could precede the clinical manifestations of the disorder and/or contribute to the development of hypertension [101].

Nonalcoholic fatty liver disease

NAFLD is a proxy of the metabolic syndrome and is growingly recognized as a marker of CVD, both directly and indirectly through its association with other cardiometabolic disorders. The mesenteric blood supply conveying to the liver drains microbial products originating from intestinal saccharolytic and proteolytic fermentation that contribute to NAFLD pathogenesis [102]. Patients with NAFLD present changes in the expression and distribution of tight junction protein critical for gut barrier permeability. This event promotes liver exposure to gut-derived endotoxins ensuing per se the development of NAFLD [103, 104]. Also, microbial activity increases TLR activation and initiates nuclear transcription factors resulting in the release of proinflammatory cytokines, which ultimately lead to hepatic injury and fibrosis. Such a proinflammatory outcome has also been observed for ethanol-producing bacteria via nuclear factor-κB (NF-κB) signaling pathways [105]. Moreover, gut microbiota modulate liver fatty acid oxidation by acting on AMPK, the enzyme involved in liver and muscle cells as a gauge of cell energy. AMPK inhibition decreases fatty acid oxidation and enhances fat accumulation. Also important is the activity of TMAO not only as a predictor of NAFLD but also for a putative role in liver triglycerides accumulation and cholesterol input into the bloodstream [106].

Cross-sectional studies in nonobese humans reported a relationship between an increased *Bacteroidetes* to *Firmicutes* ratio and NAFLD progression. A decrease in butyrate-producing *Ruminococcaceae* has been observed in patients with NAFLD independent of obesity. Complementing these findings, intervention studies found that hepatic mitochondria are the main target of the beneficial effect of butyrate-based compounds in reverting insulin resistance and fat accumulation in diet-induced obese mice [107], and supplementation of SCFAs in animals reduced liver fat accumulation, inflammation, and cholesterol synthesis via mechanisms relating to the AMPK–acetyl-CoA carboxylase pathway and hepatic fatty acid synthase activity [108–110].

Atherosclerosis and vasculopathies

Atherosclerosis is a chronic inflammatory disease and a leading cause of vascular disease worldwide [111, 112]. It mainly affects large and medium-sized arteries and is characterized by the presence of plaques (atheromas) leading to vasculopaties. Atherosclerosis often remains asymptomatic until arterial narrowing reaches thrombotic occlusion. CAD includes all conditions associated with insufficient blood flow and consequent oxygen depletion of the heart muscle. Koren et al. [113] suggested that the gut microbiota of CVD patients produce more proinflammatory molecules. These authors found that individuals with atherosclerotic plaques display similarities in bacterial representation between the atherosclerotic plaque and oral cavity/intestine, suggesting that some microbial communities may contribute to plaque instability. Equally, Calandrini et al. [114] documented higher abundance of oral microbacterial spp. *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* in atheromas. Also important is the role of TMAO. It acts on monocytes/macrophages by promoting the uptake of cholesterol and thus increasing the potential thrombogenic effect via formation of foam cells [83]. Moreover, TMAO has been claimed to yield proatherogenic actions via production of inflammatory molecules [115] that play a central role in atherosclerosis development, such as IL-6, cyclooxygenase (COX)-2, E-selectin, and intercellular adhesion molecule-1. Recently, Zhu et al. showed that circulating levels of TMAO directly modulate platelet hyperreactivity (e.g., activation, adhesion,

and aggregation) and the rate of clot formation in vivo [116]. Qualitative and quantitative alterations in microbiota can, in turn, also be induced by acute myocardial infarction (AMI). Wu et al. [117] found microbial and gut barrier alterations in a rat model with increased levels of *Synergistetes* pylum and *Lachnospiraceae* family until 7 days post AMI. The comparison of gut microbiota in CAD patients revealed higher abundance of *Lactobacillales* and lower levels of *Bacteroides* and *Prevotella* than controls [118]. These findings indirectly suggest that an appropriate richness and diversity of human microbiota could be crucial for primary prevention in patients prone to CAD.

Chronic kidney disease

Although the prevalence of chronic kidney disease (CKD) is globally varied, its incidence is increasing worldwide and represents a major public health burden [119]. CKD patients exhibit increased all-cause and CV mortality in comparison with the general population when standardized by age and gender [120]. In the last decade, a growing number of studies have focused on the alterations of gut microbiota in CKD patients. Accumulation of uremic toxins alters the gut microenvironment and impairs the host immune response, resulting in a condition of gut dysbiosis [121]. Dysbiosis in CKD induces bacterial proteolysis with further production of uremic toxins such as indoxyl sulfate, p-cresyl sulfate, and TMAO. In particular, indoxyl sulfate acts as a predictor of CV and all-cause mortality in CKD patients. An inverse correlation between indoxyl sulfate and glomerular filtration rate (GFR), and a direct correlation with endothelial function tests, such as pulse wave velocity and the aortic calcifications, is observed in CKD patients [122]. Likewise, plasma levels of p-cresyl sulfate are associated with an increased risk of death and CV events in hemodialysis patients [123].

Evidence of a correlation between TMAO levels and the decrease of GFR exists in patients affected by moderate to severe CKD [124]. The increased levels of these uremic toxins originating from the gut microbiota are not only associated with an enhanced risk of CVD but also with a faster progression of CKD [125]. Understanding the specific mechanism/s by which the CKD toxic compounds can impair gut microbiota composition should be a goal of future investigations [126].

Cardiomyopathies and heart failure

An association has been described between gut microbiota and proteomic/metabolomic determinants of cardiomyopathy phenotypes [127], and host–microbe interactions have been found to impact proteins involved in epithelial function, lipid metabolism, and central nervous system function relating to CVD [128]. Interestingly, succinate, a tricarboxylic acid intermediate metabolite, can cause murine cardiac hypertrophy in a GPR91-dependent manner and its levels increase in patients with hypertrophic cardiomyopathy, the condition of left ventricle wall thickening leading to defective pump function [129]. Likewise, indoxyl sulfate can stimulate hypertrophy and fibrosis of cardiomyocytes in vitro and in vivo [130]. With regards to ischemic cardiomyopathy, it has been observed that patients with ischemic cardiomyopathy harbor higher levels of TMAO and betaine that those with dilated cardiomyopathy, potentially reflecting a more negative prognosis in the former [131].

Several studies focused on the relationship between gut microbiota and HF, a multisystem disorder resulting from cardiomyopathies of different origin. In HF, hemodynamic alterations can impair gut epithelial function and lead to the translocation of bacteria-derived endotoxins across the gut epithelial barrier, which can in turn induce systemic inflammatory responses [132, 133] via increased LPS concentrations [134, 135]. The severity of HF has been associated with the disadvantageous overgrowth of *Campylobacter*, *Shigella*, *Salmonella*, as well as *Candida* spp [136]. Using bacterial 16S rRNA gene sequences, lower diversity indices and core intestinal microbiota (*Coriobacteriaceae*, *Erysipelotrichaceae*, and *Ruminococcaceae*) were found in HF patients compared with controls [137]. Changes in core intestinal microbiota, depletion in butyrate-producer *Lachnospiraceae* family, as well as correlations between microbial changes and increased levels of soluble CD25, a marker of T cell and macrophage activation, partly explain the immune abnormalities seen in HF patients [138]. When further analyzed according to age, lower proportions of *Bacteroidetes* and larger quantities of *Proteobacteria* have been described in older compared with younger patients with HF [139].

HF patients show an imbalanced production of butyrate and TMAO, which associates with distinct metabolomic signatures relating to enhanced expression of microbial genes associated with LPS biosynthesis [140]. In experimental HF, TMAO directly acts on inflammatory pathways known to contribute to CVD [115, 141, 142], and its pharmacologic manipulation has been shown to blunt diet-induced inflammation, cardiac dysfunction, fibrosis, and atherosclerosis [143].

Cardiovascular mortality

Studies on mortality predictors have focused on circulating products activity rather than microbiota strains. TMAO is by far the most investigated product, with particular reference to its prognostic impact in patients with established atherosclerosis. A study in medically treated patients with stable CAD showed that high TMAO predicted a fourfold

increased mortality risk in 5 years; after multiple adjustments, the mortality risk remained nearly doubled [144]. Parallel findings were obtained in medically treated patients with peripheral artery disease [145]. Also, TMAO levels predicted a poor prognosis in patients with HF and a threefold increase in 5-year mortality risk (HR, 3.4) even after multiple adjustments [146]. In contrast, a study on patients with venous thromboembolism (VTE) found no change in the risk of recurrent VTE across TMAO categories, although a marginally significant U-shaped association was reported between TMAO and mortality risk, with the lowest mortality risk observed for TMAO levels of 4 μmol/L [147]. In a systematic review and meta-analysis of prospective studies (19,256 participants, 3315 incident cases), elevated TMAO was associated with increased relative risk (RR) for major adverse CV events (MACE; RR, 1.62) and all-cause mortality (RR, 1.63), independent of traditional risk factors [148]. The dose–response study showed that increasing TMAO levels by 1 μmol/L conferred a significant 2–5% higher risk of MACE. In another meta-analysis of 14 studies on 16 cohorts enrolling 15,662 subjects, TMAO levels were associated with all-cause mortality (HR, 1.91) and major adverse cardio- and cerebrovascular events (MACCE; HR, 1.67). The dose–response subanalysis documented a 7.6% increased RR for all-cause mortality for each 10 μmol/L increment in TMAO levels [149]. Lastly, TMAO predicted mortality and multiple CVR more strongly in individuals with diabetes than in those without. In patients with diabetes and acute coronary syndrome, high TMAO levels were associated with increased mortality (HR = 2.7), myocardial infarction (HR = 4.0), HF (HR = 4.6), unstable angina (HR = 9.1), and all CV events (HR = 2.0), while in patients without diabetes, associations were "only" significant for death (HR, 2.7) and HF (HR, 1.9) [150].

Modulation of gut microbiota as a therapeutic strategy

Interventions during neonatal life

Early postnatal life is critical for adult health. Microbiota colonization of the host occurs early, i.e., during prenatal life, birthing process and upon postnatal exposure to external factors [151–153]. Birth mode and infant gut microbiota mediate the association between maternal prepregnancy overweight and early childhood overweight [154]. They are also correlated with children's BMI at age 12 years [155]. Altered α- and β-diversity of the offspring fecal microbial community and abnormal *Firmicutes*/*Bacteroides* ratio have also been observed in association with maternal HFD, maternal obesity, and overnutrition possibly via SCFAs production and energy extraction from the diet [156–160].

The use of probiotics during pregnancy is a promising tool to circumvent the problem. In a double-blind study, administration to mothers of *Lactobacillus rhamnosus* from 4 weeks before delivery to 6 months after delivery alleviated the initial, but not late, weight gain among children who then became overweight compared with placebo [161]. Also, prebiotics have shown encouraging results in modulating the offspring gut microbiota, the development of the intestinal tract, and the expression of satiety hormones and genes associated with healthy glucose metabolism. In 2–12-week-old infants, supplementation with short-chain oligosaccharides with or without long-chain oligosaccharides showed a strong bifidogenic effect compared with traditional infant formulas [162].

Dietary approaches: prebiotics, probiotics, postbiotics, and polyphenols

Preventive strategies aimed at reducing the burden of obesity and noncommunicable diseases should consider genetic makeup and its interaction with dietary intake as a continuum. The association between unhealthy nutrition and inflammation or oxidative stress applies to chronic diseases consequent to abnormal microbiota colonization of the gut. The HFD is paradigmatic for its ability to trigger systemic inflammation via inflammatory mediators, such as activated NF-κB, as well as products of leukocyte activation, such as CD11A, CD11B, and CD62L [163]. In postprandial conditions, the inflammatory response related to endotoxemia and bacterial LPS synthesis exerts forceful inflammatory and proatherogenic effects [164]. Likewise, a meat-based diet can increase bile-tolerant microorganisms (e.g., *Alistipes, Bilophila*, and *Bacteroides*) and decrease the abundance of *Firmicutes*, which metabolize dietary plant polysaccharides (*Roseburia, Eubacterium rectale*, and *Ruminococcus bromii*) [165]. Inversely, diets rich in polyunsaturated (PUFA) and monounsaturated (MUFA) fatty acids, and poor in animal fats and glucose-dense food have been largely shown to advantage microbiota and benefit CV health.

Healthy dietary approaches expressing this peculiar micronutrient profile include Mediterranean, Japanese, and vegetarian diets [166, 167]. The usefulness of the Mediterranean Diet (MD) in preventing CVD risk and other noncommunicable chronic diseases [168, 169] has been extensively shown owing to high contents of vegetables, fresh fruit, cereals, olive oil, resveratrol-containing foods and other antioxidant-rich compounds. A simple change in the meal energy load from lipids to carbohydrates equivalent to ≈25% improves postprandial proatherogenic factors [170], while adherence to the MD can reduce LDL oxidized

proteins and promote significant variation in gene expression of antioxidant and prooxidant genes [171].

It is also recognized that dietary interventions can modify gut microbiota in a fast, diet-specific fashion [165]. A plethora of compounds have been found to modulate the gut microbiota and activate specific patterns of gene expression that, in turn, act to restore the hormetic mechanisms capable of decreasing cellular stress and inflammation [172–175]. As such, four classes of compounds constitute effective nutritional interventions: prebiotics, probiotics, postbiotics, and phytochemicals [176].

Prebiotics belong to fiber, vitamins A, B1, B2, B6, B3, B12, D, α, β, γ, δ-tocopherol family, α, β, γ, δ-tocotrienol, MUFA, and PUFA (ω-9, ω-6), iron, zinc, phytosterols, and inulin, which act to control and re-establish innate and adaptive immune efficiency, improving immune functions, and stress response [177].

Probiotics, such as *Bacteroides, Clostridium, Faecalibacterium, Eubacterium, Peptococcus, Peptostreptococcus*, and *Bifidobacterium* can correct the altered intestinal microbiota and restore innate and adaptive immunity [178]. Clinical trials have been conducted to evaluate the effects of probiotics on BP and NAFLD. There is indirect evidence that probiotic treatment could be a new target in the treatment of hypertension, since reversing dysbiosis could solve one of the mechanisms underlying hypertension. A meta-analysis of nine randomized trials showed a significant decrease in both systolic and diastolic BP in patients who consumed a daily dose of ≥109 CFU of probiotics [179]. Li et al. demonstrated that probiotic supplementation improves insulin resistance, hepatic histology, and total fatty acid content in mice with steatohepatitis [180]. In humans, supplementation with fructo-oligosaccharide (or fructo-oligosaccharide and *Bifidobacterium longum*) was associated with reductions in NAFLD and TNFα levels [181, 182]. Furthermore, the use of a mix of probiotic strains decreased levels of TNFα and reduced hepatic inflammatory signaling in liver steatosis suggesting that probiotic administration could ameliorate oxidative and inflammatory liver damage associated with NAFLD.

Postbiotics can improve epithelial barrier function, increase the production of mucins by the goblet cells, and are able to decrease inflammatory processes through downregulation of proinflammatory cytokine production by intestinal epithelial cells [183–185]. Such phytochemicals include curcumin, polyphenols like caffeic acid, flavonoids like catechin, epicatechin, quercetin, procyanidins, and phenolic acids, hydroxytyrosol and resveratrol, which are highly effective in blocking NF-κB activation, hence peroxidation of low density lipoprotein cholesterol [173, 186, 187]. Many of these compounds yield anti-inflammatory activity by modulating the gut-associated lymphoid tissues, responsible for upregulation of caspases, p53, NF-E2-related factor, Bcl-2-associated X, and IL-10 and downregulation of protein kinase-C, protein kinase-D, lipoxygenase, COX-2, sirtuins, TNF-α, uncoupling protein-2, dual-oxidase 2 gene, IL-1 receptor-associated kinase-2 gene, catalase, and C-X-C motif chemokine ligand 12 genes [34, 188, 189].

Fecal transplant

One emerging strategy to modulate the intestinal microbiota in patients with dysbiosis is to use a fecal microbiota transplant (FMT) [190]. This is a key treatment for *Clostridium difficile* infections [191–193]. Studies have shown the possibility of transmission of obesity, inflammatory bowel disease, depression [194], mood disorders [195], and other conditions in animal through FMT, giving strength to the argument that microbiota may be actively implicated in the pathogenesis of metabolic diseases. Gregory et al. [196] showed that atherosclerosis susceptibility can be transmitted with a gut microbial transplant through TMAO-induced effects, while others observed that *Akkermansia muciniphila* can reverse western diet-induced atherosclerosis and endotoxemia in ApoE-knockout mice [197]. This approach can prevent inflammation and suppress the formation of atheroma via reduced macrophage infiltration [198]. In humans, the use of FMT from metabolically healthy donors to subjects with metabolic syndrome prompted improvements in peripheral and hepatic insulin sensitivity measured by the hyperglycemic clamp, suggesting the possibility of manipulating microbiota to treat diabetes [199].

Conclusions

CVD is intimately associated with alterations in microbiota. Lifestyle changes and elimination of associated risk factors remain the main strategy to reduce CV morbidity and mortality. The complex interaction between gut microbiota and the CV system warrants further research to clarify the intra- and interindividual variations in this relationship and plan intervention strategies. There is, however, emerging evidence that chronic inflammation, CVD and CV mortality can be reduced by improvements in long-term composition of the gut microbiota. In this perspective, manipulation of intestinal microbiota could represent a novel therapeutic option for the treatment of CVD, even if further studies are necessary to clarify the long-term effects of gut microbiota in prevention and treatment of CV disease.

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