MetS and Gut Microbiota Metabolites

Subjects: Microbiology

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Metabolic syndrome (MetS) is a complex pathophysiological state with incidence similar to that of a global epidemic and represents a risk factor for the onset of chronic non-communicable degenerative diseases (NCDDs), including cardiovascular disease (CVD), type 2 diabetes mellitus, chronic kidney disease, and some types of cancer. A plethora of literature data suggest the potential role of gut microbiota in interfering with the host metabolism, thus influencing several MetS risk factors.

metabolic syndrome gut microbiota dysbiosis nutrition inflammation probiotics prebiotics

1. Introduction

Metabolic syndrome (MetS) is defined by WHO as a pathological condition characterized by obesity, insulin resistance, hypertension, hyperlipidemia and waist-to-hip ratio; MetS is present if three or more of the above-mentioned criteria are present [1].

The complex ecosystem of microorganisms (including bacteria, viruses, protozoa, and fungi) living in different districts of the human body (gastrointestinal tract, skin, mouth, respiratory and urogenital systems) is defined as microbiota. Most microbiotas reside in the gastrointestinal tube [2]. The microbiota contains over 100 times more unique genes than those codified in the human genome [3]: it encompasses over 100 trillion microbes and 5000 different species, accounting for 5 million genes.

The habitual diet plays an important role in defining the composition of the intestinal microbiota and determining the microbial metabolites that can affect the host metabolism. In the literature, several studies have shown positive effects of some dietary models in MetS management. For example, adherence to the Mediterranean diet (MD) leads to significantly higher levels of total short-chain fatty acids (SCFAs), important gut microbiota metabolites that modulate immune–endocrine processes [4].

2. SCFA Beneficial Metabolic Effects

Intestinal bacteria play an important role in regulation of the host metabolism (influencing energy homeostasis, appetite and food eating behavior) and modulation of the immune system, through the production of SCFAs, vitamins, metabolites, and neuropeptides (Figure 1) [5][6].

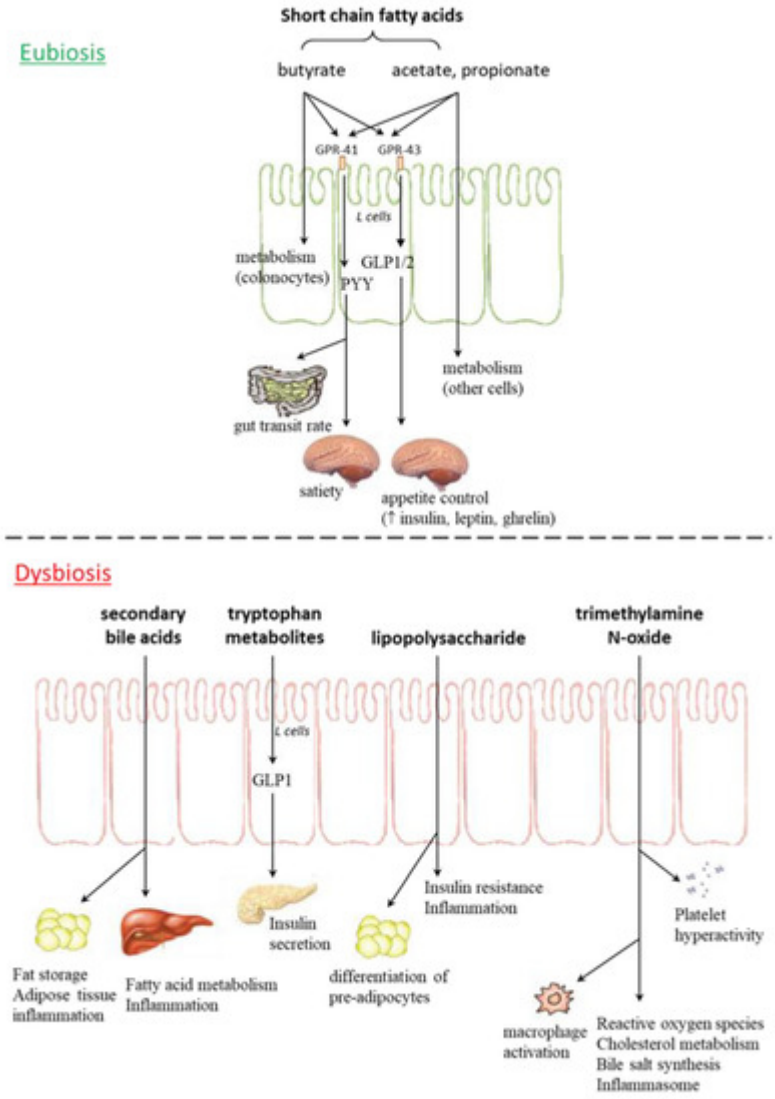

Figure 1. Gut microbiota metabolites in eubiosis and dysbiosis. GPR: G protein coupled receptor; GLP: glucagon-like peptide; PYY: peptide YY.

3. LPS and Endotoxemia

In healthy conditions, the integrity of the intestinal epithelial barrier, guaranteed by a tight junction network, blocks passage of antigens or microbe-derived endotoxins. Some pathological conditions give rise to gut microbiota perturbations (referred to as dysbiosis) and a subsequent impairment of intestinal barrier function (due to disorganized tight junction proteins, zonulin and occludin, in colonocytes); in these circumstances, microbial metabolites can cross the intestinal barrier and move to the bloodstream, triggering systemic pro-inflammatory signaling that, in turn, causes metabolic alterations (peripheral insulin resistance, hyperglycemia and non-alcoholic fatty liver disease (NAFLD)) in distant tissues [7][8].

Obesity, insulin resistance, and NAFLD, linked to MetS, are usually associated with low diversity in the gut microbiome and chronically higher levels of pro-inflammatory and microbiota derived lipopolysaccharide (LPS) in circulation [9]. A growing body of evidence suggests the potential role of LPS in obesity, insulin resistance, hepatic

steatosis, and systemic and local inflammatory processes [7]. The ability of LPS to induce proliferation and adipogenesis is supported by in vitro and in vivo (mice models and human subjects) studies.

4. Nonalcoholic Fatty Liver Disease (NAFLD) and Microbiome

NAFLD is the hepatic manifestation of cardiometabolic syndrome. Systemic LPS concentration is significantly elevated in NAFLD compared to control groups, in both human and animal studies [10][11][12][13]. The gut microbiota contributes to liver fat deposition through modulation of the nuclear farnesoid X receptor (FXR), responsible for regulation of bile acid synthesis, and hepatic triglyceride accumulation [14][7][15]. After a meal, primary bile acids (chenodeoxycholic and cholic acids), stored in the gall bladder, are secreted in the duodenum, where they can be deconjugated by gut microbes, thus being metabolized into secondary bile acids in the colon [16]. Bacteria with the capability of producing secondary bile acids belong to *Clostridium* (clusters XIVa and XI) and *Eubacterium* [17][18].

Gut microbiota involvement in NAFLD genesis has been demonstrated by microbiota transplantation in recipient germ-free mice, as it generates fasting hyperglycemia, insulinemia and NAFLD; in particular, *Lachnospiraceae bacterium 609* and *Barnesiella intestinihominis* species were specifically related to NAFLD [19].

5. Role of Bacterial TMAO and Development of Atherosclerosis

Trimethylamine N-oxide (TMAO) is a biomarker of risk for major adverse cardiovascular and cerebrovascular events, such as myocardial infarction and stroke (Figure 2): increased plasma TMAO concentrations have indeed been correlated with the accumulation of fatty depots in blood vessels, fatty liver, visceral obesity, and atherosclerosis [20][21][22][23][24][25][26][27][28].

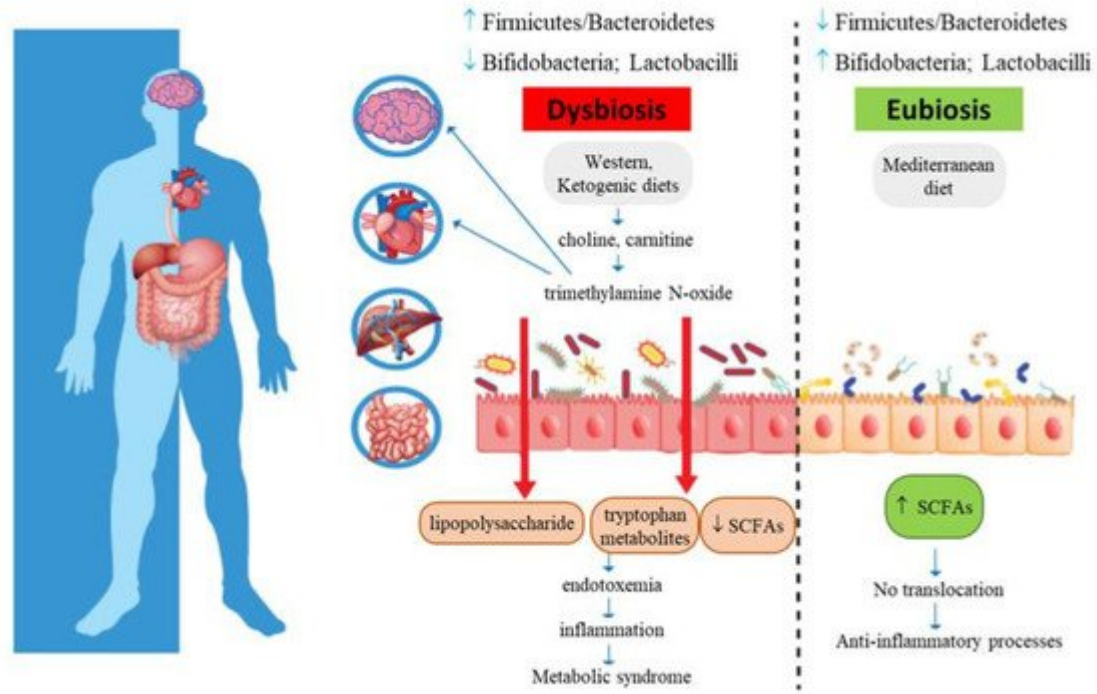

Figure 2. Metabolic syndrome and gut microbiota intestinal dysbiosis. Increased intestinal permeability causes translocation of lipopolysaccharide and tryptophan-derived metabolites, with subsequent metabolic endotoxemia and chronic low-grade systemic inflammation.

High TMAO serum levels are related to MetS and cardiovascular risk. TMAO may promote dyslipidemia by regulating hepatic lipogenesis and gluconeogenesis [3], macrophage scavenger receptors [29], while downregulating cholesterol and bile acid metabolism [30], as well as impairing macrophage reverse cholesterol transport [31], promoting movement of activated leukocytes to endothelial cells [32], activating NF-κB signaling [32], and enhancing platelet activation, thus promoting a pro-thrombotic phenotype [33] and inducing endothelial dysfunction through activation of the NLRP3 inflammasome [34]. In addition, TMAO also affects brain functions, as it induces neuronal senescence, increases oxidative stress, impairs mitochondrial function, inhibits mTOR signaling and upregulates expression of macrophage scavenger receptors and CD68, all phenomena that contribute to brain aging and cognitive impairment [32][28][35].

6. Gut Microbiota and Tryptophan Metabolism

Bacteria-derived indoles, produced from Trp metabolism, can modulate host physiological and pathological pathways, thus contributing to cardiovascular, metabolic, and brain disorders [36]. Trp metabolites are also involved in MetS. Indeed, in human patients with MetS, overactivation of indoleamine 2,3-dioxygenase and increased serum levels of kynurenine have been reported [37]. Indoxyl sulfate and p-cresyl sulfate are two other Trp metabolites that stimulate GLP-1 in L cells and subsequent insulin secretion from pancreatic β cells [38][39]. These two metabolites seem to be also related to chronic kidney disease, a MetS complication, and related risk factors (cardiovascular disease (CVD); hypertension, diabetes and hyperhomocysteinemia) [40][41].

7. Dietary Strategies for MetS Management and Gut Microbiota Modulation

In MetS patients, nutritional intervention should firstly aim at reducing CVD and type 2 diabetes risk and usually includes reduction of body weight by 7–10%, followed by weight maintenance and lifestyle changes (such as increases in physical activity and stopping cigarette smoking). Losing as little as 5% of initial weight results in insulin sensitivity improvement, serum triglycerides and LDL-cholesterol reduction and decrease in systolic and diastolic blood pressure [42][43].

Obesity is one of the five fundamental features of MetS; the relationship between obesity and microbes is clearly established. Colonization of germ-free mice with gut microbiotas derived from obese subjects led to increases in total weight, compared with transplantation of lean gut microbiotas [44]. Similar results have been observed in humans, where obesity developed after fecal microbiota transplantation from overweight donors [45], whereas transplantation of lean microbiotas into individuals with MetS improved insulin sensitivity [46]. In obese subjects, main microbiota changes concern the reduction of Bacteroidetes and a proportional increase in Firmicutes and

Actinobacteria [47][48][49][50]; increase in Bacteroidetes in overweight subjects has also been reported [51]. However, conflicting data still exist [48][52][53], especially considering differences in age, sex, physiological state, and ethnicity; therefore, we are far away from understanding the real Firmicutes/Bacteroidetes ratio in obesity, and further studies are recommended.

Several in vivo studies have underlined the relevance of dietary fat quality on metabolic health and gut microbiota composition. Patterson and co-workers [54] demonstrated that mice fed with high-fat diets of different compositions displayed peculiar microbial ecosystems: dietary saturated fatty acids (palm oil) were associated with a low abundance of Bacteroidetes, obesity and MetS; mono-unsaturated fatty acids (MUFAs; olive oil) led to an increase in the Bacteroidaceae family; ω-3 PUFAs (flaxseed/fish oil) increased EPA and DHA concentrations, as well as the intestinal abundance of *Bifidobacterium* genus.

MD adherence reduces chronic inflammation, improves lipid profile, insulin sensitivity and endothelial function, while decreasing CVD incidence and all causes of mortality (myocardial infarction, stroke, cancer) [128,129]. High adherence to MD positively impacts the gut microbiota composition and microbial metabolomes.

Some findings indicated that nutritional ketosis, induced by very low carbohydrate ketogenic diets (VLCKD; <10% carbohydrates per day), allowed weight management and improved metabolic and inflammatory markers, including lipids, glycated hemoglobin, high-sensitivity C-reactive protein, fasting insulin and glucose levels [55][56].

A diet rich in proteins and low in carbohydrates promotes dysbiosis, causing an increase in pro-inflammatory bacteria and a reduction in SCFA-producing bacteria, with subsequent changes in bacterial metabolites; indeed, increased branched-chain fatty acids, indoxyl sulfate, p-cresol sulfate and TMAO have been observed with this dietary regimen [57][58][59].

Epidemiological evidence identifies the benefits of vegetarian dietary patterns (rich in fiber, but low in EPA and DHA) in both the prevention and treatment of MetS, CVD mortality and risk of coronary heart disease [60][61].

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