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Obesity, non-alcoholic fatty liver disease, and atherothrombosis: a role for the intestinal microbiota?

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Abstract

Whereas the association between intestinal microorganisms and health has been widely accepted in the area of infectious disease, recent advances have now implied a role for the intestinal microbiota in human energy balance. In fact, numerous studies support an intricate relationship between the intestinal microbiota and obesity, as well as subsequent insulin resistance and non-alcoholic fatty liver disease. Intestinal microorganisms also seem to be involved in haemostatic tone and atherogenesis. However, as most of the findings stem from observational data, intervention studies in humans using interventions selectively aimed at altering the composition and activity of the intestinal microbiota are crucial to prove causality. If substantiated, this could open the arena for modulation of the intestinal microbiota as a future target in obesity-associated disease, both as a diagnostic test for personalized algorithms and for selective therapeutic strategies.

Keywords: Atherosclerosis, atherothrombosis, intestinal microbiota, non-alcoholic fatty liver disease, obesity, thrombosis
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Introduction

Obesity is an increasingly important public health issue, as it is expected that, by 2030, one-third of the population of the western world will be obese [1]. The term 'metabolic syndrome' is widely used as a clinical definition of overweight individuals at increased risk of a large series of comorbidities, such as insulin resistance, cardiovascular disease (CVD), venous thromboembolic events, and non-alcoholic fatty liver disease (NAFLD) [2] (Fig. 1) . Apart from many other genetic risk factors that play a role in the development of obesity [3], metabolic syndrome is increasingly thought to be a chronic inflammatory disease driven by chronic intestinal bacterial translocation resulting in endotoxaemia [4,5]. Endotoxaemia is characterized by Gram-negative bacterial capsule fragments in the plasma, and is linearly associated with the concentration of lipopolysaccharide-binding protein in plasma. In this regard, plasma lipopolysaccharide-binding protein was found to be a marker of chronic inflammation associated with the development of obesity and insulin resistance in both mice and humans [6,7]. Moreover, there is increasing evidence that the intestinal microbiota might contribute to host metabolism and obesity [8], a process that is thought to stem from impaired gut barrier function in obese subjects [9].

The average human bowel is home to trillions of microorganisms, mainly bacteria, but also viruses and a low number of fungi, which outnumber the cells of their human host by a factor of ten to one [10]. In fact, their genes even outnumber the human genes by >100-fold. Microbial colonization starts soon after birth and, although the initial composition of the microbiota varies, it becomes relatively stable after the age of 3–4 years, and remains so into advanced age [10]. The intestinal microbiota serves as an 'exteriorized' organ, complementing and interacting with human metabolism, and so giving rise to novel therapeutic targets. In this respect, the composition of the intestinal microbiota and its collective

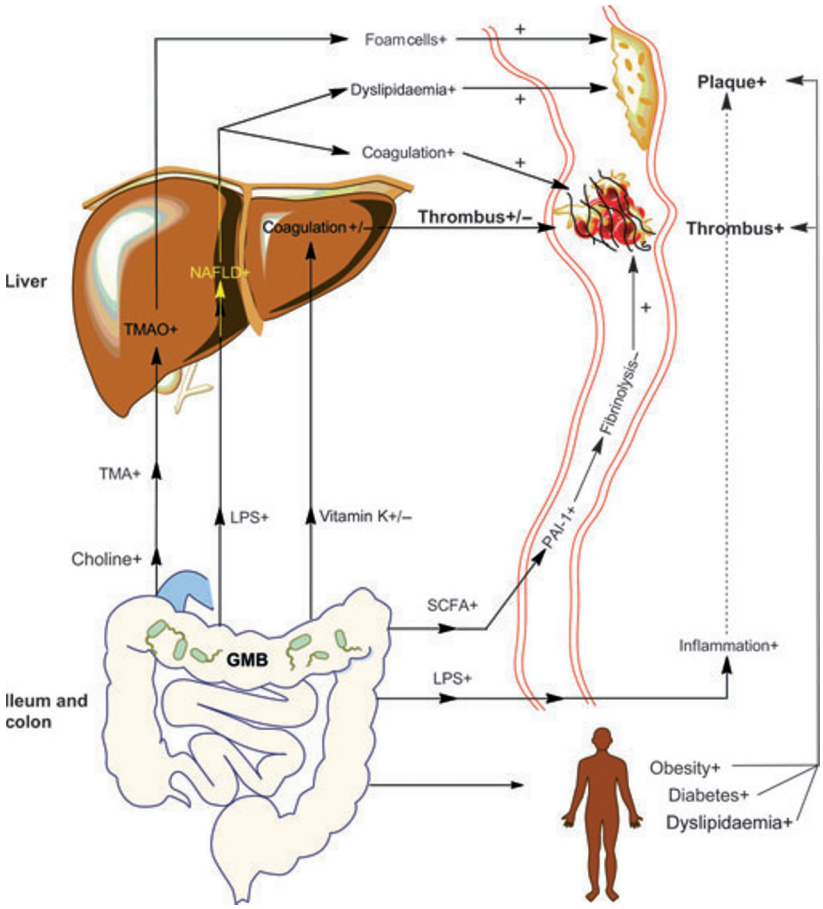

FIG. 1. Potential associations between the intestinal microbiota and obesity-related comorbidities, comprising insulin resistance, cardiovascular disease, venous thromboembolic events and non-alcoholic fatty liver disease (NAFLD). GMB, Gut microbiota; LPS, lipopolysaccharide; PAI-1, plasminogen activator inhibitor-1; SCFA, short-chain fatty acid; TMAO, trimethylamine-*N*-oxide.

genome (also known as the microbiome) is considered to be an important factor in various diseases, ranging from gastrointestinal tract disease to obesity [11]. Bacterial numbers and composition vary considerably along the human gastrointestinal tract. In the oral cavity, there are approximately 10^{12} bacteria; the numbers in the stomach and small intestine are significantly lower, owing to the rapid transit times and the secretion of gastric acid, and bile and pancreatic juice. Bacterial numbers range from 10^{0} to 10^{4} per gram in the stomach, whereas the proximal small intestine and the ileum harbour 10^{5}–10^{7} and up to 10^{7}–10^{8} bacteria per gram of intestinal content, respectively. The highest number of bacterial cells is found in the large intestine, with approximately 10^{11} per gram of intestinal content [12]. Quantitatively, the most important phyla of the intestinal microbiota include the *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*, the representatives of which are often regarded as strict anaerobes (except for the *Proteobacteria*, which can be facultative anaerobes) [12]. Older literature has suggested that germ-free animals are less susceptible to obesity [13] and atherosclerotic plaque [14] and thrombus formation [15], suggesting that the intestinal microbiota may play a role in these cardiometabolic diseases [16]. Until recently, knowledge of the intestinal microbiota was limited, mainly because of the lack of methods for growing and identifying their representatives. The introduction of culture-independent approaches based on analysis of 16S rRNA and its corresponding genes has profoundly changed the landscape; these topics have already been covered in recent reviews [11,17,18]. Nevertheless, owing to the use of different analysis platforms, reproducibility issues, and other biases, including concomitant medication use in selected subjects, inconsistent results have been generated by these observational studies, and this calls for caution in their interpretation [17]. In the present article, we will discuss the potential influence of the intestinal microbiota on the development of obesity-associated parameters such as NAFLD and hypercoagulability. The underlying pathophysiological processes, including microbiota-associated chronic low-grade inflammation, and potential therapeutic targets are also described.

Gut microbiota, inflammation and lipid metabolism

It is widely acknowledged that obesity and subsequent insulin resistance are closely related to the presence of adipose tissue inflammation. As adipose tissue is important for the production of various inflammation cytokines [19], there is ample