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Review Article

Gut microbiota and obesity: Concepts relevant to clinical care

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ABSTRACT

The composition and function of gut microbiota play a role in obesity and metabolic disease, yet the mechanisms have not been fully described. As new discoveries and advances in the field have occurred, the relevance of gut microbiota in clinical care has become more substantial. There is promising potential for manipulation of the gut microbiota as treatment of obesity and associated health complications, both as a standalone therapy and as part of interventions such as weight loss. In this review we have compiled knowledge and concepts that are important in the consideration of gut microbiota for clinical care.

1. Introduction

Even though there have been notable scientific advances in the study of gut microbiota and obesity, a causal relationship between the two remains undefined [1]. Although promising mechanistic links have been uncovered in rodents, the myriad factors underlying human obesity and related-metabolic dysfunction (including genetics/epigenetics and lifestyle) make it difficult to demonstrate an independent role for gut dysbiosis. Studies have measured composition, functional potential, metabolomics, and ecologic dynamics of the gut microbiota, but we still do not know their relative contribution to complex disease pathophysiology and their concrete applicability to clinical care.

We, here summarize key discoveries made thus far that could have relevance in the management of obesity and its co-morbidities (Fig. 1).

2. Cross-talk between microbiota and host in metabolic disorders

Composition and function of the microbiota differ between healthy lean and obese subjects [2]. Gut microbiota is modified in obesity per se and related-comorbidities, including type 2 diabetes (T2D) [3–7], non-alcoholic steatohepatitis [8], and cardiovascular diseases [9]. The mechanisms believed to link the gut microbiota with obesity, at least in animals, include energy extraction capacity from food, influence on the integrity of the gut barrier, modulation of chronic inflammation and the immune system, and production of specific metabolites that, besides having a local effect on the gut-associated immune system and intestinal barrier, also signal to other tissues and organs including the brain, liver and adipose tissue.

2.1. Factors influencing gut microbiota and metabolic diseases

Metabolic diseases stem from a combination of factors, including host intrinsic characteristics, lifestyle and environment, genetic/epigenetic factors and gut microbiota composition and function. Diet has been widely studied in connection with the gut microbiota in obesity. For example, microbiota enterotypes, which have been used to group people according to their dominant phyla, are associated with long-term dietary habits [10]. Fermented foods and fiber consumption are associated with a healthier and more diverse microbiota [11]. As shall be described below, people living in more industrialized environments tend to have lower microbial diversity than people living in a more traditional manner.

Exchange of microbiota between individuals is another factor that shapes the microbial ecosystem. Adults consuming Western or restricted diets had distinct gut microbiota compositions, and lower richness was found in Western diet consumers. The microbes from these individuals were transplanted onto mice. Upon co-housing and enabling the transfer of gut microbiota (i.e. mice are coprophagic) recipients of the Western diet microbiota acquired traits of the restricted diet [12]. Similar results were seen in Ridaura et al. [13], showing the phenotypic transmissibility of some microbiota properties from humans to mice.

Pharmacology has an important effect on gut microbiota composition. Antibiotic treatment leads to profound and long-lasting modifications in the gut ecosystem [14]. Metformin, a key antidiabetic agent, has been identified as a confounder of microbiota observations in diabetes studies. These studies have suggested that the effect of metformin on the host may be partially induced through the gut microbiota

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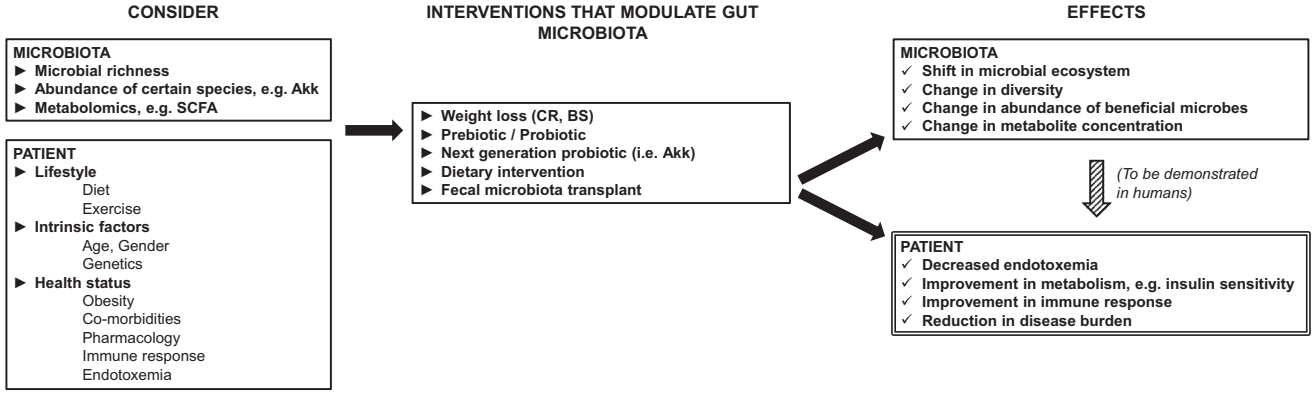

Fig. 1. Potential of gut microbiota in clinical care. Several aspects of gut microbiota composition and function have been implicated in metabolic diseases. Taking into consideration intrinsic patient characteristics, health status and environmental factors, manipulation of the gut microbiota could eventually be used in a wide array of treatments for metabolic disease, such as calorie restriction, bariatric surgery, prebiotic/probiotic intake and fecal microbiota transplantation. These treatments have shown changes in gut microbiota, which have been in turn associated with positive health outcomes, although causation remains to be demonstrated in humans. CR = calorie restriction, BS = bariatric surgery, Akk = *Akkermansia muciniphila*.

[15–17]. It is not excluded, however, that microbial composition may modify the pharmacology of drug compounds frequently used in metabolic disease leading in some circumstances to differential clinical effect as it was shown for example for digoxin, a well-known antiarrhythmic agent [18].

2.2. The gut microbiota influences host intestinal barrier and immune response

There is an association between gut dysbiosis and disruption of the intestinal barrier's integrity, specifically mucus production and layer thickness, tight junctions, insulin sensitivity, and inflammation. Disruption of the intestinal architecture may lead to leaking of gut-derived compounds that would otherwise stay in the gut lumen. Cani et al. termed the detection of lipopolysaccharide (LPS) in circulation 'metabolic endotoxemia,' and found it to be associated with chronic inflammation and disruption of metabolic homeostasis, particularly insulin sensitivity, in mice. LPS acts by activating Toll-like receptor 4 (TLR4) and inducing an inflammatory cascade. LPS from certain bacterial groups is more inflammatory than others, and it may be translocated in chylomicrons or by leaking through a permeable gut. High fat diets are associated with endotoxemia [19,20].

There is a complex interplay between microbiota, intestinal epithelium and the gastrointestinal immune system, with many metabolites and microbial components having a direct influence on the host's immunity. The production of metabolites from nutrients or modification of host-produced metabolites has a direct effect on immune cells and on both the integrity and permeability of the intestinal epithelium. The enteric immune system is constantly assessing and responding to the gut microbiota. A healthy gut ecosystem is needed in the development of immune tolerance, for example by promoting regulatory T cell (T_{reg}) differentiation and expansion [21], and prevention of autoimmune disease or chronic inflammation.

The most studied metabolites in connection with microbiota and host are short chain fatty acids (SCFA). They are synthesized from fiber metabolism by certain bacterial groups. SCFA act on the host in different ways. They serve as a source of energy for colonocytes, they have a critical influence on glucose homeostasis by inducing gluconeogenesis on colonocytes, as histone deacetylase (HDAC) inhibitors they impact epigenetic modifications, and they influence incretin secretion, specifically glucagon-like peptide 1 (GLP-1), through activation of G protein-coupled receptors GPR41 and GPR43 [22,23]. SCFA are elevated in obesity [24,25], where it is believed microbiota is more efficient at extracting energy from otherwise indigestible fibers, although this has not been fully demonstrated. Acetate may also have a role in central signaling of hunger and satiety [26,27]. SCFA have an anti-inflammatory effect through different pathways via both innate and adaptive immunity; they may inhibit pro-inflammatory cytokine production and promote T_{reg} expansion. They also maintain the integrity of the intestinal epithelial barrier [21]. Since differences were found in immune cells of the jejunum layer in severe obesity [28], it would be of major importance to examine the interaction between obesity-related immune dysfunction, the intestinal tract and gut microbiota. One example pertains to lymphocyte subtypes known to be modified in obese condition [29]. Mucosal-associated invariant T (MAIT) cells are innate-like T cells that recognize bacterial ligands. They are present in blood and enriched in mucosal and inflamed tissues [30]. We showed a depletion of circulating MAIT cells in obese and diabetic subjects [108]. MAIT cells in metabolic disorders have an exacerbated pro-inflammatory phenotype (increased IL-17). Furthermore, MAIT cell activation is directly influenced by metabolites synthesized from vitamin B2 and B9 by gut bacteria [30].

There are various other examples of microbiota metabolites and co-metabolites that have been implicated in metabolic disease. For example, trimethylamine (TMA) is generated from dietary choline and carnitine by certain bacterial taxa, and converted in the liver to trimethylamine N-oxide (TMAO). This compound has been consistently associated with increased risk of cardiovascular disease and mortality in humans and found to promote atherosclerosis in mice [31–33], though the mechanism remains unknown. Importantly, certain microbiomes (e.g. vegans and vegetarians) are unable to produce TMA. Another example is the production of branched chain amino acids (BCAA) by microbiota. A microbiome with a higher potential to produce BCAA has been associated with obesity [13], and insulin resistance [34]. This is relevant because high circulating concentrations of BCAA may disrupt glucose homeostasis and have been associated with T2D and obesity [35]. These findings call for detailed studies not only of microbiota composition but also of functional potential and metabolomics.

2.3. Gut microbiota diversity is decreased in metabolic diseases

A lower microbial diversity has been shown in populations where the burden of obesity and metabolic disease is greater [36–39]. When comparing fecal microbiota between groups from urban areas in the United States, rural areas in Malawi, and Amerindians from the Venezuelan Amazon it was found that subjects from the United States had the least diverse microbiota and the Amerindians had the highest diversity [36], suggesting a link between urbanization, low fiber content of Western diets, microbiota and metabolic diseases.