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Influence of High-Fat-Diet on Gut Microbiota: A Driving Force for Chronic Disease Risk

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Abstract

Purpose of review—This review will examine the recent scientific literature surrounding high-fat-diet (HFD)-induced alterations in gut microbiota and subsequent development of obesity and chronic disease risk.

Recent findings—Excessive consumption of HFDs has undoubtedly contributed to the obesity epidemic. However, the mechanisms responsible for this relationship are likely to be more complex than the simple concept of energy balance. In fact, emerging literature has implicated HFD-induced alterations in gut microbiota in the obesity epidemic. HFD consumption generally leads to a decrease in *Bacteroidetes* and an increase in *Firmicutes*, alterations that have been associated with obesity and subsequent development of chronic diseases. Potential mechanisms for this effect include 1) an improved capacity for energy harvest and storage and, 2) enhanced gut permeability and inflammation. We highlight the most important recent advances linking HFD-induced dysbiosis to obesity, explore the possible mechanisms for this effect, examine the implications for disease development, and evaluate the possibility of therapeutic targeting of the gut microbiome to reduce obesity.

Summary—A better understanding of the mechanisms linking HFD to alterations in gut microbiota is necessary to allow for the regulation of dysbiosis and ensuing promotion of anti-obesity effects.

Keywords

high-fat-diet; obesity; gut microbiome; chronic disease

Introduction

In the United States, it is estimated that 34.9% of the adult population is obese while 68.5% are classified as either overweight or obese [1]. This is of critical public health concern given the link between obesity and chronic diseases such as cancer, diabetes, cardiovascular disease, and central nervous system disorders. The global acceptance and widespread

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Conflicts of interest

None

availability of energy dense foods along with the lack of physical activity are largely responsible for the dramatic increase in obesity rates. However, this may present an over simplistic view of this mechanism as it's now evident that the causes of obesity involve contributions from the environment and host genetics in addition to an imbalance between food intake and energy expenditure. As such, emerging evidence provides an argument for a role of the gut microbiome in the control of body weight and energy homeostasis. This is thought to be driven, at least in part, by high-fat-diet (HFD) induced alterations in gut bacterial composition; HFD feedings have been associated with modifications in the gut microbial profile as well as decreased diversity [2,3]. This review will examine the recent literature on HFD-induced alterations in microbiota composition, the propensity for this to lead to an obese phenotype, the consequences for disease risk, and the potential to target HFD-induced dysbiosis for obesity prevention.

Influence of High-Fat-Diet on Dysbiosis

The composition of gut microbiota is unique to each individual, is variable between persons, and is reasonably stable following the first year of life. Despite this, emerging literature implicates diet as an important influence on the gut microbial profile. As such, lack of adequate nutrition has been linked to dysfunctional microbiota and dysbiosis.

Recent research has focused on the influence of HFD consumption on gut microbial composition. For example, it has been reported that HFD promotes a decrease in *Bacteroidetes* and an increase in both *Firmicutes* and *Protebacteria* [2,3]. Similar phylum-level shifts were reported following high-fat and high-sucrose feedings [4]. Specifically, it was reported that body fat percentage growth was negatively associated with the abundance of *Akkermansia* (phylum *Verrucomicrobia*) but positively associated with the relative abundances of *Lactoococcus* from phylum *Firmicutes* and with the genera *Allobaculum* (phylum *Bacteroidetes*) [4]. Carmody et al., used over 200 strains of mice to determine whether variations in gut microbiota are primarily driven by host genetics or by dietary factors [5*]. Their findings indicate that a high-fat and high-sugar diet reproducibly altered the gut microbiota despite differences in host genotype [5*]. More specifically, the gut microbiota exhibited a linear dose response to dietary perturbations, taking an average of 3.5 days for each diet-responsive bacterial group to reach a new steady state [5*]. However, repeated dietary shifts demonstrated that most changes to the microbiome are reversible, while the abundance of certain bacteria depends on prior consumption [5*]. Arguably the most convincing evidence for an impact of HFD-induced gut microbial changes in obesity comes from an investigation to determine whether shifts in the microbial profile during obesity are a characteristic of the phenotype or a consequence of obesogenic feeding [6**]. Huang et al., reported that obese-prone rats display a gut microbiota distinct from obese-resistant rats fed the same HFD [6**]. Transfer of obese-prone but not obese-resistant microbiota to germ-free mice replicated the characteristics of the obese-prone phenotype, increased weight gain and adiposity, intestinal permeability and inflammation, and enhanced lipogenesis and adipogenesis [6**]. Interestingly, HFD-induced changes in gut microbiota and resulting metabolic perturbations appear to be dependent on the fat content as milk fat-based, lard-based (saturated fatty acid sources), or safflower oil (polyunsaturated fatty acid)-based HFDs induced dramatic and specific 16S rRNA phylogenic profiles that were associated

with different inflammatory and lipogenic mediator profiles of mesenteric and gonadal fat depots [7]. However, not all the data supports a positive association as a few studies have reported that the absence of intestinal microbiota does not protect mice from diet-induced obesity [8]. Inconsistences in the literature are likely due, at least in part, to microbial adaptation to diet and time [9].

Mechanisms Linking High-Fat-Diet-Induced Dysbiosis to Obesity

The consequences of HFD-induced dysbiosis are potentially significant as the majority of evidence links this to the promotion of obesity and ensuing metabolic disorders. For example, in a study of obese and overweight individuals it was reported that reduced microbial richness was associated with more pronounced dys-metabolism [10]. Potential mechanisms for this effect include 1) an improved capacity for energy harvest and storage and 2) enhanced gut permeability and inflammation.

1. Improved capacity for energy harvest and energy storage

It has been reported that the microbiome from an obese mouse has an increased capacity to harvest energy from the diet [11]. This trait is transmissible as colonization of germ-free mice with an ‘obese microbiota’ results in an increase in body fat compared with colonization with a ‘lean microbiota’ [11]. This phenomenon is reportedly due to fermentation of undigested food components by gut microbes leading to increased short-chain fatty acids (SCFAs), an important energy source for the host [12]. In support of this, Schwiertz et al., found significant differences in SCFA concentrations between lean and obese individuals [13]. Similarly, overweight/obese women with metabolic disorder had a higher proportion of bacteria belonging to *Eubacterium rectale-Clostridium coccoides*, a bacterium associated with efficient energy harvest from nutrients in the gut, than overweight/obese women without metabolic disorder and normal weight women [14].

In addition, gut microbiota reportedly play a role in the modulation of genes associated with fat storage. Conventionalization of germ free mice with a normal microbiota produces a 60% increase in body fat content and insulin resistance within 14 days despite reduced food intake. A decrease in fasting-induced adipocyte factor (Fiaf) is thought to play a role in this process as it is selectively suppressed in the intestinal epithelium of normal mice by conventionalization and studies using knockout mice show that it is necessary for the microbiota-induced deposition of triglycerides in adipocytes [15]. Similarly, adenosine monophosphate-activated protein kinase (AMPK) is thought to influence fat storage as germ-free mice consuming a western-style diet have increased levels of AMPK and its downstream targets involved in fatty acid oxidation in the skeletal muscle and liver compared to conventionalized mice [16].

2. Enhanced gut permeability and inflammation

HFD-induced obesity is associated with low-grade chronic inflammation. The initiating events for this process are thought to be due to an increase in intestinal LPS-bearing bacterial species and subsequent activation of toll like receptors (TLRs) on immune cells [17]. Further, HFD can alter intestinal barrier structure via a reduction of tight junction

proteins [18]. An increase in bacterial translocation ensues leading to elevations in circulating LPS and metabolic endotoxemia [17]. A study by Burcelin's group reported that HFD modulates gut microbiota in association with increased plasma LPS [19]. Interestingly, when antibiotic treatment was used to deplete gut microbiota, plasma LPS as well as cecal LPS was reduced and this was associated with reduced glucose intolerance, body weight gain, fat mass development, increased inflammation and macrophage accumulation [19]. Similarly, Ding et al., reported an increase in inflammatory mediators in the ileum and colon of mice following HFD-feedings in conventionally raised mice but not in germ free mice [20] . Interestingly, these effects preceded weight gain and obesity and showed strong and significant associations with progression of obesity and development of insulin resistance [20]. In addition, rats that exhibited an obesity prone phenotype following HFD feedings showed an increase in TLR4 activation, ileal inflammation, intestinal permeability, and plasma LPS but these effects were not reported for obesity resistant rats [21]. Further, an increase in *Enterobacteriales* was reported in the obese prone rats, which is known to be associated with inflammation [21].

HFD-Induced Dysbiosis and Disease Risk

Obesity has been associated with cancer, diabetes, cardiovascular disease, and central nervous system disorders to name a few. The mechanisms that link obesity to disease risk are undoubtedly multifactorial in origin. However, recent evidence provides a compelling argument to include gut microbiota as a potential player.

1. Cancer

Recent studies provide evidence to support a role of the gut microbiome in driving obesity-induced cancers. For example, Schulz et al., examined the effects of HFD on tumor progression in the small intestine using a genetically susceptible K-ras^{G12Dint} mouse model and found a shift in the composition of the gut microbiota, which was associated with increased tumor progression [22**]. The transfer of fecal samples from HFD-fed mice with intestinal tumors to healthy K-ras^{G12Dint} mice resulted in enhanced tumorigenesis, while the use of antibiotics blocked this effect, directly implicating microbiota in disease progression [22**]. These effects occur independent of obesity as the K-ras^{G12Dint} mice were resistant to HFD-induced obesity [22**]. Similarly, Yoshimoto et al., reported that both HFD-induced and genetic obesity causes alterations in gut microbiota leading to increased deoxycholic acid (DCA), a gut bacterial metabolite known to cause DNA damage [23]. Enterohepatic circulation of DCA resulted in secretion of various inflammatory and tumor-promoting factors in the liver, thus facilitating chemically induced-HCC development in mice [23].

2. Cardiovascular Disease

Current literature supports an influence of gut microbiota on cardiovascular disease. This is thought to occur via sensing of gut microbial-derived products by the host receptor system [24]. Li et al., reported that a 'western-type' diet induced atherosclerosis progression in association with altered gut microbiota functions among others. Switching to a normal diet reversed this process implicating a crucial role of gut microbiota in atherosclerosis

development [25]. In addition, it was reported that atherosclerosis susceptibility may be transmitted via transplantation of gut microbiota and that this may be influenced by intestinal microbial metabolism of certain dietary nutrients producing trimethylamine N-oxide [26*]. Similarly, Ghosh et al., treated LDLR deficient mice with antibiotics and reversed the effects of a western diet on development of atherosclerosis [27]. A human study found that bacteria from the oral cavity and the gut correlated with plasma cholesterol levels and may correlate with disease markers of atherosclerosis [28]. Likewise, Karlsson et al., reported that patients with symptomatic atherosclerosis harbor characteristic changes in the gut metagenome [29].

3. Diabetes

It's well recognized that obesity can lead to diabetes, thus it's no surprise that studies have examined a link between HFD-induced dysbiosis and insulin resistance. Mice fed a HFD that were classified as diabetic or diabetic resistant displayed a gut microbial profile specific to each metabolic phenotype despite having the same background and nutritional status [30]. These findings were consistent in humans as insulin-resistant versus insulin-sensitive obese subjects had a segregated microbial DNA profile based on their degree of insulin action [31]. In an effort to find bacterial predictors of type 2 diabetes, it was discovered that blood levels of 16S rDNA are elevated well before development of diabetes [32]. Mechanistic support for this relationship comes from antibiotic treatment in HFD fed mice where reduced levels of fasting glucose and insulin and improved glucose and insulin tolerance were reported [33]. A recent study by Denou et al., reported that NOD2 plays a role in this process as defective NOD2 peptidoglycan sensing promotes dysbiosis and insulin resistance [34*]. Similarly, the SCFA receptor GPR43 is likely to be involved as it has been reported that the gut microbiota suppresses insulin-mediated fat accumulation via this receptor [35].

4. Central Nervous System Disorders

Accruing evidence indicates that the gut microbiota can communicate with the central nervous system (CNS), thus influencing brain function and behavior. Germ free mice display increased motor activity and reduced anxiety behavior in conjunction with altered expression of associated genes [36]. Hsiao et al., demonstrated microbial alterations in a mouse model that is known to display features of autism spectrum disorder. Interestingly, treatment of these mice with the human commensal *Bacteroides fragilis* ameliorates the defects in communicative, stereotypic, anxiety-like and sensorimotor behaviors [37]. Additionally, disruption of the gut microbiota in early-life selectively affects visceral pain in male rats [38]. A recent study of Parkinson's patients indicated that the intestinal microbiome is altered in Parkinson's disease and is related to motor phenotype [39]. Although it's clear that gut microbiota can influence CNS disorders, studies implicating HFD-induced microbiome alterations in this process are currently limited. However, a study by Bruce-Keller et al., reported that mice transplanted with microbiota from HFD fed mice had significant selective disruptions in exploratory, cognitive, and stereotypical behavior in association with increased neuroinflammation and disrupted cerebrovascular homeostasis [40*].

Targeting High-Fat-Diet-Induced Dysbiosis for Obesity Prevention

Recent studies have evaluated the possibility of therapeutic targeting of the gut microbiome to reduce obesity. Although still in its infancy, several studies have reported promising findings.

The majority of studies to date have employed probiotics to target HFD-induced dysbiosis. For example, Stenman et al., treated HFD fed mice with Bifidobacterium animalis ssp. lactis 420 and found a decrease in fat mass along with improved glucose tolerance, decreased LPS levels, and reduced inflammation [41]. Similarly, Saccharomyces boulardii Biocodex, a probiotic yeast, reduced body weight, fat mass, hepatic steatosis and inflammatory tone in leptin-resistant obese and type 2 diabetic mice in accordance with dramatic changes in the gut microbial composition [42]. In another study, the prebiotic oligofructose, reduced energy intake, weight gain and fat mass and both oligofructose and the probiotic Bifidobacterium animalis subsp. lactis BB12 improved glycemia [43]. Park et al., reported that HFD fed mice treated with Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032 had reduced weight gain and fat accumulation as well as lowered plasma insulin, leptin, total-cholesterol and liver toxicity biomarkers, which was associated with changes in gut bacterial composition and diversity [44]. Although, Lactobacillus salivarius UCC118 Bac(+) changed the microbiome composition in HFD-induced obese mice this was not reflected by an improvement in the metabolic profile [45]. However, in a follow-up time course study this group reported that Lactobacillus salivarius UCC118 Bac(+) does in fact result in a decrease in weight gain but the effects appear to be time dependent [46].

Recent evidence supports a possible beneficial effect of plant components in altering gut microbial composition in obesity models. Quercetin but not resveratrol was effective at reducing dysbiosis induced by a high-fat sucrose diet [47]. Although this was associated with reduced serum insulin and insulin resistance, these effects were also reported for resveratrol which scarcely modified the profile of gut bacteria [47]. Similarly, fermented green tea extract was reported to alter the composition of gut microbiota and this was linked to a decrease in fat mass, reduced inflammation and alleviation of glucose intolerance [48]. Further, a polyphenol-rich cranberry extract was reported to protect mice from diet-induced obesity and metabolic perturbations, which was associated with a proportional increase in Akkermansia spp. population [49].

Conclusion

While it’s clear that HFD can result in significant changes in gut microbial composition, a large number of studies to date are simply associations between HFD consumption, altered gut bacterial composition, and promotion of obesity. Significant mechanistic research is needed to link specific gut phylotypes to obesity traits and subsequent risk for chronic disease. Although the available literature on therapeutic targeting of the microbiota to counteract diet-induced obesity appears promising, whether this presents a realistic approach is unclear. Viable agents have yet to be fully recognized, and specifics on the dose, timing and frequency of administration are still unknown.

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Key Points

- Emerging evidence has implicated high-fat-diet-induced alterations in gut microbiota in the obesity epidemic.
- High fat diet-induced dysbiosis is thought to promote obesity through an improved capacity for energy harvest and storage as well as enhanced gut permeability and inflammation.
- High fat diet-induced alterations in the gut microbiome have been associated with increased disease risk.
- Therapeutic targeting of the gut microbiome may reduce obesity and subsequent chronic disease risk.