

Microbiota in Obesity

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Abstract

The obesity epidemic is globally considered as one of the topmost health concern whose multifactorial etiology involves sedentary life style, poor dietary habit, individual's genetic peculiarity, environmental factors, adipose tissue inflammation and many more. More recently, researchers are intensively focusing on the role of gut microbiome in the manifestation and pathogenesis of obesity and associated complications. Microbiomes modulation of inflammatory responses associated to physiology of obesity implicated the involvement of the Toll-like receptors (TLRs), Short-chain fatty acids (SCFAs) response, gut fermentation mechanisms, as well as passive immune defense exerted by refining of mucous barriers in response to bacterial presence. We reviewhere the role of gut microbiota in the pathogenesis and management of obesity as it relates to metabolic inflammation. Accurate alteration of the gut microbiome appears to be a potential therapeutic intervention that may impede white adipose tissue inflammation and in the long run prevent obesity.

Keywords: Etiology; Microbiomes; Microbiota; Firmicutes; Bacteroidetes

Introduction

Obesity is a metabolic product of long-term imbalance between energy intake and expenditure with a heterogeneity characterization involving several health threatening co-morbidities [1]. Its pathogenesis is dependent on host genetics, environmental factors, diet/caloric intake, lifestyle, and adipose tissue inflammation [2]. Comorbidities of obesity includes insulin resistance, type 2 diabetes, atherosclerosis, hypercholesterolemia, fatty liver disease, hypertension, and low grade systemic inflammation [3], which all together translates towards metabolic syndrome [2].

Recently, researches focusing on the involvement of intestinal microbiota in the manifestation and management of obesity reflected the need to critically examine the lineage of microbiome-obesity-adipose tissue inflammation link.

Gut Microbiota Profile and Obesity

The gut consist of approximately 1014 bacteria with an estimated 150-fold more accumulated genes than the entire single human genome. Among the established human gut microbiota (which are mostly Gram-positive and anaerobic), Firmicutes and Bacteroidetes predominates, accounting for more than 90% of physiologically important microbiomes [4-6]. Apart from the substantial beneficial digestive function of the gut microbiota, it was suggested to be an important environmental factor involved in the regulation of body weight, energy homeostasis and consequently obesity [7,8].

Substantial difference in flora composition exist between obese animals and human subjects as compared to their leaner counterparts [4], showing a greater representation of Firmicutes and fewer Bacteroidetes, as well as reduced bacterial diversity at large [8]. A number of studies on microbiota profile of obese rats clearly

supported patterns of greater Firmicutes/Bacteroidetes ratios [5]. Furthermore, some specific proteobacteria (Halomonas and Sphingomonas) as well as lower bifidobacterial and total bacteria counts were associated with the obese phenotype [8].

The Firmicutes and Bacteroides are both affected by modality of diet [6]. Microbiome - diet hygiene interactions influences host biology through variety of mechanisms [7], a common example include the phenotypic obese trait expression that accompanies gut microbiota alterations [8]. The mechanisms through which this phenotype is developed is quite intricate, as a number of underlying mechanisms are thought to coalesce within the host microbiome to result in obesity and these underlying mechanism includes the role played by gut microbiome in energy homeostasis, food intake and its interaction with biomolecules that were proven to be implicated in the pathogenesis of obesity [9,10].

Improper dietary habit involving consumption of insulinogenic foods, proteotoxins, gluten, zein, low intake of fruits and vegetable predisposes individuals to dysfunctional microbiota, dysbiosis, chronic inflammation, increased production and leakage of endotoxins through the various tissue barriers as commonly observed in obesity and chronic diseases [9]. The great majority of Western diet has been reported to be absorbed in the upper small intestine and thus have limited benefit to the microbiota which is mostly populated in the colon. Most of the Firmicutes predominantly exist in the upper intestinal areas while the Bacteroides and Bifidobacteria are more in the colon. It can be suggested that this distribution (see table 2) added to the fact that that industrialized foods are absorbed in the upper part of the small intestine favors some firmicutes overgrowth and Bacteroides suppression in obese individuals. It is can also be postulated that the overgrown gut microbiome mediates epigenetic modifications that may implicate the development of obesity. Table 1 illustrates the alterations in microbiome in relation to normal lean flora architecture upon exposure to dietary and non-dietary dependent obesity etiologies.

Microbiome	Increased	Decreased	Reference
<i>Bacteroidetes</i>			
<i>Bacteroides vulgates</i>			[46,47]
<i>Bacteroides uniforms</i>			[47]
<i>Alistipes (genus)</i>			[47]
<i>Firmicutes</i>			
<i>Lactobacillus reuteri</i>			[48]
<i>Clostridium cluster XIVa</i>			[47]
<i>Roseburia intestinalis</i>			[47,49]
<i>Eubacterium dolichum</i>			[50]
<i>Eubacterium rectale</i>			[49,51]
<i>Lactobacillus (genus)</i>			[46,52]
<i>Actinobacteria</i>			
<i>Bifidobacterium</i>			[11]
<i>Euryarchaeota</i>			
<i>Methanobrevibacter smithii</i>			[53,11]

Table 1: Microbiome profile alterations in obese subjects.

Microbiota, Lipogenesis and Energy Homeostasis

In response to over nutrition, gut microbiota promotes fat deposition and storage in adipocytes by suppression of the intestinal expression of an inhibitor of lipoprotein lipase (LPL) termed as fasting-induced adipose factor (FIAF), otherwise known as Angiopoietin like 4 (ANGPTL4). The main function of LPL is hydrolysis of triglycerides to fatty acids, the fatty acids get transported into adipocytes, subsequently re-esterified into triglycerides and stored as fat in the adipose tissue cells. ANGPTL4 carry out its anti-obesogenic function by antagonizing LPL activity, thus suppression of ANGPTL4 by gut microbiota leads to a higher LPL activity, followed by increased cellular uptake of fatty acids and triglyceride accumulation in adipocytes laying the foundation for development of obese phenotype [8]. This indicates that amplification of ANGPTL4 activity may serve as a potential means of depleting excess fat stores among the obese.

Microorganisms	Stomach	Jejunum	Ileum	Colon
Total Count	0-103	0-105	103-107	1011-1012
Aerobic or facultive microorganisms				
Enterobacteria	0-102	0-103	102-106	104-1010
Streptococci	0-103	0-104	102-106	105-1010
Staphylococci	0-102	0-103	102-105	104-107

Lactobacilli	0-103	0-104	102-105	106-1010
Fungai	0-102	0-102	102-103	102-106
Anaerobic microorganism				
Bacteroides	rare	1-102	103-107	1010-1012
Bifidobacterium	rare	0-103	103-105	108-1012
Peptostreptococcus	rare	0-102	103-107	1010-1012
Clostridium	rare	rare	102-104	106-1011
Fusobacterium	rare	rare	rare	109-1010
Eubacterium	rare	rare	rare	109-1012

Table 2: Composition, distribution and number of microbiome per milliliter of gastrointestinal content [55].

The microbiota play a significant role in energy processing and regulation of nutrient harvest, one mechanism through which this is achieved includes hydrolysis and fermentation of non digested dietary polysaccharides to monosaccharides and short chain fatty acids (SCFAs) which functions as sources of energy to various organs (e.g. colon, liver and adipose tissues) [10]. Fermentation activity of gut microbiomes and subsequent SCFAs production was reported to be higher in obese and overweight subjects. This occurs as a result of incomplete digestion of complex dietary polysaccharides by glycoside hydroxylase [11]. Changes in the population of the two dominant bacterial phyla (Firmicutes and Bacteroidetes) as observed in obese subjects, may explain the variation and contribution of microflora to energy homeostasis because the microbes differ in energy harvest capacities [8,12]. Additionally the increased level of SCFAs was associated with increased lipogenesis in the liver as well as increased production of very low density lipoprotein (VLDL) [8].

The colonic epithelia derive 60–70% of their energy supply from SCFAs, particularly butyrate [13]. SCFAs (e.g. propionate, butyrate, acetate etc) signaling cascades are mediated by membrane surface G protein- coupled receptors (GPCRs), explicitly free fatty acid receptors 2 and 3 (FFAR2 and FFAR3). FFAR2 promotes +ve energy balance by stimulating adipogenesis, inhibiting lipolysis and decreasing expenditure of stored energy [14]. Its deficiency is associated with lower body fat mass, increased lean body mass, high energy expenditure, high core body temperature, increased insulin sensitivity, low triglyceride and hypocholesterolemia [15]. FFAR2 contained in the colon, regulates host energy homeostasis through effects that are microbiota dependent and they do regulate intestinal motility and satiety via a gut hormone known as glucagon-like peptide GLP-1 [16].

GLP-1, an incretin hormone that is secreted by L-enteroendocrine cells, it communicates with the hypothalamic centers to promotes satiety and suppress energy intake. Additionally it regulates insulin and glucagon secretion [5]. This suggests that manipulation of SCFA activation of GPCRs could, theoretically, serve as a therapeutic target, modulating efficiency of caloric extraction from a polysaccharide-rich diet.

Another important regulator of energy homeostasis is the Adenosine monophosphate-activated protein kinase (AMPK) is an enzyme that is expressed primarily by brain, liver and skeletal muscle cells in response to disruption of AMP: ATP or NAD: NADH ratios, which are indicators of metabolic stress. In an energy deprived state, AMPK stimulates fatty acid oxidation, ketogenesis, glucose uptake, and insulin secretion while inhibiting cholesterol synthesis, lipogenesis, and triglyceride synthesis. The gut microbiome has suppressive effect on AMPK-driven fatty acid oxidation activity thereby predisposing subjects to obesity and insulin resistance [17]. As earlier mentioned, the gut microbiota suppresses the intestinal expression of ANGPTL4, which not only regulates LPL but also is a potent regulator of fatty acid oxidation [5]*. So far, there is no dependable established fatty acid oxidation link between the ANGPTL4 and AMPK but it is possible that their expression is initiated by a similar factor onto which the microbiome targets. Nevertheless concurrent activation of the two unrelated pathways may increase fatty acid metabolism and properly reverse fat storage.

The gut communicates with the hypothalamus via neural and hormonal pathways. The gut hormones are produced by enteroendocrine cells in the intestinal epithelium in response to dietary intake. Enteroendocrine cells express the SCFA receptor and this gives the gut microbiota the opportunity to regulate host metabolism by induction of gut hormones released by L-cells especially glucagon-like peptide (GLP) and peptide YY (PYY) in response to GPCRs activation [14]. These hormones control satiety by regulating the production and release of digestive enzymes [18]. In addition to its effect on satiety, PYY decreases pancreatic secretions, suppresses gastric motility and slows gastric emptying thus enhancing digestion. Several lines of evidence suggest that low circulating PYY concentrations predisposes individuals to obesity and vice versa. Mice lacking PYY are hyperphagic and have obese phenotype, conversely, chronic PYY3-36 (one of the two major forms of PYY) administration to obese rodents reduces adiposity [19]. Reduced expression of PYY in FFAR3 deficient mice resulted in lower body fat mass and increased lean body mass [15]. This indicates that targeting the PYY system by alteration of the microbiome may serve as an important therapeutic approach to treating obesity.

Microinflammation and Microflora

Obesity is associated with a low- grade inflammatory state affecting energy homeostasis. Development of adipose tissue in obesity is characterized by increased plasma levels of some inflammatory and acute phase proteins such as C-reactive protein, interleukin(IL)-6, IL-8, serum amyloid A (SAA), monocyte chemotactic protein (MCP)-1 and decreased anti-inflammatory adipokines such as adiponectin [4]. Adipocyte necrosis was suggested to be the basis for the pro-inflammatory responses in obesity simply because caloric intake and energy expenditure result in adipocyte hypertrophy, which may be accompanied by local hypoxia and apoptosis [20]. Hypertrophic adipocytes secrete TNF- α which stimulates chemotactic response and attracts macrophages as a in response to increased adipocyte turnover. Metabolic endotoxemia as a result of microbiota-derived LPS may be the trigger involved in the onset and progression of inflammation in obesity [1]. This is strongly supported by the explicitly increased insulin resistance and adipose tissue weight gain similar to high-fat diet induced obesity alongside observed elevated levels of inflammatory markers following continuous LPS infusion [21].

Toll-like receptors (TLRs) are a type recognition receptor, which function in innate immunity by interacting with interleukin-1 receptors to form “interleukin-1 receptor/TLR super family.” TLRs have since been implicated in the pathogenic process of diabetes through increase in the level of blood sugar, non-esterified free fatty acids, cytokines secretion and reactive oxygen species. This results in pro-inflammatory state that manifests diabetes [22].

The bacterial microbiota modulates gut motility through afferent nerve terminals or signaling peptides, which alters gut hormones secretion and modifies gut permeability. Bifidobacteria decreases serum LPS translocation and increases its colonic level by reducing gut permeability through glucagon-like peptide-2 [21].

LPS was reported to trigger the development of chronic systemic inflammation through increased pro-inflammatory cytokines production by binding TLR4 to elicit downstream signaling cascades that exert negative effect on glucose tolerance, which leads to insulin resistance and increased body weight [23]. This occurs in a pattern that mimic the activation of TLR4 signaling in chronic inflammation of adipocytes by increased circulating levels of fatty acids in obesity and insulin resistance [24]. Since hypoxia inducible factor-1 α (HIF-1 α) upregulates TLR4 expression in macrophages, hypoxic stress at inflammatory sites may enhance bacterial mediated innate cellular responses [2].

In the view of enhancing host defense and survival, TLR5 activates innate immunity by recognition of pathogen through the microbe-associated molecular patterns (MAMPs) expressed on bacteria, viruses and fungi [25] leading to induction of inflammatory cascades and downstream transcription of various inflammatory cytokines and mediators through a number of transcription factors, most notably NF κ B, which plays crucial role in immune and inflammatory responses [26]. A number of obesity risk factors such as hyperlipidemia, hypertension, and insulin resistance were observed in TLR5 deficient mice, in addition, severe hyperphagia and increased adiposity were also reported [27]. Another important finding linking microbiome dependent LPS level with inflammation was the observation that Co-administration of high-fat diet and antibiotics decreased levels of endotoxin, inflammatory markers, reduced weight gain and improved glucose tolerance [23]. Thus, the manipulation of the gut microbiota may provide a novel therapeutic target for obesity.

Potential Therapeutic Perspectives

Since excessive fat accumulation results not only from positive energy balance and sedentary life style, identifying specific nutritional and biomolecular components that has linkage to microinflammation in obese state can lead to therapeutic strategies that will allow manipulation and restoration of healthy state gut microbiota may provide lasting solution [28]. Microbiota can be modulated using prebiotics, probiotics, diet, stem cell infusion or fecal microbiota transplant [29] Dominant obese microbiome (i.e. Firmicute) contain more genes associated with lipid and carbohydrate metabolism and the breakdown of indigestible polysaccharides than dominant lean microbiome (i.e Bacteroidetes) [30]. One of the gut microbiome that has received so much attention is the Bifidobacterium. It play a pivotal role in physiology of inducing weight loss and it function by antagonizing the pro-inflammatory action of gut microbiota in response to a high fat diet, which normally predisposes subjects to obesity [31]. In diet induced obesity, increase in fecal level of Firmicutes (obesogenic) and a decrease in Bacteroides (anti-

obesogenic) was observed, this supported the influence of diet in alteration of gut microbiome. Induction of obesity by high fat diet is independent of presence or non presence of gut microbiota, nevertheless the extent of obesity induced is higher in germ-free subjects devoid of microbiota. Prebiotics on the other hand increases Bacteroides and conversely decreases Firmicutes gut population, and promote SCFA production [20].

Probiotics are live microorganisms that, when ingested in adequate quantities alter and reconstitute gut microbiota to a profile that is beneficial to host health. They exert this beneficial effect by stimulating the growth of other microorganisms, modulating immunity (mucosal and systemic), and improving microbial balance in the gastro-intestinal tract [32]. Various probiotic strains has been tested for anti-obesity effects, example includes Bifidobacterium, Lactobacillus, Saccharomyces, Streptococcus, and Enterococcus [33,34] Probiotics such as Lactobacillus decreases body weight, subcutaneous fat, BMI, waist, and hip circumference. A number of the human trials conducted using probiotics were encouraging and very promising [35].

Prebiotics are non-digestible polysaccharides that selectively stimulate the growth and/or activity of one or a limited number of gut bacteria (usually Bifidobacterium and Lactobacillus) to exert beneficial health effects to the host [36]. Some classical examples of prebiotics include the inulin-type fructooligosaccharides (FOS), wheat arabinoxylan, oligofructose, oat, bran, pectin, and resistant starch. Modification on the overall structure of the gut microbiome and resultant shift in the fecal metabolic profiles characterized by marked increase in SCFA, ketones, carbon disulfide, and methyl acetate, suggests potential positive health effects of pro and prebiotics [37]. Some prebiotics exerts their anti-obesogenic function by decreasing appetite and increasing satiety, leading to a lowered total energy intake, as well as a reduced hepatic de novo lipogenesis [38-45] In a 12 week randomized control trial conducted to study the influence of oligofructose on body weight in obese and overweight subjects, a reduction in caloric intake which coincided with increased PYY and decreased ghrelin levels were recorded, this indicatings the potential weight loss effect of oligofructose in treatment of obesity [46-50]

Faecal transplantation is yet another suggested means of combating obesity. Promising findings were obtained after transplantation of stools from lean subjects to achieve weight loss [40,50-56].

Conclusion and Recommendations

Obesity and its related complications are a major detriment on the current state of healthcare and have significant health implications. The evidence presented herein strongly suggests/indicates that the gut microbiota plays a pivotal role in regulating energy homeostasis and the development of obesity and its associated low grade inflammation. It appears that manipulation of the gut flora may be a potential therapeutic target and it is also logical to try modulating gut flora towards increasing ANGPTL4 expression, an action that may promote leanness. In addition to studies conducted on life-style, exercise, dietary composition, identification of susceptibility genes from GWAS studies and epigenetic factors associated with obesity, research on human gut microbiota seems to allow the positive manipulation of the interior milieu of a human being by means of using the appropriate microbiome that exerts antiobesity effects and/or administering the right substrate (prebiotic and/or probiotics) to promote its growth.

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