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Dietary-Induced Alteration in the Gut Microbiome and Its Potential Role in Obesity

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Abstract:

The gut microbiome, a key constituent of the colonic environment, has been implicated as an important modulator of human health. Obesity has become a major health problem due to its increasing prevalence and its association with chronic disorders that include type 2 diabetes, atherosclerosis, cardiovascular disease, and cancer. Although obesity is a result of a long-term imbalance between dietary intake and energy expenditure, dietary-induced alterations in the gut microbiome play an important role in the onset and development of this condition. Many studies have shown that by manipulating diet, it is possible to favor the engraftment of a specific bacterial strain over others to control obesity using the approach of prebiotics, probiotics, and synbiotics. Metabolic changes due to the altered microbiome in obesity include enhanced energy extraction from food, lipogenesis, and insulin resistance. These therapeutic approaches to prevent and treat obesity by microbiome manipulation are being pursued in laboratories and are of growing interest to commercial companies and governments.

1. Introduction:

1.1. The Function of Gut Microbiota: The human gut microbiome consists of several trillion microbes, which reside in the gastrointestinal tract with their genes that code for a wide array of effects on human physiology. Gut microbes ferment non-digestible polysaccharides, thereby producing short-chain fatty acids (SCFAs), which bind to the GPR 41/43 receptors on gut epithelial cells and stimulate peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) production. PYY and GLP-1 are gut-derived hormones that attenuate gut motility and facilitate the aggregation of the constitutive flora to ferment more. These gut-hormones also suppress appetite by delaying gastric emptying and centrally promoting satiation. SCFAs also promote gut barrier integrity and antagonize local and systemic inflammation, which drives insulin resistance and lipogenesis. The adiposity in the liver and skeletal muscles is also regulated by gut microorganisms via phosphorylated adenosine monophosphate-activated protein kinase (AMPK) levels. In health, constitutive gut microbes maintain immunoglobulin A (IgA) levels to prevent colonization by enteric pathogens.[1]

1.2. The Association between Gut Microbiome and Obesity: When it comes to obesity, there are several ways gut microbes might influence matters, including through appetite, production of gases, efficiency of using food, and impact on the immune system and inflammation.[2] There is a large body of evidence demonstrating the link between the gut microbiome and obesity, with one of the most frequently-cited contributing factors being a shift in the proportion of bacterial flora belonging to the Firmicutes relative to Bacteroidetes phyla.[1] A diet that is high in both fat and sugar correlates with an increased proportion of Firmicutes microbes, which are efficient in harvesting energy from food, over the less efficient Bacteroidetes, potentially leading to obesity.[3] The harvested energy is generated from otherwise indigestible polysaccharides fermented by microbiome enzymes that are not encoded in the human genome. Fermentation products include monosaccharaides and short-chain fatty acids that are absorbed into the circulation, stimulating synthesis of triglycerides in the liver and their incorporation into adipocytes or

acting as regulatory molecules.[2] Hence the obesogenic diet shapes the microbiome prior to the development of obesity, leading to altered bacterial metabolite production which predisposes the host to obesity.[4]

1.3. Dietary Manipulation of Gut Microbiota: The ability to engineer a favorable metabolic environment by dietary modulation makes the gut microbiome an attractive target in the war against obesity. Dietary modulation of the gut microbiome includes three kinds of foods: prebiotics, probiotics and synbiotics. **Prebiotics** are nonviable food components associated with the favorable modulation of the gut microbiota, such as inulin, fructo-oligosaccharides, galacto-oligosaccharides, resistant starch, xylo-oligosaccharides and arabinoxylan-oligosaccharides. **Probiotics** are living microorganisms, such as *Lactobacillus* and *Bifidobacterium*, which, when ingested, provide health benefits, either directly or through interactions with the host or other microorganisms. The combination of pre- and pro-biotics has been termed **synbiotics.**[1]

1.4. The Aim of the Report: To assess the relation between dietary-induced alteration in gut microbiome and obesity using the approach of prebiotics, probiotics and synbiotics and to identify the role of antibiotics in the development of obesity.

2. Discussion:

2.1. The Overall Effect of Pre-, Pro- or Syn-Biotics on Body Mass Index, Body Weight and Fat Mass: The use of probiotics led to significant reductions in body mass index (BMI), body weight and fat mass when compared to the placebo. A subgroup analysis in five studies using single species probiotic agents revealed that *Lactobacillus* probiotics showed significant reductions in BMI and the greatest reductions in body weight and fat mass. A subgroup analysis also demonstrated significant body weight and BMI reductions in studies using low or medium probiotic doses of greater than 12 weeks in duration. Prebiotics have been shown to reduce appetite, improve insulin sensitivity and improve lipid metabolism in animal and human studies. Prebiotics only had a marginal effect on the reduction of BMI, However, there was a significant reduction in body weight and no significant loss fat mass. They improves the gut barrier by allowing the proliferation of commensal gut flora and has been shown to reduce the levels of inflammatory cytokines in animal studies. However, there are several factors, such as baseline gut microbiome profile (i.e., *Firmicutes/Bacteroidetes* ratio) and diet, which could influence the success of a prebiotic since its action is primarily the creation of a favorable environment for the growth of specific bacteria. Synbiotics didn't show an effect.[1]

2.2. Gut Microbiome and Its potential Role in Obesity: The role of the microbiome in obesity was noted by observing that germ-free mice lacking a microbiome are leaner than conventionally bred mice. The introduction of the gut microbiome from conventionally bred mice into germ-free mice (a process called *conventionalization)* produced a rapid 60% increase in body fat within 14 days despite a lower intake of chow, normalizing adiposity to the levels of conventionally raised mice. The leaner state of mice that lacked a microbiome was attributed to their inability to ferment polysaccharide- rich food to the short-chain fatty acids that are a source of energy and lipogenesis. Transferring the microbiome from the conventional mice

to the germ-free mice reversed the situation, increasing adiposity and insulin resistance. The ability to transfer the obese or lean phenotype to germ-free mice by means of the microbiome was further observed in a study using the microbiome of human female twins divergent in obesity. Gut microbiome harvested from the obese twin and transferred via gavage to germ-free mice on a low-fat diet resulted in the mice becoming obese; mice colonized with the microbiome from the lean twin remained lean.[2]

2.3. Antibiotics, Gut Microbiome and Obesity: with the increasing use of antibiotics, we are now faced not only with the increasing threat of antibiotic resistance, but also with a rising concern about potential long-term effects of antibiotics on human health, including the development of obesity. Dysbiosis (imbalance in gut microbiota) has been linked to the development of obesity by multiple mechanisms, via either direct effects on the gut or indirect regulation of distal organs. These bacteria are able to break down indigestible polysaccharides to short-chain fatty acids (SCFAs), which provide 80-200 kcal/d of energy to normal adults. Dysbiosis (e.g. a 20% increase in Firmicutes and a corresponding 20% decrease in Bacteroidetes) can result in an additional 150 kcal of energy harvested per day. Dysbiosis also reduces the production of angiopoietin-like protein 4 (ANGPTL4) that inhibits lipoprotein lipase, leading to excess deposition of triglycerides in the adipose tissue, liver, pancreas and heart. Other metabolic effects of the gut bacteria are caused by changes in behavior, including appetite modulation, food intake and energy expenditure. It's shown recently that obese humans have fewer *Bacteroides thetaiotaomicron* (glutamate-fermenting bacteria) in their gut, with an associated increase in serum glutamate concentrations. Transfer of *B. thetaiotaomicron* led to a reduction in serum glutamate levels, significantly reducing total fat mass and increasing lean body mass in mice on normal diet, and preventing further weight gain and adiposity in mice on a high-fat diet. Antibiotics have been linked to a dysbiotic gut microbiome, which in turn have been proposed to lead to obesity. The mechanisms by which antibiotics modulate weight gain are unclear, but several hypotheses have been proposed, which include the following: (i) increased ability from gut bacteria to extract energy from indigestible polysaccharides; (ii) reduction in the number of bacteria that are metabolically protective against obesity; (iii) altered hepatic lipogenesis; (iv) altered metabolic signaling; and (v) reduction in intestinal defence and immunity.[5]

Conclusion:

The normal gut microbiome imparts specific functions in host metabolism, including immunity, maintenance of the intestinal barrier, and protection against pathogens. The composition and activities of the microbiome are altered in obese individuals compared with their lean counterparts. The utilization of gut microbiome-modulating dietary agents (prebiotic/ probiotic/ synbiotic) shows significant decreases in BMI, weight and fat mass. Further studies are needed to identify the ideal dose and duration of supplementation and to assess the durability of this effect. There are strong data supporting the role of antibiotics in the development of obesity in well-controlled animal models, but evidence in humans remains inconclusive.

References:

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