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Management of obesity and other metabolic disorders through faecal microbiota transplant technology

Abstract

The microbiota regulates health and many diseases both infectious and metabolic. The makeup and density of intestinal microbiota can be influenced by diet and therefore, they play a major role in the development of obesity by regulating energy metabolism. Recent evidence, primarily from investigations from animal models, suggests that the gut microbiota affects nutrient acquisition and energy regulation. Gut microbiota regulates obesity by regulating energy absorption, central appetite, fat storage, chronic inflammation, and circadian rhythms. Several members of phylum Proteobacteria, were reported to be obesity-associated. Among non-antibiotic therapeutic method, the faecal microbiota transfer technology seems to be one of the effective therapeutic and management techniques to treat and/or manage some of the metabolic disorders in particular obesity.

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Introduction

In order to avoid the ill effects of antibiotics scientists were in search of alternative therapies for infectious diseases.[1] Antimicrobial Proteins, Bacteriocins, Bacteriophages, Plant-Derived Antimicrobial Compounds, Probiotics. and Prebiotics have been identified to suit the requirements as an efficient alternative to antibiotics.[2] In faecal microbiota transplant technology (FMT) the faecal matter of a healthy human to a patient via colonoscopy, enema, nasogastric (NG) tube, or in capsule is delivered. FMT is highly effective, safe, and cost-effective treatment option at least for recurrent *Clostridioides difficile* infection (CDI) with a success rate around of 90%. From animal models and human trials this technique is also proved to be an effective in several diseases such as, Carbapenem-resistant *Interobacteriaceae* (CRE), Alzheimer's, arthritis, diabetes mellitus, inflammatory bowel disease, autism, polycystic ovary syndrome and obesity.[3–5]

Obesity is a public health issue, due to disequilibrium in energy balance, with energy intake exceeding energy expenditure resulting in a state of chronic inflammation. Obesity also proves to be a triggering factor for the prognosis of metabolic diseases such as, type 2 diabetes, cardiovascular diseases, osteoarthritis and certain cancers. Globally, the prevalence of obesity is increasing at an alarming rate. Further to increasing the onset of metabolic imbalances, obesity is one of the nine contributory factors for aging as well as for reducing the life span. The increasing rate of aging due to obesity, affects all aspects of physiology and thus shortening life span and health span.[6] Obesity is also associated with depression, suffers from sleep issues, insomnia and increased risk for developing asthma. At present, there are more than 500 million adults worldwide who are considered to be with overweight [body mass index (BMI) of 25.0-29.9 kg/m2] and 250 million people saluted as obese (BMI ≥30 kg/m2) globally.[7]

Out numbering the human genome by 150:1, bacteria is involved in the development and evolution of human beings with a constant turnover from birth till death. Diversity as well as adaptability of these organisms and their by-products change drastically throughout life in human beings.[8–10] The bacterial populations residing in the digestive system are observed to co-develop along with the human host and also depend on the mode of birth,[11] breastfeeding and early diet and nutrition, environmental and other factors including antibiotic exposure ultimately leading to bacterial disequilibrium and variations in prognostic outcomes. Gut microbes are involved in polysaccharide breakdown, nutrient absorption, inflammatory responses, gut permeability, and bile acid modification. In addition to changes in energy balance discussed earlier, other defined factors are also identified to be responsible for the increased incidence of obesity and related metabolic diseases worldwide. One such crucial factor is the dysbiosis of the gut microbiota due to their capability to utilize more energy from the diet.[12–14]

Role of the gut microbiota in obesity

In depth studies provide concrete proof for the close association between the microorganism present inside the digestive system and obesity as well as obesity-associated abnormalities. Elevated energy harvest from the diet, fatty acid regulation within the tissues, chronic as well as low-grade inflammation are linked as causal factors to induce obesity.[7] When these bacteria and their metabolites interfere with the host carbohydrate metabolism, obesity and imbalance of their number ultimately results in metabolic syndrome.[4,15] There exists a drastic difference between the bacterial population of the digestive system of lean and obese individuals which came to lime light only from metagenomic studies.[16] The altered microbiota found in obese individuals could be responsible for re-disposing them to obesity through increased energy extraction, or possibly through an interaction with the gut–brain access leading to decreased energy output or through influencing fullness.[17] The hypothesis for the involvement of the intestinal bacteria to induce obesity could through increasing dietary energy harvest, increase adipose tissue formation, altering the loco motor activity of the host, having central effects on a feeling of fullness, and triggering systemic inflammation.[7]

Reports are available for the high fat diet to induce chronic systemic inflammation. As a result shifts in the balance of gut microbiota composition toward high in unfavourable bacterial species that may predispose an individual to weight gain.[11] Decrease in the fractional proportion of *Bacteroidetes* species relative to *Firmicutes* in obese subjects compared with lean individuals was a valid observation but vice versa could be observed regarding the relative proportion of *Bacteroidetes* species and microbial diversity. Similarly, diversity of the genes was decreased in obese compared with lean individuals. Management of obesity and other metabolic disorders through FMT can be manage effectively.[7] Many studies have given a clue that the methanogenic *Archaea* may contribute to altered metabolism and weight gain in the host. In fact the point to be focussed is that there may be difference between the content of the stool or colonic samples with which studies are performed compared to the metabolically active small intestine.[6]

In depth studies has proved that alterations in intestinal bacterial population is capable of reducing intestinal barrier integrity but to increase the oxidative stress and mucus degradation by reducing the production of butyrate (known to be associated with obesity and pain sensation and plays an important role in colonic function). *Akkermansia muciniphila* was reported to reduce the insulin resistance index, control fat storage, adipose tissue metabolism, intestinal levels of acylglycerols, and glucose homeostasis. When the diet was altered increase in *Clostridium leptum, Bacteroides fragilis, and Bifidobacterium catenulatum* and decreased abundance of *Lactobacillus, Clostridium coccoides, and Bifidobacterium* was noticed. Only quality of the diet and not the quantity hardly had the impact in the experiment.[18] also reported that the gut of obese subjects had more H_2-producing bacterial groups. Probably these bacteria are capable of absorbing H_2 rapidly by methanogens resulting in the fermentation of carbohydrates and increase the hydrolysis efficiency of usually indigestible organic matter.[18–20] It is interesting to note that pure form of lipopolysaccharide and endotoxin, the only bacterial product when subcutaneously infused in a mice, obesity and insulin resistance could be induced via an inflammation-mediated pathway.

Not all bacterial strains have the capacity to induce obesity since some pro and some are anti-obesity depending on the fibre utilization (Anti-obesity) like *A. muciniphila* commonly linked to anti-obesity characteristics.[21,22] To ensure efficacy during obesity treatments, alterations of intestinal bacteria is very essential. With a good knowledge gained about the influence of the commensal microbes, obesity could be therapeutically treated by changing bacteria in the gut accordingly.[7] Metabolic syndrome is due to altered gut barrier function and leakage of bacteria and/or bacterial components into the circulatory system resulting in an inflammatory state. For example endotoxemia, is an indication for translocation of gram-negative bacteria contributory factor in many diseases, including metabolic syndrome.[23] Inflamed gut that allows fatty acids into the circulatory ultimately gets esterifies into triglycerides and stored within the adipocytes. Some strains of gut bacteria can influence ANGPTL4 levels that decrease triglyceride storage and increases circulating plasma triglyceride levels.

Other metabolic diseases

Some strains of bacteria can harvest energy from specific monosaccharides through specialized proteins resulting in the imbalance of host's weight and metabolic energy.[16] Liver sterol response element binding protein type-1 (SREBP-1), a transcriptional regulator of lipogenic gene expression is found to have a close association with bacteria in the digestive system to involve in bacteria-induced lipogenesis as well as remodelling of adipose tissue storage. Indeed, treatment with, specific bacteria strains such as A. muciniphila, probiotics or prebiotics has been shown to down regulate high-fat diet or high cholesterol-induced SREBP-1c expression in the liver. Conclusion can be drawn that metabolic imbalance seen in obese subjects could possibly be linked to the nutritional manipulation of these energy-extracting, lipogenic bacteria and their respective proteins.[11] Along with inflammatory mechanisms they are capable of producing signalling molecules anticipated to affect gut integrity, the immune system and may influence host metabolism. Short-chain fatty acids (SCFAs), such as acetate, propionate and butyrate, are small molecules metabolized by gut microbes from dietary fibres. Location of receptors in the human body for these SCFAs are still is an enigma and therefore may induce complex effects.

Bile acids (BA) are identified to aid in microbiota-host communication through nuclear receptor farnesoid X receptor (FXR) to maintain metabolic health. This interesting conclusion was drawn from a study where, FXR-deficient mice fed with high-fat diet or those mice genetically predisposed toward obesity have better glucose regulation than control mice with normally functioning FXR. This observation in human trials is still pending. Association among fatty liver disease (non-alcoholic fatty liver disease [NAFLD] and non-alcoholic steatohepatitis [NASH]), the intestinal microbiota, and obesity is not surprising because NAFLD and NASH are associated with obesity and insulin resistance. Data from human studies also support the concept that changes in the intestinal microbiota contribute to the development of fatty liver diseases. Increase in intestinal permeability, LPS-binding peptide levels in the plasma, endotoxemia, and numbers of *Gammaproteobacteria,* reduced numbers *Bacteroidetes* compared with healthy subjects could be noticed in patients with NAFLD. Microbiota strains differ in subjects with non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD), compared with healthy controls. More human trials are wanting to ascertain the functional role of microbiota in all aspects of the metabolic syndrome including insulin resistance, dyslipidemia, atherosclerosis, hepatic steatosis and elevated blood pressure. Nevertheless, confirmation on the effect of FMT in NASH or NAFLD in human studies is wanting.[23]

FMT therapy/management for obesity

Obesity can happen for a number of reasons, including diet, a sedentary lifestyle, genetic factors, a health condition, or the use of certain medications. A number of treatment options can help people to achieve and maintain a suitable weight. However, recent experiments performed by microbiologists have demonstrated that alteration in the relative level of the two dominant bacterial populations (*Bacteroidetes* and *Firmicutes*) could be associated with obesity, namely, the population of *Bacteroidetes* was lower, while *Firmicutes* was higher in obese individuals. These *Firmicutes* better in efficiency to absorb energy from diet compared to the bacteria from lean subjects.[16] from their in-depth study in which the faecal microbiota of obese C57BL/6J donors was transplanted into germ-free C57BL/6J recipients. Germ-free mice colonized with an bacteria from obese subjects exhibited a significant increase in total body fat compared with germ-free mice colonized with a microbiota from lean subjects suggesting that intestinal bacteria could be an additional contributing factor to the patho-physiology of obesity. In their human trials patients with metabolic syndrome were randomly assigned to groups and given small intestinal infusions of allogenic or autologous microbiota to study the effect of FMT. Patients who received an infusion of microbiota from lean donors were observed to have a significant increase in insulin sensitivity and butyrate producing intestinal microbiota (e.g. *Eubacterium hallii or Roseburia intestinalis*). Interestingly in subjects with high microbial gene richness at baseline and when FMT donors that are metabolically compromised are used, no metabolic improvement is seen.

Roux-en-Y gastric bypass (RYGB) an effective therapeutic agent in treating obesity also ultimately induce a significant alteration

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in the intestinal bacteria profiles. In obese subjects the caecal concentrations of butyric acid and iso-butyric acid were significantly lower indicating altered microbial activity Evidences from studies unequivocally establish the beneficial effects of FMT treatment in obesity and the metabolic syndrome function.[7] In addition to examining the role of FMT in metabolic disorders, scientists focussed their attention towards testing the efficacy of FMT in other disease processes that have similar pathogenicity as metabolic syndrome including allergen-related GI disease like Celiac disease. The complex relationship between different bacterial populations depends on individual conditions, disease status, dietary habits, development, physiological status, gut microbial composition, and other. Since effective colonization using FMT depends on the microbiota profile of the recipient that differs between patients suffering with metabolic syndrome.[24] The gut microbiota is also susceptible to alter due to change in the external environment as a result of industrialization and modern life style. Engineering a customized bacterial population to restore microbial profile through FMT might represent future remedy to restore a healthy gut microbiota. FMT in therapeutics has to go a long way although; new discoveries will continue to fill up the lacuna in our understanding how effectively FMT can be used to improve metabolic disorders related to gut dysbiosis like obesity and metabolic syndrome.[24]

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Conflicts of interest

The authors declare there is no conflict of interest.

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