Available online at http://www.ijims.com
ISSN: 2348 – 0343

Gut Microbiota Modulation Can be an Alternative Approach to Ameliorate Obesity and Diabetes: A Review

Desai Ishani and Desai Toral *
Department of Biotechnology, Shree Ramkrishna Institute of Computer Education and Applied Sciences, Surat, Gujarat, India
*Corresponding Author: Desai Toral

Abstract

The human intestinal tract has been colonized by thousands of species of bacteria during the coevolution of man and microbes. Gut-borne microbes outnumber the total number of body tissue cells by a factor of ten. Evidence for various beneficial roles of the intestinal microbiota in human health and disease is expanding rapidly. Perturbation of the intestinal microbiota may lead to chronic diseases such as autoimmune diseases, colon cancers, gastric ulcers, cardiovascular disease, functional bowel diseases, diabetes and obesity. Restoration of the gut microbiota may be difficult to accomplish, but the use of probiotics has led to promising results in a large number of well-designed (clinical) studies for example diabetes and obesity. Animals models of obesity connect an altered microbiota composition to the development of obesity, insulin resistance, and diabetes in the host through several mechanisms: increased energy harvest from the diet, altered fatty acid metabolism and composition in adipose tissue and liver, modulation of gut peptide YY and glucagon-like peptide (GLP)-1 secretion, activation of the lipopolysaccharide toll-like receptor-4 axis, and modulation of intestinal barrier integrity by GLP-2.

Keywords: Obesity, Diabetes, Intestine, Microbiota, Probiotic, Resistant

Introduction

Bacteria, unicellular eukaryotes, and other organisms inhabit the human body in large numbers. The human gut is dominated by several bacterial phyla including Bacteroidetes, Firmicutes, and Actinobacteria. It is estimated that the human microbiota contains as many as 10^{14} bacterial cells, a number that is 10 times greater than the number of human cells present in our bodies[1-3]. Virtually every surface of the human body starting from the skin surface to the genitourinary tract, oral cavity, respiratory tract, ear, and the gastrointestinal tract is colonized heavily by various species of bacteria. By far, the most heavily colonized organ is the gastrointestinal tract (GIT) which houses a huge microbial ecosystem; the colon alone is estimated to contain over 70% of all the microbes in the human body. The gut microbiota or microflora has a crucial role in human health and disease [1, 3].

The greatest health challenge of the 21st century is obesity. Indeed, it is reaching epidemic proportions in much of the developed world and in areas of the developing world where Western-style diet and lifestyle have been adopted. Globally, an estimated 300 million people are obese [body mass index (BMI) ≥30 kg/m2] and more than 1 billion people are overweight (BMI ≥25 kg/m2) [4]. Obesity is associated with a range of disease states including a collection of related metabolic diseases such as type 2 diabetes, nonalcoholic fatty liver disease, cardiovascular disease, and some cancers.

There is strong epidemiological data supporting the link between certain diets or dietary components and obesity, with diets high in fat and refined carbohydrates predisposing to body weight gain and, conversely, diets rich in fiber, whole plant foods and certain dairy products being inversely related to overweight. Similarly, there is a growing body of

evidence mainly from animal studies that certain fibers, prebiotics and resistant starch (RS) may reduce biomarkers of metabolic disease associated with obesity such as dyslipidemia, insulin resistance and the chronic low-grade systemic inflammation thought to play an etiological role in type2 diabetes and non-alcoholic fatty liver disease. Interestingly, prebiotics and RS act through modulation of the gut microbiota or their activities, which has itself now been identified as a putative contributor to the obesogenic environment [5, 6].

The human gut microbiota and diet-microbe interactions

All mammals have symbiotic relationships with the microbial community inhabiting their gastrointestinal tracts. This collection of microorganisms, or microbiota, consists of a diverse and highly metabolically active consortium of species. Intestinal bacteria occupy diverse ecological niches and life strategies which, in health, result in a stable and homeostatically controlled commensal community [7, 8]. Early studies on the composition of the gut microbiota were limited by the shortcomings of conventional culture-based microbiology, which relies upon the ability of bacteria to grow in pure culture under defined environmental conditions [9]. However, the vast majority of bacteria within the gut are recalcitrant to growth in pure culture and are not represented in studies using traditional, culture based methodology [9, 10]. Recognition of the 16S rRNA gene as a universal chronometer and its adoption in bacterial phylogenetics led to the development of a range of molecular tools which have opened up the complex gut microbiota to ecological study [11]. Techniques such as fluorescence in situ hybridization (FISH) using 16S rRNA-targeted oligonucleotide probes and quantitative PCR (qPCR) using 16S rRNA gene primers sets allow direct enumeration of bacterial populations without the need for isolation and cultivation of bacteria [12, 13]. Species richness may be assessed using fingerprinting techniques like PCR-denaturing gradient gel electrophoresis (DGGE) [14] or similar approaches including temperature gradient gel electrophoresis, TGGE and temporal temperature gradient gel electrophoresis (TTGE), which give a snapshot of the dominant species present within a mixture of amplified 16S rRNA gene fragments. Recently, DNA microarrays have been developed as innovative, information-dense, rapid tools for studying the gut microbiota [15].

The gut microbiota comes in contact with a wide range of food components which escape digestion in the upper gut. These include carbohydrates, proteins, plant polyphenols and – to a lesser extent – dietary fat and lipid, which escape hydrolysis in the stomach and small intestine, and reach the colon. Non-digestible carbohydrate is the major substrate for microbial fermentation in the colon, providing both the energy and carbon source for the majority of gut bacteria. Carbohydrate fermentation results in increased bacterial biomass and fermentation end-products such as acetate, propionate and butyrate. These short-chain fatty acids (SCFAs) have diverse and far reaching biological roles in the host[16].

Mechanisms linking gut microbiota to obesity, IR, and type 2 diabetes

Beside an increased energy harvest from the diet, further mechanisms linking gut microbiota to obesity have been subsequently proposed, including chronic low-grade endotoxinemia , regulation of tissue biologically active fatty acid composition and modulation of gut-derived peptide secretion.

1. Chronic inflammation induced by low-grade endotoxinemia

Metabolic pathways are functionally integrated with immune responses, and the relevance of the innate immune system for the pathogenesis of metabolic disorders is increasingly recognized, e.g., in mice fed a high-fat diet, the activation of liver resident macrophages Kupffer cells promotes hepatic IR and glucose intolerance. The selective depletion of these cells, without affecting adipose tissue macrophages, restores hepatic insulin sensitivity and improves whole-body and hepatic fat accumulation along with glucose metabolism [17, 18]. Recent work has shown that gut

bacteria can initiate the inflammatory state of obesity and IR through the activity of lipopolysaccharide (LPS), a component of the gram-negative bacterial cell walls, which can trigger the inflammatory process by binding to the CD14 toll-like receptor-4 (TLR-4) complex at the surface of innate immune cells.

2. Regulation of adipose tissue and liver fatty acid composition by gut microbes

Gut microbiota can also affect host metabolism and inflammatory state by modulating the tissue fatty acid composition: mammalian intestinal Lactobacilli and Bifidobacteria can synthesize from free linoleic acid bioactive isomers of conjugated linoleic acid, which have antidiabetic, anti-atherosclerotic, immunomodulatory, and anti-obesity properties [19]. The supplementation of Bifidobacterium breve and linoleic acid to different mammalian species resulted in a two- to threefold higher intestinal, hepatic, and adipose tissue content of cis-9, trans-11 conjugated linoleic acid, eicosapentaenoic acid, and docosahexaenoic acid, concomitantly with a reduced proinflammatory cytokines TNF-α, IL-6, and interferon-γ expression, than the linoleic acid-alone supplemented diet [20].

3. Gut microbiota modulates gut-derived peptide secretion PYY

Gut microbiota synthesizes a large amount of glycoside hydrolases that break down complex plant polysaccharides to monosaccharides and short-chain fatty acids, mainly acetate, propionate, and butyrate. Beside representing an important source of energy for de novo lipogenesis, these short-chain fatty acids are ligands for two G-protein–coupled receptors, Gpr41 and Gpr43, of gut enteroendocrine cells[18]. Upon ligand binding, these G-protein–coupled receptors stimulate secretion of PYY, which inhibits gut motility and slows intestinal transit thereby enhancing nutrient absorption. Consistent with these properties, conventionally raised Gpr41-deficient mice or germ-free Gpr41-deficient mice colonized with Bacteroidetes theatiotaomicron and Methanobrevibacter smithii (two common commensals of human distal gut) were significantly leaner than wild-type littermates, whereas there were no genotype-related differences in germ-free mice. Gpr41 deficiency was associated with decreased expression of PYY, faster intestinal transit rate, and reduced harvest of energy from the diet[21].

Modulation of the gut microbiota towards reduced obesity and metabolic disease

1. Antibiotics

The composition and metabolic potential of the gut microbiota may be modified using pharmaceuticals or through dietary means. Antibiotics, especially broad spectrum antibiotics and those with low absorption in the upper gut can dramatically influence the bacteria in the colon. In an effort to determine whether changes within the composition of the gut microbiota could directly impact on metabolic endotoxemia[22]. However, the use of antibiotics to treat obesity in humans is not realistic considering the dramatic impact of broad-spectrum antibiotics on the normal gut microbiota and consequent diminution in colonization resistance to invading pathogens and the emergence of multidrug-resistant bacteria. Therefore other ecological strategies, especially dietary strategies, may constitute a more viable alternative for the treatment of obesity.

2. Dietary microbiota modulation

Certain foods, particularly dairy foods and foods rich in fiber (e.g. whole plant foods), are recognized to be protective against overweight, obesity and the diseases of obesity [23, 24]. Dairy foods include a wide array of different products from raw milk, fermented cheeses and yoghurts to high saturated fat products like butter but overall intake of low saturated fat products appears to be inversely related to heart disease risk, markers of the metabolic syndrome and obesity in various epidemiological studies[25, 26]. Dairy products are complex foods and it is difficult to single out particular components which may be responsible for these health effects, although several intrinsic factors such as calcium, beneficial lipids (e.g. sphingomyelin oleic acid, short- and medium-length fatty acids) and bioactive peptides

have potential health promoting activities[24]. While calcium is independently associated with reduced risk of metabolic disease and improved gut health. Indeed fermented dairy products have long been associated with improved health and have formed the basis of the modern probiotic functional foods industry. Probiotic bacteria, defined by the WHO as "live microorganisms which when administered in adequate amount confer a health benefit on the host," appear to impact on metabolic parameters related to obesity and the metabolic syndrome [27]. High level consumption of yoghurt (about 10% w/w of diet) has recently been shown to produce significant differences in body composition (less weight gain and less body fat) in yoghurt-fed animals compared to control animals on an isocaloric diet [28]. In models of diabetes, probiotic intervention has been examined for its ability to impact on metabolic biomarkers of disease. Studies using the traditional Indian yoghurt, dahi, or dahi supplemented with probiotic strains of Lactobacillus acidophilus and L. casei have shown that this product can improve markers of diabetes, including hyperglycemia, hyperinsulinemia, dyslipidemia and oxidative stress [29-31]. In humans, dietary intervention with yoghurts containing probiotics (such as L. acidophilus, Bifidobacterium longum, L. plantarum and/or B. lactis) have been shown to significantly reduce total serum cholesterol and LDL cholesterol and to improve the LDL:HDL cholesterol ratio [32-34].

3. Dietary fiber, prebiotics and RS

Current recommendations for the management of obesity and diabetes include increased intake of dietary fiber and foods rich in fiber [35]. These recommendations are based on epidemiological links between high dietary fiber intake and improved markers of metabolic disease and reduced body weight. However, recent studies suggest that these effects may not hold in the absence of a concomitant reduction in energy intake or through reduced energy density of foods. Indeed, in practice, it is very difficult to significantly increase dietary fiber intake without reducing energy intake Similarly, it is often difficult to identify the underlying mechanisms of action of diets rich in fiber, as these diets are composed of complex foodstuffs of plant origin which contain many different classes of biologically active compounds including fermentable carbohydrates, bioactive peptides and polyphenolic compounds, all of which may impact on biomarkers of metabolic health.

Conclusion

The intestinal microbiota has emerged as a possible contributor to the obesogenic environment that is driving increased rates of obesity in westernized societies. Close interactions between diet and the gut microbiota on the one hand, and the gut microbiota and host physiology on the other, appear to be adulterated in the obese. In humans, the gut microbiota of obese people appears to differ from that of the lean. Early events in the successional development of the gut microbiota may play an important role, with anomalous colonization in infancy implicated in high body weight in later life. Obesity per se appears to be characterized by a gut microbiota with enhanced capacity for harvesting energy from the diet and this obese-type microbiota disappears with weight loss upon adoption of diets designed to induce weight loss or following gastric bypass surgery. However, not all studies agree that the gut microbiota of the obese shows an altered Bacteroidetes/Firmicutes profile and further studies comparing the gut microbiota of lean and Dietary approaches for microbiota modulation are now well established, and, interestingly, many of these same microbiota-modulatory foods have long been associated with reduced risk of obesity and the diseases obese individuals are needed, especially by means of a combination of techniques to overcome the limitations of individual molecular approaches of obesity in epidemiological research.

In the only follow-up study prospectively connecting gut microbiota to the development of obesity, other factors, including dietary habits, were not assessed, making causal inference uncertain. The assessment of pro/prebiotic efficacy in free-living humans is far more complex than under standardized experimental conditions because different

confounding factors, including antibiotic use, background diet and physical activity, endotoxin content of ingested food, and even meal frequency, may affect gut microbiota, energy balance, and ultimately body weight. Understanding these factors may allow researchers to design future trials and better understand the relative impact of pre/probiotics on the treatment of obesity, which is a complex disease deriving from the interaction of largely unknown multiple genetic and environmental factors. The ongoing double-blind, randomized, controlled trial, FATLOSE, is assessing the effect of healthy donor feces transplantation on glucose homeostasis and intestinal inflammation in subjects with metabolic syndrome and will hopefully help address these issues. Furthermore, the long-term safety of gut microbiota manipulation needs assessment.

References

(1) Ley, R. E., Peterson, D. A., & Gordon, J. I. (2006). Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell, 124(4), 837-848.

(2) Kennedy, M. J. (1989). Regulation of Candida albicans populations in the gastrointestinal tract: mechanisms and significance in GI and systemic candidiasis. In Current topics in medical mycology (pp. 315-402). Springer New York.

(3) Whitman, W. B., Coleman, D. C., & Wiebe, W. J. (1998). Prokaryotes: the unseen majority. Proceedings of the National Academy of Sciences, 95(12), 6578-6583.

(4) Huang, T. T., Drewnowski, A., Kumanyika, S. K., & Glass, T. A. (2009). A systems-oriented multilevel framework for addressing obesity in the 21st century. Preventing Chronic Disease, 6(3).

(5) Zaneveld, J., Turnbaugh, P. J., Lozupone, C., Ley, R. E., Hamady, M., Gordon, J. I., & Knight, R. (2008). Host-bacterial coevolution and the search for new drug targets. Current opinion in chemical biology, 12(1), 109-114.

(6) Turnbaugh, P. J., Ley, R. E., Hamady, M., Fraser-Liggett, C., Knight, R., & Gordon, J. I. (2007). The human microbiome project: exploring the microbial part of ourselves in a changing world. Nature, 449(7164), 804.

(7) Cani, P. D., Lecourt, E., Dewulf, E. M., Sohet, F. M., Pachikian, B. D., Naslain, D. & Delzenne, N. M. (2009). Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. The American journal of clinical nutrition, 90(5), 1236-1243.

(8) Russell, W. R., Gratz, S. W., Duncan, S. H., Holtrop, G., Ince, J., Scobbie, L.,& Flint, H. J. (2011). High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. The American journal of clinical nutrition, 93(5), 1062-1072.

(9) Neish, A. S. (2009). Microbes in gastrointestinal health and disease. Gastroenterology, 136(1), 65-80.

(10) Wilson, K. H., Ikeda, J. S., & Blitchington, R. B. (1997). Phylogenetic placement of community members of human colonic biota. Clinical infectious diseases, S114-S116.

(11) Seksik, P., Rigottier-Gois, L., Gramet, G., Sutren, M., Pochart, P., Marteau, P. & Dore, J. (2003). Alterations of the dominant faecal bacterial groups in patients with Crohn's disease of the colon. 52(2), 237-242.

(12) Gaskins, H. R., Croix, J. A., Nakamura, N., & Nava, G. M. (2008). Impact of the intestinal microbiota on the development of mucosal defense. Clinical infectious diseases, 46(Supplement 2), S80-S86.

(13) Amor, K. B., Vaughan, E. E., & de Vos, W. M. (2007). Advanced molecular tools for the identification of lactic acid bacteria. The Journal of Nutrition, 137(3), 741S-747S.

(14) Kurakawa, T., Kubota, H., Tsuji, H., Matsuda, K., Asahara, T., Takahashi, T., & Nomoto, K. (2012). Development of a sensitive rRNA-targeted reverse transcription-quantitative polymerase chain reaction for detection of Vibrio cholerae/mimicus, V. parahaemolyticus/alginolyticus and Campylobacter jejuni/coli. Microbiology and immunology, 56(1), 10-20.

(15) Wall, R., Marques, T. M., O'Sullivan, O., Ross, R. P., Shanahan, F., Quigley, E. M., & Stanton, C. (2012). Contrasting effects of Bifidobacterium breve NCIMB 702258 and Bifidobacterium breve DPC 6330 on the composition of murine brain fatty acids and gut microbiota. The American Journal of Clinical Nutrition, 95(5), 1278-1287.

(16) Simrén, M., Barbara, G., Flint, H. J., Spiegel, B. M., Spiller, R. C., Vanner, S., & Zoetendal, E. G. (2013). Intestinal microbiota in functional bowel disorders: a Rome foundation report. 62(1), 159-176.

(17) Mai, V., & Draganov, P. V. (2009). Recent advances and remaining gaps in our knowledge of associations between gut microbiota and human health. World journal of gastroenterology: WJG, 15(1), 81.

(18) Lanthier, N., Molendi-Coste, O., Horsmans, Y., van Rooijen, N., Cani, P. D., & Leclercq, I. A. (2010). Kupffer cell activation is a causal factor for hepatic insulin resistance. American Journal of Physiology-Gastrointestinal and Liver Physiology, 298(1), G107-G116.

(19) Vrieze, A., Holleman, F., Zoetendal, E. G., De Vos, W. M., Hoekstra, J. B. L., & Nieuwdorp, M. (2010). The environment within: how gut microbiota may influence metabolism and body composition. Diabetologia, 53(4), 606-613.

(20) Salas-Salvado, J., Marquez-Sandoval, F., & Bullo, M. (2006). Conjugated linoleic acid intake in humans: a systematic review focusing on its effect on body composition, glucose, and lipid metabolism. Critical reviews in food science and nutrition, 46(6), 479-488

(21) Marchesi, J., & Shanahan, F. (2007). The normal intestinal microbiota. Current opinion in infectious diseases, 20(5), 508-513.

(22) Serino, M., Luche, E., Gres, S., Baylac, A., Bergé, M., Cenac, C., & Burcelin, R. (2012). Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. 61(4), 543-553.

(23) Konstantinova, S. V., Tell, G. S., Vollset, S. E., Nygård, O., Bleie, & Ueland, P. M. (2008). Divergent associations of plasma choline and betaine with components of metabolic syndrome in middle age and elderly men and women. The Journal of nutrition, 138(5), 914-920.

(24) Beydoun, M. A., Gary, T. L., Caballero, B. H., Lawrence, R. S., Cheskin, L. J., & Wang, Y. (2008). Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. The American journal of clinical nutrition, 87(6), 1914-1925.

(25) Duffey, K. J., Gordon-Larsen, P., Steffen, L. M., Jacobs, D. R., & Popkin, B. M. (2010). Drinking caloric beverages increases the risk of adverse cardiometabolic outcomes in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. The American journal of clinical nutrition, 92(4), 954-959.

(26) Siri-Tarino, P. W., Sun, Q., Hu, F. B., & Krauss, R. M. (2010). Saturated fat, carbohydrate, and cardiovascular disease. The American Journal of Clinical Nutrition, 91(3), 502-509.

(27) Reid, G. (2006). Safe and efficacious probiotics: what are they?. TRENDS in Microbiology, 14(8), 348-352.

(28) Yan, L., Combs Jr, G. F., DeMars L. C., & Johnson, L. K. (2011). Effects of the physical form of the diet on food intake, growth, and body composition changes in mice. Journal of the American Association for Laboratory Animal Science: JAALAS, 50(4), 488.

(29) Jain, S., Yadav, H., Sinha, P. R., & Marotta, F. (2009). Modulation of cytokine gene expression in spleen and Peyer's patches by feeding dahi containing probiotic Lactobacillus casei in mice. Journal of digestive diseases, 10(1), 49-54.

(30) Amnah, M. A. (2013). Chemical and biological study on the effect of yoghurt on most common consumed ready meat products. Journal of Applied Sciences Research, 9(3).

(31) Kelishadi, R., Farajian, S., & Mirlohi, M. (2013). Probiotics as a novel treatment for non-alcoholic Fatty liver disease; a systematic review on the current evidences. Hepatitis monthly, 13(4).

(32) Gill, H. S., & Guarner, F. (2004). Probiotics and human health: a clinical perspective. Postgraduate Medical Journal, 80(947), 516-526.

(33) Koebnick, C., Wagner, I., Leitzmann, P., Stern, U., & Zunft, H. F. (2003). Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation-The aim of the present study was to investigate the effect of a. Canadian Journal of Gastroenterology, 17(11), 655-660.

(34) Lepercq, P., Relano, P., Cayuela, C., & Juste, C. (2004). Bifidobacterium animals strain DN-173 010 hydrolyses bile salts in the gastrointestinal tract of pigs. Scandinavian journal of gastroenterology, 39(12), 1266-1271.

(35) Jones, M. L., Tomaro-Duchesneau, C., Martoni, C. J., & Prakash, S. (2013). Cholesterol lowering with bile salt hydrolase-active probiotic bacteria, mechanism of action, clinical evidence, and future direction for heart health applications. Expert opinion on biological therapy, 13(5), 631-642.