Special Article

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The role of intestinal microbiota in energetic metabolism: new perspectives in combating obesity

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ABSTRACT

The knowledge that the composition of intestinal microbiota is different in lean and obese humans indicates that the microbiota plays an important role in the pathophysiology of obesity. Studies show that diet composition promotes the modification of intestinal bacterial species, favoring the increase of energy extraction from the diet, insulin resistance and obesity. Unbalanced diets, with overload fat and low fiber content, lead to increased *Firmicutes* and *Proteobacteria* phyla favoring dysbiosis, endotoxemia and inflammation. The use of probiotics, prebiotics and symbiotics, in order to modulate the composition of intestinal microbiome, may be a promising therapy for the reduction of the metabolic complications of obesity; however, further studies should be conducted to establish which probiotic species are suitable to help in the treatment of obesity.

Keywords: *Obesity; dysbiosis; obesogenic microbiota; inflammation; probiotic; prebiotic*

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The increasing prevalence of obesity has led the World Health Organization (WHO) to consider it as the world's largest epidemic of the century, being referred to as the most important nutritional disorder in developed and developing countries[1]. Prevalence of obesity and related diseases, such as metabolic syndrome, non-alcoholic fatty liver disease, diabetes, cardiovascular diseases, and cancer, has increased dramatically worldwide[2,3]. Recent insights have generated an entirely new perspective, suggesting that the microbiota may be involved in the development of these disorders[4]. Clarke et al. demonstrated through fecal transplantation experiments that obesity and metabolic syndrome may be associated with alterations of the intestinal microbiota composition[5]. Components of the intestinal microbiota can facilitate the extraction of calories from substances ingested in the diet, which provides nutrients for the growth of microbes or can be stored as fat[6]. Studies in germ free animals demonstrated that the composition of the intestinal microbiota has a profound influence on the onset and progression of human diseases, including obesity, and on the regulation of energy harvest and fat storage[6-8]. The so called "obesogenic microbiota" promotes more efficient energy extraction from the diet and predisposes to the development of obesity.

INTESTINAL MICROBIOTA AND ITS RELATION TO OBESITY

The human gut is the natural habitat of an extraordinary bacterial community[9,10]. The main functions of the intestinal microbiota include metabolic activities that result in energy and absorbable nutrient storage, important trophic effects on the intestinal epithelium, immune function and protection of the host against pathogenic microorganisms[10,11].

Studies with germ-free animals revealed the role of the microbiota as a major environmental factor that affects the collection and storage of energy derived from ingested nutrients[8,12]. Backhed et al. showed that implantation of the intestinal microbiota of conventionally raised mice into germ-free mice resulted in a 60% increase of body fat in transplanted animals[8]. Ridaura et al.[12] transplanted fecal microbiota from obese and lean mice into germ-free mice

and observed an increase in body weight and fat mass, as well as in metabolic phenotypes associated with obesity, in those which were transplanted with microbiota from obese mice. An interesting observation from this study was that the mice which were transplanted with the microbiota from obese animals developed less body fat in comparison to the animals that received microbiota from the lean mice. The presence of specific bacteria of lean animals in obese animals was also observed. These results revealed transferable and modifiable effects of microbiota and the interactions between diet and microbiota[12]. Turnbaugh et al. demonstrated that the microbiota of obese mice was more efficient in energy utilization from food and that there was an increase in adiposity after transplantation of the microbiota from obese to germ-free animals[7].

A study to evaluate the influence of diet on the composition of the intestinal microbiota found that the shift to a high-fat diet caused a decrease in *Bacteroidetes* phylum and an increase in *Firmicutes* and *Proteobacteria* phyla. This strengthens the hypothesis that the diet is a determining factor for the composition of the intestinal microbiota[13]. Carilicci et al. found that the *Firmicutes* phylum may be related to insulin resistance and obesity[14]. Increased ratio of *Firmicutes* in the microbiota seems to influence the onset of diabetes and obesity in two ways: first, by increasing the capacity to extract energy from food (some species of *Firmicutes* break polysaccharide molecules) and/or increasing its absorption; second, by favoring the increase of intestinal permeability and the passage of LPS (lipopolysaccharides) into the bloodstream and leading to the inflammatory state of obesity[6,7,14,15].

After comparing bacterial 16S rRNA gene sequences from intestinal microbiota of genetically obese *ob*/*ob* mice, lean *ob*/+ and wild-type siblings, and their *ob*/+ mothers, Ley et al. observed that the composition of the intestinal microbial community can promote increased fat deposition[16]. These authors concluded that the intentional manipulation of community structure may be useful for the regulation of energy balance in obese individuals[16].

PREBIOTICS AND PROBIOTICS IN THE MODULATION OF OBESOGENIC MICROBIOTA

Accumulating evidence of the strong relationship between intestinal microbiota and obesity led to the hypothesis that the manipulation of the microbiota may contribute to obesity prevention strategies. Studies on this issue in animals and human beings have been conducted in order to evaluate the action of prebiotics and/or probiotics on obesity and overweight treatment[17-19].

A study conducted by Million et al. was designed to investigate which species of bacteria – *Firmicutes, Bacteroidetes, Methanobrevibacter smithii, Lactococcus lactis, animalis Bifidobacterium and Lactobacilli* – were associated with obesity or normal weight[20]. This study showed that obesity is associated with decreased presence of *M. smithii* and increased presence of *L. reuteri* in microbiota composition. In addition, higher levels of *B. animalis*, *L. paracasei*, *L. plantarum*, were associated with normal weight[20].

To highlight the modulation effect of the intestinal microbiota in the host metabolism, a double-blind intervention was performed: 30 placebo-controlled obese women were treated with prebiotics (inulin-type fructans) for 3 months (16 g/day). The treatment increased the number of *Bifidobacterium* and *Faecalibacterium prausnitzii*; both bacteria were negatively correlated with serum levels of lipopolysaccharides. Prebiotics also decreased the proportion of *Bacteroides intestinalis*, *B. vulgatus* and *Propionibacterium*, an effect associated with a slight decrease in fat mass[21].

According to Vrieze et al., the manipulation of the gut microbiota may be considered as a therapeutic agent, since dysbiosis is associated with obesity and insulin resistance in humans[22]. The administration of prebiotics, probiotics or symbiotics can improve gut barrier integrity, rebalance microbiota composition and reduce the inflammation state, thus ameliorating metabolic balance and promoting weight loss.

DYSBIOSIS HIGH FAT DIET AND INFLAMMATORY CONDITION

Eating behavior can be considered as one of the factors that most influence quality of life. Eastern people have always believed that all diseases begin in the gut and there is a fundamental relationship between the intestines and health. Excessive consumption of processed foods, beverages, sugar, and fat, as well as undesirable interactions between nutrients, contribute to change intestinal microbiota leading to dysbiosis[23,24].

Ingestion of a high fat diet promotes low-grade inflammation, which contributes to the development of obesity-associated diseases[24]. Clinical studies showed associations between obesity, intestinal microbiota composition, and endotoxemia[24-27]. Unbalanced diets, with overload fat and low fiber content, lead to increased levels of LPS, favoring endotoxemia. Nutrient load is a key variable that can influence the structure of the intestinal bacterial community. Individuals with a low bacterial diversity are characterized by more adiposity, insulin resistance, and dyslipidemia, and a pronounced inflammatory

phenotype when compared to individual with a higher bacterial richness[26].

The impact of dietary fat in the intestinal microbiota and the development of a low grade inflammation have been studied by Cani et al.[28]. They observed that administration of a high fat diet caused changes in the composition of the microbiota, which contributed to a significant increase in intestinal permeability, reduced the expression of genes encoding proteins of the tight junctions, and increased plasma concentrations of LPS, contributing to the development of endotoxemia[28]. Furthermore, an increase in the levels of blood glucose, fasting insulin, body weight, and fat mass, which was related to increased levels of proinflammatory cytokines (tumor necrosis factor-alpha, interleukin [IL] 6, IL-1b, macrophage inflammatory protein-1) in plasma, adipose tissue, liver and muscle[28]. These results suggest that modulation of the microbiota for the reduction of plasma levels of LPS can be a therapeutic strategy to control processes associated with inflammatory diseases.

CONCLUSION

Obesity is a systemic disease and new approaches are needed for its treatment. Evidence related to the role of intestinal microbiota in obesity shows that this is an important issue to address in obese patients, together with approaches that include diet, physical activity, psychological treatment, medications, and sometimes surgery.

Conflicts of interest

None to declare.

REFERENCES

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9945):766-81. http://dx.doi.org/10.1016/S0140-6736(14)60460-8. PMid:24880830.

2. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Mol Sci*. 2014;15(4):6184-223. http://dx.doi.org/10.3390/ijms15046184. PMid:24733068.

3. Howe LR, Subbaramaiah K, Hudis CA, Dannenberg AJ. Molecular pathways: adipose inflammation as a mediator of obesity-associated cancer. *Clin Cancer Res*. 2013;19(22):6074-83. http://dx.doi.org/10.1158/1078-0432.CCR-12-2603. PMid:23958744.

4. Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. *Mol Aspects Med*. 2013;34(1):39-58. http://dx.doi.org/10.1016/j.mam.2012.11.001. PMid:23159341.

5. Clarke SF, Murphy EF, Nilaweera K, Ross PR, Shanahan F, O'Toole PW, et al. The gut microbiota and its relationship to diet and obesity. *Gut Microbes*. 2012;3(3):186-202. http://dx.doi.org/10.4161/gmic.20168. PMid:22572830.

6. DiBaise JK, Zhang H, Crowell MD, Krajmalnik-Brown R, Decker A, Rittmann BE. Gut microbiota and its possible relationship with obesity. *Mayo Clin Proc*. 2008;83(4):460-9. http://dx.doi.org/10.4065/83.4.460. PMid:18380992.

7. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444(7122):1027-31. http://dx.doi.org/10.1038/nature05414. PMid:17183312.

8. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci USA*. 2004;101(44):15718-23. http://dx.doi.org/10.1073/pnas.0407076101. PMid:15505215.

9. Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet*. 2003;361(9356):512-9. http://dx.doi.org/10.1016/S0140-6736(03)12489-0. PMid:12583961.

10. Duca F, Gérard P, Covasa M, Lepage P. Metabolic interplay between gut bacteria and their host. *Front Horm Res*. 2014;42:73-82. http://dx.doi.org/10.1159/000358315. PMid:24732926.

11. Greer RL, Morgun A, Shulzhenko N. Bridging immunity and lipid metabolism by gut microbiota. *J Allergy Clin Immunol*. 2013;132(2):253-62, quiz 263. http://dx.doi.org/10.1016/j.jaci.2013.06.025. PMid:23905915.

12. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science*. 2013;341(6150):1241214. http://dx.doi.org/10.1126/science.1241214. PMid:24009397.

13. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY, et al. High fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology*. 2009;137(5):1716-24. http://dx.doi.org/10.1053/j.gastro.2009.08.042. PMid:19706296.

14. Caricilli AM, Picardi PK, de Abreu LL, Ueno M, Prada PO, Ropelle ER, et al. Gut microbiota is a key modulator of insulin resistance in TLR 2 knockout mice. *PLoS Biol*. 2011;9(12):e1001212. http://dx.doi.org/10.1371/journal.pbio.1001212. PMid:22162948.

15. Weisberg SP, Mccann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW JR. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003;112(12):1796-808. http://dx.doi.org/10.1172/JCI200319246. PMid:14679176.

16. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci USA*.

2005;102(31):11070-5. http://dx.doi.org/10.1073/pnas.0504978102. PMid:16033867.

17. Silva ST, Santos CA, Bressan J. Intestinal microbiota; relevance to obesity and modulation by prebiotics and probiotics. *Nutr Hosp*. 2013;28(4):1039-48. PMid:23889619.

18. Blaut M, Bischoff SC. Probiotics and obesity. *Ann Nutr Metab*. 2010;57(1 Suppl):20-3. http://dx.doi.org/10.1159/000309079. PMid:20829589.

19. Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des*. 2009;15(13):1546-58. http://dx.doi.org/10.2174/138161209788168164. PMid:19442172.

20. Million M, Maraninchi M, Henry M, Armougom F, Richet H, Carrieri P, et al. Obesity-associated gut microbiota is enriched in Lactobacillus reuteri and depleted in Bifidobacterium animalis and Methanobrevibacter smithii. *Int J Obes*. 2012;36(6):817-25. http://dx.doi.org/10.1038/ijo.2011.153. PMid:21829158.

21. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut*. 2013;62(8):1112-21. http://dx.doi.org/10.1136/gutjnl-2012-303304. PMid:23135760.

22. Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. 2012;143(4):913-6. http://dx.doi.org/10.1053/j.gastro.2012.06.031. PMid:22728514.

23. Almeida LB, Marinho CB, Souza CS, Cheib VBP. Disbiose intestinal [revisão]. *Rev Bras Nutr Clin.* 2009;24(1):58-65.

24. Clemente-Postigo M, Queipo-Ortuño MI, Murri M, Boto-Ordoñez M, Perez-Martinez P, Andres-Lacueva C, et al. Endotoxin increase after fat overload is related to postprandial hypertriglyceridemia in morbidly obese patients. *J Lipid Res*. 2012;53(5):973-8. http://dx.doi.org/10.1194/jlr.P020909. PMid:22394503.

25. Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am J Clin Nutr*. 2011;94(1):58-65. http://dx.doi.org/10.3945/ajcn.110.010132. PMid:21543530.

26. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature*. 2013;500(7464):541-6. http://dx.doi.org/10.1038/nature12506. PMid:23985870.

27. Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L, et al. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. *Am J Clin Nutr.* 2011;93(5):1062-72. http://dx.doi.org/10.3945/ajcn.110.002188. PMid:21389180.

28. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet induced obesity and diabetes in mice. *Diabetes*. 2008;57(6):1470-81. http://dx.doi.org/10.2337/db07-1403. PMid:18305141.

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