Intestinal Microbiome In Obesity

ebook.ecog-obesity.eu/chapter-biology/intestinal-microbiome-in-obesity

Grzegorz Telega
Children's Hospital Of Wisconsin Since 2000
Program director, Liver Transplant Hepatology, Children's Hospital of Wisconsin

Introduction

Human intestine is a complex ecosystem maintained by interactions of numerous species of microbiota, human organism and the ingested substrates. It's estimated that number of bacterial cells colonizing human intestine exceeds the number of human cells in the rest of the body. Between 10 to 100 trillion of bacteria existing inside the intestine belong to 10 phyla and at least 15000 recognized species. Two phyla dominate numerically intestinal microbiome: *Firmicutes* and *Bacteroides* (3).

Phages and viruses serve as predators of intestinal ecosystem. They are important in interspecies gene transfer. Such gene transfer has been documented in many in-vitro systems and may be responsible for development of new traits including antibiotic resistance, or change in immunological properties of bacterial proteins (1,2).

Human intestine is also a host to *Archaea*, newly discovered kingdom of organisms known to inhabit thermal vents at the bottom of the sea, or hot volcanic springs. *Methanobrevibacter smithii* is a dominant species of *Archaea* in human intestine (1,2).

Recent progress in understanding of intestinal microbiome is associated with development of ribosomal RNA (SSU rRNA; 16S rRNA) sequencing in *Bacteria* and *Archaea*. Importance of this technology stems from the fact that majority of intestinal microbiota is cannot survive in-vitro. Sequencing of ribosomal RNA allows classification and study of bacteria without isolating them in culture (1).

In healthy individuals composition of intestinal bacteria is also remarkably stable through the lifespan. In particular there are only minor changes in bacterial composition from the time of weaning from breast milk till adulthood. Intestinal flora tends to return to homeostatic balance after disturbance. Environmental factors such as exposure to antibiotics, change in diet or surgery can affect composition of bowel flora, but after disturbance is removed composition of bacterial species returns to baseline within 6-52 weeks (1,2). Intestinal microbiome is adaptable in a sense that expression of bacterial genes and activity of metabolic pathways is influenced by host developmental stage, nutrient availability and presence of other microbial species (2).

In contrast to stability of individual's flora there is significant variation in the composition of bacterial flora between the individuals (1,2).

Intestinal microbiome has enzymatic capabilities that are not encoded in human or animal genome. This allows organism access to extended array of biochemical pathways which depend on microbial genetic make up. Metagenomic analysis focuses on all biochemical pathways which are active in given ecosystem with an understanding that different organisms have capacity to perform only limited number of chemical reactions (Figure 1). Some pathways can be redundant with many species performing same chemical reactions frequently competing for limited resources. Some pathways will be available only to few species frequently making otherwise unavailable substrates enter circulation within ecosystem. From metagenomic perspective intestinal microbiome is a system of biochemical reactions in which human and bacteria complement each other.

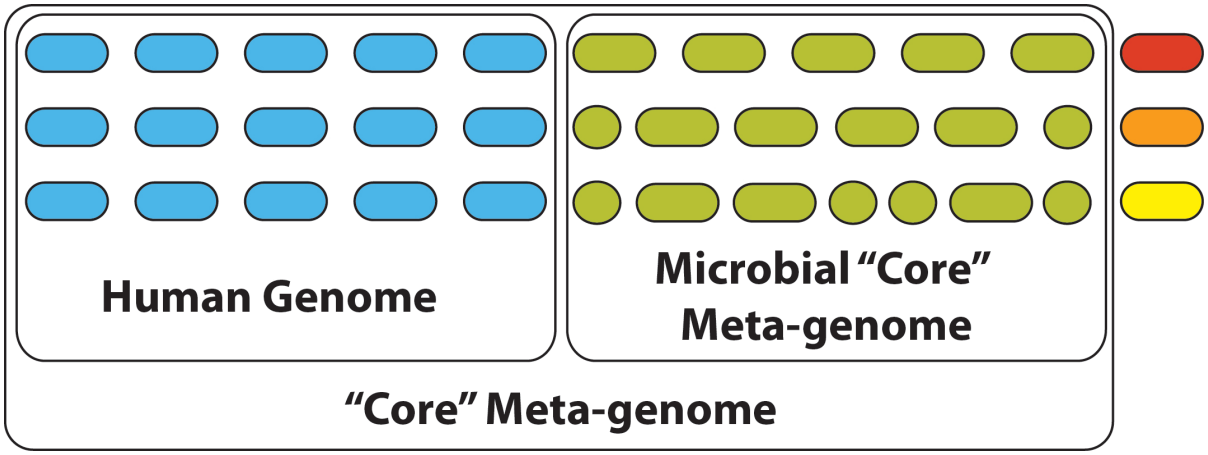

Figure 1. *Concept of meta-genomic complementary metabolic pathways in ecosystem consisting of human and intestinal microbiota. From biochemical perspective humans are nearly identical. Many metabolic pathways are common when microbioms of different individuals are compared. Frequently different organisms may participate in different aspects of the same metabolic pathway. In general diversity of microbial metabolic pathways greatly exceeds differences between individual humans.*

Within intestinal ecosystem multiple human/bacteria and bacteria/bacteria relationships have been described. These relationships span all known interspecies relationships ranging from pathogenic to commensal and mutualistic.

Intestinal microbiome and energy metabolism – animal studies

Germ free mice model provides opportunity to study energy metabolism in absence of intestinal bacteria. In comparison with conventionally raised mice, germ free mice have approximately 40% lower weight. This discrepancy is not related to a difference in food intake or in resting energy expenditure. Germ free mice will achieve normal body weight once it's transferred to normal (non-sterile) environment and becomes colonized by intestinal microbiota. Based on this experiment researcher hypothesized that intestinal microbiota may increase bioavailability of some dietary substrates. Indeed further studies showed increased uptake of dietary monosaccharides. Interestingly intestinal microbiota also increase insulin resistance, increase hepatic lipid production, change bile acid composition and increase integrity of intestinal epithelium. These metabolic and endocrine changes result in increased deposition of body fat. Mechanism of these changes is not yet fully understood (10).

Fasting-induced adipose factor (Fiaf) is one of the mediators linking intestinal flora with adipose tissue. Germ-free mice have increased levels of circulating Fiaf. Fiaf inhibits endothelial lipoprotein lipase which is responsible for releasing triglycerides from circulating chylomicrons and VLDL. Consequently less triglyceride is available for deposition in adipose tissue (Figure 2). Colonization of germ-free mice by conventional intestinal flora leads to suppression of Fiaf through yet unknown mechanism. Subsequently transfer of triglycerides from chylomicrons and VLDL into adipose tissue increases (Figure 3). Confirmation of Fiaf hypothesis comes from similar experiments on Fiaf knockout mice (Fiaf -/-). In this model germ-free Fiaf -/- mice had weigh not different from conventionally raised mice. This suggests that effect of intestinal bacteria on deposition of fat is mediated by Fiaf (Figure 4).

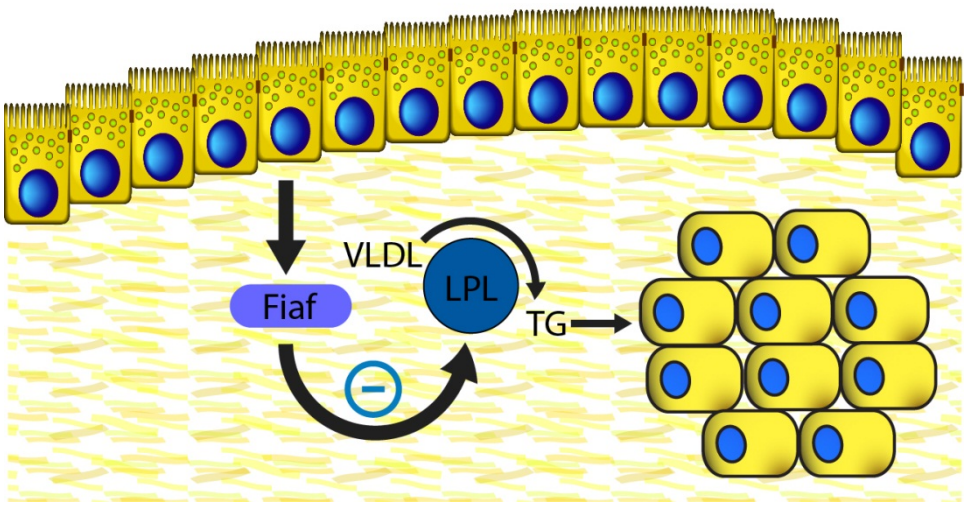

Figure 2. *Germ free mice has high levels of Fiaf (Fasting-induced adipose factor). Fiaf acts as an inhibitor to LPL (lipoprotein lipase) and decreases uptake of TG (tigliceride) by adipocyte.*

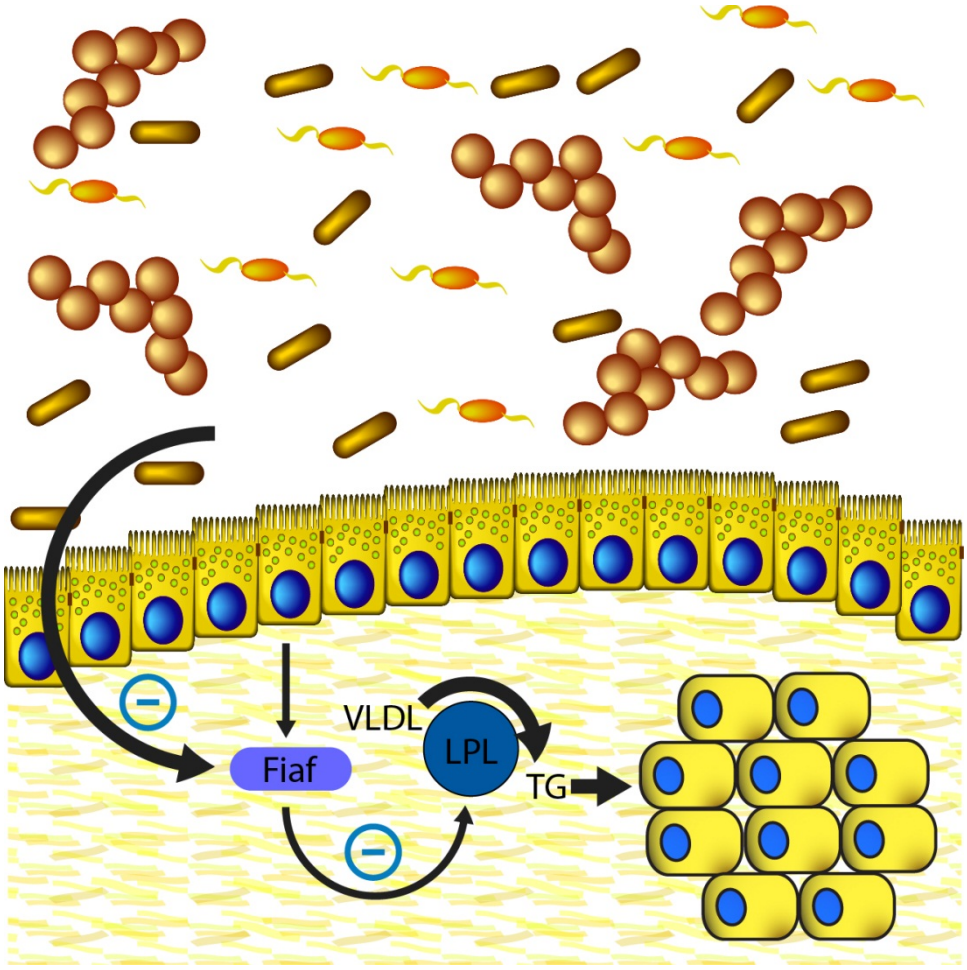

Figure 3. *Colonization of intestine decreases levels of Fiaf and leads to activation of LPL and transfer of triglycerides to adipose tissue.*

Adenosine monophosphate-activated protein kinase (AMPK) is activated as intracellular molecular mediator of metabolic stress. AMPK is up regulated in times of metabolic stress it increases energy utilization and decreases energy storage. AMPK increases beta oxidation of fatty acids leading to depletion of fat and glycogen stores. AMPK activity is increased in a germ-free mouse which leads to decreased fat deposition despite of normal caloric intake. The mechanism of AMPK activation in germ free environment is yet unknown .

Humans have limited gene repertoire for digestion and absorption of complex carbohydrates. Bacteria are able to metabolize complex carbohydrates and produce short chain fatty acids (SCFA) such as acetate, propionate and butyrate. Short chain fatty acids can be easily absorbed by diffusion and contribute to increased caloric yield of food. SCFA can bind to G-protein coupled receptor (Gpr41/42), this molecule up regulates secretion of peptide YY (PYY). PYY slows down motility of GI tract and enhances absorption of SCFA. Increased energy harvest leads to positive energy balance and over time result in obesity (Figure 4). SCFA which are produced by intestinal microbiota can have effect brain-gut neural communication .

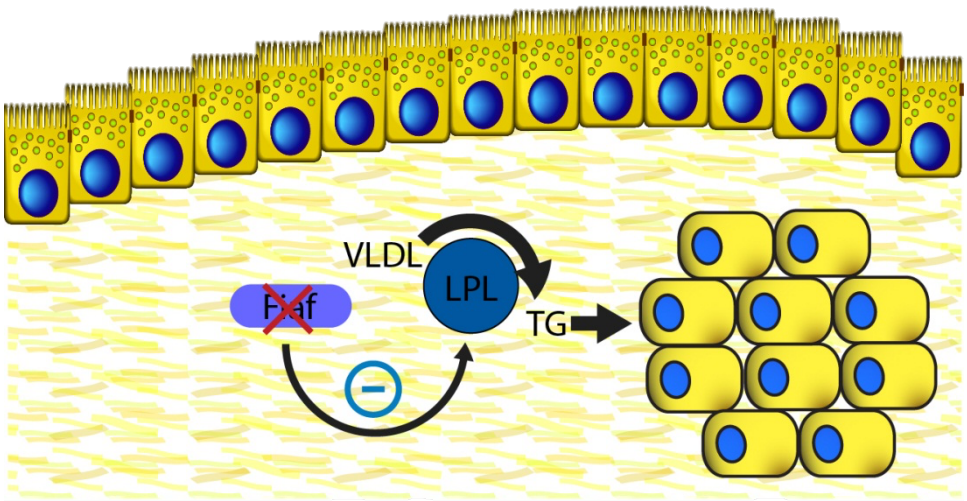

Figure 4. *Germ free Fiaf -/- mice gain weight at similar rate as conventionally raised mice.*

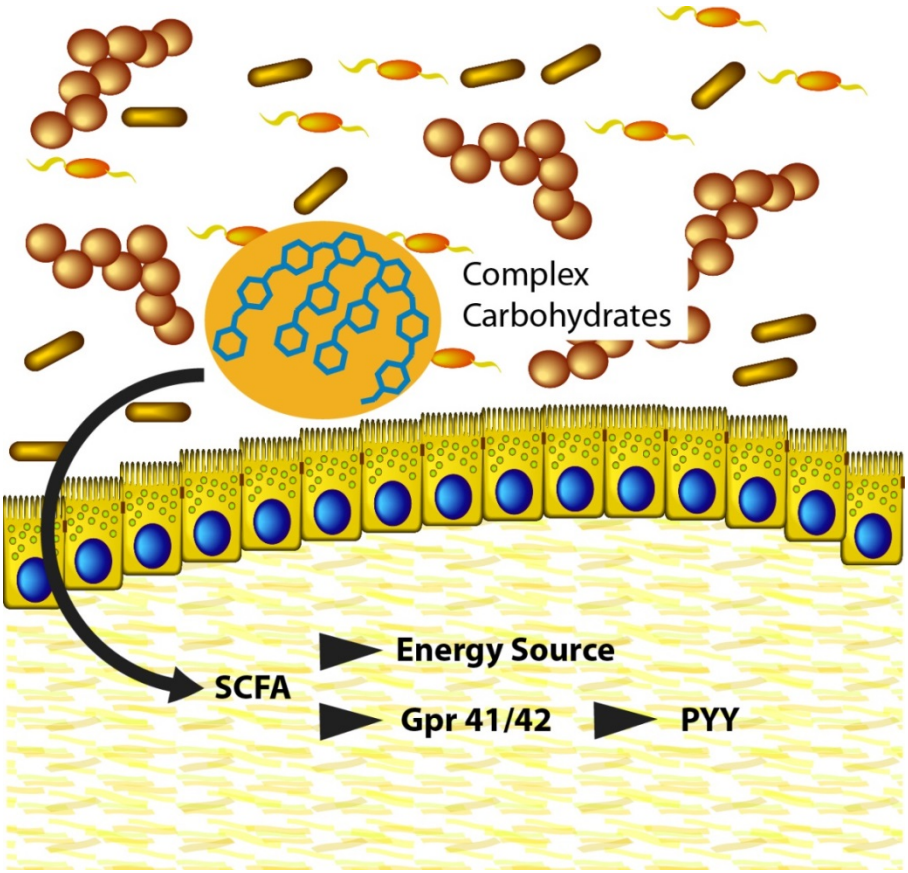

Figure 5. *Short chain fatty acids are produced by intestinal bacteria. Poorly absorbable complex carbohydrates serve as substrates. Additionally they interact with Gpr 41/42 protein and affect PYY secretion.*

Insight into nature of individual variation in energy harvest is provided by co-colonization studies. Germ free mice model allows colonization of mice with selected species of microbes. This allows study of contribution of species of microbes to energy harvest from the diet. Some bacterial species collaborate to increase energy harvest. For example *M. smithi* and *B. Thetaiotaomicron* harvest more energy from standard diet when animal is colonized with combination of these two than when each species colonizes animal separately. Addition of *Arhaea* to most of bacterial colonization models increases efficiency of fermentation by removal of H_2 (3).

Interactions between organism, diet and microbiota can result in alteration of energy harvest. Genetically obese ob/ob mice have homozygous mutation of leptin gene and as result they have increased caloric intake. Interestingly ob/ob mice bowel flora is different from that of wild type or heterozygote ob/+ mice. Ob/ob mice have increased population of *Firmicutes* and *Arhaea*. Bowel flora of ob/ob mice has increased capacity to break polysaccharides, increased CCFA production and increased fermentation efficiency. As consequence energy harvest in ob/ob mice from standard diet may be up to 50% higher than in wild type mice. Transmission of bowel flora from ob/ob mice into germ free mice increases body mass and body fat. This effect exceeds weight gain and body fat in germ free mice colonized with bowel flora of wild type mice. In conclusion microbiota of ob/ob mice contribute to excessive weight gain by increasing energy harvest .

Diet alone may have impact on energy harvest. Mice fed high fat high sugar diet (meant to simulate "western diet") expanded *Mollicutes* population at the expense of *Bacteroides*. Change in composition of microbiota results in increased energy harvest. Increase in efficiency of fermentation of fructose and N-acetyl-galactosides appear to be mechanism of enhanced energy harvest .

Of course intestinal microbiota are not the only, not even main cause of obesity. After all germ free ob/ob mice are still obese, and germ free mice can become obese on high fat diet.

Intestinal microbiome and energy metabolism – human data.

Bacterial flora is mostly inherited from the mother, though there is some transmission of bacteria between family members. Tis hypothesis is supported by the evidence that there is no significant difference in composition of bowel flora between monozygotic and dizygotic tweens. Impact of maternally inherited flora on development of human obesity has been postulated. Effect of microbiota may be partially responsible for increased rate of obesity in children born via cesarean section.

Role of microbiota in increasing energy harvest have been demonstrated in humans. Obesity correlates with lower levels of *Bacteroides* and higher levels of *Actinobacteria*. Metagenomic analysis of microbiota shows overexpression of genes responsible for carbohydrate processing in obese subjects. Bacteroides/Firmicutes ratio has been postulated to be a factor in development of the obesity. Weight loss and persistent use of low calorie diet results in changes in bacterial composition, but metabolic significance of that is unknown.
Some skepticism is warranted regarding impact of microbiota on obesity in humans as recent analysis of stool microbiomes from large metagenomic samples sets found no association between BMI and taxonomic microbiome composition. In this analysis the Bacteroidetes to Firmicutes ratio was not associated with obesity or BMI and gut microbiome community diversity was not associated with BMI.

Obesity and Inflammation.

Bacterial lipo-polysacharides (LPS) are known to induce inflammatory responses. These responses are mediated through CD14 molecule which serves as LPS receptor. Intestinal flora is a main source of circulating LPS. Changes in bowel flora can affect LPS levels. In mice after 4 weeks of high fat diet LPS levels increase in proportion to the number of LPS producing bacteria in the intestine. I humans even 3 days of high fat diet can result in increase in LPS levels. Antibiotics reduce LPS levels in mice fed high fat diet. In this animal model antibiotics reduced markers of inflammation and improved intestinal permeability. Antibiotics also improved glucose intolerance, reduced weight gain, and decreased visceral adipose tissue.

Role of LPS in human disease is suggested by observation that patients with short gut and documented intestinal bacterial overgrowth LPS levels are elevated. In this patient group LPS level correlates with the severity of TPN related liver disease. There is increasing support for the role of intestinal microbiota in development of inflammatory response in obesity.

Intestinal flora and complications of obesity

Intestinal bacteria seem to influence several factors leading to development of non-alcoholic steatohepatitis in humans. Fatty acid synthesis, insulin resistance, C- reactive protein levels and VLDL production have been correlated with changes in bowel flora. Short chain fatty acids generated by microbiota acting through GPR43 receptor are one of the main mechanisms implicated in improvement in insulin mediated fat deposition . Similarly risk factors for cardiovascular disease have been correlated with probiotics and composition of intestinal flora.

Composition of microbiota have been correlated with insulin resistance and increased HOMA index.

Probiotics

Several species of bacteria, particularly species performing lactic fermentation are considered beneficial for gastrointestinal health. These species are widely used in fermentation based food preservation such as yoghurt and cheese making, production of pickled food etc. Despite of their wide spread use health benefits are not yet clear in management of obesity.

Several species of bacteria shown promise to have beneficial effect on processes implicated in pathophysiology of obesity in animal models. Supplementation of *Bifidobacteria* in mice led to lower lipo-polysaccharide levels. *Bifidobacteria* increase de-conjugation of bile acids leading to depletion of bile acid pool and decrease in the cholesterol levels as cholesterol is a substrate in bile acid production. Probiotics seem to improve insulin sensitivity and fatty acid oxidation. *Lactobacillus paracasei* reduced effects of high fat diet in rats . Similar effect was shown for *Agaricus blazei* in rats. Modification of microbial composition of GI tract showed protective effect on obesity associated with “western” (high fat, high carbohydrate) diet in mice . Again, the impact of pro-biotics is not settled even in animal studies as probiotics however did not affect obesity in several other studies.

Pre-biotics are defined as dietary supplements (poorly absorbable oligosaccharides) able to influence intestinal environment and change composition of bacterial flora. For instance fructo-oligosaccharides fed to mice had increased number of *Bifidobacteria*. Metabolic effects of pre-biotics were similar to that of *Bifidobacteria* supplementation.

There is no conclusive data on the effects probiotics in human obesity.

Questions surrounding the role of the microbiota in obesity.

Intestinal microbiota are relatively new subject in the study of obesity. There are multiple methodological questions regarding testing and analyzing intestinal microbiota. New insights bring however several intriguing questions which may be resolved by future research.

Energy harvest which depends on composition of bacterial flora put into question current evaluation of caloric value of food. According to models incorporating metagenomic concepts caloric value of food can

change from individual to individual as energy harvest depends on composition of bowel flora.

It is clear that host related factors and diet can affect microbiota and microbiota can affect host in return. Although animal studies elucidated several potential mechanisms involved we know very little about of these interactions in humans. It is not clear if obesity and high calorie diet lead to adverse changes in bowel flora or if individual variation in bowel flora predisposes to development of obesity. The research is in its early stages and should not be over-interpreted into clinical recommendations.

References

1. Turnbaugh PJ, Ley RE, Hamady M, et al. The human microbiome project. Nature 2007;449:804–810.
2. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 2006;124:837–848.
3. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. Science 2001;292:1115–1118.
4. Neish AS. Microbes in Gastrointestinal Health and Disease. Gastroenterology 2009;136:65–80.
5. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. Science 2005;308:1635–1638.
6. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. Science 2001;292:1115–1118.
7. Flint HJ, Bayer EA, Rincon MT, et al. Polysaccharide utilization by gut bacteria: potential for new insights from genomic analysis. Nat Rev Microbiol 2008;6:121–131.
8. Hooper LV, Wong MH, Thelin A, et al. Molecular analysis of commensal host-microbial relationships in the intestine. Science 2001;291:881–884.
9. Backhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial mutualism in the human intestine. Science 2005;307:1915–1920.
10. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA 2004;101:15718–15723
11. Kahn BB, Alquier T, Carling D, et al. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. Cell Metab 2005;1:15–25.
12. Samuel BS, Shaito A, Motoike T, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fattyacid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci USA 2008;105:16767–16772.
13. Sonnenburg JL, Xu J, Leip DD, et al. Glycan foraging in vivo by an intestine-adapted bacterial symbionta. Science 2005;307:1955–1959.
14. De Vadder F. Kovatcheva-Datchary P. Goncalves D. Vinera J. Zitoun C. Duchampt A. Backhed F. Mithieux G. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 2014;156(1-2):84-96.
15. Samuel BS, Gordon JI. A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. Proc Natl Acad Sci USA 2006;103:10011–10016.
16. Ley RE, Backhed F, Turnbaugh P, et al. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA 2005;102:11070–11075.
17. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006;444:1027–1031.
18. Ferraris RP, Vinnakota RR. Intestinal nutrient transport in genetically obese mice. Am J Clin Nutr 1995;62:540–546.
19. Turnbaugh PJ, Backhed F, Fulton L, et al. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe 2008;3:213–223.
20. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature 2009;457:480–484.

21. Luoto R. Collado MC. Salminen S. Isolauri E. Reshaping the gut microbiota at an early age: functional impact on obesity risk? Annals of Nutrition & Metabolism. 63 Suppl 2013;2:17-26.
22. Blustein J. Attina T. Liu M. Ryan AM. Cox LM. Blaser MJ. Trasande L. Association of caesarean delivery with child adiposity from age 6 weeks to 15 years. International Journal of Obesity. 2013;37(7):900-6.
23. Ley RE, Turnbaugh PJ, Klein S, et al. Microbial ecology: human gut microbes associated with obesity. Nature 2006;444:1022–1023.
24. Knights D, Costello EK, Knight R (2011) Supervised classification of human microbiota. FEMS Microbiology Reviews 35: 343–359.
25. Finucane MM, Sharpton TJ, Laurent TJ, Pollard KS (2014) A Taxonomic Signature of Obesity in the Microbiome? Getting to the Guts of the Matter. PLoS ONE [Electronic Resource] 9(1): e84689.
26. Neish AS. Microbes in Gastrointestinal Health and Disease. Gastroenterology 2009;136:65–80.
27. Verdam FJ. Fuentes S. de Jonge C. Zoetendal EG. Erbil R. Greve JW. Buurman WA. de Vos WM. Rensen SS. Human intestinal microbiota composition is associated with local and systemic inflammation in obesity. Obesity. 2013;21(12):E607-15.
28. Graessler J. Qin Y. Zhong H. Zhang J. Licinio J. Wong ML. Xu A. Chavakis T. Bornstein AB. Ehrhart-Bornstein M. Lamounier-Zepter V. Lohmann T. Wolf T. Bornstein SR. Metagenomic sequencing of the human gut microbiome before and after bariatric surgery in obese patients with type 2 diabetes: correlation with inflammatory and metabolic parameters. Pharmacogenomics Journal. 2013;13(6):514-22.
29. Mehal WZ. The Gordian Knot of dysbiosis, obesity and NAFLD. Nature Reviews Gastroenterology & Hepatology. 2013;10(11):637-44.
30. Kimura I. Ozawa K. Inoue D. Imamura T. Kimura K. Maeda T. Terasawa K. Kashihara D. Hirano K. Tani T. Takahashi T. Miyauchi S. Shioi G. Inoue H. Tsujimoto G. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43 Nature communications . 2013;4:1829.
31. Ebel B. Lemetais G. Beney L. Cachon R. Sokol H. Langella P. Gervais P. Impact of probiotics on risk factors for cardiovascular diseases. A review. Critical Reviews in Food Science & Nutrition. 2014;54(2):175-89.
32. F S Teixeira T. Grzeskowiak LM. Salminen S. Laitinen K. Bressan J. Gouveia Peluzio Mdo C. Faecal levels of Bifidobacterium and Clostridium coccoides but not plasma lipopolysaccharide are inversely related to insulin and HOMA index in women. Clinical Nutrition. 2013;32(6):1017-22.
33. Serino M. Fernandez-Real JM. Garcia-Fuentes E. Queipo-Ortuno M. Moreno-Navarrete JM. Sanchez A. Burcelin R. Tinahones F. Managing the manager: gut microbes, stem cells and metabolism. Acta Diabetologica. 2013;50(5):753-61.
34. Lee BH, Lo YH, Pan TM Anti-obesity activity of *Lactobacillus* fermented soy milk products. J Funct Foods 2013;5:905–913
35. Vincent M. Philippe E. Everard A. Kassis N. Rouch C. Denom J. Takeda Y. Uchiyama S. Delzenne NM. Cani PD. Migrenne S. Magnan C. Dietary supplementation with *Agaricus blazei* murill extract prevents diet-induced obesity and insulin resistance in rats. Obesity. 2013;21(3):553-61.

36. Poutahidis T. Kleinewietfeld M. Smillie C. Levkovich T. Perrotta A. Bhela S. Varian BJ. Ibrahim YM. Lakritz JR. Kearney SM. Chatzigiagkos A. Hafler DA. Alm EJ. Erdman SE. Microbial reprogramming inhibits Western diet-associated obesity. PLoS ONE [Electronic Resource]. 2013;8(7):e68596.
37. Yin YN, Yu QF, Fu N, Liu XW, Lu FG (2010) Effects of four *Bifidobacteria* on obesity in high-fat diet induced rats. World J Gastroenterol 16:3394–3401
38. Arora T, Anastasovska J, Gibson G, Tuohy K, Sharma RK, Bell J, Frost G (2012) Effect of *Lactobacillus acidophilus* NCDC 13 supplementation on the progression of obesity in diet-induced obese mice. Br J Nutr 108:1382–1389
39. Respondek F. Gerard P. Bossim M. Boschat L. Bruneau A. Rabot S. Wagner A. Martin JC. Short-chain fructo-oligosaccharides modulate intestinal microbiota and metabolic parameters of humanized gnotobiotic diet induced obesity mice. PLoS ONE [Electronic Resource]. 2013;8(8):e71026.
40. Raoult D. Henrissat B. Are stool samples suitable for studying the link between gut microbiota and obesity? European Journal of Epidemiology. 2014;29(5):307-9
41. DeWeerdt S. Microbiome: A complicated relationship status. Nature. 2014;508(7496):S61-3.

~ About the Authors ~

Grzegorz W Telega

Children's Hospital Of Wisconsin Since 2000
Program director, Liver Transplant Hepatology, Children's Hospital of Wisconsin
Associate professor, the Medical College of Wisconsin

Office Locations

Children's Hospital of Wisconsin-Main Campus
8915 W. Connell Ave
Milwaukee, WI 53226
(414) 266-3690
(877) 607-5280 (appointment)

Education

- 1989, N Copernicus Academy of Medicine (Krakow, Poland), MD
  Residency

- 1997, Schneider Children's Hospital (NY) – Pediatrics
  Fellowship

- 2000, The Children's Hospital of Philadelphia – Ped Gastroenterology
  Awards

- Best Doctors for 10 consecutive years since 2003

Recent Publications

1. Lerret S, Mavis A, Biank V, Telega G. Respiratory syncytial virus and pediatric liver transplant: one center's experience. *Prog Transplant.* 2013 Sep;23(3):253-7.
2. Mazur A, Matusik P, Revert K, Nyankovskyy S, Socha P, Binkowska-Bury M, Grzegorczyk J, Caroli M, Hassink S, Telega G, Malecka-Tendera E. Childhood obesity: knowledge, attitudes, and practices of European pediatric care providers. 2013 Jul;132(1):e100-8.

3. Telega G, Cronin D, Avner ED. New approaches to the autosomal recessive polycystic kidney disease patient with dual kidney-liver complications. *Pediatr Transplant.* 2013 Jun;17(4):328-35.
4. Greenley RN, Kunz JH, Biank V, Martinez A, Miranda A, Noe J, Telega G, Tipnis NA, Werlin S, Stephens MC. Identifying youth nonadherence in clinical settings: data-based recommendations for children and adolescents with inflammatory bowel disease. *Inflamm Bowel Dis.* 2012 Jul;18(7):1254-9.
5. Loomba RS, Telega GW, Gudausky TM. Type 2 Abernethy malformation presenting as a portal vein-coronary sinus fistula. *J Pediatr Surg.* 2012 May;47(5):E25-31.
6. Lerret SM, Garcia-Rodriguez L, Skelton J, Biank V, Kilway D, Telega G. Predictors of nonalcoholic steatohepatitis in obese children. *Gastroenterol Nurs.* 2011 Nov-Dec;34(6):434-7.
7. Jensen MK, Biank VF, Moe DC, Simpson PM, Li SH, Telega GW. HIDA, percutaneous transhepatic cholecysto-cholangiography and liver biopsy in infants with persistent jaundice: can a combination of PTCC and liver biopsy reduce unnecessary laparotomy? *Pediatr Radiol.* 2012 Jan;42(1):32-9.
8. Sultan MI, Biank VF, Telega GW. Successful treatment of autoimmune hepatitis with methotrexate. *J Pediatr Gastroenterol Nutr.* 2011 Apr;52(4):492-4.
9. Venkatasubramani N, Telega G, Werlin SL. Obesity in pediatric celiac disease. *J Pediatr Gastroenterol Nutr.* 2010 Sep;51(3):295-7.
10. Mazur A, Ostański M, Telega G, Malecka-Tendera E. Is epicardial fat tissue a marker of metabolic syndrome in obese children? 2010 Aug;211(2):596-600.

~ How To Use This article ~

You are **free to use, share and copy this content** by quoting this article as follow:

Telega G (2015). Intestinal Microbiome In Obesity. In M.L. Frelut (Ed.), The ECOG's eBook on Child and Adolescent Obesity. Retrieved from ebook.ecog-obesity.eu

Also make sure to **give appropriate credit** when using this content. Please visit ebook.ecog-obesity.eu/terms-use/summary/ for more information.

~ Final Word ~

Thank you for reading this article.

If you have found this article valuable, please share it with someone that will be interested in.

Also make sure to visit ebook.ecog-obesity.eu to read and download more childhood obesity-related articles.