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EDITORIAL

High-Fat Diet, Dysbiosis, and Gastrointestinal and Colonic Transit: Is There a Missing Link?

In a series of elegant studies reported in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Anitha et al[1] report that a high-fat diet results in slowing of gastrointestinal transit (by geometric center of fluorescein isothiocyanate distribution after gavage), total gastrointestinal transit (by first arrival of a blue dye in stool), and distal colonic transit (by the time taken to expel a bead through the last 2 cm of colon). This retardation of transit is associated with increased numbers of fecal *Firmicutes* and reduced numbers of *Bacteroidetes*. The high-fat diet also was associated with an increase in serum lipopolysaccharide, reflecting increased permeability of the digestive tract, and reductions in numbers of enteric nervous system neurons, with specific loss of neurons expressing nitric oxide synthase. Anitha et al[1] hypothesize that a reduction in nitric oxide synthase–expressing neurons was the cause of retarded transit. Oligofructose partly corrected transit rate, serum lipopolysaccharide, microbial perturbations, and a reduction in enteric nervous system nitrergic neurons. Parallel in vitro studies have suggested that dietary fat causes neuronal apoptosis by activating Toll-like receptor 4.[1]

The data provided by the animal model lead to a number of intriguing questions, some of which will require investigation in human beings while others can be addressed based on prior reports in the literature.

Is the Retardation of Transit the Result of Obesity or the High-Fat Diet Per Se?

Both epidemiologic studies and actual measurements of colonic transit in human beings suggest that a body mass index greater than 30 kg/m^2 are associated with diarrhea rather than constipation, and with faster colonic transit.[2,3] Obesity typically is associated with normal or accelerated gastric emptying.[4] This would suggest that the observed retardation of transit is the result of the diet rather than the obesity per se. However, in human studies, a high-fat diet was not associated with retardation of colonic transit.[5] The blue dye and fluorescein isothiocyanate method to evaluate overall gut and small-intestinal transit in the study by Anitha et al[1] started with gastric gavage of the marker. Given the known retardation of gastric emptying by high-fat loads[6] and evidence of adaptation to the effects of fat,[7] it would be interesting to further evaluate the contributions of gastric transit to changes in overall and distal colonic transit observed in the mouse model.

Does a High-Fat Diet Increase Intestinal Permeability in Human Beings?

There is human evidence that a high-fat diet increases serum lipopolysaccharide levels.[8] Serum lipopolysaccharide levels can be increased by direct diffusion owing to increased intestinal paracellular permeability or by absorption across enterocytes during chylomicron secretion; the precise mechanisms are being investigated actively.[9] Consumption of a high-fat diet results in increased production of bile, observed in both obese and lean animals.[10] This was associated with reduced expression of claudin-1, claudin-3, occludin, and junctional adhesion molecule-1 in small, but not large, intestinal epithelial cells; consistent with this, in vitro exposure of Caco-2 cell monolayers to bile juice and fat emulsion increased tight junction permeability and reduced tight junction protein expression.[10]

Are There Other Perturbations Resulting From a High-Fat Diet That May Result in the Observed Changes in the Microbiome?

It is intriguing that the increase in *Firmicutes* and the reduction in *Bacteroidetes* observed with a high-fat diet have been reported with administration of the primary bile acid cholic acid.[11] Further studies are needed to better understand the mechanisms of this shift in microbial composition as well as its impact on metabolism and intestinal function.

What is the Mechanism by Which Oligofructose Corrects Fat-Induced Functional Perturbations?

Oligofructose is a prebiotic fructan that, similar to inulin, is not hydrolyzed or absorbed in the upper gastrointestinal tract but undergoes variable degrees of fermentation in the colon.[12] The beneficial effects are particularly interesting given that diets low in fructans and other fermentable oligo-di-monosaccharides and polyols are beneficial in patients with irritable bowel syndrome,[13] although such diets are not superior to traditionally recommended diets.[14] Nonetheless, it is clear that low fermentable oligo-di-monosaccharides and polyols diets modify the gut microbiome,[15] and that oligosaccharides increase fecal *Bifidobacteria*.[16] Moreover, in mice, oligofructose feeding increases the *Bacteroidetes* abundance with a concomitant decrease in *Firmicutes*,[17] similar to the changes observed by Anitha et al.[1] Once again, it is intriguing to note that dietary oligosaccharide supplementation results in increased fecal bile acid levels in rats, hamsters, and mice.[18,19]

Finally, Anitha et al[1] focused on dysbiosis as a contributor to the effects of a high-fat diet. An alternative hypothesis is that the effects are mediated at least in part by bile

acids. Thus, triggering the TGR5 (G-protein–coupled bile acid) receptor with the bile acids chenodeoxycholic acid or deoxycholic acid activated the main mitogen-activated protein kinases (extracellular signal–regulated kinase 1/2, p38, and c-Jun-N-terminal kinase), as well as the nuclear factor-κB signaling pathway in a monocyte cell line.[20] Once again, it is interesting to speculate that bile acids may be the missing link.

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References

1. Anitha M, Reichardt F, Tabatabavakili S, et al. Intestinal dysbiosis contributes to the delayed gastrointestinal transit in high-fat diet fed mice. Cell Mol Gastroenterol Hepatol 2016;2:328–339.
2. Delgado-Aros S, Locke GR 3rd, Camilleri M, et al. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. Am J Gastroenterol 2004;99:1801–1806.
3. Delgado-Aros S, Camilleri M, Garcia MA, et al. High body mass alters colonic sensory-motor function and transit in humans. Am J Physiol Gastrointest Liver Physiol 2008; 295:G382–G388.
4. Acosta A, Camilleri M, Shin A, et al. Quantitative gastrointestinal and psychological traits associated with obesity and response to weight-loss therapy. Gastroenterology 2015;148:537–546.
5. Cummings JH, Wiggins HS, Jenkins DJ, et al. Influence of diets high and low in animal fat on bowel habit, gastrointestinal transit time, fecal microflora, bile acid, and fat excretion. J Clin Invest 1978;61:953–963.
6. Heddle R, Collins PJ, Dent J, et al. Motor mechanisms associated with slowing of the gastric emptying of a solid meal by an intraduodenal lipid infusion. J Gastroenterol Hepatol 1989;4:437–447.
7. Cunningham KM, Daly J, Horowitz M, et al. Gastrointestinal adaptation to diets of differing fat composition in human volunteers. Gut 1991;32:483–486.
8. Pendyala S, Walker JM, Holt PR. A high-fat diet is associated with endotoxemia that originates from the gut. Gastroenterology 2012;142:1100–1101.
9. Moreira AP, Texeira TF, Ferreira AB, et al. Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. Br J Nutr 2012; 108:801–809.
10. Suzuki T, Hara H. Dietary fat and bile juice, but not obesity, are responsible for the increase in small intestinal permeability induced through the suppression of tight junction protein expression in LETO and OLETF rats. Nutr Metab 2010;12:7–19.
11. Islam KB, Fukiya S, Hagio M, et al. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. Gastroenterology 2011; 141:1773–1781.
12. Flamm G, Glinsmann W, Kritchevsky D, et al. Inulin and oligofructose as dietary fiber: a review of the evidence. Crit Rev Food Sci Nutr 2001;41:353–362.
13. Halmos EP, Power VA, Shepherd SJ, et al. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology 2014;146:67–75.
14. Böhn L, Störsrud S, Liljebo T, et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology 2015;149:1399–1407.
15. Halmos EP, Christophersen CT, Bird AR, et al. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut 2015;64:93–100.
16. Stiverson J, Williams T, Chen J, et al. Prebiotic oligosaccharides: comparative evaluation using in vitro cultures of infants' fecal microbiomes. Appl Environ Microbiol 2014;80:7388–7397.
17. Massey VL, Stocke KS, Schmidt RH, et al. Oligofructose protects against arsenic-induced liver injury in a model of environment/obesity interaction. Toxicol Appl Pharmacol 2015;284:304–314.
18. Levrat M, Favier M, Moundras C, et al. Role of dietary propionic acid and bile excretion in the hypocholesterolemic effects of oligosaccharides in rats. J Nutr 1994; 124:531–538.
19. Trautwein E, Rieckhoff D, Erbersdobler H. Dietary inulin lowers plasma cholesterol and triacylglycerols and alters biliary bile acid profile in hamsters. J Nutr 1998; 128:1937–1943.
20. Mobraten K, Haugbro T, Karlstrom E, et al. Activation of the bile acid receptor TGR5 enhances LPS-induced inflammatory responses in a human monocytic cell line. J Recept Signal Transduct Res 2015;35:402–409.

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Conflicts of interest
The author discloses no conflicts.

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