Disharmony in Gut Microbiota – Should This Be a Priority for Public Health Nutrition?

Amanda Avery
lead author on behalf of the EFAD PH specialist group, Division of Food, Nutrition & Dietetics, University of Nottingham, Sutton Bonington Campus, Leicestershire, United Kingdom

Abstract from Malesza IJ, Malesza M, Walkowiak J, et al.: High-Fat, Western-Style Diet, Systemic Inflammation, and Gut Microbiota: A Narrative Review. Cells. 2021;10(11):3164.

Keywords
LPS · NF-κB · TLR4 · Bile acids · Dysbiosis · Endoplasmic reticulum stress · Endotoxemia · Leaky gut · Oxidative stress · Postprandial inflammation

Abstract
The gut microbiota is responsible for recovering energy from food, providing hosts with vitamins, and providing a barrier function against exogenous pathogens. In addition, it is involved in maintaining the integrity of the intestinal epithelial barrier, crucial for the functional maturation of the gut immune system. The Western diet (WD) – an unhealthy diet with high consumption of fats – can be broadly characterized by overeating, frequent snacking, and a prolonged postprandial state. The term WD is commonly known and intuitively understood. However, the strict digital expression of nutrient ratios is not precisely defined. Based on the US data for 1908–1989, the calory intake available from fats increased from 32% to 45%. Besides the metabolic aspects (hyperinsulinemia, insulin resistance, dyslipidemia, sympathetic nervous system and renin-angiotensin system overstimulation, and oxidative stress), the consequences of excessive fat consumption (high-fat diet-HFD) comprise dysbiosis, gut barrier dysfunction, increased intestinal permeability, and leakage of toxic bacterial metabolites into the circulation. These can strongly contribute to the development of low-grade systemic inflammation. This narrative review highlights the most important recent advances linking HFD-driven dysbiosis and HFD-related inflammation, presents the pathomechanisms for these phenomena, and examines the possible causative relationship between pro-inflammatory status and gut microbiota changes.

© 2021 The Author(s)
Knowledge Transfer

Background
Over the past three decades, we have seen a global increase in the prevalence of several non-communicable diseases. This well-established observation has led to a continuum of different healthy eating policies that have tried to reverse the situation. However, the prevalence of obesity has continued to increase globally, along with its associated comorbidities of diabetes, hypertension, cardiovascular disease, certain cancers, non-alcoholic fatty liver disease, neurological disorders, and musculoskeletal disease. So, what do we need to do differently – what might be the missing piece of the puzzle that may make a difference and reduce the prevalence of obesity and non-communicable diseases? Perhaps the area of study where we might find this missing piece is the further exploration of the role of the gut microbiome.

We are all beginning to appreciate that a diverse community of microorganisms live in the human gut, referred to as ‘microbiota’ and comprising more than 250 different species of bacteria, fungi, viruses, and archaea [1, 2]. The microbiota of an adult may include around 1,013 bacterial cells [3] and is a dynamic, highly individualised system that changes across the life course. The amount of bacteria species varies depending on genetics, age, diet, pharmacotherapy, including antibiotics, and other environmental factors [4, 5]. We are also appreciating the extensive role that a healthy gut microbiota plays in maintaining good health. We know that it helps in the digestion of polysaccharides [6] and provides a number of B vitamins as well as vitamin K; it has been suggested that up to 50% of the daily vitamin K requirement is acquired by the microbiota [7]. Furthermore, the microbiota is protective against exogenous pathogens, contributing to maintaining the integrity of the intestinal epithelial barrier [8, 9], and is pivotal in the functional maturation of the gut immune system [10]. The microbiota also influences other organs, and we now refer to the interaction between the intestinal microbiome and the brain as the gut-brain axis. This interaction helps to regulate satiety and hormone levels and may impact mood and behaviour [11–13].

Some gut bacteria have anti-inflammatory or proinflammatory properties and have been found to reduce low-grade inflammation in human and animal models [14–17], in some cases due to the generation of short-chain fatty acids (SCFA). For example, butyrate, one of the most abundant SCFA in the gut, has known anti-inflammatory properties [18]. Microbiota species related to increased SCFA production include Bifidobacteria which maintain intestinal microvilli integrity, promote anti-inflammatory cytokine production, cause maturation of immune cells, stimulate IgA secretion, and have antioxidant properties [19].

Exactly what is a ‘healthy microbiota’ or eubiosis remains a challenge to define but generally refers to a balanced intestinal microbial ecosystem with a dominance of potentially beneficial bacteria species [20]. Although the gut microbiota is highly variable between individuals, any alterations in the composition can disrupt the complex host-microbiota relationship. Disarray in the composition of the microbiota is called dysbiosis and has been linked to the development of several diseases including obesity and type 2 diabetes [21].

Study Results
Diet influences the composition of the gut microbiota. Dietary fibre, in all its different forms, is acknowledged to promote a healthy microbiota [22]. A recent review concluded that dairy products such as milk, yogurt, and kefir may regulate the gut microbiota composition in favour of the host [23]. Malesza et al., in their narrative review, consider the relationship between a high-fat western-style diet, systemic inflammation, and the gut microbiota [24]. They appreciate that it is very difficult to define what is meant by a westernised diet although generally characterised by overeating energy-dense foods, frequent snacking, high intake of refined sugars, high intake of saturated fats with an imbalance between omega-6 and omega-3 fatty acids, and low levels of dairy fibre. The narrative review, underpinning this knowledge exchange, presents the evidence linking dietary fats, colonic microbiota composition, and inflammation. Obesity-related dysbiosis can be directly linked to a high-fat diet (HFD) and presents with a reduced overall microbiota count, a shift in the dominating bacteria species, an increased stimulation of the inflammatory pathway, and an overall increase in gut permeability [25, 26] with the implications of a leaky gut fully explored in the review. Of further interest is that a HFD in animal models leads to the development of microbiota profiles similar to those of males with obesity [13, 27, 28]. The HFD-driven dysbiosis in animal and human models primarily includes an increase in the Firmicutes/Bacteroidetes ratio [29], and is often related to a reduction in Bifidobacterium species [30].

Whilst the literature does suggest some inconsistencies in the microbiota changes driven by a HFD, this inconsistency might be due to different types of fat used in the various studies [31]. In mice, dysbiosis related to HFD is caused by palm oil- but not olive or flax/ fish oil-based diets [32]. In humans, changes in the intestinal microbiota have also been found to be related to the type of fatty acids ingested – with omega-3 polysaturated fatty acid (PUFA) intake associated with an increase in Lactobacillus, whilst monounsaturated fatty acids (MUFA) and omega-6 PUFA were associated with reduced Bifidobacterium [33]. According to other researchers, inconsistencies in the results investigating the association between HFD and microbiota may be due to the different fibre content in the applied diets [34].

A westernised diet also has other features, one being a relatively high intake of processed foods. There is emerging interest in the extensive use of emulsifiers in processed foods leading to dysbiosis and subsequent changes in adiposity, resulting in metabolic syndrome and chronic inflammatory disease states [35]. Due to the wide use of emulsifiers in many processed foods and the inability to measure the actual amounts present and being consumed, it is suggested that the actual quantity of emulsifiers being consumed daily has now far exceeded what was once accepted [36]. As part of the drive to reduce energy intake whilst appeasing peoples liking for sweet foods, there has been an increased use of non-caloric artificial sweeteners (NAS). However, several studies have suggested that commonly used NAS lead to negative metabolic effects. Researchers have demonstrated...
that consumption of commonly used NAS formulations causes positional and functional alterations to the gut microbiota that drives the development of glucose intolerance [37].

**Conclusion for Clinical Practice**

There have been several proposed hypotheses as to the cause of the obesity epidemic with the main proposed thoughts linked to changes in dietary habits and the increased intake of energy-dense foods, a more sedentary lifestyle, and decreased energy expenditure. However, whilst there have undoubtedly been changes in dietary habits, perhaps the main cause of the obesity epidemic are the changes that result in disharmony in the gut microbiota and lead to low-grade inflammation, altered metabolism, and modified satiety regulation. Perhaps we should be focussing less on creating an energy deficit and more on providing guidance on how people can maintain a healthy gut microbiome through a diet containing plenty of wholegrains, vegetables, fruits, pulses, nuts, water to drink, some dairy, fewer processed foods containing emulsifiers, and fat in moderation with an increased focus on improving the balance between omega-3 and omega-6 fatty acids. People would likely benefit from curbing their fondness for sweet foods and only have small amounts of sugar on occasion. The conclusion of this knowledge exchange has to be that much more research is required; however, the insights to date suggest that harmony in the gut microbiota is likely to be pivotal in our mission to address obesity and associated non-communicable diseases.

**Disclosure Statement**

I hereby declare that there are no conflicts of interest with regards to this commentary.

**References**

1. Allam-Ndoul B, Castonguay-Paradis S, Veilleux A. Gut Microbiota and Intestinal Trans-Epithelial Permeability. *Int. J. Mol. Sci.* 2020;21:6402.
2. Salazar J, Angarita L, Morillo V, et al. Microbiota and Diabetes Mellitus: Role of Lipid Mediators. *Nutrients*. 2020;12:3039.
3. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Symbiotic Bacteria in the Body. *PLoS Biol.* 2016;14:e1002533.
4. Graf D, Di Cagno R, Fåk F, et al. Contribution of Diet to the Composition of the Human Gut Microbiota. *Microb. Ecol. Health Dis.* 2015;26:26164.
5. Faith JJ, Guruge JL, Charbonneau M, et al. The Long-Term Stability of the Human Gut Microbiota. *Science*. 2013;341:123743.
6. Sonnenburg ED, Sonnenburg JL, Manchester JR, et al. A Hybrid Two-Component System Protein of a Prominent Human Gut Symbiont Couples Glycan Sensing in Vivo to Carbohydrate Metabolism. *Proc. Natl. Acad. Sci. USA* 2006;103:8834–8839.
7. Hill MJ. Intestinal Flora and Endogenous Vitamin Synthesis. *Eur. J. Cancer Prev. Off. J. Eur. Cancer Prev. Organ. ECP*. 1997;6 (Suppl. 1):543–545.
8. Buffle CG, Pamer EG. Microbiota-Mediated Colonization Resistance against Intestinal Pathogens. *Nat. Rev. Immunol.* 2013;13:790–801.
9. Alakomi HL, Skytta E, Saarela M, et al. Lactic Acid Permeabilizes GramNegative Bacteria by Disrupting the Outer Membrane. *Appl. Environ. Microbiol.* 2000;66:2001–2005.
10. Kamada N, Seo S-U, Chen YG, Núñez G. Role of the Gut Microbiota in Immunity and Inflammatory Disease. *Nat. Rev. Immunol.* 2013;13:321–335.
11. Diaz Heijtz R, Wang S, Anuar F, et al. Normal Gut Microbiota Modulates Brain Development and Behavior. *Proc. Natl. Acad. Sci. USA* 2011;108:3047–3052.
12. Sudo N, Chida Y, Alba Y, et al. Postnatal Microbial Colonization Programs the Hypothalamic-Pituitary-Adrenal System for Stress Response in Mice. *J. Physiol.* 2004;558:263–275.
13. Sen T, Cawthorn CR, Ihsa BT, et al. Diet-Driven Microbiota Dysbiosis is Associated with Vagal Remodeling and Obesity. *Physiol. Behav.* 2017;173:305–317.
14. Everard A, Lazarevic V, Derrien M, et al. Responses of Gut Microbiota and Glucose and Lipid Metabolism to Prebiotics in Genetic Obese and Diet-Induced Leptin-Resistant Mice. *Diabetes*. 2011;60:2775–2786.
15. Everard A, Belzer C, Geurts L, et al. Cross-Talk between Akkermansia muciniphila and Intestinal Epithelial Cells Controls Diet-Induced Obesity. *Proc. Natl. Acad. Sci. USA* 2013;110:9966–9971.
16. Collado MC, Isern A, Lavin K, Salminen S. Distinct Composition of Gut Microbiota during Pregnancy in Overweight and Normal-Weight Women. *Am. J. Clin. Nutr.* 2008;88:894–899.
17. Karlsson CL, Onnerfält J, Xu J, et al. The Microbiota of the Gut in Preschool Children with Normal and Excessive Body Weight. *Obes. Silver Spring Md.* 2012;20:2257–2261.
18. Bach Knudsen KE, Lærke HN, Hedemann MS, et al. Impact of Diet-Modulated Butyrate Production on Intestinal Barrier Function and Inflammation. *Nutrients*. 2018;10:1499.
19. Else A, Amato F, Zarrilli F, et al. Butyrate Modulating Effects on Proinflammatory Pathways in Human Intestinal Epithelial Cells. *Biol. Microbes*. 2017;8:841–847.
20. Ielsba V, Tortino V, Gagliardi A, et al. Eubiosis and Dysbiosis: The Two Sides of the Microbiota. *New Microbiol.* 2016;391–12.
21. Patterson E, Ryan PM, Cryan JF, et al. Gut Microbiota, Obesity and Diabetes. *Postgrad. Med. J.* 2016;92:286–300.
22. Myhyrdad M, Tunjö H, Charnock C, Telle-Hansen VH. Dietary Fiber, Gut Microbiota, and Metabolic Regulation-Current Status in Human Randomized Trials. *Nutrients*. 2020;12:859.
23. Aslam H, Marx W, Rocks T, et al. The effects of dairy and dairy derivatives on the gut microbiota: a systematic literature review. *Nutr. Metab.* 2020;12(1):1799533.
24. Maleša U, Maleša M, Walkowiak J, et al. High-Fat, Western-Style Diet, Systemic Inflammation, and Gut Microbiota: A Narrative Review. *Cells*. 2021;10(11):3164.
25. Turnbaugh PJ, Ridaura VK. Faith JJ, et al. The Effect of Diet on the Human Gut Microbiota: A Metagenomic Analysis in Humanized Gnotobiotic Mice. *Sci. Transl. Med.* 2009;1:6ra14.
26. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial Ecology: Human Gut Microbes Associated with Obesity. *Nature*. 2006;444:1022–1023.
27. De La Serre CB, Ellis CL, Lee J, et al. Propensity to High-Fat Diet-Induced Obesity in Rats Is Associated with Changes in the Gut Microbiota and Gut Inflammation. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2010;299:G440–G448.
28. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-Induced Obesity Is Marked to But harbour Reversals in the Mouse Distal Gut Microbiome. *Cell Host Microbe*. 2008;3:213–21.
29. Molt D, Firmino O, Lévenez F, et al. The Firmicutes/Bacteroidetes Ratio of the Human Gut Microbiota Changes with Age. *BMC Microbiol.* 2009;9:123.
30. Shin N-R, Whon TW, Bae JW, et al. Butyrate: Microbial Signature of Dysbiosis in Gut Microbiota. *Trends Biotechnol.* 2015;33:496–503.
31. Mucio JR, Baccan GC, Georheva A, et al. Changes in Gut Microbiota Due to Supplemental Fatty Acids in Diet-Induced Obese Mice. *Br. J. Nutr.* 2013;110:711–720.
32. Patterson E, O’Doherty RM, Murphy EF, et al. Impact of Dietary Fatty Acids on Metabolic Activity and Host Intestinal Microbiota Composition in C57BL/6J Mice. *Br. J. Nutr.* 2014;111:1905–1917.
33. Wolters M, Ahrens J, Romani-Pérez M, et al. Dietary Fat, the Gut Microbiota, and Metabolic Health—A Systematic Review Conducted within the MyNewGut project. *Clin. Nutr. Edinb. Scand.* 2019;38:2504–2520.
34. Wang B, Kong G, Li X, et al. A High-Fat Diet Increases Gut Microbiota Biodiversity and Energy Expenditure Due to Nutrient Difference. *Nutrients*. 2020;12:3197.
35. Chassaigne B, Van de Wiele T, De Bodt J, et al. Dietary emulsifiers directly alter human microbiota composition and gene expression ex vivo potentiating intestinal inflammation. *Gut*. 2017;66:1414–1427.
36. Laster J, Bonnes SL, Rocha J. Increased Use of Emulsifiers in Processed Foods and the Links to Obesity. *Curr. Gastroenterol. Rep.* 2019;21:61.
37. Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature*. 2014;514(7521):181–186.

Correspondence to: Amanda Avery, amanda.avery@nottingham.ac.uk