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EDITORIAL

Does the gut microbiota hold the key to the obesity crisis? A perspective piece

Djamila Eliby[1] and Julian G. Simmons[2]

1. Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, VIC, Australia
2. Melbourne School of Psychological Sciences, Centre for Adolescent Health, Murdoch Children's Research Institute, University of Melbourne, Melbourne, VIC, Australia

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Corresponding Author:
Djamila Eliby
Melbourne School of Psychological Sciences
University of Melbourne
Melbourne, VIC, Australia
djamila.eliby@unimelb.edu.au

SUMMARY
Emerging evidence indicates that the gut microbiota relate to the onset and maintenance of obesity via several pathophysiological mechanisms, all of which are influenced by the host diet. The rapid shift towards Western-typical diets at a global scale may be contributing to gut dysbiosis, and consequently fuelling the global obesity crisis. Further mechanistic understanding of the influence of the gut microbiota in weight regulation in humans may lend itself to the development of more efficacious treatments.

Key Words
Obesity; gut microbiome; metabolism; diet; ultra-processed foods

INTRODUCTION

The alarming increase in the obesity prevalence worldwide poses a substantial public health crisis, with roughly one-third of adults deemed overweight (body mass index [BMI] 25 to <30) or obese (BMI > 30).[1] Obesity rates are disproportionally higher in affluent regions, including the USA, Europe, and Australasia, although a more recent surge in overweight and obesity in low-to-middle income countries, especially among children and adolescents, has been observed.[1,2] The health and societal burden of obesity is reflected in its contribution to the global incidence of non-communicable diseases (NCDs), including heart disease, type 2 diabetes mellitus, certain cancers, osteoarthritis, sleep apnea, and work-related afflictions.[1] An increase in sedentary living and a greater uptake of highly processed Western-style diets are known contributors to the obesity epidemic.[2] Yet, despite increased importance placed on the prevention of obesity at a national and policy level, rates of worldwide obesity continue to rise.[1] As such, to postulate that alterations in dietary habits and physical activity are the only contributing factors in the staggering growth of worldwide obesity rates may miss key causal factors and underlying mechanisms.

One area of research that has garnered increasing attention over the last few decades in relation to the obesity crisis has been the gut microbiota, which describe the collective ecosystem of gastrointestinal microorganisms comprising mostly bacteria, as well as fungi, viruses, archaea, and protozoa (the gut *microbiome* refers to the indigenous microbes, as well as their collective gene pool). Microorganisms populate almost every inch of the human body, with the most abundant

and diverse collection of microbes in the gut estimated to exceed 10^{14}, which is roughly 10 times the amount of human cells, and over 100 times the genetic material relative to the human genome.[3] Our gut microbiota have coevolved alongside humans (ie, the host) for over thousands of years to create a symbiotic relationship: the innate and adaptive immune systems coordinate and cooperate with the gut microbiota by tolerating commensal bacteria and staging a defensive response towards invasive pathogens.[4] In addition to their role in immune homeostasis, the gut microbiota are also critical in regulating digestion and host metabolism[4], all of which are influenced by diet.

The gut microbiota derive their nutrition from what is ingested by its host, including carbohydrates, lipids, and proteins, and through host-derived constituents, such as shed epithelial cells and mucus.[5] In turn, these substrates are used by the intestinal microbes to produce the energy necessary for cellular activity, growth, and survival which—as a by-product—leads to the production of several beneficial nutrients (including metabolites and certain vitamins) known to influence human metabolism and health.[5] For instance, dietary polysaccharides (ie, the main dietary substrate for intestinal bacteria) that are not digested in the small intestine are then fermented by the gut microorganisms into metabolites in the large intestine, notably, short-chain fatty acids (SCFAs). For instance, butyrate and propionate constitute an integral source of energy for the epithelial cells and play a critical role in gluconeogenesis, with positive effects on energy and glucose homeostasis.[6] By contrast, acetate, which is the most ubiquitous SCFA, is transferred to the peripheral tissues in the human body where it is involved in lipogenesis and cholesterol metabolism.[6]

In the context of obesity, dietary alterations often include high intakes of ultra-processed foods with excess sugar, salt, and fats—often replacing the intake of dietary plant fibre and other beneficial food substrates[12]—which may have adverse influences on the gut microbiota. The earliest evidence linking the gut microbiota to adiposity and energy regulation comes from animal work, which demonstrated that germ-free mice (ie, mice genetically bred to be sterile) colonised by microbes increased in weight and body fat.[13] Despite higher food intake, the germ-free mice had around 40 per cent less total body fat compared to the conventional mice, which increased by 57 per cent over two weeks after receiving the faecal microbiota transplants (FMTs).[14] This finding suggested that the intestinal microbiota improved the ability of the host to gather energy from the diet and store it in adipocytes, which ultimately brought about weight gain.[7] Furthermore, germ-free mice that received FMTs from obese humans saw a noticeably higher rate of weight gain relative to mice that received transplants from individuals of a normative weight, demonstrating a causal relationship between the gut microbiota and weight gain.[15]

Although much of the ensuing research investigating the involvement of gut microbes in the establishment and maintenance of obesity comes from pre-clinical mouse models, the successful transfer of an obese phenotype from humans via faecal transplant suggests there might be a common mechanism between mice and humans.[9] Long-term weight gain in humans has also been associated with lower microbial diversity, which is further exacerbated by inadequate dietary fibre intake.[16] Microbiota diversity is measured as the number and relative distribution of microbial species that are present, where lower diversity is generally regarded as a marker of

dysbiosis (ie, microbial imbalance).[8] This reinforces the idea that an alteration in the host microbiota may precede the onset of obesity, hence contributing to a growing number of studies that have started to analyse the pathophysiological processes through which the gut microbiome may influence obesity.

Researchers have hypothesised that gut dysbiosis fosters diet-induced obesity and metabolic dysregulation through numerous mechanisms, including 1) altered energy regulation, 2) immune dysregulation and pro-inflammatory mechanisms, and 3) alterations in gut hormone regulation.[8] Other factors beyond the scope of the present editorial include genetic and epigenetic influences, taste sensing, anaerobic resting metabolism, and thermogenesis—which may also be involved in the association between the microbiota and obesity predisposition and/or energy metabolism.[10]

1) Altered energy regulation

Researchers have established that the gut microbiota are involved in underlying processes related to energy homeostasis, which could potentially contribute to obesity development. Intestinal microbiota provide enzymes that are involved in various dietary metabolic pathways, most notably by facilitating fermentation of complex carbohydrates that would remain inaccessible to the host otherwise. This process results in the generation of SCFAs, which increases the host's capacity to obtain energy from ingested food, supplying up to 70 per cent of the daily energy source for herbivores and about 10 per cent of the daily energy source for omnivores.[17] Furthermore, SCFAs contribute to additional fat deposition throughout the body and are ligands for several G-protein coupled receptors (GPRs) that are involved in regulating energy expenditure.[18] Other processes linking SCFAs to the onset of obesity include the regulation of lipid metabolism (ie, through fasting-induced adipose factor), de novo fatty acid and triglyceride synthesis, regulation of glucose homeostasis and leptin secretion, and modulation of the satiety response, described in detail in previous reviews.[10]

Accordingly, there is literature to suggest that the elevated levels of SCFAs observed in obese children and adults relative to their non-obese counterparts may be due to higher colonic fermentation, or reduced absorption of SCFAs as a result of low-grade inflammation.[19,20] This finding is not consistent, however, with research indicating that fibre- and SCFA-rich diets could potentially prevent obesity onset.[9] As opposed to the function of SCFAs serving as additional energy supplies and adipogenic factors, researchers instead hypothesise that SCFAs derived from dietary fibre could be beneficial in obesity prevention, such as through regulating satiety responses and lipid metabolism[10] and by decreasing the total energy density of the diet.[9] Both butyrate and propionate may also exert beneficial effects on glucose metabolism by inducing gluconeogenesis, which may be related to improved glucose tolerance[21] and by improving insulin sensitivity.[22] As such, while SCFAs are involved in energy harvesting and regulating host metabolism, there is research to indicate that these metabolites may confer a protective role in the onset of obesity, warranting further attention in the context of weight regulation.[10]

2) Immune dysregulation and pro-inflammatory mechanisms

The gut microbiota's critical role in immune regulation is partly reliant on the integrity of the epithelial lining and normal production of intestinal mucus, which are supported by fibre-rich diets.[23] By contrast, the typical Western diet is low in fibre and may therefore contribute to the degradation of the colonic mucin barrier.[8] This breakdown contributes to a heightened gut permeability, causing a transfer of bacterial lipopolysaccharides (LPS) into the bloodstream.[10] LPS are endotoxins which, in elevated levels, contribute to a cascade of pro-inflammatory processes and metabolic perturbations relevant to obesity.[10] The consumption of high-fat diets, which are a characteristic feature of Western-typical diets, is associated with the overgrowth of gram-negative pathogenic bacteria, which lead to increased plasma levels of LPS[9]; over this time, this increase leads to metabolic endotoxemia, which accelerates the development of insulin resistance, inflammation, and fatty liver.[9]

Although the precise mechanisms by which intestinal microbiota influence metabolic endotoxemia and the subsequent contribution to obesity are not well understood, it has been suggested that heightened gut permeability and lowered gene expression in relation to tight junction proteins may drive the development of endotoxemia.[24] In fact, observational studies in humans have indicated tight junction impairments in severely obese individuals.[25] Additionally, researchers have associated high-fat diets with a decline in *Bifidobacterium* species and an overactivation of the endocannabinoid system, which can have unfavourable effects on gut microbiota composition and gut permeability.[10] LPS are additionally involved in the activation of the immune pathway of NF-κB in the bloodstream where, along with the pro-inflammatory cytokine CD14, LPS serves as a ligand for Toll-like receptor 4 (TLR4); researchers have identified this signalling pathway as one of the main triggers in increasing the obesity-induced inflammatory response.[26] In the context of high-fat diets, these observations suggest that the translocation of bacterial endotoxins may bring about the systemic low-grade inflammation induced by obesity.[27]

3) Alterations in gut hormone regulation

The final hypothesised pathway through which gut microbiota may exert an influence on obesity development is through a cascade of hormonal mechanisms that are involved in the activation of GPRs and host appetite control.[28] The gut microbiota are thought to influence the synthesis and function of neuropeptides and hormones that are produced by the nervous system, as well as the enteroendocrine cells of the colonic mucosa and peripheral organs, all of which are crucial to energy balance homeostasis.[7] Researchers have observed higher serum levels of leptin in obese individuals, which is linked to a heightened state of hunger and decreased energy expenditure.[29] Elevated levels of leptin may further bring about the synthesis of pro-inflammatory cytokines that contribute to the systematic inflammation characteristic of obesity.[29] Evidence suggests that binding between SCFAs with GPR41, which are expressed along the intestinal tract and adipocytes, promotes the expression of peptide hormones involved in appetite and energy metabolism, upon activation.[30]

Furthermore, gut-derived hormones are involved in the transfer of signals from the gut to the regulatory appetite centres in the brain.[31] Researchers have suggested that commensal bacteria may be able to modulate biochemical functioning of the brain and behaviour via the synthesis of metabolites and by modulating the vagus nerve, as summarised in a previous review.[10] The bi-directional pathway known as the gut-brain axis represents a crucial mediating link in the intricate neuroendocrine modulation of appetite and energy homeostasis.[32] Hence, it is plausible that gut dysbiosis brought on by the intake of a Western-typical diet could result in an altered synthesis of neurotransmitters that leads to overconsumption and weight gain.[32] The regulation of gut hormone release could therefore be a target of interest in relation to satiety/appetite signals and energy balance mechansisms.[10]

Further Considerations

Other important factors to consider in relation to the Western-typical diet are the ingredients (or effects on ingredients through processing) of ultra-processed foods, including food additives, artificial sweeteners, emulsifiers, high-fructose corn syrup, and thermal processing[11], which may be particularly deleterious to gut microbial balance. While discussion around these factors is beyond the scope of this editorial and have been summarised previously[11], the overarching evidence points towards ultra-processing of food contributing to obesity, metabolic syndrome, and a host of other non-communicable diseases through a disturbance of the gut microbiota. Although the mechanisms by which the processing of foods may impact weight gain and obesity remains incompletely understood, the intestinal microbiome may be a significant modulator of these relations and warrants further investigation.[11]

The link between host diet and obesity appears to be significantly influenced by the gut microbiota. A state of gut dysbiosis may precede the onset of obesity, potentially due to over-adherence to the Western-typical diet, which confers deleterious impacts on the gut microbiota's health. Accordingly, this sequence of events leads to a cascade of pathophysiological mechanisms via complex and interrelated metabolic, immune, and endocrine pathways, which potentially create a negative feedback loop that further predisposes individuals to weight gain, obesity, and its related comorbidities. Beyond diet, various other factors (eg, antibiotic usage, mode of natal delivery, breastfeeding, stress, sleep, etc.) modulate the make-up and function of the intestinal microbiome (and intestinal membrane function) in relation to obesity, which also require further research.[10]

With the understanding that the gut microbiota could be a modifiable target for weight loss, a growing number of studies have been conducted looking into interventional approaches in relation to dietary and lifestyle changes, probiotics, prebiotics, and FMTs.[8,10] However, while some of these studies have shown promise, most of the research to date has been conducted in animals, with inadequate or inconsistent evidence in humans.[10] Furthermore, although the gut microbiota is responsive to rapid shifts in the diet, it has been shown that the restoration of microbial diversity after dysbiosis through prolonged intake of excess simple sugars and lack of prebiotic dietary fibre could only be achieved through FMTs, and not simply by changing dietary habits.[33] Accordingly, researchers have postulated that the rapid shift towards Western-typical diets could have contributed to a steady reduction of bacterial diversity in the last few decades, at

a pace that far surpassed our body's evolutionary ability to adapt to the negative effects on the gut microbiota—hence, resulting in surplus fat storage and weight gain.[33] The restoration of a healthy gut ecosystem via means of replenishing and reintroducing beneficial microbes is therefore an attractive prospect but will require further rigorous consideration, such as identifying and targeting the precise bacterial taxa that promote or reduce the development of obesity.[9] In the meantime, trials for weight loss using FMTs delivered via oral capsules have already begun[34], which may present a less invasive and more efficacious mode of delivery that should be explored further.

While safe and effective pharmacological, surgical, and lifestyle therapies for childhood and adulthood obesity exist, challenges remain in the widespread implementation of these interventions.[35] For instance, the notion of obesity as a "disease" remains controversial among many healthcare workers, with a common view that individuals with obesity simply lack the willpower or self-control to restrict their food intake.[35] Further issues around cost, availability, and potential side effects remain as barriers for effective and sustained weight loss.[35] The view that simply eating less and increasing physical activity will lead to a weight-loss transformation has been criticised due to a disregard for more recent research implicating the importance of energy balance regulation in body weight.[34] Based on the established evidence base so far, it is critical to acknowledge the importance of the relatively understudied gut microbial ecosystem as part of our "modern" understanding of obesity.

Concluding Remarks

Emerging discoveries of the central role of the gut microbiome in obesity etiology, particularly in consideration of evidence related to physiological cascades, supports the idea that we need to move beyond simply blaming personal responsibility for how and why certain individuals develop obesity. Furthermore, our understanding of the significant inter-individual differences in microbiota composition, as well as highly individualised responses to dietary changes, points to the future of personalised nutrition in more effectively preventing and reducing the incidence of obesity and other metabolic conditions.[10] For instance, it is already possible to accurately predict an individual's blood glucose response based on personal and microbial features, which has been shown to significantly reduce postprandial responses with consistent alterations in gut microbiota signatures.[36] Understanding the importance of people's unique physical, emotional, and environmental circumstances, as well as the distinct make-up of their gut microbiome and physiology, will lend itself to a future of precision medicine that optimises clinical health care.

The gut microbiome may hold promise as a suitable target for intervention in the treatment and prevention of obesity and related comorbidities. However, the mechanisms underlying the connection between the gut microbiome, human nutrition, and host metabolic processes as it relates to obesity are not fully elucidated in humans. As such, further rigorous research in the form of basic science, epidemiological, and human experimental studies (including in vivo) are needed to better understand the underlying mechanistic processes relating the gut microbiota to obesity.

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