

# The impact of the gut microbiota on human metabolism

## EDUCATION

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### ABSTRACT

The increasing prevalence of obesity is a global health problem due to the associations of obesity with co-morbidities such as diabetes, cancer and stroke. Current obesity management strategies and public health measures are doing little to fight the ever-growing burden of obesity in today's obesogenic environment, therefore new approaches are clearly required. The gut microbiota has long been implicated in the pathophysiology of a number of diseases and is emerging as an important player in the pathogenesis of obesity, diabetes and metabolic syndrome, however the exact nature and mechanism behind how gut bacteria can influence host metabolism is an area of intense debate. This article explores how the gut bacteria can influence energy metabolism and whether our knowledge of this can be converted into useful clinical interventions at a time when better care for obese and metabolically unhealthy patients is fast becoming an urgent necessity.

## INTRODUCTION

In 2016, there were over 650 million obese adults worldwide, with global obesity burden doubling from 1980. (1) Obesity is a strong risk factor for type 2 diabetes, cardiovascular disease and cancer, with the burden of these diseases following the same trend as obesity. (2) The increasing burden of obesity therefore represents a huge global challenge, so it is of critical importance that the prevention and management of the condition is improved.

The gastrointestinal tract contains a vast number of bacteria, with an estimated 10 trillion to 100 trillion microorganisms populating the adult intestines. (3) The genome of these bacteria (the microbiome) is around 150 times the size of our own with around 500 times the coding potential. (4) Hippocrates, often referred to as the ‘father of medicine’, stated that ‘all disease starts in the gut’ following his observations of the influence of the diet and gut health on human pathology. Furthermore, along with the gut influencing our physiology, we in turn influence the composition of our gut, primarily through our diet. Diet-induced changes to gut microbiota were first observed almost 100 years ago, when Herter and Kendall found increases in *Bifidobacterium* and ‘proteolytic bacteria’ in response to high-fat and high-protein based diets in dogs. (5) We have only recently begun to understand the powerful impact that the microbiota has on our physiology, with alterations to the microbiota being implicated in a host of conditions from depression, sleep apnoea, abnormal social interactions, cognitive flexibility and schizophrenia, (6–10) to autoimmune diseases, (11) inflammatory disorders, (12) and obesity (13). However, the mechanisms behind these interactions, and whether they can be manipulated with any significant clinical benefit, remains a highly controversial subject.

Recent technological advances such as the advent of bacteria rRNA shotgun sequencing have revolutionised the study of the microbiota, resulting in a surge of interest in the field. With this in mind, this review will address some of the many known changes implicated in host metabolism and the impact these have on obesity, diabetes and metabolic syndrome. It will argue that this is a field not to be overlooked and that it may provide therapeutic benefits in our management of obesity. Throughout, there will be references to bacterial populations at all taxonomic levels. Accordingly, the reader is referred to the taxonomy diagram in Supplementary Figure 1 to aid understanding of the relevant bacterial ecology.

### How does the microbiota influence metabolism?

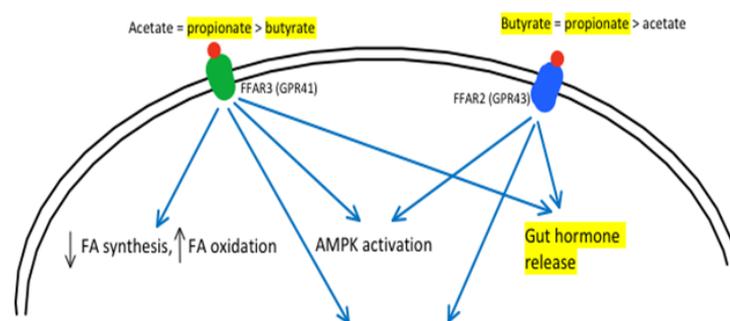
#### Short chain fatty acids

The gut microbiota ferments dietary fibres into short chain fatty acids (SCFAs) and is therefore responsible for extracting energy from the approximately 30g of complex carbs and 13g of undigested protein the gut receives each day. (14) The importance that colonic fibre fermentation has on energy consumption is shown in gnotobiotic (germ-free) mice. These mice are much leaner than their normal counterparts and are protected from obesity when fed a Western (high fat) diet. (15) This highlights the principle that gut

microbiota are involved in energy extraction from food, as these animals are unable to extract energy from these food products, preventing the uptake of around 10% of the energy from a standard diet. (16) As obesity is the long-term consequence of an energy imbalance, changes to this energy extraction process through gut microbiota alterations are an important factor to consider in the management of obesity. (17)

The major products of fibre fermentation are the SCFAs acetate, propionate and butyrate which constitute nearly 95% of the SCFAs in the gut at a ratio of around 60:20:20. (18,19) As well as being absorbed, these bind to free fatty acid receptors (FFARs), modulating L-cell incretin secretion and communicating with the brain via the vagus nerve; this gut-brain axis is essential to how the microbiota impacts our physiology and is excellently reviewed elsewhere. (20) For example, the binding of FFAR1 by dietary-derived fatty acids leads to GLP-1 release from L-cells, which positively modulates insulin secretion. (21) The knock-out of FFAR2 in rats significantly reduced GLP-1 secretion both in vitro and in vivo, further highlighting the key role that SCFAs play in host metabolism. (22) Figure 1 shows a schematic representation of some of the effects of FFAR binding and thus the effects that SCFAs have on our metabolism.

Each of the major three SCFAs have specific metabolic roles, with butyrate and propionate appearing to be mainly anti-obesogenic. Butyrate is the major metabolic substrate for the colonic epithelium and stimulates the growth of this layer, as well as stimulating peripheral tissue mitochondria. (23, 24) Butyrate supplementation in mice improved insulin sensitivity and increased energy expenditure through increasing fatty acid oxidation and stimulating mitochondrial function and biosynthesis. Although butyrate supplementation at 5% of a high fat diet is far from physiological, and thus may not demonstrate the normal function of butyrate, this indicates a beneficial role for butyrate in the diet. (25,26) Butyrate also has known anti-inflammatory effects through downregulation of NF- $\kappa$ B, a key transcription regulator of cellular stress responses. (27) Inflammation leads to the development of insulin resistance, metabolic syndrome and diabetes, so increasing butyrate absorption from the gut may help to prevent the aberrant inflammation that contributes to these diseases. (28,29)



**Figure 1:** A diagram representing some of the known responses to FFAR binding, with the binding affinities of FFAR3 and FFAR2 shown (74) and those actions restricted to butyrate and propionate highlighted in yellow (19, 75–77)

Propionate is another SCFA with apparent anti-obesogenic benefits. This was first suggested by Chen et al., who found a reduction in liver and serum cholesterol levels in cholesterol-fed rats supplemented with 0.5% sodium-propionate supplementation, vs control. (14) They suggested that propionate may (in part) be responsible for the hypocholesterolaemic effects of certain soluble plant fibres, which was supported by a study finding the same reduction in liver cholesterol pool, as well as reduced fasting plasma glucose and urinary glucose excretion, in obese hyperinsulinemic (fa/fa) rats on propionate supplementation. (15) Propionate, along with butyrate, is a strong stimulator of FFAR2 (see Figure 1). Binding to this receptor leads to release of gut incretins such as GIP from K cells and GLP-1 from L cells, in addition to release of other satiety signals such as CCK-1 and PYY. (16,17)

Acetate is absorbed into the peripheral circulation where it is the basis for cholesterol synthesis, however whether or not acetate is beneficial or detrimental to host metabolic health is still unclear. Many labs have reported positive health outcomes associated with acetate; dietary acetic acid reduces serum cholesterol and triglycerides in rats on a high cholesterol diet, and the acetic acid in vinegar reduces body weight, body fat mass and serum triglyceride levels in obese Japanese men. (18,19) Recently, Prof Frost's lab followed the uptake of dietary <sup>11</sup>C-acetate into hypothalamus with PET-CT, and found that it stimulated parasympathetic nerve fibres and decreased appetite. (20) However, some labs have suggested that acetate may negatively affect host metabolism. In 1993, it was shown that plasma acetate levels are higher in diabetic subjects than obese normoglycaemic and healthy controls, with significant correlations seen between glycosylated haemoglobin (HbA1C), plasma glucose and acetate levels. It was not reported whether or not these changes in acetate matched changes in the other SCFA levels (i.e. whether total SCFA level was increased or just acetate level), which somewhat limits the strength of conclusions drawn from the study. (21) However, subsequent work has shown that acetate supplementation via addition of an acetate-producing prebiotic leads to an increase in plasma LDL and cholesterol vs control. (22) Finally, Perry et al. have shown that acetate stimulates ghrelin secretion, leading to hyperphagia and thus predisposing to obesity, further suggesting that acetate has detrimental effects on host metabolism. (23)

### Bacterial metabolites

As well as fermenting fibres, the gut microbiota produces metabolites that can influence host metabolism. Trimethylamine (TMA) is metabolised from cheese, seafood and red meat by gut bacteria and is enzymatically oxidised by flavin-containing monooxygenase-3 in the liver to TMA N-oxide, or TMAO. (24) Serum levels of TMAO correlate with obesity, atherosclerosis and poor cardiovascular health, suggesting that these TMA-producing bacteria have a negative impact on host metabolic health. (25) TMA-producing bacteria are distributed over Firmicutes, Actinobacteria, Proteobacteria and Gammaproteobacteria, and are particularly highly expressed in *Escherichia* and *Shigella*, as found by detection of TMA-synthesis gene expression. (26) Whilst it may be early to draw conclusions, the pathogenicity of the changes in microbiota with obesity described in the next section may in part be played by

the increase in production of TMA by these bacteria. Drugs such as 3,3-dimethyl-1-butanol that reduce TMAO levels by inhibition of TMA production or conversion to TMAO are under development, and can reduce cardiac dysfunction in Western diet-fed mice. (27) It is hoped that as our understanding of TMA and other microbiota metabolites increases, we can use this knowledge to improve obesity care.

### Changes to gut microbiota seen in obesity and diabetes

#### Changes at the phylum level

The major change seen in the obese patient's microbiota is a relative increase in the *Firmicutes* phyla relative to the *Bacteroidetes* (see Supplementary Figure 1), along with an increase in abundance of *Proteobacteria*. (3,28–32) For example, ob/ob mice - which develop obesity through hyperphagia - have almost 50% lower *Bacteroidetes* compared to *Firmicutes*. (33) Whilst it is unclear whether obesity causes the change in bacteria or the bacteria change results in obesity, it is thought that the diet can alter the bacteria which then predisposes people to obesity due to a higher efficiency of energy extraction by the unhealthy microbiota. This is supported by Hildebrandt and colleagues, who studied the effects of high fat diets (HFD) on wildtype and the obesity-resistant RELM-b mouse strain. Switching from standard chow to HFD caused obesity in wildtype mice but not in the RELM-b mice, however the *Firmicutes*:*Bacteroidetes* ratio was altered in both independently of any gain in weight. (4,28)

The relative composition of these phyla appears to impact on the ability of the gut to harvest energy from food. Jeffrey Gordon's lab found that colonising genetically identical gnotobiotic mice with the microbiota of a diet-induced obese mouse results in more total body fat gain than colonising the mouse with lean mice microbiota. This 'obese microbiota' appears to be adapted to ferment fibres more efficiently, as seen by higher expression of fermentation enzymes in the obese microbiome. The faeces of the obese microbiota mice had less energy remaining when measured with bomb calorimetry vs control, further supporting this theory. (31) The gut concentration of butyrate and acetate is higher in patients with this altered microbiota, (34) so it is unclear how these 'obese microbiota' appear to be detrimental to host health despite increasing the production of butyrate which is known to be beneficial to host health. It is possible that the increase in butyrate is simply a change that was measured in these experiments which indicates an increase in whole energy harvesting, or that in these patients and animals, there is a different source of butyrate (such as undigested protein vs carbohydrates) which somehow confers the obesity phenotype. Or perhaps the satiety signals and other SCFA responses are aberrant in these patients, thus predisposing to obesity? This apparent contradiction is a source of debate and needs to be understood to elucidate the interactions between diet, health and gut bacteria.

### Changes to specific bacteria

Certain bacteria have specific effects on host metabolism. *Akkermansia muciniphila* appears to have a protective effect on metabolic profiles, with orally-administered muciniphila protecting against obesity and enhancing glucose tolerance in mice. (50) This protective effect is also seen in humans, with the abundance of the bacteria inversely correlated to fasting plasma glucose level, waist:hip ratio and subcutaneous fat diameter. Furthermore, amongst obese patients, those with a higher *A. muciniphila* abundance had the best metabolic profiles (as determined by parameters such as plasma triglycerides and fasting glucose) and displayed the greatest improvement in insulin sensitivity in response to a 6-week calorie restriction. (51) Interestingly, diabetic patients treated with metformin have changes in the gut microbiota which include an increase in *A. muciniphila* compared to untreated diabetics, potentially suggesting that some of the benefits of metformin may be mediated through the drug's impact on gut bacterial populations. (52) A number of other changes to bacterial populations are shown in Supplementary Table 1, which describes a number of different bacteria of nearly all major phyla and their apparent roles in altering host metabolism.

### Therapeutic modulation of the gut microbiota

#### Prebiotics

The dietary supplementation of propionate as a weight control therapy is currently being investigated by the Frost lab, who have developed an inulin-propionate ester that can be added to food. The conjugation to inulin (a fibre) ensures targeted delivery of propionate to the colon, as the propionate is only released upon fermentation of inulin resulting in a gram-level delivery of the SCFA to the colon that wouldn't be feasible through diet alone. As discussed above, propionate stimulates GLP-1 and PYY secretion and seems to prevent hepatic lipidosis. In a 24-week study, overweight adults were given the inulin-propionate ester, which significantly reduced weight gain and reduced gain of intra-abdominal adipose tissue vs an inulin control. Interestingly, whilst acutely the propionate-inulin ester stimulated an increase in GLP-1 and PYY secretion, by the end of the 24-week study, no significant difference in the release of these gut hormones was found, even though subjective rankings of postprandial appetite were lower in the propionate group. Clearly, the gut microbiota's influence of satiety and therefore obesity is complex, however this study indicates that dietary interventions targeting the microbiota could emerge as a novel management of obesity. (53)

Although the exact benefits or problems associated with acetate aren't clear, the role of fibre in improving metabolic health is vastly understated. The average Western diet is deficient in fibre, with the UK guidance on consumption of fibre being (inadequately so) to 'eat lots', which fails to stress how beneficial dietary fibre is. (54) Howarth et al demonstrated that when subjects were left to eat as they pleased, the addition of fibre to this diet resulted in a 10% average decrease in energy intake, resulting in nearly 2kg weight loss over 4 months vs control. (55) Clearly, fibre has overall benefits to host health, so improving public education of benefits of dietary fibre could help reduce the burden of obesity.

#### Faecal microbial transplantation

Faecal transplant is an established treatment in recurrent *C. difficile* and has an excellent safety profile. Numerous animal studies have shown that a metabolic profile can be transferred through faecal microbiota transplant (FMT) as discussed above, (56) with a limited number of studies now beginning to show some efficacy in humans. Max Nieuwdorp's group have shown that FMT from lean donors resulted in a significant improvement in insulin sensitivity at 6 weeks in insulin-resistant obese males with metabolic syndrome. In this 2012 study, they found that the improvement in insulin sensitivity correlated with an increase in butyrate-producing bacteria. (57) This is thought to improve host health through the mechanisms described above, although the contradiction between the benefits of butyrate production and the increase in energy extraction through this SCFA need to be examined. However, the group's most recent trial showed that whilst they could replicate this positive change in phenotype at week 6, by week 18 after FMT the effects on insulin sensitivity had worn off, which was associated with a return to baseline faecal microbiota composition. (58) This raises the idea of a 'personal core faecal microbiome', suggesting perhaps that host immune system interactions resulted in this return to baseline microbiome from the foreign gut flora. If FMT is to become a successful future intervention for metabolic syndrome and/or obese patients, this issue needs to be further understood to allow us to cause lasting change in the patient flora. On top of this, we need to better understand what makes a good faecal donor and what predicts the level of patient response, with lower initial bacterial diversity in the patient and higher levels of butyrate-producing bacteria in the donor appearing to be good markers of success. (56,57) Other bacteria implicated in degrees of FMT success can be found in Supplementary Table 1, and as such development of more sophisticated algorithms to better select patients and donors to maximise responses is required if this treatment is to become mainstream.

#### Clinical outlook/concluding remarks

The role that the gut microbiota plays in a number of different disease states is an area of extensive research and intense debate. It is clear that there is a significant relationship between changes in the gut microbiota and obesity, diabetes and metabolic syndrome, and that this is often overlooked in weight and diabetes management strategies. The extent to which potential microbiota-focused interventions such as FMT and pro- and prebiotics may play in our management of obesity and diabetes remains to be seen. In an age where fad diets commonly direct patients' weight loss strategies in an unscientific manner, greater appreciation and understanding of the importance of gut bacteria and how our diet can influence these will assist patients in making more informed lifestyle choices. Overall, obesity along with its associated co-morbidities is a complex disease and there is not a single approach which will offset the rise in obesity. This paper does not aim to present the gut microbiota as the answer to obesity care, however it is an important factor to consider when addressing the global problem of obesity.

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## APPENDIX

Bacteria/bacterial metabolite	Metabolic indication
<b>Akkermansia (Cerrucomicrobia)</b>	Increased after Roux-en-Y gastric bypass surgery. [35]
<b>Akkermansia muciniphila</b>	Appears to have beneficial metabolic effects. Found to increase in FMT responders [36] and inversely correlated fasting glucose and body fat mass in mice and fasting glucose, waist:hip ratio, plasma triglycerides subcutaneous adipocyte diameter in humans. [37] Increased by metformin treatment. [38]
<b>Bacteriodes vulgatus</b>	BCAA producing species found in higher abundance in insulin-resistant patients vs control. [39]
<b>Clostridium scindens</b>	Found to be strongly negatively correlated with body weight in mice. [40]
<b>Dorea longicatena</b>	Correlated with better FMT response. [36]
<b>Enterobacteriales</b>	Increased after Roux-en-Y gastric bypass surgery. [35]
<b>Escherichia coli</b>	A G- bacterium that produces LPS. E. coli and LPS are both elevated in diabetes patients and LPS is able to induce inflammation of fat tissue and reduce insulin sensitivity in mice. [41-43]
<b>Eubacterium sp.</b>	Produce butyrate. Administration of live E. halii to obese and diabetic mice improved insulin sensitivity and increased energy expenditure. [44]
<b>Eubacterium ventriosum</b>	Inversely correlated with better FMT response. [36]
<b>Euryachaeota and Crenarchaota</b>	Increase the efficiency of bacterial fermentation by removing H <sub>2</sub> , found in higher abundance in ob/ob mice vs normal. [33]
<b>F. prausnitzii</b>	Suggested to be involved in strengthening the gut barrier whereby reducing inflammation and diabetes progress.[38] Found in lower abundance in patients with type 2 diabetes.[45]
<b>Lactobacillus fermentum</b>	Found to lower cholesterol and triglycerides when given as a microencapsulated probiotic to hypercholesterolaemic hamsters. [46]
<b>Lactobacillus reuteri</b>	Found to be strongly positively correlated with body weight and obesity in mice; elevated in obese humans. [40,47-49]
<b>Lactobacillus brevis</b>	Produces GABA. L. brevis supplementation improves glucose homeostasis in insulin-resistant rats, [50] correlating with direct GABA supplementation improving insulin resistance through reducing inflammation. [51]
<b>Leuconostoc</b>	Found in a higher abundance in patients who regained more weight in a 6-week diet followed by 6-week restabalisation study. [33]
<b>Mucispirillum schaedleri</b>	Found to be strongly positively correlated with body weight in mice. [40]
<b>Pediococcus</b>	Found in a higher abundance in patients who regained more weight in a 6-week diet followed by 6-week restabalisation study. [33]
<b>Prevotella</b>	Enrichment of Pr. linked to improved tolerance to glucose on whole-grain diets. [52]
<b>Prevotella copri</b>	BCAA producing species, found in higher abundance in insulin-resistance patients vs control. Administration of P. copri induced insulin resistance in mice. [39]
<b>Roseburia intestinalis</b>	Produces butyrate. Negatively correlated with subcutaneous adiposity, body weight, liver weight and serum insulin in mice, [40] negatively correlated with human plasma glucose [47] and less abundant in T2DM patients. [41]
<b>Ruminococcus torques</b>	Inversely correlated with better FMT response. [36]
<b>Subdoligranulum variabile</b>	Correlated with better FMT response. [36]
<b>Verrucomicrobiales</b>	Significantly increased after Roux-en-Y gastric bypass surgery. [35]

Supplementary Table 1: Bacteria implicated in host metabolism



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