

Gut microbiota: Its role in diabetes and obesity

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Article points

1. The role of the gut microbiota in certain disease progressions has been postulated, particularly its role in diabetes and obesity.
2. There is much greater genetic diversity between people's gut microbiota than between their genomes.
3. Improved understanding of the mechanisms by which the human microbiota contributes to the development of type 1 and type 2 diabetes offers the potential for novel interventions.

Key words

- Bacteria
- Gut
- Microbiota

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The gut microbiota is a community of microorganisms that live in the gut and intestinal tract. The microbiota consists of bacteria, archaea and eukarya, as well as viruses, but is predominantly populated by anaerobic bacteria. Relationships between gut microbiota constituents and a wide range of human conditions such as enterocolitis, rheumatoid arthritis, some cancers, type 1 and type 2 diabetes, and obesity have been postulated. This article covers the essentials of the gut microbiota as well as the evidence for its role in diabetes and obesity.

The human gut microbiota is “an ecological community of commensal, symbiotic and pathogenic micro-organisms that literally share our body space” (Lederberg and McCray, 2001). It is made up of between 10 and 100 trillion micro-organisms (with a mass weight of 1.5 kg) and is found in the distal intestine (Allin et al, 2015). The microbial community acts in concert with the body to provide important functions that the body cannot provide alone. The gut microbiota is involved in the following:

- It is a key component of the immune system.
- Protection against pathogens.
- Regulation of intestinal hormone secretion.
- Modulation of gastrointestinal nerve function.
- Synthesis of vitamin K, folate and B12.
- Generation of short-chain fatty acids through fermentation of non-digestible carbohydrates.
- The breakdown of toxins and medications.

Interest in the association between constituent elements of the human microbiota and disease dates back to the 1680s around the time of the birth of the study of microbiology itself (Dobell, 1920). In his research into the diversity of the human microbiota, Antonie van Leeuwenhoek (1684) compared his own oral and faecal microbiota and noticed significant differences in microbes between these different sources. He went on to examine and compare microbiota from others in good health, as well as those with established disease, also noting significant differences between sample sites.

Identifying microbiota constituents

Until relatively recently, bacteria could only be identified by direct microscopy and culture. This proved particularly problematic with most anaerobic commensal gut flora (Ursell et al, 2012). It has only been in recent years that advances in gene sequencing and analytical techniques have made it possible to define and classify microbial DNA from faecal collections – generally considered to reflect the distal bowel microbiota (Kuczynski et al, 2012). Two detection methods are currently employed; targeted 16S ribosomal RNA gene sequencing and un-targeted whole-genome shotgun sequencing (otherwise known as metagenomic sequencing; Weinstock, 2012). The former generates information about the bacteria themselves (i.e. types, numbers and relationships), while the latter provides a picture of the collective genome of the gut microbiota (i.e. the gut microbiome).

Gene diversity in the human microbiome dwarfs that of the entire human genome. The MetaHIT Consortium found 3.3 million non-redundant genes in the microbiome compared to 22 000 genes in the human genome (Qin et al, 2010). More recently a microbial gene catalogue of 9.9 million genes from European, Chinese and American samples has been published (Li et al, 2014). Importantly, the genetic diversity of the microbiome between individuals is far greater than that of the human genome. People are 99.9% identical to each other in terms of their human genome but can be 80–90% different from each other in terms of their gut microbiome (Turnbaugh

et al, 2009). In an age of personalised medicine, the variation within the microbiome presents a potentially useful avenue for future interventions in disease processes.

Does the microbiota change throughout life?

Birth and childhood

The relative bacterial composition of the microbiota is influenced by several factors throughout life and in childhood in particular.

Babies delivered vaginally develop microbial populations within 20 minutes of birth, mirroring those of their mother's vagina and rectum (*Lactobacillus*, *Prevotella* or *Sneathia*), while the microbiota of babies born by Caesarian section are derived from microbes on the hands that touch and hold the baby after birth (*Staphylococcus*, *Corynebacterium* and *Propionibacterium*; Dominguez-Bello et al, 2010).

The gut microbiota of infants tends to be narrow and unstable. Breast feeding, formula milk, antibiotic treatment, illness and travel can all contribute to the changeable milieu of the microbiota in the young (Koenig et al, 2011). After the age of 3 years, diet, including variations in solid food ingestion, and illness are the predominant determinants of the microbiota (Power et al, 2014).

By the age of 7 years, *Firmicutes* and *Bacteroidetes* comprise about 90% of the microorganisms present in a child's microbiota, with the remaining 10% being made up by *Tenericutes*, *Cyanobacteria* and *Proteobacteria*. The microbiota becomes more stable at this stage and begins to resemble that of adults (Dominguez-Bello et al, 2011).

Adulthood

In healthy adults, the microbiota is stable and is related to long-term diet patterns. Three enterotypes are found in adults globally: *Bacteroides* (the predominant class in the phylum *Bacteroidetes*), *Prevotella* and *Ruminococcus* (Wu et al, 2011). All three can be linked to diet and living conditions. For instance, *Bacteroides* are found in those with high animal protein and saturated fat intake (western diet), while *Prevotella*, by contrast, are found in those in agricultural and vegetarian communities where high consumption of carbohydrates and sugars is the norm, and remain so until older

age when immune-related changes in the gut microbiota can occur (Arumugam et al, 2011).

What is the relationship between the microbiota and diabetes?

Relationships between gut microbiota constituents and human conditions, including enterocolitis, rheumatoid arthritis, muscular dystrophy, multiple sclerosis, some cancers and a range of psychiatric disorders, have been postulated. Of key interest to the endocrine world is the possible link with type 1 diabetes, type 2 diabetes and obesity.

What is the relationship between the microbiota and type 1 diabetes?

The involvement of the microbiota in the development of type 1 diabetes in animals was first proposed in 1987 by Suzuki et al. A recent Finnish human study used age and HLA-DQ genotype to match four children who went on to develop type 1 diabetes with four children who remained healthy. Comparison of their microbiomes revealed a lesser diversity and stability of faecal microbiota in the first year of life in children in the former group (Giongo et al, 2011). The children who developed type 1 diabetes were subsequently found to have a decreased ratio of *Firmicutes* versus *Bacteroidetes* (de Goffau et al, 2013). Other studies have also reported a greater proportion of *Bacteroidetes* in islet body-positive children than in auto-antibody-negative children (de Goffau et al, 2014).

The mechanisms through which the microbiota may precipitate type 1 diabetes in susceptible individuals relate to alterations in intestinal permeability and modification of intestinal immunity. In the healthy state, the intestinal epithelium prevents food antigens, as well as commensal and pathogenic bacteria, from inducing systemic immune responses (Mazmanian et al, 2005).

In type 1 diabetes, the development of a more permeable intestinal barrier (a key component of human defence mechanisms) may be attributable to metabolites of gut microbiota, as much as to any direct action of microbes themselves. Children with type 1 diabetes have low numbers of *Bifidobacteria*, which are lactate-producing microorganisms (de Goffau et al, 2013). Butyrate, a short-chain fatty acid, is derived from lactate and

Page points

1. In an age of personalised medicine, the variation within the microbiome from person to person presents a potentially useful avenue for future interventions in disease processes.
2. The microbiota and its bacterial composition is influenced by several factors throughout life. There are variations from birth to adulthood.
3. The mechanisms through which the microbiota may precipitate type 1 diabetes in susceptible individuals relate to alterations in intestinal permeability and modification of intestinal immunity.

Page points

1. The microbiota may precipitate type 1 diabetes in susceptible individuals through alterations to intestinal permeability and modification of intestinal immunity.
2. Improved understanding of the mechanisms by which the human microbiota contributes to the development of type 1 diabetes in genetically susceptible individuals offers the potential for novel interventions in the prevention or amelioration of type 1 diabetes.

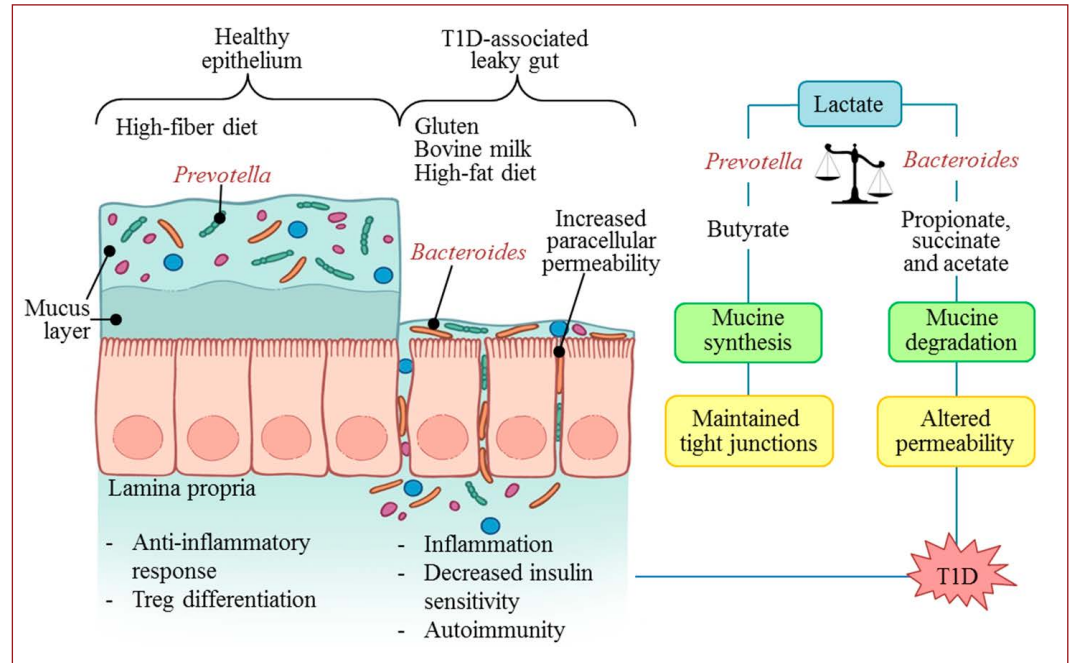


Figure 1. Diet and microbiota-associated mechanisms in autoimmunity and type 1 diabetes development (Mejía-León and Calderón de la Barca, 2015).

is a potent anti-inflammatory agent promoting gut barrier function by ensuring tight junctions between epithelial cells. Its relative deficiency may contribute to the increased intestinal permeability seen in children developing type 1 diabetes (Hague et al, 1996).

Intestinal immunity is significantly impaired in type 1 diabetes. Activation of immune responses, with generation of auto-reactive T cells, may occur due to bacterial cell components (auto-antigenic mimics) in the microbiota. Mechanisms that mediate such immune changes may include activation of Toll-like receptors (proteins that play a key role in immune systems) by gut bacteria themselves or through G protein-coupled receptor (GPCR) stimulation by bacterial metabolites (Round et al, 2011). In addition, gut bacteria-derived pathogen-associated molecular patterns (PAMPs) can induce inflammation and lead to beta-cell destruction by inflammatory

cytokines. Lastly, bacteria that permeate a “leaky” intestine may cause further inflammation and beta-cell destruction (Figure 1).

Improved understanding of the mechanisms by which the human microbiota contributes to the development of type 1 diabetes in genetically susceptible individuals offers the potential for novel interventions in the prevention or amelioration of type 1 diabetes.

What is the relationship between the microbiota and type 2 diabetes?

The microbiota may influence human metabolism through a number of mechanisms. Lipopolysaccharides (LPS) from the capsule of gram-negative bacilli activate inflammatory signalling pathways, via Toll-like receptor 4, resulting in inflammation and diminishing insulin sensitivity (Cani et al, 2007). High-fat diets can affect the microbiota and increase LPS levels

G-protein coupled receptors (GPCR)=A large family of molecules (from small to large) on the cell membrane that trigger cellular responses due to particular molecules outside the cell.
Lipopolysaccharides (LPS)=Large molecules consisting of a lipid and a polysaccharide that are found in the outer membrane of Gram-negative bacteria, and elicit strong

immune responses.
Pathogen-associated molecular patterns (PAMPs)=Molecules associated with pathogens that are recognised by cells of the innate immune system, which triggers inflammation.
Toll-like receptor 4=A receptor responsible for activating the innate immune response.

either through increased epithelial permeability or enhanced uptake in chylomicrons from the intestinal epithelium itself (Hildebrandt et al, 2009; *Box 1A*).

There are also gut microbial mechanisms that counter this adverse metabolic effect and reduce inflammation and increase insulin sensitivity. Short-chain fatty acids (e.g. butyrate, acetate and propionate) arising from bacterial fermentation of insoluble dietary fibre in the bowel can bind to GPR41 and GPR43 (Brahe et al, 2013). In immune cells, this results in reduced inflammation while in the L-cells, along the digestive tract, it leads to increased glucagon-like peptide (GLP)-1 and peptide YY (PYY) secretion and improved insulin sensitivity (Tolhurst et al, 2012). The short-chain fatty acid butyrate exerts key effects as an energy substrate in mucosal cells lining the colon, whereas acetate and propionate enhance hepatic gluconeogenesis and lipogenesis (*Box 1B*).

In addition, bacteria can metabolise de-conjugated bile acids to secondary bile acids (Thomas et al, 2009). Secondary bile acids bind to the GPCR TGR5, which, in turn, increases GLP-1 production from L-cells and increases energy expenditure in muscles leading to further improvements in insulin sensitivity (*Box 1C*).

Current evidence linking the microbiota to type 2 diabetes suggests that changes in the gut microbiota (termed dysbiosis) can lead to epithelial dysfunction and leakage. The increased intestinal epithelial permeability results in absorption of large molecules from the bowel and, subsequently, to low-grade inflammation, immune dysfunction and alterations in glucose and lipid metabolism via signalling changes. These changes combine to increase insulin resistance and enhance the

Box 1. The influence of microbes on metabolism (Allin et al, 2015).

- A. Increased lipopolysaccharides increasing inflammation:** A high-fat diet increases lipopolysaccharides (due to increased epithelial permeability or increased uptake of chylomicrons from the intestinal epithelium). Lipopolysaccharide from the capsule of gram-negative bacteria, interact and bind with Toll-like receptor 4 (TLR4), which increases inflammation and in turn reduces insulin sensitivity.
- B. Bacteria in the colon ferment dietary fibres to short-chain fatty acids:** Short-chain fatty acids (e.g. butyrate, acetate, propionate) bind to G-coupled receptor protein and increase glucagon-like peptide (GLP)-1 and peptide YY, which decrease inflammation and increase insulin sensitivity.
- C. Increased secondary bile acids:** Gut bacteria are capable of deconjugating primary bile acids, hindering their recirculation to the liver from the gut, and further metabolising them to secondary bile acids. Secondary bile acids bind to the G protein-coupled receptor TGR5, which results in increased energy expenditure in muscles and GLP1 secretion, both of which lead to improved insulin sensitivity.

likelihood of developing type 2 diabetes (Allin et al, 2015).

What has yet to be answered in humans is whether the gut microbiota is a cause – or result – of type 2 diabetes. Only prospective studies will determine an association, and randomised controlled treatment trials comparing placebo to health-promoting bacteria causality are ongoing.

What is the relationship between the microbiota and obesity?

There is increasing evidence linking the changes in the bacterial composition of the microbiota to obesity. Gut microbiota, for instance, that are transplanted from wild mice into germ-free mice result in an increase in adiposity of the germ-free mice without increased food intake (Backhed et al, 2004). Obese mice have decreased *Bacteroidetes* and increased *Firmicutes* compared to lean mice

Chylomicrons=Small particles that transport dietary lipids from the intestines to other parts of the body, such as muscles and the liver. They are made of lipoprotein particles.

Deconjugation=The disruption of conjugated bacterial cells, thus making them unstable.

Dysbiosis=A microbial imbalance or maladaptation on or inside the body.

L-cells=Cells found mainly in the small and large intestines that secrete glucagon-like peptide (GLP)-1, peptide YY, oxyntomodulin and GLP-2.

Peptide YY=A small peptide released by cells in the small intestines and colon in response to food. It acts to reduce appetite.

Primary bile acids=Bile acids synthesised by the liver.

Short-chain fatty acids=Produced by bacteria in the gut during fermentation of insoluble fibre from dietary plant matter (e.g. acetate, propionate and butyrate).

TGR5=A cell surface receptor for bile acids, the receptor is implicated in the suppression of macrophage functions and regulation of energy homeostasis by bile acids.

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1. The correlation between the microbiota and weight loss has been demonstrated; however, the correlation between the microbiota and weight gain is still to be conclusively determined.
2. The effect of antibiotics on the gut microbiota is still unknown, with past studies suggesting positive and negative effects.
3. Improving the understanding of the association between the microbiota and the development of type 1 diabetes, type 2 diabetes and obesity will allow the development of useful methods for prevention or amelioration of these disease states.

(Ley et al, 2005). Moreover this tendency to increase weight can be transferred to germ-free mice by transplantation of the microbiota of the genetically obese mice. The transplanted mice then ingest more energy from their diet and lose less in excretions (Turnbaugh et al, 2006).

In obese humans, gene-encoded enzymes that enhance breakdown of indigestible polysaccharides in the diet have been found in the microbiome, thus enabling greater energy extraction from a given food intake. It is also recognised that intestinal permeability to LPS and change in bile acid signalling accompany greater energy efficiency seen in studies of obese participants (Musso et al, 2010). In addition, the use of the probiotic *Lactobacillus reuteri* in a small randomised controlled trial of lean and obese humans without diabetes revealed an increase in plasma GLP-1 and GLP-2 – albeit with no change in glucose tolerance. The significance of this is uncertain. Whether this effect is mediated via bacterial stimulation of the L-cells (either through direct contact or through bacterially secreted substances) also remains unclear (Ferrannini, 2015).

An experiment where mice were transplanted with the bowel contents from human twins discordant for obesity demonstrated that the obesity phenotype was transmissible. Interestingly, when obese and lean mice were placed together (mice are coprophagic*), no additional weight gain was seen when the mice were fed a healthy mouse chow diet, but weight gain was recorded when they were fed human cafeteria food. This underlines the tendency of the microbiota to adjust according to the changing milieu of the intestinal tract (Ridaura et al, 2013).

In addition, the correlation between the microbiota and weight loss has been demonstrated. Modulation of the microbiota by either fat or carbohydrate restriction results in an increase in *Bacteroidetes* as weight loss progresses. This offers potential therapeutic options for both overweight and underweight people.

What effect do antibiotics play?

The relationship between antibiotic therapy and the gut microbiota has attracted much interest.

*Eat their own faeces.

Use of antibiotics in the early years of life has been shown to disturb a healthy microbiota, with adverse metabolic consequences, while other studies report that antibiotics move a disturbed microbiota to a healthier state (i.e. in an opposite direction). It is argued, however, that the microbiota of the very early infant is particularly susceptible to microbial perturbation after antibiotic therapy (Ley et al, 2006).

How might what we know about the microbiota influence future clinical practice?

Improved understanding of the association between the microbiota and the development of type 1 diabetes, type 2 diabetes and obesity points to potential useful methods for prevention or amelioration of these disease states.

Current evidence suggests that adverse changes in the microbiota increase the risk of developing type 1 diabetes through reduced bacterial diversity, leaky gut barriers and increased inflammation. Various interventions including early administration of antibiotics that target Gram-negative bacteria, dietary modification including the use of prebiotics, administration of genetically altered *Lactococcus lactis*, use of bacterial metabolites such as acetate, butyrate and propionate, and transplantation of microbiota have been shown to modulate the development of type 1 diabetes in animal models. It remains to be seen how effective such strategies can be in human beings.

In respect of type 2 diabetes and obesity, there also remains much uncertainty of the value of chosen interventions. Transplantation of donor microbiota into the intestine of people with recurrent *Clostridium difficile* infection is a successful and established therapy (van Nood, 2013). Using the same technique, improvements in insulin sensitivity have been recorded when the microbiota of insulin-sensitive people, with low BMIs, are transplanted into obese individuals with metabolic syndrome. How useful this pioneering technique may prove to be in the future remains to be demonstrated and is not without its conceptual challenge for those receiving donor transplants (Vrieze et al, 2012). The value of *Lactobacilli* supplementation as a treatment modality for dysbiosis (based on the premise that they are the

first to colonise the sterile neonatal intestinal tracts during vaginal delivery and initial breast feeding) has not been confirmed in systematic reviews and meta-analyses to date (Ruan et al, 2015).

So where does this leave us?

Much has been learned about diabetes and obesity through better understanding of the influence of the gut microbiota on metabolism in humans. While treatment methods based on present understanding of the interaction between nutrition and the microbiota have yet to prove of significant benefit to those with diabetes or obesity, it is likely that interest in interventions based on reversal of these changes will continue.

We all recognise the link between food and our health. The unfolding role of the microbiota and its effect on our metabolism makes intrinsic sense. Further research into the microbiota may provide, in time, important new strategies in the management, amelioration and possible prevention of diabetes and obesity. ■

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