

Gut microorganisms as promising targets for the management of type 2 diabetes

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Abstract Each human intestine harbours not only hundreds of trillions of bacteria but also bacteriophage particles, viruses, fungi and archaea, which constitute a complex and dynamic ecosystem referred to as the gut microbiota. An increasing number of data obtained during the last 10 years have indicated changes in gut bacterial composition or function in type 2 diabetic patients. Analysis of this ‘dysbiosis’ enables the detection of alterations in specific bacteria, clusters of bacteria or bacterial functions associated with the occurrence or evolution of type 2 diabetes; these bacteria are predominantly involved in the control of inflammation and energy homeostasis. Our review focuses on two key questions: does gut dysbiosis truly play a role in the occurrence of type 2 diabetes, and will recent discoveries linking the gut microbiota to host health be helpful for the development of novel therapeutic approaches for type 2 diabetes? Here we review how pharmacological, surgical and nutritional interventions for type 2 diabetic patients may impact the gut microbiota. Experimental studies in animals are identifying which bacterial metabolites and components act on host immune homeostasis and glucose metabolism, primarily by targeting intestinal cells involved in endocrine and gut barrier functions. We discuss novel approaches (e.g. probiotics, prebiotics and faecal transfer)

and the need for research and adequate intervention studies to evaluate the feasibility and relevance of these new therapies for the management of type 2 diabetes.

Keywords Diabetes · Glycaemia · Gut microbiota · Obesity · Prebiotic · Review

Abbreviations

AX	Arabinoxylans
AXOS	Arabinoxylan oligosaccharides
BSH	Bile salt hydrolase
DIO	Diet-induced obesity
FGF19	Fibroblast growth factor 19
GLP	Glucagon-like peptide
GPR	G protein-coupled receptor
HFD	High-fat diet
ITF	Inulin-type fructans
LPS	Lipopolysaccharides
PRR	Pattern recognition receptor
PYY	Peptide YY
RYGB	Roux-en-Y gastric bypass
SCFA	Short-chain fatty acid
TLR	Toll-like receptors
TGR5	Transmembrane G protein-coupled receptor 5
VSG	Vertical sleeve gastrectomy

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Introduction

The onset of type 2 diabetes is clearly associated with both host genetics and environmental factors (e.g. diet, physical activity). Emerging evidence indicates that the risk of developing type 2 diabetes may involve a particular environmental factor, specifically, the collection of microorganisms that inhabit our intestine.

Each human intestine harbours not only hundreds of trillions of bacteria, but also bacteriophage particles, viruses, fungi and archaea, which constitute a complex and dynamic ecosystem with which we live in symbiosis throughout our lifetime [1]. Given that host genetics is thought to contribute to the profile of the gut microbiome, all living conditions, including dietary habits, exposure to xenobiotics (such as drugs, toxicants and additives) or stresses (such as surgery and infections) will modulate the gut microbiota, occasionally for a limited period of time due to the resilience of this ecosystem [2]. This review starts with a description of the human studies relating the changes in the gut microbiota to glycaemia in type 2 diabetic patients.

Dysbiosis related to type 2 diabetes and hyperglycaemia

Several clinical trials are ongoing to obtain more precise and more reliable information about the changes in the composition and function of the gut microbiota that may be specifically associated with hyperglycaemia and type 2 diabetes, independently of other contributing factors (e.g. body weight) (for a recent review, see [3]).

Metagenomic data have revealed that patients with type 2 diabetes exhibit a moderate degree of gut microbial dysbiosis compared with patients with inflammatory bowel disease [4]. The proportions of the phylum Firmicutes and the class Clostridia are significantly reduced, whereas the class of the gram-negative Betaproteobacteria is highly enriched in the faeces of type 2 diabetic patients compared with non-diabetic individuals, and the proportion of Betaproteobacteria is positively correlated with plasma glucose levels [5].

Interestingly, the microbiome of type 2 diabetic patients are characterised by the depletion of several butyrate-producing bacteria, including *Clostridium* species, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis* and *Roseburia inulinivorans* [4, 6, 7], and an enrichment of opportunistic pathogens [4]. Bacteria increased in the gut of type 2 diabetic patients also include the sulphate-reducing bacteria *Desulfovibrio*, as well as *Lactobacillus gasseri*, *Lactobacillus reuteri* and *Lactobacillus plantarum* [6, 7]. Curiously, the treatment of Japanese type 2 diabetic patients with α -glucosidase inhibitors has been shown to increase *Lactobacillus* spp. [7]. In accordance with these findings, an increasing number of observational studies have reported changes in the gut microbiota associated with type 2 diabetes, but the outcomes are not always concordant. Zhang et al found a decreased abundance of *Akkermansia muciniphila*, a mucus-colonising bacterium that plays a role in gut barrier function, in diabetic and glucose-intolerant patients [8]; this observation has been reported in several studies of obese individuals. Data on a Chinese population indicated the opposite effect, specifically, an increase in *A. muciniphila* in type 2 diabetic patients

[4]. Thus, it appears that genetic background and/or medication can influence the gut microbiota, which might explain discrepancies between studies.

Many articles have reported a correlation between changes in the gut microbiota and markers of type 2 diabetes. *Lactobacillus* species correlate positively with fasting glucose and HbA_{1c} levels whereas *Clostridium* species correlate negatively with fasting glucose, HbA_{1c} and insulin levels [6]. A recent study suggests that a higher blood glucose concentration may be predicted by a reduction in the proportion of anaerobes, particularly *Bacteroides* [9].

Importantly, different features of metabolic disorders, including markers of glucose metabolism disorders (i.e. insulinaemia and HOMA-IR), but not BMI or body weight, are significantly associated with the gene count of the microbiome, suggesting that individuals with a low gene count are characterised by metabolic disturbances known to increase the risk of diabetes [10].

The functions of the microbiome are also affected in type 2 diabetic patients, such as an increase in membrane transport of sugars or branched amino acids, the activity of enzymes involved in xenobiotic or carbohydrate metabolism, or sulphate reduction [4, 6]. In contrast, functions involved in cell motility, butyrate synthesis and cofactor and vitamin metabolism are decreased in type 2 diabetic patients [4, 6]. Importantly, markers related to oxidative stress resistance are also enriched in type 2 diabetic patients, suggesting a type 2 diabetes-associated increase in defence mechanisms in the gut microbiota [4, 6].

Important questions remain unanswered regarding the long-term persistence of the changes specifically associated with diabetes and the cause–effect relationship of dysbiosis with the occurrence or progression of type 2 diabetes in humans. Clearly, because the alterations in glucose metabolism can be transmitted by gut microbiota transfer in germ-free mice [11], some gut microbial populations/functions may play an active role in the pathogenesis of glucose metabolism disorders. For evident ethical reasons, the ‘transfer’ of the diabetic phenotype via the gut microbiota has never been tested in humans.

Bacterial components and metabolites prone to interact with glucose homeostasis: an overview of the molecular mechanisms underlying microbe–host interactions in the context of diabetes

A chronic low-grade inflammation in type 2 diabetes appears to be a driver of metabolic alterations linked to obesity. The inflammation in the different tissues contributes to insulin resistance. The triggers of the inflammatory response include endoplasmic reticulum stress, inflammasome activation and Toll-like receptors (TLRs). The involvement of TLRs implicates a response to bacterial elements present in the gut microbiota [12, 13].

Bacterial components involved in diabetes Gut microbes are able to communicate with the host via specific cell membranes or related molecules that may activate pattern recognition receptors (PRRs). These PRRs are involved in the recognition of molecular patterns (known as pathogen-associated molecular patterns or PAMPs) that are specific to bacteria and other microorganisms. The most studied PRRs are the TLRs. It is understood that the stimulation of TLR-4 by bacterial lipopolysaccharides (LPS) results in an inflammatory response, cytokine production and chemokine-mediated recruitment of acute inflammatory cells [14]. In 2007, our laboratory first discovered that the gut microbiota also contributes to the onset of insulin resistance and type 2 diabetes via mechanisms associated with an increase in plasma LPS, defined as metabolic endotoxaemia [15]. In experimental obesity and type 2 diabetes, metabolic endotoxaemia is associated with an altered composition of the gut microbiota and with increased intestinal permeability [15–17]. Several human studies also reported an increase in LPS or LPS-binding protein levels in association with type 2 diabetes [18]. Taken together, these data highlight a strong relationship between the gut microbiota, inflammation and metabolic perturbations, including hyperglycaemia. More recently, we discovered that specifically inactivating a protein of the innate immune system that is involved in the signalling of most TLRs (i.e. deleting the protein myeloid differentiation primary response gene 88 [MyD88]) in intestinal cells induces body weight loss and improves type 2 diabetes associated with obesity in mice fed a high-fat diet (HFD). Importantly, this phenomenon is mediated by gut microbiota-dependent mechanisms, and these data clearly suggest that intestinal cell walls play a crucial role in the systemic metabolic response to bacterial elements [19]. The efficacy of the gut barrier is controlled by numerous pathways and cell types, including mucus-producing goblet cells, tight junction proteins, the endocannabinoid system and immune responses [20]. In addition, other bacterial components, such as peptidoglycans, which bind nucleotide-binding oligomerisation domain-containing protein 2 (NOD2) receptors, are likely to play a protective role in the control of insulin resistance and obesity. Indeed, experimental data have recently shown that inhibition of peptidoglycan signalling in *Nod2*^{−/−} mice fed an HFD provokes dysbiosis and promotes bacterial adherence in the mucosae and bacterial accumulation in the liver, thereby contributing to systemic inflammation, insulin resistance and adiposity [21]. Similarly, TLR5-deficient mice, which lose their response to bacterial flagellin in the intestinal mucosa, show mild loss of glycaemic control, which is likely to be driven by insulin resistance and partially compensated for by increased insulin production—conditions typically observed in

humans with the metabolic syndrome [11]. In humans, a nonsense polymorphism (R392X) in TLR5 appears to protect against obesity but, as consistent with findings in animals, predisposes individuals to type 2 diabetes [22].

Bacterial metabolites and glucose homeostasis Metabolites produced by gut microbes may also be related to the development, or the control, of insulin resistance and type 2 diabetes. Most of the data illustrated in Fig. 1 have been obtained using mouse models of diabetes and obesity. As explained below, several metabolites can modulate the endocrine function of the gut, potentially affecting glucose homeostasis.

Short-chain fatty acids (SCFAs; e.g. butyrate, propionate and acetate) are among the most widely investigated metabolites produced by the gut microbiota that interfere with host metabolism. These molecules are produced by the microbial fermentation of specific oligo- or polysaccharides (i.e. non-digestible carbohydrates) via distinct metabolic pathways [23]. The effect of SCFAs on insulin sensitivity and energy metabolism is now widely accepted, although various physiological pathways have been suggested. Indeed, SCFAs are able to modify the levels of several gut peptides involved in glucose metabolism, gut barrier function and energy homeostasis [24–26]. For example, butyrate and propionate were shown to suppress weight gain in mice with HFD-induced obesity (DIO), and acetate was shown to reduce food intake in healthy mice [27, 28]. The majority of the pathways underlying these effects remain unknown. Several studies have suggested that the effects of SCFAs are mediated by the members of a recently identified G protein-coupled receptor family that includes G protein-coupled receptors 43 and 41 (GPR43 and GPR41, respectively) (for a review, see [29]). The binding of SCFAs to GPR43 and GPR41 increases the plasma levels of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), leading to improved glucose homeostasis and reduced appetite (for a review, see [30]). Interesting studies in animals have shown that butyrate activates the expression of genes involved in intestinal gluconeogenesis via a cAMP-dependent mechanism, whereas propionate, already known as a substrate for gluconeogenesis, promotes intestinal gluconeogenic gene expression via a gut–brain neural circuit involving GPR41. The subsequent release of glucose into the portal vein contributes to the regulation of glycaemia and insulin sensitivity [31].

Recent data have indicated that the production of indole, a metabolite produced by gut bacteria from tryptophan, may also contribute to the secretion of GLP-1 by intestinal enteroendocrine cells [32, 33]. Chimere et al discovered that indole inhibits voltage-gated K⁺ channels, thereby changing the action potential properties of L cells and leading to enhanced Ca²⁺ entry, which acutely triggers GLP-1 secretion [34]. More importantly, it has been found that over a longer period of stimulation indole acts as an inhibitor of

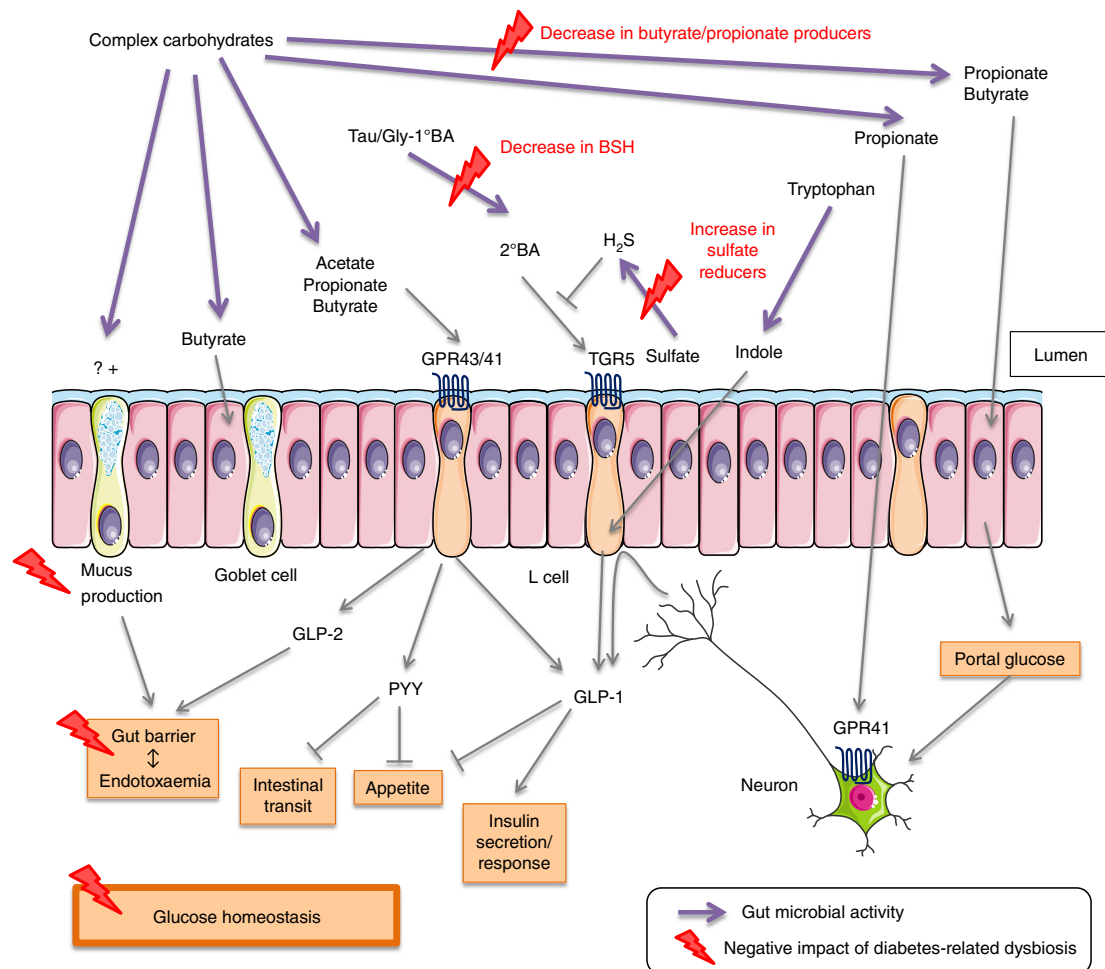


Fig. 1 Metabolites produced by gut microbes may be related to the development or the control of insulin resistance and type 2 diabetes. The figure presents several pathways by which microbial metabolites can influence various physiological processes (such as gut barrier function, appetite, insulin secretion and response and intestinal

gluconeogenesis) and thereby affect glucose homeostasis. For more details, please refer to the main text. Most of the findings illustrated in the figure have been obtained using mouse models of diabetes and obesity. The figure was produced using Servier MedicalArt (www.servier.com). 1°BA, primary bile acids; 2°BA, secondary bile acids

mitochondrial metabolism, resulting in a reduction in the intracellular ATP concentration, which induces the opening of ATP-sensitive K^+ (K_{ATP}) channels, thereby hyperpolarising the plasma membrane and slowing GLP-1 release [34]. Interestingly, we recently demonstrated that among alcoholic individuals, those with higher gut permeability, higher metabolic endotoxaemia and low-grade inflammation exhibit a lower abundance of indole and 3-methyl indole [35]. Taken together, the discovery that indole may trigger GLP-1 secretion and the finding that gut barrier function is reinforced by indole, lead us to suggest that GLP-2 is involved in the control of gut barrier [36] and that its co-secretion with GLP-1 by L cells may be controlled by indoles.

Over the last 10 years, studies have demonstrated that not only are bile acids important in the digestion of dietary lipids, but they also act as signalling molecules in the context of energy, glucose and lipid metabolism [37]. A recent study has reported that pretreatment of DIO mice with antibiotics

(vancomycin and bacitracin), which reduces the levels of the major bacterial phyla (Bacteroidetes and Firmicutes) in the gut and changes the production of bacterial metabolites, improves glucose intolerance and insulin resistance. The authors proposed GLP-1 as a mediator of these effects and noted an increase in primary conjugated bile acid (taurocholic acid) levels as a potential key driver of GLP-1 secretion and a key regulator of host glucose homeostasis [38]. TGR5, a G protein-coupled receptor primarily localised to intestinal enteroendocrine cells, is primarily activated by secondary bile acids produced by the gut microbiota (lithocholic and deoxycholic acids). Activation of this receptor has been associated with improved liver function and glucose tolerance in obese mice by regulating intestinal GLP-1 production [37, 39, 40] (for a review, see [41]). Interestingly H₂S, which can be produced by bacteria expressing sulphate-reducing enzymes, may counteract TGR5 activation and exert an inhibitory effect on GLP-1 and PYY release [42]. Moreover, studies conducted

in mice have demonstrated that the gut microbiota regulate the expression of fibroblast growth factor 15 (for which the orthologous protein in humans is fibroblast growth factor 19 [FGF19]) in the gut by activating the farnesoid X receptor—these hormones are responsible for transmitting bile acid-induced signals in targeted tissues to regulate weight gain and insulin resistance [40, 43, 44]. Joyce et al have shown that promoting the activity of bile salt hydrolase (BSH)—an enzyme distributed across the major bacterial divisions and archaea that catalyses the deconjugation of bile acids to produce secondary bile acids—in the gut microbiota may directly control body weight, blood cholesterol levels, hepatic lipid levels and fat mass gain [45]. Interestingly, a recent intervention study involving the administration of a BSH-active *L. reuteri* strain to healthy volunteers led to an increase in total plasma (conjugated and unconjugated) bile acid levels that correlated with the serum FGF19 levels [46]. The impact of changing the availability and the profile of bile acids on host glucose homeostasis remains to be clearly established in humans, but these metabolites appear to function as important mediators of host metabolism.

Thus, although the influence of the gut microbiota on energy metabolism is multifactorial, different targets involving immunity and/or specific metabolites have been emphasised in recent studies, clearly demonstrating the rationale for searching for novel therapeutic targets based on compounds derived from or produced by bacteria.

Potential contribution of the gut microbiota to the pharmacological or surgical treatment of type 2 diabetes

The discovery of the gut microbiota as a metabolic partner in the management of type 2 diabetes also led to the publication of studies investigating whether gut microbes play a role in the benefits of type 2 diabetes therapies.

Metformin is the most widely used glucose-lowering drug. However, its mechanism of action remains unclear [47]. A first clue regarding the involvement of the gastrointestinal tract in the benefits of metformin came from the observation that intravenous administration of metformin was unable to reduce glycaemia [48]. A second clue came from the finding that the improvement in glucose tolerance induced by metformin was abrogated in mice treated with broad-spectrum antibiotics [49]. Strikingly, Shin et al reported that metformin induced a profound shift in the microbial ecosystem in favour of *Akkermansia* spp. and that oral administration of *A. muciniphila* improved glucose tolerance [49], thereby confirming the results obtained at our laboratory [50]. The authors thus suggested that a modulation of the gut microbiota (likely an increase in the *Akkermansia* spp. population) may contribute to the glucose-lowering effects of metformin. A

few months later, Lee et al confirmed that metformin treatment induces an increase in the *A. muciniphila* population and demonstrated a negative correlation between glycaemia and *A. muciniphila* abundance. Interestingly, co-incubation of metformin and mouse stool samples led to an enrichment in *A. muciniphila* [51], suggesting that metformin directly interacts with the gut microbiota to foster the growth of *A. muciniphila*.

Acarbose, an α -glucosidase inhibitor that is almost exclusively used in Asia, is another type 2 diabetes drug with effects that could be related to the gut microbiota. In Chinese patients, the inclusion of acarbose as part of their glucose-lowering medication has been reported to increase faecal *Bifidobacterium* spp. and reduce LPS levels [52].

Interestingly, new therapeutic agents proposed for the treatment of type 2 diabetes (sitagliptin and exenatide) exploit the GLP-1 pathway. As mentioned earlier, GLP-1 secretion can also be stimulated by metabolites produced by the gut microbiota [25]. Reimer et al demonstrated that co-administration of sitagliptin and a viscous fermentable fibre, which is broken down into SCFA, more effectively reduced fasting glycaemia in obese Zucker rats than either treatment alone [53]. Similar results were obtained in the same model when this fibre was combined with metformin or with metformin and sitagliptin [54].

Currently, the combination of medical therapy with bariatric surgery (vertical sleeve gastrectomy [VSG] or Roux-en-Y gastric bypass [RYGB]) appears to more effectively control glycaemia than medical therapy alone in obese patients with uncontrolled diabetes [55]. In this context, studies have found that RYGB restructures the gut microbiota in humans and rats [56, 57]. Transfer of the gut microbiota of mice that underwent RYGB to non-operated germ-free mice resulted in weight loss and decreased fat mass but no change in fasting glycaemia, providing the first evidence that changes in the gut microbiota contribute to the metabolic improvements conferred by RYGB [56]. As explained above, bile acids might link the gut microbiota to the host. Their levels are modified after bariatric surgery, and VSG does not improve hyperglycaemia in mice carrying a targeted genetic deletion of the farnesoid X receptor, implicating bile acids as bacterial modulators of host homeostasis in this context [58]. Bile acids are without doubt very interesting mediators. However, the differences in bile acid and cholesterol metabolism between mice and humans make it difficult to translate the data from the animal models to the human situation.

Novel therapeutic approaches of type 2 diabetes based on the understanding of gut microbiota–host interactions

Aside from the classical treatments, the recently recognised implication of gut microbes in the pathophysiology of type 2

diabetes opens a novel area of research for developing new strategies to tackle this disease using gut microbes.

Microbiota transfer An original study recently investigated this approach using an infusion of faecal microbiota from lean donors to recipients with the metabolic syndrome [59]. The transfer of a microbiota sample from healthy patients was able to increase the levels of butyrate-producing bacteria and insulin sensitivity in insulin-resistant recipients [59], thus suggesting that the isolation of the microbiota from faecal content might be developed as a therapeutic strategy to increase insulin sensitivity in humans. However, this type of experiment assessing the role of the gut microbiota in the control of diabetes in humans is currently a proof-of-concept rather than a potential therapy. Additional studies are needed to confirm the lack of harmful effects linked to the transfer of faecal microorganisms, most of which are unidentified and uncharacterised at present.

Probiotic approach More specific approaches may also be considered for type 2 diabetic patients. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host (i.e. humans) [60]. To date, the major probiotic strains that have shown beneficial effects on glucose metabolism in humans belong to the *Lactobacillus* genus (i.e. *L. plantarum* 299v, *Lactobacillus acidophilus* NCFM and *L. gasseri* SBT2055) [61–63]. These observations may appear to be discordant, as some *Lactobacillus* species have been shown to be increased in type 2 diabetic patients, as previously discussed. However, the increase in *Lactobacillus* species in type 2 diabetes has never been demonstrated to have a direct impact on the disease. Moreover, the effects obtained using probiotics are probably strain-specific; thus, different strains of the same species may exert distinct effects. Importantly, it could be interesting to investigate other ‘beneficial’ microorganisms that are decreased in diabetic patients.

Among the bacteria that could potentially be used for the treatment of type 2 diabetes, *A. muciniphila* appears to be of particular interest. By administering *A. muciniphila* Muc^T (ATTC BAA-835) in a diet-induced mouse model of type 2 diabetes, we demonstrated the direct beneficial effects of this bacterium on glucose metabolism [50]. First, *A. muciniphila* is able to counteract fasting hyperglycaemia in diet-induced mouse model of type 2 diabetes by preventing the increase in *G6pc* (glucose-6-phosphatase) mRNA expression [50]. This suggests that *A. muciniphila* thwarts the deleterious increase in gluconeogenesis in diabetic mice. Moreover, administration of live *A. muciniphila* alleviates glucose intolerance in HFD-induced diabetic mice [49, 50]. However, additional studies are needed to establish whether *A. muciniphila* can be used as a probiotic for patients with type 2 diabetes, and of these, intervention studies in humans are of utmost

importance. Finally, *A. muciniphila* is probably not the sole bacterium that could be beneficial for the treatment of these patients; other bacteria, such as *F. prausnitzii*, which plays an important role in the maintenance of the gut barrier and in the control of inflammation, could also be interesting to investigate (for a review, see [64]).

Non-bacterial ‘colonisers’ of the gut of potential interest In addition to the classical probiotic bacteria, several other types of living organism might contribute to the therapeutic arsenal for treating hyperglycaemia in the future. Here, we consider the current knowledge on fungi, archaea and helminths regarding their relationship with host glycaemia.

Our understanding of the contribution of the mycobiota (fungal community) to health and disease remains in its infancy [65]. Our laboratory recently provided the first evidence supporting the hypothesis that fungi can influence host metabolism. The yeast *Saccharomyces boulardii* changed the gut microbiota and reduced certain features of the metabolic syndrome in genetically obese and diabetic mice. However, this yeast did not change fasting glycaemia in these mice [66]. Improving our understanding of the mycobiota and its relationship with the host might lead in the future to the development of new therapies for the metabolic syndrome.

The predominant archaeon member in the human gut is *Methanobrevibacter smithii*. How this methanogenic archaeon collaborates with saccharolytic bacteria such as *Bacteroides thetaiotaomicron* to metabolise complex carbohydrates was elegantly established almost 10 years ago [67]. This symbiotic association increases adiposity when inoculated into germ-free mice [67]. In humans, methanogenic archaea are increased in obese vs lean individuals [68], and intestinal methane production in obese individuals is associated with a higher BMI [69]. However, this association cannot be generalised to all archaea [70], and their relationship with glycaemia has not been reported.

Helminths are known to induce T helper type 2-oriented immunity in association with eosinophilia. For this reason, *Nippostrongylus brasiliensis* has been used in a mouse model of DIO to maintain eosinophil homeostasis in adipose tissue, and this intervention led to reduced adipose macrophage counts and fasting glucose levels [71]. In accordance with these results, metabonomic investigation of mice infected with *Schistosoma mansoni* suggested a stimulation of glycolysis, which might also contribute to the glucose-lowering effect associated with helminth infection [72]. Moreover, as helminths influence the gut microbiota (e.g. increased lactobacilli) [73, 74], we cannot exclude an indirect effect of helminths on host metabolism via modulation of the gut microbiota. Voluntary infection with helminths might not constitute an appropriate therapeutic approach to reducing blood glucose levels. However, unravelling the biological mechanisms underlying the beneficial effects of helminths on

glucose metabolism (such as the induction of eosinophilia or the stimulation of the growth of lactobacilli) should reveal new therapeutic targets and would help to identify how the gut ecosystem plays a role in the control of host metabolism.

A place for nutrition in the management of glycaemia-related dysbiosis

Inulin-type fructans Nutrition plays an important role in the management of diabetes. Indeed, some nutrients are able to decrease the postprandial glucose response. Cereals, legumes, fruits and spices are four important food groups that contain active ingredients (such as dietary fibre and polyphenols) that are able to reduce glycaemia and insulin responses in humans [75]. The glucose-lowering effect of fibre intake may depend on the fibre type, amount and/or source. Dietary inulin-type fructans (ITF), which are present in various fruits and vegetables, are fermentable carbohydrates that display prebiotic properties, as their metabolism by gut microorganisms modulates the composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host [76]. ITF increase the number of endocrine L cells in the jejunum and colon of rodents and promote the production and release of the active forms of GLP-1, thereby decreasing glycaemia [77–81]. A systematic review conducted to evaluate the effectiveness of dietary ITF on serum glucose in humans revealed that four out of 13 eligible randomised controlled trials published from 1984 to 2009 reported a decrease in serum glucose concentrations [82]. Interestingly, in healthy volunteers, 2 weeks of treatment with ITF (16 g per day) increased the postprandial release of gut peptides (specifically GLP-1 and gastric inhibitory peptide), modified eating behaviour (increased satiety and decreased energy intake) and decreased postprandial glycaemia [83]. One study performed on a limited number of patients at risk for cardiovascular disease did not support the effect of ITF on insulin sensitivity [84]. Short-chain-enriched inulin (10 g/day) caused a significant decrease in the levels of fasting plasma glucose, HbA_{1c} and inflammatory markers (IL-6, TNF- α and LPS) compared with maltodextrin in a trial of 52 overweight type 2 diabetes women over a period of 8 weeks [85]. In a study of the correlations between glycaemic control by ITF in obese women and gut bacteria, changes in *Clostridium* cluster IV group (which was increased by ITF) were negatively correlated with fasting glycaemia, insulinaemia and HOMA-IR [86]. In contrast, changes in *Propionibacterium* spp., *Bacteroides intestinalis* and *Bacteroides vulgatus*, all three of which were significantly decreased by prebiotic treatment, were positively correlated with the changes in glucose homeostasis. Serum LPS levels were negatively correlated with several bacterial phyla and species, specifically Firmicutes, Actinobacteria, *Bifidobacterium* and *F. prausnitzii*, all of which were

promoted by ITF. The promotion of *Bifidobacterium* by ITF is logical since these bacteria express β -fructosidase, but the other changes, such as the interesting increase in *F. prausnitzii*, remain unexplained.

Arabinoxylans Other non-digestible carbohydrates are gradually fermented throughout the colon, and these might have beneficial health effects by acting as substrates for certain microbes. Arabinoxylans (AX), the most abundant non-digestible carbohydrates in wheat, are predominantly present in bran and aleurone fractions [87, 88]. AX are selectively degraded in the colon by intestinal bacteria expressing xylanases and arabinofuranosidases and represent a new class of prebiotics [89–91]. Table 1 summarises the findings of studies on AX and AXOS (short-chain AX produced via enzymatic processing) in animal models and in humans. In our studies, AX and AXOS supplementation induced caecal and colon enlargement, increased *Bifidobacterium* spp., *Bacteroides/Prevotella* spp. and *Roseburia* spp. and improved insulin resistance in a diet-induced mouse model of type 2 diabetes [92, 93]. Importantly, correlation analysis revealed that the *Roseburia* spp. levels are inversely correlated with HOMA-IR and inflammatory markers. AXOS increased the level of GLP-1 and counteracted the HFD-induced increase in HOMA-IR. In addition, AXOS reduced HFD-induced metabolic endotoxaemia [92]. Most human intervention studies, including those of type 2 diabetic patients, assessing the effects of wheat-derived AX(OS) on glucose metabolism demonstrated a decrease in glycaemia (Table 1). Additional studies are needed to determine whether the effect of AX(OS) on gut microbiota is linked to the improvement in glucose homeostasis.

Polyphenols Some phenolic compounds abundant in fruit, vegetables, chocolate, nuts and beverages (tea, coffee, wine and soy milk) may be poorly absorbed in the upper part of the gut and are fermented by bacteria in the colon. Our laboratory has demonstrated that supplementation with pomegranate peel extract, which is rich in ellagitannins and anthocyanins, modulates the gut microbiota in favour of bifidobacteria [94]. Although this effect was accompanied by the reduced expression of key inflammatory factors, it did not significantly modify glycaemia or glucose tolerance. Of note, several recent studies have highlighted the importance of gut microbiota modulation in the metabolic effects of polyphenols on glucose homeostasis. One such polyphenol is resveratrol, a natural phytoalexin present in red grapes, peanuts, and berries that displays antioxidant and anti-inflammatory properties. In one study, resveratrol increased GLP-1 production via a mechanism that was dependent on the alteration of the intestinal microbiota and required the GLP-1 receptor to mediate its antidiabetic effect on DIO mice. In particular, it was shown that *Parabacteroides johnsonii*, *Alistipes putredinis* and

Table 1 Effects of wheat AX(OS) consumption on glucose homeostasis related or not related to changes in gut microbiota

Study design	Delivery method	Results	References
Animals			
24 mice fed an HFD to induce obesity	Mice were fed an HFD enriched with AX (10%) ($n=8$)	= fasting glycaemia, = fasting insulinaemia, ↓ insulin resistance index, ↓ IL-6, ↓ MCP-1, ↑ <i>Bifidobacterium</i> spp., ↑ <i>Roseburia</i> spp., ↑ <i>Bacteroides/Prevotella</i> spp., = total bacteria	[93]
24 mice fed an HFD to induce obesity	Mice were fed an HFD enriched with AXOS (7.5%) ($n=8$)	↓ HOMA-IR, ↓ fasting insulin, ↓ endotoxaemia, ↓ IL-6, ↑ GLP-1, ↑ <i>Bifidobacterium</i> spp., ↓ <i>Lactobacillus</i> spp., = <i>Bacteroides/Prevotella</i> spp.	[92]
48 healthy rats	Rats were fed a diet (2.5 g) enriched with AX that were either native or cross-linked and either prehydrated or not ($n=8$)	↓ glucose response area after the meal	[101]
6 healthy female pigs	Pigs were catheterised via the portal artery and were fed with 5 experimental breads (one of which was enriched with AX) on separate days in a randomised 5 × 6 incomplete crossover design with washout periods, resulting in 6 observations per diet	↓ postprandial glucose, ↓ insulin secretion, = GLP-1, = GIP, = glycaemic index, = insulinaemic index	[102]
60 Zucker diabetic fatty rats	Rats were fed one of 5 wheat breads (one of which was enriched with AX) for 7 weeks ($n=12$)	↓ glucose response areas after the OGTT, ↓ fasting glucose, ↓ HbA _{1c} , ↑ insulin, = glucagon	[103]
Humans			
14 healthy individuals	Bread containing 0, 6 or 12 g of AX 3 breakfasts on 3 days	↓ postprandial glycaemia, improvement in the insulin response	[104]
15 individuals with type 2 diabetes; randomised crossover intervention	Bread and muffins containing 14% AX for 5 weeks	↓ fasting glycaemia, ↓ glycaemia and insulinaemia 2 h post OGTT	[105]
11 individuals with impaired glucose tolerance; single-blind, controlled, crossover intervention over 18 weeks	15 g AX supplied daily via bread and powder for 6 weeks, followed by a 6 week washout period	↓ fasting glycaemia, = insulin, After LMCT: ↓ postprandial glycaemia, ↓ insulin	[106, 107]
15 healthy individuals; crossover intervention	Breakfast containing 6 g of AX	= postprandial glycaemia, ↓ postprandial insulinaemia	[108]
55 healthy individuals; double-blind, randomised crossover intervention	Ready-to-eat cereal containing AXOS (0, 2.2 or 4.8 g/day) for 3 weeks	= fasting glycaemia, ↓ fasting insulinaemia (by 2.2 g/day vs control), ↑ faecal bifidobacteria = total bacteria, = <i>Bacteroides</i> , = <i>Lactobacillus</i> spp., = <i>Clostridium coccoides</i> , = group <i>R. intestinalis/E. rectale</i> , = <i>F. prausnitzii</i> , = <i>Clostridium</i> clusters I and II	[109]
15 individuals with the metabolic syndrome; acute, randomised, crossover study	50 g of semolina porridge supplemented with AX, rye kernels or concentrated AX combined with rye kernels	↓ acute glucose, ↓ insulin responses, = GLP-1 response to AX vs the control food, ↓ GLP-1 response to AX vs rye kernel-supplemented food, ↑ plasma butyrate and acetate	[110]

GIP, glucose-dependent insulintropic polypeptide; LMCT, liquid meal challenge test; MCP-1; monocyte chemoattractant protein-1; = means no significant changes vs controls

Bacteroides vulgatus, the levels of which were increased by HFD treatment, disappeared 5 weeks after resveratrol supplementation [95]. In another study, mice fed an HFD supplemented with 4% green tea powder for 8 weeks had a significantly increased insulin response compared with control mice [96]. In addition, fasting plasma glucose, insulin and HOMA-IR levels were lower in mice fed the green tea supplement for 11 or 22 weeks. In a third study, the administration of cranberry extract, which is rich in proanthocyanidins, improved insulin sensitivity in high-fat/high-sucrose diet-fed mice. In this study, cranberry extract treatment markedly increased the proportion of *Akkermansia* and decreased intestinal inflammation [97]. Finally, a double-blind trial revealed that changes in the gut microbiota are associated with the glucose-lowering effects of a traditional berberine-containing Chinese herbal formula in type 2 diabetic patients [98]. Indeed, this decoction significantly increased *F. prausnitzii*, which was negatively correlated with fasting blood glucose, HbA_{1c} and postprandial blood glucose levels and was positively correlated with HOMA of beta cell function.

Importantly, energy-free artificial sweeteners were extensively introduced to our diets with the intention of reducing energy intake and normalising blood glucose levels without ‘sweet-toothed’ humans having to compromise. A recent study demonstrated that the consumption of commonly used artificial sweetener formulations drives the development of glucose intolerance via the induction of compositional and functional alterations to the intestinal microbiota [99]. Whether the bacterial populations or metabolic pathways altered by the consumption of artificial sweeteners are similar to those described in individuals with or developing diabetes remains to be elucidated [99, 100].

Conclusions

Type 2 diabetes, a complex disease that is often associated with obesity, develops via the interaction between genetic and environmental factors. We believe that the gut microbiota represents an environmental factor of type 2 diabetes that was neglected in the past due to the complexity of its analysis and to the lack of an understanding of the mechanisms underlying the interactions between gut microbes and host metabolism. The current interest in the gut microbiota as a potential target for the management of non-communicable diseases such as type 2 diabetes partially relies on the novel methodologies available for analysing the composition and function of the gut microbiota, as well as on the recent discoveries of host molecular targets that are prone to ‘respond’ to bacterial metabolites/components. To those who might question the relevance of gut dysbiosis in the occurrence of type 2 diabetes, we would say that all of the data supporting a causative role of dysbiosis in type 2 diabetes have been obtained using germ-

free animals into which the intestinal content of diabetic mice was transferred. As far as the development of novel therapeutic approaches is concerned, intervention studies using probiotic, prebiotic, or microbial transplantation have been successful in a very limited number of published reports. Nutritional advice is crucial in the management of diabetes. We believe that a better characterisation of the nutrients that are able to modulate the gut microbiota in favour of anti-inflammatory bacteria or bacterial metabolites is needed to provide adequate advice to patients who are at risk for type 2 diabetes development.

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