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Review

Role of gut microbiota in type 2 diabetes pathophysiology

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ABSTRACT

A substantial body of literature has provided evidence for the role of gut microbiota in metabolic diseases including type 2 diabetes. However, reports vary regarding the association of particular taxonomic groups with disease. In this systematic review, we focused on the potential role of different bacterial taxa affecting diabetes. We have summarized evidence from 42 human studies reporting microbial associations with disease, and have identified supporting preclinical studies or clinical trials using treatments with probiotics. Among the commonly reported findings, the genera of *Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia and Roseburia* were negatively associated with T2D, while the genera of *Ruminococcus, Fusobacterium,* and *Blautia* were positively associated with T2D. We also discussed potential molecular mechanisms of microbiota effects in the onset and progression of T2D.

1. Introduction

The microbiome has been associated with pathophysiology of most chronic diseases. Type 2 diabetes (T2D) is no exception to this rule. Indeed, there is evidence for the effects of microbiota on glucose metabolism in both preclinical animal models of T2D and in healthy animals. Therefore, there is considerable interest in potential use of microbiota in clinical applications for understanding and treating T2D. At first glance, however, the microbiome literature on T2D appears chaotic and concerns have been raised about variability of the results. Different taxa are reported to be associated with T2D in different studies. Furthermore, a recent large study observed that different microbes were found associated with the same metabolic outcomes in different geographical areas [1]. While this might appear somewhat discouraging it is important to remember that discrepancies between results and disagreements about interpretations are common features of any emerging field in science. As a research community, we should not shy away from these problems, rather understand which aspects of the current literature are robust and which ones are not. A key issue moving forward is to identify properties of the microbiome and T2D that contribute to this apparent lack of reproducibility. In this review, we researched recent literature regarding microbiome in type 2 diabetes patients and summarize the most reliable findings.

2. Bacteria involved in T2D

Out of 42 human observational studies that investigated T2D and the bacterial microbiome, the majority of studies reported associations between specific taxa and disease or its phenotypes (see Supporting Table 1 and "Search strategy and selection criteria" below). However, only a handful reported similar results. Among the commonly and consistently reported findings, the genera of *Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia and Roseburia were negatively associated with T2D, while the genera of Ruminococcus, Fusobacterium,* and *Blautia* were positively associated with T2D (Fig. 1). *Lactobacillus* genus, while frequently detected and reported, shows the most discrepant results among studies. Interestingly, different macro-metrics of microbial communities, such as several indexes of diversity and the Bacteroidetes/Firmicutes ratio that have been previously suggested as markers of metabolic disease did not show consistent associations with T2D (Table 1).

Bacteroides and *bifidobacterium* represent beneficial genera most frequently reported in studies of T2D.

Bifidobacterium appears to be the most consistently supported by the literature genus containing microbes potentially protective against T2D. Indeed, nearly all papers report a negative association between this genus and T2D [2–9]; while only one paper reported opposite results [10]. Furthermore, some studies also found a

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Table 1
Number of reports examining association between T2D and diversity of microbiota or Bacteroides/Firmicutes ratio.

Index		# Reports	No association	References (PMID)	Positive	References (PMID)	Negative	References (PMID)
Alpha diversity	Shannon	13	9	24013136, 29998997, 29280312, 29922272, 29596446, 27151248, 26756039	2	30397356, 26941724	2	27974055, 27151248
	Chao1	8	6	24013136, 29998997, 29280312, 29922272, 26756039, 27151248	2	26941724, 29789365	0	
	Simpson	3	1	29998997	1	26941724	1	29789365
Beta diversity		8	7	24988476, 28530702, 24997786, 29280312, 29922272, 29596446, 27151248	0		1	27974055
Bacteroides/Firmicutes ratio		14	6	24013136, 26756039, 29789365, 29434314, 29657308, 29998997	3	20140211, 29434314, 23032991	4	23657005, 27974055, 26919743, 22293842

negative association between specific species such as *B. adolescentis, B. bifidum, B. pseudocatenulatum, B. longum, B. dentium* and disease in patients treated with metformin or after undergoing gastric bypass surgery [6,11]. According to our literature search, *Bifidobacterium* has not been used alone as probiotics for T2D. However, almost all animal studies that tested several species from this genus (*B. bifidum, B. longum, B. infantis, B. animalis, B. pseudocatenulatum, B. breve*) showed improvement of glucose tolerance [12–16]. Thus, animal studies strengthen the idea that *Bifidobacterium* naturally habituating the human gut or introduced as probiotics play protective role in T2D.

The second most commonly reported genus was ***Bacteroides***. Eight studies have reported associations between the abundance of this genus and T2D. Among these, five cross-sectional studies [3,17–20] show negative associations with disease while three other studies [6,11,21] that involved some type of treatment reported positive associations. This apparent inconsistency can be explained by previously reported antibiotic effect of metformin [22] and/or potential feedback mechanisms on gut microbiota resulting from improved human physiology. Interestingly, in He et al. [1,23] 21 out of 23 OTUs of Bacteroides detected in their study were negatively associated with T2D. Accordingly, in investigations that analyzed this genus on the species level, *Bacteroides intestinalis, Bacteroides 20–3 and Bacteroides vulgatus* were decreased in T2D patients and *Bacteroides stercoris* were enriched after sleeve gastrectomy (SG) surgery in T2D patients with diabetes remission [5,11,17,24]. We also found only two experimental animal studies testing the ability of *Bacteroides* to treat diet induced metabolic disease. In these studies, administration of *Bacteroides acidifaciens* [25] and *Bacteroides uniformis* [26] improved glucose intolerance and insulin resistance in diabetic mice. Together, these studies indicate that *Bacteroides* plays a beneficial role on glucose metabolism in humans and experimental animals.

While ***Roseburia, Faecalibacterium,* and *Akkermansia*** were not reported as frequently as the two genera above mentioned (Bifidobacterium, Bacteroides) in the 42 studies we reviewed, but those genera were also found to be consistently negatively associated with T2D in human studies.

In five case-control studies *Roseburia* was found in lower frequencies in T2D group than in healthy controls [3,17,27–29]. Accordingly, investigations that were able to assign *Roseburia* to a species level also reported a negative association with disease for *Roseburia inulinivorans, Roseburia_272,* and one unclassified OTU from this genus [11,17,24]. Only one paper reported an opposite result for *Roseburia intestinalis* [17].

Two case-control studies reported lower frequencies in the disease group for *Faecalibacterium* [2,28]. Nevertheless, this genus was also found to be decreased after different types of antidiabetic treatments ranging from metformin and herbal medicine [30] to bariatric surgery [11]; only one study reported an opposite effect [31]. Moreover, studies that were able to analyze this genus at species level usually detected *F. prausnitzii.* This species was found to be negatively associated with T2D in four out five human case control studies [17,24,32–34]. While it is a popular probiotic for colitis [35], there were few attempts to use *F. prausnitzii* as a probiotic for metabolic disease.

Interestingly, in one study the administration of *F. prausnitzii* resulted in improvement of hepatic function and decreased liver fat inflammation in mice with diet-induced metabolic disease without affecting blood glucose [36]. Finally, it was also shown that another species of this genus, *Faecalibacterium cf,* was associated with remission of diabetes after bariatric surgery [11].

Akkermansia muciniphila is a relatively recently discovered member of commensal microbiota [37]. Its beneficial effect on host glucose metabolism was first reported in animal models [38,39]. In agreement with animal studies, the negative association between the abundance of this bacterium and T2D has been reported in human studies [17,38].

In summary, a decrease in at least one of these five phylogenetically distant genera (*Bacteroides, Bifidobacterium, Roseburia, Faecalibacterium, and Akkermansia*) in patients was found in approximately half of T2D microbiome studies suggesting their potential role beyond serving as a biomarker. Supporting this notion, the majority of these bacteria have been tested as probiotics for metabolic disease in mice, but more rarely in humans [12–16,25,26,36–42]. The potential mechanisms of interaction between these microbes and mammalian organisms are discussed later in this paper.

Lactobacillus genus presents a complex case of apparently discordant results when considering all association studies, i.e. including those that analyzed changes after treatments (Fig. 1). However, cross-sectional studies of patients versus controls reported positive association between abundances of this genus and T2D in five out of six papers [3–5,29,43]. Furthermore, several associations of this genus tend to be species-specific. For example, while *L. acidophilus* [34], *L. gasseri* [24], *L. salivarius* [24] were increased, *L. amylovorus* [29] was decreased in T2D patients suggesting a high diversity in functional impact on host metabolism by bacteria from this genus. Moreover, several species from this genus have been also tested as probiotics. Experimental studies in mice show mostly beneficial effects in the models of T2D such as *L. plantarum* [44–47], *L. reuteri* [48], *L. casei* [49], *L. curvatus* [50], *L. gasseri* [51], *L. paracasei* [52], *L. rhamnosus* [53], *L. sakei* [54]. More importantly, twenty-five human clinical trials [55–79] employed twelve different species of *Lactobacillus* with ten of those studies [55-62,64,79] adding other probiotics. Out of eleven studies [58–64,72,76,77,79] that showed some protective effect, the majority combined other genera, most frequently *Bifidobacterium* [58–62,64,79], suggesting that *Lactobacillus* and *Bifidobacterium* may work in a synergistic manner. Species *L.*

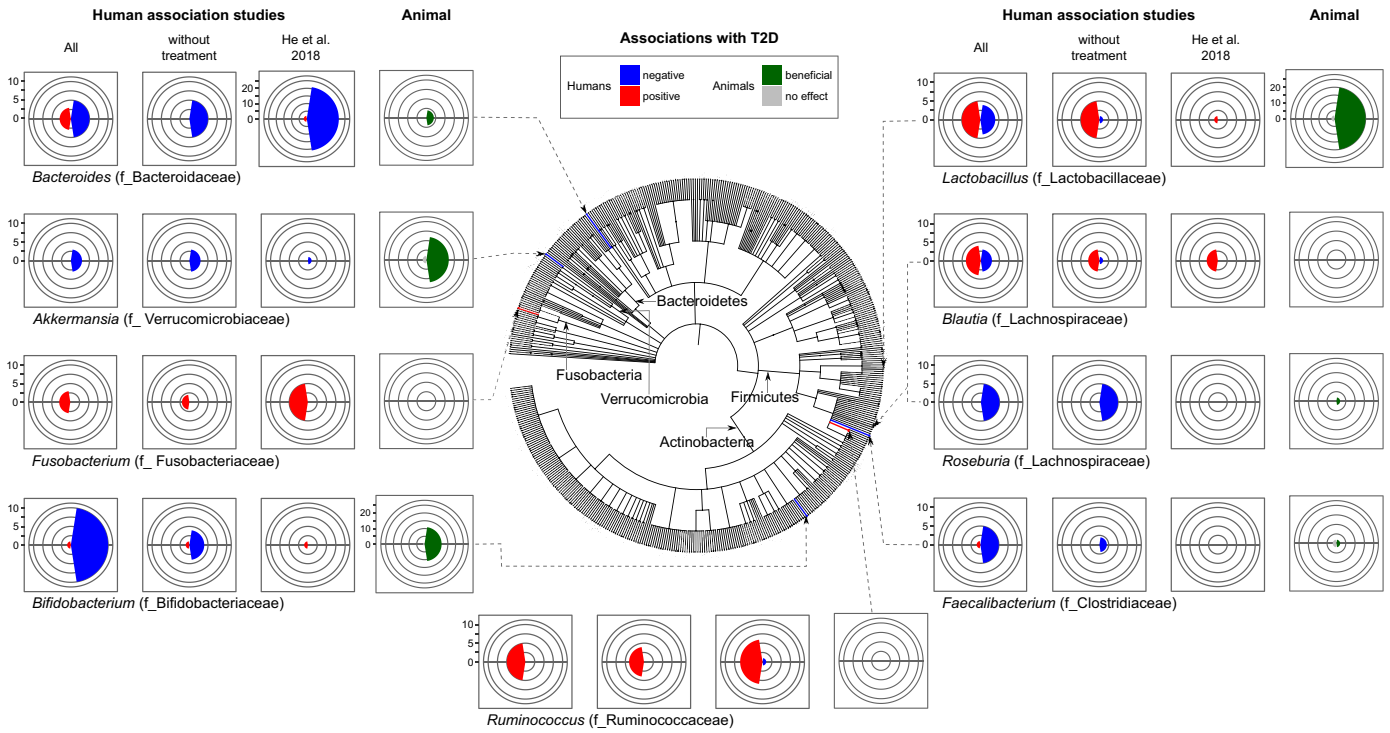


Fig. 1. Microbial genera most frequently found to be associated with T2D. Number of studies reporting one of the indicated genera in association with T2D (without treatment), and including anti-diabetic therapy (All) in addition to the largest human study by He et al., 2018 [1].

sporogenes [76,77], *L. casei Shirota* [63], *L. reuteri* [72] used as monoprobiotics have been reported to improve T2D related symptoms in humans.

L. plantarum, bacteria found in fermented food products, is intensively studied in animal systems, with many studies showing that *L. plantarum* improves glucose metabolism in diet-induced and genetic models of T2D [44–47] mice; only one reported with no significant effect of this treatment [80]. However, this species had no significant effect on glucose metabolism in four clinical trials [68–71]. Thus, it seems that *Lactobacilli* anti-diabetic effect is seen more frequently when they are a part of probiotic cocktail rather than administered individually [58,61,62,64].

Overall, *Lactobacillus* genus is highly diverse and contains the highest number of OTUs in the human gut among potentially probiotic bacteria. Its effects on T2D seems to be species-specific or even strain-specific, which might explain why genus level analysis lacks consistency amongst studies using this bacteria (Fig. 1).

Fewer studies (11 out of 42) reported positive associations (increase in disease) of microbiota with T2D and/or hyperglycemia. Specifically, ***Ruminococcus, Fusobacterium***, and ***Blautia*** have been reported in a positive association with T2D. On one hand, consistent findings have been reported in 5 studies on *Ruminococcus* genus [3,17,28,31,81] and 3 studies on *Fusobacterium* [2,4,6]. On the other hand, the studies reporting species levels of these bacteria reported conflicting results [6,11,34]. For example, while one study demonstrated that Ruminococcus sp. SR1/5 enriched by metformin treatment [6], another found *Ruminococcus bromii* enriched and *Ruminococcus torques* decreased after bariatric surgery and diabetes remission [11]. It is possible that different types of treatments might be a major reason for the inconsistences between results of these studies.

Blautia genus has been found increased in disease groups in three out of four cross-sectional studies for T2D [17,18,82,83] and reduced after bariatric surgery [31]. Disagreeing with these reports, Blautia spp. were reported to increase after treatment with metformin in another study [30]. Importantly, results by He et al. 2018 [1], are concordant with the genus level analyses demonstrating positive associations between T2D and several OTUs of all three of these genera. The question still remains whether these bacteria play a causal role in T2D since there are no studies investigating these potentially harmful bacteria in animal models of T2D.

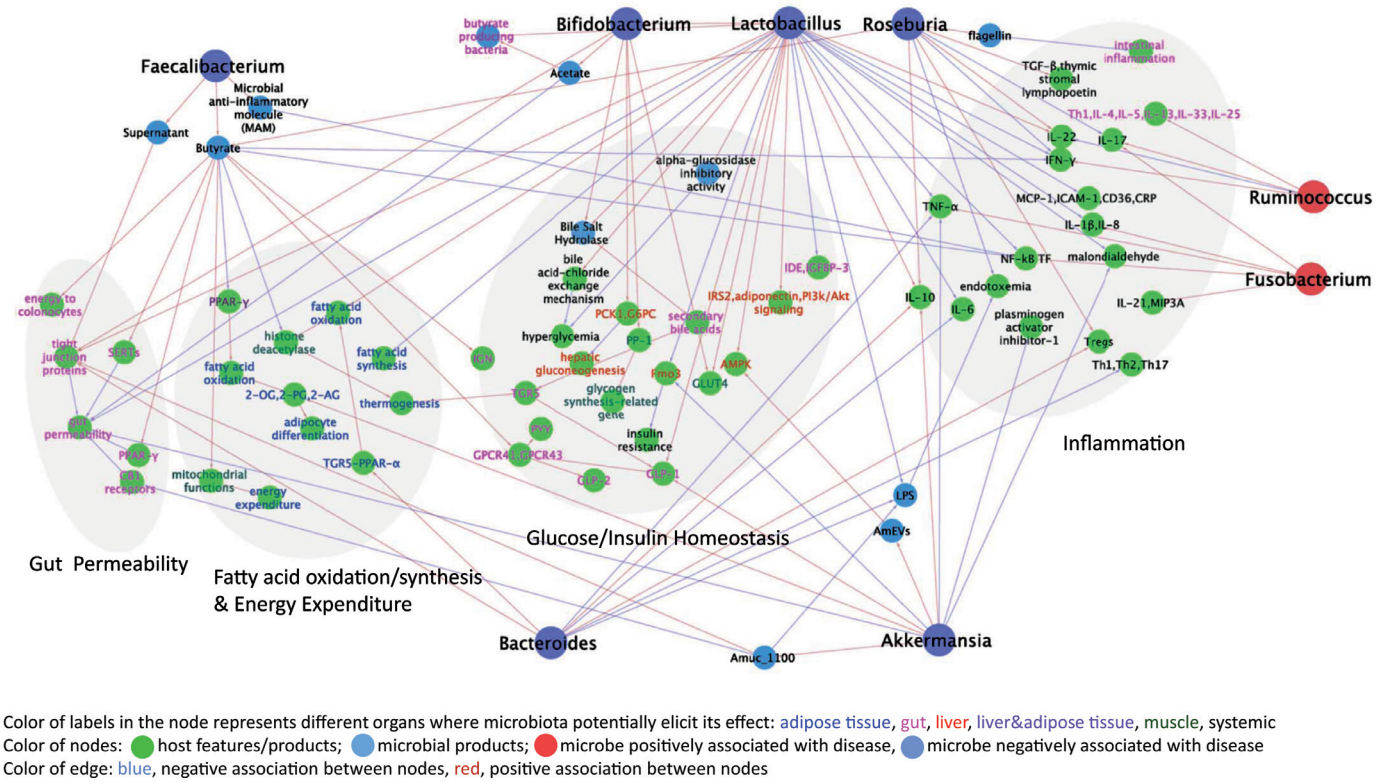
In summary, our review of literature regarding overall diversity and other macro-metrics of microbial communities failed to show a relation to diabetes (Table 1). However, some taxa have been systematically implicated in T2D. Surprisingly, some taxa are consistently associated with protection from T2D at genus level (e.g. *Bacteroides, Bifidobacterium*, etc.) or even phylogenetically at higher levels (e.g. Actinobacteria [7,17]) whereas others (e.g. *Lactobacilli*) show only species- or strain-specific effects. This phenomenon might be to be associated with a diversity of a given genus habituating the human gut (i.e. the larger a number of strains of a given genus found in human gut, the more strain-specific effects are observed). Importantly, several of these microbes are currently tested as probiotics in mouse and human studies.

3. Potential mechanisms of microbiota effects on metabolism in the T2D patient

Multiple molecular mechanisms of gut microbiota contribution to metabolic disease and T2D have been recently reviewed elsewhere [84]. Microbiota modulates inflammation, interacts with dietary constituents, affects gut permeability, glucose and lipid metabolism, insulin sensitivity and overall energy homeostasis in the mammalian host (Fig. 2). Herein, we summarize the mechanisms whereby specific taxa highlighted earlier in this review can affect T2D.

3.1. Modulation of inflammation

Overall, T2D is associated with elevated levels of pro-inflammatory cytokines, chemokines and inflammatory proteins. While some



Color of labels in the node represents different organs where microbiota potentially elicit its effect: adipose tissue, gut, liver, liver&adipose tissue, muscle, systemic
Color of nodes: host features/products; microbial products; microbe positively associated with disease, microbe negatively associated with disease
Color of edge: blue, negative association between nodes, red, positive association between nodes

Fig. 2. Literature-based network analysis of potential effects on metabolism of bacterial taxa consistently found in association with human T2D (shown in Fig. 1). References corresponding to each edge can be found in the text.

gut microbes and microbial products especially lipopolysaccharides (LPS) promote metabolic endotoxemia and low-grade inflammation, others stimulate anti-inflammatory cytokines and chemokines. For example, induction of IL-10 by species of *Roseburia intestinalis, Bacteroides fragilis, Akkermansia muciniphila, Lactobacillus plantarum, L. casei* [37,85–88] may contribute to improvement of glucose metabolism since overexpression of this cytokine in the muscle protects from ageing-related insulin resistance [89]. *R. intestinalis* can also increase IL-22 production, an anti-inflammatory cytokine [90,91] known to restore insulin sensitivity and alleviate diabetes [92]. It can also promote T regulatory cell differentiation, induce TGF-β and suppress intestinal inflammation [85,90,91]. Likewise, *Bacteroides thetaiotaomicron* induces expression of T regulatory cell gene expression [90].

Inhibition of pro-inflammatory cytokines and chemokines is another route used by beneficial microbes to prevent inflammation. Various species of Lactobacillus (*L. plantarum, L. paracasei, L. casei*) can decrease IL-1β, Monocyte Chemoattractant Protein-1, Intercellular adhesion molecule-1, IL-8, CD36 and C-reactive protein [93,94]. *L. paracasei* and *B. fragilis* inhibit expression of IL-6 [86,95]. Similarly, Lactobacillus, Bacteroides and Akkermansia have been found to suppress TNF-α [96,86–88,95,97,98]. *L. paracasei* and microbial anti-inflammatory molecule from *F. prausnitzii* inhibit the activity of NF-kB [95,99]. Similarly, Roseburia and Faecalibacterium are butyrate producing bacteria and butyrate is also known to inhibit the activity of NF-kB [100,101]. *Lactobacillus casei* and *Roseburia intestinalis* decrease another pro-inflammatory cytokine IFN-γ [90,91,102] whereas *Roseburia intestinalis* can inhibit IL-17 production [90,91]. *Bacteroides thetaiotaomicron* reduces Th1, Th2 and Th17 cytokines in mono-associated mice [90].

Potentially detrimental microbes in T2D (pathobionts), like *Fusobacterium nucleatum* and *Ruminococcus gnavus* can increase several inflammatory cytokines, albeit in other inflammatory diseases [103,104].

3.2. Gut permeability

Increased intestinal permeability is a characteristic of human T2D. It results in translocation of gut microbial products into the blood and causes metabolic endotoxemia [105]. Two species (*Bacteroides vulgatus* and *B. dorei*) from the potentially beneficial for T2D genera have been found to upregulate the expression of tight junction genes in the colon leading to reduction in gut permeability, reduction of LPS production and amelioration of endotoxemia in a mouse model [106]. Another probiotic bacterium, *Akkermansia muciniphila,* decreased gut permeability using extracellular vesicles which improve intestinal tight junctions via AMPK activation in epithelium [42]. The outer membrane protein (Amuc_1100) of this bacterium enhances the expression of occludin and tight junction protein-1 (Tjp-1) and improves gut integrity [37]. Amuc_1100 also inhibits cannabinoid receptor type 1 (CB1) in the gut, which in turn, reduces gut permeability and systemic LPS levels [37]. While a specific bacterial component was not determined for *Faecalibacterium prausnitzii*, it was shown that the supernatant from the cultured bacterium enhances the expression of tight junction proteins improving intestinal barrier functions in colitis model [107]. Finally, butyrate, produced by *Faecalibacterium, Roseburia*, also have potential to reduce gut permeability through serotonin transporters and PPAR-γ pathways [101].

3.3. Glucose metabolism

Gut microbiota may also affect T2D by influencing glucose homeostasis and insulin resistance in major metabolic organs such as liver, muscle and fat, as well as by affecting digestion of sugars and production of gut hormones that control this process. For example, one of the potential probiotics discussed above (*Bifidobacterium lactis*) can increase glycogen synthesis and decrease expression of hepatic gluconeogenesis-related genes [108]. In the same report, *B. lactis*

improved the translocation of glucose transporter-4 (GLUT4) and insulin-stimulated glucose uptake.

Lactobacillus gasseri BNR17 also increases GLUT-4 expression in the muscle with potential anti-diabetes effect [109]. *Akkermansia muciniphila* and *Lactobacillus plantarum* reduce the expression of hepatic flavin monooxygenase 3 (Fmo3) [37,93], a key enzyme of xenobiotic metabolism, whose knockdown has been found to prevent development of hyperglycemia and hyperlipidemia in insulin resistant mice [110]. *Lactobacillus casei* can ameliorate insulin resistance by increasing the mRNA level of phosphatidylinositol-3-kinase (PI3K), insulin receptor substrate 2 (IRS2), AMPK, Akt2 and glycogen synthesis in the liver [97,111]. The effect of this particular microbe is not limited to the effects on liver. Indeed, *L. casei* also reduces hyperglycemia via a bile acid-chloride exchange mechanism involving the up regulation of multiple genes, i.e., ClC1-7, GlyRα1, SLC26A3, SLC26A6, GABAAα1, Bestrophin-3 and CFTR [112]. It also decreases the insulin-degrading enzyme (IDE) in the caco-2 cells and insulin-like growth factor binding proteins-3 (IGFBP-3) in the white adipose tissue [97,111,113]. *L. rhamnosus*, another lactobacillus species, increases adiponectin level in the epididymal fat, thus, improving insulin sensitization [98].

Some species of Lactobacillii and *Akkermansia muciniphila* possess potent alpha-glucosidase inhibitory activity that prevents the breakdown of complex carbohydrates and reduces postprandial hyperglycemia [52]. Microbiota and their products can modulate gut hormones and enzymes and improve insulin resistance and glucose tolerance. Butyrate can act as ligand for G-protein coupled receptors (GPCR41 and GPCR43) in the gut and promotes the release of gut hormones GLP-1, PYY and GLP-2 from entero-endocrine L-cells (reviewed in [114,115]). *Bifidobacterium* and *Lactobacillus* produce bile salt hydrolases, which convert primary conjugated bile salts into deconjugated bile acids (BA) that are subsequently converted into secondary BA. Secondary BAs activate the membrane bile acid receptor (TGR5) to induce the production of GLP-1 (reviewed in [114]).

3.4. Fatty acid oxidation, synthesis and energy expenditure

Increasing fatty acid oxidation and energy expenditure and reducing synthesis of fatty acids ameliorates obesity and consequently T2D [116]. *Akkermansia muciniphila, Bacteroides acidifaciens, Lactobacillus gasseri* and short chain fatty acids have been reported to increase fatty acid oxidation in the adipose tissue.

For example, *Akkermansia muciniphila* has been found to increase the levels of 2-oleoyl glycerol (2-OG), 2-palmitoylglycerol (2-PG), 2-acylglycerol (2-AG) in the adipose tissue which increase the fatty acid oxidation and adipocyte differentiation [39]. Furthermore, *Bacteroides acidifaciens* also improves fatty acid oxidation in the adipose tissue via TGR5-PPAR-α pathway [25]. Likewise, butyrate can promote fatty acid oxidation and thermogenesis by inhibiting the histone deacetylation process in the muscle which increases energy expenditure partially by promoting mitochondrial functions in the muscle [117]. In liver and adipose tissue, butyrate and other two SCFAs, propionate and acetate, decrease the expression of PPAR-γ [118] which in turns increases fatty acid oxidation. *Lactobacillus gasseri* has been shown to reduce obesity by increasing the fatty acid oxidation genes and reducing fatty acid synthesis related genes [109]. Serum level of malonidialdehyde, a marker of oxidative damage of lipids, has been found to be reduced by *Akkermansia muciniphila* and *Lactobacillus casei* in diabetic rodents [87,96]. Hence, members of microbiota with beneficial effect on T2D modulate fatty acid metabolism and associated energy expenditure in the host that results in alleviation of obesity and accompanying T2D.

3.5. Combined effects of bacteria

Besides the above-mentioned mechanisms, some microbes can also affect the host physiology by increasing other potential beneficial microbiota or by cross-feeding. Several species of Bifodobacterium were shown to have cross feeding interaction with other microbiota like Faecalibacterium and Roseburia [119,120]. *Lactobacillus rhamnosus* can increase Bifidobacterium abundance in the cecum of rats [98]. *L. casei* has been found to increase the butyrate producing bacteria [97,111].

4. Contribution of microbiota to the success of drug therapy for T2D

The interplay of drugs and gut microbiota is receiving much-deserved interest (reviewed in [121]). It is well known that antibiotics [122,123], non-antibiotic drugs [124] and anti-diabetic drugs (Table 2) can modulate microbiota and improve diabetes. Similarly, the baseline microbiota can positively and negatively affect the pharmacokinetics and pharmacodynamics of drugs and numerous chemicals via a variety of mechanisms (reviewed in [125]). Fewer studies, however, have examined how altering gut microbiota (via pre- and/or probiotics) changes the effects of anti-diabetic drugs.

One recent study examined effects of a probiotic *Bifidobacterium animalis* ssp. *lactis* 420, prebiotic polydextrose and their combination with sitagliptin in diabetic mice [126]. The combination of sitagliptin with pre- and probiotics was effective in reducing several T2D parameters. A similar study in Zucker diabetic rats observed that combining prebiotic polysaccharide with the antidiabetic drugs metformin and sitagliptin reduced hyperglycemia and adiposity compared to using only the drugs [127]. In another study, streptozotocin-induced diabetic mice were treated with a combination of a prebiotic and metformin. Improvements in fasting blood glucose, glucose tolerance and insulin resistance were observed with the combined therapy, as compared to metformin or MOS alone [128]. Thus, a new direction in the microbiome research has emerged focused on the interaction between anti-diabetic drugs and microbiota. These studies should answer important questions such as (1) how different anti-diabetic drugs affect microbiota; (2) which characteristics of gut microbiota are underlying different responses to anti-diabetic drugs; and (3) which co- pre- and probiotics are needed to improve response to medication.

5. Outstanding questions

T2D is a multi-organ, heterogeneous, multi-factorial disease making the dissection of causative microbes from the gut microbiome challenging. In human studies, confounding factors like geographic location, race, culture, health status and drug-use lead to inconsistency in identifying microbiota associated with T2D [1]. Moreover, due to challenges in sampling from the intestine of humans, most studies use stool samples for microbiota analysis. However, the stool microbiota profile does not fully reflect the gut microbiome. Furthermore, most studies focused on genomics, rarely studying the transcriptome, proteome or metabolome. Even at the genomic level, deep shotgun sequencing is expensive, making marker-based amplicon sequencing such as 16S rRNA gene prevailing. Further, the existing sequencing and analysis technologies rarely identify (annotate) microbes at species or strain levels. Considering that the functional capacity varies between strains from the same species, identification of microbes and microbial genes associated with disease is challenging.

A significant problem in the field is that the majority of human association studies do not attempt to infer microbes that may have contributing and/or causal role in T2D. Although inference of causality is a complex statistical problem, it is possible for host-microbiome interactions. Indeed, new approaches, such as Transkingdom Network Analysis [122] and novel application of Mendelian Randomization methods [129], have been recently developed and validated to answer which microbes and microbial genes/pathways are in control of host physiological processes.

Table 2
Contribution of microbiota to the success of therapy of T2D.

Anti-diabetic Drug	Effects on Microbiota Promotes	References (PMID)	Reduces	References (PMID)
Biguanides (Metformin)	*Akkermansia muciniphila, Escherichia,Bifidobacterium adolescentis, Lactobacillus, Butyrivibrio, Bifidobacterium bifidum, Megasphaera, Prevetolla, Escherichi-Shigella, Erysipelotrichaceae incertate sedis, Fusobacterium, Flavonifractor, Lachnospiraceae, Lachnospiracea incertae sedis, and Clostridium XVIII and IV*	23804561, 28530702, 25038099, 27999002, 29056513, 30261008, 30815546, 29789365	*Intestinibacter, Romboutsia, Peptostreptococcaceae_unclassified, Clostridiaceae_1_unclassified, Asaccharospora, Alistipes, Oscillibacter, Bacteroides, Parabacteroides, un-Ruminococcaceae*	28530702, 30261008, 29789365
Alpha-glucosidase Inhibitors (eg. Acarbose, voglibose, miglitol)	Lactobacillus, Faecalibacterium, Dialister,Subdoligranulum, Allisonella, *Megasphaera,* Bifidobacterium, Enterococcus, faecalis	28130771, 29176714, 25327485	*Butyricicoccus, Phascolarctobacterium,Ruminococcus, Eggerthella, Bacteroides, Oribacterium, Erysipelotrichaceae,Coriobacteriaceae*, Bacteroides	28130771, 28349245, 29176714, 25327485
GLP-1 Receptor agonist(eg. Liraglutide)	*Akkermansia muciniphila, Bacteroides acidifaciens, Lachnoclostridium, Flavonifractor, Ruminococcus_gnavus,Allobaculum, Turicibacter, Anaerostipes, Lactobacillus, Butyricimonas, Desulfovibrio*	30815546, 30292107, 29171288, 27633081	*Helicobacter, Prevotella, Ruminococcaceae, Christensenellaceae, Roseburia, Candidatus Arthromitus, Marvinbryantia,Incertae Sedis*	30292,107,29171288, 27633081
Thiazolidinediones (Pioglitazone)			Proteobacteria	27751827
DPP-4 Inhibitors (Vildagliptin, sitagliptin,saxagliptin)	Lactobacillus, *Streptococcus, Bacteroides acidifaciens, Streptococcus hyointestinalis, Erysipelotrichaceae, Allobaculu, Turicibacter,Roseburia*	29797022, 29036231, 27633081, 27631013	Oscillibacter, Ruminiclostridium_6, *Anaerotruncus, Kurthia,Christensenellaceae, Prevotellaceae, Bacteroides, Prevotella,Blautia,*	29797022, 29036231, 27633081, 27631013
SGLT2 Inhibitors (eg. Dapagliflozin)	Akkermansia, Enterococcus	29703207	*Oscillospira*	29703207

Finally, challenges related to animal studies testing effects of microbiota on diabetes hamper progress. First, discrepancies between results caused by differences between microbiomes of otherwise genetically identical animals is one problem. Second, current advanced technologies in gnotobiotics such as studies of germfree and mono/oligo-colonized animals are currently incompatible with functional metabolic studies employing metabolic cages and hyperinsulinemic-euglycemic clamp techniques. Our research community should overcome these technical challenges and develop robust experimental systems to validate predictions coming from human studies and investigate mechanisms of host-microbiota interactions in metabolic diseases.

Future research is needed to develop new diagnostic, preventive and therapeutic microbiota tools for personalized/precision medicine of T2D. First, design of microbiome studies will need to account for clinical, molecular, and genetic as well as drug response diversity of T2D patients stratifying patient populations for analyses. Second, non-invasive approaches to collect microbiota samples from different sites of intestinal tract are needed as fecal material is limited in representation of gut microbiota. Third, while it is easier to focus on individual causal microbes, identifying combination of microbes is required to truly capture the community-level dynamics of the gut microbiota. In addition to taxon-based analysis, grouping microbes by function regardless of taxonomic similarity and function-based analysis should be pursued. Accordingly, we anticipate development of a new generation of analytical methods that will model cause-effect relationships and infer targets of therapeutic interventions. Finally, in order to test new drugs and probiotics as well as drug-microbiota interactions, well-defined gnotobiotic models, specifically humanized microbiota, will become a main tool in animal studies.

6. Conclusion

Despite multiple studies supporting the importance of gut microbiota in pathophysiology of T2D, the field is in early stage. Currently, we have reached a point in our understanding that some microbial taxa and related molecular mechanisms may be involved in glucose metabolism related to T2D. However, the heterogeneity of T2D and redundancy of gut microbiota do not promise simple interpretations (e.g. low diversity) and easy solutions (such as fecal transplant from non-diabetic/non-obese donor). In contrast, we should work towards precision/personalized medicine selecting anti-diabetics and probiotics for a given patient based on the combination of her/his mammalian and microbial genomes.

7. Search strategy and selection criteria

PubMed and Google Scholar literature searches were performed. To identify gut microbiome composition of T2D patients, articles between 2006 and 2018 were included with combinations of the terms “T2D”, “Glucose”, “gut” “Microbiome” “16S rRNA”, “metagenomics”, and “sequencing”. Additional papers relevant to our research were manually sought through bibliography search. Inclusion criteria in our review were (1) Human case-controlled studies; (2) articles focused on T2D (3) gut microbiota quantified from stool samples; (4) Glucose testing performed during the study (5) Either 16S rRNA gene sequencing or metagenomic sequencing performed in stool samples.

Google scholar and PubMed found 42 papers relevant to our focus. Articles were rejected if it was determined from the title and the abstract that the study failed to meet the inclusion criteria. Any ambiguities regarding the application of the selection criteria were

resolved through discussions between at least 3 researchers involved. Each publication was an academic and peer-reviewed study.

Majority (79%) of studies utilized 16S rRNA gene sequencing with V3 and V4 regions most frequently (33% and 42%, respectively) targeted for sequencing (Supporting Table 1). Human subjects across all studies had mean age of 53 years (standard deviation 10 years) and were equivalently distributed between sexes. On average, patients had body mass index 28.3 ± 3 whereas controls 25.8 ± 4.

We searched for mouse colonization studies for the top 8 microbes found in the human-case studies. Articles between 1997 and 2018 were included with combinations of the terms "Mouse", "Glucose", "[*selected microbe*]". Selected microbes included: Bacteroides, Bifidobacterium, Lactobacillus, Blautia, Faecalibacterium, Ruminococcus, Roseburia, and Fusobacterium. Inclusion criteria were (1) Mouse colonization studies; (2) Articles focused on T2D; (3) Glucose testing performed during the study. We also analyzed the literature on *Akkermansia muciniphila*, though it is in the species level, because of its recent emergence as an important potential probiotic microbe.

Similar to the mouse colonization study literature search, we searched for results from clinical trials with microbes/probiotic supplementation. Inclusion criteria were: (1) Human Clinical study w/ microbes/probiotic supplementation; (2) Glucose testing performed during the study; and (3) Microbes or Probiotics from genera identified in our papers as frequently found in human association studies.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2019.11.051.

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