Bi-directional drug-microbiome interactions of anti-diabetics

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Abstract

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Type 2 diabetes (T2D) has become a global epidemic. Although several drugs are available to manage T2D, problems associated with person-to-person variability in drug efficacy and potential side-effects remain unresolved. Owing to the emerging role of the gut microbiome in obesity and T2D, the interaction between gut microbes and anti-diabetic drugs and its influence on drugs’ functions remains of immediate research interest. On one hand, drugs can manipulate gut microbiome composition and metabolic capacity. Conversely, the metabolic activities of the microbiome and its metabolites can also influence drug metabolism and effects. Hence, understanding this bi-directional drug-microbiome interaction and how it influences the clinical outcomes of antidiabetic drugs can pave the way to develop next-generation strategies to ameliorate diabetes. This review presents evidences demonstrating the putative interactions between anti-diabetic drugs and the gut microbiome, and discusses the potential of microbiome modulators to manipulate drug-microbiome interactions and the drug metabolism.

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Abbreviations: AGIs, α-Glucosidase inhibitors; AMP, adenosine monophosphate; AMPK, AMP-kinases; BCCA, branched-chain amino acid; cAMP, cyclic AMP; DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like protein-1; HbA1c, hemoglobin A1c; HFD, high-fat diet; HIF-HSD, high-fat-high-sucrose diet; IR, insulin resistance; LPS, lipopolysaccharide; MS, multiple sclerosis; PPAR, peroxisome proliferator-activated receptor; SCFAs, short-chain fatty acids; SGLT, sodium-glucose cotransporters; SGLT2, sodium-dependent glucose transport-2; T2D, type-2 diabetes; IR, insulin resistance; TLR, toll-like receptor; T2Ds, thiazolidinediones.

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1. Introduction

Type-2 diabetes (T2D) has recently become a global pandemic, largely due to increasing degrees of obesity and a sedentary lifestyle. T2D is a multifactorial syndrome characterized by carbohydrate/fat metabolism abnormalities and often includes hyperglycemia, hypertension, and abnormal cholesterol profiles. Different metabolic organs regulate/influence diabetic hyperglycemia differently, e.g., brain via appetite, kidney via glucose reabsorption, liver via gluconeogenesis, muscle/adipose tissue via glucose uptake, pancreas via insulin, and gut via sugar absorption and gut hormones (Fig. 1). Many anti-diabetic drugs normalize blood glucose by targeting these organs: e.g., gut hormones (e.g., glucagon-like protein-1; GLP-1) mimetic and dipeptide-4 (DPP-4; a GLP-1 degrading enzyme) inhibitors suppress appetite in brain; sodium-dependent glucose transport-2 (SGLT2) inhibitors block renal glucose reabsorption; metformin (a biguanide) reduce hepatic gluconeogenesis; thiazolidinediones (TZDs; PPAR-γ agonists) increase glucose uptake in skeletal muscles and adipose tissues and lipolysis; sulfonylureas (SU) increase pancreatic insulin secretion (Fig. 1). Emerging discoveries indicate that the gut microbiota (bacterial communities inhabiting our intestine) play an important role in the development of obesity, metabolic syndrome and T2D.

Human gut microbiota is predominated by bacterial phyla Firmicutes and Bacteroidetes, followed by Actinobacteria, Proteobacteria and Verrucomicrobia [1]. These bacteria affect host metabolism, immunity, and brain function, manifesting their indispensableness to human health. One main function of gut microbiota is to metabolize non-digestible carbohydrates into short-chain fatty acids (SCFAs; e.g., acetate, propionate, butyrate) and regulate host metabolism. Hence, perturbations in microbiota (gut dysbiosis) can instigate diseases not only of gut but also of other organs including brain, heart, pancreas, liver, adipose tissues, muscles and kidneys [2]. Gut dysbiosis is known to instigate obesity and T2D [2]. For example, energy-rich diets and obesity involve increased intestinal Firmicutes-Bacteroidetes ratio in rodents and humans [1,3,4]. Likewise, T2D patients have altered gut microbiota with reduced butyrate-producing genera (e.g., Roseburia, Subdoligranulum, Clostridiales) wherein metformin-treatment reduces/reverses changes in Firmicutes population [5]. While T2D treatments

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Fig. 1. Metabolic organs contributing in diabetic hyperglycemia, and targeted mechanisms of antidiabetic medications. (a) Increased appetite by the brain can contribute to hyperglycemia, and is inhibited by glucagon-like peptide-1 receptor agonists (GLP1-RA). (b) Elevated glucose reabsorption by the kidneys participates in hyperglycemia, and SGLT2i (Sodium-Glucose co-transporter 2 inhibitors) blocks glucose reabsorption in kidneys. (c) Enhanced endogenous hepatic glucose production leads to hyperglycemia, and TZDs (thiazolidinediones); Met (metformin), and GLP1-RA inhibit this process. (d) Decreased blood glucose uptake by the skeletal muscle contributes to hyperglycemia, and its inhibition is targeted by TZDs and GLP1-RA. (e) Augmented lipolysis in adipose tissue increases hyperglycemia, and is inhibited by TZDs and Orlistat. (f) Abnormal insulin secretion from pancreas contributes in diabetic hyperglycemia, and is inhibited by SUs (sulfonylureas) and GLP1-RA. Glucagon secretion by pancreas can also lead to hyperglycemia and is inhibited by GLP1-RA and DPP-4i (dipeptidyl peptidase-4 inhibitors). (g) DPP-4 enzymatic activity in circulation participates in blood hyperglycemia, and is inhibited by GLP1-RA. (h) Increased glucose absorption in the gut can contribute to hyperglycemia, and is inhibited by AGIs (alpha-glucosidase inhibitors).
focus primarily on achieving normoglycemia by restoring insulin availability/sensitivity, carbohydrate gastrointestinal absorption, or glucose urinary excretion; some T2D therapies might be functioning via gut dysbiosis amelioration. For example, metformin, alters gut microbiome in rodents and humans, in a way that contrasts with high-fat diet (HFD) effects [6]. Not only do anti-diabetic drugs influence the gut microbiome, but gut microbiome also influences the metabolism of drugs and xenobiotics, thereby affecting patients’ responses. Several orally-administered drugs and xenobiotics, before being absorbed in bloodstream, are encountered/processed by intestinal microbial enzymes, and hence, the gut microbiome’s metabolic capacity could influence the absorption and function of these drugs by making them pharmacologically active, inactive or even toxic [7]. Thus, this drug-microbiome interface could also influence host’s overall health. The present review discusses such potential interactions between the anti-diabetic drugs and gut microbiome, and contemplates how gut microbiome can contribute to drugs’ efficacy and variability in clinical practice. Indeed, the decipherment of this drug-microbiome interface can facilitate novel precision-medicine approaches against T2D.

2. Role of gut bacterial metabolites in the regulation of host metabolism

Gut microbiome affects host metabolism through several mechanisms, viz. catabolism of dietary toxins/carcinogens, fermentation of indigestible nutrients, synthesis of micronutrients, and facilitating the absorption of electrolytes and minerals [8]. SCFAs are one of the most studied bacterial products due to their suggested health benefits. For example, fiber-rich diet is associated lower risk of obesity [9], whereas gut microbiome of diabetic patients has fewer SCFA-producing bacteria [10]. In mice, the dietary supplementation of butyrate (one of the most-studied and beneficial SCFAs) prevents weight gain and improves insulin sensitivity by increasing energy expenditure and decreasing food intake [11], suggesting that SCFAs might prevent HFD-induced obesity and insulin resistance (IR) by causing a shift from lipogenesis to fatty-acid oxidation in liver and adipose tissue [12]. Furthermore, butyrate and propionate may also induce intestinal gluconeogenesis, which can act through an intestine–brain neural circuit to improve peripheral glucose production and insulin sensitivity [13]. Interestingly, acetate can also act on the parasympathetic nervous system to increase food intake and promote glucose-stimulated insulin secretion in rodents [14,15]. Whereas, in HFD-fed mice, intravenous and colonic administration of acetate reduces food intake and weight gain [16]. However, it remains undetermined if these contradictory effects of acetate in rats vs. mice are due to host species-specific responses to acetate. For instance, in humans, acetate is associated with increased short-term subjective satiety ratings [17] and reduced body-weight [18].

Besides increased energy harvest and bacterial metabolites produced during food metabolism, other potential mechanisms linking gut microbiome to obesity may include chronic low-grade inflammation and endotoxemia. Gut bacteria can instigate obesity- and IR-associated inflammatory state through lipopolysaccharide (LPS; a component of gram-negative bacterial cell-wall), which triggers inflammation by binding to toll-like receptor-4 (TLR-4) complex at the surface of innate immune cells. Deletion of TLR-4 prevents HFD-induced IR, suggesting that TLR-4 is implicated in metabolic diseases [19]. HFD-induced obese mice demonstrate fewer gut bifidobacteria and eubacteria and increased circulating LPS levels [20]. In humans, a similar-grade endotoxemia associated to IR, and a high-fat-high-carbohydrate meal induces significant elevations in postprandial plasma LPS [21], hinting that endotoxemia might play a pathological role in obesity-associated inflammatory state and that the food ingestion may affect plasma endotoxin levels. Studies have also demonstrated the association between fasting serum branched-chain amino acid (BCAA) levels and incident T2D [22], the normalization of BCAA levels in obese individuals after bariatric surgery [23], and the development of IR in rats after BCAA-diet supplementation [24], suggesting a potentially causative role of BCAAs or their metabolites in metabolic disorders. Gut microbiome might also independently contribute to the elevated serum BCAA levels in humans with IR [25]. Association between gut microbiome functions—including BCAA biosynthesis—and IR are largely driven by specific species including Prevotella copri and Bacteroides vulgatus, suggesting that these species may directly influence host metabolism [25]. Hence, gut dysbiosis may potentially affect serum metabolome and contribute to IR through pathways involving BCAAs.

3. Impact of antidiabetic drugs on the gut microbiome configuration

Given the importance of drug-microbiome interactions, we assembled evidences demonstrating the interactions of some of the most commonly used antidiabetic drugs with the gut microbiota while treating hyperglycemia or T2D (summarized in Fig. 2 and Table 1).

3.1. Biguanides

Among biguanides, metformin is used as first-line treatment in newly diagnosed T2D patients (Fig. 1c), and ameliorates glycemic control and cardiovascular mortality in overweight T2D patients and can even prevent T2D. Although, the precise mechanism(s) of action remains unclear, metformin’s glucose-lowering effects are known by decreased hepatic gluconeogenesis, increased glycogenesis, reduced intestinal glucose absorption, and increased glucose uptake by muscle cells and adipocytes, via activation of AMP-kinase dependent and independent pathways [reviewed in [26–29]]. In addition, accumulating evidences suggest that metformin also acts through pathways in the gut and its microbiome [30]. Multiple evidences suggest that metformin modulates gut microbiota [30] in humans and HFD-fed rodents and improves glycemia along with increased abundance of mucus-degrading gut bacteria, namely Akkermansia muciniphila [6]. Similarly, other studies have demonstrated that metformin increases the abundance of A. muciniphila and Clostridium cocleatum in HFD-fed mice [31]. Increased abundance of A. muciniphila by metformin may not only be correlated, since administration of A. muciniphila alone improves glucose tolerance in HFD-fed mice [6]. A recent study demonstrated that A. muciniphila’s cell-wall consists of an active ingredient that mimics metformin’s action to reduce obesity and diabetes in a rodent model [32].

Although, several studies have identified A. muciniphila as a potential mediator of the glucoregulatory effects of metformin, other studies report that the abundance of Akkermansia in the upper small intestinal luminal contents remain unchanged in response to 3-day HFD-feeding with or without metformin pretreatment [33]. The differences between these findings could be due to a lower abundance of this genus in the upper small intestine, as Akkermansia has been documented to colonize more efficiently in the cecum and colon compared to the small intestine [34]. In addition, a longer metformin treatment regimen and HFD-feeding may be required to induce significant changes in Akkermansia abundance, as previous studies detailing the effect of metformin on Akkermansia have used a chronic treatment protocol [5]. Still, another study has observed a decrease in Akkermansia in T2D patients after metformin treatment, and hence, further research is required to specify the role of Akkermansia with reference to metformin and T2D [35]. Other studies, instead, have found that HFD decreases the upper small intestinal abundance of Lactobacillus, while this effect is partially reversed with metformin pretreatment [33]. This is consistent with previous work showing that metformin increases the abundance of Lactobacillus in HFD-fed rodents [31]. Thus, in addition to increasing the abundance of A. muciniphila in the lower intestinal tract [36], metformin may increase the abundance of Lactobacillus in the upper small intestine, which could both contribute to the anti-diabetic effect of metformin.

Along with the modulation of microbiome composition, metformin treatment can also improve the microbiome metabolic function i.e., by
increasing the population of SCFA-producing bacteria including *Allobacum*, *Bacteriodes*, *Blautia*, *Butyricoccus*, and *Phascolarctobacterium* in the gut [37]. These studies indicate that metformin can modify bacterial diversity, which contrasts the effects of a HFD, and selectively increases the abundance of specific bacteria in HFD-fed mice, while also altering multiple metabolic pathways in the gut microbiota, such as increasing those for sphingolipid and fatty acid metabolism [31]. One study involving treatment-naive T2D individuals showed that metformin administered over varying amounts of time results in altered abundance of *Escherichia* and *Intestinibacter* as well as SCFA-producing bacteria such as *Bifidobacterium adolescentis* [36]. This study involving newly diagnosed T2D individuals showed that metformin, but not calorie restriction, had rapid effects on gut microbiota composition and function in association with reduced HbA1c and fasting blood glucose levels. Fecal analysis demonstrated dramatic shifts in the composition of the gut microbiota after 2 and 4 months of metformin treatment in individuals with newly diagnosed T2D, particularly significant changes in *Escherichia* and *Intestinibacter* abundance across all sampling points in the metformin-treated group [36]. It was also shown that metformin promoted the growth of *B. adolescentis* both in-vivo and in-vitro using pure cultures which can be significant because previous findings have shown that supplementation with *B. adolescentis* in a rodent model of the metabolic syndrome can increase insulin sensitivity [38]. Interestingly, the study did not observe any significant correlations between HbA1c levels and *A. muciniphila* abundance. In addition, it was found that the transfer of the fecal microbiota from metformin-treated individuals to germ-free mice resulted in improved glucose tolerance in recipients. This indicates that metformin-adapted microbiota could contribute to the beneficial effects of metformin on glucose homeostasis. To examine the microbial mediation of the therapeutic effects of metformin, one study compared metformin-treated and -untreated T2D subjects to characterize the effect of the treatment in more detail. Univariate tests of the effects of metformin treatment showed a significant increase of *Escherichia* spp. and a reduced abundance of *Intestinibacter* spp. [5]. These significant microbiome alterations were consistent with well-known side effects of metformin treatment, including reduced intestinal lipid absorption, LPS-triggered local inflammation, and butyrate production, which has been shown to increase the intestinal gluconeogenesis gene expression [13]. In rodents, the net result of increased intestinal gluconeogenesis is a beneficial effect on glucose and energy homeostasis with reductions in hepatic glucose production, appetite and body-weight [5]. Another recent study examined the contributions that some intestinal microbes have on the host intestinal nutrient pool. The four intestinal microbes examined were *Escherichia* spp., *A. muciniphila*, and *Subdoligranulum variabile*, which were previously found to be increased after metformin, as well as *Intestinibacter bartlettii*, which was found to be decreased after metformin treatment [39]. Using Genome-scale metabolic models to elucidate bacterial metabolism and effect on the host intestinal nutrient pool, this study suggested that *Escherichia* sp. and *S. variabile* may contribute to the production of important SCFAs such as acetate and butyrate, respectively, involved in the host physiology. Hence, the

Fig. 2. Effects of antidiabetic drugs on the relative abundance of gut microbes. ↑: increased relative abundance; ↓: decreased relative abundance; TZD: Thiazolidinedione; AGI: Alpha-glucosidase inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; DPP-4i: Dipeptidyl peptidase-4 inhibitor; ITF: Inulin-type fructans; SCFA: short-chain fatty acids.
Summary of the effects of antidiabetic drugs on the gut microbiota.

| Drug                        | Model                  | Major findings                                                                 | Reference |
|-----------------------------|------------------------|-------------------------------------------------------------------------------|-----------|
| Metformin                   | Rodent: C57BL/6 mice N = 24 | • Improvement in glucose tolerance, fasting glucose levels in HFD-fed mice       | 7         |
|                             |                        | • Decreased proportion of Akkermansia and Alistipes genera and increased Anoerenoruncus, Lactobacillus, Porabacteroides, Odoribacter, Lawsonia, Blautia, and Lactonifactor see in HFD control mice were reversed by Metformin |           |
|                             |                        | • HFD decreased abundance of Akkermansia                                        |           |
|                             | Rodent: C57BL/6 mice N = 41 | • Decreased serum glucose levels after metformin treatment in HFD mice         | 33        |
|                             |                        | • Decreased serum total cholesterol levels in female mice, no change in male mice with HFD |           |
|                             |                        | • Metformin in HFD group increased composition of phylum Bacteroidetes, Verrucomicrobia |           |
|                             |                        | • In HFD group treated with metformin, Coprococcus spp. increased in males while Clostridium spp., Bacteroides spp., and members of family Lactobacillaceae and the class Bacteroides increased in females |           |
|                             |                        | • A. muciniphila negatively correlated with serum glucose levels                |           |
|                             |                        | • Clostridium orbiscindens showed negative correlation with body weight        |           |
|                             |                        | • Decreased bacterial diversity during metformin treatment, even more significant than dietary change |           |
|                             |                        | • Increased abundance of A. muciniphila and Clostridium cocleatum with metformin treatment in HFD group |           |
|                             | Rodent: SPF Wistar rats N = 50 | • Attenuated increase of body weight and inhibited accumulation of body fat in HFD rats | 40        |
|                             |                        | • Metformin significantly reduced richness and diversity of gut microbiota    |           |
|                             |                        | • Significant enrichment of Blautia, Bacteroides, Butyricoccus, Phascolarctobacterium, and Parabacteroides, most of which are SCFA-producing bacteria |           |
|                             |                        | • Inhibiting effects on Clostridium XIVa, Flavonifractor, Lachnocloacae incertae sedis, Roseburia, Clostridium XI |           |
|                             | Rodent: Sprague-Dawley Rats N = 20 | • Abundance of Akkermansia in the upper small intestinal luminal contents remained unchanged in response to a 3-day HFD feeding, both with and without metformin treatment | 64        |
|                             |                        | • HFD feeding decreases upper small intestinal abundance of Lactobacillus, which is partially reversed by metformin pre-treatment |           |
|                             | Rodent: C57BL/6 mice N = 40 | • Composition of Bacteroidetes in HFD group was significantly lower than that in normal diet (ND) group | 62        |
|                             |                        | • Metformin administration to HFD group resulted in increased composition of Bacteroidetes, similar to that in ND group |           |
|                             |                        | • Abundance of A. muciniphila and C. cocleatum increased during metformin treatment of mice on a HFD |           |
| Human: T2D Patients N = 40  |                        | • Metformin promoted the growth of B. adolescentis in vivo                     | 67        |
|                             |                        | • Incubation of fecal samples from treatment-naïve participants with metformin resulted in increased abundance of A. muciniphila |           |
|                             |                        | • Significant increase in A. muciniphila in individuals who received metformin for 4 months |           |
|                             |                        | • Fecal transfer to germ-free mice resulted in improved glucose tolerance in recipients of metformin-altered microbiota |           |
| Human: T2D patients N = 450 |                        | • Metformin treatment significantly inhibited including Alistipes, Oscibibacter, and Bacteroidetes | 66        |
|                             |                        | • Increase in Blautia spp. in metformin-treated group |           |
| Human N = 784               |                        | • Decrease in Akkermansia in T2DM patients after metformin |           |
|                             |                        | • Metformin-untreated T2D was associated with a decrease in Roseburia, Subdoligranulum, and a cluster of butyrate-producing Clostridiales spp. |           |
|                             |                        | • Metformin treatment associated with a significant increase of Escherichia spp. and a reduced abundance of Intestinibacter |           |
| Thiazolidinediones          | Rodent: Male SD rats n = 32 | • HFD led to increase in relative abundance of Proteobacteria | 46        |
|                             |                        | • Pioglitazone administration in HFD rats led to a reduction in relative abundance of Proteobacteria, but not effect on Enterobacteriaceae and Desulfovibrionaceae |           |
|                             | Rodent: C57BL/6 mice N = 21 | • HFD altered spatial segregation of bacteria and microbiota composition. Increased Firmicutes, Verrucomicrobia. Decreased Bacteroidales. | 48        |
|                             |                        | • Treatment with rosiglitazone did not restore microbiota composition of HFD mice to that of Standard Diet mice |           |
|                             |                        | • Treatment of HFD mice with rosiglitazone restored spatial distribution of ileal microbiota compared to SD mice |           |
| α-Glucosidase inhibitors    | Rodent: C57BL/6 mice n = 30 | • Miglitol decreased hepatic cellular lipid accumulation, inflammation and fibrosis in HFHSD fed mice | 51        |
|                             |                        | • Miglitol decreased intestinal transit time |           |
|                             |                        | • Miglitol did not reduce body weight but reduced insulin resistance |           |
|                             |                        | • HFHSD diet decreased percentage of Bacteroidetes and increased percentage of Actinobacteria |           |
|                             |                        | • Increased percentage of Coriobacteriaceae within the Actinobacteria phylum and Erysipefilorichaeae within the Firmicutes phylum were suppressed in the HFHSD fed mice treated with Miglitol |           |
|                             |                        | • Increased abundance of Dialister following acarbose, which was negatively correlated with Hba1c. | 53        |
|                             |                        | • Butyricoccus, Phascolarctobacterium, and Ruminococcus were inhibited |           |
|                             |                        | • When Acarbose was added to anti-diabetic treatment, Bifidobacterium longum was significantly increased compared to anti-diabetic treatment without acarbose | 58        |
|                             |                        | • No significant difference in content of Enterococcus faecalis between group receiving Acarbose and group without acarbose along with anti-diabetic therapy |           |

(continued on next page)
Historically, biguanide, due to its anti-microbial activities, has been used to treat infections in natural healing practices, and such properties of metformin may be the main reason why it modulates the gut microbiome. One clinical trial has shown that the metformin treatment in humans significantly inhibits two functional groups containing potential pathogen-like genera, including Alistipes, Oscillibacter, and Bacteroides, and this inhibition is significantly correlated with improved glucose homeostasis by metformin [35], suggesting that the inhibition of potential pathogen-like bacteria may be involved in some of the commensal and competing behaviors in bacteria and its relation to the production of extracellular compounds such as SCFA and amino acids may play a role in the effects of metformin in the treatment of T2D.

Overall, these studies suggest that the glucose-lowering effect of metformin can be partly attributed to certain species within the gut microbiota that helps metformin function more efficiently. As the mechanisms by which metformin influences the gut microbiota becomes more elucidated, it is likely that the oral administration of metformin has both direct and indirect effects on the gut microbiota.

**Table 1 (continued)**

| Drug                  | Model                          | Major findings                                                                                      | Reference |
|-----------------------|--------------------------------|-----------------------------------------------------------------------------------------------------|-----------|
| GLP-1 Receptor Agonists | Rodent: ApoE −/− C57BL/6 mice N = 60 | • Lagalglutide decreased body weight gain in both normoglycemic and hyperglycemic mice                | 69        |
|                       |                                | • Mean blood glucose level was significantly lower in Lagalglutide-treated mice compared with control |           |
|                       |                                | • Mice being treated with Lagalglutide had the lowest food intake                                    |           |
|                       |                                | • Decreased microbial diversity in Lagalglutide-treated mice on a normal glucose diet; may be          |           |
|                       |                                | attributed to prominent enrichment of Firmicutes, decreased proportion of Bacteroidetes.             |           |
|                       |                                | • Relative abundance of only one obesity-related phylotype (the genus Candidatus Arthomitus)          |           |
|                       |                                | affected by Saxagliptin                                                                             |           |
|                       |                                | • Sitagliptin resulted in a significant reduction of blood glucose while having no impact on body    | 70        |
|                       |                                | weight in HF/HC fed rats                                                                             |           |
|                       |                                | • Relative abundance of Firmicutes treated with Sitagliptin was significantly less than that in the   |           |
|                       |                                | diabetic condition.                                                                                  |           |
|                       |                                | • Relative abundance of Bacteroidetes and Proteobacteria increased in Sitagliptin condition           |           |
|                       |                                | • After Sitagliptin treatment of diabetic rats, Roseburia increased, Blautia decreased, and Clostrid- |           |
|                       |                                | ium showed no change in stools                                                                       |           |
| DPP-4 inhibitors      | Rodent: C57BL/6 J male mice N = 27  | • Vildagliptin decreased Oscillibacter spp., increased Lactobacillus spp. and propionate             | 68        |
|                       |                                | • Reduced ligands of Toll-like receptors 2 and 4                                                    |           |
|                       |                                | • Promoted antimicrobial peptide production and increased cryp depth in the ileum                   |           |
|                       |                                | • Vildagliptin reduced expression of proinflammatory cytokines in the liver                         |           |
| SGLT2 Inhibitors      | Rodent: C57BLKS male mice N = 24 | • Dapagliflozin improved hyperglycemia and reduced circulating markers of inflammation              | 82        |
|                       |                                | • Microbiota richness and diversity reduced in diabetic mice treated with dapagliflozin            |           |
|                       |                                | • Reduced Firmicutes/Bacteroidetes ratio in diabetic mice treated with dapagliflozin                |           |
|                       |                                | • Increased A. muciniphila in diabetic mice treated with dapagliflozin relative to diabetic control  |           |
| Sulfonylurea           | Rodent: Sprague-Dawley male rats N = 24 | • Glibenclamide treatment have mild effects on microbiome α-diversity in Streptozotocin induced   | 75        |
|                       |                                | diabetic rats                                                                                        |           |
|                       |                                | • Glibenclamide treatment increased abundance of Paraprevotellaceae and Prevotella in Streptozotocin|           |
|                       |                                | induced diabetic rats                                                                                  |           |
|                       |                                | • Glipizide have not shown any significant differences on gut microbiome in diabetic patients        |           |
|                       |                                | after 3 months of intervention                                                                       |           |
| Combination therapy (PGX + S/MET) | Human: diabetic N = 43 | • Rats given PolyGlycoPlex (PCX) in conjunction with Sitagliptin and Metformin (S/MET) maintained   | 74        |
|                       |                                | the lowest body weight than all other groups                                                         |           |
|                       |                                | • Rats treated with PCX + MET and PCX + S/MET had the lowest blood glucose concentrations           |           |
|                       |                                | • PCX + S/MET and PCX + ET delayed the progression of diabetes in ZDF rats                            |           |
|                       |                                | • PCX + S/MET was associated with the greatest degree of insulin sensitivity                         |           |
|                       |                                | • Rats treated with PCX + S/MET displayed the highest β-cell mass in the pancreas                    |           |
|                       |                                | • Marked and sustained increase in active GLP1 with PCX + S/MET that was higher than all monotherapies|           |
|                       |                                | • Greatest reduction of C. coccoides (Firmicutes) seen in rats treated with PCX with S/MET           |           |
|                       |                                | • Bacteroides abundance was significantly higher in rats treated with S/MET and control, compared   |           |
|                       |                                | with MET, PCX, and PCX + S/MET                                                                      |           |
|                       |                                | • Bacteroides decreased in the genus Bacteroides, increased in the genus Bacteroides                  |           |
| Prebiotics (inulin-type fructans) | Human: obese women N = 30 | • Treatment with ITF prebiotics, but not placebo, led to an increase in Bifidobacterium and Faecalibacterium prausnitzii, which were both negatively correlated with serum LPS levels. | 108       |

|                          |                          | • ITF prebiotics decreased Bacteroides intestinal, Bacteroides vulgatus, and Propionibacterium       |           |

HFD: high-fat diet; HFHSD: high-fat-high-sucrose diet; ITF: Inulin-type fructans; LPS: lipopolysaccharide; SCFA: short-chain fatty acids; SD: standard diet; SPF: specific-pathogen free; T2D: type-2 diabetes; TG: triglycerides.
beneficial effects of metformin. Interestingly, it was found that metfor-
min impairs folate metabolism in bacteria such as E. coli, and hence,
this may be one potential mechanism through which metformin exerts
its effects on the gut microbiota [40].

### 3.2. Thiadidoniones

Thiadidoniones (TZDs), or glitazones, attenuate and improve IR
in T2D. Because of their ability to restore peripheral insulin sensitivity,
TZDs such as pioglitazone are commonly used clinically in the manage-
ment of T2D. The effects of TZDs, which are attributed to their agonistic
action on the peroxisome proliferator-activated receptor-(PPAR)\(\gamma\), are
detailed in other studies [41–43].

In addition to their antidiabetic properties, TZDs also possess anti-
bacterial activities and may consequently affect gut bacteria. HFD feed-
ing increases the abundance of Proteobacteria, Enterobacteriaceae and
Desulfovibrionaceae in rodents [44], and pioglitazone treatment reduces
the abundance of Proteobacteria in the HFD-fed rats, with no significant
decline in Enterobacteriaceae and Desulfovibrionaceae [44], suggesting
that pioglitazone only partially reverse the HFD-induced gut dysbiosis.
Another study has demonstrated that the gut-associated butyrate-
producing microbes can activate PPAR-\(\gamma\) signaling and prevent a
dysbiotic expansion of potentially pathogenic bacteria belonging to the
genera Escherichia and Salmonella [45], suggesting that antidiabetic
drugs affecting the composition of butyrate-producing microbes in the
gut may play an important role through PPAR-\(\gamma\) signaling pathway.
Lastly, a study found that the HFD-induced gut microbial dysbiosis in-
cluding increased Firmicutes, Proteobacteria and Verrucomicrobia and
decreased Bacteroidetes abundance could be reversed by switching the
mice back to the standard diet or treating them for one week with
rosiglitazone, another TZD [46]. These studies indicate that there is an
interaction between gut microbiota and TZDs, which may possibly be
involved in the antidiabetic effects of TZDs.

### 3.3. \(\alpha\)-Glucosidase inhibitor

\(\alpha\)-Glucosidase inhibitors (AGIs) delay the intestinal absorption and
digestion of non-absorbable complex carbohydrates into absorbable
monosaccharides and reduce postprandial hyperglycemia (Fig. 1h)
[47]. Acarbose, an AGI initially isolated from bacterial cultures, gives a
selective advantage to their bacterial producers in a community where
there is competition for similar nutrients [48].

Given that AGIs impact the nutrient sources of bacteria by altering the
composition and length of time that carbohydrates remain in the in-
testines, it is unsurprising that AGIs can influence the gut microbiota
composition as well. It has been shown that in mice that are fed a
high-fat high-sucrose diet (HHSFD), treatment with Miglitol, an AGI,
not only suppresses IR and liver fat accumulation and shortens
intestinal transit time, but can also result in gut microbiota changes,
thereby suppressing HHSFD-induced increase in the composition of
Erysipelotrichaceae within the phylum Firmicutes and Coriobacteriaceae
within the phylum Actinobacteria [49]. In addition, an in-vitro study
demonstrated that the Acarbose can specifically inhibit the growth of
E. coli (when grown on maltose) by blocking the maltose importer
[50]. In a randomized-double-blind controlled study, Acarbose treat-
ment in 52 Chinese prediabetic patients was shown to increase SCFA-
producing bacteria such as Faecalibacterium, Prevotella, and Lactobacillus
[51], and Lactobacillus treatments are known to ameliorate glycemia
[52–55]. An increase in the abundance of Dialister has also been found
following the Acarbose treatment, which was negatively correlated with HbA1c [51]. Hence, some Dialister species may potentially play a
role in the regulation of glucose metabolism. Another study suggested
that the addition of Acarbose to antidiabetic treatment leads to increase
in the abundance of Bifidobacterium longum [56]. A similar effect was
also seen in the fecal microbiota of hyperlipidemic patients that are ad-
ministered Acarbose, with a significant increase in Lactobacillus and

### 3.4. GLP-1 receptor agonist

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) used in the
treatment of T2D have demonstrated efficacy in improving glycemic
control through numerous physiological effects (Fig. 1c, d, f, g); how-
ever, the precise molecular mechanisms remain largely unclear
[reviewed in [58–61]]. Studies have demonstrated that the GLP-1 RA
can also modulate the gut microbiota. Liraglutide (an injectable GLP-1
RA) has been shown to produce substantial gut microbiota changes
in mice compared to non-treated controls [62], with enrichment of
genera Allobaculum, Turicibacter, Anaerostipes, Blautia, Lactobacillus,
Butyricimonas, and Desulfovibrio accompanied by reduced abundance of
phytotypes mainly within the order Clostridiales (phylum Firmicutes)
and Bacteroidales (phylum Bacteroidetes) [62]. Interestingly, the relative
abundance of all obesity-related phytotypes (viz. Erysipelotrichaceae
Incertae Sedis, Marvinbryantia, Roseburia, Candidatus Arthromitus, and
Parabacteroides) were substantially decreased under liraglutide admin-
istration [62]; whereas in terms of phytotypes associated with leanness,
liraglutide seemed to induce enrichment of Lactobacillus and
Turicibacter [62]. In addition, we have previously demonstrated that a
multi-strain probiotic cocktail called VSL#3 (now Visbiome) can pre-
vent and treat obesity and T2D in mice models via modulating gut
microbiome and its metabolites viz. SCFAs (specifically butyrate) and
increasing intrinsic GLP-1 production from L-cells [55].

### 3.5. DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4), is a proteolytic enzyme found in the
cell membrane of most of the cells in human body with the primary
function of inactivating GLP-1 [63]. Inhibition of DPP-4 with gliptins
such as sitagliptin, vildagliptin, and saxagliptin, prolongs the circulating
half-life of GLP-1, thus enhancing its insulinogetic and glucoregulatory
abilities (Fig. 1f, g). The effects of gliptins are reviewed in previous stud-
ies [64,65]. It is also known that certain commensal gut bacteria exert
DPP-4-like activity [66]. Saxagliptin-treatment in mice increased
Firmicutes abundance, especially in the genus Lactobacillus along with the
genera Allobaculum and Turicibacter [62]. A decrease in the phylum
Bacteroidetes was also observed and was mainly from the genus
Bacteroides and Prevotella [62]. In addition, when comparing liraglutide,
a GLP-1 receptor agonist, saxagliptin treatments have milder effects on
gut microbiome signature. The relative abundance of all obesity-related
phytotypes significantly decreased with liraglutide, while only one phy-
lotype, the genus Candidatus Arthromitus, was affected by saxagliptin
[62]. In observing the relative abundance of phytotypes associated with
a decrease in body-weight, both liraglutide and saxagliptin were
shown to enrich Lactobacillus and Turicibacter [62]. Interestingly,
Lactobacillus possesses inhibitory activity against DPP-4 [67]. Mice receiving a
Western-diet (45% kilojoules from fat and 17% kilojoules from sucrose)
with vildagliptin found that vildagliptin modulates the gut microbiota
composition and its metabolic activities [66]. Vildagliptin decreased
Oscillibacter spp., increased Lactobacillus spp., promoted antimicrobial
peptide production in the ileum, and indirectly reduced hepatic expres-
sion of proinflammatory cytokines [66]. Thus, it is possible that the DPP-
4 inhibitory activity of saxagliptin partially involves the enrichment of
Lactobacilli and decrease in other species such as Oscillibacter. In another
study, administration of sitagliptin in T2D rats decreased abundance of
Firmicutes and Blautia, while increased Bacteroidetes, Proteobacteria and
Roseburia [68]. These studies indicate that the DPP-4 inhibitor mediated
changes in gut microbiome may interact with mechanism(s) that bene-
fit the host in maintaining better glucose homeostasis [68].
3.6. Sulfonylureas

The sulfonylureas (SU) have been important in the treatment of T2D over the past 50 years for their ability to stimulate insulin release in a glucose-independent manner [Fig. 1f] [69–71]. To our knowledge, no study has hitherto examined the direct impact of sulfonylureas on the gut microbiota; however, indirect studies have demonstrated that patients treated with sulfonylureas have increased hippurate (a normal metabolite found in urine, mainly derived from the breakdown of plant phenolics and aromatic amino acids by the gut microflora) and aromatic amino acids in the urine, suggesting that the sulfonylureas may have some effect on the gut microbiota and their ability to metabolize plant phenolics and aromatic amino acids [72]. In addition, some recent studies indicate that SUs like Glebclamide and Glipizide have interactions with gut microbiome [73,74], wherein Glibenclamide showed minor impact on the rat gut microbiome [74] while Glipizide showed no effects on gut microbiome in diabetic human subjects [73]. However, these studies were not focused specifically to illustrate the effects of these sulfonylureas on gut microbiome and hence studies that are more direct are warranted to establish the impact of sulfonylureas on the gut microbiome and vice-versa.

3.7. SGLT2 inhibitors

The two major sodium-glucose cotransporters (SGLTs) i.e., SGLT-1 and –2, found in the kidney, are responsible for the reabsorption of glucose in the renal tubules [75]. Various SGLT2 inhibitors are used as a T2D therapy due to their ability to improve glycemic control by inhibiting re-absorption of glucose filtered through the renal glomerulus [Fig. 1b] [76]. The effects of SGLT2 inhibitors on the gut microbiota or specific gut microbial species remain to be elucidated. As of yet, one recent study found that the dapaglifozin treatment reduces microbiome diversity and richness in control mice, with no effects in diabetic mice. Firmicutes:Bacteroidetes ratio is reduced in dapaglifozin-treated diabetic mice [77]; notably, previous studies have associated reduction in this ratio with a lean phenotype. This study reported that the dapaglifozin-treated diabetic mice show significantly increased body-weight compared to the control mice. The increase in body-weight, however, was thought to be protective because diabetic mice tend to lose weight as the severity of diabetes progresses and medications that improve health outcomes in diabetic mice are known to preserve or even increase the body-weight [78,79]. At species level, A. muciniphila abundance was increased in dapaglifozin-treated diabetic mice, which may be associated with improved metabolic outcomes [77]. Hence, the impact of SGLT2 inhibitors on the gut microbiota is an area of active research.

3.8. Orlistat

Orlistat is a pancreatic and gastric lipase inhibitor that is used in the management of obesity to facilitate weight loss [Fig. 1e]. Orlistat has been shown to reduce the progression of diabetes, especially in those with impaired glucose tolerance [80–82].

Considering the mechanism of Orlistat, there may be an indirect effect on the gut bacteria through a higher input of dietary fat into the colon. However, a study examining the effects of increased dietary fat reaching to the colon after Orlistat treatment reported only minor, non-significant changes in gut microbiome, suggesting that the increased dietary fat does not modify the microbiota composition [83]. However, this study remains inconclusive due to the limitation of short period of Orlistat intervention. Furthermore, while HFD administration has been reported to decrease Bifidobacterium spp. in mice, administration of Orlistat prevented this decline [83]. Another study employing batch-culture fermentation experiments demonstrated no effect of Orlistat in the presence or absence of olive oil on the composition of bacterial communities [84] Hence, the impact of Orlistat on gut microbiome is still uncertain and further studies are needed to establish these facts.

3.9. Combination therapy

Because T2D is a progressive disorder characterized by increasing degree of hyperglycemia and a need to gradually increase the dose to maintain glycemic control, combination therapy has been used to target multiple mechanisms. The most commonly used combinations are those of DPP-4 inhibitors and metformin, metformin-sulfonylureas, and metformin-thiazolidinediones [85]. At present, however, there is limited research on the effects of different combination therapies on the gut microbiome. One study found that the administration of prebiotic polysaccharide PolyGlycopleX (PGX) with metformin alone (MET) or with a combination of sitagliptin and metformin (S/MET) in rodents increases the abundance of Bacteroides, compared to MET, PGX, and PGX + S/MET [86]. All treatments reduced the population of Clostridium coccoides compared to cellulose, with C. coccoides being the lowest in PGX + S/MET-treated rats, suggesting that combination therapy was dominant in decreasing C. coccoides abundance. Bifidobacterium were also very low across all groups [86]. Significantly higher levels of bifidobacteria were seen in MET and PGX compared with C, S/MET and PGX + MET [86]. Lastly, Enterobacteriaceae was significantly higher in PGX compared with all other groups, indicating that different combination therapies used to treat diabetes/hyperglycemia can impact the gut microbiota [86]. However, whether and how these changes help different combination therapies work better or delay resistance in their efficacy in the long term remains unclear.

4. Metabolism of anti-diabetic drugs by the gut microbiome

Orally-administered drugs are absorbed into the circulation through gut epithelia and the fate/efficacy of this course is influenced not only by drug characteristics (e.g., solubility, stability, permeability) but also by the drug metabolism capacity of host and microbiome enzymes [87]. Host enzymes influencing the drug metabolism are well studied but the dynamics of gut microbiome in drug metabolism and efficacy remain unclear. Gut microbiome might play a central role - perhaps even analogous to that of the liver or any other potential organ in the human body - in the efficacy and metabolism of drugs including xenobiotics and other endogenous/exogenous compounds [88,89]. For instance, gut microbes produce hydrophobic by-products via reductive and hydrolytic metabolisms, thus facilitating their absorption from gut into the circulation [88]. Further, the effect, if any, of gut microbiome on drug metabolism may also be influenced by drug- as well as host-related elements, viz. drug absorption in the upper gut, drug’s quantity reaching the distal gut, and enzymes secreted by the gut microbiome [90]. Given that the drug-microbiome interactions could make a drug pharmacologically active, inactive or even toxic, it is imperative to decipher these drug-microbiome interactions pertaining to differences in the absorption and metabolic fates of different drugs and xenobiotics, as well as individual-specific gut microbiome disparities [7] (Figs. 3 and 4).

Nevertheless, due to inadequate data on the metabolism of TZDs, GLP-1 RAs, DPP-4 inhibitors, sulfonylureas, and SLGT2 inhibitors by the gut microbiome, it remains unclear how anti-diabetics are metabolized by the gut microbiome. For example, Acarbose is metabolized exclusively within the gastrointestinal tract, principally by the intestinal bacteria and digestive enzymes [91]. Acarbose, in contact with α-
Amylases and cyclodextrin glucanotransferases (a bacterial enzyme commonly found in the genus *Bacillus*), is converted to longer-chain derivatives and can be regarded as a pro-drug since it can form more active inhibitors by the catalytic activity of its target site [92]. Voglibose, another α-glucosidase inhibitor, is poorly absorbed and is rapidly excreted in stools with no metabolites identified to-date [93]. In contrast, Miglitol is fully absorbed in the gut and cleared unchanged by kidneys [94]. Lastly, though no specific study has linked microbiome with Orlistat metabolism, it is speculated that Orlistat is metabolized primarily within the gastrointestinal wall, forming relatively inactive metabolites [95].

5. Probiotics and prebiotics for the modulation of gut microbiome and metabolism

Probiotics are live microorganisms that, when administered in sufficient amounts, can offer health benefits to the host, including improvements in immune system function. A meta-analysis assessing the efficacy of probiotics in glucose metabolism shows that probiotics can decrease fasting blood glucose and HbA1c levels and improve glucose metabolism [96]. However, how different probiotics and their combinations with different anti-diabetics interact with the gut microbiome remain unclear. The term prebiotics, on the other hand, refers to non-digestible dietary ingredients such as fibers and related oligosaccharides (e.g., inulin, fructo-oligosaccharides, galacto-oligosaccharides) that selectively modulate the growth of beneficial bacteria in the large intestine. For instance, inulin has been associated with positive gut microbiome changes; wherein inulin-type fructans prebiotics, but not placebo, fostered *Bifidobacterium* and *Faecalibacterium prausnitzii* population and decreased *Bacteroides intestinalis*, *Bacteroides vulgatus* and *Propionibacterium*, an effect that associated with lower fat mass, plasma lactate, and phosphatidylcholine levels and suggested that prebiotics can induce subtle changes in the gut microbiome that may impact several key metabolites implicated in diabetes [97].

6. Conclusion and future prospects

Besides gut eubacterial community, various commensal archaea, viruses, and fungi, which otherwise remain understudied, might also influence human health. Archaea such as *Methanobrevibacter* genus and *Methanobrevibacter smithii* have been linked with obesity [98] and increased energy harvest [99], respectively. Thus, such groups may also be a therapeutic target to prevent obesity and T2D. Fecal DNA and RNA viral population has been correlated positively with *Firmicutes* and negatively with *Bacteroidetes* and bifidobacteria [100]. T2D patients also demonstrate higher carriage of specific gut phages [101]. These studies hint that direct or indirect interaction of viral population with host cells might modulate host metabolism. Intestinal fungi are also associated with gut inflammation and Crohn’s disease [102]. HFD-feeding increased dysbiosis in bacterial and fungal taxa [103]. Although the data on gut archaea, fungi and eukaryotes are relatively limited, these studies suggest their possible role in obesity-gut microbiome association and indicate that these microbes together with eubacteria form a highly complex ecosystem in the gut and hence can also influence T2D and drug effects.

Drugs can change the gut microbiome and its metabolites, thus affecting the host metabolic functions (drug-microbiome-metabolism axis). However, the interactions of microbiome with host is bidirectional. For example, Bariatric surgery, a common treatment for morbid obesity, improves host metabolic functions that are tightly correlated with specific GM changes. Furthermore, certain anti-diabetic (e.g., insulin, GLP-1R agonists) may first impact host metabolic function than microbiome. Diabetic people who maintain better glycemia using insulin injections have better health outcomes like reduced cardiovascular diseases and may also have different gut microbiome; hence, such studies are highly warranted. However, Liraglutide primarily improves diabetes that are associated with microbiome changes too, suggesting that drug-metabolism-microbiome axis may also explain the drug-microbiome interactions in regulating diabetes and obesity.
However, more studies are warranted to establish such facts that can help in deciphering these interactions in clinical practice.

Interestingly, supplementation with specific bacteria such as *Bifidobacterium adolescentis* and *A. muciniphila* has shown beneficial effects in T2D rodents. Hence, it would be interesting to examine whether and how such bacteria and probiotics/prebiotics can help increase drug efficacy, eliminate side-effects, and/or ameliorate diabetic complications in humans. Given that the microbiome dysbiosis is implicated in T2D and obesity, research on the characterization of gut bacteria and their metabolites involved in these pathologic states would provide important insights for the development of novel drugs and even personalized medicine. Thus, the modulation of gut microbiome by drugs can represent a target to improve, modify, or reverse the efficiency of current medications for T2D.

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Authors contributions

AW: conducted literature search, compiled and analyzed reports, and wrote parts of manuscript; RN: compiled and wrote part of manuscript; GG: analyzed and interpreted reports, and conceptual and linguistic editing: HY: conceived the idea, helped to analyze and interpret reports, and conceptual and linguistic editing; AW: conducted literature search, compiled and analyzed reports, conceptual and linguistic editing.

Competing interests

Authors declare that they have no competing interests.

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