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## Crosstalk between gut microbiota and antidiabetic drug action

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### Abstract

Type 2 diabetes (T2D) is a disorder characterized by chronic inflated blood glucose levels (hyperglycemia), at first due to insulin resistance and unregulated insulin secretion but with tendency towards global spreading. The gut microbiota is recognized to have an influence on T2D, although surveys have not formed a clear overview to date. Because of the interactions between gut microbiota and host homeostasis, intestinal bacteria are believed to play a large role in various diseases, including metabolic syndrome, obesity and associated disease. In this review, we highlight the animal and human studies which have elucidated the roles of metformin,  $\alpha$ -glucosidase inhibitors, glucagon-like peptide-1 agonists, peroxisome proliferator-activated receptors  $\gamma$  agonists, inhibitors of dipeptidyl peptidase-4, sodium/glucose cotransporter inhibitors, and other less studied medications on gut microbiota. This review is dedicated to one of the most widespread diseases, T2D, and the currently used antidiabetic drugs and most promising new findings. In general, the gut microbiota has been shown to have an influence on host metabolism, food consumption, satiety, glucose homeostasis, and weight gain. Altered intestinal microbiota composition has been noticed in cardiovascular diseases, colon cancer, rheumatoid arthritis, T2D, and obesity. Therefore, the main effect of antidiabetic drugs is on the microbiome composition, basically increasing the short-chain fatty acids-producing bacteria, responsible for losing weight and suppressing inflammation.

**Key words:** Type 2 diabetes; Gut microbiota; Metformin;  $\alpha$ -glucosidase inhibitors; Glucagon-like peptide-1 agonists; Peroxisome proliferator-activated receptors  $\gamma$  agonists; Dipeptidyl peptidase-4 inhibitors; Sodium/glucose cotransporter inhibitors

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**Core tip:** Gut microbiota was found to have an influence on host metabolism, food consumption, satiety, glucose homeostasis, and weight gain. Altered intestinal microbiota composition has been noticed in cardiovascular diseases, colon cancer, rheumatoid arthritis, type 2 diabetes, and obesity. Therefore, the main effect of antidiabetic drugs is on the microbiome composition, basically increasing the short-chain fatty acids-producing bacteria, responsible for losing weight and suppressing the inflammation.

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## INTRODUCTION

Over the last few decades, diseases related to metabolic processes, such as type 2 diabetes mellitus (T2D), obesity, dyslipidemia, hypertension and cardiovascular diseases (CVD) have become the main health problems around the world<sup>[1]</sup>. T2D is a disorder characterized by chronic inflated blood glucose levels (hyperglycemia), at first due to insulin resistance and unregulated insulin secretion but with a tendency towards global spreading. Environmental and genetic factors' contribution are known, but sedentary life style and dietary habits are not the least constituents. Influence of gut microbiota on T2D is also recognized<sup>[2-4]</sup>, although findings differ between surveys. Because of the interactions between gut microbiota and host homeostasis, gut bacteria are thought to play a great role in diseases, including metabolic syndrome<sup>[5-7]</sup>.

The composition and richness of the gut microbiota is modulated by diet, host health, age, ethnicity and genetics, and thus are unique and highly variable among individuals<sup>[3,4]</sup>. Turnbaugh *et al*<sup>[8]</sup> suggest that there is a "core gut microbiome" that could be responsible for proper gut functioning. That core gut microbial profile predominantly consists of bacteria, which belong to the Gram-positive Firmicutes and the Gram-negative Bacteroidetes<sup>[5]</sup>. Nevertheless, the increase of intestinal Firmicutes/Bacteroidetes ratio is observed in both obesity and during consumption of energy-rich diets in humans and animal models<sup>[5,9,10]</sup>. Similar to obesity outcomes, T2D induces a dysbiosis, mainly by reduction in butyrate-producing bacteria<sup>[11,12]</sup> and in *Akkermansia muciniphila*, which is now considered a biomarker for glucose intolerance<sup>[4]</sup>.

The bacterial phylotypes found to be correlated with weight are associated with the phyla Firmicutes (2 families and 11 genera), Bacteroidetes (1 family and 2 genera) and Tenericutes (1 family and 1 genus)<sup>[3,13]</sup>. Among them are five genera affiliated with an increase in weight, including *Erysipelotrichaceae incertae sedis*, *Marvinbryantia*, *Roseburia*, *Candidatus arthromitus*, and *Parabacteroides*<sup>[3,13]</sup>. The phylotypes associated with weight loss were of the genera *Lactobacillus*, *Turicibacter*, *Anaerostipes*, *Coproccoccus*, *Blautia*, *Oscillibacter*, and *Clostridium*<sup>[3,13]</sup>. For instance, Vrieze *et al*<sup>[14]</sup> showed that obesity was associated with modifications in the abundance, diversity, and metabolic function of the gut microbiota, mostly represented as a higher quantity of Firmicutes and a reduced abundance of Bacteroidetes in animal experiments.

Furthermore, one main function of the gut microbiota is to devastate nondigestible carbohydrates into short-chain fatty acids (SCFAs), mostly propionate, acetate and butyrate<sup>[15]</sup>. Lines of evidence have suggested that intestinal microbiota and SCFAs exert positive effects on glucose-lowering agents in T2D. Glucose-lowering agents can also alter gut microbiota<sup>[16]</sup>, thus meliorating glucose metabolism and energy balance; they also have an influence on the production of SCFAs, thereby providing beneficial effects<sup>[12]</sup>. Perhaps mechanisms may also affect gene expression, levels of inflammatory cytokines, and the regulation of SCFA synthesis. Furthermore, gut microbiota may attenuate side effects caused by glucose-lowering agents, which is an advantage for diabetic patients. It has even been suggested that human gut microbiota express some enzymes which are capable of binding to and transforming a wide spectrum of bioactive substances<sup>[17,18]</sup>.

Orally-taken medicines reach the gastrointestinal tract and encounter the intestinal microbiota. It has been shown that microbiota-encoded enzymes have the ability to metabolize xenobiotics and to impact the pharmacogenetics of drugs and their

bioavailability<sup>[19,20]</sup>. Accordingly, the gut microbiota may have an influence on drug effectiveness.

Moreover, supplementation with probiotic strains and their combination with nutraceuticals has been demonstrated to provide health benefits in obesity and associated diseases in both animal<sup>[21,22]</sup> and human studies<sup>[23-25]</sup>.

In this review, we will focus on gut microbiota alterations in obese and T2D patients and its response to currently used antidiabetic drugs (Figure 1). Below, we highlight the animal and human research that has begun to elucidate the role of metformin (1,1-dimethylbiguanide hydrochloride), alpha-glucosidase inhibitors ( $\alpha$ -GIs), glucagon-like peptide-1 (GLP-1) agonists, peroxisome proliferator-activated receptors (PPARs) activators, inhibitors of dipeptidyl peptidase-4 (DPP-4) and sodium/glucose cotransporter (SGLT-2), and other less studied medications on gut microbiota.

## GUT MICROBIOTA AND METFORMIN

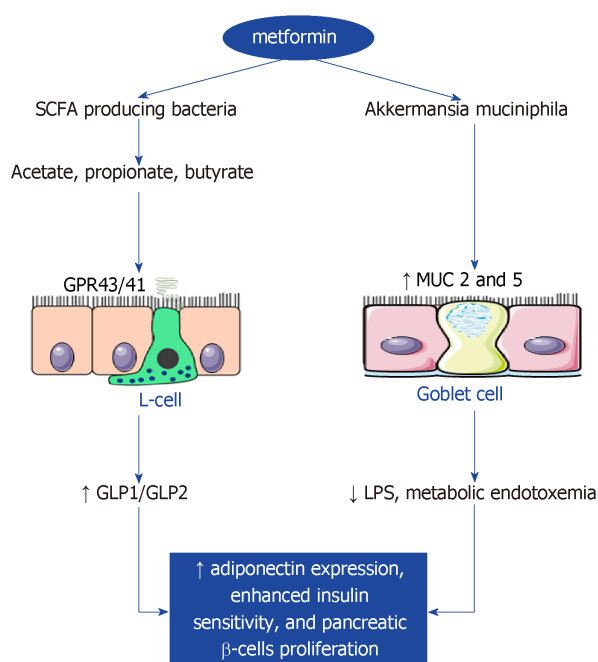
Metformin is the most used nonmetabolizable compound from the biguanide class that patients take orally. It is currently the drug of choice recommended by the American Diabetes Association and the European Association for the Study of Diabetes. Metformin has blood glucose-lowering and insulin sensitizing effects and inhibits liver glucose production. Also, this drug modulates the incretin pathway by improving the expression of GLP-1 receptor in the pancreatic islets and raising plasma levels of GLP-1<sup>[5,26,27]</sup>. A recent study suggested that inhibition of mitochondrial glycerophosphate dehydrogenase, an enzyme in the glycerophosphate shuttle, could be the main system involved in the metformin-induced inhibition of gluconeogenesis<sup>[28]</sup>.

Treatment with metformin also alters bile acid recirculation<sup>[6]</sup>, suggesting that the primary actions of metformin could be in the gut<sup>[11]</sup>; however, the absorption of metformin mainly occurs in the small intestine. Moreover, T2D patient treated with metformin can experience improvement in their lipid levels, which would contribute to the reduction of chronic micro- and macrovascular complications. Most of metformin's pleiotropic effects are predetermined by adenosine monophosphate-activated protein kinase (AMPK) activation in the skeletal muscle and liver<sup>[29]</sup>. In addition, AMPK activation is known to upregulate autophagic activity through direct phosphorylation of unc-51-like kinase and Beclin 1, key molecules involved in the initiation of autophagy; consequently, metformin can magnify autophagy<sup>[30]</sup>. Autophagy is valuable for nutrient supply in the case of energy deficiency, has a significant impact on body metabolism, and is also essential for the proper turnover of organelles, such as mitochondria and the endoplasmic reticulum<sup>[28]</sup>. These organelles play critical roles in pancreatic  $\beta$ -cell physiology and insulin sensitivity. Although, a global increase in autophagic activity is likely to improve the metabolic profile under metabolic stress conditions<sup>[28,31]</sup>, which might be related to attenuation of the chronic low-grade tissue inflammation associated with obesity<sup>[28,32]</sup>.

Metformin treatment is accompanied by the enrichment of SCFA-producing bacteria, such as *Blautia*, *Bacteroides*, *Butyrivoccus*, *Bifidobacterium*, *Prevotella*, *Megasphaera*, *Butyrivibrio*<sup>[33]</sup> or *Phascolarctobacterium*, and has positive effects on the Proteobacteria phylum as well as the *Allobaculum* and *Lactobacillus* genera<sup>[5,32]</sup>. Additionally, the composition of the phylum Verrucomicrobia in a high-fat diet (HFD)-Met-treated experimental group was notably raised. Metformin treatment was also shown to have an effect on the gut microbiota in mice on normal diet. Furthermore, the families *Rikenellaceae*, *Ruminococcaceae*, and *Verrucomicrobiaceae*, as well as *Alistipes* spp., *Akkermansia* spp., and *Clostridium* spp., were found to be more abundant with normal diet plus metformin treatment than in the control experimental group<sup>[34]</sup>.

At the genera level, an increase of *Escherichia* and a decrease of *Intestinibacter* has been detected in a metformin-treated group<sup>[33]</sup>. The number of positive connections among microbial genera, especially those within Proteobacteria and Firmicutes, was also found to be increased after 2 mo of metformin treatment<sup>[33]</sup>. After 4 mo of treatment with metformin, there were significantly larger increases in fecal concentrations of lactate and a trend toward a larger increase in fecal concentrations of succinate<sup>[33]</sup>. In addition, Shin *et al.*<sup>[35]</sup> showed significant differences in the abundance of Firmicutes and Bacteroidetes and gut microbiota composition between metformin-treated and non-treated mice but only under HFD conditions. Correspondingly, Lee *et al.*<sup>[34]</sup> observed that metformin caused a decrease in bacterial diversity in mice on HFD.

Recently, the degradation of mucin was reported in mice on HFD<sup>[36]</sup> and suggested



**Figure 1 Crosstalk between metformin action and gut microbiota.** GLP1: Glucagon-like peptide-1; GLP2: Glucagon-like peptide-2; LPS: Lipopolysaccharide; SCFA: Short-chain fatty acid.

as possibly related to metabolic disorders. After metformin treatment in female mice, but not in male mice, expression of the genes *MUC2* and *MUC5* in the small intestine became remarkably increased<sup>[34]</sup>. This is a beneficial effect of the drug, because gastrointestinal mucins produced by goblet cells protect the underlying epithelium from pathogens. Moreover, female hormones are known to exert a protective effect against metabolic disorders<sup>[37]</sup> and to be involved in lipid and glucose metabolism. Therefore, the observed differences in the gut microbiota between male and female mice during metformin treatment might be caused by differences in hormone levels, which might be associated with metabolic phenotypes<sup>[34]</sup>.

Nevertheless, the abundance of *Akkermansia*, which are mucin-degrading bacteria, is positively correlated with the quantity of goblet cells. Studies have highlighted that metformin multiplies the number of goblet cells, irrespective of diet<sup>[5,35]</sup>. Another study showed that treatment with *A. muciniphila*, which was identified from enterotype gut microbiota, improved metabolic parameters<sup>[34,36]</sup>. Albeit, approximately 30% of patients report experiencing side effects with metformin, including diarrhea, nausea, vomiting, bloating, and lactic acidosis.

## GUT MICROBIOTA AND ALPHA-GIs

The  $\alpha$ -GIs are oral hypoglycemic antidiabetic drugs that postpone the digestion of carbohydrates such as disaccharides and starch in the small intestine, and which reduce postprandial hyperglycemia<sup>[5]</sup> and delay the absorption of glucose, thereby managing blood glucose levels and related complications. To this class belong acarbose, voglibose (also naturally occurring in *Streptomyces*) and miglitol. Thus,  $\alpha$ -GIs alter the nutrient sources of bacteria by segregating complex carbohydrates.

Acarbose delays the enzymatic carbohydrates decaying in the small intestine and thereby diminish postprandial hyperglycemia. Clinical studies have shown that acarbose significantly enhances glycemic control and lowers known CVD risk factors, including triglycerides' levels, body mass index, insulin levels, and systolic blood pressure<sup>[38-40]</sup>. The prominent mechanisms for this cardiovascular protective function are only partially understood, but they can be attributed to the ability of acarbose to neutralize oxidative stress by increasing H<sub>2</sub> production in the gastrointestinal tract<sup>[38,41]</sup>. Panwar *et al.*<sup>[42]</sup> found that *Lactobacillus* strains exert effects of glucosidase-inhibitors and regulate blood glucose responses to carbohydrates *in vivo*. As mentioned above, SCFAs play a crucial role in diabetes. In individuals with impaired glucose tolerance, acarbose was found to increase serum butyrate levels. The underlying mechanism for this effect might be that acarbose increases the fermentation of insoluble fibers in the colon. Interestingly, oral supplementation of

butyrate was found to improve insulin sensitivity and increase energy expenditure by enhancing mitochondrial work in mice<sup>[38,43]</sup>. To minimize the known gastrointestinal side effects of acarbose (*e.g.*, flatulence, diarrhea, or abdominal cramps), the drug was administered in small proportions. Zhang *et al.*<sup>[39]</sup> compared treatment for T2D with acarbose and metformin and showed that both treatments notably increased GLP-1 concentration and decreased glucagon after 24 wk. However, additional benefits of acarbose besides its antidiabetic effect remain unknown.

Acarbose is effective in lowering blood glucose level in patients with T2D by delaying the digestion of complex carbohydrates through the inhibition of pancreatic  $\alpha$ -amylase and a variety of  $\alpha$ -glucosidases<sup>[38]</sup>. Later, microbiota will ferment these carbohydrates, which will alter the composition of the intestinal microbiota. The features of gut microbiota in patients with prediabetes (before treatment) are genera abundance of *Bacteroides* (belonging to Bacteroidetes) and *Faecalibacterium* (belonging to Firmicutes). The most plentiful phyla include Firmicutes (68.53% of all reads), Bacteroidetes (27.85% of all reads), Proteobacteria (1.98% of all reads), and Actinobacteria (0.98% of all reads)<sup>[38]</sup>.

After the treatment with acarbose, five genera, including *Lactobacillus* and *Dialister*, flourished. In response to acarbose, *Lactobacillaceae*, *Ruminococcaceae* and *Veillonellaceae* increased and six genera, including *Butyricoccus*, *Phascolarctobacterium* and *Ruminococcus*, decreased. Likewise, many of the operational taxonomic units that greatly increased in response to acarbose belong to SCFA-producing taxa, such as *Faecalibacterium*, *Prevotella*, and *Lactobacillus*<sup>[38]</sup>. Some species of *Megasphaera* also thrived following acarbose treatment. They can transform carbohydrates into SCFAs, including butyrate, formate, acetate, valerate, and caproate, a process which is valuable for *Lactobacillus* development<sup>[38]</sup>. Consequently, the effect of acarbose on body weight might be related to reorganized microbiota structure. It is supposed that SCFAs such as acetate, butyrate and propionate and their concentrations are prognostic of lifespan<sup>[38]</sup>. Thus, the increased levels of SCFAs in acarbose-treated mice may lead to the beneficial effect on the lifespan<sup>[44]</sup>. However, studies have shown that the weight loss in female mice on acarbose was more dramatic than in males, while the longevity effect is much stronger in males<sup>[45]</sup>.

Another  $\alpha$ -GI, voglibose, changes dysbiosis in diet-induced obese mice<sup>[46]</sup>. These changes could increase the production of bile acid metabolites and have an advantageous systemic outcome. Specifically, scientists have found favorable effects of voglibose on several cardiovascular end-points, as it improves glycemic control in mice with cardiac overpressure<sup>[47]</sup>. Voglibose has anti-obesity effects on diet-induced obese mice. Possibly, the effects of incretins in voglibose, activation of neuroendocrine linked to leptin, and inducement of the genes responsible for magnified energy metabolism cause the reduction in energy intake and improvement of mitochondrial function<sup>[48]</sup>. The reduction in food intake is possibly derived from increased GLP-1 levels due to voglibose supplementation or from direct modulation of hypothalamic genes which lead to the satiety response.

Miglitol shortens the intestinal transit time and suppresses histological and molecular markers of inflammation, for which concentrations are elevated by a high-fat and high-glucose diet and which shifts with the increases in *Erysipelotrichaceae* and *Coriobacteriaceae* induced by the energy-rich diet<sup>[49]</sup>. Miglitol is able to alter human gut microbiota because of the transit time reduction.

The development of nonalcoholic steatohepatitis (NASH) could be dependent on the gut environment as well. As  $\alpha$ -GIs change the gut environment, they might also protect against NASH development, because of its sensibility to changes in the gut environment<sup>[49]</sup>. NASH is characterized by hepatocellular lipid accumulation along with inflammation and fibrosis that is a precondition for oxidative stress, inflammatory cytokines, and endotoxins. There is an essential need for therapeutic interventions considering that NASH can lead to cirrhosis and liver cancer. In addition, acarbose was also demonstrated to have a protective effect against NASH development in HFD-induced obese rats<sup>[50]</sup>. However, the underlying mechanisms should be further investigated.

Miglitol was shown to restrain the accumulation of lipid droplets and inflammatory cell infiltration, and to lead to a decrease in the numbers of ballooning hepatocytes as well as to stoppage of the activation of stellate cells, which plays a role in liver fibrosis<sup>[49]</sup>.

The administration of an  $\alpha$ -GI has been found to increase the levels of butyric acid in the intestines of healthy individuals. Indeed, the administration of butyric acid was demonstrated to suppress intestinal inflammation in mice<sup>[51]</sup>. These findings suggest that miglitol administration increases the butyric acid level in the intestine and suppresses colon inflammation.

Human gut bacterium *Blaubia* (*Ruminococcus*) *obeum* expresses enzymes, such as  $\alpha$ -glucosidases (Ro- $\alpha$ G1), which have specific crystal structures with free active site(s) to

bind and interact with volatile substrates. Therefore, the proposed theory is that  $\alpha$ -GIs (acarbose, voglibose, miglitol) can affect the bacterial Ro- $\alpha$ G1 in human gut and exert positive effects or create adverse gastrointestinal symptoms<sup>[52]</sup>. The  $\alpha$ -GIs bind to the active site of Ro- $\alpha$ G1 and change the enzyme's activity. Acarbose was found to slightly inhibit the gut bacterial  $\alpha$ -glucosidases as well as other currently used  $\alpha$ -GIs.

## GUT MICROBIOTA AND GLP-1 AGONIST

Intestinal endocrine cells (L cells) respond to food ingestion by secreting GLP-1, an incretin hormone<sup>[53]</sup>. This hormone can intensify glucose-induced insulin from pancreatic  $\beta$ -cells and suppress glucagon secretion; in addition, it can protect pancreatic  $\beta$ -cells from apoptosis and promote  $\beta$ -cell proliferation. Together, incretins are liable for 50%–60% of postprandial insulin secretion. In addition, GLP-1 plays critical roles in gastrointestinal motility as well as in metabolism; moreover, GLP-1 can possibly suppress gastrointestinal motility, thus affecting the absorption of digested food<sup>[54]</sup>. However, the natural GLP-1 is degraded rapidly, primarily through enzymatic destruction by DPP-4. Therefore, another pharmaceutical approach to treat T2D is to increase GLP-1 function, either by the administration of GLP-1 peptide mimetics or suppressing its degradation by DPP-4. GLP-1 expression could be stimulated by binding of SCFAs and secondary bile acids (lithocholic acid and deoxycholic acid) with the G-coupled protein receptor FFAR2 (formerly GPR43)<sup>[53]</sup>. Many studies have shown that satiety and glucose homeostasis are modulated by the gut microbiota that induces the secretion of GLP-1<sup>[55,56]</sup>.

The body weight control induced by GLP-1 is maintained by reduced food intake and inhibition of appetite and gastric emptying<sup>[57]</sup>. However, restricted dietary intake supplemented with GLP-1 results in more significant weight loss. Interestingly, the microbial diversity after GLP-1 increment seemed to be dependent on the glycemic state of the mice studied. In normoglycemic mice treated with liraglutide and saxagliptin, bacterial variety significantly decreased, while in transiently hyperglycemic mice it rose to the normal level<sup>[13]</sup>. Of late, scientists have proposed liraglutide as a prospective anti-obesity drug because of its additional impact on weight loss in obese and diabetic individuals. The daily injection of liraglutide has been shown to significantly improve glucose tolerance and insulin tolerance in diabetic rats rather than in nondiabetic rats. Although, it was found to alter the microbial composition in both simple obese and diabetic obese rats. The genera *Candidatus*, *Roseburia*, *Arthromitus* and *Marvinbryantia* may promote weight gain, while the genera *Coproccoccus* and *Lactobacillus* are associated with weight loss<sup>[58]</sup>.

Liraglutide administration has been shown to decrease the relative abundance of all of the obesity-related phylotypes (such as *Romboutsia*, *Ruminiclostridium*, and *Erysipelotrichaceae*) and to enrich the lean-related genera *Blautia* and *Coproccoccus*<sup>[59]</sup>. After liraglutide intervention, the abundance of Firmicutes was also found to tend towards decrease in obese rats, whereas the finding was contrary when the study was carried out in human volunteers under field conditions without restriction<sup>[60]</sup>. Patients with long duration of T2D show a significantly reduced *Akkermansia* variety. After comparison of the gut microbiota of subjects receiving a GLP-1 agonist and metformin, higher *Akkermansia* abundances were detected in the liraglutide-treated patients<sup>[61]</sup>. At first, the genus *Akkermansia* and some genera in the family *Christensenellaceae* increased prominently under liraglutide, unlike that seen under metformin, with the latter of which leading to a greater expansion of *Dorea* and *Sutterella* genera.

GLP-1 receptors are placed on neurons innervating the portal vein, on  $\beta$  cells of the pancreas, and the central nervous system<sup>[62]</sup>. GLP-1 after its release can affect afferent neurons innervating the gastrointestinal tract which signal to the caudal brainstem or enteric neurons, and/or they can enter the circulation to functionate centrally, or on peripheral targets to regulate metabolic disorders<sup>[59,63]</sup>. Thus, the weight-loss and glucose-controlling effects of liraglutide are possibly mediated by the gut-brain axis. In addition, the GLP-1 analog liraglutide reduces visceral hypersensitivity and acts as a sort of pain-killer<sup>[64]</sup>. ROSE-010, another GLP-1 analog, has been shown to diminish visceral pain in patients suffering from irritable bowel syndrome<sup>[65]</sup>.

Long-term HFD intake has been shown to result in a lack of energy substrates, reduced acetylcholine synthesis, membrane deterioration and oxidative stress, and consequently is valid in intestinal myenteric neurons loss in mice<sup>[66]</sup>. Grasset *et al.*<sup>[67]</sup> revealed that gut microbiota dysbiosis causes the loss of enteric neurons, attenuated nitric oxide production and following GLP-1 resistance. Nitric oxide produced by nuclear nitric oxide synthase has been generally expected to have a protective effect on enteric neurons that is greater than its damaging effect. The GLP-1 secretagogue l-

arginine oral administration has also been shown to improve glucose tolerance by influencing GLP-1R signaling<sup>[68]</sup>. L-arginine is a substrate of nuclear nitric oxide synthase which improves GLP-1 sensitivity in HFD-fed mice and increases the glucose-induced insulin secretion. In consequence, L-arginine supplementation could have beneficial effects on postprandial GLP-1 response and GLP-1 sensitivity in patients with T2D.

## GUT MICROBIOTA AND DPP-4 INHIBITORS

Protein CD26 present on the lymphocyte cell surface was first described to have a proteolytic activity in 1966 and was later named as DPP-4. The potential substrates of DPP-4 activity are gut hormones, like incretins, GLP-1 and gastric inhibitory polypeptide, neuropeptides, chemokines, and dietary proteins<sup>[69]</sup>. Through the cleavage of key hormones and peptides, the DPP-4 activity influences behavioral, intestinal and metabolic disorders<sup>[70]</sup>. DPP-4 can enhance the agonistic activity of gut hormones, like neuropeptide Y and peptide YY (PYY), by cleaving off the N-terminal dipeptide. As PYY has an influence on the ileal and colonic brake of digestion and on the induction of satiety *via* activation of hypothalamic Y2 receptors, these effects could be enhanced by DPP-4<sup>[71]</sup>. However, the capacity of DPP-4 in the regulation of satiety has not yet been fully elucidated.

An experiment on Dpp-4 knockout mice showed an increased GLP-1 level and improved glucose tolerance associated with it. This effect was achieved in humans by administration of DPP-4 inhibitors, antidiabetic agents that maintain incretins in their active form<sup>[72]</sup>. Moreover, Ahmed *et al*<sup>[73]</sup> revealed that overweight and obese patients, in comparison to normal-weight patients, have increased DPP-4 activity, which decreases the activity of GLP-1. The administration of prebiotics led to decreased DPP-4 activity, which was explained by double concentration in the active form of GLP-1<sup>[74]</sup>.

Some studies have acknowledged that some commensal bacteria, such as *Prevotella* or *Lactobacillus*, can express human DPP-4 homologs<sup>[70,75]</sup>. Two groups of scientists published findings of DPP-4 expression being higher in gnotobiotic mice colonized with feces of a lean subject than in germ-free mice, which strongly indicates that their intestinal microbiota produced DPP-4-like activity<sup>[70,76]</sup>. The overall literature affirms that DPP-4 encoded by the gut microbiota could compose an innovative mechanism to alter protein digestion, host metabolism, and behavior.

The novel type of DPP-4 inhibitors are sitagliptin, saxagliptin and vildagliptin, which are administrated orally. Sitagliptin increases insulin and suppresses glucagon secretion. In patients with T2D, therapies which include DPP-4 inhibitors promote healing of colitis and diminish depression symptoms. DPP-4 was proposed as a possible target for treating autoimmune diseases, including inflammatory bowel disease as it has an influence on the immune system, particularly on T cell function<sup>[77]</sup>. Obese dams with adverse pregnancy outcomes have been reported as having decreased *Lactobacillus spp.* compared with dams with normal litters. Secondly, maternal obesity and reduced fertility are related to bad pregnancy outcomes, gestational diabetes, and preeclampsia<sup>[78]</sup>. Sitagliptin or prebiotic consumption during pregnancy could normalize gestational weight gain, increase *Bifidobacterium spp.*, reduce fasting glucose levels, and possibly alleviate pregnancy termination associated with maternal obesity while improving offspring metabolic health and composition of the intestinal microbiome<sup>[79]</sup>.

Saxagliptin, another DPP-4 inhibitor, appears to act only on a small target group of gut microbes, mainly on the Firmicutes/Bacteroides ratio. It has been shown to enhance the development of the genus *Lactobacillus* within the class *Lactobacillaceae*, the genera *Allobaculum* and *Turicibacter* within class *Erysipelotrichaceae* and suppresses the genus *Bacteroides* within the class *Bacteroidaceae*, and the genus *Prevotella* within the class *Prevotellaceae*. As compared to the GLP-1 agonist liraglutide, saxagliptin reduced the enrichment of the genus *Blautia* and of the genus *Coproccoccus*. Moreover, despite the fact of similar food intake reduction, saxagliptin had a neutral effect on body weight, with subjects on liraglutide having significantly lower weight regardless of their glycemic control<sup>[83]</sup>.

Another DPP-4 inhibitor, vildagliptin, affects the gut microbiota composition and its metabolic activity. Vildagliptin has been shown to reduce the fasting blood glucose and HbA1c levels. In obese murine models, vildagliptin reduced *Ruminococcaceae*, such as the genera *Oscillibacter*, *Ruminiclostridium\_6*, *Anaerotruncus*, and *Ruminococcaceae\_UCG\_007*, as well as the families *Planococcaceae*, *Christensenellaceae*, and *Prevotellaceae*. The enriched phylotypes were of the *Streptococcaceae* family, the genera *Bacteroides*, and the family *Bacteroidaceae*. In general, it modified the

Firmicutes/Bacteroides ratio, reduced DPP-4 activity in the portal vein and increased the concentration of active GLP-1, improving gastrointestinal function according to AMPs' expression restoration and the depth of the crypts in the ileum<sup>[80]</sup>. Vildagliptin also has a potential effect on inflammation, due to reduction of TLR and cytokine expression. Zhang *et al.*<sup>[80]</sup> suggested that vildagliptin enriches SCFA-producing bacteria and ameliorates gastrointestinal health and could ultimately mediate their beneficial effects on the host, especially in diabetes.

The DPP-4 inhibitor PKF-275-055 improves glucose/cholesterol metabolism, decreases Firmicutes/Bacteroidetes ratio, and drops mass gain and mesenteric adipose accumulation. Moreover, mice on HFD with PKF-275-055 treatment showed enriched butyrate-producing *Ruminococcus* and of the acetogen *Dorea* compared to the control group<sup>[81]</sup>.

## GUT MICROBIOTA AND SGLT-2 INHIBITORS

The sodium/glucose cotransporters SGLT1 and SGLT2 are generally expressed in the small intestine and are regulated by a sodium gradient created by Na<sup>+</sup>/K<sup>+</sup> ATPase. SGLT1 transports glucose and galactose across the apical membrane of enterocytes, whereas SGLT2, and at some extent SGLT1, reabsorbs glucose in the renal tubule. SGLT2-selective inhibitors are a new class of treatment for T2D<sup>[82]</sup>. SGLT2 differs from other antidiabetic medications because it ameliorates vascular function and thus has advantageous effects on CVD. Among the numerous T2D consequences, CVD is the most widespread and dramatic. Data characterize the gut microbiota as an important regulator of vascular function<sup>[83]</sup>. Indeed, people with diabetes have vascular dysfunction and heightened risk of CVD. Distinct signs of diabetes-related CVD are arterial stiffness, endothelial dysfunction, and vascular smooth muscle functional disorder. Reduction in endothelium-independent dilation is present in T2D patients and is a marker of cardiovascular complications.

After 8 wk of treatment with a selective SGLT2 inhibitor dapagliflozin, diabetic mice showed lower arterial stiffness and blood glucose level, and improvements in endothelial and vascular smooth muscle dysfunctions compared to nontreated diabetic mice. In addition, reductions in circulating inflammatory markers, such as MCP-1, IL-1 $\beta$  and IL-6, and hyperglycemia improvement were detected<sup>[84]</sup>. Animals with diabetes treated with dapagliflozin showed decreased Firmicutes/Bacteroidetes ratio and Oscillospira, and increased *Akkermansia muciniphila*.

The dual SGLT1/2 inhibitor has been shown to reduce blood glucose levels and HbA1c and to increase total GLP1 in mice fed a high-sucrose diet<sup>[85]</sup>. The higher doses of SGLT1/2 inhibitor accelerated body weight gain and increased Bacteroidetes and decreased Firmicutes quantity, but the *Akkermansia* spp. was not modified<sup>[82]</sup>. SGLT1/2 inhibitors or SGLT2-selective drugs like canagliflozin guarantee intestinal SGLT1 inhibition in T2D<sup>[86]</sup>. They enhance GLP-1 and PYY secretion and delay the glucose excursion after carbohydrate intake. The dual SGLT1/2 inhibitor LX4211/sotagliflozin, in clinical testing, has the same effects as the medicine described directly above<sup>[87]</sup>. However, SGLT1 cannot be completely inhibited as long as changed Na<sup>+</sup> homeostasis and elevated colonic carbohydrates can lead to the opposite gastrointestinal effects and diarrhea.

## GUT MICROBIOTA AND PPAR

The PPARs belong to the nuclear receptor family of regulatory factors that are ligand-activated transcription factors. There are two PPAR $\gamma$  isoforms: PPAR $\gamma$ 1 and PPAR $\gamma$ 2. They form a heterodimeric complex with the retinoid X receptor, which binds to PPAR-responsive elements and then regulates transcription. Its main functions are linked to maintaining homeostasis in the intestine, inducing adipocyte growth and differentiation<sup>[88]</sup>, cellular apoptosis<sup>[89]</sup>, regulation of genes involved in glucose and lipid metabolism<sup>[90]</sup>, and inflammatory responses. PPAR $\gamma$  is expressed mainly in several tissues such as of the lungs, breast, ovaries, placenta and at most in the colon, where it regulates colonocyte metabolism and cell cycle<sup>[91]</sup>.

PPAR $\gamma$  is considered to have anti-inflammatory effects and to be a molecular target for cancer chemoprevention<sup>[92]</sup>. It also enhances insulin sensitivity and regulates the genes involved in hypertension and contributing to atherosclerosis. There are lines of evidence indicating reduction of intestinal inflammation and colon cancer development and T2D<sup>[93]</sup> by specific PPAR $\gamma$  agonists.

Nepelska *et al.*<sup>[91]</sup> engineered a colonic epithelial HT-29-PPAR $\gamma$  reporter cell line to control the influence of bacterial metabolites on transcriptional activity of PPAR $\gamma$ .

Two main metabolites of intestinal bacteria, butyrate and propionate, were linked to activation of PPAR $\gamma$  transcriptional activity. Notwithstanding, phylogenetic affiliation of the strains were found to not rigorously correspond to reporter gene activities, among them the most general stimulating effect was noticed for Firmicutes and Fusobacteria, while Actinobacteria exerted moderate or no modulation.

The strongest potential of PPAR $\gamma$  activation is exerted on *Roseburia hominis*, *Roseburia intestinalis*, and *Fusobacterium naviforme*. These are well-known producers of butyrate, therefore the response pattern of PPAR $\gamma$  reporter cells is exposed to the composition of organic acids of conditioned media. Gene regulation in intestinal epithelial cells is known to be regulated by the SCFAs, especially butyrate<sup>[94]</sup>. Acetate negatively affected the PPAR $\gamma$  reporter system, demonstrating a reverse correlation. Moreover, butyrate and propionate stimulated PPAR $\gamma$  activity, even at such low concentrations as 0.5mM. Acetate, however, showed an insignificant activation starting from 8 mM, and lactate did not affect the activity but was cytotoxic from 2 mM, which lead to cell detachment<sup>[95]</sup>. In general, high concentrations of all organic acids, especially acetic and lactic, have a deleterious effect on the viability of cells, possibly because of decrease in pH.

Some species can activate the expression of PPAR $\gamma$  target genes even without presence of butyrate and propionate in their conditioned media. To them belong *Atopobium parvulum* and *Prevotella copri*. These bacteria were shown to increase ANGPTL4 and ADRP expression in HT-29 cells. Their underlying mechanisms are probably different, because stimulation with conditioned media of *A. parvulum* showed its influence after 6 h and *P. copri* in 12 h<sup>[91]</sup>. The induction of ANGPTL4 by the PPAR $\gamma$ -specific ligand troglitazone was weaker in either case. In addition, *A. parvulum* and *P. copri* promote PPAR $\gamma$  phosphorylation *via* ERK1/2<sup>[91]</sup>. Studies confirmed that bacterial upregulation of PPAR $\gamma$  in enteral epithelial cells occurs by phosphorylation<sup>[96]</sup>. Though, high levels of *P. copri* and *A. parvulum* in the intestine has been connected to arthritis<sup>[97]</sup> and linked to periodontitis<sup>[98]</sup> accordingly.

However, the elevated risk of cardiovascular ischemic events is affiliated with the use of such PPAR $\gamma$  ligands as rosiglitazone. PPAR $\gamma$  agonists are used in clinics despite the fact that they have serious adverse effects, such as heart failure, weight gain, and increased bone fracture<sup>[99]</sup>. At present, natural products could be found as a source of drugs<sup>[100]</sup>.

Fish oil has established favorable effects in diabetes, CVDs, autoimmune inflammatory diseases, and inflammatory bowel diseases. Neschen *et al.*<sup>[101]</sup> revealed advantageous effects of fish oil on glucose and lipid metabolism, improvement of insulin sensitivity, and reduction of triglycerides. Additionally, the n-3 polyunsaturated fatty acids of fish oil, eicosapentaenoic acid and docosahexaenoic acid, are endogenous ligands for PPAR; consequently, even small changes in their structures affect PPAR activation. These fatty acids adjust the insulin-sensitizing, anti-inflammatory and lipid-lowering properties of fish oil<sup>[102]</sup>.

## GUT MICROBIOTA AS A TREATMENT OPTION FOR T2D: FUTURE PERSPECTIVES

Over the past 10 yr, an increasing body of literature has suggested that the gut microbiota plays a crucial role in the host immune system, modulation of inflammatory processes, extraction of energy from the host diet, and alterations of human gene expression, and is considered to make an important impact on obesity/insulin resistance development. Several mechanisms that contribute to explaining the link between altered gut microbiota and pathogenesis of insulin resistance have been described<sup>[7]</sup>. They control the fermentation and absorption of dietary polysaccharides to produce SCFAs, which may explain their importance in the regulation of fat accumulation. SCFAs can stimulate the secretion of GLP-1 and GLP-2, thus increasing insulin and adiponectin expression, which might contribute to enhanced insulin sensitivity and pancreatic  $\beta$ -cells proliferation<sup>[103,104]</sup>. Another mechanism by which the microbiome may contribute to insulin resistance is compromised gut barrier function with an increased intestinal permeability, accumulation of lipopolysaccharide, and metabolic endotoxemia development<sup>[105]</sup>.

Lactobacillus and Bifidobacterium are commonly used as probiotics and are the most studied strains in the treatment and prevention of obesity-associated disorders<sup>[15]</sup>. Moreover, several potential bacterial candidates, such as *Saccharomyces cerevisiae* var. *boulardii*, *Parabacteroides goldsteinii*, *Enterobacter halii* or *Akkermansia muciniphila*, have been identified and innovative mechanisms of action overriding their beneficial effects for insulin resistance/obesity have been elucidated<sup>[106,107]</sup>.

The abundance of *Akkermansia muciniphila*, which is a mucin-degrading bacterium

that resides in the mucus layer, has been found to be decreased in obese/T2D and inversely correlated with body weight in both rodents and humans<sup>[34]</sup>. Metformin treatment<sup>[35,36]</sup>, consumption of oligofructose<sup>[108]</sup>, dietary concord grape polyphenols<sup>[109]</sup>, and gastric bypass surgery in humans<sup>[110]</sup> and mice<sup>[111]</sup> leads to a marked increase in *A. muciniphila* abundance with subsequent weight loss and reversed metabolic disorders, including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance<sup>[34]</sup>.

*F. prausnitzii* plays an important role in preserving the gut barrier and controlling inflammation and T2D progression<sup>[112]</sup>. A traditional Chinese berberine-containing herbal formula given to T2D patients<sup>[112,113]</sup> changed the gut microbiota by increasing *F. prausnitzii*, which was negatively correlated with fasting blood glucose, HbA1c and postprandial blood glucose levels, and positively correlated with homeostasis model assessment of  $\beta$ -cell function (commonly known as the HOMA-B).

*Parabacteroides goldsteinii* is a commensal bacterium with reduced level in HFD-fed mice. Oral treatment of HFD-fed mice with live *P. goldsteinii* reduced obesity and was found to be associated with increased adipose tissue thermogenesis, enhanced intestinal integrity, and reduced levels of inflammation and insulin resistance<sup>[106]</sup>.

Identifying the most important microbiota-related metabolic pathways could lead to the development of integrated strategies using new prebiotics or beneficial bacterial strains to prevent and treat these metabolic disorders in the near future<sup>[112]</sup>.

## CONCLUSION

This review is dedicated to one of the most widespread diseases, diabetes, and the currently used antidiabetic drugs and possible promising new findings in this field. The gut microbiota has been found to have an influence on host metabolism, food consumption, satiety, glucose homeostasis, and weight gain. Altered intestinal microbiota composition has been noticed in CVDs, colon cancer, rheumatoid arthritis, diabetes, and obesity. Therefore, the main effect of antidiabetic drugs is thought to be on the microbiome composition, basically increasing the SCFA-producing bacteria responsible for losing weight and suppressing inflammation. Scientists have found that some drugs for T2D also elicit favorably effects on several cardiovascular end points and have anticancer as well as anti-aging effects. However, further detailed experimental and clinical investigations should be conducted to gain a deeper understanding of antidiabetic drugs' functions.

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