



Gut microbiota interactions with anti-diabetic medications and pathogenesis of type 2 diabetes mellitus

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Abstract

Microorganisms including bacteria, viruses, protozoa, and fungi living in the gastrointestinal tract are collectively known as the gut microbiota. Dysbiosis is the imbalance in microbial composition on or inside the body relative to healthy state. Altered Firmicutes to Bacteroidetes ratio and decreased abundance of Akkermansia muciniphila are the predominant gut dysbiosis associated with the pathogenesis of type 2 diabetes mellitus (T2DM) and metabolic syndrome. Pathophysiological mechanisms linking gut dysbiosis, and metabolic diseases and their complications include altered metabolism of short-chain fatty acids and bile acids, interaction with gut hormones, increased gut microbial metabolite trimethylamine-N-oxide, bacterial translocation/Leaky gut syndrome, and

endotoxin production such as lipopolysaccharides. The association between the gut microbiota and glycemic agents, however, is much less understood and is the growing focus of research and conversation. Recent studies suggest that the gut microbiota and anti-diabetic medications are interdependent on each other, meaning that while anti-diabetic medications alter the gut microbiota, the gut microbiota also alters the efficacy of anti-diabetic medications. With increasing evidence regarding the significance of gut microbiota, it is imperative to review the role of gut microbiota in the pathogenesis of T2DM. This review also discusses the interaction between gut microbiota and the various medications used in the treatment of T2DM.

Key Words: Metabolic disease; Gut microbiota; Cardiovascular disease; Short chain fatty acid; Dysbiosis; Trimethylamine-N-oxide

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Core Tip: Gut microbiota influence the pathogenesis of type 2 diabetes mellitus (T2DM) and metabolic syndrome through multiple mechanisms. The role of dysbiosis and various pathophysiological mechanisms such as altered metabolism of short-chain fatty acids, interaction with gut hormones, increased gut microbial metabolite trimethylamine-N-oxide and bacterial translocation in the pathogenesis of T2DM and cardio-metabolic diseases have been extensively studied. With increasing evidence regarding the significance of gut microbiota, it is imperative to review the role of gut microbiota in the pathogenesis of T2DM. This review also discusses the interaction between gut microbiota and the various medications used in the treatment of T2DM.

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INTRODUCTION

Diabetes mellitus is a common chronic endocrine disorder with an estimated global burden of 537 million adults worldwide and projections indicate that the number of diabetic patients worldwide, will reach 700 million by 2045[1]. Diabetes is characterized by raised blood glucose levels arising as a consequence of decreased insulin production, resistance to insulin action or both. Traditional risk factors of developing type 2 diabetes mellitus (T2DM) include family history of diabetes, advancing age, obesity, sedentary lifestyle and poor-quality diet. Over the last decade, multiple studies have indicated a possible causal role of alterations in gut microbiota with development of T2DM[2-4]. Various studies are exhaustively exploring the role of gut microbiota as a biomarker for T2DM and a possible therapeutic intervention to treat T2DM[5-9].

Microorganisms including bacteria, viruses, protozoa, and fungi living in the gastrointestinal tract (GI) are collectively known as the gut microbiota. Over 100 trillion microbes live in our gut, particularly in the large intestine[10]. Taxonomically bacteria are classified as species, genus, family, order and phylum. Human gut microbiota is primarily composed of 5 phyla namely Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria and Cerrucomicrobia[11]. Firmicutes (*i.e.*, *Bacillus* spp.) and Bacteroidetes (*i.e.*, *Bacteroides* spp.) account for 90% of the gut microbiota community[11]. Their primary physiological roles in humans include protection against pathogens, producing vitamin B and K as well as bile acids, and a very pivotal role in host metabolism and immune modulation[12,13]. The composition of gut microbiota is regulated by factors such as genes, diet, geographical factors and medication use[13-15].

The development of PCR-based techniques has shown the way for the characterization and quantification of bacterial composition *via* sequencing of bacterial genes in human fecal sample. This has enabled scientists and physicians around the world to understand the role of gut microbiota and its interplay with multiple pathological conditions. In this review article we discuss the role of gut microbiota in the development of T2DM and therapeutic action of anti-diabetic drugs.

GUT DYSBIOSIS AND ITS ROLE IN PATHOPHYSIOLOGY OF T2DM

Dysbiosis is the imbalance in microbial composition on or inside the body relative to healthy state. Dysbiosis is associated with several autoimmune and inflammatory pathological conditions including allergies, central nervous system disorders, cancers, metabolic syndrome, diabetes mellitus, polycystic ovarian syndrome and cardiovascular disease[16,17]. Altered Firmicutes to Bacteroidetes ratio and decreased abundance of Akkermansia muciniphila are the predominant gut dysbiosis associated with the pathogenesis of T2DM and metabolic syndrome (Figure 1).

The ratio of Firmicutes to Bacteroidetes is increased in obese patients and during consumption of high calorie diets[2,18-21]. The altered ratio of these two major phyla leads to impaired glucose metabolism and an increase in obesity[22]. Decreasing the amount of Firmicutes and increasing the proportion Bacteroidetes leads to weight loss and reduced inflammation. T2DM is also associated with dysbiosis and have shown decreased abundance of Bacteroides[3,19] and propionate-producing bacteria such as Akkermansia muciniphila[3,4,19,23].

Akkermansia muciniphila is an anaerobic gram-negative bacteria that has shown to affect glucose metabolism, lipid metabolism and promote intestinal immunity[24]. Akkermansia muciniphila is found in abundant quantity in gut mucosa which utilizes mucin as its energy source and produces mucin degrading enzymes[25] thereby playing a crucial role in gut barrier function. Goblet cells in the gastrointestinal tract produce a thick layer of mucus which serves as a protective barrier against pathogens. The breakdown of intestinal mucosal barrier seen in patients with diabetes can be altered by this microbiota *via* its mucus secreting action. Akkermansia-induced extracellular vesicles may help regulate gut permeability[24]. Lipopolysaccharide (LPS) is an endotoxin derived from gram negative bacteria and plays a role in increasing gut permeability and thereby promoting the inflammatory process[26]. LPS level in blood has been shown to be elevated in high fat diet (HFD) mice and mice with diabetes, which decreases following the administration of Akkermansia[26].

Akkermansia muciniphila also upregulates the endogenous production of GLP1 thereby increasing postprandial insulin secretion[27]. In humans, levels of Akkermansia muciniphila were found to be decreased in diabetes mellitus and obesity whereas the levels of Akkermansia muciniphila increased with treatment with anti-diabetic drugs and weight loss bariatric surgery[28-30]. Akkermansia muciniphila, in fact, is considered a next generation probiotic as there is large body of evidence linking decreased abundance of Akkermansia muciniphila with development of diabetes and obesity[31,32].

Research over last couple of decades have elucidated several pathophysiological mechanisms by which gut microbiota influences the pathogenesis of T2DM and metabolic syndrome. Pathophysiological mechanisms linking gut dysbiosis, and metabolic diseases and their complications include altered metabolism of short-chain fatty acids (SCFAs), interaction with gut hormones, increased gut microbial metabolite trimethylamine-N-oxide (TMAO), bacterial translocation/Leaky gut syndrome, and endotoxin production such as LPS.

Complex sugars are metabolized into SCFA in the colon by gut microbiota, which are known to reduce inflammation and improve glucose homeostasis (Figure 2). These SCFA specifically butyrate, acetate and propionate modulate the insulin release and hunger by increasing endogenous Glucagon like peptide1 (GLP1) and Protein YY (PYY) secretion[33]. The mechanism of action of this process is based on the interaction between SCFAs and G-protein-coupled free fatty acid receptors GPR41 and GPR43. SCFAs directly bind to receptor GPR41 and GPR43 to mediate release of GLP1 and PYY from intestinal L cells[34].

GLP-1 secreted by intestinal L cells increases the secretion of glucose-induced insulin from pancreatic β -cells, decreases the secretion of glucagon and delays gastric emptying[35]. GLP1 receptor analogs are an established method of treating T2DM nowadays. Pancreatic islet-derived PYY plays an important role in controlling glucose homeostasis through the modulation of β -cell mass as well as by increasing insulin secretion[36].

Researchers and clinicians have been cautiously optimistic that gut microbiota modulation has the potential to be a novel therapeutic target for T2DM treatment. It has been noted that ingestion of fermentable dietary fibers increased SCFA concentration, whereas the high-fat diet reduced formation of SCFAs[33]. Chambers *et al*[37] showed that SCFA propionate supplementation significantly reduced weight gain in overweight adults by increasing their postprandial secretion of GLP-1 and PYY. A previous study also showed that per rectal administration of SCFA significantly raised the plasma GLP1 and PYY concentrations, thereby further suggesting the beneficial effects of gut microbiota modulation in patients with T2DM[38,39].

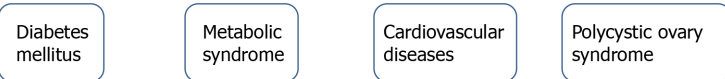
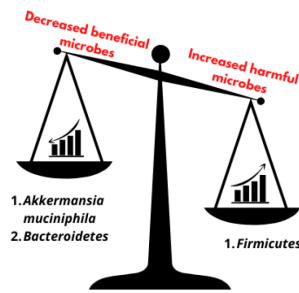
Dysbiosis also leads to increased inflammation and atherogenesis through the gut microbial metabolites, TMAO and its precursors. Choline is an important nutrient which is found in foods such as red meat, fish, poultry and eggs. Gut microbiota metabolizes choline into Trimethylamine (TMA) which is further transported to liver *via* portal venous circulation where TMA is oxidized into TMAO³⁹. Plasma levels of TMAO are positively associated with degree of atherosclerosis in a dose dependent manner[40]. Several studies have implicated TMAO levels as a risk factor for cardiovascular disease and mortality[17,41]. However, recent studies have also shown association of higher TMAO levels with diabetes, gestational diabetes and obesity[42-44].

Gut dysbiosis

Reduction in *Akkermansia muciniphila*
Increased firmicutes to bacteroidetes ratio

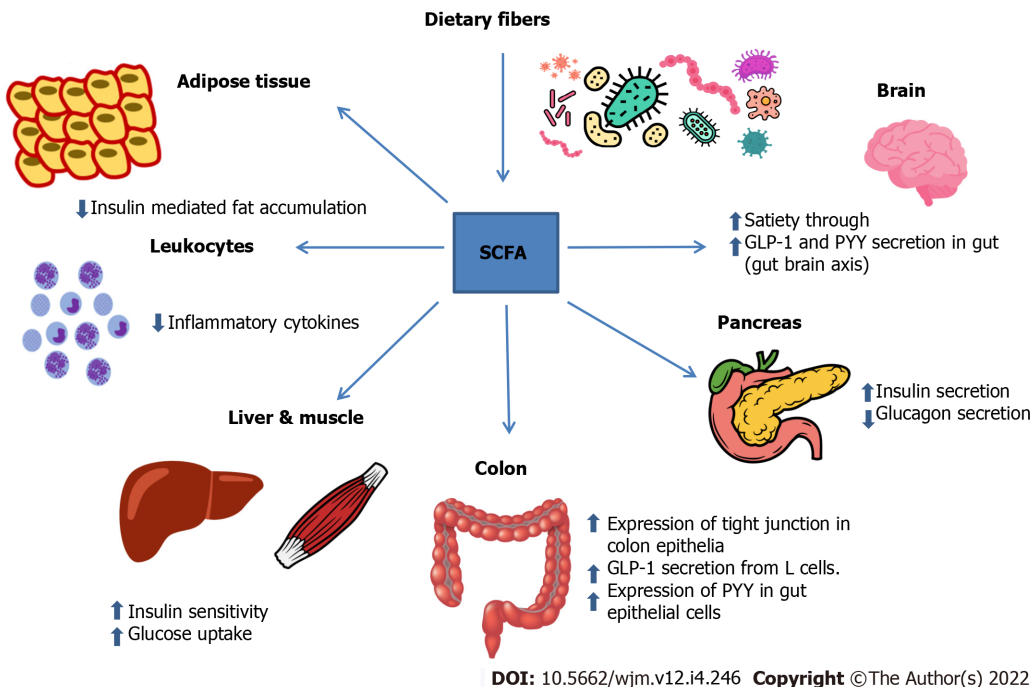
Pathophysiological mechanisms

Alteration in short chain fatty acid metabolism
Interaction with gut hormones.
Altered mucosal permeability or leaky gut syndrome
Increased trimethylamine-N-oxide levels
Lipopolysaccharide endotoxin production



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Figure 1 Gut dysbiosis and its role in pathophysiology of type 2 diabetes mellitus and cardio-metabolic diseases.



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Figure 2 Role of gut microbiota and short-chain fatty acids in the pathophysiology of diabetes mellitus. SCFA: Short-chain fatty acids; GLP-1: Glucagon-like peptide-1; PYY: Peptide YY.

Dysbiosis also leads to disruption of gut epithelial barrier leading to excessive absorption of gut microbiota produced LPS. LPS is a strong endotoxin present in the outer membrane of gram-negative bacteria that can trigger an immune response associated with inflammation. Continuous absorption of LPS evokes a chronic inflammatory response and increased LPS levels are associated with diabetes and insulin resistance[45].

IMPACT OF GUT MICROBIOTA ON ANTI-DIABETIC DRUGS

The composition of an individual's gut flora is known to have an influence on metabolism and glucose homeostasis. The association between the gut microbiota and glycemic agents, however, is much less understood and is the growing focus of research and conversation. Recent studies suggest that the gut microbiota and anti-diabetic medications are interdependent on each other, meaning that while diabetic medications alter the gut microbiota, the gut microbiota also alters the efficacy of diabetic medications. Below, the results of various studies surrounding the relationship between various glycemic

medications and the gut microbiota will be reviewed.

Since the composition of gut flora is known to influence glucose homeostasis, it is vital to understand the impact of anti-diabetic medications on the gut microbiota to fully comprehend their mechanism of action (Table 1).

METFORMIN

Metformin has the strongest data regarding impact of gut microbiota on its therapeutic effects among all anti-diabetic medications. Metformin use has shown to promote the growth of various SCFA-producing healthy bacteria[5,30]. In a double-blinded randomized control trial, Wu Hao and colleagues included treatment-naïve patients with T2DM to receive either 4 months (mo) of metformin or placebo[5]. Treatment with metformin for 4 mo, compared to placebo, showed an increment in the following SCFA producing bacteria such as *Blautia*, *Bacteroides*, *Butyricoccus*, *Bifidobacterium*, *Prevotella*, *Megasphaera* and *Butyrivibrio*, and increase in fecal concentration of lactate as well as a trend towards an increase in the fecal concentration of succinate. In the same study, metformin treatment for 2 mo, led to an increase in the microbial genera such as *Proteobacteria* and *Firmicutes*[5].

Metformin use is also associated with an increase in the mucin degrading microbiota, *Akkermansia muciniphila*[29,30,46]. As described in detailed earlier in this article, *Akkermansia muciniphila* affects glucose metabolism through regulating gut permeability, decreasing LPS and increasing postprandial insulin secretion through interaction with GLP-1[24,26,27]. A study involving community-dwelling Colombian adults showed that participants with diabetes taking metformin not only had high abundance of gut microbiota known for production of SCFAs (*Butyrivibrio*, *Bifidobacterium bifidum*, *Megasphaera*, and an operational taxonomic unit of *Prevotella*) but also had higher relative abundance of *Akkermansia muciniphila*, in comparison to participants without diabetes[30].

Studies in mice have shown an association between metformin treatment and an increase in the abundance of *Akkermansia muciniphila* in the gut flora of mice that were placed on a high fat diets[29, 46]. Metformin use has also shown to have a positive effect on the gut microbiota in mice on a normal diet[46]. An abundance of microbes belonging to families such as *Rikenellaceae*, *Ruminococcaceae*, and *Verrucomicrobiaceae*, and an abundance of microbes belonging to species such as *Alistipes*, *Akkermansia*, and *Clostridium* were noted in the experimental mice with normal diet plus metformin treatment than in the control group[46,47].

There is also a suggestion that the cardiovascular protective effects of metformin may be mediated by gut microbiota. Metformin treatment in db/db mice with T2DM resulted in a twofold reduction in the concentration of TMAO and also decreased bacterial production rate of TMAO precursors[44]. Authors postulated that reduction in TMAO levels with metformin use may contribute to cardiovascular benefits of the drug.

Based on the large body of evidence summarized above, it is safe to say that metformin has consistently shown a beneficial effect towards improving the gut health and cardiovascular health.

GLP-1 RECEPTOR AGONISTS

GLP-1 is an incretin hormone secreted by the intestinal endocrine cells known as the L cells, in response to food ingestion and causes glucose-mediated insulin secretion from the beta cells of the pancreas, concomitant suppression of glucagon from the alpha cells of the pancreas and a decrease in gastric emptying[6]. GLP-1 receptor agonists (GLP-1 RAs) use in patients with T2DM not only results in improved glycemic control but has also shown to promote weight loss, favorable effects on blood pressure and cholesterol, and decreased cardiovascular morbidity and mortality[48]. Therefore, there has been a great interest in the research community to understand underlying mechanisms resulting in GLP-1 RAs therapeutic benefits.

Limited data available on impact of GLP-1 RAs on gut microbiota suggests that clinical benefits of GLP-1 RAs may be mediated by modulation of gut microbiota. Current data suggests that GLP-1 expression could be stimulated by the binding of SCFAs, which are produced by the degradation of carbohydrates by the gut bacteria, to the free fatty acid receptor 2[19]. GLP-1 RAs have shown to be associated with decreased dysbiosis particularly increase in *Bacteroidetes* to *Firmicutes* ratio, decrease in obesity-related and an increase in lean-related microbiota phenotypes, and an increase in abundance of *Akkermansia*[49-52].

Gut microbiota in obese people lack microbial diversity and specifically there is a decline in the *Bacteroidetes* population along with an abundance in the *Firmicutes* population resulting in decreased *Bacteroidetes* to *Firmicutes* ratio[46]. This was shown in a recent study which compared the fecal microbiota of European children (EU) and the children from Burkina Faso (BF), a rural African village where the diet is rich in fiber. There was a significant abundance in *bacteroidetes* and a reduction in *Firmicutes* in the BF children in comparison to the EU children. In one study, several mouse models that were subjected to a probiotic known as VSL#3, led to a suppression of weight gain and insulin

Table 1 Impact of anti-diabetic medications on the gut microbiota

Drug	Changes in microbiota
Metformin	Increase in SCFA producing bacteria[5,30], Akkermansia muciniphila[29,30,46], Firmicutes[5] and Proteobacteria[5]; Increased fecal concentrations of lactate and succinate[5]; Decreased concentration of TMAO and its precursor metabolites[44]
Liraglutide	Increase in Bacteroidetes to Firmicutes ratio[49] and Akkermansia[50]; Increase in lean related phenotypes (Blautia and Coprococcus) [49]; Decrease in Obese related phenotypes (Romboutsia, Ruminiclostridium and Erysipelotrichaceae)[49]
Dulaglutide	Increase in Bacteroidetes to Firmicutes ratio[51]
Sitagliptin	Increase in Bacteroidetes to Firmicutes ratio[7]; Increase in SCFAs and other organic acids like succinate[54]
Saxagliptin	No change in Bacteroidetes to Firmicutes ratio[49]; Obesity related phylotype= Decrease in only one genus Candidatus Arthromitus[49]; Lean related phenotype= Increase in the family Lactobacillaceae but Decrease in genus Blautia and Coprococcus[49]
Vildagliptin	Increase in lactobacillus species and propionate[8]; Decrease in Oscillibacter species[8]
Linagliptin	Increase in Bacteroidetes and decrease in Proteobacteria species[8]
Empagliflozin	Increase in Bacteroidetes to Firmicutes ratio[51]
Dapagliflozin	Increase in Bacteroidetes to Firmicutes ratio[9]; Increased Oscillospira and Akkermansia muciniphila species[9]
Canagliflozin	Increase in Bacteroidetes to Firmicutes ratio[57]; Increase in Olsenella[57], Alistipes[57], Alloprevotella[57] and Lactobacillus species[58]; Decrease in Helicobacter and Mucispirillum species[57]
PPAR γ agonists	Firmicutes and Fusobacteria stimulate PPAR gamma activity[63]
Acarbose	Increase in Lactobacillus and Dialister genera[66]; Decrease in Butyricoccus, Phascolarctobacterium, and Ruminococcus genera[66]; Increase in the ratio between primary bile acids and secondary bile acids[70]
Sulfonylureas	Glicazide have not shown any significant differences on gut microbiome in diabetic patients after 12 wk of intervention[68]

SCFA: Short chain fatty acid; TMAO: Trimethylamine N-oxide.

resistance by altering the gut microbiota. VSL#3 specifically decreased the quantity of Firmicutes and increased the quantity of Bacteroidetes, a change which was associated with an increase in Butyrate production which in turn increased the secretion of GLP-1 from the intestinal L-cells[53].

The above beneficial alteration of gut microbiota is also seen with liraglutide administration. A study showed an increase in the Bacteroidetes to Firmicutes ratio leading to weight loss regardless of the glycemic status in mice with liraglutide use[49]. This study also showed a decrease in obesity-related phylotypes such as Romboutsia, Ruminiclostridium and Erysipelotrichaceae, and an increase in lean-related phylotypes such as Blautia and Coprococcus in mice treated with liraglutide[49].

Like metformin, liraglutide has also been associated with an increased in the presence of Akkermansia[50]. In fact, one study comparing the effect of metformin *vs* liraglutide on the gut microbiota in patients with T2DM, showed higher concentrations of Akkermansia in subjects receiving Liraglutide compared to metformin[50].

Dulaglutide is another GLP-1 agonist used in the treatment of T2DM. Currently, there is limited data on the impact of dulaglutide use on gut microbiota. However, one recent study showed a decrease in the pro-inflammatory pathways and microbiota dysbiosis, specifically an increase in the Bacteroidetes to Firmicutes ratio, in non-diabetic mice with non-alcoholic steatohepatitis after treatment with either dulaglutide or empagliflozin, or both (NASH)[51].

To date, there are no studies looking at the effect of Semaglutide and Exenatide on gut microbiota.

Given the literature showing favorable modulation of gut microbiota with GLP-1 agonists use and our current understanding of role of gut microbiota in the pathophysiology of T2DM and metabolic syndrome, it is not unreasonable to hypothesize that GLP-1 agonists may exert their therapeutic benefits in patients with T2DM through alteration of gut microbiota. However, further studies are needed, particularly in human subjects, to validate these findings and improve our understanding of this topic.

DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS

Sitagliptin has shown to exert a beneficial effect on the gut microbiota. Liao X *et al*[7] analyzed the effects of Sitagliptin and acarbose on the gut microbiota in mice on high fat diet. The alteration in 24 genera induced by high fat diet were protected by sitagliptin. A total of 75% of genera increased by sitagliptin belonged to Bacteroidetes and 87.5% of genera decreased by sitagliptin belonged to Firmicutes thus resulting in increased Bacteroidetes to Firmicutes ratio[7]. This study also performed metabolomics analysis which demonstrated that DPP-4 inhibitors changed the pattern of metabolites

linked to carbohydrate, amino acid and nucleic acid metabolism. There was a trend towards an increase in SCFAs and other organic acids like succinate, both of which are already known to improve glucose tolerance and insulin sensitivity[54].

Saxagliptin was compared with liraglutide in one study to evaluate their individual effects on gut microbiota in mice[49]. Although liraglutide showed a prominent effect on the microbial diversity as mentioned in the subsection of GLP-1 RAs above, saxagliptin did not show any significant shift of the microbial composition. Among the liraglutide treated group, there was a significant reduction in all the obesity-related phylotypes whereas only one phylotype (genus *Candidatus Arthromitus*) decreased with saxagliptin. With regards to the lean-related phylotypes, although both medications led to a similar enrichment in the family Lactobacillaceae and the genera *Lactobacillus* and *Turicibacter*, only liraglutide caused an enrichment of the genus *Balutia* and the genus *Coprococcus* and these two were decreased in the saxagliptin group. There were also no significant changes in the phyla Firmicutes and Bacteroidetes [49].

Vildagliptin has also shown to impact the composition of the gut microbiota and its metabolic activity. In one study, male mice placed on a western diet plus vildagliptin not only showed a significant reduction in DPP-4 activity in the feces but also a reduction in *Oscillibacter* spp, and an increase in *Lactobacillus* spp and propionate[8].

Linagliptin was studied along with a sulfonylurea in diabetic patients already on treatment, to evaluate their impact on human gut flora. Following 4 wk of treatment with either medication in a total of 5 patients with MODY and 19 patients with T2DM, there was no significant changes in the gut microbiota[55]. Another study evaluated the changes caused by linagliptin and a purified Peroxisome proliferator-activated receptor- alpha (PPAR-alpha) agonist (WY14643) on various GI parameters such as gut microbial composition, intestinal barrier integrity, endotoxemia, and hepatic energy metabolism in mice on a high-fructose fed diet (HFRU). The HFRU group showed glucose intolerance, endotoxemia, dysbiosis with increased Proteobacteria and a parallel decrease in Bacteroidetes, significant liver inflammation and steatosis. The Linagliptin and PPAR-alpha agonist group in comparison to the control group, had a positive impact on all the above pathological changes which included restoration in the abundance of Bacteroidetes, a significant decrease in Proteobacteria species, protection of the intestinal ultrastructural damage, restoration of the intestinal permeability and improvement in hepatic steatosis *via* beta oxidation[56].

Based on the current evidence summarized above, not all DPP4 inhibitors seem to have a positive impact on gut microbiota. The limited studies involving Linagliptin may have shown a benefit due its combination with a PPAR- alpha agonist, which is known to play a role in intestinal cell metabolism, differentiation, and inflammation. Although, the studies involving Sitagliptin and Vildagliptin have shown a benefit, they were conducted in mice. Future studies in humans are awaited to see if the results from the current studies can be replicated or not.

SGLT-2 INHIBITORS

Empagliflozin has been studied along with liraglutide in non-diabetic mice with NASH, to examine their effects individually or in combination, on inflammatory pathways, hepatic steatosis and microbiome dysbiosis[51]. After placing the mice on a high-fat-high-fructose diet with cholesterol surplus for 12 wk, they were randomized to receive either empagliflozin or dulaglutide or both. Neither medication showed an effect on hepatic steatosis in the non-diabetic mice. Only dulaglutide, as a single agent and in combination with empagliflozin showed a beneficial effect on weight loss, glucose homeostasis, anti-inflammatory, and anti-fibrotic pathways. There was no beneficial effects seen with empagliflozin alone. Nevertheless, both medications, alone and in combination, showed a beneficial effect on gut microbiota with an increase of Bacteroidetes and a decrease of Firmicutes[51].

Dapagliflozin has also shown to mildly alter the gut microbiota composition in mice with T2DM. Eight wk after being randomized to receive either a standard diet *vs* a standard diet with dapagliflozin, male diabetic mice in the dapagliflozin group increased the Bacteroidetes to Firmicutes ratio, and increased *Oscillospira* and *Akkermansia muciniphila*. It also significantly lowered arterial stiffness and caused a reduction in hyperglycemia and inflammatory markers[9].

Canagliflozin was studied in male mice after inducing T2DM in them by giving a HFD for 24 wk[57]. Various cardio-metabolic parameters and changes in the colonic gut microbiota were assessed. Following treatment with canagliflozin, there were reductions in the lipid profile which was associated with lowering the index for atherogenesis and arteriosclerosis, a reduction in the vascular basement membrane thickness and markers of oxidative stress. It also altered the ratio of Firmicutes to Bacteroidetes from 230% to 98%, increased the abundance of *Olsenella*, *Alistipes* and *Alloprevotella*, and decreased the abundance of *Helicobacter* and *Mucispirillum* in mice with diabetic cardiovascular disease[57].

Another study assessed the effect of canagliflozin on the gut microbiota and the serum concentrations of gut-derived uremic toxins in 5/6th nephrectomized (Nx) rats[58]. Canagliflozin improved the concentration of *Lactobacillus* bacteria, a bacterium which is known to have the ability to maintain the

expression of tight junction proteins and thereby prevent the accumulation of uremic toxins in the serum of chronic kidney disease patients. Indeed, this study showed that canagliflozin increased the expression of the tight junctions' proteins in the ascending colon which were low in the Nx rats. Consequently, the serum concentration of gut-derived uremic toxins which were significantly elevated in the Nx rats were lowered significantly by Canagliflozin[58].

Based on the literature evidence summarized above, SGLT-2 inhibitors have a positive impact on the gut microbiota. It is well known that SGLT-2 inhibitors are effective in treating DM and in providing CV protection. Future studies are awaited to understand whether these beneficial effects are in part due to their action on the gut microbiota.

PPAR AGONISTS

PPAR gamma, a nuclear receptor is vastly present in the colon[59] where it is involved in the intestinal cell metabolism, differentiation and inflammation[60]. It is closely linked to various pathological conditions including diabetes which is linked to the gut microbiota. Evidence shows the PPAR gamma agonists can help reduce gut inflammation, colon cancer and diabetes[61,62]. PPAR-gamma activity has been shown to be induced by gut microbiota. A study in humans assessed the involvement of various gut bacterial strains belonging to the major phyla such as Firmicutes, Bacteroides, Actinobacteria and Fusobacteria on PPAR gamma activity located within the intestinal epithelial cells[63]. These bacteria were anaerobically cultured and a specific reported cell line called HT-29-PPAR gamma was used to identify the bacteria with PPAR gamma activity regulation. At the level of phyla, Firmicutes and Fusobacteria showed the strongest effect while Actinobacter showed mild to no effect. Roseburia hominis and Roseburia intestinalis within the Firmicutes phyla and Fusobacterium naviforme within the Fusobacteria phyla exhibited the strongest capacity to stimulate PPAR gamma activity.

As shown above, an agonistic effect on PPAR gamma receptors that are widely present throughout the colon, can have a positive impact on gut health. However, the current evidence is limited, and it is compounded by the infrequent use of medications belonging to this class. Hence, it will be interesting to see if future studies look more closely into the relationship between PPAR gamma receptor agonism and gut microbiota.

ALPHA GLUCOSIDASE INHIBITORS

SCFA's, including butyrate play an important role in pathophysiology of diabetes. Patients with T2DM have a decline in the abundance of butyrate-producing bacteria[64]. Acarbose has shown to increase the serum butyrate levels in patients with impaired glucose tolerance. Oral supplementation of butyrate in mice, has shown to improve insulin sensitivity and increase energy expenditure *via* mitochondrial action[65]. Zhang *et al*[66] performed a study in 52 Chinese patients with prediabetes, who were assigned randomly to receive either acarbose or placebo, to characterize the gut microbiota. The baseline gut microbiota composition in the fecal samples of these prediabetic patients showed an abundance in the genera Bacteroides (19.4%) and Faecalibacterium (8.97%), and an abundance in Firmicutes (68.53%), Bacteroidetes (27.85%), Proteobacteria (1.98%) and Actinobacteria (0.98%) at the level of phyla. Acarbose treatment led to an enrichment in five genera, including Lactobacillus and Dialister and there was a corresponding decline in six genera, including Butyrivibrio, Phascolarctobacterium, and Ruminococcus[66]. The same study also showed that some species of Megasphaera thrived following acarbose treatment. This species has shown to have many beneficial effects such as conversion of carbohydrates to SCFA's, including butyrate, acetate, valerate and formate. It also utilizes lactate, a harmful end product of carbohydrate metabolism and converts it into SCFA's, including propionate, acetate and butyrate[67].

SULFONYLUREAS

The data so far, suggest a lack of positive effect on the gut microbiota by the use of sulfonylurea. In one study, type 2 diabetic patients treated with metformin were randomized to receive either glipizide or dapagliflozin to analyze their effect on gut microbiome. At the end of 12 wk, neither treatment significantly changed the gut microbiome alpha diversity or composition[68].

Bile acid metabolism and signaling is important for maintaining metabolic health. Changes in the composition and content of plasma bile acids are seen in patients with diabetes and/or obesity[69]. Gu Y *et al*[70] assigned treatment-naïve type 2 diabetes patients to receive either acarbose or glipizide to analyze the plasma bile acids and choose the appropriate anti-diabetic medication for treatment. Acarbose, but not glipizide, led to an increase in the ratio between primary bile acids and secondary bile acids. In the same study, acarbose caused an increase in the abundance of Lactobacillus and Bifidobac-

terium in the gut microbiota[70].

The lack of an alteration in the gut microbiota by sulfonylureas may be partly due to the limited studies that have investigated its role in gut health. However, current literature has shown no organ protection action including cardiovascular protection from the use of a sulfonylurea. This poses a question about its role in gut health and future studies are needed for a better clarification.

CONCLUSION

Recent studies have remarkably improved understanding of the role of the gut microbiota in the pathophysiology of T2DM and metabolic diseases. The role of dysbiosis in the various pathophysiological mechanisms related to altered metabolism of SCFAs, interaction with gut hormones, increased gut microbial metabolite TMAO and endotoxemia in the pathogenesis of T2DM and cardio-metabolic diseases have been demonstrated in numerous studies. The impact of gut microbiota on the therapeutic effects of anti-diabetic medications is becoming increasingly recognized. Altering the gut microbiota is proposed as an attractive method to decrease inflammation and weight gain, improve glucose homeostasis, and prevent cardio-metabolic diseases. The current review has outlined the role of the microbiota in the pathophysiology of T2DM and highlighted the interplay between anti-diabetic medications, the microbiota and some of the known pathophysiological mechanisms. In future, the gut microbiota may be a novel target for new drug development to prevent and treat T2DM and metabolic diseases. However, further studies are needed prior to successful clinical application of gut microbiota modulation.

FOOTNOTES

Author contributions: Kant R, Chandra L and Antony MA designed the outline, performed the writing, prepared the figure and edited the paper; Verma V, Nain P, Bello D and Patel S performed the writing, and prepared the table and figure; Ala S and Chandra R provided the input in writing the paper, performed the writing and edited the paper.

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