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Contents

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Holistic perspective of the role of gut microbes in diabetes mellitus and its management

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Abstract

The gut microbiota (GM) plays a role in the development and progression of type 1 and type 2 diabetes mellitus (DM) and its complications. Gut dysbiosis contributes to the pathogenesis of DM. The GM has been shown to influence the efficacy of different antidiabetic medications. Intake of gut biotics, like prebiotics, probiotics and synbiotics, can improve the glucose control as well as the metabolic profile associated with DM. There is some preliminary evidence that it might even help with the cardiovascular, ophthalmic, nervous, and renal complications of DM and even contribute to the prevention of DM. More large-scale research studies are needed before wide spread use of gut biotics in clinical practice as an adjuvant therapy to the current management of DM.

Key Words: Probiotics; Prebiotics; Synbiotics; Diabetes mellitus; Microbial dysbiosis; Antidiabetic drugs

Core Tip: The emerging role of the gut microbiome on diabetes development, progression as well as prevention has been discussed in this manuscript. The significance of gut dysbiosis in the aetiopathogenesis of diabetes mellitus and its complications has been reviewed. A bidirectional relationship exists between the antidiabetic drugs and the gut microbiome. Faecal transplantation, and bariatric surgery, typically used to treat morbid obesity, have also been shown to improve commensal gut microbiota changes. Diabetic outcomes and management can improve with better understanding of the drug-gut microbiome interactions. There is emerging evidence pointing out that gut biotics can be an add-on therapy with the antidiabetic management. To our knowledge, there is no evidence about the role of gut microbes of diabetic patients who had pancreatic cell transplantation, as well as the role of gut

biotics influencing the management in this group.

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INTRODUCTION

Globally diabetes mellitus (DM) is a common medical disorder and is seen in pandemic proportions[1] with the global prevalence in adult subjects is roughly 10% [2]. The International Diabetes Federation projected by 2035, there will be 592 million cases of diabetes in the world[3]. DM type 1 is secondary to auto-immune- mediated loss of beta-cell function and is seen in 5% of the diabetic population. DM type 2 is mainly due to insulin resistance and is seen in 95% of diabetic subjects[4]. The 2016 US National Health Interview Survey data showed roughly 8.58% of the population had type 2 DM and 0.55% had type 1 DM[5].

Various research has been done in the last decade since the study of the human microbiome in 2012[6,7]. Microbes contribute to 2% of human body weight and the bacterial genomes exceeds human genes by a factor of 150[8,9]. Gut microbiota (GM) varies with age, diet, geographical location, life style, and the use of xenobiotics[10-12]. In the recent years there have been more focus on the GM in the development, progression, and distant organ complications due to DM[13]. Many studies have shown the role of the gut microbiome in DM[14-17].

The gut microbiome starts to develop with the mode of birth and it is influenced by environmental factors, diet, as well as certain medications, including antibiotics[18]. There are differences between the gut microbes seen between non-diabetic and diabetic subjects[20] (Table 1). Gut dysbiosis plays a role in numerous diseases including DM. Both altered GM and endocrine disrupters can influence the development of DM[21]. In this literature review, we analyzed the evidence for the role of GM in the development, pathogenesis, complications, management, and prevention of DM.

LITERATURE SEARCH

A literature search was performed using the electronic databases MEDLINE (1966–February 2021), EMBASE and SCOPUS (1965–February 2021), and DARE (1966–February 2021). The main search items were gut bacteria, GM, intestinal flora, gut dysbiosis, type 1 DM, type 2 DM, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, probiotics, prebiotics, synbiotics, bariatric surgery, and faecal transplantation. Non-English articles were excluded.

GM IN TYPE 1 DM

Studies have shown that Firmicutes/Bacteroides ratio is altered in type 1 DM[22]. In the study by Huang *et al*[23] (2018) negative association was seen with gut microbe *Faecalibacterium* and *Ruminococcacea* and hemoglobin A1c (HbA1c), whereas in the study by Fassatoui *et al*[24]. (2019) a negative association was seen between HbA1c and *Akkermansia muciciniphia*. A systematic review of studies done in Hispanic populations showed that patients with newly diagnosed type 1 DM have high levels of *Bacteroides* with a reduced proportion of *Prevotella*, *Megamonas*, and *Acidaminococcus*. With the initiation of insulin treatment these subjects showed an increase of *Prevotella* levels. Prior to the development of type 1 DM, inverse relationship of Firmicutes/Bacteroidetes ratio has been reported[25].

Table 1 Changes in the microbiome in type 1 and type 2 diabetes mellitus

Location	Change in microbiome	Ref.
Type 1 diabetes		
Gastrointestinal tract	(1) Decreased: *Prevotella*; *Megamona*; *Acidaminococcus*; and (2) Increased: *Bacteriodes*	Elena *et al*[25], 2019
Gastrointestinal tract	(1) Decreased: *Bifidobacterium adolescentis*; *Bifidobacteria*; and (2) Increased: *Clostridium perfingens*; *Bacteroides*	De Goffau *et al* [122], 2013
Gastrointestinal tract	Increased: *Leptotrichia goodfellowii*; *Bacillus cerus*; *Enterobacter mori* LMG 25706	Tai *et al*[123], 2016
Gastrointestinal tract	Increased: *Bacteroidetes/Firmicutes*	Giongo *et al*[124], 2011
Gastrointestinal tract	(1) Decreased: *Faecalibacterium prausnitzii*; and (2) Increased: *Bacteroides dorei*; *Bacteroides vulgatus*	De Goffa *et al* [125], 2014
Gastrointestinal tract	(1) Decreased: *Prevotella*; *Akkermansia*; *Bifidobacterium adolescentis*; *Roseburia faecis*; *Faecalibacterium prausnitzii*; and (2) Increased: *Dialister invisus*; *Gemella sanguinis*; *Difidobacterium longum*	Brown *et al*[126], 2011
Type 2 diabetes		
Gastrointestinal tract	(1) Decreased: *Clostridium coccoides*; *Clostridium leptum*; and (2) Increased: *Lactobacillus*	Chen *et al*[28], 2019
Gastrointestinal tract	(1) Decreased: *Bifidobacterium*; *Bacteroides*; *Faecalibacterium*; *Akkermansia*; *Roseburia*; and (2) Increased: *Ruminococcus*; *Fusobacterium*; *Blautia*	Gurung *et al*[30], 2020
Gastrointestinal tract	(1) Decreased: *Bifidobacterium*; *Akkermansia*; and (2) Increased: *Dorea*	Li *et al*[127], 2020
Gastrointestinal tract	(1) Decreased: *Bifidobacterium*; and (2) Increased: *Lactobacillus*	Sedighi *et al*[31], 2017
Blood	(1) Decreased: *Aquabacterium*; *Xanthomonas*; *Pseudonocardia*; and (2) Increased: *Actinotalea*; *Alishewanella*; *Seiminibacterium*; *Pseudoclavibacter*	Qiu *et al*[38], 2019

GM IN TYPE 2 DM

The type of gut microbes and the changes seen with them influence the development of DM. The prominent GM seen in the intestine are the gram-positive Firmicutes and gram-negative Bacteroidetes and it is influenced by dietary changes[26]. A change in the ratio of Bacteroidetes to Firmicutes is associated with DM[27]. A case-control study done by Chen *et al*[28] (2019) in newly diagnosed type 2 DM subjects, *Lactobacillus* faecal count was significantly higher whereas *Clostridium coccoides* and *Clostridium leptum* was lower, and these changes in the microbes was positively correlated with glycated hemoglobin with higher *Lactobacillus* count subjects, and negatively correlated with decreased *Clostridium* count subjects when compared with healthy controls. Another study found that patients with DM showed an affiliation with the following phyla of bacteria: Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria[29]. Alterations in the gut microbe population may be related to DM, and gut microbes *Ruminococcus* and *Fusobacterium* has been shown with the development of type 2 DM, when compared to healthy adults[30]. A study by Sedighi *et al*[31] (2017) found that patients with type 2 DM has increased levels of *Lactobacillus*, while healthy controls showed increased *Bifidobacterium*. With respect to the *Lactobacillus* genus, there are various mixed results suggesting its association with type 2 DM. Certain strain such as *L. acidophilus, L. gasseri*, and *L. salivarius* have been increased where as *L. amyloyorus* has been decreased[30]. However, many species from this genus, such as *L. plantarum, L. casei*, and *L. rhamnosus* are often involved in probiotic preparation and have shown to be beneficial in diabetic mice models[30]. Overall, it looks that there may be a strain-specific association with DM.

Further changes in the microbiome in patients with DM are listed in Table 1. Nutrient imbalance by affecting the GM can influence the development of type 2 DM. With newly diagnosed type 2 DM different measurement parameters like age, blood lipids, body-mass index, blood pressure, and dietary nutrient intake was related to the gut microbiome composition[32].

RELATIONSHIP BETWEEN GUT AND BLOOD MICROBIOME AND ITS ASSOCIATION WITH TYPE 2 DM

Cani *et al*[33] (2008) in their animal study showed lipopolysaccharide produced by gram negative intestinal bacteria can translocate into systemic circulation through a leaky gut and can result in endotoxemia causing metabolic dysfunction and obesity. Recent evidence points out in addition to gut microbiome, the blood microbiome plays a role in DM. Blood is usually considered to be sterile, but the research suggests the presence of a microbe or microbial component in healthy humans is known as a blood microbiome. The evidence for blood human microbiome is slowly growing[34-36].

In a study by Sato *et al*[37] (2014) with Japanese type 2 DM subjects, blood micro-biome translocation from gut microbiome was detected at a higher rate (28%) in type 2 diabetic subjects when compared with healthy controls (4%) (*P* < 0.01). A recent nested case control study by Qiu *et al*[38] (2019) showed the blood microbe *Sediminibacterium* is associated with increased risk of type 2 DM [Odd ratio (OR) = 14.098, 95%CI: 1.358-146.330] where as the microbe *Bacteroides* in blood have a reduced risk for type 2 DM (OR = 0.367, 95%CI: 0.151- 0.894).

GM AS A COMPLEX ENDOCRINE ORGAN

The regulation of the GI system is done by short-chain fatty acids (SCFA) derived from the metabolism of carbohydrates, and GM plays a role in this function. In addition, the gut microbes produce hormone like chemicals that can act at distant targets. Neuroactive compounds like tryptophan and neurotransmitters like serotonin, dopamine, noradrenaline, GABA, and hormones like leptin, ghrelin and glucagon-like peptide 1 (GLP-1) are indirectly regulated by SCFAs *via* enteroendocrine cells. Overall, the gut microbes produce several substances of a hormonal nature into the circulation which act as distant sites. Because of the GM's ability to influence distant organs and systems as mentioned above it is considered as an endocrine organ. Overall GM functions as an autonomous endocrine organ and plays a role in bodily endocrine actions including neuroendocrine and immunoendocrine regulations[39-42].

DM AND GUT DYSBIOSIS

Gut dysbiosis, is a state of increased or altered prevalence of gut bacteria which might in turn result in many disorders such as gastrointestinal, obesity, DM, immunological, and neurobehavioral diseases[43]. Shifts in the GM's composition with more pathogenic species and phyla can contribute to the above-mentioned diseases. Hyperglycemia was associated with changes of microbiota composition, preferring the non-commensal ones, on the detriment of beneficial phyla such as Bacteroidetes, Proteobacteria, and Actinobacteria. The ratio of Firmicutes/Bacteroidetes has been found to be correlated with plasma glucose concentration. Microbiota are capable to ferment undigested carbohydrates, fiber, and other dietary and xenobiotic compounds to produce SCFAs, which through their ubiquitous receptor play an important role in host glucose metabolism[37,44,45]. The Human Microbiome plays a role in gut permeability, modification of bile acids, glucose breakdown and in the absorption of nutrients[46,47].

Normal commensal bacteria are helpful in maintaining the gut wall integrity, innate immunity, insulin sensitivity, metabolism, and in communication with the brain functions, as well as help to prevent the penetration of harmful microorganisms in the bowel. Bidirectional relationship exists between the GM and the brain. This chain of communication depends on the interaction of gut microbe through immune and neuroendocrine system with the central nervous system. Short-chain fatty acids, such as butyrates, acetates and propionates, produced by the GM are beneficial to different metabolic processes. The imbalance between the microbiome and host organism lead to dysbiosis. Gut microbiome dysbiosis through inflammation and metabolic dysregu-lation increases insulin resistance and influence the development of type 2 DM[48] (Figure 1).

Microbial dysbiosis can also be the result of nutritional imbalance which can lead to a low-grade inflammatory state, obesity, and other metabolic disorders[49]. Gut microbes affect gut permeability, glucose and lipid metabolism, energy homeostasis, and insulin sensitivity. Like any other medical conditions, gut microbes play a role in
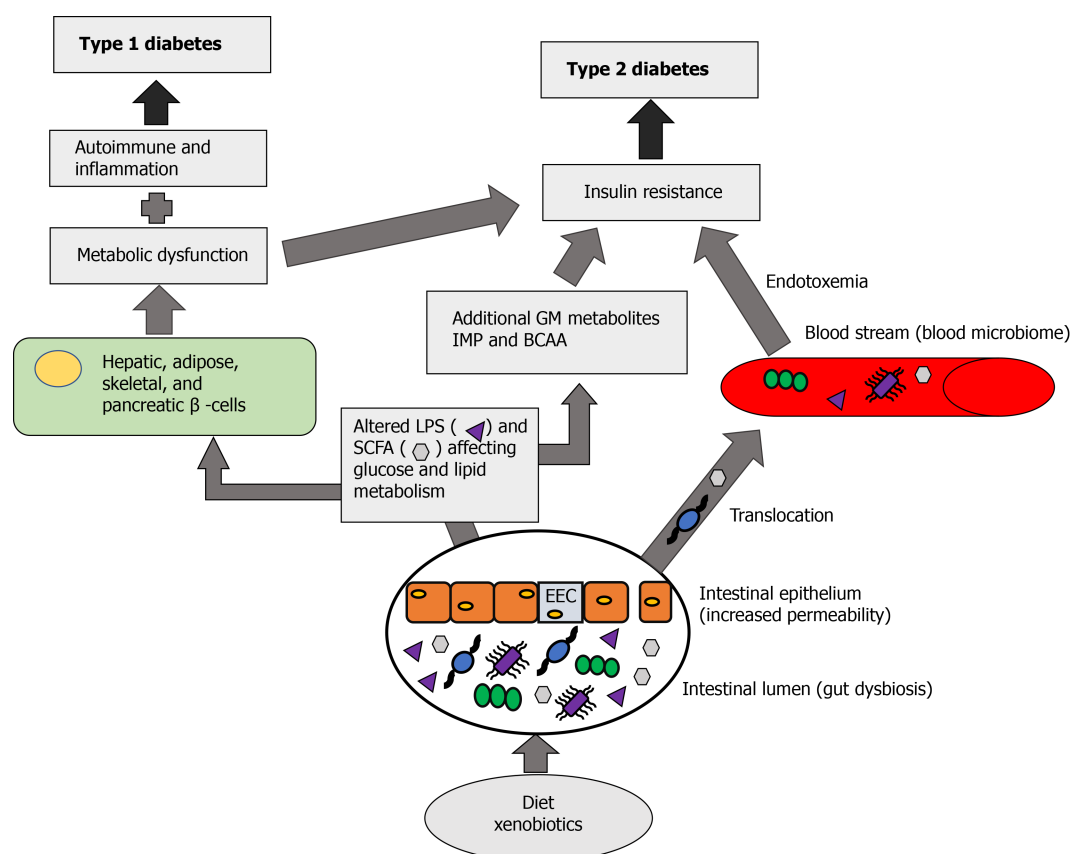
Figure 1 The role of gut dysbiosis in diabetes mellitus. The ingestion of a diet rich in carbohydrates and fats along with certain xenobiotics can lead to a disruption of the gut microbiome (dysbiosis). Under normal conditions, the gut bacteria produce metabolic products such as short chain fatty acids (SCFA) (Hexagons) that act locally and have a positive benefit on metabolism. Under conditions of dysbiosis there can be a disruption to the enteroendocrine cells and lead to gut permeability. This can lead to an increase in these metabolic products as well as bacterial translocation to the bloodstream, leading to endotoxemia resulting in metabolic dysfunction and insulin resistance contributing to type 2 diabetes. Gut dysbiosis also results in altered production of SCFA and release of lipopolysaccharides (LPS) (Triangles) and an increase production of other metabolites such as imidazole propionate and bacteria derived amino acids. These metabolites can act directly to affect insulin resistance. Excess SCFA and LPS can act on hepatic, skeletal, adipose, and pancreatic cells leading to metabolic dysfunction, altered inflammation and immune response which can influence insulin resistance. These factors can contribute to the development of type 1 and type 2 diabetes. SCFA: Short chain fatty acids; EEC: Enteroendocrine cells; LPS: Lipopolysaccharides; BCAA: Bacteria derived amino acids; IMP: Imidazole propionate; GM: Gut microbiota.

inflammation and immunity[50]. A diet rich in fat and sugar may lead to an abundance of lipopolysaccharide (LPS) release from GM and this LPS, by entering into systemic circulation, can affect β-cells, leading to decreased insulin release, and thereby altering systemic insulin sensitivity, resulting in insulin resistance, and potentially leading to DM[51].

Diets rich in carbohydrates and fat as well as xenobiotics (medications affecting the gut microbes) can cause gut dysbiosis. Normally GM produces metabolic products like SCFA, acetate, butyrate and propionate which acts locally leading to beneficial effects on different metabolic process. When there is gut dysbiosis, it can affect the enteroendocrine L-type cells in the intestinal epithelium and increase the gut permeability (leaky gut) causing these metabolic products to enter into the systemic circulation, as well as translocation of the gut microbiome into the circulation leading to the formation of the blood microbiome. This blood microbiome can cause endotoxemia and affect both metabolic dysfunction and insulin resistance. Gut dysbiosis results in excessive production of SCFA and LPS, as well as additional GM metabolites like imidazole propionate (IMP), derived from histidine, and bacteria derived amino acids. Excessive SCFA and LPS by acting on hepatic, adipose, skeletal and pancreatic cells causes metabolic dysfunction, inflammation and altered immune response. When there is a metabolic dysfunction due to gut dysbiosis combined with inflammatory and altered immune response it can cause type 1 DM, and when combined with insulin resistance due to gut dysbiosis as well as the effect of blood microbiome it can lead to the development of type 2 DM (Figure 1).

GUT MICROBES AND METABOLIC NETWORKS

The human gut contains a wide variety of microbial communities that carry out a wide range of biochemical functions that can influence the human body through metabolite production, physiological regulation, and interacting with the host's cellular response and immunity[52]. It has also been found that the host's own genetics can influence the composition of their gut microbiome, making each host a unique ecosystem[53]. Dynamic changes in the gut microbiome have been seen within individuals often in various disease states, such as obesity, and DM[19,54-56]. The GM has been found to cause enhanced transcriptional changes in the intestinal cells and protein biosynthesis in the crypts within the intestine[57].

SCFAs produced by GM can serve as signaling molecules that can influence the host's lipid and glucose levels, liver, skeletal muscle, and even immunity[52]. When there is a disruption of the gut microbiome, the altered mixture of SCFA may influence obesity, insulin sensitivity, weight gain and other comorbidities[58,59]. Obese individuals with type 2 DM have shown changes in the GM that are distinct, from non-diabetic subjects. It was found that individuals with type 2 DM showed an increase level of *Proteobacteria* and *Bacteroides* with a decreased level of *Firmicutes*[19].

The GM has been found to influence the host's metabolism and show great adaptability to the changing environment within the intestines based on diet, genetics, and various physiological cues from the host[52]. The human gut microbiome can modulate absorption as well as nutrient availability within the host. This can be achieved through gene expression changes, alteration of hormones and immunity[52].

ASSOCIATION BETWEEN MICROBIOME, OBESITY AND DM

Microbial diversity and the production of SCFA as well as products such as butyrate, propionate, and acetate have been found to have a protective role against obesity and insulin resistance[60,61]. SCFAs are able to act as signaling molecule that can activate a variety of pathways that are involved in cholesterol, lipid, and glucose metabolism [58]. Modifications of the microbiome can influence metabolic parameters, in particular when there is a higher abundance of Firmicutes leading to a higher Firmicutes/Bacteroidetes ratio that may be linked to obesity[62]. This may in part be due to the fact that Firmicutes are more efficient at promoting the nutrient absorption leading to subsequent weight gain compared to Bacteroidetes[63].

A study showed the GM composition is different in obese subjects with and without type 2 DM[20]. A recent study also showed for the first time in subjects with type 2 DM the relationship between body composition and GM[64]. Faecal microbiota of obese subjects without DM had increased numbers of SCFA producing microbes, whereas obese subjects with type 2 DM had less beneficial SCFA butyrate producing microbes[65].

ROLE OF GUT MICROBES IN THE PROGRESSION OF DM

The progression of DM is seen as macrovascular[66] and microvascular complications like retinopathy, nephropathy, and neuropathy[67]. Gut microbes seem to play a role in the progression of DM and also shown to play a role in these complications. Diet induced diabetic animal models helps to study these complications[68]. Studies have shown that subjects with DM and eye complications have higher bacterial conjunctival flora when compared to subjects without DM[69-72]. Beli *et al*[73] (2018) in their animal study showed the association between the GM and diabetic retinopathy (Table 2). More research is needed to understand the mechanism how GM causes diabetic retinopathy[74].

Diabetic neuropathy is seen as autonomic neuropathy as well as distal sensory and motor neuropathy and correlate with diabetic control, and GM also seems to play a role[75]. In a human study with early diabetic nephropathy, Barrios *et al*[76] (2015) showed an increase in colonic GM, whereas with end-stage renal disease patients microbes producing urease, uricase, p-cresol and indole-forming enzymes were seen [77]. The proposed mechanisms for progression of kidney disease could be due to GM imbalance, metabolic shifts, immunosuppression, inflammation, as well as accumulation of uremic toxins[78].

Table 2 Selected animal studies showing the effect of various interventions on the gut microbiome and the role of gut microbiota in diabetes mellitus management

Intervention	Organism	Health benefit	Change in microbiome	Ref.
Intermittent fasting	Mice	Protection from diabetic retinopathy by increasing Tauroursodeoxycholate (a neuroprotective bile acid) producing microbes	Increased Firmicutes and decreased Bacteroidetes and Verrucomicrobia in diabetic mice undergoing intermittent fasting	Beli *et al* [73], 2018
Antibiotic treatment (ampicillin, metronidazole, neomycin, vancomycin, or their cocktail)	Mice	Reduction in fasting glucose. Change in glucose tolerance (seen with ampicillin, vancomycin, or cocktail)	Alterations in the α- and β- diversity. An association with *Akkermansia mucinipjila* with decrease fasting glucose. The effect is mediated through systemic changes in glucose metabolism	Rodrigues *et al*[94], 2017
Prebiotic: Acorn and sago	Mice	Mice fed acorn and sago derived prebiotics had an amelioration of the glucose intolerance and insulin resistance induced by a high-fat diet feeding. Intake of both novel prebiotics as well as inulin increases SCFAs levels in the mouse gut		Ahmadi *et al*[103], 2019
Combination of a functional fibre [PolyGlycopleX (PGX) with metformin (MET) or sitagliptin and metformin (S/MET)]	Mice	PGX + MET and PGX + S/MET showed reduced glycemia compared to controls and single treatment (P = 0.001). HbA1c was lower in PGX + S/MET compared to all other treatments (P = 0.001)		Reimer *et al* [93], 2014
Artificial sweetener (Neotame)	Mice	Decreased butyrate synthetic genes in Neotame group. Higher concentrations of cholesterol ($P < 0.05$) and fatty acids ($P < 0.05$) in Neotame treated mice feces	Reduction in α-diversity and altered β-diversity. Reduced Firmicutes ($P < 0.01$) and increased Bacteroides ($P < 0.01$)	Chi *et al* [85], 2018
Combination of metformin and a prebiotic [konjac mannan-oligosaccharides (MOS)]	Mice	Combination of metformin and MOS help ameliorate insulin resistance and improved glycemic control ($P < 0.05$) and repair islet and hepatic histology	Metformin and MOS change the microbiome ($P < 0.0001$) with: Decreased: Rikenellaceae and Clostridiales; Increased: *Akkermansia muciniphila* and *Bifidobacterium pseudolongum*	Zheng *et al* [96], 2018

MANAGEMENT

In DM, normal GM can be restored using diet, gut biotics, faecal transplantation, and bariatric surgery, which may help with the proper management of DM.

Faecal transplant, bariatric surgery

There is some evidence from human studies, that both faecal transplant and bariatric surgery improved the glucose and metabolic parameters by altering the GM[48]. A meta-analysis done by Magouliotis *et al*[79] (2017) showed some discrepancy between the human studies and the benefits witnessed from bariatric surgery. Another study looking at obese insulin resistant subjects who received allogenic faecal transplants from a lean insulin sensitive donor show improved insulin sensitivity for a short period of 6 weeks, however the benefit was not seen past 12 weeks[80] (Table 3).

Nutritional therapy

Diet can modulate the GM and play a role in the management of DM by preventing gut dysbiosis[81] (Table 2). Fruits and vegetables contain polyphenols which can increase beneficial GM like *A. muciniphila*, *Lactobacilli* and *Bifidobacteria*[82]. Unbalanced dietary intake can affect the structure and abundance of GM which can play a role in the development of DM[83].

Artificial sweeteners

Artificial sweeteners are no-calorie sugar substitutes, may induce glucose intolerance by affecting the gut microbes. In an animal study with saccharin-fed mice showed an increase in Bacteroides and a reduction in *Lactobacillus reuteri* leading to GM dysbiosis and glucose intolerance[84]. Similar effects were seen in another study by Chi *et al*[85] (2018) using the artificial sweetener, Neotame. In a cross-sectional human study by Frankenfeld *et al*[86] (2015), showed sweeteners like aspartame or acesulfame-K found no effect on gut bacterial abundance. A recent randomized-blinded crossover study in healthy participants did not demonstrate measurable changes in the GM or in SCFAs after 14 d daily intake of aspartame and sucralose[87]. These preliminary observations

Table 3 Selected human studies showing the effect of diet, gut biotics, faecal transplantation and bariatric surgery on gut microbiome and the role of gut microbiota in diabetes mellitus management

Intervention	Organism	Health benefit	Change in microbiome	Ref.
Probiotics	Human	Decreased fasting blood glucose and HbA1c levels. Increased HDL levels, however no significant effect on BMI and LDL levels were found		Kocsis *et al*[112], 2020
Artificial sweeteners (aspartame and acesulfame-K)	Human		Compared to controls, aspartame and acesulfame-K had different bacterial diversity ($P < 0.01$, $P = 0.03$ respectively), compared to controls	Frankenfeld *et al* [86], 2015
Probiotics, Prebiotics, or synbiotics	Human (meta-analysis)	The use of probiotics, prebiotics, or synbiotics showed a decrease in FBG ($P < 0.01$), total cholesterol ($P = 0.02$), triacylglycerols ($P = 0.01$) and insulinaemia ($P < 0.01$), as well as increased HDL-cholesterol levels ($P < 0.01$. Even though HbA1c reduction is seen it is not statistically significant. No effect on LDL-cholesterol was seen		Bock *et al*[115], 2020
Laparoscopic sleeve gastrectomy	Human	Decreased weight and BMI. Restored insulin tolerance and type 2 DM remission	Increased: *Bacteroidetes/Firmicutes* ratio at 1- and 3-months post surgery. *Lactobacillales*	Kikuchi *et al* [128], 2018;Li *et al*[129], 2013
Roux-en-Y gastric bypass	Human	Type 2 DM remission and improved BMI and weight loss. Improved gastric emptying and bile acid metabolism	Decreased: *Bacteroidetes/Firmicutes* ratio. Improved probiotic supplementation effects due to lowered pH environment	Selber-Hnatiw *et al*[52], 2020; Li *et al*[129], 2013

BMI: Body mass index; HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

needed to be established in future human research studies.

ALTERATION OF GM BY ANTIDIABETIC DRUGS AND ITS ROLE IN DM MANAGEMENT

Antidiabetic drugs can influence the gut microbiome by affecting the drug microbiome interface, whereas the gut microbiome also influences the metabolism and play a role in the efficacy of antidiabetic drugs. The interactions of antidiabetic drugs and microbiota is getting more attention as it may play a role in the management of DM [88]. Antidiabetic agents cause alteration of the specific gut microbes. Metformin increases the population of *Akkermansia muciniphila* by 18-fold, enhancing the digestion of mucin and increasing SCFA[89]. Metformin, in addition to *Akkermasia*, causes increase in *Lactobacillus* and *Bifidobacterium*, whereas insulin increase *Fusobacterium* [90]. This first line antidiabetic agent in type 2 DM modifies the GM, alter the bile acid circulation and thereby a possibility that primary site of action may be gut and the GM [91].

Understanding the pharmacokinetics, pharmacodynamics and pharmacomicro-biomics of antidiabetic medications and gut microbes can help to understand drug-gut microbiome and its potential benefit with antidiabetic drugs. Overall, it may help to better manage the DM management[92].

Antidiabetic drugs have been shown to affect the different gut microbes and their metabolic effects through the medication-microbiome-metabolism axis. GM can influence the pharmacokinetics of various antidiabetic drugs such as drug absorption, drug metabolism which can affect the potency of these medications. Overall, there is a bidirectional relationship exist between antidiabetic drugs and gut microbes[88].

Different combinations of antidiabetic drugs are used to better control DM. The commonly used combination is metformin with sulphonylureas, thiazolidinediones, DPP-4 inhibitors and insulin. One animal study showed some delay in the progression of DM when sitagliptin/metformin combination given with a prebiotic fibre[93]. Currently, there is a need for more research of different combination therapies on GM.

GUT BIOTICS AND DM

Animal studies

Several animal studies have showed that gut biotics, like prebiotics and probiotics, can improve the efficacy of antidiabetic drugs. Treatment with individual or a cocktail of antibiotics reduced dysbiosis and decrease fasting glucose but did not affect body weight, as well as antibiotic treatment also changed gene expression in the ileum and liver, and shifted the alpha (α) and beta (β) diversities of GM[94]. In an animal study with mice, combining probiotics and/or prebiotics with antidiabetic medications showed an improvement in glycemic control and insulin sensitivity[95]. A study by Reimer *et al*[93] (2014) found that using a combination of sitagliptin and metformin with a functional fiber can delay DM progression. In an animal study usage of mannan-oligosaccharides by altering the GM increased the hypoglycemic effects of metformin[96]. Yang *et al*[97] (2020) found that Genistein found in soybeans and soy derived foods (prebiotic) helped to improve glucose and lipid metabolism by altering GM composition[97]. In another animal study, certain GM like *Bacteroides fragilis, A. muciniphila, L. plantarum*, *L. casei* can induce interleukin 10 (IL-10), which has been shown to improve both insulin resistance and glucose metabolism[98] (Table 2).

Human studies

Many gut microbes have been shown to have antidiabetic effect in humans by different mechanisms including effect on insulin sensitivity[99]. *Roseburia intestinalis* can improve insulin sensitivity by increasing IL-22 production[100]. Some strains of *Lactobacilli* act like acarbose and have been shown to inhibit alpha glucosidase[101]. Prebiotics can feed the gut microbiome and increase the population of L-cells in the intestine and thereby increase the amount of GLP-1[102] and prevent high fat diet induced insulin resistance[103]. In the recent PREMOTE randomized control trial (RTC) study, probiotics showed antidiabetic effect by altering metabolic homeostasis [104]. Thus, GM may be useful in the management of DM[105]. Jafarnejad *et al*[106] (2015) and Asemi *et al*[107] (2014), in their two studies showed multi-probiotic supplement as well as synbiotic *(L. sporogenes* plus inulin) product helps to reduce glucose and other metabolic parameters. Tonucci *et al*[108] (2015) in their double-blind RCT study comparing fermented milk containing *L. acidophilus (LA-5)* plus *B. animalis (Lactis BB-12)* with plain fermented milk in 45 type 2 DM subjects showed decreased in HbA1c as well as low-density lipoproteins cholesterol and inflammatory cytokines. Multiple RTCs and the meta-analysis of these RCT's with different gut microbes demonstrated antidiabetic effect as well as effect on different metabolic parameters [109-111] (Table 3).

A recent meta-analysis of 14 RCTs showed significant decrease in HbA1c in the probiotic group compared to placebo controls, weighted mean difference (WMD) is -0.33%, 95%CI -0.53 to –0.13, $P = 0.001$. In this meta-analysis, probiotics significantly reduced fasting blood glucose, insulin, lipid profile and inflammatory marker in addition to blood pressure levels[112]. Another meta-analysis showed similar result with reduction in HbA1c% (WMD = - 0.24, 95%CI: - 0.44 to - 0.04, $P = 0.02$), fasting blood glucose (WMD = - 0.44 mmol/L, 95%CI: - 0.74 to - 0.15, $P = 0.003$)[113,114]. A meta-analysis study done in 2021 with probiotics, prebiotics or synbiotics on type 2 DM also showed significant improvement in glucose and other metabolic parameters [115]. Prebiotic inulin improves glycemic control in young adults with type 1 DM [116]. Certain specific species of probiotic microbes as well as certain prebiotics by altering the GM was shown to improve the auto-immune condition, which plays a major role in the pathogenesis of type 1 DM[117].

A study by Didari *et al*[118] (2014) looked at the safety of probiotics and synbiotics and found that certain populations, such as patients who are immunocompromised, with cardiac valvular disease, having a central venous catheter, or those with short-bowel syndrome may have an increased risk for systemic infections. Thus, caution may be warranted when using these products in diabetic patients and a risk-benefit analysis should be considered.

GUT MICROBES AND THE PREVENTION OF DM

Some preliminary evidence in animal studies indicates altering GM may help to prevent DM[119,120]. A recent study by Gurung *et al*[30] (2020) showed with certain gut microbes like *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Akkermansia* and *Roseburia* have a negative association with DM and appears to be protective. In 42

healthy adults, GM *Lactobacillus johnsonii* seems to reduce the risk of type 1 DM[121].

CONCLUSION

Gut dysbiosis plays a role in the development and progression of DM. The current evidence also points out that the GM can play a role in DM related complications. Modulation of the gut bacteria or dysbiosis can be corrected by fibre, diet, antidiabetic medications, and by using gut biotics like prebiotics, probiotics, and synbiotics as well as by bariatric surgery and faecal transplantation. The interaction between gut microbes and antidiabetic agents is a promising field that may change the landscape of DM management in the future. There is some preliminary evidence to show that GM may play a role in the prevention of DM. More research is needed on a large scale to confirm these findings.

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