Review

Role of Gut Microbiota in Pathogenesis and Treatment of Type 2 Diabetes

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Abstract

In developing countries, Type-2 Diabetes mellitus accounts for 80% of premature mortality. T2DM is characterized by a combination of low production of pancreatic beta cell insulin and peripheral resistance to insulin. The gut microbiota is well known for its function in human health preservation. Altering the composition of the microbiota affects the host reaction to the metabolism of lipids, glucose and carbohydrates. Alteration in gut microbiota composition is associated with T2DM through diminished beneficial effects of short chain fatty acids. There have been reports that suggest the effect of antidiabetics occurs through gut modulation. Modern probiotics have been developed, and the mechanisms underlying their beneficial effects on T2DM have been elucidated. By restoring intestinal functional integrity and reversing gut dysbiosis, manipulating the gut microbiota may be advantageous in T2DM. Human intestinal microbiota is thought to be a possible source of novel therapies for metabolic disorders like T2DM. This treatment is completely safe, reliable, and has no side effects and also it is also very easy to obtain. More evidence from human trials is needed to validate the beneficial effects of probiotics.
Keywords: Antidiabetics, gut dysbiosis, probiotics

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Among metabolic disorders, Type 2 diabetes mellitus (T2DM) alone leads to 80% premature mortality in developed countries due to metabolic disorders.[1] In the previous 3-4 decades, the incidence of diabetes has increased significantly due to lifestyle changes like unhealthy eating habits, less physical activity and exposure to adverse environmental factors such as stress, vitamin D deficiency.[2] Metabolic disorders pathophysiology is complex and multifaceted and is not well understood.[3] However, such conditions may be caused by genetic, epigenetic, environmental and medical variables.[4] The gut microbiota is well known to play a major role in preserving human health and the immune system. Microbiota is known as an endocrine organ controlling the human body's activity.[5] Altering the composition of the microbiota affects the host reaction to the metabolism of lipids, glucose and carbohydrates. The imbalance or dysbiosis can cause various disease conditions or can exacerbate the severity of diseases such as ulcerative colitis, crohn's disease, inflammatory bowel disease, colorectal cancer food allergy and non-alcoholic steatohepatitis.[6-14] In addition, intestinal microbiota (IM) changes have also been linked with the progression of chronic low-grade inflammation which is associated with T2DM.[15] Modern probiotics have been developed and their mechanisms have been elucidated that are responsible for their beneficial effects on metabolic disorders. Research studies have shown that an increased intake of dietary fibre can be a potential alimentary strategy for IM

modulation that can alleviate and prevent the phenotypes of T2DM.[16] The growth of IM is supported by dietary fibres and in exchange, these bacteria produce Short chain fatty acids (SCFAs) for instance acetate, butyrate, and propionate, for the fermentation of these dietary fibres. SCFAs are thought to mediate the beneficial effects of dietary fibre by reducing inflammation and controlling glucose and energy homeostasis, among other things and by providing energy sources to the luminal colon cells.[17] Insulin sensitivity is shown to be enhanced in persons at risk of T2DM after faecal microbiota transplantation (FMT) from health donors.[18,19] Metformin, the first-line antidiabetic drug, has been shown to exert some of its effects through the alteration of microbiota in naive T2DM.[20] A complete account of species diversity and their functional mechanisms needs to be further clarified for therapeutic purposes due to the complex association between gut microbiota and health.

Gut Microbiota and Their Role in Metabolism

The gut microbiota is a complicated network of microbes that is vital to the health of the host. *Actinobacteria* (*Bifidobacteria*), *Bacteroidetes* (*Porphyromonas*, *Prevotella*, *Bacteroides*) and irmicutes (*Ruminococcus*, *Clostridium*, *Lactobacillus*, and *Eubacteria*) are the three main group of organisms present in gut. These microbes carry an important role in the development of SCFAs, control of bile acid metabolism and induction/protection of metabolic endotoxemia.[21] In the fermentation of dietary fibres, gut microbiota has been involved. This approach contributes to the production of propionate, acetate, and butyrate i.e., SCFAs. Propionate is an important energy source for the host by de novo lipid and liver glucose synthesis. Acetate is used in peripheral tissues as a medium for cholesterol synthesis, and butyrate is a rich energy source for the epithelial cells that line the colon. In addition to playing a key role in host metabolism, studies indicated that gut microbiota often play a modulatory role in obesity by regulating energy balance, food intake, and satiety through gut peptide signalling, hormonal effects in the blood, or by directly modulating the nervous system.[22] Obesity leads to increased levels of inflammation and fatty acids, leading to resistance to insulin, which can lead to T2DM.[23] T2DM is characterized by a combination of low production of pancreatic β-cell insulin and peripheral resistance to insulin. Insulin resistance results in increased plasma fatty acids, resulting in reduced glucose transport through muscle cells, as well as increased fat breakdown, resulting in increased hepatic glucose production.[24] It suggests that dietary or other manipulation of the gut microbiota can provide beneficial effects by restoring intestinal functional integrity and reverse dysbiosis, and therefore, human IM is thought to be a source of novel therapies for the management of metabolic disorders.

Role of Short Chain Fatty Acids in Pathogenesis of T2DM

SCFAs are small molecule metabolites produced by dietary fibres microbial fermentation.[25] Colonocytes rapidly absorb the SCFAs produced in the digestive tract, with only less than 10 percent excreted in faeces.[26] SCFAs were being used as substrates in mitochondrial β-oxidation and the citric acid cycle to produce energy after absorption by colonocytes.[27] SCFAs that are not used as substrates for energy in colonocytes are transferred through the portal circulation to the liver and can be used by hepatocytes as energy substrates.[28] Besides this, the liver uses acetate and butyrate as substrates for the production of cholesterol and long-chain fatty acids[29] and propionate is converted via the tricarboxylic acid (TCA) cycle into glucose.[30] To remind the brain about the intestinal metabolic condition, SCFAs can cross the blood-brain barrier (BBB),[31] but the brain uptake of SCFAs is very low. A depletion of SCFAs plays a central role in the growth of T2DM.[32] T2DM pathogenesis is dependable with overexpression and abnormal recruitment of Histone deacetylases (HDACs) and the SCFAs are natural inhibitors of HDACs (group of proteases that are responsible for deacetylation of histone and non-histone proteins which ensure that DNA is negatively charged and inhibit gene transcription).[32,33] By entering cells through transporters, SCFAs may either act directly on HDACs or indirectly through G-Protein coupled receptor (GPR) activation. The beneficial effects of SCFAs in T2DM pathogenesis are mediated by GPR interaction and/or HDAC inhibition.[34]

SCFAs even regulate the brain's energy homeostasis by controlling metabolic hormone secretion, intestinal gluconeogenesis (IGN) induction, vagal afferent neurons stimulation and central nervous system regulation (CNS).[35] SCFAs can monitor the secretion of metabolic hormones associated with appetite and energy intake, i.e., leptin and ghrelin.[36] Leptin is an anorexic hormone that is secreted by adipose cells and reduces food consumption by activating hypothalamic proopiomelanocortin neurons.[37] The key hunger hormone is ghrelin which is produced in the stomach and duodenum by ghrelin cells and stimulates hypothalamic somatostatin neurons to control feeding.[38] SCFAs can cause enteroendocrine-L cells to secrete GLP-1 (Glucagon like peptide-1) and PYY (Peptide YY).[39] Glucose dependent insulin secretion is enhanced by GLP-1 which is an anorexic incretin hormone.[40] The anorexic neuropeptide PYY works by inhibiting peristalsis, suppressing appetite, and improving pancreatic-cell resilience and function, which is a beneficial in management of T2DM.[41] Therefore, by regulating metabolic hormones such as GLP-1, PYY, leptin, and ghrelin, SCFAs can have beneficial effects on ap-

petite suppression and lower energy intake.[42] SCFAs can induce inhibition of appetite and influence energy homeostasis by regulating hormone-regulating appetite secretion and inducing intestinal gluconeogenesis metabolism (Fig. 1).[42] Therefore, SCFAs can regulate glucose homeostasis by decreasing gluconeogenesis, improving glucose uptake and glycogen synthesis in the liver, increasing pancreatic-cell mass, and regulating insulin secretion.

Probiotics and Their Impact on Diabetes Mellitus

There is an immense amount of literature on the role of probiotics in human health. For multiple diseases, probiotics deliver a tempting preventive treatment, the most striking proof of the possibilities of microbiota modulation to treat diseases.[43] With passive or active strategies, gut microbiota can be modulated and probiotics are becoming new preventative and medicinal instruments.[44] IM changes are closely related to the development of intra-intestinal and extra-intestinal diseases, as well as many immunological diseases. [45] The technique of modulating the function of the gut microbiota has been under intensive study to shed more light to address these difficulties. The role of specific bacteria in modulating blood glucose levels in T2DM is known by today. [46] To clarify the role of probiotics in diabetes, several other principles are suggested. Some forms of probiotic bacteria may have immune-modulatory effects to counteract chronic inflammation due to changes in the gut microbiome.[47-49] The effect of low-grade chronic inflammation in the progression of T2DM is well established.[50] Probiotic strains can also increase the development of Interleukin-10 (IL-10), which in diabetic mice model is a very significant regulatory and anti-inflammatory cytokine. Increases in IL-10 have been reported to down-regulate proinflammatory cytokines such as Interferons-γ (IFN-γ) and IL-2/IL-1β, contributing to low-grade inflammation prevention and the onset of diabetes. [51] The use of *Lactobacillus* reuteri GMNL-263 in a recent study was found to decrease T2DM markers such as serum glucose, glycated haemoglobin and C-peptide 46. Inflammatory cytokines IL-6 and Tumour necrosis factor-α (TNF-α) levels in adipose tissue were also found to be lower in the same research along with Glucose transporter type-4 (GLUT-4) and Peroxisome proliferator activated receptor- γ (PPAR-γ) down-regulation. In order to minimize the high-sensitivity C-reactive protein level, which is also involved in T2DM, daily intake of probiotic yoghurt can reduce inflammatory markers.[52,53] In addition to these results, certain probiotic strains are capable of reducing pancreatic tissue oxidative stress, thereby decreasing chronic inflammation and apoptosis of pancreatic cells.[54] Probiotic strains have been found to decrease LDL cholesterol and total serum cholesterol by modulating lipid metabolism, which can be viewed as a risk reduc-
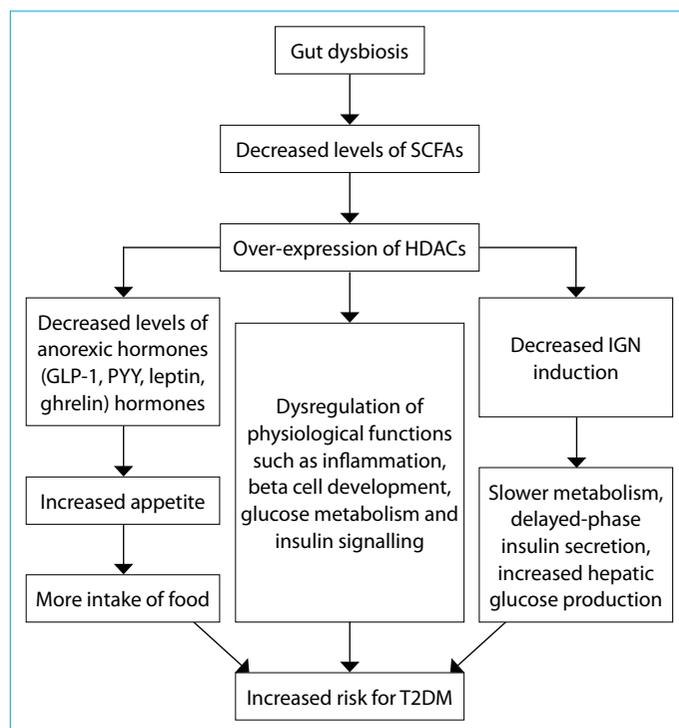

Figure 1. Association between gut dysbiosis and increased risk for T2DM.

tion factor for T2DM.[55] Oral administration of *Lactobacillus casei* Shirota increased lipopolysaccharide-binding protein expression in plasma and alleviated endotoxemia in a murine model of obesity and T2DM.[50] *Bifidobacterium* animalis subsp. lactis 420 has been shown to limit bacterial translocation in the intestinal tissues and to decrease metabolic bacteraemia in the early stages of T2DM.[56] Administration of L. casei Zhang[57] to animals with high fructose-induced hyperinsulinemia has been found to enhance impaired tolerance of glucose. The interrelationship between the gut microbiome and metabolic functionality and their role in diabetes mellitus is confirmed by these findings.

Antidiabetics and Their Effect on Gut Microbiota
Metformin

Metformin is the first-line treatment for T2DM patients to be used by physicians to control hyperglycaemia without causing side effects such as hypoglycaemia or weight gain or other cardiovascular complications.[58] Metformin mainly acts by blocking mitochondria-mediated respiratory chain complexes, resulting in decreased production of glucose in the liver.[59] Several studies show that metformin triggers GLP-1 secretion and suppression of serum bile acid and correlates well with changes in the *Bacteroidetes/Firmicutes* ratio.[60,61] Metformin contributes to the glucose metabolism by the help of IM.[62] Metformin has been shown in some studies to improve the dysbiosis of IM and induce mucin

expression in the same way as *Akkermansia muciniphila* does.[63] *A. muciniphila* is a common microbe found in the human gut, accounting for around 1%-3% of the total gut microbiota. *A. muciniphila* has the ability to be a biomarker for a number of metabolic and inflammatory diseases. The mechanism by which *A. muciniphila* work is discovered to be an immunomodulatory protein called "Amuc 1100," which is embedded in the bacterial outer membrane. The endocannabinoid (eCB) system is also affected by *A. muciniphila*, which is an important regulatory mechanism in the battle against obesity, type 2 diabetes, and inflammation.[64] According to reports, the eCB system controls glucose and energy metabolism.[65] The administration of both *Akkermansia* and metformin to mice fed a high-fat diet results in a decrease in IL-1 and IL-6 expression in adipose tissue. These studies show that *Akkermansia* and metformin are similar in terms of enhancing the metabolic profile by reducing tissue inflammation in diet-induced obesity.[60] Metformin promotes the development of SCFA-producing bacteria that include *Blautia*, *Bacteroides*, *Butyricoccus*, and *Phascolarctobacterium*, as well as the *Proteobacteria phylum*; the genera *Allobaculum* and *Lactobacillus*.[66] Therefore, during hyperglycaemic conditions the bacterial population in combination with metformin can control glucose metabolism.

Alpha-Glucosidase Inhibitors

The absorption of carbohydrates, such as disaccharides and starch, in the small intestine is slowed by the class of medication called alpha-glucosidase inhibitors (α-GIs), reducing postprandial hyperglycaemia. As a consequence, α-GIs impact bacteria's nutrient sources by partitioning complex carbohydrates/dietary fibres.[67] The α-GI i.e., Acarbose can prevent *E. coli* from growing on maltose by blocking the maltose importer.[68] Miglitol can alter the human gut environment by reducing transit time and reversing the rise in *Erysipelotrichaceae* and *Coriobacteriaceae* caused by an energy-dense diet.[69] Acarbose raises starch and butyrate concentrations in the faeces while lowering propionate levels. This indicates that acarbose inhibits starch use by propionate-producing bacteria while preventing production and absorption of starch, as well as improving bacteria that ferment starch and produce butyrate.[70] *Bifidobacterium* and *Lactobacillus*, along with other bacterias that produce SCFA including *Faecalibacterium* and *Prevotella*, were found to increase after acarbose was given to T2DM patients.[71] The increased concentration of Dialister following acarbose treatment is negatively associated with HbA1c, suggesting that species belonging to this taxon may play a role in glucose metabolism regulation. Ultimately, acarbose treatment was related to a decrease *Enterobacteriaceae*, *Bacteroidaceae*, and lecithinase positive *Clostridum* in human faeces.[72]

Incretin-Based Drugs

After a meal, intestinal cells secrete incretins, which are small peptide hormones.[73] Currently, two peptides are known as incretins: GIP (gastric inhibitory peptide) and GLP-1.[74] Both incretins are mainly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) and exist in the body in both active and inactive forms.[75] Two types of incretin-based drugs have been developed to improve the beneficial effects exerted by incretins: DPP-4 inhibitors (DPP-4i) and GLP-1 receptor agonists (GLP-1 RA).[76] Incretin secretion is also influenced by gut microbiota fermentation products. The G-protein-coupled free fatty acid receptors FFAR2 and FFAR3 activate GLP-1 secretion which is stimulated by acetate and propionate in primary murine colonic cultures.[77]

i. GLP-1 Receptor Agonists

GLP-1 RA are modified peptides homologous to subcutaneously injected GLP-1.[78] GLP-1 levels, which affect gut transit time and gastric emptying rate, may alter the internal environment of the gut lumen (local pH value and nutrient composition), affecting microbiota composition. A GLP-1 RA drug i.e., Liraglutide the improved the concentration of *Firmicutes*, while the *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* phylas are depleted. Liraglutide treatment increases the abundance of 13 phylotypes in the genera *Allobaculum*, *Turicibacter*, *Anaerostipes*, *Blautia*, *Lactobacillus*, *Butyricimonas*, and *Desulfovibrio*, while decreasing the abundance of 20 phylotypes in the orders *Clostridiales* and *Bacteroidales*.[79] Liraglutide has been shown to increase the growth of *Blautia*, *Coprococcus*, *Lactobacillus*, *Turicibacter*, and bacteria, as well as decrease the no of obesity-related phylotypes (*Candidatus Arthromitus*, *Erysipelotrichaceae* incertae sedis, *Marvinbryantia*, *Roseburia*, and *Parabacteroides*).[80] Just a few investigations have looked at the impact of GLP-1 RA on gut microbiota, and details on some other GLP-1 RA, such as albiglutide, dulaglutide, exenatide or lixisenatide is absent.

ii. DPP-4 Inhibitors

A DPP-4i called Sitagliptin has been shown to restore IM structure at the phylum level without altering body weight. Sitagliptin raises the relative abundance of *Bacteroidetes* and *Proteobacteria* while decreasing the relative abundance of *Firmicutes*. Sitagliptin has an effect on SCFA-producing bacteria at the genus level, that, it prevents *Bifidobacterium* reduction and increase *Lactobacillus* reduction.[81] One phylotype associated with weight gain i.e., *Candidatus Arthromitus*, was able to minimize the abundance of the Saxagliptin.[79] There are currently no reports on the impact of other DPP-4i on the gut microbiota, such as alogliptin, vildagliptin, or linagliptin.

Role of Other Antidiabetic Drugs on Gut Microbiota

Any studies on the effect of sodium glucose co-transporter-2 (SGLT-2) inhibitors or meglitinides on the gut microbiota is limited, as is knowledge of sulfonylureas and thiazolidinediones. Sulfonylureas influence on the composition of the gut microbiota is uncertain. Just one study looks at the impact of thiazolidinediones on the gut microbiota and findings suggests that diet-induced obesity in rats is related to a growth in inflammatory markers like TNF-α, IL-6 and Monocyte Chemoattractant Protein (MCP-1) as well as a decrease in the anti-inflammatory cytokine IL-10. Pioglitazone administration decreases the abundance of *Proteobacteria* in high fat fed rats, which appears to be related to lower plasma endotoxin, TNF-α, IL-6, and MCP-1 levels. Pioglitazone only tends to partly relieve gut dysbiosis and inflammation caused by a high fat diet.[82]

Gut Microbiome and Antibiotics

Antibiotics suppress not only pathogenic bacterial activity, but also the activity of the commensal microbial community in the gut. A change in the gut microbial population as a result of antibiotic use has been related to the progression of DM in several studies.[83] As treatment with antibiotics can suppress IM, therefore it may decrease SCFA levels.[84] The relationship between the gut microbiome and T1D, on the other hand, is poorly known. While several studies show that antibiotics usage alters the composition of gut microbiota i.e., depletes the levels of Enterovirus, which protects against virus-induced T1D and because of that children with diabetes have a smaller variety of gut microbiota.[85] When compared to genetically prone children that do not have diabetes, there is also a decline in *Bifidobacterial* spp. and a rise in *Bacteroides* spp.[86]

Conclusion

Metabolic problems are often linked to dysbiosis of the gut microbiota. The primary treatment for metabolic disorders is lifestyle modification. The best way to treat metabolic disorders is to manipulate or modulate the dysbiosis of the gut microbiota. Probiotic treatment can affect glucose metabolism, insulin sensitivity, body weight, and inflammation by modifying the gut microbiota. This treatment is completely safe, reliable, and has no side effects. It is also very easy to obtain. Metformin and α-glucosidase inhibitors have been shown to have a positive effect on the microbiome and its influencers, which is important for human health. Other anti-diabetic medications, on the other hand, have limited or no data. More evidence from human trials is needed to validate probiotics' beneficial effects on metabolic disorders. So, there is still a long way to go before these candidates can be used in clinical settings.

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