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Review

Gut microflora: the unheeded factor in type 2 diabetes mellitus: a review

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Abstract

Type 2 Diabetes Mellitus is rising globally. The pathogenesis of Type 2 Diabetes Mellitus remains unclear. Recent research indicates that the composition of the intestinal microbiota is linked to obesity and type 2 diabetes. This article provides an overview of the involvement of intestinal microbiota in the etiology of type 2 diabetes. The intestinal microbiota affects body weight, bile acid metabolism, inflammation, insulin resistance, and gut hormones. Modifying the gut microbiota using probiotics and fecal microbiota transplantation may improve glucose metabolism and insulin resistance. Research to understand the intricate interactions between gut microflora and the pathogenesis of Type 2 Diabetes Mellitus will help develop newer, effective therapeutic modalities.

Keywords: Diabetes Mellitus, insulin resistance, gut microflora.

Abbreviations: AMPK – AMP-activated protein kinase; BCAA – Branched-chain amino acids; CDI – recurrent *Clostridium* difficile infection; eCB – Endocannabinoid; FMT – Faecal microbiota transplantation; GIT – Gastrointestinal Tract; GPRs – G-protein-coupled receptors; IKK-β – IκB kinase; IRS – Insulin receptor substrate; JNK – c-Jun N-terminal kinase; lipopolysaccharide – Lipopolysaccharide; OGIS – Oral Glucose Insulin Sensitivity; PYY – Peptide YY; SCFAs – Short-chain fatty acids; T2DM – Type 2 Diabetes Mellitus; TLR – Toll-like receptor.

Introduction

The International Diabetes Federation estimates that 382 million people worldwide have diabetes, with an estimated increase of around 592 million by the year 2035. Type 2 diabetes (T2DM) affects approximately 85 to 95 percent of people with diabetes. Numerous risk factors are connected to T2DM, including genetics, age, obesity, and poor lifestyle habits. Recent research indicates that the intestinal microbiota may contribute significantly to the onset of T2DM [1, 2].

Former Nobel Prize awardee Joshua Lederberg originally defined the "human microbiome" in 2001 as an ecological community consisting of symbiotic, commensal and pathogenic bacteria that cohabit in the bodily space. Microbiota coexisting with our bodies have a significant impact on human health. The human gastrointestinal tract (GIT) is cohabited by approximately 100 trillion microorganisms, with the colon housing the highest number of these contributors [3, 4]. Recent evidence suggests a connection between gut microbiota composition and obesity and T2DM. Firmicutes make up 64% of the gut microbiota under normal physiological conditions, with Bacteroidetes (23%), Proteobacteria (8%), and Actinobacteria (3%) in order of prominence. The gut microbiota may directly or indirectly affect human health, and disruption of stable communities may increase the prevalence of

proinflammatory disorders such as obesity, inflammatory bowel disease, T2DM, arthritis, and cancer. The species present in T2DM microbiota communities include *Eggerthella lenta*, *Escherichia coli*, *Clostridium hathewayi*, *Clostridium ramosum*, *Clostridium symbiosum*, and *Bacteroides caccae* [5].

Studies have also looked into alterations in the gut microbiome composition of patients with T2DM. In the diabetic group, researchers found that the abundance of Firmicutes and *Clostridium* was much lower than that of the control group. At the same time, the proportion of Bacteroidetes and Betaproteobacteria was relatively increased. Zhang and colleagues discovered that the T2DM patients had a greater percentage of Firmicutes and *Clostridium* than the normal glucose group. Betaproteobacteria levels were noticeably higher in patients in the pre-diabetic and T2DM population groups than in those with normal glucose levels [6]. Qin *et al.* observed that the T2DM population exhibited a modest degree of gut microbial dysbiosis, a decline in several butyrate-producing bacteria, and an abrupt rise of opportunistic infections [7]. Karlsson *et al.* found that the T2DM group had significantly lower levels of five *Clostridium* species and significantly greater levels of four *Lactobacillus* species [8]. According to Sato *et al.*, stool samples from diabetic patients exhibited a notable increase in levels of *Lactobacillus* counts and a substantial reduction in the *Clostridium coccoides* group, Atopobium cluster, and *Prevotella* when compared to healthy people [9].

This article provides an overview of the gut microbiota trait in the T2DM population and the molecular patterns that connect host and gut microflora in the diabetic population, thereby paving the way for novel therapeutic approaches.

Body weight and gut microflora

Humans lack enzymes for digesting plant polysaccharides like cellulose, xylans, resistant starch, and inulin. Microbes inhabiting the intestine can ferment indigestible carbohydrates, producing energy and short-chain fatty acids (SCFAs). In addition to lipid and carbohydrate metabolism, variations in bile acid profiles are caused by the gut microbiome's modulation of bile acid signaling. About 5–10% of bile acids are converted by anaerobic gut bacteria such as *Clostridium*, *Eubacterium*, and *Bacteroides*. In the colon, intestinal bacteria produce Acetate, propionate, butyrate, fermenting proteins and non-metabolized polysaccharides. Estimates suggest that SCFA may supply up to 70% of the energy required for colonic epithelial cells to breathe and up to 10% of daily energy needs. An accumulation of excess energy over time may cause the body to store more fat. Studies on both humans and animals have shown that the obese phenotype is associated with an increased amount of SCFA in fecal and cecal samples compared to non-obese people [10].

The availability of substrate, gastrointestinal transit, mucosal absorption, gut health, gut microbiota development, and symbiotic relationships among various gut microbiota species are some factors that predict the increased SCFA production in obese phenotypes. Because the gut microbiota produces SCFA, it plays a significant role in energy metabolism. Microorganisms produce SCFAs, which are microbial waste products, to support gut homeostasis. Consumption of resistant starch and dietary fibers induces the production of SCFAs, which can enhance insulin sensitivity, maintain glucose homeostasis, and positively impact body weight, lipid metabolism, and insulin sensitivity in general. It can also activate the free fatty acid receptor 2 and promote the hormone peptide YY (PYY) synthesis. An individual's likelihood of becoming obese or experiencing an increase in body fat is predicted by the Firmicutes to Bacteroidetes ratio (F: B ratio). The gut microbiota composition may be altered by a wide range of factors, including fasting, food type and calorie content, antibiotic usage, age, location, amount and frequency of physical exercise, and genetic, technical, and clinical factors [11].

Metabolism of glucose, insulin and intestinal microflora

The gut microbiota can influence glucose homeostasis through a number of processes involving the generation of metabolites and their subsequent effects, activation of cascades of the inflammatory process, disruption of the intestinal mucosal barrier, and secretion of incretins. Patients with T2DM have improved branched-chain amino acid (BCAA) transport across the membrane, methane metabolism, xenobiotic breakdown, and sulfate reduction. Microbial byproducts generated during anaerobic fermentation in the gut, such as succinate, indole, imidazole, SCFAs, and BCAAs, play important roles in microbe-host signaling networks. *Ackermansia*, *Prevotella*, *Ruminococcus*, *Coprococcus*, *Faecalibacterium*, *Eubacterium*, *Roseburia*, *Clostridium*, *Bacteroides*, *Lactobacillus*, *Streptococcus*,

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Propionibacterium, and *Fusobacterium* are among the microbiota species that primarily produce these compounds [12].

The most prevalent SCFAs produced by intestinal fermentation of dietary fibers are butyrate, acetate, and propionate. Firmicutes produce butyrate, whereas Bacteroidetes primarily produce acetate and propionate. SCFAs function as a signaling molecule in the body's circulation as well as an energy source for intestinal mucosal cells. SCFAs interact with G-protein-coupled receptors (GPRs) to significantly impact glucose metabolism. These are mostly present in immunological cells, the stomach, and adipose tissue. Enteroendocrine L-cells produce more incretin GLP-1 when GPR43 and GPR119 are stimulated.GLP-1 slows intestinal transit, protects β-cells from apoptosis, increases β-cell proliferation, decreases glucagon secretion, and enhances the release of insulin from β-cells. Intestinal gluconeogenesis is triggered by butyrate and propionate stimulating the GPR41 receptor through two distinct mechanisms. It first increases the expression of the intestinal gluconeogenesis gene by acting as a GPR41 agonist. Second, it triggers GPR41 and other neurons in the gut-brain circuit. By increasing glycogen synthesis, decreasing plasma fatty acid levels, and reducing glycolysis and gluconeogenesis, SCFAs may have an impact on hepatic glucose metabolism. SCFAs increase appetite and glucose-stimulated insulin production by promoting parasympathetic activity[13, 14].

SCFAs improve glucose absorption peripherally by boosting GLUT4 expression and enhancing the activity exhibited by AMP-activated protein kinase (AMPK). Second, SCFAs in the skeletal musculature reduce glycolysis, resulting in increased glucose-6-phosphate accumulation and glycogen production. The most prevalent SCFA, acetate, is transported to the intestinal epithelium, exported to the liver by the portal vein, and then distributed to other tissues for metabolism. Acetyl-CoA carboxylase can be activated by systemic acetate, which can cross the blood-brain barrier and lead to increased neuropeptide synthesis, hypothalamic neuron activity, and appetite suppression. 60–70% of the energy required for colonic mucosa growth and differentiation is provided by butyrate, which is the main energy source for colonocytes. Butyrate prevents reactive oxygen and nitrogen species from being produced under oxidative stress, which helps to preserve colonic epithelial homeostasis [15].

Propionate, a preferred glucogenic precursor, is generated in the intestine, accounting for roughly 50 percent of its use. Increased intestinal propionate supply improves the function of β-cell and glucose-stimulated release of insulin, regardless of GLP-1 levels. Propionate preserves human islets by inhibiting apoptosis caused by inflammatory cytokines. A diet enriched in fibers has been shown to boost SCFA-producing microbiota and reduce HbA1c levels by increasing GLP-1 production, thereby regulating T2DM. Postprandial plasma butyrate concentrations were observed to increase the number of Intestinimonas butyriciproducens and Akkermansia muciniphila. The OGIS model, i.e., Oral Glucose Insulin Sensitivity, revealed a direct correlation between butyrate concentrations and postprandial insulin sensitivity [16].

Succinate promotes glycemic control by activating intestinal gluconeogenesis, similar to butyrate and propionate. The chance of acquiring T2DM in the future has been found to increase fivefold with a slight increase in the levels of BCAAs and aromatic amino acids, which constitute the essential amino acid group. Increased plasma levels of BCAAs are interconnected to insulin resistance and two particular bacterial species: *Bacteroides vulgatus* and *Prevotella copri* [17].

A product of bacterial catabolism of aromatic amino acids, indolepropionic acid, is strongly correlated with fiber consumption and may reduce the incidence of T2DM. It may shield pancreatic β-cells from oxidative and metabolic stressors in view of their strong radical scavenging activity. GLP-1 secretion may result from inhibiting voltage-gated potassium channels, which may alter the generation of incretin from enteroendocrine L-cells. Imidazole propionate, which is generated when the gut microbiota breaks down histidine, inhibits the intracellular insulin receptor signaling cascade, making it more difficult for cells to react adequately to insulin [18]. Figure 1 shows the influence of gut microflora on glucose homeostasis.

Influence of intestinal microflora on insulin resistance

T2DM, insulin resistance, and obesity are closely associated with low-grade inflammation, characterized by abnormal cytokine production and the activation of the network of signal pathways pertaining to inflammation. Low-grade inflammation is brought on due to a shift in the gut microbiota that promotes endotoxemia at the metabolic level and initiates the inflammatory process through a mechanism reliant on lipopolysaccharide (LPS) and CD14/toll-like receptor (TLR). Inflammatory substances like peptidoglycan

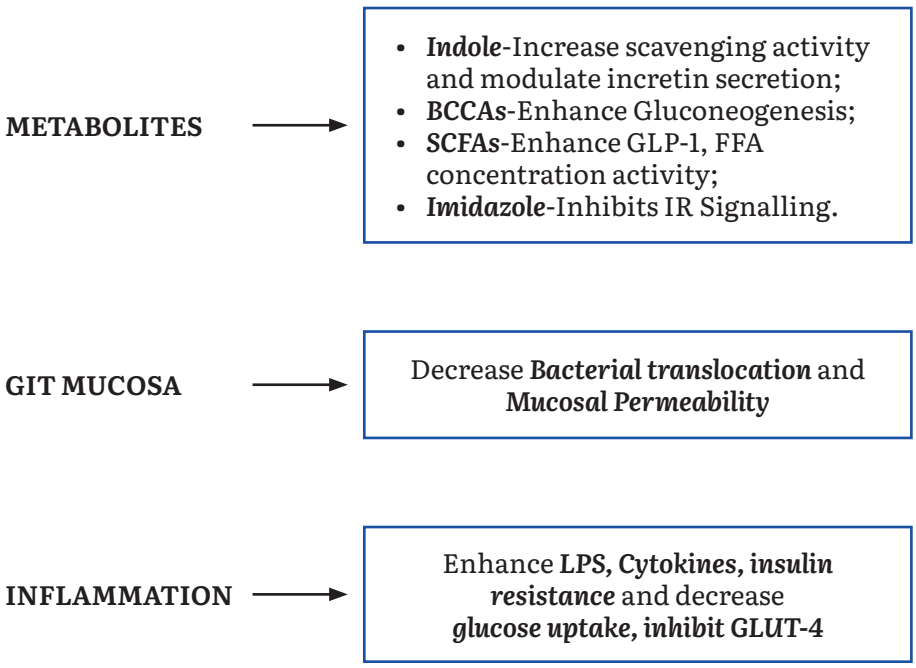

Figure 1: Influence of Gut microflora in glucose homeostasis.

and LPS are found to be prevalent in the gut microbiome. The production of LPS by the gut microbiota contributes to developing and advancing inflammation and metabolic diseases [19].

CD14 is portrayed as a key player in innate immunity. LPS attaches itself to the complex of the mCD14 and TLR4 on the surface of innate immune cells, which sets off the cascade reaction of the inflammatory process. The IκB kinase (IKK)-β and c-Jun N-terminal kinase (JNK) pathways are intracellularly activated by a variety of common proinflammatory stimuli, including chemokines, lipids, fatty acids, and LPS. In addition to stimulating the nuclear factor (NF)-κB transcription factor family, IKKβ activation increases the synthesis of several inflammatory mediators that may be involved in insulin resistance.JNK activation may result in insulin resistance by inhibiting normal signal transmission across the insulin receptor/IRS-1 axis and by promoting the phosphorylation of insulin receptor substrate (IRS)-1 at serine sites. Thus, the endotoxemia caused by LPS generated from the gut microbiota at the metabolic level is associated with insulin resistance and inflammation. Increased intestinal permeability is associated with elevated endotoxemia. Employing prebiotics to alter the makeup of the gut microbiota improves gut permeability, lowers inflammation, lessens metabolic endotoxemia, and alleviates glucose intolerance [20].

It is currently believed that diabetes and inflammation are related to the endocannabinoid (eCB) system. Intestinal microbiota colonies influence gut eCB expression via the CB1 receptor, which in turn controls the permeability of gut and plasma levels of LPS. By increasing the distribution and localization of tight junction proteins (occludin and ZO-1), blocking the CB1 receptor enhances the function of the intestinal barrier. This indicates that the distribution and localization of tight junction proteins allow the eCB system to regulate intestinal permeability. Changes in CB2 receptor expression have a negative correlation with intestinal counts of *Clostridium* and a positive correlation with intestinal counts of *Lactobacillus* species [21, 22].

The gut mucosa protects against dangerous substances and regulates the immune system.T2DM causes increased intestinal permeability, leading to bacterial translocation as well as low-grade inflammation. The consequences can cause β-cell destruction and insulin resistance. *Faecalibacterium*, *Roseburia*, and *Bifidobacterium* are known for their ability to inhibit the translocation of bacterial species and reduce intestinal permeability. It has been proven that people with T2DM have reduced levels of these particular bacteria [23]. The role of gut microflora in the permeability of the gut and insulin resistance is summarised in Figure 2.

Modulation of intestinal microflora from a therapeutic viewpoint

Recent studies indicated that the gut microbiome may influence T2DM. Probiotics are live bacteria that

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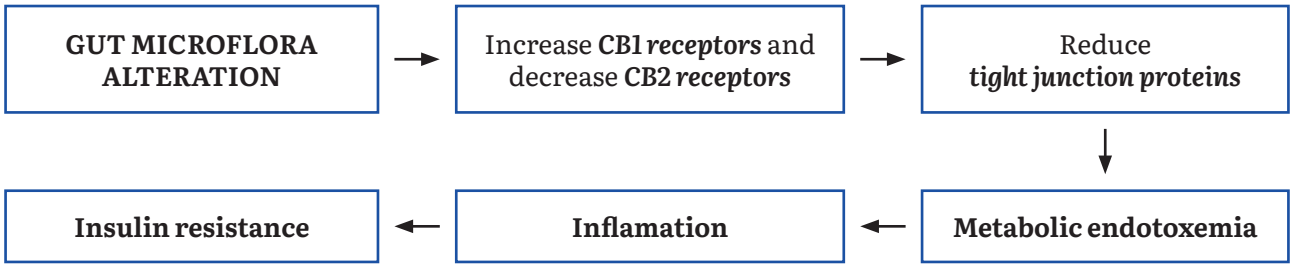

Figure 2: Alterations in the intestinal microbiota promote insulin resistance and metabolic endotoxemia by increasing gut permeability and decreasing tight junction proteins of gut epithelial cells.

can provide health benefits to the host. Researchers discovered that when diabetic rats were exposed to high fructose levels, fermented milk products containing probiotic bacteria considerably deferred the emergence of glucose intolerance, hyperglycemia, and hyperinsulinemia. It has been demonstrated that probiotics improve intestinal microbiota, which in turn improves peripheral insulin sensitivity, lowers circulating LPS levels, improves intestinal integrity, and lessens endoplasmic reticulum stress and T2DM [24].

Faecal microbiota transplantation (FMT) involves transferring pre-screened donor stool into a gut of "diseased" patient in order to rectify dysbiotic conditions, increase diversity, and restore microbial functionality. FMT is solely approved for the management of recurrent *Clostridium* difficile infection (CDI), having a rate of resolution above 89 percent. Numerous studies have been currently conducted to investigate additional possible indications, including in the field of T2DM. FMT is thought to be more effective in comparison to probiotics because it can transfer entire microbiota communities of the donor, including their metabolites, and can correct microbiota disruption over specific targets. Metabolic syndrome patients who were given small intestinal infusions of fecal microbiota obtained from healthy allogeneic donors for about six weeks experienced improved insulin sensitivity and increased butyrate-producing intestinal microbiota. Manipulating the gut microbiota with procedures like FMT could be a promising therapeutic option for T2DM patients [25].

Conclusion

The intestinal microbiota can impact T2DM through its influence on gut hormones, body weight, metabolism of bile acids, proinflammatory activity, and insulin resistance. Incorporating probiotics and fecal microbiota transplantation can improve metabolism of glucose and insulin resistance in the host. More research is needed to better understand the relationship between intestinal microbiota and T2DM, leading to the development of more effective therapeutic options.

Conflict of interest

The authors declare no conflict of interest.

References

1. International Diabetes Federation. IDF Diabetes Atlas, Sixth Edition. 2013. Available from: URL: http://www.idf.org/ sites/default/files/EN_6E_Atlas_Full_0.pdf
2. Prevention of diabetes mellitus. Report of a WHO Study Group. World Health Organ Tech Rep Ser 1994; 844: 1-100
3. Lederberg J, McCray A. Ome sweet omics—a genealogical treasury of words. Scientist. 2001;15(7):8.
4. Relman DA, Falkow S. The meaning and impact of the human genome sequence for microbiology. Trends Microbiol. 2001;9(5):206–8.
5. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007;449(7164):804–10
6. Zhang X, Shen D, Fang Z, Jie Z, Qiu X, Zhang C, Chen Y, Ji L. Human gut microbiota changes reveal the progression of glucose intolerance. PLoS One 2013; 8: e71108
7. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012; 490: 55-60
8. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature 2013; 498: 99-103
9. Sato J, Kanazawa A, Ikeda F, Yoshihara T, Goto H, Abe H, et al. Gut dysbiosis and detection of "live gut bacteria" in the blood of Japanese patients with type 2 diabetes. Diabetes Care 2014; 37: 2343-2350
10. Noor J, Chaudhry A, Batool S, Noor R, Fatima G. Exploring the Impact of the Gut Microbiome on Obesity and Weight Loss: A Review Article. Cureus. 2023 Jun 25;15(6): e40948.
11. Gut microbes and health: a focus on the mechanisms linking microbes, obesity, and related disorders. Rastelli M, Knauf C, Cani PD. Obesity (Silver Spring) 2018;26:792–800

12. Dai ZL, Wu G, Zhu WY. Amino acid metabolism in intestinal bacteria: links between gut ecology and host health. Front Biosci (Landmark Ed). 2011; 16:1768–86
13. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016;165(6):1332–45.
14. Cummings JH. Short chain fatty acids in the human colon. Gut. 1981;22(9):763–79.
15. Tazoe H, Otomo Y, Kaji I, Tanaka R, Karaki SI, Kuwahara A. Roles of short chain fatty acids receptors, GPR41 and GPR43 on colonic functions. J Physiol Pharmacol. 2008;59(Suppl 2):251–62
16. Bloemen JG, Olde Damink SW, Venema K, Buurman WA, Jalan R, Dejong CH. Short chain fatty acids exchange: Is the cirrhotic, dysfunctional liver still able to clear them? Clin Nutr. 2010;29(3):365–9
17. Zhao L, Zhang F, Ding X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science. 2018;359(6380):1151–6.
18. Gribble FM, Reimann F. Function and mechanisms of enteroendocrine cells and gut hormones in metabolism. Nat Rev Endocrinol. 2019;15(4):226–37.
19. Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. Curr Pharm Des 2009; 15: 1546-1558
20. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006; 116: 1793-1801
21. Scherer T, Buettner C. The dysregulation of the endocannabinoid system in diabesity-a tricky problem. J Mol Med (Berl) 2009; 87: 663-668
22. Cani PD, Geurts L, Matamoros S, Plovier H, Duparc T. Glucose metabolism: focus on gut microbiota, the endocannabi noid system and beyond. Diabetes Metab 2014; 40: 246-257
23. Cani PD, Possemiers S, Van de Wiele T, et al. Changes in gut microbiota control infammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut. 2009;58(8):1091– 103
24. Balakumar M, Prabhu D, Sathishkumar C, et al. Improvement in glucose tolerance and insulin sensitivity by probiotic strains of Indian gut origin in high-fat diet-fed C57BL/6J mice. Eur J Nutr. 2018;57(1):279–95
25. Tariq R, Pardi DS, Bartlett MG, Khanna S. Low cure rates in controlled trials of fecal microbiota transplantation for recurrent Clostridium diffcile infection: a systematic review and meta-analysis. Clin Infect Dis. 2019;68(8):1351–8

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