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# Link of Gut Microbiome with Risk of Type 2 Diabetes Mellitus

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**Abstract**
The gut microbiota presented in the human digestive system plays an active role in maintaining host health. Recent studies that rely on the use of high throughput metagenomic sequencing (MGS) revealed the association of dysbiosis in the intestinal microbial community and many chronic diseases, specifically type 2 diabetes (T2D). This disease is considered one of the most prevalent metabolic diseases worldwide comprising up to 90%. This article presents the most prominent research in this field and summarizes the method used to study the diversity of the gut microbiome through the use bioinformatics tools. We highlight the role of gut metabolic products in the development of T2D, as many studies have proven the influence of microbial metabolite products, such as LPS and SCFAs, on blood glucose levels through the microbial-host cross-talk. In addition, this article underlines the interaction of epigenetic mechanisms and the gut microbiome in regulating and developing T2D. The latter can be an appropriate preventative or therapeutic approach for several human metabolic diseases. Therefore, future research is required to build new type of T2D therapy based on epigenetic mechanisms, microbial composition, and microbial metabolites.
**Keywords:** Gastrointestinal microbiome, diabetes mellitus, type 2, microbial metabolites, epigenomics

## Introduction

One of the alarming human health issues in the world is diabetes mellitus, which is a metabolic disorder through which patients are unable to regulate glucose absorption. The most common diabetes type is type 2 diabetes (T2D), representing about 90% of cases globally, while type 1 diabetes (T1D) represent only 10%.[1] In developing countries, 85% of the early death is related to metabolic disorders, of which deaths due to diabetes constitute about 80%.[2] According to the Internation Diabetes Federation (2019), 463 million people have diabetes worldwide, of which 55 million people live in the Middle East and North Africa region. These numbers are speculated to rise to 108 million in year 2045. In 2019, Saudia Arabia became one of the top five countries for diabetes with 4.3 million patients, and the diabetes prevalence reached 18.3 (Internation Diabetes Federation, 2019).[3]

Patients with T2D commonly suffer from damage or lack of insulin secretion.[4] The disease is recognized by hyperglycemia caused by a deficiency of insulin production, which exhaustion results of pancreatic beta cells function after establishing insulin resistance.[5] Several studies indicated that obesity and unhealthy lifestyles, such as the lack of exercise and poor dietary habits, are linked to T2D.[6]

Previously, it was believed that only genetic and environmental factors can influence the pathogenicity of T2D.[7] However, recent studies on the human microbiome have found evidence that supports the effect of the intestinal microbiome in stimulating inflammation, insulin resistance, obesity, and T2D.[8] Findings of the latter report indicated differences in the gut microbiome in T2D patients compared with healthy individuals. These results have led to the investigation of gut microbiota as an essential factor in diabetes risk development.[9] Gut microbiota has a wide range of functions that impact human physiology, e.g., vitamin synthesis, regulation of the intestinal mucosal barrier, protection against pathogens, host nutrition alteration, energy harvest modulation, fermentation of indigestible carbohydrates, and development of the host immune system.[10]

In humans, the gastrointestinal (GI) tract contains bacteria, viruses, archaea, and eukaryotes. This dynamic population has more than 1014 microbial cells with 35,000 species and over 10 million non-redundant genes.[11] These collective genomes of gut microbiota present enormous metabolic properties to the host because the gut microbiome has at least 100 times more encoded genes than those of the human genome.[12] Researchers found that the human gut microbiome contains six prime phyla, e.g., Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Verrucomicrobia, and Proteobacteria.[13] Moreover, most bacterial species in the adult gut belong to Firmicutes and Bacteroidetes, constituting more than 90% of the gut microbial community and related to obesity and T2D.[13] Barengolts (2016) reported that a healthy gut microbiome consists of 64% Firmicutes, 23% Bacteroidetes, 8% Proteobacteria, and 3% Actinobacteria.[14] Furthermore, the alteration in the bacterial diversity of the gut microbiome leads to the overgrowth of Proteobacteria, resulting in dysbiosis. Metabolic diseases such as diabetes, obesity, multiple sclerosis, Crohn's disease, rheumatoid arthritis, and inflammatory bowel disease are correlated with gut microbiome dysbiosis.[15,16]

The development of gut microbiota can be impacted by many factors, as illustrated in Figure 1. The maternal nutrition of the mother during pregnancy, embryonic environment, and mode of birth are the first elements in obtaining the gut microbiota. Then, it is completely formed during the age of 2–3 years, similarly to the adult microbiome, and remains relatively stable in adulthood.[17] Additionally, dietary patterns such as breast feeding, diet, and diet components play a critical role in maintaining the gut community and maturity. All these factors, along with an individual's genetic and environmental factors (such as drug or antibiotic intake, infections, lifestyle patterns, and migration to a different location), contribute to shaping the microbial gut population.[18]

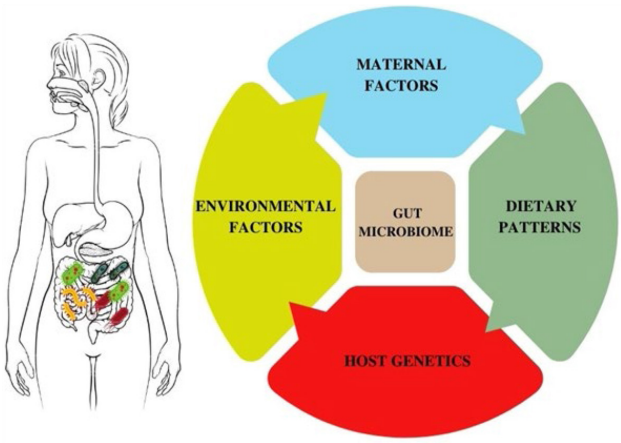


Fig. 1 **Factors influencing the development of gut microbiome.**

## Diversity in the Human Gut Microbiome

During the last two decades, the gut microbiome received considerable attention from researchers because of its participation in several medical and psychological disorders.[19] Scientists considered it as another body organ that interacts with the host to health promotion and, in some cases, triggers the disease. In this context, it is noted that the microorganisms that inhabit the GI tract are referred to as gut microbiota, while the genomes of the microbiota is known as the gut microbiome. In microbiome research, the diversity of microorganisms within a specific body area is used as a measurable outcome and defined based on species richness and eveness as well as microbial relative abundance and distribution among different organs.[20-22]

Microbiome studies aim currently to understand the mechanical role of microbial diversity in disease etiology and public health. To achieve these objectives, scientists focused on identifying the factors that lead to differences in microbiome environments. Age is one of the factors that shape or effect the microbiome, where microbiota appears to be volatile in the infancy stage and then becomes more stable after the initial three years.[13] Also, environment, genetic factors, and lifestyle factors such as diet and smoking seem to impact the composition of human gut microbiome.[23,24]

Understanding human gut microbiome and factors that drive its variability composition could lead to important insights into mental and physical health. In this context, many studies proposed a cross-talk between the brain and the GI tract allowing each to influence the other.[25] This interaction, called the gut-brain axis, may cause the symptom of the disease health disorders.[26] Besides, the gut microbiome composition has a crucial role in the gut-brain axis.[27] Consequently, understanding the etiology and consequences of mental and physical health disorders and the development of efficient treatments depends on studying the gut microbiome composition.

Recently, the new developments in the technologies of high throughput metagenomic sequencing (MGS) enhanced the understanding of the symbiotic correlation between the host and the gut microbiome.[28] MGS allows researchers to recognize the pathogenic mechanisms of the microbiome that associate with the host's disease and thus provide ways to modify the microbial community in the gut for therapeutic and even preventive objectives.

Metagenomics and metatranscriptomics are nucleic acid sequencing-based methods used for microbiota characterization. Sequencing portions or whole gene of bacterial 16S ribosomal RNA subunit is one of these methods. It is utilized as a phylogenetic marker to predict the bacterial population structure, support microbiota preliminary investigation, and determine variations in the diversity and abundances of individual bacterial species between microbiota samples.[29] In living organisms, mRNA translating to proteins through the complex called the polysome that is made of several ribosomes. Ribosomes are composed of several proteins besides several RNAs called ribosomal RNAs (rRNA). In prokaryotes, rRNA is identified as a 16S rRNA subunit, while in eukaryotes is known as the 18S rRNA subunit.[30] Both rRNA subunit types have evolutionarily conserved regions surrounding nine variable regions.[31] Usually, the conserved regions are used to design the universal primers for PCR to amplify the targeted variable regions; and the resulting amplicons are sequenced for phylogenetic analysis. Finally, the sequences of the variable regions are compared to a set of reference sequences with pre-assigned taxonomy to conduct the phylogenetic analysis, which allows estimating the composition of taxonomic units in the community. Indeed, data is used to assess the composition of the bacterial population when completing the sequencing of partial- or full-length 16S rRNA gene. After the sequences is completed, the data quality filtering steps apply, and the bioinformatics tooles (the Qiime (Caporaso et al., 2010))[32] or Mothur (Schloss et al., 2009)[33] are used to assign the taxonomy by mapping sequences to the reference databases GreenGene (DeSantis et al., 2006)[34] or Silva (Quast et al., 2013).[35] Subsequently, several statistics are applied to the resulting operational taxonomic unit (OTU) table, which evaluates the diversity of bacterial communities and shows the similarities or differences between these communities.

Numerous studies have indicated the clinical relevance of estimating microbiota diversity within the intestinal tract, where the decrease of microbiome diversity is often associated with alterations in the gut microbiota composition, called dysbiosis. Alpha and beta diversity are two types of measures used to analyze the diversity of the microbiome. The number of unique taxa (richness) and their distribution (evenness) in a specific sample is defined as alpha diversity, which evaluates by many indices involving Chao1, Shannon Index, and the Simpson index. In addition, the number of species that are different among the groups, known as beta diversity, evaluates the differences in species composition between two groups of samples.[36]

## Eubiosis and Dysbiosis in the Gut Microbiome

Eubiosis is a term that refers to a healthy composition of the intestinal microbiome that maintains host health. In contrast, dysbiosis refers to an unhealthy microbiome composition that induces the risk for certain diseases. The gut microbiome in a state of eubiosis has various roles in producing metabolic products such as short-chain fatty acids (SCFAs), branched-chain amino acids (BCAAs), and impacting the metabolism of lipid. Moreover, the gut in eubiosis consists of 95% Bacteroidetes and 5% Firmicutes, which is considered a standard B/F ratio in the gut bacterial community, thus, enhances intestinal health, regulates opportunistic pathogens, and participates in the whole body's good health.[37] Changes in the desirable

microflora in a healthy gut can lead to a dysbiosis state (Petersen and Round, 2014), which force a negative effect that causing obesity and multiple diseases such as T2DM and subsequent CVD (Figure 2).[37]

For instance, Turnbaugh et al. (2007) carried out his piou neering experiment on germ-free (GF) mice in which they colonized gut microbiota from conventionally raised (CONV) mice. Then, they observed changes in body weight.[21] Regardless of the reduction in food intake, the GF mice exhibited increased body fat within 10–14 days. This increase in body fat has been attributed to microbial fermentation of undigestible polysaccharides, absorption of monosaccharides, and the microbiome genes that stimulate the growth of adipocytes. These discoveries guided the researchers to support the claim that obese persons are usually more efficient at energy harvest because of their microbiome than thin counterparts, explaining the weight gain.

## The Influence of Gut Microbiome in Type 2 Diabetes

Recent studies found that the development risk of obesity and T2D is connected with the composition imbalance in gut microbiome populations (Moreno-Indias et al., 2014),[38] in addition to increasing insulin resistance, lipid levels, adiposity, and inflammation linked to decreasing gastric microbial diversity, known as the bacterial species number or richness.[39] Amar et al. (2011) found that Proteobacteria (gram-negative bacteria) translocate out of the intestinal lumen preceding the advent of abdominal adiposity and T2D.[40] Besides, microbial metabolites could contribute to the risk of obesity through slowing intestinal transit and boosting energy absorption.[38] Various studies have been performed in microbiome profiling of T2D cases and controls in humans. In 2010, Larsen et al. compared the gut microbiome between diabetic and non-diabetic individuals by using principal component analysis, finding that T2D is associated with the changes in the composition of gut microbiota at the phylum level (Larsen et al., 2010).[41] They reported that T2DM shows a reduced abundance of Firmicutes phylum and Clostridia class contrasted with the control group, while increasing abundance of Betaproteobacteria class, which correlates with plasma glucose concentration. In the human GI tract, several bacteria producing butyrate belong to the Firmicutes phylum, specifically class Clostridia.[42,43]

The massive metagenomic species (MGS) research in Chinese and European cohorts showed that butyrate-producing bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia intestinalis* known for their anti-inflammatory properties (Vrieze et al., 2012),[44] were less abundant in patients with T2D disease.[45,46] Moreover, the combined analysis of these two datasets showed that butyrate-producing taxa were reduced in T2D and remained after controlling microbiome-modifying impacts of metformin.[47] Another study found that increasing *F. prausnitzii* is associated with an anti-diabetic impact, which was remarked instantly after gastric-bypass surgery, regardless of significant weight reduction.[48] Also, in a Danish study that included 277 non-diabetic individuals, scientists found an increase in serum BCAAs levels in people who had insulin resistance, caused by an increase in the production of BCAA and a decrease in the transportation into bacterial cells.[49] The most important species that leading the biosynthesis of BCAAs are *Prevotella copri* and *Bacteroides vulgatus*. In mice, the researchers noted that *P. copri* can stimulate insulin resistance and promote BCAAs circulating levels. They also indicated that gut microbiota plays a crucial role in insulin resistance and might be a significant resource for increasing BCAAs levels. Radwan et al. (2020) examined the bacterial microbiome composition and abundance in patients with T1D and T2D and characterized the gut microbiota features to find the possible differences associated with this population.[50] The results emphasized a substantial increase in abundance in gram-negative bacteria, possibly opportunistic pathogenic taxa such as *Pseudomonas* and *Prevotella* in all patients with diabetes compared to healthy individuals. They also found that the *Gemella* (gram-positive bacteria) related to increased the risk of diabetes and significantly had an increase in abundance in all groups of people with diabetes. The control group has more abundant commensal bacterial taxa as *Turicibacter*, *Terrisporobacter*, and *Clostridium* than the T1D group.

In 2013, Zhang et al. used 16S ribosomal DNA (rDNA)–based sequencing and discovered that prediabetes people who were recently diagnosed with T2D had a lower abundance of *Akkermansia muciniphila,* which may be considered as a biomarker of glucose intolerance.[51] In obese adults, Dao et al. (2016) proved that a healthier metabolic condition associate with the presence of *A. muciniphila* in a high abundance.[52] *A. muciniphila* is a human gut mucin-degrading bacterium that represents 3–5% of the human intestinal microbial population. Moreover, the study showed that optimal clinical outcomes as glucose homeostasis, blood lipids, and body composition had linked to the presence of *A. muciniphila* in higher abundance in the baseline after caloric restriction. In addition, increasing *A. muciniphila* levels were observed due to treatment with metformin, which could intercede with many of its metabolic benefits.[53] The latest research found that patients with T2D have a significantly higher Firmicutes/Bacteroidetes ratio than healthy controls.[54] On the contrary, the Chinese, European, and Danish cohort studies observed that patients with T2D have a lower Firmicutes/Bacteroidetes ratio.[45,46] The contradiction among these studies is perhaps because of perplexing influences such as different techniques of sequencing, study populations, using a medication, and diet. Additional controlled studies are needed to study these confusing variables. These unrelated disease variables can substantially influence the result of the microbiome.[55] Overall, research outcomes to date recognized a relationship between the gut microbiome and T2D.

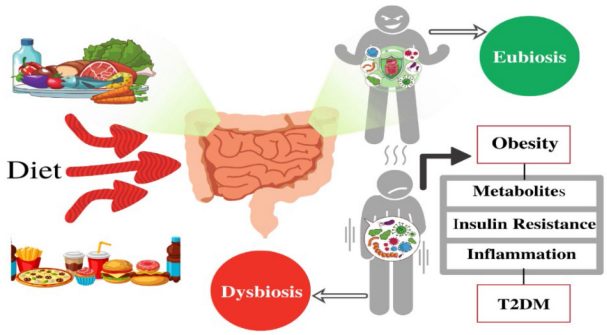


Fig. 2 **Influence of diet on the gut microbiome and risk of T2D.**

## Type 2 Diabetes and Microbial Metabolites

Microbial metabolites are responsible for regulating host metabolism and gut integrity. Therefore, they can be considered as a vital link connecting the gut microbiome to insulin resistance, which can result into T2D. Some of the metabolites are beneficial, e.g., SCFA, indole derivatives, sulfur-containing amino acids, bile acids, and vitamins, while others are harmful, e.g., lipopolysaccharide (LPS), methane, BCAA, phenol, amines, p-cresol, and ammonia.[56] The essential metabolites of interest are mentioned below.

## Short Chain Fatty Acids (SCFAs)

The most metabolites produced by the gut microbiota are short-chain fatty acids (SCFAs) such as butyrate, propionate and acetate representing in the human intestinal lumen at the ratio of 1:1:3.[57,58] Nevertheless, the ratio of these types of SCFAs depends on both the composition of microbes and the diet. The bacteria-derived SCFAs have a different destiny, where most butyrate is used locally as their primary energy source through colonocytes. Also, propionate is metabolized by the liver upon absorption, while acetate is easily absorbed and distributed to peripheral tissues through the blood circulation.[59] A recent study documented that metabolites have interacted with host metabolism. Gut microbiota ferment the indigestible carbohydrates such as oligosaccharides or polysaccharides to generate SCFAs by various metabolic pathways.[60] Insulin sensitivity and energy metabolism are effected by SCFAs. Previous reports supposed that SCFAs can change the concentrations of several gut peptides involved in glucose metabolism, gut barrier function, and energy homeostasis.[61,62] While, more recent reports have documented that butyrate and propionate suppress the weight gain in mice with high fat diet-induced obesity, and acetate has been proven to reduce food intake in healthy mice.[63,64] Also, Perry et al. (2016) reported that acetate plays a vital role in parasympathetic activity to increase food intake and support glucose-stimulated insulin secretion in a rodent model.[64] Bindels et al. (2013) have recognized a G protein-coupled receptor family, which is responsible for the effects of SCFAs.[65] Examples of GPRs include G protein-coupled receptors 43 (GPR43) and G protein-coupled receptors 41 (GPR41). When SCFAs bind to GPR43 and GPR41, this leads to increased plasma levels of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), improved glucose homeostasis, and reduced appetite due to their central nervous system interventions.[66] Gut microbiota can also produce indole from tryptophan, which contributes to the secretion of GLP-1 by intestinal entero-endocrine cells.[67]

## Secondary Bile Acids (SBAs)

Bile acids are amphipathic molecules produced from cholesterol by hepatocytes and released into the gastrointestinal lumen to facilitate dietary lipids solubilization and absorption.[68] Gut microbiota is implicated directly in the host metabolism of bile acids. The bile salts are efficient in enterohepatic recycling, which depends on bile acid deconjugation and dihydroxylation by microbial-derived bile salt hydrolases (BSH), causing a rise in the secondary bile acids.[69] The latter are more hydrophobic and can, therefore, be reabsorbed by passive diffusion, thus limiting the loss of bile acid via the feces. In the human gut microbiota, the specific activity of BSH varies in different phyla, where BSH of Firmicutes and Actinobacteria can metabolize all conjugated bile salts, while its activity in Bacteroidetes is restricted to Tauro-conjugated bile acids.[69] Additionally, bile acids are signal molecules are involved in peripheral metabolism and play significant roles via their action on both bile acid receptors, e.g., the G-protein coupled receptor TGR5 (Gpbar1), and the nuclear receptor FXR, both of which express in enteroendocrine cells.[68] Moreover, the affinity and potency of the receptor vary considerably among the different bile acids. In this way, the microbiome in the intestinal tract can profoundly impact the host metabolism by modifying bile acid pool composition across modified synthesis and reuptake of bile acid.[68]

## Lipopolysaccharide (LPS)

Membrane-bound lipopolysaccharide (LPS) is a structural component of the gram-negative bacterial membrane. LPS acts as a signaling molecule via numerous cellular pattern-recognition receptors (PRRS).[70] Furthermore, the first step in the cascading pro-inflammatory response is the translocation of LPS. One of the most PRRS reviewed are the Toll-like receptors (TLRs).[71] TLR-4 invigorated by bacterial lipopolysaccharides (LPS), resulting in inflammatory responses, cytokine production, and chemokine-mediated recruitment of inflammatory cells.[61] Previous reports suggested that plasma concentrations of gut microbiota-derived lipopolysaccharide (LPS) are increased due to the gut microbiota alterations which triggers the creation of the abovementioned inflammatory factors, by means of the CD14-dependent mechanism.[72,73] Several other studies found that LPS elevation levels (endotoxemia) are clinically correlating with insulin resistance and obesity.[74]

## Epigenetics, Gut Microbiome, and Type 2 Diabetes Mellitus

Newly different researches proved a direct link between the gut microbiome and epigenetic mechanisms in the pathogenesis of all diabetes types.[75] Epigenetics is identified as a heritable phenotype modifications that control gene expression without altering the DNA sequence. The epigenetic mechanisms in eukaryotes include mainly DNA methylation,

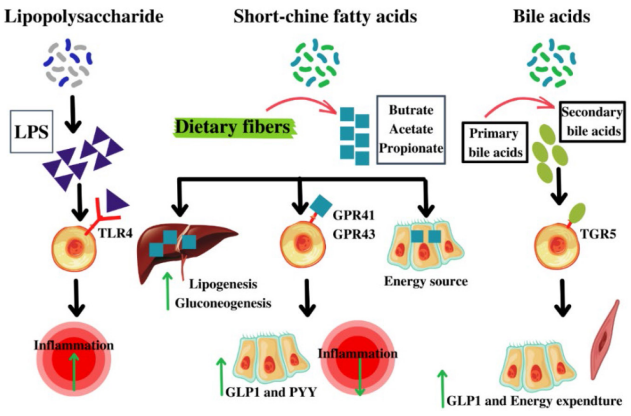


Fig. 3 **Microbes and host metabolism in T2D, modified from (Kristine et al., 2015).[77]**

chromatin restructuring, post-transcriptional histone modifications, and gene expression regulation through non-coding RNAs.[76]

Many factors are involved in regulating epigenetic mechanisms like the cross-talk of microbial metabolites, environmental influences including pH, oxygen, and temperature, and external influences such as antibiotics and diet, thus causing alteration of many metabolic diseases in humans.[78] The last findings provide new opportunities for using epigenetic regulations in altering the gut microbiota and thus their use in treating or delaying autoimmunity in patients. As mentioned earlier, evidence has emerged confirming that the community of gut microbiota is connected with type 2 diabetes as a Chinese study indicated a reduction in species of *Roseburia* and *Faecalibacterium* besides the rise in *Escherichia coli* in patients with type 2 diabetes than non-diabetic people (Qin et al., 2012)[45] which possess anti-inflammatory attributes.[51,79] The microbial-produced SCFA metabolites, like butyrate, play a crucial role in epigenetic modifications, such as HDAC inhibition.[80] Furthermore, butyrate has a vital role in the differentiation of T cells (Tregs) through acetylation of non-coding regions of the Foxp3 locus.[81] Newly, experiments have emerged looking at the relationship between changes in the gut microbial community in people with type 2 diabetes and their association with metabolic and epigenetic mechanisms have undoubtedly demonstrated that epigenetic modulations such as DNA methylation are linked to type 2 diabetes.[6]

Genome-wide association studies (GWAS) have shown an association between single nucleotide polymorphisms (SNPs) in type 2 diabetes and the defect in insulin secretion, which links with the defect in the cells of the pancreatic islet.[82] In 2014, Dayeh et al. suggested contributing epigenetic mechanisms with insulin resistance regulation and developmental process in type 2 diabetes through pancreatic cells. This study has analyzed the levels of DNA methylation of CpG sites and transcriptome in pancreatic islets in both patients with type 2 diabetes and healthy individuals. The authors have analyzed the levels of DNA methylation of CpG sites and transcriptome in pancreatic islets in both patients with type 2 diabetes and healthy individuals. Therefore, they identified 1,649 CpG sites and 853 genes involving KCNQ1, TCF7L2, and FTO, with differential DNA methylation in islets from type 2 diabetes patients. Their findings also involve 102 genes exhibiting differential DNA methylation and differential gene expressions such as CDKN1A, PDE7B, SEPT9, and EXOC3L2 genes in islets from type 2 diabetes. Those genes are crucial for regulating insulin secretion in b-cells and glucagon secretion in pancreatic α cells.[83]

## Conclusion

Gut bacteria have an essential role in developing many diseases, especially type 2 diabetes, as available evidence indicated the association between microbiome dysbiosis and T2D. Several studies have demonstrated that gut microbial composition differs significantly between type 2 diabetics and healthy individuals. Host glucose metabolism was shown to be affected by microbial metabolites produced by gut microbes, which are involved in different metabolic pathways. Also, several studies have revealed that people with type 2 diabetes have a less abundant gut microbial community of SCFAs butyrate-producing bacteria, which reflects their dietary pattern that depends on consuming a high-fat high-glycemic index, and low-fiber dietary compared to a healthy diet. Future efforts should integrate microbial metabolites with metagenomic sequencing (MGS) studies, search for causes affecting their production, and identify possible pathogenic metabolites. In addition, various studies have implicated the gut microbiome's interactions with the epigenome of the host, which indicates the possible role of gut microbiome in controlling host metabolism. Modulation of gut microbiome to the host epigenome might result from the direct and repeated contact with the host and various metabolites derived from microbes that are generated in the intestine. Moreover, many studies have a focus on the gut microbiome's epigenetic mechanisms and its impact on T2D. This new field may hold a promising future for discovering new therapeutic solutions that can convert gut microbiome dysbiosis to a healthy and balanced state and thus provide new insights towards preventing and treating T2D in the future.

## Conflict of Interest

None.

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