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Contents

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REVIEW

- 7508 Gut microbiome: New perspectives for type 2 diabetes prevention and treatment
Li SX, Guo Y

MINIREVIEWS

- 7521 Endoscopic management of benign biliary strictures: Looking for the best stent to place
Colombo M, Forcignanò E, Da Rio L, Spadaccini M, Andreozzi M, Giacchetto CM, Carrara S, Maselli R, Galtieri PA, Pellegatta G, Capogreco A, Massimi D, Khalaf K, Hassan C, Anderloni A, Repici A, Fugazza A
- 7530 Antibiotic resistance in patients with liver cirrhosis: Prevalence and current approach to tackle
Liakina V

ORIGINAL ARTICLE

Retrospective Study

- 7543 Analysis of risk factors for postoperative deep vein thrombosis after craniotomy and nomogram model construction
Su ZJ, Wang HR, Liu LQ, Li N, Hong XY
- 7553 Value of ultrasound and magnetic resonance imaging combined with tumor markers in the diagnosis of ovarian tumors
Yang Q, Zhang H, Ma PQ, Peng B, Yin GT, Zhang NN, Wang HB
- 7562 Measurement of combined flap thickness for reconstruction of decubitus ulcer using computed tomography
Kim EC, Park JD, Wee SY, Kim SY
- 7570 Does the advantage of transcutaneous oximetry measurements in diabetic foot ulcer apply equally to free flap reconstruction?
Lee DW, Hwang YS, Byeon JY, Kim JH, Choi HJ

Clinical Trials Study

- 7583 Effects of ulinastatin therapy in deep vein thrombosis prevention after brain tumor surgery: A single-center randomized controlled trial
Tao YN, Han Q, Jiao W, Yang LK, Wang F, Xue S, Shen M, Wang YH

Observational Study

- 7593 Network pharmacological and molecular docking study of the effect of Liu-Wei-Bu-Qi capsule on lung cancer
Yang Q, Li LY

- 7610** Efficacy of β_2 -adrenergic receptor agonist combined with corticosteroid in the treatment of children with cough variant asthma

Cao JY, Wang YC, Deng XX

Randomized Controlled Trial

- 7619** Protective effect of sevoflurane on lung function of elderly chronic obstructive pulmonary disease patients undergoing total hip arthroplasty

Yao Y, Zhang MS, Li YB, Zhang MZ

CASE REPORT

- 7629** Sunitinib-induced hyperammonemic encephalopathy in metastatic gastrointestinal stromal tumors: A case report

Hayakawa T, Funakoshi S, Hamamoto Y, Hirata K, Kanai T

- 7635** Simultaneous lateral and subxiphoid access methods for safe and accurate resection of a superior vena cava aneurysm: A case report

Kim SP, Son J

- 7640** Ultrafast power Doppler imaging for ischemic encephalopathy: A case report

Huang LJ, Jiao JF, He Q, Luo JW, Guo Y

- 7647** Intermittent spontaneous ovulation in patients with premature ovarian failure: Three case reports and review of literature

Zhang WY, Wang HB, Deng CY

- 7656** Sneddon's syndrome concurrent with cerebral venous sinus thrombosis: A case report

Heng Y, Tang YF, Zhang XW, Duan JF, Shi J, Luo Q

- 7663** Carcinosarcoma of the deep lobe of the parotid gland in the parapharyngeal region: A case report

Tang YY, Zhu GQ, Zheng ZJ, Yao LH, Wan ZX, Liang XH, Tang YL

- 7673** Malignant peripheral nerve sheath tumor with hemophilic syndrome and bone marrow fibrosis: A rare case report

Li H, Wang L, Wu YH, Chen G, Li HX, Fan LF, Gu M, Jiang CH

- 7680** Comparison of drug concentrations in blood and gastric lavage fluid before and after gastric lavage: A case report

Zhou Y, Tong JL, Peng AH, Xu SY

- 7684** Recurred forehead osteoma disseminated after previous osteoma excision: A case report

Lee DY, Lim S, Yoon JS, Eo S

- 7690** Renal pelvis sarcomatoid carcinoma with renal vein tumor thrombus: A case report and literature review

Guan HY, Wang J, Wang JX, Chen QH, Lu J, He L

- 7699** Ultrasonographic identification of lateral femoral cutaneous nerve anatomical variation in persistent meralgia paresthetica: A case report

Park HW, Ji KS, Kim JH, Kim LN, Ha KW

- 7706** Biliary hemorrhage caused by a malignant small round cell tumor in the common bile duct: A case report
Jin YL, Ruan YJ, Lu GR
- 7712** Successive development of ischemic malignant strokes in a patient with multiple fusiform aneurysms: A case report
Shin DS, Yeo DK, Choi EJ
- 7718** Isolated axillary tumor deposit consistent with primary breast carcinoma: A case report
Li T, Zhang WH, Liu J, Mao YL, Liu S
- 7724** Multiple inflammatory pseudotumor formation after craniopharyngioma resection *via* an extended nasal endoscopic approach: A case report
Wu H, Ding YW, Yan ZC, Wei M, Wang XD, Zhang HZ
- 7732** Huge Bartholin's cyst managed by primary marsupialization: A case report
Li HY, Ding DC

LETTER TO THE EDITOR

- 7738** Do not forget diet and exercise during Ramadan
Ilias I, Tselebis A

ABOUT COVER

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Gut microbiome: New perspectives for type 2 diabetes prevention and treatment

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Abstract

Type 2 diabetes mellitus (T2DM), which is distinguished by increased glucose levels in the bloodstream, is a metabolic disease with a rapidly increasing incidence worldwide. Nevertheless, the etiology and characteristics of the mechanism of T2DM remain unclear. Recently, abundant evidence has indicated that the intestinal microbiota is crucially involved in the initiation and progression of T2DM. The gut microbiome, the largest microecosystem, engages in material and energy metabolism in the human body. In this review, we concentrated on the correlation between the gut flora and T2DM. Meanwhile, we summarized the pathogenesis involving the intestinal flora in T2DM, as well as therapeutic approaches aimed at modulating the gut microbiota for the management of T2DM. Through the analysis presented here, we draw attention to further exploration of these research directions.

Key Words: Microbial metabolites; Intestinal flora; Probiotics; Insulin resistance; Type 2 diabetes

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Core Tip: In this review, we summarized the pathogenesis that intestinal flora is involved in type 2 diabetes mellitus (T2DM), as well as therapeutic approaches aimed at modulating the gut microbial for the management of T2DM.

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INTRODUCTION

Diabetes, a metabolic disease with a rapidly increasing incidence, is characterized by deficiencies in insulin secretion, diminished sensitivity of target organs to insulin and metabolic disorders. According to the statistics supplied by the International Diabetes Federation, 463 million individuals suffer from this condition worldwide, and a conservative estimate of the global population of adult patients with diabetes indicates that it may reach 700 million by 2045[1]. Diabetes is broadly divided into three major types: Gestational diabetes, type 1 diabetes, and type 2 diabetes mellitus (T2DM), which represent over 90% of all diagnosed cases[1,2]. Therefore, the acquisition of knowledge of the unclear etiology and effective treatment strategies is crucial. Extensive discussions have revealed that the primary contributing factors include genetics, excessive caloric intake, and a lack of effective exercise[3]. Meanwhile, developing T2DM is closely related to obesity, which is recognized as the principal pathogenetic factor[4]. Furthermore, mounting evidence has proven that T2DM is linked to inadequate insulin production or insulin resistance (IR)[5].

Recently, increasing evidence has indicated that the intestinal microbiota is the essential element for maintaining health and the main pathogenic factor for various diseases that significantly influences the normal development of physiological systems[6,7]. Certainly, intensive discussions have identified the intestinal flora and the factors contributing to and mechanisms of T2DM as key factors in the advancement of metabolic diseases and the progression of T2DM[8]. According to many studies, T2DM patients have compositional differences in the characteristics of the intestinal microbiota compared to healthy people. Hence, for the purpose of preventing and improving T2DM and complicating diseases, as well as to provide literature references for the participation of the intestinal flora in the treatment of T2DM, this review summarizes the relevance and focuses on the systems in which the gut flora are engaged in the pathogenesis of this condition. These findings have allowed us to identify the significance of the intestinal flora as a candidate target for managing T2DM and related metabolic diseases.

OVERVIEW OF GUT MICROBIOME

The intestinal flora in the digestive system is currently considered an emerging 'organ' with immunologic, endocrinological, and energy-metabolic-like functions[9], and it consists of a vast quantity of bacteria, fungi and other parasitic organisms. The mature microbial ecosystem in the gut is originally formed during the introduction of solid food, which generally materializes between the ages of one and three years[10]. Once established, the overall structure and function of the intestinal flora remain relatively unchanged until old age. The adult intestine is a place of residence for a wide variety of bacterial species, has a range of approximately 500-1000 of bacterial classes, a large quantity of approximately 10¹²-10¹⁴, and a total scale of approximately 1-2 kg. Additionally, researchers have estimated that the human body comprises close to 30 to 40 trillion cells. In contrast, research shows that the number of bacterial cells in the intestinal microbiome exceeds 10 times the total number of cells composing the human body[7]. Meanwhile, compared to the human genomic sequence, the human microbiome encompasses a significantly higher number of genes: more than 150 times that of the human genome[9]. These numbers indicate the abundance and complexity of the intestinal flora. According to research, the majority of the normal gut microbiota is composed of anaerobic bacteria. These bacterial species are well adapted to flourish in the oxygen-depleted environment of the gut tract. The majority of the total intestinal microbiota, accounting for nearly 98% of the microbial population, is subjugated by the following four key bacterial phyla: Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes[11]. Within these four phyla, Firmicutes constitutes the highest proportion, reaching up to 64%, and mainly includes *Lactobacillus*, *Enterococcus*, and *Clostridium*, which are involved in numerous metabolic processes. Proteobacteria comprises *Escherichia*, *Salmonella*, and *Helicobacter*. *Bifidobacterium*, *Corynebacterium*, and *Mycobacterium* are considered the core constituents of Actinobacteria. Bacteroidetes includes bacterial genera such as *Bacteroides*, *Prevotella*, and *Parabacteroides*. Certain studies indicate that Verrucomicrobia might be involved in the augmentation of glucose regulation and insulin responsiveness.

The gut microbiome, which is broadly identified as a critical factor for human health, is intimately correlated with various aspects of human physiological function, the immune response and metabolic nutrition. These aspects encompass but are not exclusively constrained by the following functions: the metabolism of nondigestible dietary residues, which subsequently supply energy for gut motility, likewise organisms through short-chain fatty acids; adjustments of epithelial cellular growth and differentiation[9], as these cells form an intestinal barrier to safeguard against pathogens and harmful substances[6]; involvement in various metabolic processes, such as fermentation of carbohydrates and dietary components, and vitamin synthesis; and modulation of the immune system and inflammatory responses[12,13]. Microbial flora have the potential to impact the absorption and transportation of saccharides across intestinal epithelial cells. Certain microorganisms can modulate the expression of glucose transporters on these cells, thus influencing the uptake and utilization of glucose[14,15]. *Akkermansia muciniphila* effectively reverses the metabolic disturbances induced by a high-fat diet, which include an increase in fat accumulation, metabolic endotoxemia, inflammation in adipose tissue, and IR[16].

THE INTESTINAL MICROBIOTA AND T2DM

Recently, the development of 16S rRNA sequencing has transformed scholars' comprehension of taxonomic studies of the gut microbiome. The initial exploration of the intestinal microbiota in individuals with T2DM was documented in 2010. T2DM is linked to alterations in the gut flora[17].

Emerging evidence suggests that the formation and structure of intestinal microbes have the potential to modulate the occurrence of diabetes, particularly T2DM[18]. Furthermore, a study analyzing bacterial gene functions reported a discrepancy in the gut flora composition at the molecular level among people with diabetes and those without the illness [19]. Many studies have noted the interconnection between T2DM and fluctuations in the microbial composition of intestinal microorganisms, predominantly at the class and phylum levels. Compared with the normal population, an interesting finding is that one of the main characteristics of the microbiota during the initial and progressing periods of T2DM is that the proportional representation of *Bacteroides* and β -proteus increases significantly with dietary alterations [20], and the remarkably higher levels of *Bacilli*, including the *Lactobacillus* group[17], specifically in the advanced stages. Furthermore, the levels of *Clostridium*, *Bifidobacteria*, and *Firmicutes* in the gut microbiota of T2DM patients exhibit meaningful decreases[17,18,21], and the number of *Verrucomicrobia* decreases significantly[15]. However, importantly, one of the main alterations related to T2DM includes a notable decrease in the frequency of specific butyrate-synthesizing bacteria, such as the species *Faecalibacterium prausnitzii* and *Roseburia intestinalis*[22]. According to the latest reports, the enrichment of the Betaproteobacteria family[17] and Proteobacteria[23] is associated with low-grade inflammation in individuals with T2DM. Alterations in the levels and variety of bacterial groups, along with other modifications in the gut flora, may cause metabolic dysregulation and IR through various mechanisms, thus generating T2DM.

The principal determinant of the risk for T2DM is obesity, which is particularly characterized by excess visceral adipose accumulation[24]. Fat accumulation could cause increased IR and decreased insulin secretion, leading to decreased glucose absorption by cells and higher blood glucose levels, which eventually trigger the occurrence of T2DM. Recently, the decrease in the diversity and proportional distribution of microbes have also been implicated in obesity[25, 26]. Numerous mechanisms have been postulated to elucidate how the intestinal colony contributes to obesity and visceral adiposity[10,27], including assimilating energy from dietary consumption, regulating metabolism and triggering low-grade inflammation. In obese individuals, several factors, such as increased intestinal permeability and dysfunction of the gut barrier and immune system characterized by a chronic low-grade immune response, might further facilitate the advancement of IR and T2DM[28,29] (Table 1).

THE MECHANISMS UNDERLYING THE EFFECTS OF THE GUT FLORA GET IN ON THE ACT THE ONSET AND DEVELOPMENT OF T2DM

Bile acid theory

Bile acid plays a crucial role as an integral component of bile, which is manufactured by the liver and stockpiled within the gallbladder, together with the cholesterol end metabolite. Bile acids enter the gastrointestinal tract. Initially, bile acids, a component of bile, are exuded into the intestine. The sophisticated processes of primary bile acid metabolism are predominantly regulated by the gut microbiota and then enzymatically transformed into secondary bile acids[30,31]. Secondary bile acids may affect amylaceum metabolism and insulin susceptibility through diverse signaling pathways [32]. Some studies have suggested that certain secondary bile acids activate a continuum of specific nuclear receptors, namely, farnesoid X receptor (FXR) and Takeda G protein-coupled bile acid receptor 1 (GPBAR1)[33], which participate in the regulation of glucose and lipid metabolism. FXR activation by secondary bile acids has been linked to increased glycemic tolerance and insulin susceptibility. By activating FXR, hepatic glucose production and insulin signaling are potentially affected in peripheral tissues, ultimately leading to an improvement in glycemic control. Fibroblast growth factor 19/15 (FGF19/15) is secreted by intestinal cells and is induced by FXR activation. FGF19/15 has been proven to optimize insulin sensitivity by facilitating dextrose uptake into cells, stimulating glycogen synthesis in the liver, and diminishing hepatic glucose production[33,34]. Secondary bile acids also activate Takeda G protein-coupled receptor 5 (TGR5). TGR5 was initially discovered in 2002[35] and subsequently characterized in 2003[36]. Through the establishment of TGR5 mice[37,38], researchers discovered that their overall reservoir of bile acids was diminished. In skeletal muscle, TGR-5 activation has been validated to increase the utilization of glucose and aliphatic acids, thereby promoting energy consumption. In intestinal L cells, TGR-5 activation stimulates the production of glucagon-like peptide 1 (GLP-1), an incretin hormone responsible for regulating glucose homeostasis. GLP-1 shows promise for therapeutic applications due to its ability to stimulate insulin secretion from pancreatic beta cells and inhibit glucagon release. Moreover, it has shown promising potential in reversing IR and correcting irregular glucose metabolism[33,39]. Both FXR and TGR5 are expressed in pancreatic β -cells and serve a purpose in accelerating glucagon synthesis and insulin discharge in reaction to glucose. Therefore, the proper functioning of the intestinal flora is vital for the synthesis, alteration, and transmission of bile acids. Recent research has indicated that an imbalance in the intestinal flora interferes with the ability of bile acids to regulate glucose metabolism[40,41], which further disturbs carbohydrate metabolism and results in the onset of T2DM.

The theory of short-chain fatty acids

Short-chain fatty acids (SCFAs), one of the metabolites that has been researched extensively, are synthesized by specific bacteria in the intestine through fermentation using a variety of substrates. Several common bacteria, such as *Bacteroides*, *Streptococcus*, *Clostridium*, *Eubacterium*, and *Bifidobacterium*, breakdown a variety of dietary fibers and cumbersome carbohydrates through zymolysis, eventually resulting in the generation of SCFAs. SCFAs belong to the group of organic carboxylic acids, including monopropanoic, lactic acid, acetic acid, isobutyric acid, isovaleric acid, isohexanoic acid, and butyrate, among others.

Gut hormones: As ligands for FFAR2 and FFAR3, the receptors that bind to free fatty acids, SCFAs can transmit signals related to the energy status and metabolic processes, including the regulation of energy balance and metabolism. Free

Table 1 Alterations of gut flora in type 2 diabetes mellitus individuals

Classification	Species of bacteria	Content
Fimicutes	<i>Eubacterium rectale</i> , <i>Lactobacillus gasseri</i> , <i>Roseburia spp.</i> , <i>Faecalibacterium</i>	Down
	<i>Streptococcus mutans</i> , <i>Clostridium ramosum</i>	Up
Bacteroidales	<i>Bacteroides spp.</i> , <i>Parabacteroides</i>	Up
Verrucomicrobia	<i>Akkermansia muciniphila</i>	Down
Proteobacteria	<i>Escherichia coli</i>	Up

fatty acids (FFAs) are always produced by colonic enteroendocrine L cells. In addition to their roles in inhibiting glucagon secretion and glucose-dependent insulin secretion, FFAs have also been validated to stimulate the production of specific hormones in the intestinal tract, such as GLP-1 and peptide YY (PYY)[42,43]. GLP-1 functions as an insulinotropic hormone to stimulate insulin secretion while also serving as an anorectic hormone to promote sensations of satiety. Through the utilization of C57BL6 mice and free fatty acid receptor 2 knockout mice, researchers have observed that propionate promotes the liberation of GLP-1 and PYY, while the absence of FFA2 negatively impacts the secretion of intestinal hormones induced by short-chain fatty acids[42]. Mice deficient in FFAR2 and FFAR3 exhibit diminished secretion of GLP-1 in response to SCFAs both *in vitro* and *in vivo*, resulting in impaired glucose tolerance[44]. Colonic infusions of SCFA mixtures (including acetate, propionate, and butyrate) lead to elevated energy expenditure and PYY levels while reducing lipolysis[45].

Energy supply: SCFAs, particularly ethanoate and propionate, can enter the bloodstream from the colon and are subsequently transported to the liver. The metabolic pathway of hepatic gluconeogenesis is directly stimulated by SCFAs, a process that entails the synthesis of glucose from noncarbohydrate sources. It contributes approximately 30% of the energy required for liver metabolism[46]. Furthermore, studies have estimated that the zymolysis of SCFAs by microbes in the colon supplies a substantial amount of the energy required for the metabolism of colonocytes, which comprise approximately one-tenth of the entire energy expenditure in the normal state[47]. Butyrate, a type of SCFA, has shown potential in improving insulin sensitivity in response to the diet, glucose metabolism and the burning of calories, potentially through several mechanisms that are still being investigated[48]. SCFAs exert various effects on fat accumulation within the human body[49,50]. In particular, SCFAs inhibit fatty acid production by suppressing the activity of key enzymes involved in fatty acid synthesis and increasing thermogenesis, which results in the burning of more calories and potentially leads to a reduction in fat accumulation.

Intestinal glucose metabolism: Butyrate and propionate, two of the major SCFAs, exert considerable effects on the process of intestinal gluconeogenesis, which involves glucose production, thereby promoting improvements in body weight and glycemic regulation. Studies have indicated that butyrate increases glucose synthesis in the intestine by promoting the activation of genes related to intestinal gluconeogenesis. Additionally, propionate and butyrate have been identified as crucial catalysts required for the activation of intestinal gluconeogenesis, which plays a major role in fostering metabolic wellness[51].

Moreover, SCFAs potentially stimulate β -cells to deliver insulin and activate G-protein coupled receptors, thereby aiding in increasing glucose metabolism or insulin sensitivity by engaging diverse pathways[44].

Intestinal barrier: SCFAs contribute to the maintenance of a healthy gut environment through multiple mechanisms, including enhancing the acidic pH in the colon to restrain the proliferation of harmful bacteria. An additional mechanism is the ability of SCFAs to prevent gastrointestinal dysfunction and regulate fluid and electrolyte equilibrium. Multiple research findings have presented supporting evidence for the beneficial effects of SCFAs on inflammatory responses, including their anti-inflammatory ability to suppress the production of proinflammatory factors[47,52]. The development of T2DM is strongly influenced by the presence of chronic inflammation[53,54]. Impaired intestinal barrier function may cause persistent inflammation, triggering the development of IR in T2DM patients[55,56]. Given these implications, the utilization of SCFAs and their associated molecular targets represents a potential avenue for therapeutic intervention in the management and treatment of these disorders.

Endotoxin theory

Some bacteria in the gut microbiota produce endotoxins, particularly lipopolysaccharide (LPS), which are constituents located in the outer membrane that are present in gram-negative bacteria. In individuals diagnosed with T2DM, endotoxins penetrate more easily due to the impaired intestinal barrier function, such as the elevated permeability of the intestinal barrier, culminating in an increased concentration of LPS in the bloodstream. After the endotoxin enters the bloodstream, it engages with the immune system, inciting the onset of inflammation. Endotoxins bind to Toll-like receptors (TLRs) and other receptors, activating immune cells to produce inflammatory mediators. Meanwhile, endotoxins may cause disorders in the host immune system. Increased systemic levels of LPS may be able to induce a

chronic low-grade inflammatory reaction, ultimately contributing to impaired glucose metabolism and insulin signaling in individuals with T2DM[57,58]. In addition, the disruption of the intestinal flora may increase the abundance of gram-negative bacteria, which in turn increases LPS production and release. LPS in the circulation forms a complex with CD14 and is subsequently identified by TLR-4. Afterward, the activation of mitogen-activated protein kinase and TLR signaling pathways triggers a cascade of nonspecific inflammatory responses that ultimately result in disturbances in insulin secretion and insulin transport[59]. Simultaneously, disturbances in the intestinal flora contribute to the impairment of gut epithelial barrier function, resulting in metabolic endotoxin-related pathogenesis. The presence of mild inflammation caused by endotoxemia implies that intestinal microbiota-derived metabolites may exert effects on initiating metabolic disturbances and the development of T2DM. Interestingly, previous research has shown that the concentration of endotoxins in individuals may serve as a prognostic biomarker for identifying humans with a higher risk of T2DM[60] (Figure 1).

THERAPEUTIC APPROACHES FOR T2DM UTILIZING THE GUT MICROBIOTA

The modulation of the intestinal microbiota has become a substantial focus as a promising area of research for preventing and treating T2DM, as numerous studies published in recent years have recognized the notable role of gut flora in the physiopathology of T2DM.

Diet

Balanced dietary choices, particularly the types of foods and nutrient contents, represent appropriate changes in shaping the health of the intestinal microbiome and metabolites derived from gut microorganisms[61], and they might prevent and lower the predisposition to obesity and T2DM[62] and promote glycemic control[63]. Over the last several decades, scientific evidence has highlighted the significant effects of dietary factors on both the prevention and healing of T2DM [64]. Altering the structure and composition of diet is regarded as a basic and essential adjunct approach for treating diabetes effectively.

Dietary fiber has received considerable attention among the various dietary factors due to its significant effect on improving glycemic control in T2DM patients[65,66]. Consuming a diet rich in dietary fiber, including whole grains and nuts, perhaps promotes positive effects on glucose regulation and insulin sensitivity, thereby decreasing the probability of developing T2DM[67,68]. By increasing the intake of fiber-rich foods, insulin susceptibility may be increased by promoting dietary fiber fermentation by the gut microbiome and the creation of prominent end products, such as short-chain fatty acids, butanoate, and propanoic acid ester[69].

Making dietary choices, such as replacing saturated and trans fats with healthier fats, selecting carbohydrates with a low glycemic index (GI) and consuming lean proteins, can enhance insulin sensitivity and lower the likelihood of developing T2DM. Closer adherence to the diets that are primarily based on plants, such as the DASH, Portfolio, and Mediterranean diets, is linked to a lower incidence of developing T2DM in the future[70,71].

Regarding traditional calorie-restricted diets, intermittent fasting (IF) by individuals affected by T2DM has shown potential advantages in glucose control, weight management and IR[72,73]. Increasing evidence suggests that intermittent fasting has the capacity to alter the composition and diversity of the gut microflora and modulate microbial metabolite products. This diet may be responsible for the maintenance of gut, glucose and lipid metabolic health[74].

Therefore, these changes in the intestinal microbial community resulting from dietary modifications might have a major impact on enhancing glycemic control in T2DM patients[75,76].

Beneficial prebiotics and probiotics

Probiotics are living microscopic organisms that provide health advantages to humans by synthesizing vitamins, assisting in the digestion of food, and suppressing the proliferation of hazardous bacteria[77]. The increasing popularity of probiotics as functional foods or dietary supplements is due to their perceived effects on the intestinal microbial community[78-80]. Changes in metabolic disorders related to T2DM are usually observed after the utilization of probiotics[81], which encompass increased insulin sensitivity[82,83], the amelioration of impaired glucose tolerance[84], improved intestinal integrity[85], modulation of the gut flora and a reduction in systemic levels of LPSs[86,87]. The mechanisms of T2DM that are affected by individuals using probiotics as a supplemental treatment have been suggested [88].

Based on accumulating evidence indicates, studies not only showcase the positive effects of various probiotic strains but also provide a valuable understanding of the effects of a few particular strains of probiotics on T2DM. The administration of *Bifidobacterium lactis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, and *Lactobacillus acidophilus* as supplements has shown promising results in enhancing glycemic control in adults diagnosed with T2DM[89]. Clinical and experimental research has revealed that *Lactobacillus gasseri*, *Bifidobacterium bifidum*, *Lactobacillus casei*, and *Lactobacillus helveticus* effectively decrease fasting blood glucose levels and HbA1c levels in individuals diagnosed with T2DM [90]. *Lactobacillus casei*, a probiotic strain that is considered beneficial for individuals with T2DM, has been shown to improve SIRT1 and fetuin-A levels, which are correlated with various metabolic processes[91]. Consequently, *Lactobacillus casei* supplementation may have the potential to effectively manage diabetes[92] and change the gut microbiota ecosystem in patients suffering from T2DM, specifically by increasing the copiousness of beneficial microflora[93]. *Lactobacillus reuteri* DSM 17938 enhances insulin sensitivity and increases the diversity of gut microorganisms[94]. Numerous studies have examined the effects of *Lactobacillus rhamnosus* GG on glycemic parameters, reporting its potential advantages in safeguarding against alterations such as decreased blood glucose levels in the fasting state, enhancing the insulin

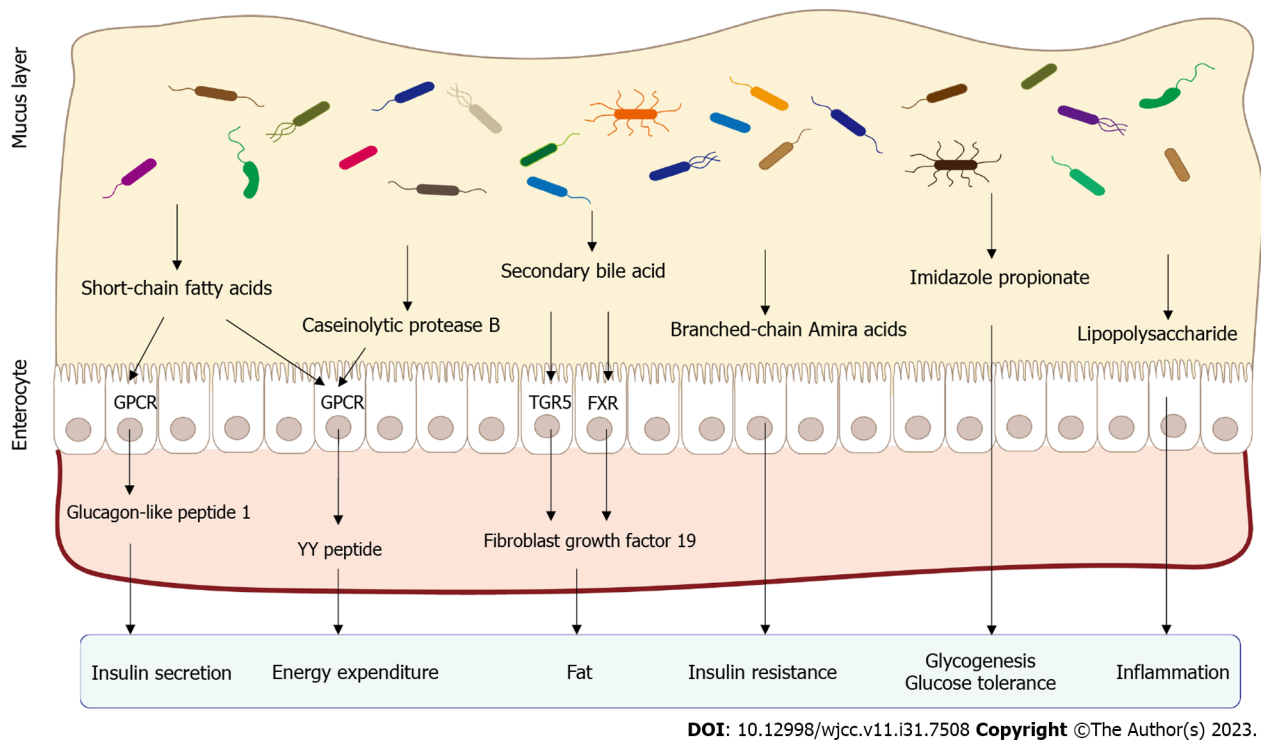


Figure 1 Intestinal flora impacts the varied ways of metabolism in type 2 diabetes mellitus. GPCR: G-protein coupled receptor; TGR5: Takeda G protein-coupled receptor 5; FXR: Farnesoid X receptor.

hormone sensitivity index, and improving glucose control, specifically in individuals with impaired glucose tolerance [95]. *Lactobacillus casei* CCFM419 shows promising potential in promoting metabolic health, exerting anti-inflammatory effects, reducing IR and improving the composition of beneficial gut microbes, possibly helping to improve the amelioration of hyperglycemia in individuals with T2DM [96]. Supplementation with *Akkermansia* probiotics improves insulin sensitivity and is associated with improving metabolic health indicators [97].

Prebiotics, which are indigestible food components, exert a beneficial effect by preferentially promoting the proliferation and function of a single or a restricted group of specific bacteria that already exist in the colon [98]. Inulin, one of the extensively researched prebiotics, tends to enhance glucose by provoking the production of the hormone GLP-1. It can help alleviate T2DM by suppressing inflammation and modulating the composition of the gut microbiota [99,100].

Importantly, the combination of prebiotics and probiotic substances may exert a greater positive effect on decreasing fasting glycemia levels and HbA1C levels in T2DM patients compared to the administration of prebiotics or probiotics individually [101,102]. The amalgamation of multiple beneficial probiotic strains promotes more encyclopedic and substantial synergistic effects on T2DM [103,104] because of their distinct mechanisms and complementary effects.

In the future, supplementation with beverages containing probiotics and/or prebiotics has the potential to emerge as a complementary approach in conjunction with medication and lifestyle modifications to effectively manage T2DM [105, 106].

Physical activity

Regular physical activity, a budget-friendly lifestyle modification for the prevention and intervention of obesity and T2DM by increasing energy consumption and the metabolic rate [107], might improve glycemic homeostasis and insulin receptor sensitivity [108]. A controlling effect of exercise on the extent and nature of the intestinal microbiota has been proposed, particularly in terms of the underlying mechanisms. The microflora of individuals who exercise exhibits higher biodiversity and metabolic aptitude, and different types and intensities of exercise promote noticeable shifts in the constitution and capacity of the intestinal bacterial population [109,110] because exercise stimulates gut motility, dietary changes and the activity of immune cells. Meanwhile, according to some references, a strong correlation exists between exercise interventions that induce transformations in gut microorganisms and improvements in metabolic improvements, including glucose homeostasis and insulin sensitivity [111]. On the other hand, a better understanding of the role of the gut bacterial population in the response to physical activity is needed and may provide valuable insights into personalized approaches and therapeutic interventions for enhancing glucose metabolism and insulin sensitivity [112].

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a technique used to restore the equilibrium of gut microbiota in clinical trials and is recognized as an effective method to rectify dysbiosis. Essentially, FMT involves transferring beneficial microbes from the healthy gut tract of donors into patients with gut microbiota dysbiosis, thereby reestablishing a harmonious microbial ecosystem in the intestinal tract to treat diseases [113].

Studies have indicated that FMT from individuals with a lean weight who were diagnosed with metabolic syndrome might result in improved insulin sensitivity, glucose levels, and the alleviation of metabolic syndrome. This positive outcome may be at least partially attributed to the increased abundance of butyrate-producing bacteria[114-116].

Similarly, research has shown that FMT from healthy Chinese individuals into mice effectively decreases fasting plasma glucose levels[117]. Similar studies have shown that reverse IR is effectively reversed by restoring the microbiota in mice with T2DM using FMT[118].

Based on the ongoing exploration of the “brain-gut-microbiota axis”, the mood of patients with diabetes, particularly those with diabetic neuropathy, may be affected by their intestinal flora. Interestingly, promising research findings have shown that patients with stable glycemic levels and well-controlled conditions who underwent fecal bacteria transplantation as a therapy for T2DM experienced positive outcomes[119]. Based on the aforementioned studies, we propose the hypothesis that fecal bacteria transplantation holds promise in ameliorating the symptoms of T2DM.

Medications

Metformin, a widely used medication for treating T2DM, was discovered in the study of *Galega officinalis*, a plant commonly known as Goat's rue, in 1922. Since then, metformin has been widely used due to its ability to lower glucose levels through its interaction with the gastrointestinal system. Moreover, numerous studies have provided supporting evidence that the modulation of gut microbiota participates in the mechanism through which metformin improves glycemic regulation[120]. Notably, metformin has been found to alter the abundance and composition of various microbial taxa. Specifically, it decreases the levels of *Clostridium* spp. and *Intestinibacter* spp. while increasing the abundance of *Bifidobacterium bifidum*, *Lactobacillus*, *Bilophila wadsworthia*, *Escherichia* and *Shigella* spp.[121,122]. Propionate helps decrease hepatic blood dextrose levels, while butyrate improves insulin sensitivity. Metformin has been observed to regulate blood glucose levels in individuals with conditions such as T2DM due to its effects on propionate and butyrate production[123,124]. Furthermore, an expanding repertoire of research has indicated that metformin exerts its effects on endocrine cell activity through diverse pathways, encompassing the regulation of bile acid conversion, intestinal barrier integrity and permeability, reductions in endotoxin levels, and increasing the production of the hormones released by endocrine cells, such as GLP-1 and PYY peptides, in the gut[125]. Furthermore, metformin has the potential to increase the population of *Akkermansia muciniphila*, a type of bacteria known for its beneficial effects on insulin sensitivity and glucose regulation[126]. *Akkermansia* protects the intestinal barrier in individuals with T2DM, aiding in the preservation of the wholeness of the intestinal mucosa and thereby reducing inflammatory reactions.

Acarbose, the other antidiabetic medication with a connection to the microorganism community, is an α -glucosidase inhibitor used to manage the condition of individuals with T2DM. Acarbose treatment represses the enzymatic transformation of complex oligosaccharides to monosaccharides and disaccharides and lowers blood glucose levels in the small intestine by modifying the diversity and abundance of designated microbial families in patients with T2DM[127].

According to recent studies, the composition of the gut microbial community changes in diabetic rats following treatment with pioglitazone, vildagliptin, DPP-4 inhibitors and sitagliptin[128-130]. Recent studies have revealed that SGLT2 inhibitors may also exert their hypoglycemic and therapeutic effects on T2DM by influencing on the intestinal microbiota[131].

Regulating intestinal phages and engineering bacteria

Bacteriophages, which are viruses that specifically target bacteria, are highly prevalent microorganisms in the gut. They have a prominent role in shaping the structure of the gut flora, ultimately impacting health[132]. An increased quantity of bacteriophages has been observed in the digestive tract of individuals with diabetes[133]. This finding highlights the significance of the presence of bacteriophages in individuals with diabetes.

The fecal virome transplant operation, which is the transfer of a healthy virome from the donor to the receiver, may induce positive changes in altering the gut microbiome and host metabolome in patients with T2DM[134].

The active artificial manipulation of gut microbial genes has the potential to control the structure and function of the intestinal ecosystem. Through a targeted manipulation, promoting the expression of beneficial metabolic genes may be feasible. For example, administering engineered *Lactobacillus gasseri* or *Escherichia coli* Nissle 1917, which produce GLP-1, may render intestinal cells responsive to glucose, making them sensitive to glucose and inducing insulin production when glucose levels increase[135,136], potentially improving glucose regulation in individuals with T2DM. The production of high-fat diet-fed mice transplanted with engineered *Escherichia coli* Nissle 1917 that generate N-acylphosphatidylethanolamines lead to a decrease in glycemia and IR.

PERSPECTIVE

A large number of emerging papers has increasingly recognized the involvement of intestinal flora in the onset and progression of T2DM. The gut microbial community plays a role in regulating T2DM through various mechanisms and multiple targets, including the regulation and production of bacterial metabolites and bile acid metabolism and inflammation mediated by LPS, which may contribute to the occurrence and extension of T2DM. By conditioning the intestinal flora as a therapeutic approach, scientists may not only be able to regulate IR and the blood glucose status but also to improve T2DM outcomes.

Our understanding of the complex field of the intestinal ecosystem is still in its nascent stages, and numerous questions remain unanswered and details remain unknown. First, currently, the majority of studies still primarily focus on bacteria while disregarding the contributions of nonbacterial microorganisms, such as viruses and fungi. Crucially, we should

delve deeper into the complete microbial ecosystem to gain a comprehensive grasp of their implications for health and diseases such as T2DM. Second, specific related microbial taxa or metabolic derivatives that fulfill a role in the pathogenesis and escalation of T2DM must be identified to provide valuable targeted interventions. Third, the establishment of standardized reference databases is expected to analyze the comparisons of microbiome data and sustain our exploration of the involvement of intestinal microbes in metabolic disorders such as T2DM. Fourth, an imperative goal is to not only concentrate on the gut microbiome at certain time points but also maintain a continuous determination of the fluctuating variations in the gut flora and metabolic products. These alterations occur throughout various stages of diabetes and its complications, which might enable us to identify potential biomarkers for improved prevention and treatment measures. Fifth, the creation of a noninvasive diagnostic technique for early detection, such as examining biomarkers in blood and feces, is formidable and challenging. In addition, maintaining the sustained presence of exogenous microbes in the gut is another challenge. Last but not least, deeper research based on the gut microbiome to predict T2DM holds the potential to formulate novel and personalized approaches to prevent and treat IR and T2DM.

CONCLUSION

Continued investigation is essential to obtain a more comprehensive understanding of the mutual influences between the intestinal ecosystem and T2DM and to provide a crucial foundation for predicting and treating diabetes in the future. Absolutely, we believe that the treatment of T2DM based on the value of the gut flora has promise as a safer and more reliable approach, which shows promise in minimizing side effects and improving long-term effectiveness.

FOOTNOTES

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