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Gut microbiota and diabetic gastrointestinal autonomic neuropathy

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Abstract: Diabetic gastrointestinal autonomic neuropathy, one of the complications of diabetes, has a widespread impact on the digestive tract. Symptoms include gastroesophageal reflux, nausea, vomiting, gastroparesis, abdominal pain, constipation, and diarrhea, among others. Currently, the pathogenesis of diabetic gastrointestinal autonomic neuropathy is not fully understood, but an increasing number of studies suggest a close connection between the gut microbiota and diabetic gastrointestinal autonomic neuropathy. This article aims to summarize the research progress and potential mechanisms of the relationship between the gut microbiota and diabetic gastrointestinal autonomic neuropathy, and to explore treatment strategies related to the gut microbiota, with the aim of providing new perspectives for the prevention and treatment of diabetic gastrointestinal autonomic neuropathy, thereby improving the quality of life for patients.

Keywords: Diabetes mellitus; Gut microbiota; Gastrointestinal autonomic neuropathy; Probiotics; Fecal microbiota transplantation

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Diabetic gastrointestinal autonomic neuropathy (GAN) is a typical gastrointestinal manifestation of autonomic nervous system dysfunction in patients with diabetes mellitus. It can involve multiple sites, including the esophagus, stomach, small intestine, and colon, leading to abnormal gastrointestinal motility [1]. Clinical manifestations include nausea, postprandial fullness, and gastroesophageal reflux. In some patients with concomitant gastroparesis, delayed gastric emptying may cause glycemic fluctuations, further aggravating the disease and reducing quality of life [2]. Existing studies suggest that pathological mechanisms such as hyperglycemic injury, autoimmune responses, oxidative stress, and vascular insufficiency may cause intestinal autonomic neuropathy and impairment of vagal afferent regulatory function, thereby inducing widespread systemic disturbances, including intestinal dysmotility, reduced secretion of local hormones or neurotransmitters, and alterations in the gut microbiota [1]. Recent studies have revealed a causal association between the gut microbiota and diabetes mellitus and its complications [3]. Under healthy conditions, lactate and butyrate produced by gut microbial metabolism can promote intestinal mucin synthesis and maintain intestinal microbial homeostasis. In diabetic mouse models, however, dysbiosis of the gut microbiota increases intestinal permeability, allowing bacteria and harmful metabolites to enter the bloodstream, inducing chronic inflammation and exacerbating the progression of diabetic GAN [4].

Therefore, whether regulation of the gut microbiota and its metabolites can prevent and treat diabetic GAN has become an issue worthy of investigation. This review summarizes progress in the relationship between the gut microbiota and diabetic GAN and discusses strategies for preventing and implementing individualized treatment of diabetic GAN through improvement of the gut microbiota.

1. Relationship Between the Gut Microbiota and Diabetic GAN

The gut microbiota refers to the microbial community colonizing the human intestine, including bacteria, a small number of archaea, and unicellular eukaryotes. It participates in key physiological processes such as host metabolic regulation, immune activation, regulation of gene expression, and maintenance of gastrointestinal motility [5-6]. Animal experiments have confirmed that germ-free rats, due to the absence of gut microbiota colonization, develop marked intestinal motility disorders. After colonization with *Clostridium*, *Lactobacillus acidophilus*, and *Bifidobacterium*, the propagation efficiency and transit speed of the small intestinal migrating motor complex are significantly improved. In contrast, *Escherichia coli* inhibits intestinal motility [4]. These findings suggest that the type and abundance of gut microbiota directly affect gastrointestinal motor function.

The incidence of diabetic GAN remains unclear. From the perspective of clinical manifestations, diabetic GAN is heterogeneous: patients with gastric dysmotility may present with gastroparesis and gastroesophageal reflux, whereas those with intestinal involvement mainly present with constipation or diarrhea. Some patients

develop malnutrition due to long-term gastrointestinal dysfunction [1]. In recent years, clinical studies have further confirmed that patients with diabetic GAN exhibit significant gut microbiota dysbiosis. Compared with patients with diabetes alone, patients with diabetic gastroparesis have increased abundance of Enterobacteriaceae in feces, whereas beneficial bacteria such as *Bacteroides*, *Bifidobacterium*, and *Lactobacillus* are significantly reduced [7-9]. Analysis of the gut microbiota structure in patients with type 2 diabetic gastroparesis showed an abnormal increase in Proteobacteria abundance, and this microbial alteration was positively correlated with disease severity, possibly accelerating disease progression by inducing intestinal inflammation [10]. In summary, gut microbiota dysbiosis in patients with diabetic GAN is characterized by an increase in harmful bacteria and a decrease in beneficial bacteria. However, which specific strains are directly involved in disease onset and progression still requires validation by more high-quality clinical studies.

2. Possible Mechanisms Linking the Gut Microbiota to the Development of Diabetic GAN

2.1 Disruption of the intestinal barrier

The intestinal barrier is a key structure for maintaining intestinal microbial homeostasis. It consists of intestinal epithelial cells, tight junction proteins, and the mucosal protective layer, and prevents intestinal bacteria and toxins from entering the bloodstream [11]. The gut microbiota bidirectionally regulates intestinal barrier function through its structural components and metabolites. On the one hand, lipopolysaccharide released by Gram-negative bacteria can disrupt adhesion structures between intestinal epithelial cells, reduce tight junction integrity, and increase intestinal permeability [12]. On the other hand, metabolites of beneficial bacteria, such as butyrate, can induce intestinal epithelial cells to express synaptopodin and promote repair of damaged epithelium. Anti-inflammatory molecules secreted by *Faecalibacterium prausnitzii* can also restore intestinal barrier function in diabetic mice by upregulating the expression of the tight junction protein ZO-1 [1,13].

When the gut microbiota is dysregulated, impairment of intestinal barrier integrity increases intestinal permeability, allowing bacterial antigens and harmful metabolites to enter the systemic circulation and induce systemic chronic inflammatory responses. Meanwhile, local intestinal inflammation can directly affect gastrointestinal smooth muscle contractile function and aggravate motility disorders [4]. Clinical studies have also confirmed that serum inflammatory factor levels are significantly higher in patients with diabetic GAN than in patients with diabetes alone, and are positively correlated with intestinal barrier markers [7], further supporting the role of intestinal barrier disruption in this disease.

2.2 Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) refers to a bacterial load in the small intestine that exceeds the normal threshold, defined as a jejunal aspirate bacterial count $>10^5$ CFU/mL. Its occurrence is closely related to slowed intestinal peristalsis, anatomical abnormalities, and impaired regulation of gastrointestinal motility, and diabetic autonomic neuropathy is one of the important risk factors for SIBO [14-15].

In patients with diabetic GAN, weakened gastrointestinal motility, such as prolonged orocecal transit time, reduces bacterial clearance efficiency in the small intestine, leading to bacterial overgrowth and production of gases such as methane and hydrogen. This causes symptoms such as abdominal distension and periumbilical pain. Some patients may also develop malabsorption and osmotic diarrhea due to bacterial competition for nutrients [16]. Clinical data show that 60% of patients with gastroparesis whose main symptoms are abdominal pain and bloating have concomitant SIBO, and the duration of gastroparesis is significantly longer in SIBO-positive patients than in SIBO-negative patients [15]. In addition, meta-analysis has shown that the detection rate of SIBO is significantly higher in patients with diabetes than in non-diabetic populations. Patients with type 2 diabetes and SIBO have higher serum levels of oxidative stress markers and inflammatory factors, lower levels of the antioxidant glutathione, and concurrent decreases in fasting insulin levels, impaired glucose tolerance, and elevated glycated hemoglobin [16-17].

At present, the incidence of SIBO in patients with diabetic GAN and the effect of SIBO eradication on symptom improvement remain unclear, and prospective studies are needed for validation.

2.3 Reduction of gastrointestinal interstitial cells of Cajal

Interstitial cells of Cajal (ICC) are specialized cells distributed throughout the layers of the gastrointestinal wall. By generating rhythmic electrical activity, they regulate myogenic contraction of gastrointestinal smooth muscle and also mediate neural signal transmission among the enteric nervous system, central nervous system, and smooth muscle cells [18].

Patients with diabetic GAN show significant abnormalities in ICC function and number. Gastric tissue biopsies from patients with gastroparesis have shown significantly reduced expression of Kit, a specific ICC marker [19]. Animal experiments have confirmed that a reduction in ICC number in the gastric fundus of diabetic mice impairs fundic relaxation, whereas a reduction in antral ICC is directly associated with decreased slow-wave frequency and delayed gastric emptying [20]. Clinical studies have further found reduced ICC numbers in the stomach, small intestine, and colon tissues of patients with diabetes and diabetic GAN, and the degree of reduction is positively correlated with the severity of gastrointestinal dysmotility [1].

ICC membranes express multiple 5-hydroxytryptamine (5-HT) receptors. Activation of the 5-HT_2B receptor can promote ICC proliferation through the

phospholipase C-intracellular calcium release-protein kinase Cγ pathway, and enhancement of this signaling pathway can also improve colonic motility in diabetic mice [21]. Experiments in germ-free mice have shown that after fecal microbiota transplantation from healthy mice, gastrointestinal transit is significantly accelerated, intestinal 5-HT-positive cell expression is increased, and transit time is negatively correlated with the number of 5-HT-positive cells [22]. In addition, *Bacteroides thetaiotaomicron* can regulate colon-specific contraction and improve intestinal motility by increasing the number of intestinal L cells and promoting 5-HT synthesis [23]. These studies suggest that the gut microbiota may affect gastrointestinal motility in patients with diabetic GAN by regulating the 5-HT/ICC pathway, although the specific pathway requires validation in in vivo studies.

2.4 Effects on the enteric nervous system and central nervous system

The enteric nervous system (ENS) is a network composed of independent neurons and glial cells. It transmits visceral sensory signals such as gastrointestinal pain, distension, and fullness through sensory neurons, and regulates gastrointestinal motility, secretion, and mucosal blood flow through sympathetic and parasympathetic efferent pathways [6].

Chronic hyperglycemia damages the supportive role of glial cells for enteric neurons through oxidative stress, inflammation, and impaired cellular signaling, leading to impaired neurotransmitter processing, disrupted cellular communication, and increased neuronal susceptibility to injury and apoptosis [1]. The gut microbiota is essential for ENS development and functional maintenance. Maturation of the mucosal enteric glial cell network occurs synchronously with microbial colonization. After germ-free mice are colonized with normal microbiota, the number of impaired enteric glial cells can be restored to normal levels [24]. In addition, microbial metabolites, namely short-chain fatty acids (SCFAs), can affect neural signal transmission in the ENS by regulating glial cell function [6], suggesting that gut microbiota dysbiosis may exacerbate diabetic GAN progression by disrupting the ENS.

Meanwhile, the microbiota-gut-brain axis theory proposes that the gut microbiota establishes bidirectional communication with the central nervous system (CNS) through pathways such as the bloodstream and vagus nerve [6]. Clinical studies have shown that bidirectional communication exists between the gastrointestinal tract and the brain, and that the CNS can also influence gastrointestinal motility [25]. The emotional motor system can perceive intestinal stimuli and regulate several intestinal functions. Clinical studies have shown abnormal activity in brain regions, such as the left superior temporal gyrus, in patients with major depressive disorder accompanied by gastrointestinal symptoms, suggesting that structural and functional CNS changes may affect gastrointestinal motility through the microbiota-gut-brain axis [25]. However, direct evidence is still lacking regarding how the gut microbiota affects the ENS and CNS in patients with diabetic GAN through the microbiota-gut-brain axis, and further exploration is needed.

2.5 Oxidative stress and inflammatory responses

Oxidative stress and chronic low-grade inflammation are core pathological bases of diabetes mellitus and its complications [4]. Under long-term hyperglycemia, reactive oxygen species production increases, whereas antioxidant systems, such as glutathione and superoxide dismutase, are weakened, resulting in an oxidant-antioxidant imbalance and subsequent damage to gastrointestinal nerves and ICC [1]. Patients with diabetes develop systemic low-grade inflammation. Current in vitro studies have shown that tumor necrosis factor (TNF)-α can reduce the number of ICC and inhibit contractility of the colonic smooth muscle layer [26]. In rat models of diabetic gastroparesis, mitogen-activated protein kinase (MAPK) inhibitors significantly reduce TNF-α levels in the gastric wall and increase the gastric emptying rate [26].

The gut microbiota plays a key role in regulating oxidative stress and inflammatory responses. SCFAs, metabolites of beneficial bacteria, can attenuate inflammation by downregulating the expression of proinflammatory factors such as TNF-α and interleukin-6 [27-28]. In contrast, an increase in harmful bacteria, such as Enterobacteriaceae, aggravates inflammatory responses through lipopolysaccharide release [4]. At present, the specific roles of the gut microbiota and its metabolites in the regulation of oxidative stress and inflammation in patients with diabetic GAN still require further clinical validation.

2.6 Effects of metabolites

Metabolites of the gut microbiota can act as signaling molecules, be absorbed, and reach almost every organ and cell of the host through the circulation, thereby influencing host physiological processes. Gut microbial metabolites, such as SCFAs, secondary bile acids, branched-chain fatty acids, and tryptophan metabolites, may also participate in the regulation of intestinal function and glucose metabolism.

2.6.1 Short-chain fatty acids

SCFAs include acetate, propionate, butyrate, and valerate. As the final metabolites of bacterial fermentation of indigestible dietary fiber, they regulate a range of host physiological processes [6], including energy metabolism, immune status, and inflammatory levels. SCFAs can regulate lipid metabolism and improve skeletal muscle insulin sensitivity through G-protein-coupled receptor (GPCR) pathways. They can also promote intestinal L cells to secrete glucagon-like peptide (GLP)-1 and regulate intestinal endocrine function [29]. In vitro experiments have shown that propionate, butyrate, and valerate can inhibit M1 macrophage activity and promote M2 macrophage polarization [30]. Macrophages in the gastrointestinal muscularis can directly or indirectly regulate gastrointestinal motility [31]. Butyrate plays an important role in maintaining intestinal barrier integrity [4],

which is beneficial for improving host inflammatory status [6]. In addition, butyrate and propionate can reduce nitric oxide production in macrophages and attenuate inflammatory responses by inhibiting the activities of nuclear factor-κB, interferon-β/signal transducer and activator of transcription (STAT) 1, and histone deacetylase [32]. In rat models of diabetic gastroparesis, SCFA levels are decreased and GPCR expression is also reduced. After pharmacological intervention, however, SCFA levels are increased, levels of gastrointestinal hormones such as GLP-1, peptide YY, and 5-HT are regulated, GPCR expression is upregulated, and intestinal motility in rats is enhanced [33].

As microbial metabolites, SCFAs have demonstrated associations among SCFAs, diabetic metabolism, and gastrointestinal motility in animal experiments and in vitro studies. Future studies should explore whether exogenous SCFA supplementation improves disease symptoms and determine the optimal dosage.

2.6.2 Bile acids

There is a significant interaction between bile acid metabolism and the gut microbiota. Studies have shown that the gut microbiota can regulate bile acid synthesis in the liver [6]. The association between secondary bile acids and diabetic GAN is mainly mediated through activation of Takeda G protein-coupled receptor 5 (TGR5). TGR5 is widely expressed in intestinal L cells, neurons, and immune cells. After activation, it enhances mitochondrial oxidative phosphorylation, increases the ATP/ADP ratio, promotes GLP-1 secretion, improves glucose homeostasis [34], and reduces gastric emptying [7]. Fecal microbiota transplantation experiments in mice have confirmed that the gut microbiota of healthy mice can improve diabetic symptoms by activating the TGR5 signaling pathway [35]. In addition, age-related microbial changes lead to increased conversion of conjugated bile acids to unconjugated bile acids, thereby reducing TGR5 expression and the number of M2 macrophages, ultimately delaying intestinal transit [36]. This suggests that abnormal bile acid metabolism may aggravate gastrointestinal dysmotility in patients with diabetic GAN through the TGR5 pathway.

Bile acids play important roles in regulating energy metabolism and inflammatory responses and participate in the pathogenesis of diabetes mellitus. Meanwhile, bile acids are also crucial in regulating gastrointestinal barrier function and immune status. Therefore, the interaction between the gut microbiota and bile acids may play an important role in the pathogenesis of diabetic GAN.

2.6.3 Tryptophan metabolites

Tryptophan is an essential amino acid that cannot be synthesized by the human body. It can be catabolized by intestinal bacteria to produce various microbial metabolites, such as 3-indolepropionic acid (3-IPA) and tryptamine, which have important effects on intestinal barrier function and gastrointestinal motility [37].

3-IPA is a metabolite produced by bacterial deamination of tryptophan and has antioxidant, anti-inflammatory, and glucose metabolism-regulating functions [37]. Clinical studies have shown that serum 3-IPA levels are significantly lower in patients with type 2 diabetes than in healthy individuals. During follow-up, 3-IPA levels further decreased in patients, whereas they increased in healthy individuals, suggesting that 3-IPA may be negatively associated with the risk of diabetes [38]. In addition, 3-IPA can enhance the intestinal barrier by promoting the expression of tight junction proteins in intestinal epithelial cells, and can indirectly affect gastrointestinal motility by regulating GLP-1 secretion from intestinal L cells [37].

Tryptamine regulates gastrointestinal motility mainly in two ways. First, as a signaling molecule, it directly regulates intestinal transit time. In vitro experiments have shown that tryptamine can alter short-circuit current in mouse colon and affect ion secretion by intestinal epithelial cells, while ion balance is an important basis for gastrointestinal peristalsis [37]. Second, tryptamine indirectly promotes gastrointestinal motility by stimulating enterochromaffin cells to release 5-HT and activating ENS neurons [37]. Animal experiments have found that 5-HT receptor agonists can attenuate diabetic enteric neuropathy by inhibiting receptor-interacting protein kinase 3 (RIPK3)-mediated necroptosis of enteric neurons and reducing diabetes-induced colonic neuronal loss and intestinal hypomotility [39]. This suggests that tryptamine may participate in the regulation of gastrointestinal motility in diabetic GAN through the 5-HT pathway. At present, direct evidence regarding the specific roles and mechanisms of tryptophan metabolites such as 3-IPA and tryptamine in diabetic GAN remains insufficient, and further clinical studies are needed.

3. Treatment

3.1 Probiotics and prebiotics

Probiotics are live microorganisms beneficial to host health, with common strains including *Bifidobacterium* and *Lactobacillus*. Prebiotics are “food” for intestinal probiotics, such as inulin, fructooligosaccharides, and polysaccharides, and can promote probiotic proliferation and activate intestinal immunity [40].

Recent studies have found that probiotics and prebiotics have positive effects in patients with diabetes. A randomized double-blind study involving patients with type 2 diabetes showed that supplementation with multi-strain probiotics for 6 consecutive months reduced the insulin resistance index by 15%-20%, while significantly lowering fasting blood glucose and glycated hemoglobin levels [41]. The mechanism may be related to regulation of gut microbiota structure, increased SCFA production, and improved intestinal barrier integrity. A multicenter study in China confirmed that after 4 weeks of treatment with bifidobacterium tetravaccine tablets combined with the prokinetic drug mosapride, patients with diabetic gastroparesis had a significantly higher gastric emptying rate than those treated with mosapride alone, and symptom scores for postprandial fullness and nausea decreased by more than 50% [42].

In summary, probiotics and prebiotics can optimize the structure and function of the gut microbiota, increase the abundance of beneficial bacteria, inhibit the proliferation of harmful bacteria, and thereby restore gut microbiota balance. This helps improve insulin sensitivity and reduce inflammatory responses in patients with diabetes. In patients with diabetic GAN, these components may also exert positive effects through similar mechanisms.

3.2 Dietary modification

Dietary habits significantly affect microbial composition. A high-fat diet increases the abundance of opportunistic pathogens and reduces microbial diversity, while high saturated fatty acid intake may damage the intestinal mucus layer [43]. Increasing dietary fiber and fermented food intake can promote the growth of beneficial bacteria and increase SCFA levels. For example, replacing refined white rice with germinated brown rice can increase fecal *Lactobacillus* abundance, reduce inflammatory factors, and improve intestinal mucosal permeability in patients with type 2 diabetes [44]. Whey and pea protein can increase *Bifidobacterium* abundance, and a high-protein diet can also reduce hepatic fat and insulin resistance in patients with type 2 diabetes [45].

Dietary intervention can adjust the composition and function of the gut microbiota and thereby exert positive effects on diabetic GAN. In clinical practice, patients with diabetic gastroparesis are generally advised to adopt small-particle, divided-meal, liquid-diet regimens to promote gastric emptying and enhance satiety [46]. However, diabetic gastrointestinal disease has diverse manifestations. Therefore, individualized dietary plans are very important. How to adjust dietary structure, whether to adopt divided meals, and whether to choose solid or liquid foods still require more clinical research data to provide scientific evidence.

3.3 Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a therapeutic approach in which functional bacteria from the feces of healthy donors are transplanted into the patient's intestine to reconstruct intestinal microbial homeostasis [4]. Recent studies have shown that FMT has potential efficacy in diabetes mellitus and gastrointestinal motility disorders. FMT alone or combined with metformin in patients with type 2 diabetes can increase gut microbiota diversity, reduce insulin resistance, and improve glycemic control [47]. A clinical report described a patient with type 1 diabetes mellitus, malnutrition, and gastrointestinal symptoms whose nausea and vomiting were markedly relieved after FMT, while constipation, nutritional status, and glycemic control gradually improved. The gut microbiota composition of the patient and that of the healthy donor showed a certain degree of similarity [48].

Therefore, FMT can reconstruct intestinal microbial homeostasis and may become a therapeutic method for delaying the progression of diabetic GAN. Larger, more detailed, multicenter studies are needed to accurately evaluate the benefits of FMT.

4. Discussion

This article systematically reviews the association between the gut microbiota and diabetic GAN and its mechanisms, and proposes therapeutic strategies based on gut microbiota regulation. Gut microbiota dysbiosis participates in the progression of diabetic GAN through multiple pathways. Disruption of microbial structure can impair intestinal barrier integrity and increase intestinal permeability. Abnormal metabolites can affect gastrointestinal hormone secretion, ENS function, and ICC activity. Meanwhile, oxidative stress and inflammatory responses triggered by microbiota dysbiosis can further aggravate nerve injury and gastrointestinal dysmotility. In addition, as a communication bridge between the gut microbiota and the CNS, the microbiota-gut-brain axis may indirectly affect gastrointestinal symptoms by regulating brain-region function, although the specific mechanisms require further investigation.

In terms of treatment, probiotics, prebiotics, dietary modification, and FMT can produce positive therapeutic effects on diabetes and its related complications by improving the structure and function of the gut microbiota. Probiotics and prebiotics may act by increasing the abundance of beneficial bacteria and reducing inflammation. Dietary intervention is a fundamental approach to microbiota regulation and can achieve long-term benefits through optimization of nutritional structure. FMT provides a strategy for rapid microbial reconstruction in patients with severe dysbiosis.

However, current studies still have limitations. First, large-sample microbiota studies specifically targeting patients with diabetic GAN are lacking, and the specific pathogenic strains and key metabolites have not been identified. Second, most therapeutic studies primarily focus on improving metabolic indicators of diabetes, while assessments of gastrointestinal manifestations of diabetic GAN are insufficient. Third, the long-term safety of microbiota-regulating approaches and individualized intervention protocols have not been established. Fourth, FMT carries a risk of infection caused by inadequate donor screening. Fifth, the intestinal colonization efficiency of long-term probiotic use and its effects on immune function also require further evaluation.

Future research should focus on three aspects. First, metagenomics, metabolomics, and other technologies should be used to identify characteristic microbiota and metabolites in patients with diabetic GAN and to screen disease diagnostic biomarkers. Second, high-quality clinical studies should be conducted to verify the effects of probiotics/prebiotics and FMT on improving diabetic GAN symptoms and to explore optimal intervention strategies. Third, the interaction mechanisms among the gut microbiota, ICC, ENS, and CNS should be investigated in depth to provide new therapeutic targets. With continued research, therapeutic strategies based on gut microbiota regulation are expected to bring new hope to patients with diabetic GAN and improve their quality of life.

Conflict of Interest: None

Reference

[1] Abdalla M M I. Enteric neuropathy in diabetes: Implications for gastrointestinal function[J]. World J Gastroenterol, 2024, 30(22): 2852-2865.

[2] Bharucha A E, Kudva Y C, Prichard D O. Diabetic gastroparesis[J]. Endocr Rev, 2019, 40(5): 1318-1352.

[3] Su Jin, Tang Yile, Yang Zisen, et al. Causal association of 473 gut microorganisms with type 2 diabetes mellitus and diabetic microvascular complications[J]. J Trop Med, 2025, 25(4): 459-464, 587.**[In Chinese]**

[4] Yuan Jiushu, Zhang Huixuan, Wang Xueru, et al. Research progress of intestinal flora and diabetic peripheral neuropathy[J]. China Mod Doctor, 2023, 61(18): 127-129, 133. **[In Chinese]**

[5] Salazar N, Valdés-Varela L, González S, et al. Nutrition and the gut microbiome in the elderly[J]. Gut Microbes, 2017, 8(2): 82-97.

[6] Longo S, Rizza S, Federici M. Microbiota-gut-brain axis: relationships among the vagus nerve, gut microbiota, obesity, and diabetes[J]. Acta Diabetol, 2023, 60(8): 1007-1017.

[7] ZHAO Xianqun, ZHANG Xuesong, LIU Xiaozheng, et al. Change of intestinal flora and inflammatory factors in patients with diabetic gastroparesis[J]. Chin J Diabetes, 2017, 25(8): 725-728. **[In Chinese]**

[8] Xue Qin. Study on distribution of intestinal flora and inflammatory factors in Pa-tients with diabetic gastroparesis[J]. Diabetes New World, 2020, 23(11): 23-25.

[9] Wang Jingmei, Yang Yunmei. Analysis of intestinal flora in elderly patients with type 2 diabetes mellitus and gastroparesis[J/OL]. Chin J Crit Care Med Electron Ed, 2020, 13(2): 106-112. **[In Chinese]**

[10] Du Yuhui, Neng Qiongli, Li Yu, et al. Gastrointestinal autonomic neuropathy exacerbates gut microbiota dysbiosis in adult patients with type 2 diabetes mellitus[J]. Front Cell Infect Microbiol, 2021, 11: 804733.

[11] Régnier M, Van Hul M, Knauf C, et al. Gut microbiome, endocrine control of gut barrier function and metabolic diseases[J]. J Endocrinol, 2021, 248(2): R67-R82.

[12] Wang Xu, Ni Jiahui, You Yan, et al. SNX10-mediated LPS sensing causes intestinal barrier dysfunction *via* a caspase-5-dependent signaling cascade[J]. EMBO J, 2021, 40(24): EMBJ2021108080.

[13] Xu Jihao, Liang Rongrong, Zhang Wang, et al. *Faecalibacterium prausnitzii*-derived microbial anti-inflammatory molecule regulates intestinal integrity in diabetes mellitus mice *via* modulating tight junction protein expression[J]. J Diabetes, 2020, 12(3): 224-236.

[14] Suárez Terán J, Guarner Aguilar F. Small Intestinal Bacterial Overgrowth (SIBO), a clinically overdiagnosed entity?[J]. Gastroenterol Y Hepatol Engl Ed, 2024, 47(9): 502190.

[15] Efremova I, Maslennikov R, Poluektova E, et al. Epidemiology of small intestinal bacterial overgrowth[J]. World J Gastroenterol, 2023, 29(22): 3400-3421.

[16] Feng Xin, Li Xiaoqing. The prevalence of small intestinal bacterial overgrowth in diabetes mellitus: a systematic review and meta-analysis[J]. Aging, 2022, 14(2): 975-988.

[17] Malik A, Morya R K, Saha S, et al. Oxidative stress and inflammatory markers in type 2 diabetic patients[J]. Eur J Clin Investig, 2020, 50(6): e13238.

[18] Kaji N, Hori M. Interstitial cells of Cajal in gastrointestinal inflammatory diseases[J]. J Smooth Muscle Res, 2023, 59: 1-13.

[19] Phillips L K, Deane A M, Jones K L, et al. Gastric emptying and glycaemia in health and diabetes mellitus[J]. Nat Rev Endocrinol, 2015, 11(2): 112-128.

[20] Choi K M, Gibbons S J, Sha Lei, et al. Interleukin 10 restores gastric emptying, electrical activity, and interstitial cells of Cajal networks in diabetic mice[J]. Cell Mol Gastroenterol Hepatol, 2016, 2(4): 454-467.

[21] Jin B, Ha S E, Wei Lai, et al. Colonic motility is improved by the activation of 5-HT_{2B} receptors on interstitial cells of Cajal in diabetic mice[J]. Gastroenterology, 2021, 161(2): 608-622.e7.

[22] Yang Mo, Fukui H, Eda H, et al. Involvement of gut microbiota in the association between gastrointestinal motility and 5-HT expression/M2 macrophage abundance in the gastrointestinal tract[J]. Mol Med Rep, 2017, 16(3): 3482-3488.

[23] Aktar R, Parkar N, Stentz R, et al. Human resident gut microbe *Bacteroides thetaiotaomicron* regulates colonic neuronal innervation and neurogenic function[J]. Gut Microbes, 2020, 11(6): 1745-1757.

[24] Kabouridis P S, Lasrado R, McCallum S, et al. The gut microbiota keeps enteric glial cells on the move; prospective roles of the gut epithelium and immune system[J]. Gut Microbes, 2015, 6(6): 398-403.

[25] Liu Penghong, Li Gaizhi, Zhang Aixia, et al. Brain structural and functional alterations in MDD patient with gastrointestinal symptoms: a resting-state MRI study[J]. J Affect Disord, 2020, 273: 95-105.

[26] Okdahl T, Wegeberg A M, Jensen A B H, et al. Systemic cytokine expression in diabetes is associated with prolonged gastrointestinal transit times and cardinal gastroparesis symptoms[J]. Biomedicines, 2023, 11(4): 1027.

[27] Bonomo R R, Cook T M, Gavini C K, et al. Fecal transplantation and butyrate improve neuropathic pain, modify immune cell profile, and gene expression in the PNS of obese mice[J]. Proc Natl Acad Sci U S A, 2020, 117(42): 26482-26493.

[28] Magnusson M K, Isaksson S, Öhman L. The anti-inflammatory immune regulation induced by butyrate is impaired in inflamed intestinal mucosa from patients with ulcerative colitis[J]. Inflammation, 2020, 43(2): 507-517.

[29] Jiang Rongsheng, Zhang Long, Guan Qifan, et al. Advances in the role of short-chain fatty acids in type 2 diabetes[J]. Chin Gen Pract, 2024, 27(24): 3031-3037. **[In Chinese]**

[30] Wang Zhen, Zhang Xiaoxia, Zhu Lili, et al. Inulin alleviates inflammation of alcoholic liver disease *via* SCFAs-inducing suppression of M1 and facilitation of M2 macrophages in mice[J]. Int Immunopharmacol, 2020, 78: 106062. **[In Chinese]**

[31] Wang Yan, Gao Xiangyue, Lin Lin, et al. Role of gastrointestinal muscularis macrophages in regulation of gastrointestinal motility[J]. Chin J Gastroenterol, 2022, 27(7): 429-433. **[In Chinese]**

[32] Park J W, Kim H Y, Kim M G, et al. Short-chain fatty acids inhibit staphylococcal lipoprotein-induced nitric oxide production in murine macrophages[J]. Immune Netw, 2019, 19(2): e9.

[33] Wei Zhaohui, Li Rongke, Zhang Lei, et al. Study on the mechanism of *Hedysarum polybotrys* polysacchcaide improving small intestinal motility in spleen qi deficiency DGP rats through SCFAs-GPCRs[J]. China J Tradit Chin Med Pharm, 2024, 39(7): 3436-3441. **[In Chinese]**

[34] Wang Qiaoling, Lin Huibin, Shen Chongrong, et al. Gut microbiota regulates postprandial GLP-1 response *via* ileal bile acid-TGR5 signaling[J]. Gut Microbes, 2023, 15(2): 2274124.

[35] Hui Suocheng, Huang Li, Wang Xiaolan, et al. Capsaicin improves glucose homeostasis by enhancing glucagon-like peptide-1 secretion through the regulation of bile acid metabolism *via* the remodeling of the gut microbiota in male mice[J]. FASEB J, 2020, 34(6): 8558-8573.

[36] Qi Ran, Yang Wei, Chen Jie. Role of enteric glial cells in gastric motility in diabetic rats at different stages[J]. J Huazhong Univ Sci Technolog Med Sci, 2013, 33(4): 496-500.

[37] Roager H M, Licht T R. Microbial tryptophan catabolites in health and disease[J]. Nat Commun, 2018, 9(1): 3294.

[38] de Mello V D, Paananen J, Lindström J, et al. Indolepropionic acid and novel lipid metabolites are associated with a lower risk of type 2 diabetes in the Finnish Diabetes Prevention Study[J]. Sci Rep, 2017, 7: 46337.

[39] Cheng Yingying, Kou Yueting, Wang Juan, et al. 5-hydroxytryptamine 4 receptor agonist attenuates diabetic enteric neuropathy through inhibition of the receptor-interacting protein kinase 3 pathway[J]. Am J Pathol, 2024, 194(5): 785-795.

[40] Yadav M K, Kumari I, Singh B, et al. Probiotics, prebiotics and synbiotics: Safe options for next-generation therapeutics[J]. Appl Microbiol Biotechnol, 2022, 106(2): 505-521.

[41] Rittiphairoj T, Pongpirul K, Janchot K, et al. Probiotics contribute to glycemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis[J]. Adv Nutr, 2021, 12(3): 722-734.

[42] Wu Xiaoye. Effect of Tetragenous Viable *Bifidobacterium* Tablets combined with Mosapride for adjustment of intestinal flora and brain-gut peptides in patients with diabetic gastric paralyze[J]. Chin J Microecol, 2019, 31(8): 923-926. **[In Chinese]**

[43] Kashtanova D A, Tkacheva O N, Doudinskaya E N, et al. Gut microbiota in patients with different metabolic statuses: Moscow study[J]. Microorganisms, 2018, 6(4): 98.

[44] Ding Qi, Ren Junli, Zhou Yingying, et al. Whole grain germinated brown rice regulates intestinal immune homeostasis and gastrointestinal hormones in type 2 diabetic patients-a randomized control trial[J]. Food Funct, 2022, 13(15): 8274-8282.

[45] Singh R K, Chang H W, Yan Di, et al. Influence of diet on the gut microbiome and implications for human health[J]. J Transl Med, 2017, 15(1): 73.

[46] Zhang Rui, Liu Ting, Li Zhenyu, et al. Research progress of diabetic gastroenteropathy[J]. Chin J Clin Res, 2020, 33(8): 1138-1142. **[In Chinese]**

[47] Zhang Juan, Wang Honggang, Liu Ying, et al. Advances in fecal microbiota transplantation for the treatment of diabetes mellitus[J]. Front Cell Infect Microbiol, 2024, 14: 1370999.

[48] Xie YC, Jing XB, Chen X, et al. Fecal microbiota transplantation treatment for type 1 diabetes mellitus with malnutrition: a case report [J]. Ther Adv Chronic Dis, 2022, 13：20406223221117449.

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·研究进展·

肠道菌群与糖尿病胃肠自主神经病变

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摘要：糖尿病胃肠自主神经病变作为糖尿病的并发症之一，对消化道产生广泛影响。其症状包括胃食管反流、恶心、呕吐、胃轻瘫、腹痛、便秘和腹泻等。目前，糖尿病胃肠自主神经病变的发病机制尚未完全明确，但越来越多的研究表明肠道菌群与糖尿病胃肠自主神经病变之间存在密切关联。本文旨在总结肠道菌群与糖尿病胃肠自主神经病变相关的研究进展及其潜在机制，并探讨与肠道菌群相关的治疗策略，以期为糖尿病胃肠自主神经病变的防治提供新的视角，进而提升患者的生活质量。

关键词：糖尿病；肠道菌群；胃肠自主神经病变；益生菌；粪菌移植
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Gut microbiota and diabetic gastrointestinal autonomic neuropathy

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Abstract: Diabetic gastrointestinal autonomic neuropathy, one of the complications of diabetes, has a widespread impact on the digestive tract. Symptoms include gastroesophageal reflux, nausea, vomiting, gastroparesis, abdominal pain, constipation, and diarrhea, among others. Currently, the pathogenesis of diabetic gastrointestinal autonomic neuropathy is not fully understood, but an increasing number of studies suggest a close connection between the gut microbiota and diabetic gastrointestinal autonomic neuropathy. This article aims to summarize the research progress and potential mechanisms of the relationship between the gut microbiota and diabetic gastrointestinal autonomic neuropathy, and to explore treatment strategies related to the gut microbiota, with the aim of providing new perspectives for the prevention and treatment of diabetic gastrointestinal autonomic neuropathy, thereby improving the quality of life for patients.

Keywords: Diabetes mellitus; Gut microbiota; Gastrointestinal autonomic neuropathy; Probiotics; Fecal microbiota transplantation
Fund program: Major Science and Technology Project of Changzhou Municipal Health Commission (ZD202317); Clinical Project of Changzhou Medical Center, Nanjing Medical University (CMCC202310)

糖尿病胃肠自主神经病变(gastrointestinal autonomic neuropathy，GAN)是糖尿病患者自主神经系统功能障碍在胃肠道的典型表现，可累及食管、胃、小肠及结肠等多个部位，导致胃肠动力异常[1]。临床表现为恶心、餐后饱胀、胃食管反流等症状，部分合并胃轻瘫者还会因胃排空延迟引发血糖波动，进一步加重病情并降低生活质量[2]。现有研究认为高血糖损伤、自身免疫反应、氧化应激和血管功能不全等病理机制可以造成肠道自主神经病变，以及迷走神经传入调节功能受损，从而引起机体广泛的紊乱，包括肠道运动障碍、局部激素或神经递质分泌减少，以及肠道微生物群的改变[1]。近年研究揭示肠道菌群与糖尿病及其并发症存在因果关联[3]。健康状态下，肠道菌群代谢产生的乳酸、丁酸可促进肠道黏蛋白合成，维持肠道微生态平衡；而糖尿病小鼠模型显示，菌群结构紊乱会增加肠道通透性，导致细菌及有害代谢物入血，诱发慢性炎症，加剧糖尿病GAN进展[4]。

因此，调控肠道菌群及其代谢产物是否能够防治糖尿病GAN，成为一个值得探讨的问题。本研究总结了肠道菌群与糖尿病GAN关系的进展，探讨通过改善肠道菌群以预防及实

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现糖尿病GAN的个体化治疗的策略。

1　肠道菌群与糖尿病GAN的关系

肠道菌群是定植于人体肠道内的微生物群落总称，包含细菌、少量古细菌及单细胞真核生物，参与宿主代谢调节、免疫激活、基因表达调控及胃肠道运动功能维持等关键生理过程[5-6]。动物实验证实，无菌大鼠因缺乏肠道菌群定植，会出现明显肠道动力紊乱；而定植梭状芽孢杆菌、嗜酸乳杆菌、双歧杆菌后，其小肠迁移运动复合体传播效率及转运速度显著提升，相反，大肠杆菌则会抑制肠道动力[4]，提示肠道菌群种类及丰度直接影响胃肠运动功能。

糖尿病GAN的发病率尚未明确，从临床表现看，糖尿病GAN具有多样性：胃动力异常者可出现胃瘫、胃食管反流，肠道受累者则以便秘或腹泻为主，部分患者因长期胃肠功能紊乱合并营养不良[1]。近年临床研究进一步证实，糖尿病GAN患者存在显著肠道菌群失衡。与单纯糖尿病患者相比，糖尿病胃轻瘫患者粪便中肠杆菌丰度升高，而拟杆菌、双歧杆菌、乳酸杆菌等有益菌数量显著减少[7-9]；2型糖尿病胃轻瘫患者的肠道菌群结构分析显示，变形菌门丰度异常增加，且该菌群变化与疾病严重程度呈正相关，可能通过诱发肠道炎症加速病程进展[10]。综上，糖尿病GAN患者的肠道菌群失衡特征为有害菌增多、有益菌减少，但具体哪些菌株直接参与疾病发生发展，仍需更多高质量临床研究验证。

2　肠道菌群与糖尿病GAN发生可能的机制

2.1　*肠道屏障破坏*　肠道屏障是维持肠道微生态平衡的关键结构，由肠上皮细胞、紧密连接蛋白及黏膜保护层组成，可阻止肠道内细菌及毒素入血[11]。肠道菌群通过其结构成分及代谢产物双向调控肠道屏障功能：一方面，革兰阴性菌释放的脂多糖可破坏肠上皮细胞间黏附结构，降低紧密连接完整性，增加肠道通透性[12]；另一方面，有益菌代谢产物如丁酸盐可诱导肠上皮细胞表达突触足蛋白，促进受损上皮修复，而普拉梭菌分泌的抗炎分子还能通过上调紧密连接蛋白ZO-1表达，恢复糖尿病小鼠肠道屏障功能[1,13]。

当肠道菌群失衡时，肠屏障完整性受损会导致肠道通透性升高，使细菌抗原及有害代谢物进入血液循环，诱发全身慢性炎症反应；同时，肠道局部炎症还会直接影响胃肠平滑肌收缩功能，加剧动力紊乱[4]。临床研究也证实，糖尿病GAN患者血清炎症因子水平显著高于单纯糖尿病患者，且与肠道屏障标志物水平呈正相关[7]，进一步支持肠道屏障破坏在疾病中的作用。

2.2　*小肠细菌过度生长*（small intestinal bacterial overgrowth，SIBO）　SIBO指小肠内细菌数量超过正常阈值（空肠液细菌计数>10^5个/mL），其发生与肠道蠕动减缓、解剖结构异常及胃肠动力调控障碍密切相关，而糖尿病自主神经病变是SIBO的重要危险因素之一[14-15]。

糖尿病GAN患者因胃肠动力减弱（如口盲肠传输时间延长），小肠内细菌清除效率下降，易导致细菌过度繁殖并产生甲烷、氢气等气体，引发腹胀、脐周疼痛等症状，部分患者还会因细菌竞争营养物质出现吸收不良、渗透性腹泻[16]。临床数据显示，60%以腹痛腹胀为主的胃轻瘫患者合并SIBO，且SIBO阳性患者的胃轻瘫病程显著长于阴性患者[15]。此外，荟萃分析表明糖尿病患者SIBO检出率显著高于非糖尿病人群，且合并SIBO的2型糖尿病患者血清氧化应激标志物、炎症因子水平更高，抗氧化剂谷胱甘肽水平更低，同时伴随空腹胰岛素水平下降、糖耐量异常及糖化血红蛋白升高[16-17]。

目前SIBO在糖尿病GAN患者中的发生率及根除SIBO对患者症状的改善效果尚未明确，需开展前瞻性研究进行验证。

2.3　*胃肠道Cajal间质细胞*（interstitial cells of Cajal，ICC）*的减少*　ICC是分布于胃肠道壁各层的特殊细胞，可以通过产生节律性电活动，调控胃肠平滑肌的肌源性收缩，同时在肠神经系统、中枢神经系统与平滑肌细胞间发挥神经信号传递作用[18]。

糖尿病GAN患者的ICC功能及数量存在显著异常：胃轻瘫患者胃组织活检显示，ICC特异性标志物Kit的表达水平显著降低[19]。动物实验证实，糖尿病小鼠胃底ICC数量减少会导致胃底舒张功能受损，胃窦ICC减少则与慢波频率降低、胃排空延迟直接相关[20]。临床研究进一步发现，糖尿病及糖尿病GAN患者的胃、小肠、结肠组织中均存在ICC数量减少，且减少程度与胃肠动力障碍严重程度呈正相关[1]。

ICC细胞膜上表达多种5-羟色胺（5-hydroxytryptamine，5-HT）受体，其中5-HT_{2B}受体激活后可通过磷脂酶C-细胞内钙释放-蛋白激酶Cγ通路促进ICC增殖，增强该信号通路还能改善糖尿病小鼠结肠动力[21]。而无菌小鼠实验显示，接受健康小鼠粪菌移植后，其胃肠转运速度显著加快，肠道5-HT阳性细胞表达增加，且转运时间与5-HT阳性细胞数量呈负相关[22]。此外，多形拟杆菌可通过增加肠道L细胞数量及5-HT合成，调节结肠特异性收缩，改善肠道动力[23]。上述研究提示肠道菌群可能通过调控5-HT/ICC通路影响糖尿病GAN患者的胃肠运动，但具体作用通路仍需体内研究验证。

2.4　*对肠神经系统*（enteric nervous system，ENS）*与中枢神经系统*（central nervous system，CNS）*的影响*　ENS是由独立的神经元和胶质细胞构成的网络，通过感觉神经元传递胃肠道疼痛、牵拉、饱胀等内脏感觉信号，同时通过交感/副交感传出通路调节胃肠动力、分泌及黏膜血流[6]。

慢性高血糖通过氧化应激、炎症和细胞信号传导受损等途径损害了神经胶质细胞对肠道神经元的支持，从而导致神经递质处理受损、细胞通讯中断以及神经元对损伤和细胞凋亡的脆弱性增加[1]。而肠道菌群对ENS发育及功能维持至关重要，黏膜肠胶质细胞网络的成熟与菌群定植同步，无菌小鼠定植正常菌群后，受损的肠胶质细胞数量可恢复至正常水平[24]；此外，菌群代谢产物[短链脂肪酸（short-chain fatty acids，SCFA）]还能通过调节神经胶质细胞功能，影响ENS的神经信号传递[6]，提示肠道菌群失衡可能通过破坏ENS加剧糖尿病GAN进展。

同时，菌群—肠—脑轴理论指出，肠道菌群可通过血液循环、迷走神经等途径与CNS建立双向通信[6]。临床研究显示，

胃肠道与大脑之间存在双向通信机制，而CNS亦能影响胃肠道的运动性[25]。情绪运动系统能够感知肠道刺激，并调节几种肠道功能。临床研究显示，伴有胃肠道症状的重度抑郁患者存在脑区（如左侧颞上回）活动异常，提示CNS结构与功能改变可能通过菌群—肠—脑轴影响胃肠道运动性[25]。然而，肠道菌群如何通过菌群—肠—脑轴影响糖尿病GAN患者的ENS与CNS，目前仍缺乏直接证据，需进一步探索。

2.5　氧化应激与炎症反应　氧化应激与慢性低度炎症是糖尿病及其并发症的核心病理基础[4]。长期高血糖状态下，机体活性氧生成增加，而抗氧化系统（如谷胱甘肽、超氧化物歧化酶）功能减弱，导致氧化-抗氧化失衡，进而损伤胃肠道神经及ICC[1]。糖尿病患者会出现全身性低度炎症，目前体外研究表明，肿瘤坏死因子（tumor necrosis factor，TNF）-α可减少ICC数量，并对结肠平滑肌层的收缩力有抑制作用[26]。而在糖尿病胃轻瘫大鼠模型中发现，丝裂原激活蛋白激酶（mitogen-activated protein kinase，MAPK）抑制剂可以显著降低胃壁的TNF-α水平，提高胃排空率[26]。

肠道菌群在调节氧化应激与炎症反应中发挥关键作用。有益菌代谢产物SCFA可通过下调促炎因子TNF-α和白细胞介素-6的表达减轻炎症[27-28]；而有害菌（如肠杆菌）增多则会通过释放脂多糖加剧炎症反应[4]。目前，肠道菌群及其代谢产物在糖尿病GAN患者氧化应激与炎症调控中的具体作用，仍需更多临床研究验证。

2.6　代谢产物的影响　肠道菌群的代谢产物作为信号分子可以被吸收并通过血液循环到达宿主的几乎每个器官和细胞，影响宿主的生理过程。肠道微生物的代谢产物，如SCFA、次级胆汁酸、支链脂肪酸及色氨酸代谢物等，它们也可能参与调节肠道的功能并且影响糖代谢。

2.6.1　SCFA　SCFA涵盖乙酸、丙酸、丁酸和戊酸等。作为细菌发酵不可消化膳食纤维的最终代谢产物，它们能够调节宿主的一系列生理过程[6]，包括能量代谢、免疫状态、炎症水平。

SCFA能够通过G蛋白偶联受体（G-protein-coupled receptor，GPCR）通路调节脂质代谢和改善骨骼肌的胰岛素敏感性，也能够促进肠道L细胞分泌胰高血糖素样肽（glucagon-like peptide，GLP）-1，调节肠道内分泌[29]。在体外实验中，丙酸、丁酸和戊酸显示出能够抑制M1型巨噬细胞的活性，并促进M2型巨噬细胞的极化[30]。而在胃肠道的肌层巨噬细胞能够直接或间接地调节胃肠的运动[31]。丁酸盐在维护肠屏障完整性中发挥重要作用[4]，而肠屏障的完整性有利于改善宿主的炎症水平[6]。此外，丁酸和丙酸可以通过抑制核因子κB、干扰素-B/信号转导及转录活化因子（signal transducer and activator of transcription，STAT）1和组蛋白去乙酰化酶的活性，减少巨细胞中一氧化氮的产生，减轻炎症反应[32]。在糖尿病胃轻瘫的大鼠模型中，SCFA的含量减少，GPCR的表达也有所下降。然而，经过药物干预后，SCFA的含量得到提升，胃肠激素GLP-1、酪酪肽、5-HT的水平得到调节，GPCR的表达上调，进而增加了大鼠肠道的动力[33]。

SCFA作为菌群代谢产物，在动物实验和体外研究中展现了SCFA、糖尿病代谢和胃肠运动的相关性，未来需探索外源性补充SCFA对疾病症状的改善效果及最佳剂量。

2.6.2　胆汁酸　胆汁酸代谢与胃肠道菌群之间存在显著的相互作用。研究表明，肠道菌群能够调节肝脏中胆汁酸的合成[6]。次级胆汁酸与糖尿病GAN的关联主要通过激活武田G蛋白受体5（Takeda G protein-coupled receptor 5，TGR5）实现：TGR5在肠道L细胞、神经细胞及免疫细胞中广泛表达，激活后可增强线粒体氧化磷酸化，提高ATP/ADP比率，促进GLP-1分泌，改善血糖稳态[34]、降低胃排空[7]；小鼠粪菌移植实验证实，健康小鼠肠道菌群可通过激活TGR5信号通路改善糖尿病症状[35]。此外，年龄相关的菌群变化会导致结合型胆汁酸向非结合型胆汁酸转化增加，进而减少TGR5表达及M2型巨噬细胞数量，最终延迟肠道转运[36]，提示胆汁酸代谢异常可能通过TGR5通路加剧糖尿病GAN患者的胃肠动力障碍。

胆汁酸在调节能量代谢和炎症反应中扮演着重要角色，并参与糖尿病的发病机制。同时，胆汁酸在调节胃肠道屏障功能和免疫状态方面的作用也极为关键。因此，肠道菌群与胆汁酸之间的相互作用可能在糖尿病GAN的发病机制中发挥着重要作用。

2.6.3　色氨酸代谢产物　色氨酸是人体无法自行合成的必需氨基酸之一，色氨酸可被肠道细菌分解代谢，产生多种菌群代谢产物如3-吲哚丙酸（3-indolepropionic acid，3-IPA）和色胺等，这些代谢产物对肠屏障功能和胃肠道运动具有重要影响[37]。

3-IPA是色氨酸经细菌脱氨作用产生的代谢产物，具有抗氧化、抗炎及调节糖代谢的功能[37]。临床研究显示，2型糖尿病患者血清3-IPA水平显著低于健康人群，且随访期间患者3-IPA水平进一步下降，而健康人群呈上升趋势，提示3-IPA可能与糖尿病发生风险呈负相关[38]；此外，3-IPA可通过促进肠上皮细胞紧密连接蛋白表达增强肠屏障，同时调节肠道L细胞分泌GLP-1，间接影响胃肠动力[37]。

色胺对胃肠动力的调控作用主要体现在两方面：一是作为信号分子直接调节肠道传输时间，体外实验显示色胺可引起小鼠结肠短路电流变化，影响肠上皮细胞离子分泌，而离子平衡是胃肠蠕动的重要基础[37]；二是通过促进肠嗜铬细胞释放5-HT，激活肠神经系统神经元，间接促进胃肠运动[37]。动物实验发现5-HT受体激动剂可通过抑制受体相互作用蛋白激酶3（receptor-interacting protein kinase 3，RIPK3）介导的肠神经细胞坏死性凋亡、减轻糖尿病所致结肠神经细胞缺失及肠道动力减退[39]，提示色胺可能通过5-HT通路参与糖尿病GAN的胃肠动力调节。目前，3-IPA、色胺等色氨酸代谢产物在糖尿病GAN中的具体作用及机制仍缺乏直接证据，需更多临床研究验证。

3　治　疗

3.1　益生菌和益生元　益生菌是对宿主健康有益的活性微生物，常见菌株包括双歧杆菌、乳酸杆菌等；益生元则是肠道益生菌的“食物”（如菊粉、低聚果糖、多糖类），可促进益生菌

增殖并激活肠道免疫[40]。

近期研究发现益生菌和益生元对糖尿病患者具有积极影响。一项纳入2型糖尿病患者的随机双盲研究显示，连续6个月补充多菌种益生菌可使患者胰岛素抵抗指数降低15%~20%，同时空腹血糖及糖化血红蛋白水平显著下降[41]；其机制可能与益生菌调节肠道菌群结构、增加SCFA产生、改善肠屏障完整性相关。我国一项多中心研究证实，糖尿病胃轻瘫患者联合使用双歧杆菌四联活菌片与胃动力药莫沙必利治疗4周后，其胃排空率显著高于单用莫沙必利患者，同时患者餐后饱胀、恶心等症状评分降低50%以上[42]。

综上所述，益生菌与益生元能够优化肠道菌群的结构与功能，提升有益菌群的数量，抑制有害菌群的增殖，从而恢复肠道菌群的平衡状态。这有助于改善糖尿病患者的胰岛素敏感性并降低炎症反应。对于糖尿病GAN患者，这些成分也可能通过类似机制发挥积极作用。

3.2 饮食调整 饮食习惯显著影响菌群构成。高脂饮食会增加机会性病原体丰度、降低菌群多样性，高饱和脂肪酸还可能损害肠道黏液层[43]；增加膳食纤维及发酵食品摄入可促进有益菌生长，提升SCFA水平——如发芽糙米替代精制白米饭可增加2型糖尿病患者粪便乳酸菌数量，降低炎症因子，改善肠黏膜通透性[44]；乳清、豌豆蛋白可增加双歧杆菌丰度，高蛋白饮食还能减少2型糖尿病患者肝脏脂肪及胰岛素抵抗[45]。

通过实施饮食结构的干预策略，可调整肠道菌群的组成和功能，进而对糖尿病GAN产生积极的作用。在临床实践中，对于糖尿病胃轻瘫患者，为了促进胃排空并增强饱腹感，通常建议采用小颗粒、分餐制、流质饮食方案[46]。然而，糖尿病胃肠病变的表现形式多样，因此，针对患者制定个体化的饮食方案十分重要。如何调整饮食结构、是否采用分餐制，以及选择固体食物还是流质食物等问题，仍需依赖更多的临床研究数据以提供科学依据。

3.3 粪菌移植 粪菌移植是将健康供体粪便中的功能菌移植到患者肠道，重建肠道微生态平衡的治疗手段[4]。近年研究显示，粪菌移植对糖尿病及胃肠动力障碍相关疾病具有潜在疗效。粪菌移植单独或联合二甲双胍治疗2型糖尿病患者，可通过增加肠道菌群多样性，降低胰岛素抵抗指数，改善血糖控制[47]。临床报道指出，一例营养不良并伴有胃肠道症状的1型糖尿病患者，在接受粪菌移植后，恶心、呕吐的症状明显减轻，便秘、营养状况、血糖控制也逐渐得到改善，患者和健康供者的肠道菌群组成显示出一定程度的相似性[48]。

因此，通过粪菌移植能重建肠道微生态平衡，有希望成为延缓糖尿病GAN进展的治疗方法，有必要进行更大规模、更细致、多中心的研究来准确评估粪菌移植的益处。

4 讨 论

本文系统综述了肠道菌群与糖尿病GAN的关联及作用机制，提出基于肠道菌群调控的治疗策略。肠道菌群失衡通过多途径参与糖尿病GAN进展。菌群结构紊乱可破坏肠道屏障完整性，增加肠道通透性；代谢产物异常会影响胃肠激素分泌、ENS功能及ICC活性；同时，菌群失衡引发的氧化应激与炎症反应会进一步加剧神经损伤与胃肠动力障碍。此外，菌群—肠—脑轴作为肠道菌群与中枢神经系统的通信桥梁，可能通过调节脑区功能间接影响胃肠道症状，但具体机制仍需深入探索。

在治疗方面，益生菌、益生元、饮食结构的调整以及粪菌移植，这些方法能够通过改善肠道菌群的结构和功能，对糖尿病及其相关并发症产生积极的治疗效果。益生菌/益生元可通过增加有益菌丰度、减少炎症发挥作用；饮食干预是调控菌群的基础手段，可通过优化营养结构实现长期获益；粪菌移植则为严重菌群失衡患者提供了快速重建微生态的方案。

然而，现有研究仍存在局限性：(1) 缺乏针对糖尿病GAN患者的大样本菌群研究，具体致病菌株及关键代谢产物尚未明确；(2) 多数治疗研究以改善糖尿病代谢指标为主，针对糖尿病GAN胃肠道的评估较为缺乏；(3) 菌群调控手段的长期安全性及个体化干预方案尚未建立；(4) 粪菌移植存在供体筛选不严导致的感染风险；(5) 益生菌长期使用的肠道定植效率及对免疫功能的影响也需进一步评估。

未来研究方向应聚焦三方面：(1) 通过宏基因组学、代谢组学等技术，明确糖尿病GAN患者的特征性菌群及代谢产物，筛选疾病诊断标志物；(2) 开展高质量临床研究，验证益生菌/益生元、粪菌移植对糖尿病GAN症状的改善效果，探索最佳干预方案；(3) 深入研究肠道菌群与ICC、ENS、CNS的互作机制，为疾病治疗提供新靶点。相信随着研究的深入，基于肠道菌群调控的治疗策略将为糖尿病GAN患者带来新的希望，改善患者生活质量。

利益冲突 无

参考文献

[1] Abdalla MMI. Enteric neuropathy in diabetes: implications for gastrointestinal function[J]. World J Gastroenterol, 2024, 30(22): 2852-2865.
[2] Bharucha AE, Kudva YC, Prichard DO. Diabetic gastroparesis[J]. Endocr Rev, 2019, 40(5): 1318-1352.
[3] 苏津, 唐溢乐, 杨紫森, 等. 473种肠道微生物与2型糖尿病及糖尿病微血管并发症的因果关系[J]. 热带医学杂志, 2025, 25(4): 459-464.
[4] 袁久木, 张慧漩, 王雪茹, 等. 肠道菌群与糖尿病周围神经病变的研究进展[J]. 中国现代医生, 2023, 61(18): 127-129, 133.
[5] Salazar N, Valdés-Varela L, González S, et al. Nutrition and the gut microbiome in the elderly[J]. Gut Microbes, 2017, 8(2): 82-97.
[6] Longo S, Rizza S, Federici M. Microbiota-gut-brain axis: relationships among the vagus nerve, gut microbiota, obesity, and diabetes[J]. Acta Diabetol, 2023, 60(8): 1007-1017.
[7] 赵先群, 张雪松, 刘晓政, 等. 糖尿病胃轻瘫患者肠道菌群分布及炎症因子水平变化的观察[J]. 中国糖尿病杂志, 2017, 25(8): 725-728.
[8] 薛芹. 糖尿病胃轻瘫患者肠道菌群分布及炎症因子研究[J]. 糖尿病新世界, 2020, 23(11): 23-25.
[9] 汪晶美, 杨云梅. 老年2型糖尿病合并胃轻瘫患者的肠道菌群分析[J/OL]. 中华危重症医学杂志(电子版), 2020, 13(2): 106-112.
[10] Du YH, Neng QL, Li Y, et al. Gastrointestinal autonomic neuropathy exacerbates gut microbiota dysbiosis in adult patients with type 2 diabetes mellitus[J]. Front Cell Infect Microbiol, 2022, 11:

804733.
[11] Régnier M, Van Hul M, Knauf C, et al. Gut microbiome, endocrine control of gut barrier function and metabolic diseases[J]. J Endocrinol, 2021, 248(2): R67-R82.
[12] Wang X, Ni JH, You Y, et al. SNX10-mediated LPS sensing causes intestinal barrier dysfunction *via* a caspase-5-dependent signaling cascade[J]. EMBO J, 2021, 40(24): e108080.
[13] Xu JH, Liang RR, Zhang W, et al. *Faecalibacterium prausnitzii*-derived microbial anti-inflammatory molecule regulates intestinal integrity in diabetes mellitus mice *via* modulating tight junction protein expression[J]. J Diabetes, 2020, 12(3): 224-236.
[14] Suárez Terán J, Guarner Aguilar F. Small intestinal bacterial overgrowth (SIBO), a clinically overdiagnosed entity?[J]. Gastroenterol Hepatol, 2024, 47(9): 502190.
[15] Efremova I, Maslennikov R, Poluektova E, et al. Epidemiology of small intestinal bacterial overgrowth[J]. World J Gastroenterol, 2023, 29(22): 3400-3421.
[16] Feng X, Li XQ. The prevalence of small intestinal bacterial overgrowth in diabetes mellitus: a systematic review and meta-analysis[J]. Aging, 2022, 14(2): 975-988.
[17] Malik A, Morya RK, Saha S, et al. Oxidative stress and inflammatory markers in type 2 diabetic patients[J]. Eur J Clin Investigation, 2020, 50(6): e13238.
[18] Kaji N, Hori M. Interstitial cells of Cajal in gastrointestinal inflammatory diseases[J]. J Smooth Muscle Res, 2023, 59: 1-13.
[19] Phillips LK, Deane AM, Jones KL, et al. Gastric emptying and glycaemia in health and diabetes mellitus[J]. Nat Rev Endocrinol, 2015, 11(2): 112-128.
[20] Choi KM, Gibbons SJ, Sha L, et al. Interleukin 10 restores gastric emptying, electrical activity, and interstitial cells of Cajal networks in diabetic mice[J]. Cell Mol Gastroenterol Hepatol, 2016, 2(4): 454-467.
[21] Jin B, Ha SE, Wei L, et al. Colonic motility is improved by the activation of 5-HT_{2B} receptors on interstitial cells of Cajal in diabetic mice[J]. Gastroenterology, 2021, 161(2): 608-622.
[22] Yang M, Fukui H, Eda H, et al. Involvement of gut microbiota in the association between gastrointestinal motility and 5-HT expression/M2 macrophage abundance in the gastrointestinal tract[J]. Mol Med Rep, 2017, 16(3): 3482-3488.
[23] Aktar R, Parkar N, Stentz R, et al. Human resident gut microbe *Bacteroides thetaiotaomicron* regulates colonic neuronal innervation and neurogenic function[J]. Gut Microbes, 2020, 11(6): 1745-1757.
[24] Kabouridis PS, Lasrado R, McCallum S, et al. The gut microbiota keeps enteric glial cells on the move; prospective roles of the gut epithelium and immune system[J]. Gut Microbes, 2015, 6(6): 398-403.
[25] Liu PH, Li GZ, Zhang AX, et al. Brain structural and functional alterations in MDD patient with gastrointestinal symptoms: a resting-state MRI study[J]. J Affect Disord, 2020, 273: 95-105.
[26] Okdahl T, Wegeberg AM, Jensen ABH, et al. Systemic cytokine expression in diabetes is associated with prolonged gastrointestinal transit times and cardinal gastroparesis symptoms[J]. Biomedicines, 2023, 11(4): 1027.
[27] Bonomo RR, Cook TM, Gavini CK, et al. Fecal transplantation and butyrate improve neuropathic pain, modify immune cell profile, and gene expression in the PNS of obese mice[J]. Proc Natl Acad Sci USA, 2020, 117(42): 26482-26493.
[28] Magnusson MK, Isaksson S, Öhman L. The anti-inflammatory immune regulation induced by butyrate is impaired in inflamed intestinal mucosa from patients with ulcerative colitis[J]. Inflammation, 2020, 43(2): 507-517.
[29] 姜荣生, 张龙, 管其凡, 等. 短链脂肪酸在2型糖尿病中的作用研究进展[J]. 中国全科医学, 2024, 27(24): 3031-3037.
[30] Wang Z, Zhang XX, Zhu LL, et al. Inulin alleviates inflammation of alcoholic liver disease *via* SCFAs-inducing suppression of M1 and facilitation of M2 macrophages in mice[J]. Int Immunopharmacol, 2020, 78: 106062.
[31] 王艳, 高祥悦, 林琳, 等. 胃肠道肌层巨噬细胞在胃肠运动调节中的作用[J]. 胃肠病学, 2022, 27(7): 429-433.
[32] Park JW, Kim HY, Kim MG, et al. Short-chain fatty acids inhibit staphylococcal lipoprotein-induced nitric oxide production in murine macrophages[J]. Immune Netw, 2019, 19(2): e9.
[33] 魏昭晖, 李荣科, 张磊, 等. 红芪多糖经SCFAs-GPCRs改善脾气虚型DGP大鼠小肠动力的机制研究[J]. 中华中医药杂志, 2024, 39(7): 3436-3441.
[34] Wang QL, Lin HB, Shen CR, et al. Gut microbiota regulates postprandial GLP-1 response *via* ileal bile acid-TGR5 signaling[J]. Gut Microbes, 2023, 15(2): 2274124.
[35] Hui SC, Huang L, Wang XL, et al. Capsaicin improves glucose homeostasis by enhancing glucagon-like peptide-1 secretion through the regulation of bile acid metabolism *via* the remodeling of the gut microbiota in male mice[J]. FASEB J, 2020, 34(6): 8558-8573.
[36] Qi R, Yang W, Chen J. Role of enteric glial cells in gastric motility in diabetic rats at different stages[J]. J Huazhong Univ Sci Technolog Med Sci, 2013, 33(4): 496-500.
[37] Roager HM, Licht TR. Microbial tryptophan catabolites in health and disease[J]. Nat Commun, 2018, 9: 3294.
[38] de Mello VD, Paananen J, Lindström J, et al. Indolepropionic acid and novel lipid metabolites are associated with a lower risk of type 2 diabetes in the Finnish Diabetes Prevention Study[J]. Sci Rep, 2017, 7: 46337.
[39] Cheng Y, Kou Y, Wang J, et al.5-hydroxytryptamine 4 receptor agonist attenuates diabetic enteric neuropathy through inhibition of the RIPK3 pathway[J]. Am J Pathol, 2024, 194(5): 785-795.
[40] Yadav MK, Kumari I, Singh B, et al. Probiotics, prebiotics and synbiotics: safe options for next-generation therapeutics[J]. Appl Microbiol Biotechnol, 2022, 106(2): 505-521.
[41] Rittiphairoj T, Pongpirul K, Janchot K, et al. Probiotics contribute to glycemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis[J]. Adv Nutr, 2021, 12(3): 722-734.
[42] 吴晓晔. 双歧杆菌四联活菌片联合莫沙必利对糖尿病胃轻瘫患者肠道菌群及脑肠肽的调节[J]. 中国微生态学杂志, 2019, 31(8): 923-926.
[43] Kashtanova DA, Tkacheva ON, Doudinskaya EN, et al. Gut microbiota in patients with different metabolic statuses: Moscow study[J]. Microorganisms, 2018, 6(4): 98.
[44] Ding Q, Ren JL, Zhou YY, et al. Whole grain germinated brown rice regulates intestinal immune homeostasis and gastrointestinal hormones in type 2 diabetic patients — a randomized control trial[J]. Food Funct, 2022, 13(15): 8274-8282.
[45] Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health[J]. J Transl Med, 2017, 15(1): 73.
[46] 张蕊, 刘婷, 李振玉, 等. 糖尿病性胃肠病研究进展[J]. 中国临床研究, 2020, 33(8): 1138-1142.
[47] Zhang J, Wang HG, Liu Y, et al. Advances in fecal microbiota transplantation for the treatment of diabetes mellitus[J]. Front Cell Infect Microbiol, 2024, 14: 1370999.
[48] Xie YC, Jing XB, Chen X, et al. Fecal microbiota transplantation treatment for type 1 diabetes mellitus with malnutrition: a case report[J]. Ther Adv Chronic Dis, 2022, 13: 20406223221117449.

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