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EDITORIAL

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- 1863 Advances in clinical applications of bioceramics in the new regenerative medicine era
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- 1885 Unexpected focal fluorodeoxyglucose uptake in main organs; pass through or pass by?
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- 1909 Splenic hamartomas in children
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ORIGINAL ARTICLE**Retrospective Study**

- 1918 Chaiqin Chengqi Decoction as an adjuvant treatment for mild/moderately severe hypertriglyceridemic acute pancreatitis: A retrospective study
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- 1929 COVID-19 pandemic amplified mortality rates among adolescents with bipolar disorder through family-related factors
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- 1940** Endovascular treatment of direct carotid cavernous fistula resulting from rupture of intracavernous carotid aneurysm: A case report
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- 1947** Concomitant treatment of ureteral calculi and ipsilateral pelvic sciatic nerve schwannoma with transperitoneal laparoscopic approach: A case report
Xiong Y, Li J, Yang HJ
- 1954** Safety and efficacy of transcatheter arterial embolization in autosomal dominant polycystic kidney patients with gross hematuria: Six case reports
Sui WF, Duan YX, Li JY, Shao WB, Fu JH
- 1960** Neurosyphilis complicated by anti- γ -aminobutyric acid-B receptor encephalitis: A case report
Fang YX, Zhou XM, Zheng D, Liu GH, Gao PB, Huang XZ, Chen ZC, Zhang H, Chen L, Hu YF
- 1967** Long-term complete response to anti-programmed-death-1 monotherapy in a patient with relapsed and refractory ovarian adenocarcinoma: A case report
Zhou GD, Li Q
- 1974** Nd:YAG water mist laser treatment for giant gestational gingival tumor: A case report
Chen HY, Xu JJ, Chang XL, Wu P
- 1980** Hematochezia due to rectal invasion by an internal iliac artery aneurysm: A case report
Li F, Zhao B, Liu YQ, Chen GQ, Qu RF, Xu C, Long Z, Wu JS, Xiong M, Liu WH, Zhu L, Feng XL, Zhang L
- 1990** Colonoscopy-assisted removal of an impaction foreign body at the rectosigmoid junction: A case report
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LETTER TO THE EDITOR

- 1996** Intestinal flora: New perspective of type 2 diabetes
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ABOUT COVER

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Intestinal flora: New perspective of type 2 diabetes

Yan Liu, Jun Chang, Li-Ding Bai

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Abstract

Diabetes comprises a group of metabolic diseases characterized by hyperglycemia stemming from various factors. Current diabetes management primarily focuses on blood glucose control, yet it is inherently progressive, necessitating increased reliance on exogenous blood glucose control methods over time. Therefore, there is an urgent need to explore novel intervention strategies addressing both diabetes and its complications. The human intestinal microbiota, often referred to as the "second genome", exhibits significant diversity and plays a pivotal role in insulin resistance, glucose and lipid metabolism, and inflammatory response. Notably, Li and Guo have elucidated the involvement of intestinal flora in the pathogenesis of type 2 diabetes mellitus (T2DM) and proposed a novel therapeutic approach targeting intestinal microbes. This advancement enhances our comprehension of the multifaceted and multi-target regulation of T2DM by intestinal microflora, thereby offering fresh avenues for understanding its pathogenesis and clinical management. This letter briefly summarizes the role of intestinal flora in T2DM based on findings from animal experiments and clinical studies. Additionally, it discusses the potential clinical applications and challenges associated with targeting intestinal flora as therapeutic interventions.

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

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Core Tip: With the global prevalence of diabetes continuing to rise, China faces a particularly high burden, with diabetes and its complications affecting up to 10% of the population. Type 2 diabetes mellitus (T2DM) constitutes over 90% of these cases. While insulin remains the primary treatment for T2DM, its efficacy is limited in addressing the chronic, progressive, low-grade inflammatory, and the simple reduction of exogenous blood glucose can no longer meet the control of diabetes and its complications, nature of the disease. Consequently, there is an urgent need to identify safe and effective new therapeutic avenues. This letter corroborates the significance of intestinal flora in T2DM, as asserted by Li and Guo. It briefly outlines the role of intestinal flora in T2DM through insights from both animal experiments and clinical studies. Additionally, it discusses the potential clinical applications and challenges associated with targeting intestinal flora as therapeutic targets.

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TO THE EDITOR

We have carefully read the review article "Gut microbiome: New perspectives for type 2 diabetes prevention and treatment" by Li and Guo[1]. We acknowledge the authors' assertion regarding the involvement of gut microbiota in the etiology and progression of type 2 diabetes mellitus (T2DM), emphasizing the potential of gut microbiota modulation as a novel therapeutic avenue for T2DM. We are grateful to the authors for their dedicated exploration of intestinal flora in T2DM, which offers new insights into the mechanisms influencing blood glucose regulation and presents innovative treatment approaches for T2DM and its associated complications.

The intestinal flora, constituting the largest microecosystem within the human body, exerts a significant impact on metabolic processes and energy homeostasis. Recent studies suggest that in addition to obesity, genetics, and islet dysfunction, intestinal flora disturbance could be an important contributor to T2DM[2]. However, long-term consumption of a high-sugar, high-fat, and high-protein diet may be attributed to changes in bacterial membrane permeability, the SOS response, and bacterial composition and diversity caused by diet-induced inflammation[3]. We concur with Li and Guo[1] on the pathogenesis of intestinal flora in T2DM, including bile acid theory, the theory of short-chain fatty acids, and the endotoxin theory. Notably, the relationship between intestinal flora and bile acid metabolism is bidirectional. Guo *et al*[4] speculated that intestinal flora regulates the metabolism, synthesis, and reabsorption of bile acids, wherein bile acids regulate the growth and diversity of intestinal flora. This important bidirectional imbalance may serve as a pivotal factor leading to various diseases, including T2DM. Moreover, short-chain fatty acids (SCFAs), a derivative of the gut microbiota, play an important role in T2DM. In addition to their roles elucidated by Li and Guo[1], SCFAs contribute to regulating liver glycogen metabolism and improving skeletal muscle insulin resistance. Moreover, hepatic insulin resistance is an early symptom of T2DM. Similarly, Zhao *et al*[5] reported that the G protein-coupled receptor 43 (GPR43)- β -arrestin2-AMPK-PGC1- α signaling pathway plays an important role in the regulation of liver glycogen metabolism by butyric acid. Importantly, skeletal muscle insulin resistance is an indicator of T2DM severity. Yang *et al*[6] observed that exercise affected the distribution of intestinal microbiota in T2DM model rats, mainly because acetic acid improved insulin resistance by increasing the autophagy of skeletal muscle, which is involved in the SCFAs/GPR43 signaling axis. Additionally, metabolic endotoxemia with altered microbiota induces systemic inflammatory responses by stimulating the immune system through bacterial translocation. Lipopolysaccharide, an endotoxin, is also an important factor in inducing T2DM and its complications. Moreover, diabetes is a risk factor for Alzheimer's disease (AD). Liu *et al*[7] reported that the CCAAT/enhancer-binding protein/asparagine endopeptidase signaling pathway of neurons activated by inflammation is associated with diabetes and AD, inducing AD pathology and cognitive impairment. Given the substantial impact of intestinal flora on T2DM onset, interventions targeting intestinal flora have merged as promising therapeutic strategies, dietary modifications, probiotics, prebiotics, and fecal bacteria transplantation.

While Li and Guo[1] focused on the basic experimental aspects of the relationship between intestinal flora and T2DM, clinical studies have garnered considerable attention in recent years. Larsen *et al*[8] reported significant differences in the intestinal flora composition between patients with T2DM and a normal population. Compared with normal people, the number of *Bifidobacteria*, *Clostridium*, and *Firmicutes* in the intestinal flora of diabetic patients was significantly reduced, while that of *Bacteroides* and β -proteus was significantly increased[9]. SCFAs can improve blood glucose, body mass, insulin resistance, and glucose tolerance in patients with T2DM[10,11]. Furthermore, clinical studies found that SCFAs affected the viability of human islet cells in a concentration-dependent manner, prevented streptozotocin-induced β cell apoptosis, and prevented streptozotocin-induced β cell oxygen consumption by supporting mitochondrial respiratory function[12]. However, the specific mechanisms underlying SCFAs and glucose-stimulated insulin secretion (GSIS) necessitate further elucidation. While animal experiments suggest that acetic acid promotes GSIS through parasympathetic nerve activation[13], clinical studies have yielded different results, likely attributable to the pharmacological properties of free fatty acid receptor 2, an important receptor of SCFAs, and the species differences of experimental subjects[14]. In addition, free fatty acid receptor 1 mediates a multitude of functions in the body including release of incretins, secretion of insulin as well as sensation of pain[15]. It is worth noting that free fatty acid receptor is a promising new therapeutic target for T2DM. Therefore, large-scale clinical trials to promote the clinical transformation of basic research results and

better serve patients are required.

In summary, T2DM represents a burgeoning global health concern, characterized by its chronic, progressive, low-grade inflammatory nature, exerting significant impacts on multiple functions of human circulation, nervous system, urinary system, digestion, and other systems. Consequently, it diminishes the patient's quality of life while imposing significant healthcare burdens. Therefore, it is imperative to study the pathological mechanism and effective prevention and treatment of T2DM. As the "second genome" of humans, intestinal flora holds promise as a new therapeutic target for T2DM, offering avenues for reducing insulin resistance, improving glucose and lipid metabolism, and mitigating inflammatory response, thereby laying the groundwork for standardized treatment approaches.

FOOTNOTES

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