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## **Gut-targeted therapies for Type 2 diabetes mellitus: A review**

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### **4 Abstract**

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia and insulin resistance. The global prevalence of T2DM has reached epidemic proportions, affecting approximately 463 million adults worldwide in 2019. Current treatments for T2DM include lifestyle modifications, oral antidiabetic agents, and insulin therapy. However, these therapies may carry side effects and fail to achieve optimal glycemic control in some patients. Therefore, there is a growing interest in the role of gut microbiota and more gut-targeted therapies in the management of T2DM. The gut microbiota, which refers to the community of microorganisms that inhabit the human gut, has been shown to play a crucial role in the regulation of glucose metabolism and insulin sensitivity. Alterations in gut microbiota composition and diversity have been observed in T2DM patients, with a reduction in beneficial bacteria and an increase in pathogenic bacteria. This dysbiosis may contribute to the pathogenesis of the disease by promoting inflammation and impairing gut barrier function. Several gut-targeted therapies have been developed to modulate the gut microbiota and improve glycemic control in T2DM. One potential approach is the use of probiotics, which are live microorganisms that confer health benefits to the host when administered in adequate amounts. Several randomized controlled trials (RCTs) have demonstrated that certain probiotics, such as *Lactobacillus* and *Bifidobacterium* species, can improve glycemic control and insulin sensitivity in T2DM patients. Mechanisms may include the production of short-chain fatty acids, the improvement of gut barrier

function, and the reduction of inflammation. Another gut-targeted therapy is <sup>6</sup> fecal microbiota transplantation (FMT), which involves the transfer of fecal material from a healthy donor to a recipient. FMT has been used successfully in the treatment of *Clostridioides difficile* infection and is now being investigated as a potential therapy for T2DM. A recent RCT showed that FMT from lean donors improved glucose metabolism and insulin sensitivity in T2DM patients with obesity. However, FMT carries potential risks, including transmission of infectious agents and alterations in the recipient's gut microbiota that may be undesirable. In addition to probiotics and FMT, other gut-targeted therapies are being investigated for the management of T2DM, such as prebiotics, synbiotics, and postbiotics. Prebiotics are dietary fibers that promote the growth of beneficial gut bacteria, while synbiotics combine probiotics and prebiotics. Postbiotics refer to the metabolic products of probiotics that may have beneficial effects on the host. The NIH SPARC program, or the Stimulating Peripheral Activity to Relieve Conditions, is a research initiative aimed at developing new therapies for a variety of health conditions, including type 2 diabetes mellitus (T2DM). The SPARC program focuses on using electrical stimulation to activate peripheral nerves and organs, in order to regulate glucose levels in the body. The goal of this approach is to develop targeted, non-invasive therapies that can help patients better manage their diabetes. One promising area of research within the SPARC program is the use of electrical stimulation to activate the vagus nerve, which plays an important role in regulating glucose metabolism. Studies have shown that vagus nerve stimulation can improve insulin sensitivity and lower blood glucose levels in patients with T2DM. Gut-targeted therapies, such as probiotics and FMT, have shown potential for improving glycemic control and insulin sensitivity in T2DM patients. However, further research is needed to determine the optimal dose, duration, and safety of these therapies.

## INTRODUCTION

<sup>3</sup> Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder, characterized by high blood sugar levels resulting from insulin resistance or impaired insulin secretion. It has become a worldwide epidemic with significant public health implications.<sup>5</sup> According to the International Diabetes Federation (IDF), in 2019, approximately 463 million adults (20-79 years) had diabetes, and more than 90% of those cases were T2DM.<sup>1</sup> It is assumed that this number will rise to 700 million by 2045<sup>[1]</sup>.

The high prevalence of T2DM can be attributed to several reasons<sup>[2]</sup>. Sedentary lifestyle, unhealthy dietary patterns like western diet, and increasing obesity rates are major contributors. Urbanization and globalization have led to increased consumption of calorie-dense, processed foods and reduced physical activity. Additionally, aging populations, coupled with longer life expectancies, contribute to the rising prevalence as T2DM is more common in older individuals. The increasing aging will lead to further deterioration of the situation, and the treatment for the elderly is more limited, so early detection and prevention are more important.

In summary, T2DM is a global public health challenge with an increasing prevalence worldwide. The multifactorial nature of its etiology requires comprehensive strategies for prevention, early detection, and effective management. Promoting healthy lifestyles, raising awareness, improving access to healthcare, and addressing social determinants of health are essential in curbing the T2DM epidemic<sup>[3]</sup>. Considering that T2DM is a disease highly associated with intestinal absorption and intestinal flora, this article will focus on the research progress in this area and discuss future therapies. Given the extensive reviews on academic papers focused on T2DM, the novelty of this article lies in the discussion of invention patents related to the gut-based treatment of T2DM, which is the highlight and distinctive feature of this article.

### **Implanted electronic devices in the intestine for the treatment of T2DM**

Implanting electronic devices in the intestine is an emerging field that holds immense potential for improving the management of T2DM. These devices, including those commonly known as "smart pills" or "digestible sensors"<sup>[4]</sup>, can be ingested orally and

provide real-time monitoring and therapeutic interventions within the gastrointestinal tract<sup>[5,6]</sup>. Although the field of implantable electronic devices for T2DM treatment is still in its early stages, preliminary studies have demonstrated their safety and efficacy. With further advancements in miniaturization, wireless communication, and material technology<sup>[7,8]</sup>, these devices are poised to revolutionize the management of T2DM by providing personalized, targeted therapy. Additionally, more devices of this kind are implanted with surgery as shown in Table 1.

Implantable gastrointestinal stimulation devices used for T2DM treatment have the following characteristics: they are often driven by electricity and directly or indirectly stimulate the intestinal nerves or alter the intestinal morphology to affect local and even systemic hormone secretion <sup>[14,15]</sup>. The advantages of these devices lie in their relatively clear treatment mechanisms, including regulation of the hormone homeostasis led by GLP-1 and GIP<sup>[16,17]</sup>, as well as the neuro-immune homeostasis composed of C-fibers and A-fibers<sup>[18,19]</sup>. These types of gastrointestinal electrical stimulation devices therefore have relatively clear target audiences and service objects, and are actively chosen by doctors and hospitals due to their clear mechanisms. However, these devices have significant drawbacks for patients. Firstly, compared to oral hypoglycemic drugs, implantable gastrointestinal stimulation devices used for T2DM treatment often require invasive surgery for implantation, which hinders more patients from choosing this type of device even if their blood glucose control abilities are similar<sup>[20]</sup>. Additionally, since these devices rely on electrical power, similar to devices like pacemakers, gastrointestinal stimulation devices also need to be replaced regularly, which can discourage patients from choosing them, even if the replacement cycle is 5 to 10 years<sup>[21]</sup>.

Based on the above discussion and thinking about the contents of Table 1, we believe that the future development trends of these devices mainly involve three aspects. Firstly, miniaturization of the devices. Whether driven by the rapid progress of the electronics industry itself or the clinical needs of patients, implantable gastrointestinal stimulation devices used for T2DM treatment will develop towards miniaturization,

especially devices that stimulate the intestinal and pancreatic nerves. Furthermore, due to the further precision of their therapeutic targets, the degree of miniaturization will continue to increase. Secondly, diversification of treatment methods. Despite having clear targets, considering the diversity of glucose-regulating hormones in the intestines, as shown in Table 1 with multiple devices involved, future gastrointestinal stimulation devices may use multiple methods such as mechanical force, electric current, and infrared to stimulate the intestines and regulate blood glucose levels [22]. Based on the higher level of technological integration symbolized by the miniaturization of the devices, future gastrointestinal stimulation devices may also include more than one physical stimulation method simultaneously, occupying less space and providing patients with more treatment options. In fact, this trend can already be seen in Table 1, as some devices are no longer standalone gastrointestinal stimulation devices, but rather a treatment system. Lastly, one of the future directions will be electrical stimulation devices with personalized feedback [23,24]. Whether it is physical mechanical pressure stimulation or stimulation from sound waves and light waves, the core therapeutic goal is to control blood glucose within the ideal range. However, the degree of control is not only based on the requirements of disease treatment guidelines, but also revolves around the individual characteristics of patients, especially since most T2DM patients are elderly individuals with multiple chronic diseases. Hypoglycemia can even be life-threatening, and since the intestine serves as a storage and digestion organ for food, integrating blood glucose monitoring devices and using device feedback to prevent excessive hypoglycemia is particularly necessary [25,26]. In this sense, the advantages of electronic gastrointestinal stimulation devices become very apparent, as they contain a power source that not only drives the gastrointestinal stimulation device itself but also ensures the energy supply for blood glucose monitoring devices and related chips<sup>[27,28]</sup>.

### **Treatment of T2DM with intestinal microflora intervention**

Therapies for T2DM starting from the gut include not only treatment devices represented by electrical stimulation devices but also another major category known as gut microbiota therapy. Intervening in blood glucose and lipid metabolism through the gut microbiota has been the focus of over a decade of clinical practice and extensive basic research. A series of studies on regulating the microbiota for glycemic control has successfully achieved the translation from the laboratory to clinical settings, covering different levels from food and health products to pharmaceuticals<sup>[29]</sup>. For example ,  
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chlorella may play an important role in improving the overall condition of diabetic patients by restoring the function of pancreatic insulin-secreting cells<sup>[30]</sup>. Combined  
1  
therapy with PIO and BMCs transplantation could potentiate the protective benefit of MSCs against diabetes and cardiac damage<sup>[31]</sup>. This approach has extensively covered potential user groups and continues to iterate and make progress. Table 2 presents some representative achievements in this field.

As shown in Table 2, intervention of T2DM through gut microbiota has presented more systematic characteristics by utilizing the gut as a medium. Firstly, the treatment of gut microbiota no longer focuses solely on the simple transplantation and replication of healthy microbiota, but takes into consideration relevant associated factors <sup>[36]</sup>. Even though existing sequencing technologies can identify low-abundance microbial communities, current studies and related products have realized the importance of reconstructing a normal microbial habitat, which is superior to directly consuming various formulations of healthy microbiota. In terms of therapeutic effects, techniques including fecal microbiota transplantation have gradually helped T2DM patients to overcome insulin dependence. Furthermore, the selection of microbial communities has become increasingly precise. Secondly, thanks to the achievements of genetic engineering, engineered bacteria rather than natural bacteria have been increasingly applied in the treatment of T2DM <sup>[37]</sup>. Although the short-term cost of this therapy is high, with the scaling-up of applications and the global sharing of treatment costs, more precise and personalized microbial therapy will become the main trend. In addition, in the manufacturing process of microbial communities, more achievements in bionics

have been systematically employed [38]. For example, devices for culturing microbial communities that mimic the structure of the human gut have started to be gradually utilized [39,40].

The use of interventions to improve the gut microbiota as a means of treating T2DM has become a long-term clinical practice. Two main approaches have emerged in relation to this intervention. One approach involves directly altering the composition of the gut microbiota by consuming various types of synthetic or cultivated gut microbiota preparations or live bacteria [41,42]. The other approach involves obtaining appropriate strains of bacteria through fecal microbiota transplantation from a relatively defined donor. In the practical application of these approaches, it has been found that effective gut interventions for T2DM, which primarily involve manipulating the gut microbiota, have specific requirements regarding the types and proportions of microbiota, as well as the administration route, dosage form, and potential need for concomitant use of antibiotics [43,44]. Furthermore, due to differing regulations of food and drug administrations across countries, products related to gut interventions may take the form of pharmaceuticals, foods, or dietary supplements. However, changes in dosage form or microbiota strains may also impact the efficacy of these interventions to some extent, which is an inevitable issue that various medical research studies face when translating to routine clinical practice in accordance with specific national legal and regulatory requirements [45,46].

### **The Future of Gut-Intervention Therapies for T2DM**

In summary, T2DM is a metabolic disorder characterized by insulin resistance and impaired glucose regulation. With the increasing prevalence of T2DM worldwide, there is a growing need for innovative treatment strategies to effectively manage this chronic condition. One emerging field of research is gut-intervention therapies, which involve modulating the composition and activity of the gut microbiota to improve metabolic health [47]. This approach has shown promising results in preclinical and clinical studies,

and the future development of gut-intervention therapies holds great potential in the management of T2DM.

One of the future trends in gut-intervention therapies for T2DM is the identification of specific gut microbiota signatures associated with the disease [48]. Research has shown that individuals with T2DM have distinct gut microbial profiles compared to healthy individuals. By further characterizing these microbial signatures, scientists can develop targeted interventions that aim to restore the balance of the gut microbiota in individuals with T2DM. This may involve the use of probiotics, prebiotics, or even fecal microbiota transplantation (FMT) to introduce specific beneficial bacteria or microbial metabolites into the gut ecosystem [49].

Another trend in the future development of gut-intervention therapies is the utilization of advanced technologies to monitor and assess the gut microbiota. Advances in DNA sequencing and bioinformatics have enabled researchers to more accurately identify and quantify the microbial composition in the gut [50]. This allows for a more personalized approach to gut-intervention therapies, as individuals can be classified into distinct microbial clusters based on their gut microbiota profiles. Such personalized treatments could have improved efficacy and reduced side effects, as they target the specific imbalances in the gut microbiota that are contributing to T2DM.

The incorporation of dietary modifications alongside gut-intervention therapies is also seen as a potential future trend. It is widely recognized that a healthy diet plays a crucial role in the management of T2DM. Certain dietary components, such as fiber, polyphenols, and omega-3 fatty acids, have been shown to promote the growth of beneficial gut bacteria and enhance metabolic health [51]. Therefore, combining gut-intervention therapies with personalized dietary recommendations may optimize treatment outcomes. This could involve the development of tailored dietary plans that aim to improve both gut microbiota composition and metabolic parameters in individuals with T2DM.

In a sense, through the overview of this article, we also consider a possibility that the combination of electrical stimulation devices and microbiota therapy is inevitable as the

feasibility of miniaturization technology continues to improve. Blood glucose regulation is an extremely complex process, influenced by rhythmic daily behaviors such as eating and sleeping, as well as fluctuating factors such as emotions. The seemingly perfect insulin therapy cannot be the sole treatment for T2DM. Stimulating a single target often implies potential and cumulative side effects, which have become evident in patients receiving long-term insulin treatment. In this sense, it is particularly necessary to adopt a multi-target strategy for treatment, with an approach through the gut microbiota.

Additionally, the future development of gut-intervention therapies may involve the use of microbial-based therapeutics. This includes the development of engineered probiotics or microbial consortia that can deliver specific therapeutic functions to the gut [52,53]. For example, scientists are exploring the use of genetically modified probiotic strains that can produce beneficial metabolites or modulate the host immune response. Such microbial-based therapeutics could provide a more targeted and sustainable approach to T2DM treatment, as they can persistently colonize the gut and exert long-term beneficial effects.

In conclusion, the future development of gut-intervention therapies for T2DM holds significant promise in improving the management of this chronic condition. The identification of specific gut microbiota signatures associated with T2DM, advancements in gut microbiota monitoring technologies, incorporation of dietary modifications, and the use of microbial-based therapeutics are some of the key trends that will shape the field. As research in this area continues to evolve, the potential for personalized and effective gut-intervention therapies for T2DM is expected to increase, ultimately benefiting individuals living with this metabolic disorder.

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