Current Status of Research on Mechanisms and Treatment of Constipation in Type 2 Diabetes Mellitus

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Abstract: Both the prevalence of Type 2 diabetes mellitus (T2DM) and the number of its complications have been rising over the past few years. Type 2 diabetes constipation (T2DC) is one of the most common gastrointestinal complications caused by diabetes mellitus, and the incidence is also increasing due to the high prevalence of T2DC. Morbidity is also increasing. This review outlines the pathogenesis of DM, which causes oxidative stress, alterations in the enteric nervous system and related structures, intestinal dysbiosis, rectal dysfunction, biochemical dysfunction, and constipation, to further characterize T2DC. At the same time, the disease is in urgent need of intervention to alleviate the pressure of constipation on the lives of patients. This overview also summarizes the understanding of T2DC by domestic and foreign medical practitioners and the therapeutic advances in the treatment of T2DC from the perspective of improving symptoms by controlling blood glucose, diet and exercise, and improving symptoms through laxatives and gastrointestinal motivation drugs in Western medicine.

Keywords: Type 2 Diabetes Mellitus; Constipation; Treatment Progress; Oxidative Stress; Enteric Nervous System

1. Introduction

Over the past 30 years, the incidence of Type 2 diabetes mellitus (T2DM) has shown a rapid increase. According to the "Global Diabetes Overview (9th Edition)" IDF states that in 2019 in the world 20-79 years old people, the total number of 116.4 million people. Globally, 578 million people are anticipated to have diabetes mellitus by 2030, accounting for about 10.2% of the total number of people in the world. The number of deaths due to DM in China in 2019 was 830,000, with about 33.4% of deaths occurring in patients under the age of 60 years. Due to the rising prevalence of DM, the complications of DM are also increasing worldwide.DM complications mainly include microvascular lesions and macrovascular lesions, of which neuropathy leading to deleterious changes in neuronal structure and function is the most common complication of the microvasculature. Among the various neuropathies, the neuropathy that causes a series of severe gastrointestinal symptoms due to changes in the enteric nervous system is called diabetic enteropathy. One of the most common symptoms of diabetic enteropathy is constipation, also known as diabetic constipation (DC), which is now being gradually recognized as a separate disease due to its high prevalence and impact on one's life. In China, up to 70% of DM patients have gastrointestinal symptoms, of which 27% are constipated. Gastrointestinal symptoms caused by hyperglycemia are similar to those of preexisting irritable bowel syndrome and chronic gastritis, and are often overlooked in clinical diagnosis. However, DC is more harmful, not only will cause anorectal disorders, such as hemorrhoids, anal fissure, etc., but also can be manifested as obvious abdominal distension, nausea, vomiting, and electrolyte disorders. In elderly patients, excessive forceful defecation can also affect blood pressure and even cause cerebrovascular disease. DC not only affects the quality of life of patients, but also adds a heavy burden to the social economy. Treating DM and its complications also puts tremendous pressure on countries' healthcare finances, with the IDF stating that China's healthcare expenditures due to DM and its complications will be $109

billion in 2019, accounting for the second highest in the world. Therefore, DM and its complications should be taken seriously, and measures such as early detection and early intervention are of great significance for both DC and other complications of DM.

2. Western Pathogenesis of Constipation in Type 2 Diabetes Mellitus

2.1 Oxidative Stress

T2DC as well as other DM complications are closely related to oxidative stress. Under the continuous stimulation of hyperglycemia, the body of the sufferer produces significantly more ROS and RNS. Both products are highly oxidizing, consuming large amounts of reducing agents in the gut and causing direct damage to the enteric nerves, and peroxides such as ROS are also involved in the formation of advanced glycosylation end products (AGEs), which are formed by the non-enzymatic reaction of substances such as proteins, amino acids, lipids, or nucleic acids, with reducing sugar moieties[1]. In the normal human body, the formation of AGEs is associated with accumulation and the aging process, but the rate of production is markedly accelerated under the influence of hyperglycemia. Induced inflammation and thrombus development in the intestine by the binding of AGEs to the receptor for advanced glycosylation end-products (RAGE) disrupt enteric nerve activity and blood flow in the gut.

Inadequate antioxidant production in the gut of DM patients also contributes to oxidative stress. Glucose is generally metabolized in the body by two pathways, aerobic oxidation and glycolysis, but in DM patients, hyperglycemia stimulates and activates another. The polyol pathway is a pathway of glucose metabolism. This pathway consumes large amounts of reduced coenzyme II (Nicotinamide adenine dinucleotide phosphate, NADPH) when metabolizing glucose. A significant reduction in NADPH results in a serious scarcity of reducing agents since this enzyme is one of the crucial raw materials needed to make glutathione. At the same time, the activation of the polyol pathway will increase some metabolites, and the osmotic pressure inside and outside the cell to maintain the balance, then cause some antioxidants such as taurine content is reduced[2].

2.2 Enteric Nervous System

Damage to the enteric nervous system (ENS) is one of the main causes of constipation.The nerves that cause lesions in the DM are the parasympathetic nerves, which are responsible for, among other things, facilitating gastrointestinal motility and secretion of digestive juices. The digestive tract has several regions that link sympathetic and parasympathetic fibers and transfer signals from afferent neurons to the parasympathetic nervous system. This intimate connection between the gastrointestinal tract and autonomic nerves is known as autonomic plexus involvement. The gastrointestinal DM symptoms are assumed to be caused by autonomic neuropathy because of this interconnectivity. Vagal fibers in the mesenteric and submucosal plexuses, as well as those beyond the gastrointestinal system, have been found to have segmental demyelination and axonal degeneration in individuals with DM, according to neurological testing of the digestive tract. Under the influence of DM, the number of neurons was reduced in the colon, stomach, ileum, and cecum. The degeneration and necrosis of enteric neurons has been studied in depth, and it has been found that intra- and extracellular lipids and proteins are glycosylated, resulting in the formation of AGEs, which act on RAGE at the cell membrane to cause secondary inflammation, which leads to neurodegenerative disease. Hyperglycemia also affects intra- and extracellular substance exchange through receptors on the cell membrane. When hyperglycemic episodes are frequent or hyperglycemia persists, K+ channels can be activated to cause hypercalcemia, which in turn activates the enteric neuron apoptotic pathway[3].

Interstitial cells of Cajal (ICC) and smooth muscle cells (SMC) are important components of the enteric nervous system. In the field of gastrointestinal dyskinesia and slow intestinal peristalsis, ICC play an important role and are currently considered to be the pacemaker cells of gastrointestinal muscles. Signal communication between ICC and SMC influences the metabolism of substances throughout the gastrointestinal tract. The

absence of insulin and insulin-like growth factor (IGF) has been discovered to be the primary factor contributing to the lower survival of ICC. While enteric neurons and smooth muscle cells both contain the insulin receptor and the IGF-1 receptor, but not the SCF receptor, ICC do not have the IGF-1 insulin receptor. It is known that insulin promotes the proliferation of colonic SMCs through the receptor and causes SMCs to secrete SCF21.The reception of SCF by the ICC transmits signals to smooth muscle cells to produce rhythmic contractions of the intestine, a mechanism that is essential for defecation. The lack of sufficient insulin to bind to receptors on SMCs and enteric neurons in DM patients results in weakened IGF-1 signaling, decreased SCF production by SMCs, and smooth muscle atrophy, which ultimately leads to decreased survival of ICCs. The decrease in ICCs results in gastrointestinal hypokinesia, which slows down peristalsis, causing symptoms such as abdominal distension and constipation.

Recent research has revealed that heme oxygenase-1 (HO-1) aids in the protection against oxidative stress and the avoidance of diabetic gastroparesis (ICC). In hyperglycemia, oxidative stress also affects ICC, causing gastrointestinal dyskinesia. HO-1 is a crucial cytoprotective molecule against oxidative stress because it may shield ICC from oxidative stress. Additionally, the enzyme can repair the pathogenic alterations brought on by DM in enteric neurons and avoid the effects of hyperglycemia on enterocytes.

The primary inhibitory neurotransmitter is nitric oxide (NO), and the enzyme determining how much NO is produced by the ENS is called neuronal nitric oxide synthase (nNOS).12425 Decreased gastric volume, delayed gastric emptying, and reduced gastric musculature relaxation are all consequences of decreased nNOS and NO generation in the stomach of DM rats. Reduced nNOS expression is a gradual progression, a condition that is reversible in early treatment with insulin. However, with the development of T2DM, the continuous accumulation of nNOS and AGEs in the cell produces oxidative stress, which, if not intervened in a timely manner, ultimately leads to irreversible damage to nitrogen-ergic neurons[4]. Acetylcholine, which is produced by enteromotor neurons at receptors on the ICC in the muscle layer and mediates the contraction of smooth muscle, is the primary excitatory neurotransmitter of the enteric nervous system. It is followed by substance P and vasoactive intestinal polypeptide (VIP), which are also released by these enteromotor neurons. DM can interfere with the expression of VIP and substance P, which can affect the neuropeptide homeostasis, and consequently result in impaired smooth muscle contraction.

2.3 Intestinal Flora

There is an association between the composition of the intestinal gut flora and intestinal metabolism in DM patients[5]. It has been found in studies of DM pathogenesis that microbial changes in DM patients may be related to DM pathogenesis and also contribute to the -series of changes in intestinal motility[6]. It has been experimentally demonstrated that elimination of the microbiota in the gut leads to dilatation of the cecum. When the gut is colonized with flora, its cecum dilatation returns to normal.B4 After the discovery of microbial effects on the gut, the specific microbial composition and changes were further analyzed. Decreased levels of bifidobacteria were found in the intestines of patients with DM, whereas the intestinal levels of Enterococcus faecalis were significantly increased. The overgrowth of Enterococcus faecalis caused localized inflammation in the gut and slowed down peristalsis. Prolonged stagnation of the flora in the intestine in turn prompts further growth of Enterococcus faecalis, resulting in a vicious cycle. This cyclic mechanism causes constant changes in the microflora in the gut of DM patients and alters the signaling of nerves within the gastric wall, and abnormal gastrointestinal nerve signaling likewise affects the function of the gut in DM patients. The function of the intestinal epithelium's adhesion junctions can also be hampered by an overabundance of dangerous microorganisms. Intestinal bacterial infections are more common as a result of bacterial breakdown of the intestinal barrier, which also increases the risk of germs moving from the gut to the bloodstream and triggering systemic inflammation[7].

2.4 Hyperlipidemia

The prevalence of dyslipidemia in DM patients is high and dyslipidemia is associated with diabetic neuropathy. It has been demonstrated by animal, experiments that dyslipidemic DM mice have fewer neurons in the ileum and there is a decrease in nerve fiber density. All these changes have an important correlation with diabetic enteric neuropathy. Lipids in the blood are often oxidized, forming oxidation products such as oxidized cholesterol. Such products are able to activate pathways that produce NADPH oxidase, which depletes reductants in the gut. It follows that hyperlipidemia provides the raw material for the generation of oxidation products, exacerbating the damage to the gut from oxidative stress.

2.5 Rectal-anal] Dyskinesia

Persistent hyperglycemia impairs DM anal sympathetic nerves as well as the physiologic function of the anal sphincter, especially in elderly patients, and is associated with abnormal anal] sphincter dynamics, anorectal synergism dysregulation, abnormal sensory function, colorectal hypodynamia, and altered colonic transit time[8]. The effect of hyperglycemia on the organism is evident in elderly patients of the same age with constipation. By comparing non-DM and DM elderly patients with constipation, Dou et al. found differences in the anorectal kinetic characteristics of the two.

2.6 Electrolytes

In animal models of DM changes in adrenergic and cholinergic neurotransmission focused on the enteric nervous system, such as the absence of noradrenergic innervation in the intestinal epithelium of DM mice, lead to a slowing of the absorption of electrolytes and fluids by the intestinal mucosa. Electrolyte disturbances and reduced water content in the intestine make defecation more difficult.

3. Modern Medical Treatment of Constipation in Type 2 Diabetes Mellitus

3.1 Glucose Control

Strict glycemic management is the key to neuropathy prevention or delay. It has been reported IV that poor glycemic control increases the prevalence of diabetic constipation, with constipation and fecal incontinence occurring four times more frequently than in patients with good glycemic control[9].In addition to the use of oral medications and insulin, dietary patterns and lifestyle changes can be used as a tool for diabetic patients to control blood glucose, and the guidelines also emphasize that the interplay between diet, exercise, and medications is the key to controlling blood glucose. Adjusting the dietary structure with carbohydrates as the mainstay, increasing vegetable intake, and arranging reasonable exercise time can not only control blood glucose better, but also have a great benefit on bowel movement.

3.2 Laxatives and Gastrointestinal Motility Applications

Capsaicin and glycerin are common laxative drugs for constipated patients, and their main function is to soften the stool, which is used to help patients who have bowel movements but are dry and difficult to pass. Besides, lactulose also has a good laxative effect, it is a disaccharide composed of galactose and fructose, which has a slight effect on the patient's blood sugar, so it is often used as one of the common laxatives for DM patients.

Mosapride is a kind of commonly used gastrointestinal power drug in China, which can strengthen the gastrointestinal peristalsis of patients with constipation and increase the frequency of defecation[10].Newer drugs such as Procapride can not only reduce the severity of constipation, but also improve the symptoms of gastroparesis. Linaclotide, on the other hand, is commonly used in the treatment of patients with irritable bowel syndrome and chronic idiopathic constipation, and also has some efficacy in patients with diabetic gastroparesis. In individuals with diabetes constipation, rubiprostenone shortens the duration of colonic transit time, enhances colonic motility, and increases the frequency of stool movements.[11].

3.3 Improvement of Intestinal Flora

Bifidobacterium triplex is a micro-ecological agent commonly used in the treatment of patients with constipation or diarrhea. It is known that diabetic patients with constipation have a decrease in the number of bifidobacteria [12]. And Bifidobacterium triplex not only increases the number of

bifidobacteria and reduces the number of competing Enterococcus faecalis, but also improves smooth muscle contraction to promote defecation.

3.4 Antioxidant Treatment

Lipoic acid, an antioxidant in diabetes-related peripheral neuropathy, has been shown to have therapeutic potential in diabetic enteric neuropathy, and is clinically effective in diabetic peripheral neuropathy[13]. In individuals with diabetic neuropathy, lipoic acid enhances blood flow, lowers oxidative stress, and enhances distal nerve transmission. In addition to this, vitamin E, which acts in diabetes, has a significant protective effect against lipid peroxidation and a less pronounced effect against protein and DNA oxidation.

3.5 Other Treatments

Vibrating capsules can be used to treat constipation by improving the patient's fecal transit time through the intestinal tract primarily through vibratory delivery methods that elicit normal waves of peristalsis in the large intestine[14].

Electrical stimulation of the gastrointestinal tract was first used to improve intestinal motility in postoperative intestinal obstruction, and then people began to use it to improve gastric emptying and gastric rhythm disturbances. In some diabetic patients with severe gastrointestinal symptoms, especially significant weight loss and difficulty in achieving results with medications, gastric electrical stimulation may be one of the indications for its use.

4. Conclusion

In outpatient clinics, T2DC is often confused with preexisting bowel syndrome and senile constipation. In recent years, as the complications of DM have gained widespread attention in the medical community, the understanding of the pathogenesis of T2DC has been deepened. People have begun to pay attention to the differential diagnosis between T2DC and common diseases in gastroenterology, and to give individualized treatment.T2DC is no longer confined to the study of a single discipline, but endocrinology, gastroenterology, neurology, and other disciplines have a more profound study of this disease.

At present, the main treatment method of western medicine is to strictly control the blood glucose of diabetic patients, taking blood glucose regulation as the fundamental treatment method, and the treatment of diabetic constipation in western medicine is similar to the treatment of functional constipation in gastroenterology in terms of the application of medicines, generally based on the use of gastrointestinal dynamics or laxative, with the use of nutritive nerves, antioxidant and other therapeutic methods.

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