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Research Progress of Diabetes and Erectile Dysfunction

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Abstract: ***In recent years, studies have shown that there is a significant correlation between diabetes and erectile dysfunction. Diabetes mellitus-induced erectile dysfunction (DMED) is one of the common microvascular complications in diabetic patients. The incidence is gradually increasing and tends to be younger, which seriously affects the quality of life of patients. This article reviews the relationship mechanism and treatment between diabetes and erectile dysfunction.***

Keywords: Diabetes, Erectile Dysfunction, Pathogenesis, Treatment**.**

1. Introduction

Erectile dysfunction (ED) is one of the common functional disorders of the male reproductive system. It refers to the inability of men to continuously obtain and maintain sufficient penile erection to complete satisfactory sexual life [1]. With the rapid development of the economy, people's dietary structure has changed, leading to a sharp increase in the number of diabetic patients. According to statistics, by 2035, the number of global DM patients will reach 592 million, and 75% of DM patients will have varying degrees of ED [2]. Diabetes mellitus-induced erectile dysfunction (DMED) is one of the common complications of diabetic patients. The overall prevalence of DMED is 52.5%, which is 3.5 times that of non-diabetic patients [3]. Moreover, the treatment is more difficult. DMEM not only seriously threatens the physical and mental health of patients, but also has an adverse impact on the overall quality of life of patients and family harmony. Multiple studies have shown that there is a significant correlation between diabetes and erectile dysfunction. The erection of the penis is a complex physiological process of interaction of multiple factors such as nerves, blood vessels, and spirit. This article reviews the relationship, mechanism, and comprehensive management between the two.

2. Clinical Research on the Relationship between Diabetes and Erectile Dysfunction

Diabetes and erectile dysfunction are closely related and share many common risk factors. Atherosclerosis, impaired endothelial function and depressive disorders coexist in both diseases. Meta-analysis shows that the prevalence of erectile dysfunction in diabetic patients is higher than that in non-diabetic patients, and this prevalence increases with age, duration of progression and blood glucose level [4]. A cross-sectional study of more than 300 diabetic male patients in Germany showed that the prevalence of erectile dysfunction in diabetic men is significantly higher than that in non-diabetic men [5]. The severity of ED largely depends on the type and duration of DM, treatment and comorbidities [6-7].

3. Related Mechanisms of Diabetes Complicated with Erectile Dysfunction

3.1 Vascular Factors

3.1.1 Hemodynamics and vascular wall damage

The penile erection process is mainly the process of blood filling in the penile cavernosum, with arterial dilation and venous occlusion. Therefore, when pathological changes occur in the penile blood vessels, ED will result. The mechanism by which DM causes vascular structural lesions may be that the long-term hyperglycemic state of DM patients causes a large amount of advanced glycation end products (AGEs) to be generated. AGEs interfere with the synthesis of protease chains, and finally lead to abnormal changes in the function and structure of blood vessels. In addition, a large amount of AGEs can also act on the surface of endothelial cells of the penile cavernous sinus and produce various cell growth factors, such as endothelial nitric oxide synthase (NOS), thromboxane A2 (thromboxane, TXA2), endothelin-1 (endothelin-1, ET-1), etc., affecting the penile erection process [8]. Finally, AGEs produced intracellularly can also directly affect DNA transcription and replication, change intracellular proteins, and then cause atherosclerosis and lumen stenosis of arterial blood vessels, resulting in insufficient perfusion of penile vascular blood flow [9], thereby causing ED.

3.1.2 Dysfunction of vascular endothelial cells

Studies have shown that NO is the most important molecule involved in penile erection. After the body is stimulated physically or centrally, NO is released from the endothelial cells of the cavernous nerve and activates soluble guanylate cyclase (sGC), increasing the level of cGMP, leading to smooth muscle relaxation and arteriolar dilation [10]. When the peripheral nerves around the penile cavernosum undergo degenerative changes, the reduction of NO production will lead to a decrease in smooth muscle relaxation and arterial dilation, affecting normal erectile function [11]. Abnormal glucose metabolism can produce excessive oxygen free radicals, cause oxidative damage to cells and inhibit the synthesis of nitric oxide (NO), and reduce cyclic guanosine

monophosphate (cGMP), ultimately leading to vascular endothelial dysfunction and impaired relaxation of cavernous arterial smooth muscle [12]. Nitric oxide (NO) and ET-1 produced by endothelial cells counterbalance each other and regulate the contraction and relaxation of smooth muscle cells. Under a hyperglycemic state, the balance between the two is out of control, resulting in a decrease in NO content and an increase in ET-1 content, which in turn makes smooth muscle cells unable to relax normally and causes ED.

3.2 Peripheral Nerve Mechanism

Neural regulation plays an important role in penile erection. When pathological changes occur in the nerve fibers involved in penile erection, ED will result. Long-term glucose metabolism disorders can cause damage to the peripheral nerves around the penis [13], manifested as different degrees of degenerative changes in unmyelinated nerve fibers and small myelinated nerve fibers, damage to the nerve fiber structure, degenerative changes in nerve fibers, and a decrease in the concentration of neurotransmitters related to erection, making the conduction function of penile nerve fibers decline. In addition, the long-term hyperglycemic state will change the sorbitol bypass metabolism. The damage to the nervous system will cause arteriosclerosis of the small arteries supplying the nerves, leading to disorder of nerve nutrition supply, demyelination of nerves, and glycogen deposition, thickening of the basement membrane of Schwann cells and axonal disintegration can cause nerve sensory and motor impairment [14]. Therefore, peripheral nerve fiber degeneration not only directly damages nerves, but also affects neurotransmitter secretion, resulting in erectile dysfunction.

3.3 Central Pathological Mechanism of DMED

3.3.1 Apoptosis of hypothalamic oxytocin neurons

Oxytocin (OT) is a neuropeptide composed of 9 amino acids. The main production sites are the supraoptic nucleus and paraventricular nucleus (PVN) of the hypothalamus [15]. OT may induce male sexual behavior by activating NO synthase in PVN [16]. Therefore, in the process of DMED occurrence, there may be excessive neuronal activation and decreased OT expression, which then promotes cell apoptosis.

3.3.2 Damage to the hypothalamic dopamine receptor pathway

Studies on ED rats found that the expression of dopaminergic neurons in the basolateral amygdala and nucleus accumbens was decreased and participated in the occurrence of ED [17]. In the early stage of T2DM, there is autonomic dysfunction in the central nervous system, mainly manifested as weakened parasympathetic nerve function and enhanced sympathetic nerve function. This autonomic disorder may be involved in the occurrence of DMED. The study by Zheng H et al. [18] found that the weakened dopamine tension in the paraventricular nucleus of T2DM rats will lead to central sympathetic nerve excitation. Therefore, the weakened function of dopaminergic neurons may lead to enhanced sympathetic nerve excitability, and then lead to DMED.

3.4 DMED and Endocrine Factors

Penile erectile function is complexly regulated by hormones of endocrine glands in the body, such as testicular function, pituitary function, thyroid function, blood prolactin and adrenal cortical hormones. Therefore, once the level of a certain hormone increases or decreases, it will trigger a series of chain reactions in the body and finally lead to the occurrence of ED. In the related research of DM inducing ED, there are different views on whether DM causes a decrease in testosterone (T) level and causes ED. CAIAFFO et al. [19] pointed out that DM can promote testicular cell apoptosis by affecting the expression of Bcl-2 and Caspase proteases, and reduce the secretion of T. However, some researchers have found that there is no significant difference in the total serum testosterone (TT) content between DM patients with ED induced by DM and DM patients without ED. Therefore, the appearance of the above different views may be because the male serum T level shows a gradual decline after the age of 50, and compared with DM patients without ED, DM patients with ED are often relatively older. Therefore, this may cause some studies to detect that there is a significant difference in TT levels between DM patients with ED and those without ED. In addition, androgens also play a crucial role in the normal erection of the penis. They can not only induce spontaneous erection of the penis, but also play a regulatory role in the process of penile cavernous body blood perfusion and reflux to maintain the penile erection state. Relevant studies have shown that the persistent hyperglycemic state caused by DM will affect the physiological function of the hypothalamus-pituitary-gonadal axis, leading to a decrease in the release of gonadotropins, a decrease in TT synthesis and endothelial cell dysfunction, thereby leading to erectile dysfunction in the body [20].

3.5 DMED and Psychosocial Factors

The process of penile erection is controlled by the hypothalamic limbic system in the brain. The anxiety of DM patients about the disease and the negative impact of glucose and lipid metabolism disorders on people's emotions make the patient's mood low, so the excitation process of the cerebral cortex, limbic system and hypothalamus will eventually inhibit the normal erection of the penis [21]. A foreign study on Chinese T2DM patients with ED found that the occurrence of T2DM with ED is positively correlated with psychological distress [22]. Quek et al. [23] found that in the population, sexual problems are related to social, psychological and organic factors. Diabetic erectile dysfunction is a type of diabetic complication. It mainly occurs in middle-aged and elderly people. Social and psychological factors may affect this function. DeBerardis et al. [24] conducted a three-year follow-up on 670 diabetic patients. Among them, the conclusion is that related factors such as blood sugar, depression, and hypercholesterolemia all have a certain role in diabetic erectile dysfunction.

4. Treatment

DMED is one of the more challenging subgroups of ED patients to treat, and despite significant advances in treatment, it still faces many difficulties. Current methods for treating DMED mainly include lifestyle interventions, psychotherapy,

oral medication, surgical treatment, and Traditional Chinese medicine (TCM) treatments. Treatment should follow the principle of individualization. On the basis of actively treating the primary disease, appropriate treatment methods should be adopted in combination with the patient's condition. Oral medication is currently the first-line treatment for DMED; if the effect is average, second-line treatments such as penile cavernous body injection, vacuum erection devices, and urethral suppositories can be used; when the above treatments still cannot achieve satisfactory results, third-line treatments such as penile prosthesis implantation can be adopted. In addition to the above traditional methods for treating ED, with the in-depth study of the mechanism of DMED, some emerging treatment methods, such as low-energy shock wave therapy, adipose-derived stem cell and urine-derived stem cell therapy, vascular activation technology therapy, and some special growth factor adjuvant therapies such as insulin-like growth factor 4 (IGF-4) have become the focus of current research[25-26].

4.1 Lifestyle Intervention.

Lifestyle modification is the first step in managing patients with DMED, which mainly includes aspects of diet and exercise [27]. Choosing a balanced diet, quitting smoking, limiting alcohol, engaging in moderate physical activity, and controlling body weight are all part of a healthy lifestyle that can enhance the overall diabetes prevention and treatment awareness within the community. This is beneficial for slowing the progression of diabetic complications, including sexual dysfunction, and for maintaining a harmonious sexual life. Research has shown that lifestyle interventions such as smoking cessation, weight loss, and increased physical exercise can significantly improve ED [28].

Currently, a plethora of studies tend to focus on medical and surgical treatments, often overlooking lifestyle interventions as a crucial measure. Changes in lifestyle are not only advantageous for alleviating symptoms of ED but also effective in preventing the onset of ED in male diabetic patients. It is essential to raise awareness among general practitioners and endocrinologists about the importance of this condition, to conduct preliminary screenings, and to educate diabetic patients about the prevalence, risk factors, and the severity of the impact of DMED. Increasing the awareness of diabetic patients regarding the association between diabetes and ED will facilitate early detection, diagnosis, and treatment.

4.2 Psychological Treatment

Patients with diabetes who also suffer from erectile dysfunction often have psychological issues, primarily manifesting as depression and anxiety. These conditions can severely impact the patient's quality of life, marital stability, and family harmony. It is essential for clinicians to accurately differentiate between psychological ED and organic ED, and to provide patients with psychological guidance and treatment. Treatment plans should be formulated based on the severity of psychological issues associated with DMED. Additionally, the care and encouragement of the patient's partner are equally important in slowing the progression of the disease.

4.3 Type 5 Phosphodiesterase (PDE-5) Inhibitor

PDE-5 inhibitors are still the first-line drugs for treating DMED. They are characterized by good safety and effectiveness, high acceptability and few side effects. The side effects of these medications include headaches, facial flushing, indigestion, myalgia, and diarrhea, among others, but the incidence is low. At present, there are mainly three types, tadalafil, sildenafil and vardenafil. Their mechanisms of action are the same. They are often used in combination with hormones and oral drugs acting on the central nervous system in clinical practice [29]. Studies have found that [30] if the efficacy of a single oral drug is not good, the single drug dose can be reduced and combination therapy can be implemented. Combination therapy has a synergistic effect and improves the efficacy. Some trials and meta-analyses have indicated that the combination therapy of PDE-5 inhibitors (PDE-5i) and selective serotonin reuptake inhibitors (SSRIs) is superior to other treatment modalities, including topical lidocaine gel, behavioral therapy, PDE-5 inhibitors, tramadol, dapoxetine 30/60mg, escitalopram, and placebo [31-32].

4.4 Testosterone Replacement Therapy

For patients with average effect of PDE-5 inhibitors, it is necessary to evaluate their serum testosterone level. The decrease of testosterone level can cause hypogonadism and erectile dysfunction. For patients with ED and hypogonadism, testosterone replacement therapy is effective, and testosterone can regulate the expression of eNOS and the production of NO, thereby helping erection [33]. In addition, studies have found that low-dose testosterone can improve the efficacy of sildenafil and can be used in combination clinically [34]. However, when applying testosterone replacement therapy, it is necessary to closely observe the patient's sex hormone level and some possible adverse reactions.

4.5 Intracavernous Drug Injection

For patients who do not respond to oral drugs, vasoactive drugs can be injected into the cavernous body. Prostaglandin E1 (PGE1), papaverine, and phentolamine are three commonly used drugs. Erection usually occurs within 5 to 15 minutes, and the duration depends on the dose injected. Injection complications include penile pain, priapism, etc [35]. PGE1 is often used alone or in combination with drugs in clinical practice. PGE1 can be made into a preparation for transurethral use. Compared with injection, it is less invasive and easier to use, but its efficacy is worse than that of cavernous body injection.

4.6 Surgical Treatment

Surgical treatment for DMED primarily involves penile prosthesis implantation (PPI). When patients with DMED do not respond to oral medications or have conditions such as Peyronie's disease or corporal fibrosis that affect erectile function, PPI may be considered with the patient's informed consent and their desire to improve erectile function through this method. The most common complication following implantation is infection. However, the mechanism, definitive efficacy, and safety of this procedure still require confirmation, and it is not currently recommended as a first

choice.

4.7 Traditional Chinese Medicine Treatment

Due to the complex pathogenesis of DMED, modern medicine currently lacks specific treatment methods and clinical medications, and the therapeutic effects are limited. Existing research has confirmed that TCM therapies can achieve good results in treating DMED. They not only help control blood sugar but also improve the hardness and duration of erections, reduce patient symptoms, enhance the quality of life, delay disease progression, and have several advantages such as few adverse reactions, a variety of medication options, and diverse treatment methods.

Diabetes falls under the category of "wasting-thirst" in TCM; ED is similar to "impotence" in TCM. TCM believes that the causes of DMED are often related to kidney deficiency, spleen deficiency, liver stagnation, blood stasis, and damp-heat. Wasting-thirst is originally closely related to kidney deficiency. In addition, improper treatment or emotional stress and melancholy can lead to the consumption of qi and yin, and over time, the essence leaks out with urine, failing to nourish the spleen and kidney's primary muscles and tendons. In patients with diabetes complicated by erectile dysfunction, diabetes (wasting-thirst) is the root, and erectile dysfunction (impotence) is the branch. Seeking the root for treatment, effectively controlling blood sugar should be a key prerequisite for treating this disease, while also considering the severity of the disease and its complications, treating both the root and the branch, and applying syndrome differentiation and treatment. TCM treatments for DMED are simple, have minimal side effects, and include oral medication, acupuncture, and plaster therapy. (1) Oral medication: TCM believes that DMED has aspects of deficiency and excess, or a combination of both, so treatment should first distinguish between deficiency and excess. Common causes of impotence due to excess include damp-heat, qi stagnation, and blood stasis. Treatment based on syndrome differentiation involves methods such as dampness removal, qi regulation, and blood activation. Common causes of impotence due to deficiency include kidney deficiency, deficiency of both heart and spleen, and deficiency of both qi and yin. Treatment based on syndrome differentiation involves methods such as nourishing kidney yin, warming kidney yang, benefiting heart and spleen, and qi and yin supplementation. Those with a combination of deficiency and excess often have kidney deficiency with blood stasis, kidney deficiency with liver stagnation, and treatment based on syndrome differentiation involves methods such as kidney supplementation, liver regulation, and kidney blood activation. (2) Studies have shown that acupuncture has the advantages of being simple, easy to perform, significantly effective, and minimally invasive for treating ED, and it has a high clinical application value.

5. Summary

The pathogenesis of DMED is caused by the pathological changes of diabetes to blood vessels, nerves, penile tissues, etc., involving many neurotransmitters, cytokines and signal transduction pathways. It is a complex process. With the increase in the incidence rate, early detection and intervention are carried out for such patients, and guidance on lifestyle intervention and consultation on psychological problems are given to patients. The treatment strategy for diabetes should include comprehensive treatment measures such as lowering blood sugar, lowering blood pressure, regulating lipids, antiplatelet, controlling weight and improving lifestyle. Long-term good blood sugar control helps to delay the aggravation of DM-induced ED. Timely diagnosis and treatment of diabetes-related erectile dysfunction helps to detect potential chronic complications of diabetes early and improve the quality of life of patients.

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