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COMPREHENSIVE MANAGEMENT OF ERECTILE DYSFUNCTION IN DIABETES MELLITUS: PATHOGENESIS, TREATMENT MODALITIES, AND FUTURE PERSPECTIVES

Olgierd Dróżdż, MD

University Teaching Hospital, Borowska Str. 213, 50-556 Wroclaw, Poland

Olgierd.drozdz@gmail.com, https://orcid.org/0009-0006-6134-9101

Marcin Dołęga, MD

University Teaching Hospital, Borowska Str. 213, 50-556 Wroclaw, Poland

Marcindolega@outlook.com, https://orcid.org/0009-0008-6082-8797

Piotr Gacka, MD

University Teaching Hospital, Borowska Str. 213, 50-556 Wroclaw, Poland

Piotr.gacka@onet.pl, https://orcid.org/0009-0002-4171-5208

Dominika Musialska

Faculty of Medicine, Wroclaw Medical University, wyb. Ludwika Pasteura 1, 50-367 Wrocław, Poland

Dom.musial.98@gmail.com, https://orcid.org/0009-0006-5886-5543

Michalina Grzelka, MD

4th Military Clinical Hospital, ul. Weigla 5, 50-981 Wrocław, Poland

Michalinagrzelka1@gmail.com, https://orcid.org/0009-0000-1515-5564

Abstract

Diabetes mellitus (DM) significantly increases the risk of erectile dysfunction (ED), affecting up to 52% of diabetic males. This review examines the epidemiology, pathophysiology, and treatment modalities of ED in diabetic patients. Key factors influencing ED in this population include poor glycemic control, obesity, hypertension, and the duration of diabetes.

Both the latest reports on treatment and well-known articles containing fundamental knowledge about this condition were analyzed, mainly using online databases like PubMed.

Effective management of ED in diabetic patients requires optimal glycemic control and lifestyle modifications such as diet, exercise, and weight management. Pharmacological treatments involve phosphodiesterase type 5 (PDE5) inhibitors like sildenafil, tadalafil, and vardenafil, which enhance erectile function by increasing cGMP levels. Alternatives for those unresponsive to oral medications include intracavernous injections, intraurethral alprostadil, vacuum constriction devices, low-intensity extracorporeal shock wave therapy (Li-ESWT), and penile prosthesis implantation. Emerging therapies like mesenchymal stem cell therapy and novel drug combinations offer promising avenues, focusing on cellular regeneration and improved vascular function.

Despite the availability of these treatments, ED remains underreported due to patient embarrassment and healthcare provider hesitation, underscoring the need for increased awareness and proactive management. As projections indicate a rising global prevalence of ED, integrating ED management into comprehensive diabetes care is essential to enhance patient quality of life and address this significant public health issue.

Introduction

Diabetes mellitus (DM) is a severe condition impacting approximately 537 million adults globally (1). Among its many complications, erectile dysfunction (ED) stands out as one of the most embarrassing and quality-of-life deteriorating issues (2). This condition is not only more prevalent among diabetics—occurring up to 2-3 times more often than in the healthy population—but also tends to manifest up to 15 years earlier (3).

Erectile dysfunction is defined by the National Institute of Health (NIH) as the persistent inability to achieve or maintain an erection sufficient for satisfactory intercourse (4). However, it should be noted that in order to diagnose this condition, the symptoms of erectile dysfunction must persist for at least 3 months (5). This issue is highly common among diabetic patients, with nearly 52% of males reporting problems (6). Factors such as age, duration of diabetes, smoking, and complications like macroangiopathy, microangiopathy, polyneuropathy, and hypertension further exacerbate the risk. Symptoms of ED often appear around three years after a diabetes diagnosis, especially in those with type 2 diabetes, and can sometimes be the first sign of the disease (3,7).

The prevalence of ED among diabetics is substantial, with a comprehensive meta-analysis indicating an overall rate of 59.1%. Notably, the prevalence is higher in type 2 diabetes patients (66%) compared to those with type 1 diabetes (37.5%) (3). Age also significantly impacts ED risk, with diabetic individuals over 50 years old being 11.21 times more likely to develop the condition compared to those under 50 (8).

Body mass index (BMI) and glucose control play crucial roles in ED prevalence. A BMI exceeding 30 kg/m^2 increases the risk of developing ED by 1.26 times, while maintaining HbA1c levels below 7% reduces the risk by 7% (9). The type of diabetes also influences ED risk: severe insulin-resistant diabetes (SIRD) presents

the highest risk (52%), followed by severe insulin-deficient diabetes (SIDD) at 31%, mild age-related diabetes (MARD) at 29%, and mild obesity-related diabetes (MOD) at 18%. The lowest risk is observed in severe autoimmune diabetes (SAID) at 7% (10).

The duration of diabetes correlates with the severity of ED symptoms. Patients with prolonged DM often exhibit more severe symptoms than those with a shorter disease duration. This relationship has been well-documented, with longer diabetes duration associated with a higher prevalence of moderate to severe ED (3).

Despite the high prevalence of ED among diabetics, many patients are reluctant to report their condition due to embarrassment. Additionally, healthcare providers may be hesitant to address sexual health, making it challenging to accurately assess the true extent of the problem. This underreporting highlights the need for increased awareness and proactive management of ED in diabetic patients (11).

Projections indicate that by 2025, the number of people suffering from ED will reach 322 million (12). Given the significant impact of ED on quality of life and its strong association with diabetes, it is crucial to address this condition as part of comprehensive diabetes care and management strategies.

Pathogenesis

The pathogenesis of erectile dysfunction (ED) in diabetes mellitus (DM) is multifaceted, involving a combination of organic, psychogenic, hormonal, environmental, and drug-related factors (2).

The primary organic cause of ED in diabetes is angiopathy, a common complication of the disease. Angiopathy can be divided into macroangiopathy, microangiopathy and endothelial dysfunction (13). Microangiopathy includes conditions like retinopathy and nephropathy, while macroangiopathy involves diseases such as coronary artery disease and vascular issues affecting the brain, pelvis, lower extremities, and carotid arteries (14). In the context of ED, the focus is on the blood vessels supplying the corpus cavernosum of the penis and their endothelial function (13). Hyperglycemia, a hallmark of diabetes, is closely linked to angiopathy and endothelial dysfunction (5). An HbA1c level above 8.1% triples the risk of developing ED (15). Elevated glucose levels lead to the formation of sorbitol, which increases osmotic pressure, disrupts electrolyte balance, and impairs the sodium-potassium pump (7). Additionally, hyperglycemia results in the production of advanced glycosylation end-products (AGEs), abnormal proteins that accumulate in blood vessels and alter their properties, particularly in the corpus cavernosum (16).

Oxygen free radicals (OFR), generated during glucose autoxidation, and AGEs contribute to vascular endothelial damage and nitric oxide (NO) dysfunction. NO deficiency, coupled with elevated levels of endothelin-1 (ET-1), leads to vascular remodeling and decreased cGMP levels, crucial for smooth muscle relaxation and proper blood flow during erection (17-19). Diabetes also affects coagulation due to endothelial impairment and reduced C-protein, which inhibits clotting and increases fibrinogen and PAI levels (20). Hyperinsulinemia, often associated with type 2 diabetes, exacerbates angiopathy by promoting lipid biosynthesis, myocyte proliferation, and PAI activity, resulting in reduced blood flow to the corpus cavernosum and penile hypotension (21).

Diabetic autonomic neuropathy (DAN), particularly parasympathetic dysfunction, further complicates ED. DAN leads to reduced NO levels, and impairing sensory impulses from the penis to the reflexogenic erectile center. This condition can precede other peripheral neuropathies and affects the innervation of muscles essential for maintaining an erection (22,23). Moreover, hypertension, atherosclerosis, and cardiovascular diseases (CVD)

associated with diabetes also contribute to ED, creating a bidirectional relationship where ED can be both a result and a predictor of CVD (3,24).

Hormonal imbalances, such as hyperprolactinemia, hyper- and hypothyroidism, and hypogonadism, significantly impact ED in diabetic patients (25). Hypogonadism, in particular, is associated with low levels of sex hormone-binding globulin, which transports testosterone (26). Visceral adiposity exacerbates hypogonadism through the enzyme aromatase, which converts testosterone to estradiol (27). Low testosterone levels activate lipoprotein lipase, increasing free fatty acids and further promoting adipose tissue development (28).

Environmental influences on ED include smoking, alcohol consumption, and excessive coffee consumption. A sedentary lifestyle and reduced physical activity also contribute by increasing adipose tissue, which disrupts testosterone metabolism. Smoking, in particular, has a direct negative impact on erectile function (2,29).

Diabetic patients often require multiple medications, some of which can negatively affect erectile function. Selective serotonin or noradrenalin reuptake inhibitors (SSRI &SNRI), tricyclic antidepressants, β-adrenolitics, cimetidine, finasteride, simvastatin, and thiazides are among the medications known to impair erection. Diuretics are notably harmful, as they are more commonly used by patients with ED and disrupt vascular smooth muscle function. β-adrenolitics, such as atenolol and metoprolol, can also lower libido and impair erection, compounding the challenge of managing ED in diabetic patients (30,31).

ED in diabetes is often referred to as a silent complication, as patients frequently feel too embarrassed to discuss it, even with their doctors. Emotional and psychological factors play a crucial role, with depression and anxiety, often exacerbated by diabetes, worsening ED symptoms. Diabetes can double the risk of depression, and the fear of not achieving an erection can be powerful enough to cause ED independently of other factors. Moreover, two genes - CLDN5 and TBC1D1 - were discovered, which at the molecular level link the comorbidity of depression and erectile dysfunction (32,33).

Treatment

The foundation of both prevention and treatment of erectile dysfunction in diabetes is proper glycemic control and the management of comorbidities. Important aspects of treatment include an appropriate diet, physical activity, weight reduction, and pharmacological therapy. Hyperglycemia is the main risk factor for erectile dysfunction in diabetic patients. It contributes to the accumulation of advanced glycation end products and free oxygen radicals, which can activate various metabolic pathways, leading to further deterioration of erectile function. Generally, the longer the duration of diabetes and the poorer the glycemic control, the greater the risk of vascular damage, which is most likely the key risk factor for the occurrence of erectile dysfunction in diabetic patients (34-36).

Phosphodiesterase Type 5 (PDE5) Inhibitors: Sildenafil, Tadalafil, and Vardenafil

One of the primary methods for treating erectile dysfunction in the course of diabetes is the use of oral medications. Most commonly used are PDE5 inhibitors such as sildenafil, tadalafil, and vardenafil. Inhibition of PDE5 activity leads to an increase in cGMP, which causes the relaxation of smooth muscles, an influx of blood into the corpora cavernosa, and subsequent improvement of erection after a prior stimulus that triggers it. These drugs are highly effective and well-tolerated by patients. Side effects include headaches, hot flashes, indigestion, nasal congestion, vision disturbances, and diarrhea. For treating erectile dysfunction in diabetic patients, the highest efficacy is seen with the maximum permissible doses of these medications: sildenafil 100 mg, vardenafil 20 mg, and tadalafil 20 mg. Vardenafil and sildenafil are more effective when taken on an empty stomach and begin to work within 30 minutes, with peak effects around 1 hour. The duration of action for these drugs is about 4–6 hours. Tadalafil, however, has an effect lasting up to 36–48 hours (13,37).

There is also a new generation of phosphodiesterase type-5 inhibitors. Drugs such as udenafil and mirodenafil have been found to be effective in the treatment of erectile dysfunction (38). Udenafil is characterized by rapid absorption, a long duration of action, and relatively high efficacy. Considering the chronic nature of the described condition, it is important that this drug is well-tolerated by patients, and its use is rarely associated with side effects such as headaches or flushing (39). Mirodenafil has also demonstrated high efficacy in the treatment of erectile dysfunction in patients suffering from diabetes during numerous clinical trials (40).

Intracavernous injection

One of the methods for treating erectile dysfunction is intracavernous injection. This is an alternative method for patients for whom treatment with phosphodiesterase type 5 inhibitors (PDE5i) is ineffective or associated with bothersome side effects (6). This treatment involves injecting vasoactive substances into the corpora cavernosa. The most commonly used drugs in this method are α-adrenoreceptor blocking agents such as phentolamine, prostaglandin E1 (PGE1), and papaverine. Phentolamine is a competitive antagonist of α1 and α2 adrenoceptors, which ultimately results in the dilation of penile blood vessels. PGE1 leads to the activation of adenylate cyclase, which increases cAMP, subsequently causing the relaxation of smooth muscles and the dilation of blood vessels. An erection typically appears within 5-15 minutes, and its duration depends on the dose used. Papaverine is a non-specific PDE inhibitor (37,41). The described medications can be used as monotherapy, but more often combined preparations are used due to the reported synergism of the drugs in publications (2). The combination of alprostadil and papaverine leads to increased levels of cAMP and/or cGMP, as well as the inhibition of calcium channels and the secretion of angiotensin II. The combination of alprostadil with phentolamine can increase the effectiveness of treatment by up to 90% (37).

Intraurethral/topical alprostadil

The mentioned method appears to be an effective alternative to intracavernous injection, as its use is more comfortable for patients and is associated with fewer side effects such as priapism and penile fibrosis. The most commonly used FDA-approved drug is alprostadil. The drug is in the form of urethral suppositories and was introduced to the market as MUSE (Medicated Urethral System for Erection). Its action involves absorption through the urethra and subsequent transport to the corpora cavernosa, where it causes blood vessel dilation and smooth muscle relaxation by acting on the prostacyclin receptor. The most commonly reported side effect by patients is penile pain, but priapism or plaque formation occurs relatively rarely(25,42,43).

Yohimbine

Yohimbine is an alpha-adrenergic receptor antagonist. This preparation is one of the alternative treatment methods, but further studies are necessary to fully evaluate its effectiveness in treating erectile dysfunction in patients with diabetes. The recommended dose is 5-10 mg three times a day. This drug has moderate efficacy. The main side effects include anxiety and headache (44).

Devices for vacuum constriction (VCD)

A highly effective alternative to pharmacological and surgical treatments, achieving efficacy rates of up to 70-80%. The procedure is relatively simple but limits patients in terms of the spontaneity of sexual intercourse. It involves placing an external cylinder over the penis, which must be tightly pressed against the body to create a hermetically sealed space. Then, using a vacuum pump, operated either manually or mechanically, the patient creates a vacuum around the penis, causing the expansion of the cavernous venous sinus, increasing perfusion of the cavernous artery, and venous blood. The final element maintaining the artificial erection is an elastic band placed at the base of the penis. The ring can be maintained for a maximum of 30 minutes (45). This method is simple, cost-effective, and effective in long-term practice, even with frequent use. Ma et al. conducted an experiment on rats in 2021, demonstrating that the described device increases the ratio of smooth muscle to collagen by reducing hypoxia-inducible factor 1 and transforming growth factor 1, thereby improving blood flow in the penis (46).

In studies conducted by Khayyamfara et al. from 2003 to 2010, it was shown that up to 87.4% of patients achieved a full erection after the first training session. For the remaining participants, it took about a week of training. 94.6% of the subjects reported successful sexual intercourse after using vacuum constriction devices. For 5.4% of patients with erectile dysfunction, this option was ineffective due to their partner's virginity. It has been proven that female factors influence the effectiveness of VCD therapy (47). The majority of study participants and their partners were satisfied with the device. However, studies showed that some users experienced significant discomfort. One cause was insufficient lubrication, which could lead to bruising on the penis, numbness and/or pain, a feeling of coldness in the penis, and an inability to ejaculate. The device and the necessity of learning how to operate it can cause some frustration and a sense of lack of autonomy, as demonstrated in studies conducted by Sultan et al (48-50).

Low-intensity extracorporeal shock wave therapy (Li-ESWT)

This method was initially used for lithotripsy of stones in the urinary system. Over time, scientists began to investigate whether it could be effective in treating other conditions (51). Thus, benefits have been demonstrated from using it in the therapy of musculoskeletal disorders, cardiovascular diseases, and wound healing (52-54). Currently, low-intensity shock wave therapy is used in combating erectile dysfunction. The mechanism improving erection remains unclear. Some researchers believe that mechanical stress plays a dominant role by stimulating neovascularization, recruiting new stem cells, and improving blood flow (54). Others report that it may stimulate the synthesis of nitric oxide in nerve, muscle, and endothelial cells, leading to the dilation of blood vessels, thereby allowing blood to flow into the corpora cavernosa in the penis (55). One

study reported a reduction in sympathetic nervous system activity as a potential mechanism of action for this method (56).

Clinical studies conducted on individuals with diabetes suffering from erectile dysfunction treated with Li-ESWT have yielded many interesting findings. For instance, Tzou et al. demonstrated that uncontrolled diabetes is a poor prognostic factor for the effectiveness of Li-ESWT (57). In another study involving patients with well-controlled diabetes and confirmed neuropathy but without severe erectile dysfunction, significant improvement in the mean IIEF-EF score was observed after 3 months. As many as 71% of the study participants achieved erections sufficient for penetration (58). Kitrey i in. wykazali, że tylko 25% mężczyzn z cukrzycą osiągnęło trwały efekt po 2 latach terapii pozaustrojową falą uderzeniową. Ponad to żaden mężczyzna z ciężkimi zaburzeniami erekcji przed rozpoczęciem leczenia nie uzyskał trwałego efektu po 2-letnim leczeniu (59). Spivak et al. focused on the improvement of erectile function after shock wave therapy in individuals who previously responded well to PDE5 inhibitors. In this case, the improvement was significantly greater compared to those who did not respond well to PDE5 inhibitors previously. However, 55% of non-responders were converted into responders (60). In all the studies described, no serious adverse effects of the therapeutic method were detected.

Many studies and observations are conducted on rat models. One such study examined the simultaneous use of Li-ESWT with sildenafil. It was found that this combination could enhance erectile function in the studied animals (61). Another combination considered was Li-ESWT with a Korean herbal mixture (KH-204), which included Cornus officinalis Sieb. et Zucc, Lycium chinense Miller, Rubus coreanus Miquel, Cuscuta chinensis Lam, and Schisandra chinensis Baillon. Significant improvement in intracavernous pressure compared to the monotherapy group was noted in rat studies. The conclusions included the finding that KH-204 protects penile progenitor cells, and when combined with shock wave therapy, it reduces overall oxidative stresss (62). Shin et al. investigated the integration of Li-ESWT with stem cell implantation. From the results obtained, the greatest improvement was observed in the content of smooth muscle in the corpus cavernosum, as well as in the expression of nNOS (neuronal nitric oxide synthase), NO (nitric oxide), and cGMP (cyclic guanosine monophosphate) (63). A year later, Liu et al. revisited the described combination. They observed that Li-ESWT promotes the proliferation of adipose tissue-derived stem cells and enhances the secretion of factors including SDF-1 (stromal cell-derived factor 1), FGF2 (fibroblast growth factor 2), and VEGF (vascular endothelial growth factor) (64).

Penile prosthesis

Both the European Association of Urology and the American Urological Association agree on penile prosthesis implantation as an alternative intervention for patients for whom more conservative methods have not achieved the desired effect, such as injections into the corpora cavernosa, vacuum devices, or phosphodiesterase inhibitors (65). Contraindications for performing such a procedure include an active infectious process anywhere in the body, urinary retention issues, serious coexisting illnesses where sexual intercourse could endanger life or health, as well as patients who are unwilling to undergo device revision after surgery (66). Currently, there are many devices on the market that belong to the inflatable or plastic group. The former accounts for 90% of new implants (65). The device consists of three parts: two cylinders placed in the corpora cavernosa, a water reservoir located submuscularly or in the space of Retzius, and a scrotal pump controlling the erection (67). For patients with a more extensive medical history, such as those who have undergone pelvic radiation or major abdominal

surgeries, it is possible to implant a two-piece prosthesis with a scrotal pump and smaller reservoirs (68). In the validation conducted by Van Huele A et al., a satisfaction rate exceeding 80% was noted after implantation with a three-piece device (69). In the case of the two-piece device, it exceeds 70% (70).

As with any surgical procedure, it is necessary to conduct a thorough patient history regarding symptoms, including an assessment using the International Index of Erectile Function (IIEF-5), previous treatments for erectile dysfunction, and past surgeries that might require modification of the incision site during the operation. Additionally, precise information about comorbidities and medications being taken should be collected (71,72). The next step is to examine the patient, assessing the length and circumference of the penis and detailing any curvatures, thickening, and deformities. Preoperatively, it is essential to optimize glycemic control, as it has been proven that patients with HbA1c >8.5% have a higher likelihood of infection following penile prosthesis implantation (73).

Among the guidelines of the American Urological Association, there is a recommendation to include prophylactic antibiotic therapy before the procedure we are discussing. The first-line therapy mentioned is a combination of aminoglycosides with vancomycin or a cephalosporin. However, a multicenter analysis published in February 2023 proved that using such prophylaxis is associated with a higher risk of infection, while the use of antifungal medications reduces this risk (74).

The procedure begins with the placement of drapes and a Foley catheter, which not only ensures the bladder is emptied but also facilitates the identification of the urethra and protects it from damage. An alternative to the traditional draping from the navel to mid-thigh is the no-touch technique, in which an iodophor drape is used, exposing only the penis and scrotum (75). When placing a three-piece inflatable prosthesis, the surgeon has two access options: infrapubic and penoscrotal. In the first approach, the surgeon directly visualizes the placement of the reservoir. In the penoscrotal approach, the procedure begins with an incision in the skin, followed by the separation of the subcutaneous tissue, Dartos fascia, and Buck's fascia to reach the tunica albuginea. A common maneuver is placing holding sutures on the corpora cavernosa to facilitate the incision and subsequent closure of the corporotomy. The corporotomy itself is performed using Bovie electrocautery. The next step is dilating the corpora cavernosa, for which the surgeon may use scissors, Hegar dilators, or Brooks dilators. It is crucial that in the distal segment, the dilation is done in a cranial and lateral direction to prevent the corpora cavernosa from crossing and to avoid damaging the urethra. In the next part of the procedure, the surgeon follows the spermatic cord upwards, passing through the external inguinal ring and palpating the pubic ramus to place the reservoir in the space of Retzius. It is necessary to test the empty reservoir to assess its positioning. In patients who have undergone major pelvic surgeries, the reservoir can be placed submuscularly (76). The next crucial step is selecting the appropriate size of the cylinders. At the distal end of each cylinder, a Keith needle is attached, loaded through the Furlow device, and passed through the glans. This process is repeated on the opposite side. To check the sizing and positioning, they are inflated again with saline solution. The surgeon closes the corporotomy using temporary and then interrupted sutures. Subsequently, a scrotal pocket is created, where the pump will be placed and the Dartos tissue is re-sutured over it. Finally, all components are connected with appropriate tubing, and the skin is closed in two layers. After the procedure, the penis is wrapped in sterile gauze and positioned upward on the abdomen to prevent downward bending postoperatively (66).

In studies conducted by Torremadé J. et al., it was demonstrated that one-day implantation of a penile prosthesis is a cost-effective and equivalent alternative to the traditional practice of hospitalizing patients for approximately 5 days. Among postoperative recommendations, doctors emphasize the importance of pulling the scrotal pump downwards several times a day to prevent migration towards the head of the penis (77).

Like any surgical procedure, penile prosthesis implantation carries risks of complications. The most fundamental risk is infection, which can sometimes necessitate removal of the implant. Another significant complication is improper sizing of the prosthesis. Implanting cylinders that are too small can result in a condition known as "supersonic transport-related deformity" or "floppy glans syndrome," leading to difficulties in vaginal penetration and poor cosmetic outcomes (78). On the other hand, cylinders that are too long can cause chronic pain and erosion, which may necessitate the removal of the prosthesis (79). One of the complications previously mentioned is the migration of the pump from the scrotal pocket. Up to 27% of patients experience urinary retention after penile prosthesis implantation. Patients may perform intermittent self-catheterization or have a Foley catheter placed. The risk of this complication is significantly higher in patients with prostate enlargement who are using alpha-blockers and 5-alpha-reductase inhibitors. After undergoing the procedure, patients receive training in operating the pump under the guidance of a urologist. This process requires practice and exercises but ultimately provides significant satisfaction and control over the timing and duration of erections. To achieve an erection, the patient presses the pump, located in the scrotum, several times, which transfers fluid from the reservoir into the cylinders in the penis. Pumping can continue until the desired stiffness of the penis is achieved. At this stage, the prosthesis provides a sensation similar to a natural erection. After intercourse, the patient locates the deflation valve on the pump and presses it. This action transfers fluid from the cylinders back into the reservoir, causing the penis to return to its flaccid state. Patients with a penile prosthesis can still achieve orgasm, provided that the nerves supplying the penis have not been damaged (80).

Mesenchymal Stem Cell Therapy

Mesenchymal stem cell (MSC) therapy can regenerate damaged nerves, endothelial cells, and smooth muscle. Researchers consider it a promising method for treating erectile dysfunction in diabetic patients.

Adipose-derived stem cells (ADSCs) are garnering significant attention as a potential tool for treating diabetic erectile dysfunction (DMED) and are highly similar to bone marrow-derived stem cells (BMSCs) in their ability to secrete a wide range of growth factors and cytokines. Garcia MM et al. demonstrated that the action of ADSCs is more indirect, improving the extracellular environment and the function of local cells through paracrine action rather than directly transforming into local cell types (81). This happens through the secretion of cytokines, signaling molecules, trophic factors, and a large quantity of exosomes by ADSCs (82). The latter group (exosomes) proved to be so significant that in 2017, Chen et al., after extracting them from the supernatant of cultured ADSCs, demonstrated a significant improvement in erection in rats with DMED (83). Exosomes can be utilized as an alternative to ADSCs themselves, avoiding the potential side effects of cell therapy. Unfortunately, these extracellular vesicles are characterized by low efficiency, significantly limiting their clinical application. Some researchers, like Liu et al., have started exploring gene therapy combined with stem cell therapy as a contemporary solution. This approach is particularly relevant because erectile dysfunction, among other issues, is associated with endothelial dysfunction and impaired secretion of vascular endothelial

growth factor (VEGF). They decided to use ADSCs genetically modified with the VEGF gene and compared its effects to those of non-modified stem cells. The results showed significantly better outcomes in the first group. However, the integration risk of exogenous genes with the host genome remains problematic, thereby limiting the broader application of gene therapy (84). Another intriguing combination involved the transplantation of stem cells along with endothelial progenitor cells (EPCs), as studied by Yang Q. et al. They demonstrated that cotransplantation significantly improves erectile function. The primary mechanism in this combination involves the interaction of VEGF and SDF-1, secreted by ADSCs, in recruiting and proliferating EPCs within the corpora cavernosa. Additionally, it leads to increased expression of smooth muscle cells and nNOS in the described location (85). Scientists observed that the action of adipose tissue-derived stem cells (ADSCs) is limited under conditions of hyperglycemia due to mechanisms involving apoptosis, oxidative stress, and free radicals. To counteract these processes, they sought modifications that could prevent these limitations. During the study, they transfected ADSCs with lentivirus carrying short hairpin RNA (shRNA) targeting the nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3), which includes leucine-rich repeat (LRR) domains and the pyrin domain-containing protein 3 (shNLRP3). Subsequently, they evaluated the levels of apoptosis and reactive oxygen species (ROS) in groups with different blood glucose levels. It was demonstrated that LV-shNLRP3 enhanced the anti-apoptotic and anti-ROS functions of ADSCs in a high-glucose environment, thereby increasing their success rate post-transplantation. Additionally, it improved anti-pyroptotic function, reduced cavernous endothelial dysfunction and smooth muscle cell damage, ultimately strengthening ASCs to enhance treatment outcomes for diabetic erectile dysfunction (DMED) (86).

Another type of stem cells considered for transplantation are urine-derived stem cells (USCs), favored for their cheaper and non-invasive extraction. Galhom et al. demonstrated in a rat model of diabetic erectile dysfunction (DMED) that USC improved the condition of the corpora cavernosa and copulatory function through paracrine action. They also compared USC with USC lysate, which exhibited greater viability and better differentiation. Therefore, USC lysate appears to be a more valuable substrate for transplantation than USC alone (87). Researchers also evaluated human umbilical cord mesenchymal stem cells (hUC-MSCs). Their anti-inflammatory, anti-fibrotic, pro-angiogenic, and immunomodulatory actions have been demonstrated (88). However, what distinguishes them from other stem cells that have been studied is their greater self-renewal capacity and lower susceptibility to rejection by the immune system (89). Mukti et al. demonstrated that these cells enhance the expression of transforming growth factor beta, alpha-smooth muscle actin, and collagen in rats with diabetic erectile dysfunction (DMED), thereby positively impacting inflammatory response and erectile function improvement (90). Additionally, Feng et al. discovered another action of hUC-MSCs, which is inhibiting ferroptosis induced by diabetes (91).

Conclusions

In conclusion, the management of erectile dysfunction (ED) in diabetic patients necessitates a multifaceted approach that addresses both the underlying pathophysiology and patient-specific factors. ED, prevalent in more than half of diabetic males, significantly impacts quality of life and remains underreported due to stigma and healthcare provider reluctance. Effective management strategies begin with optimizing glycemic control and addressing comorbidities like obesity and hypertension, which exacerbate ED risk. Pharmacological interventions, particularly PDE5 inhibitors like sildenafil and newer agents like udenafil, offer reliable efficacy

with manageable side effects. For patients unresponsive to oral therapies, intracavernous injections and vacuum constriction devices provide viable alternatives, albeit with different considerations for comfort and ease of use. Advanced treatments such as low-intensity shock wave therapy and stem cell therapy show promise in reversing underlying vascular and tissue damage associated with ED in diabetes. Surgical options like penile prostheses remain a last resort but offer high patient satisfaction rates when other therapies fail. Ultimately, comprehensive care requires proactive screening, patient education, and tailored treatment plans to mitigate the profound impact of ED on diabetic patients' well-being and overall health outcomes.

Disclosure

Author's Contribution:

Conceptualization, OD, DM and MG; methodology, MD and PG; check, OD and MD; formal analysis, OD; resources, OD, PG and MG; data curation, MD; writing - rough preparation, OD, MG, DM and PG; writing - review and editing, OD, MD, PG, MG and DM; visualization, MD; supervision, OD; project administration, OD; All authors have read and agreed with the published version of the manuscript.

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