

·Review·

Pathophysiology and treatment of diabetic erectile dysfunction

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Abstract

The pathophysiology of diabetes is multifactorial and no single etiology is at the forefront. The proposed mechanisms of erectile dysfunction (ED) in diabetic patients includes elevated advanced glycation end-products (AGEs) and increased levels of oxygen free radicals, impaired nitric oxide (NO) synthesis, increased endothelin B receptor binding sites and ultrastructural changes, upregulated RhoA/Rho-kinase pathway, NO-dependent selective nitrergic nerve degeneration and impaired cyclic guanosine monophosphate (cGMP)-dependent kinase-1 (PKG-1). The treatment of diabetic ED is multimodal. Treatment of the underlying hyperglycemia and comorbidities is of utmost importance to prevent or halt the progression of the disease. The peripherally acting oral phosphodiesterase type 5 (PDE5) inhibitors are the mainstay of oral medical treatment of ED in diabetics. Vacuum erection devices are an additional treatment as a non-invasive treatment option. Local administration of vasoactive medication via urethral suppository or intracorporal injection can be effective with minimal side-effects. Patients with irreversible damage of the erectile mechanism are candidates for penile implantation. Future strategies in the evolution of the treatment of ED are aimed at correcting or treating the underlying mechanisms of ED. With an appropriate vector, researchers have been able to transfect diabetic animals with agents such as neurotrophic factors and nitric oxide synthase (NOS). Further studies in gene therapy are needed to fully ascertain its safety and utility in humans. (*Asian J Androl* 2006 Nov; 8: 675–684)

Keywords: erectile dysfunction; diabetes; mechanism; treatment

1 Introduction

More than 6% of the USA population has diabetes mellitus, of this, approximately 8 million people have impaired erections [1]. Erectile dysfunction (ED) occurs in 32% of type 1 and 46% of type 2 diabetic men [2]. Fifty percent of men with diabetes are afflicted with ED

within 10 years of their diagnosis. ED might be the initial presentation in 12% of patients subsequently diagnosed with diabetes [3]. Between the ages of 30 to 34 years, ED is present in 15% of diabetics. This number increases to 55% by the age of 60 years [4]. The Massachusetts Male Aging Study noted that diabetics have a three-fold increased incidence of ED as compared with non-diabetics [5]. Additionally, a population-based study in Minnesota showed that diabetes was associated with diminished sexual drive, ejaculatory function and sexual satisfaction [6].

2 Pathophysiology

The etiologies of ED in diabetic patients are

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multifactorial. The end-organ damage secondary to hyperglycemia, as well as the comorbidities in the patients and side-effects of the various medications (i.e. antihypertensives) they consume, all contribute to their ED. The proposed mechanisms of ED in diabetics include: elevated advanced glycation end-products (AGEs) and increased levels of oxygen free radicals, impaired nitric oxide (NO) synthesis, decreased and impaired cyclic guanosine monophosphate (cGMP)-dependent kinase-1 (PKG-1), increased endothelin B (ETB) receptor binding sites and ultrastructural changes, upregulated RhoA/Rho-kinase pathway, and NO-dependent selective nitrenergic nerve degeneration (Figure 1) [8–11, 13, 14, 16, 18–21, 24, 26–28, 30, 31, 33–36, 38–42, 44–46, 51].

2.1 AGEs

AGEs develop in diabetics secondary to hyperglycemia. AGEs are the products of non-enzymatic reactions between glucose and lipids, proteins or nucleic acids [7]. Glucose reacts with the amino groups of proteins, resulting in Schiff bases. These bases undergo a reversible reaction to form more stable Amadori products. Some

of these glycosylation products undergo further chemical modifications and ultimately become irreversible glycosylation end-products, termed AGEs [7, 8].

AGEs form covalent bonds with vascular collagen, which leads to vascular thickening, decreased elasticity, endothelial dysfunction and atherosclerosis [9, 10]. AGEs accumulate in aging and diabetic tissues, and form at an accelerated rate when glucose is elevated [9, 11]. AGEs are elevated in rat and human diabetic corpus cavernosal tissue [7, 11]. Studies have shown impaired smooth muscle relaxation in the corpus cavernosum and ED in diabetic rat penises in the presence of AGEs [7, 12]. AGEs decrease compliance in the corpus cavernosum and impair smooth muscle relaxation by generating free radicals or reactive oxygen species (ROS) that react with NO [7]. ROS and superoxide anion have been shown to be elevated in diabetic rat penises. Additionally, superoxide dismutase (an enzyme that accelerates the breakdown of superoxide anion) activity was not increased in these diabetic rat penises [13]. The product of the reaction of ROS and NO is peroxynitrite, which does not elicit smooth muscle relaxation, and it might be involved

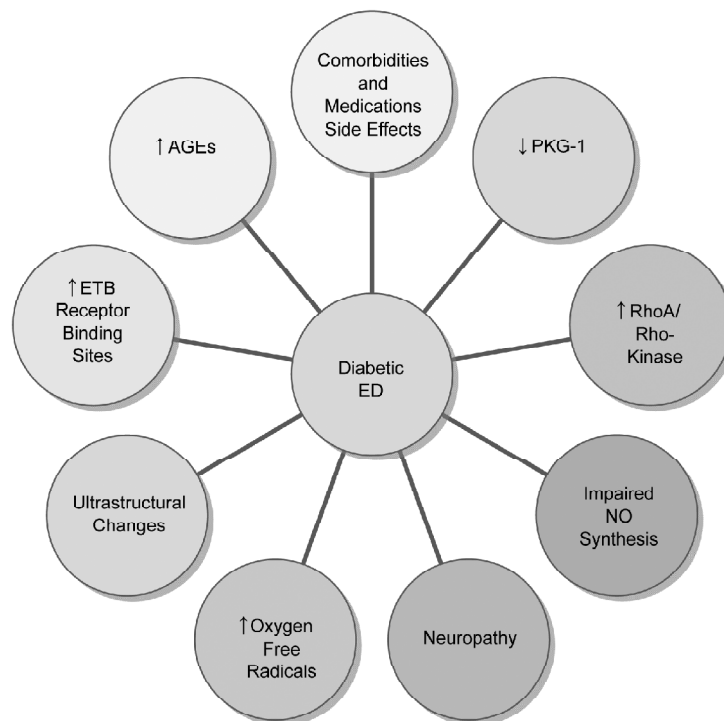


Figure 1. Mechanisms contributing to diabetic erectile dysfunction (ED). AGEs, advanced glycation end-products; ETB, endothelin B; NO, nitric oxide; PKG-1, cyclic guanosine monophosphate (cGMP)-dependent kinase-1.

in peroxide-induced cell damage and death [7]. AGEs might contribute to diabetic ED by generating oxygen free radicals, which induce oxidative cell damage and quench NO, culminating in decreased cGMP and impaired cavernosal smooth muscle relaxation [7, 13,14].

2.2 NO

NO is produced by the endothelium of the arteries of the penis and nitrenergic neurons utilizing endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS), respectively. NO mediates relaxation of the corpus cavernosum by the formation of cGMP [15–17]. Studies have shown a reduction in eNOS- and nNOS-mediated cavernosal smooth muscle relaxation in diabetic animals [18–20]. Research has shown that corpus cavernosum relaxation might be primarily mediated by nNOS activity in the nitrenergic neurons of the penis [7, 16, 19, 21–23]. Investigation has shown a reduction in nNOS activity in diabetic rats [24]. Additionally, a decrease in NOS activity in human penile tissue isolated from patients with diabetic ED has been shown [17]. It is also hypothesized that diabetes impairs the activity of guanylyl cyclase, thereby decreasing the production of cGMP [11]. Furthermore, stimulators of guanylyl cyclase have been shown to improve endothelial and neuronal functions in corpora cavernosa in diabetic mice [25]. Thus decreased NO and its effector molecule, cGMP, participate significantly in the development of diabetic induced ED.

2.3 PKG-1

cGMP causes cavernosal smooth muscle relaxation primarily through PKG-1, which alters intracellular calcium levels and opens calcium-dependent potassium channels leading to hyperpolarization of smooth muscle cells [26, 27]. PKG-1 exists in two isoforms: α and β . PKG-1 α has a higher affinity for cGMP and is highly expressed in the Purkinje cell of the cerebellum, platelets, lung and smooth muscle cells, whereas, PKG-1 β is primarily expressed in smooth muscle cells and has a lesser affinity for cGMP [27]. Studies have illustrated that PKG-1 knock-out mice have impaired cavernosal smooth muscle relaxation in response to neuronal and endothelial NO [28]. Further, *in vitro* studies have shown that both isoforms of PKG-1 protect cGMP from hydrolysis, albeit PKG-1 α protected cGMP from hydrolysis more effectively than PKG-1 β [29]. In diabetic rabbit corpus cavernosum, both isoforms of PKG-1 were significantly reduced (PKG-1 α was de-

creased more than PKG-1 β) as detected by decreased mRNA and protein using reverse transcriptase-polymerase chain reaction (RT-PCR) and Western blot analysis, respectively. In addition, immunofluorescence showed decreased PKG-1 in corporal cavernosal smooth muscle cells of diabetic rabbits. Furthermore, *in vitro* experiments showed a decrease in PKG-1 activity in the corporal cavernosum of diabetic rabbits as compared with normal rabbits [27]. The quantitative and qualitative decrease in PKG-1 might augment diabetic ED by diminished activity of the cGMP intracellular pathway.

2.4 ETB receptor and ultrastructural changes

There is evidence to suggest that ED in diabetics is linked to an imbalance toward increased penile vasoconstriction as the result of endothelin (ET) and its receptors, and ultrastructural changes in the endothelium. ET is a constrictor of vascular and non-vascular smooth muscle. ET has three isopeptides (1, 2, and 3) and two G protein coupled receptors (ETA and ETB). ET-1 is produced by the vascular endothelium and is a potent vasoconstrictor in the penis [26, 30, 31]. ET-1 has been shown to be elevated in the plasma of diabetic patients [32]. ETA receptors are located on smooth muscle and mediate vasoconstriction and cellular proliferation. ETB receptors are located predominantly on vascular endothelium, where they mediate vasodilation through the production of NO and prostacyclin [26, 33]. ETB receptors have also been shown to mediate vasoconstriction in the coronary arteries of canines and the mammary arteries of humans [34, 35]. The ETB receptors have been shown to be upregulated in the corpus cavernosum of diabetic rabbits. Although the effect of the ETB receptors in cavernosal tissue has not been fully characterized, it is hypothesized that ETB receptors in cavernosal tissue have a vasoconstricting role. Thus, the elevation of the ETB receptor and its ligand might cause the penile vasculature to have an imbalance toward vasoconstriction [33]. Furthermore, the promitogenic effects of the ETB receptor coupled with the upregulation of the receptor in diabetic cavernosal tissue, are believed to account for an early ultrastructural change of atherosclerotic-like lesions in diabetics [33]. Additionally, it has been shown that the tunica albuginea from diabetic rats is diminished and irregularly arranged. The structural alteration in the tunica albuginea is hypothesized to contribute to diabetic ED by impairing the veno-occlusive function of the penis [36].

2.5 RhoA/Rho-kinase

Recent research has shown that the transduction pathway for the ET and its receptor might play a role in diabetic ED. The pathway is composed of a GTP-binding protein, RhoA, and its effector agent, Rho-kinase. ET-1 induced vasoconstriction has been shown to be linked to the RhoA/Rho-kinase pathway [37–39]. The activation of the pathway suppresses eNOS, decreasing the production of NO [40]. Rho-kinase is present in rat, rabbit, and human cavernosal tissue, and it has been shown to be upregulated in diabetic rats. It is proposed that the RhoA/Rho-kinase pathway mediates ED through decreased production of NO in the penis [41–43].

2.6 Neuropathy

Neurologic testing has shown that diabetics with ED have abnormal nerve conduction, sphincter electromyography and vibratory testing more commonly than diabetics without ED [44, 45]. Further, patients with diabetic and neuropathic ED have been noted to have similar frequencies of somatic and autonomic neuropathies, suggesting that neuropathy contributes significantly to diabetic ED [45]. A recent study has elaborated on the connection between diabetic and neuropathic ED, showing that apoptotic pathways are present in the cavernous nerves in both disease processes [46]. The underlying etiology of ED that is the result of diabetic neuropathy might be linked to selective nitrenergic degeneration in diabetics, which has been seen in diabetic rat penises [16]. This selective neurodegeneration appears to result in decreased nNOS activity and diminished NO production, resulting in impaired nitrenergic relaxations in the corpus cavernosum of diabetics [16, 19, 21]. Additionally, NO might play a role in the selective nitrenergic degeneration through the formation of oxygen free radicals. It has been proposed that oxidative damage secondary to the production of peroxynitrite from NO might contribute to the neurodegeneration [7, 16]. Studies have shown that inhibition of NO synthase and the production of NO prevents nitrenergic degeneration, suggesting that this is a NO-dependent process. Furthermore, a blunted effect on the neuropathy seen in the noradrenergic neurons has been appreciated. The impairment in vasodilatory neurons versus the unaltered sympathetic neurons could contribute to a basal vasoconstricting tone in the penises of diabetics [16].

3 Treatment

The treatment of diabetic ED is multimodal. Treatment of the underlying hyperglycemia and comorbidities is of utmost importance to prevent or halt the progression of the abnormalities noted above. As evidenced by the British cross-sectional study, glycemic control correlated inversely with impotence [47]. Additionally, the choice of medications with the least adverse impact on erectile function to treat the patient's comorbidities should be sought (e.g. antihypertensives and antidepressants).

The cardiovascular system of all patients should be assessed prior to the initiation of any treatment for ED. According to the Second Princeton Consensus Conference (June 11–12, 2004, Princeton, NJ, USA), patients with ED and cardiovascular disease are assigned to one of three risk levels based on their cardiovascular risk factors (age, being male, hypertension, diabetes mellitus, smoking, dyslipidemia, sedentary lifestyle and family history of premature coronary artery disease). The panel recommends that high-risk patients should not receive the treatment for sexual dysfunction until their cardiac condition stabilizes or a decision by a cardiologist and/or internist that sexual activity can be safely resumed, intermediate-risk patients should have an evaluation by a cardiologist prior to the treatment for their sexual dysfunction, and low-risk patients can be considered for all first-line therapies [48]. After addressing the above offending factors on erectile function, one might consider additional medical and surgical treatment of ED.

3.1 Phosphodiesterase inhibitors

The peripherally acting oral phosphodiesterase type 5 (PDE5) inhibitors are the mainstay of oral medical treatment of ED in diabetics. At the present time, this class of agents consists of sildenafil, vardenafil and tadalafil. These agents inhibit PDE5, the primary phosphodiesterase in cavernosal tissue responsible for the degradation of cGMP [49, 50]. During sexual stimulation, NO activates guanylate cyclase, which catalyzes guanosine triphosphate to cGMP. Cyclic GMP activates serine protein kinases, which then phosphorylates proteins and ion channels, leading to the opening of potassium channels, hyperpolarization of muscle cell membranes, sequestration of intracellular calcium within the endoplasmic reticulum and the blocking of calcium influx by the inhibition of calcium channels; culminating in a decrease in cytosolic calcium concentration and the relaxation of smooth

muscle [51]. Thus, by inhibiting PDE5, there is a prolonged level of cGMP and improved smooth muscle relaxation.

Sildenafil has been noted to improve erections and attempts at successful intercourse in patients with diabetic ED. In a study comparing sildenafil versus placebo in type 1 diabetics, there were significant improvements from baseline in the ability to achieve erections [International Index of Erectile Function question number 3 (IIEF Q3)] (35.7% vs. 19.9%), ability to maintain erections (IIEF Q4) (68.4% vs. 26.5%), improved erections with treatment [Global Assessment Question (GAQ)] (66.6% vs. 28.6%), and successful attempts at intercourse (patient event log) (63% vs. 33%) [52]. Safarinejad also compared sildenafil to placebo in diabetic men and noted significant improvements from baseline in IIEF Q3 (55% vs. 29%) and IIEF Q4 (61% vs. 25%) [53]. The exemplary study by Rendell *et al.* was a 12-week randomized controlled trial in diabetics. Sildenafil versus placebo showed significant improvements from baseline in IIEF Q3 (78% vs. 25%) and IIEF Q4 (93% vs. 14%). Sixty-one percent of the sildenafil-treated patients versus 22% of the placebo group reported at least one successful attempt at intercourse (patient event log) [54].

Vardenafil was evaluated in a double-blind, placebo-controlled study in diabetics. Eighty-eight percent of the participants had type 2 diabetes mellitus. Demographics and baseline characteristics were similar among the groups. Patients who had previously taken sildenafil were included in the study, except those who had discontinued sildenafil as the result of significant side-effects or a lack of efficacy. The baseline erectile function (EF) domain of IIEF score was 11.2, and it increased to 19.0 (69.6%), 17.1 (52.7%) and 12.6 (12.5%) for vardenafil 20 mg, vardenafil 10mg and placebo, respectively. The GAQ (Has the treatment improved your erections?) was 72% for vardenafil 20 mg, 57% for vardenafil 10 mg, and 13% for placebo. According to the Sexual Encounter Profile (SEP) question number 3 (Did your erection last long enough for you to have successful intercourse?), 54% vs. 23% of the patients were able to maintain an erection for sufficient time to complete intercourse with vardenafil 20 mg versus placebo, respectively. Furthermore, evaluation of patients based on severity of ED showed that patients with severe ED (EF score < 11) had a 40% rate of successful intercourse with vardenafil 20 mg versus 11% for placebo and patients with mild ED (EF score 22–25) had a 75%

success rate with vardenafil 20 mg versus 47% for placebo. In conclusion, increases in IIEF score, in men reporting improved erections, and successful intercourse rates were significant [55].

In a retrospective analysis from 12 placebo-controlled trials evaluating tadalafil, the mean patient age was 57 years and 56 years and body mass index (BMI) was 28.1 kg/m² and 27.2 kg/m² for the diabetic group versus the non-diabetic group, respectively. Hypertension, hyperlipidemia and coronary artery disease were more common in the diabetic group. The mean baseline IIEF domains and baseline ED severity were similar in the diabetic versus the non-diabetic groups. Sildenafil non-responders were excluded from most studies. Patients with diabetes had a baseline of 12.6 for the EF domain of IIEF. Tadalafil 10 mg and 20 mg treatment resulted in an increase in the IIEF EF domain score of 6.2 and 7.4, respectively, versus 0.9 for placebo. The GAQ was 60.6% for tadalafil 10 mg, 74.5% for 20 mg and 29.7% for placebo, respectively. There was a 30%, 37% and 4% increase from baseline in intercourse completion for tadalafil 10 mg, 20 mg, and placebo, respectively, based on SEP3. Notably, the study showed that tadalafil treatment resulted in significant improvements of successful intercourse from 0.5 to 36 hours from the original dose for tadalafil 20 mg (50–63%) and 10 mg (45–61%) vs. placebo (22–30%) [56].

Overall, the phosphodiesterase inhibitors are well tolerated and boast good efficacy. However, special mention is made to the contraindication of PDE5 inhibitors and co-administration with nitrates. NO causes vasodilation through the production of cGMP and PDE5 inhibitors inhibit the breakdown of cGMP, thus there is the possible synergistic effect of the two agents, resulting in hypotension [57].

3.2 Vacuum erection device

Vacuum erection devices are an additional treatment for diabetic-induced ED. The device consists of a cylinder chamber with an opening at one end and a pumping mechanism at the other end (manual or battery pump). The base of the penis is lubricated and the pump is placed over the penis creating a tight seal against the base of the penis. The pump is activated, and it creates negative pressure (200–250 mmHg) within the pump, resulting in blood filling the corporal bodies of the penis. After penile engorgement, a tension ring is placed at the base of the penis to trap the blood in the corporal bodies. The pump is removed and an erection is maintained. The

constriction ring should remain in place no longer than 30 min. There are no specific conditions that are contraindicated with the use of vacuum erection devices. However, the devices should be used with caution in patients using blood thinners or who have a history of bleeding disorders, diminished penile sensation, significant penile curvature, priapism or risk factors for developing priapism. The use of the device might be associated with a decrease in penile temperature (1°C), superficial vein swelling and penile bruising/trauma. Further, the cosmetics of its use and incorporating the use of the device might limit patient satisfaction with the application of the device [58]. Vacuum erection devices achieve satisfactory erections in more than 70% of diabetic men, however, up to 30% of patients discontinue use as the result of inadequate rigidity, penile pain, failure to ejaculate and appearance of the penis while using the device [59, 60].

3.3 Intraurethral suppository

Alprostadil urethral suppository (Muse™) is prostaglandin E₁ (PGE₁). The proposed mechanism of action is that intraurethral alprostadil is absorbed by the urethra and transported to the corpus cavernosum, whereby it causes vasodilation and relaxes smooth muscle through the interaction of it with a prostacyclin receptor. In a double-blind study of 1511 men, the efficacy of transurethral alprostadil was evaluated. Alprostadil produced successful intercourse at least once in 64.9% vs. 18.6% of patients receiving placebo. The efficacy of alprostadil was similar regardless of the etiology of ED [61]. The open-label study showed 69% of the patients randomized to transurethral alprostadil had intercourse at least once during the 3-month home therapy compared with 11% of the patients receiving placebo. Only 18% of the patients in the home therapy group had diabetic ED, of whom, 46% of the patients with diabetes achieved intercourse at least once in the 3-month interval compared with 1% of patients receiving placebo [62].

3.4.1 Intracavernosal injection

The most common injectable agents for ED include papaverine, phentolamine and PGE₁. They can be used alone or in combination. Papaverine is a non-specific PDE inhibitor resulting in increased levels of cyclic adenosine monophosphate (cAMP) and/or cGMP, inhibition of calcium channels, and angiotensin-II secretion. The ultimate effect is vasodilation of penile vasculature

and smooth muscle relaxation with erection [63, 64]. Phentolamine is a competitive antagonist of α_1 and α_2 adrenoreceptors. Antagonism of the α_1 receptors results in vasodilation of the penile vasculature and antagonism of the pre-synaptic α_2 receptors is hypothesized to result in decreased intracorporeal norepinephrine [63, 65]. PGE₁ stimulates adenylate cyclase increasing the level of cAMP, resulting in smooth muscle relaxation, vasodilation and inhibition of platelet aggregation [65]. In an open-label study evaluating the efficacy of PGE₁ monotherapy for the treatment of diabetic ED, 83% of patients entered home therapy phase and had data available for evaluation. Ninety-nine percent of injection-induced erections were rigid enough for intercourse [66]. Intracavernosal injections have been shown to be an effective long-term treatment modality for diabetic ED regardless of the type of diabetes. During the 10-year follow-up, type 1 and 2 diabetics used a similar number of injections and combinations of intracavernosal medications for the treatment of their ED. Interestingly, insulin dependent diabetics progressed more quickly to the final standardization treatment than non-insulin dependent diabetics, possibly owing to their familiarity with self-injections and willingness to utilize intracavernosal injection therapy. Also, during the 10-year follow-up of intracavernosal injection therapy, both types of diabetics required larger doses of medications and multidrug therapy to achieve satisfactory erections [67]. Current recommendations for intracavernosal injections are an initial trial of alprostadil monotherapy, if this fails or pain at the injection site limits patient satisfaction, a trial of a combination of papaverine/phentolamine or a combination of all three agents should be tried in an effort to reduce the individual dosage and minimize adverse effects [65]. The incidence of priapism and cavernosal fibrosis among various intracavernosal treatments are summarized in Table 1. It is noted that both side-effects occur with a higher incidence in the papaverine and papaverine/phentolamine groups versus the PGE₁ and papaverine/phentolamine/PGE₁ groups. Further, the incidence of priapism is greater in the test dose versus that in the home dose, which is typical of the increased incidence of priapism occurring during the titration phase as reported in other studies [68, 69]. Additionally, it has been shown that diabetics have an increased incidence of penile fibrosis, possibly owing to their microangiopathic disease and increased propensity for fibrosis [69].

Intracavernosal injection therapy for ED is plagued

Table 1. Comparison of priapism and cavernous fibrosis occurring with the use of intracavernosal injection agents for erectile dysfunction (ED). PGE₁, prostaglandin E₁.

Agent (s)	Priapism (%)	Fibrosis (%)
Papaverine [68]	7.1	5.7
Papaverine [69]	10 (Test dose) 3.3 (Home therapy)	15.2 (Clinically and ultrasound)
Papaverine/Phentolamine combination [68]	7.8	12.4
PGE ₁ [68]	0.36	0.8
PGE ₁ [69]	0 (Test dose and home therapy)	0 (Clinically) 1.7 (Ultrasound)
Papaverine/Phentolamine/PGE ₁ [69]	1.88 (Test dose and home therapy)	3.77 (Clinically) 5.66 (Ultrasound)

with high dropout rates. Various studies have shown that between 46–76% of people discontinue its use due to various reasons, such as lack of efficacy, occurrence of side-effects and the requirement for penile injections [70, 71].

3.5 Penile prosthesis

Penile implants are suitable for patients with ED when pharmacologic therapy fails or is contraindicated and/or patients do not tolerate vacuum erection devices. Approximately 15% of patients seeking treatment for ED have irreversible damage of the erectile mechanism and are candidates for penile prosthesis implantation [72]. Penile implants are generally classified into two different types; malleable (or non-inflatable) and inflatable. The inflatable implant offers the patient the ability to achieve near normal erection and flaccidity [73]. Two recent surveys evaluated patient satisfaction with their implantable prosthesis. The surveys included patients with malleable and inflatable implants. Overall satisfaction with penile prosthesis was 69–81% [74, 75]. Ninety-five percent of the patients would recommend similar therapy to others [76]. Malleable implants should be avoided in diabetics secondary to their increased risk of erosion [73]. Studies have documented a 2–10% incidence of penile prosthetic infection in diabetics, but there was no significant difference between diabetics and non-diabetics [77, 78]. Historically, glycosylated hemoglobin greater than 11.5% was considered a contraindication to implantation [77, 79]. However, prospective and retrospective analyses of penile implants in diabetics have failed to find an increase in the infection rates of penile implants in diabetics with elevated glycosylated hemoglobins [77, 80]. In light of these conflicting findings between diabetics and increased risk of penile prosthetic infections, the

practitioner must assess each patient on an individual basis until conclusive data is reached.

3.6 Future treatments

Future strategies in the evolution of the treatment of ED are aimed at correcting or treating the underlying mechanisms involved in diabetic ED. Various targets of investigation include gene therapy with neurotrophic factors, eNOS, nNOS and superoxide dismutase. Through the use of an appropriate vector, researchers have been able to transfect diabetic animals with these agents. Injections into the cavernous sheath of diabetic rats with neurotrophin-3 (NT3) using the herpes simplex virus as the vector have been carried out. Immunoreactive stains showed a significant increase in nNOS neurons in the major pelvic ganglia and electrical stimulation of the cavernosal nerves resulted in a significant increase in the intracavernosal pressure [81]. Diabetic rats have also been injected in their corpus cavernosum with adenoviruses containing eNOS. Stimulation of the cavernous nerve in these animals resulted in increased intracavernosal pressures. Also, there was an increase in eNOS, as measured by western blot analysis and an increase in NOS biosynthesis, as measured by an increase in cavernous nitrate and nitrite formation [82]. Additionally, intracavernosal injection of adenoviruses containing superoxide dismutase into diabetic rats resulted in a decrease in superoxide anion levels, increase in NO bioavailability, increase in cGMP levels and increase in intracavernosal pressure [13]. Diabetic rats have been transfected with intracavernosal injections of *hSlo* (calcium-sensitive potassium channel), resulting in increased intracavernosal pressures after cavernosal nerve stimulation, as compared with controls. It is hypothesized that there might be a diabetes-induced alteration in these potassium channels and by utilizing gene

therapy, the molecular events of these channels might be normalized, thus improving erections in diabetic patients [83].

3.7 Other treatment modalities

Current American Urologic Association guidelines do not recommend the use of testosterone for the treatment of ED in men with normal serum testosterone, nor the use of trazodone, yohimbine or herbal remedies [84].

4 Conclusion

ED affects between 32% and 46% of people with diabetes [2]. The pathophysiology of diabetes is multifactorial and no single etiology is at the forefront. Treatment ranging from medical management to surgical implantation of a penile prosthesis is the standard at this time. Gene therapy using vectors appears to offer interesting and novel approaches to the treatment of the underlying pathophysiology of diabetic ED. However, further study in gene therapy is needed to fully ascertain its safety and utility in humans.

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