Diabetes-induced erectile dysfunction: epidemiology, pathophysiology and management

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Abstract

Erectile dysfunction (ED) is defined as the inability of the male to attain and maintain erection of penis sufficient to permit satisfactory sexual intercourse. Prevalence of impotence in diabetic men is ≥50%. The pathophysiology of diabetes-induced erectile dysfunction (DIED) is multifactorial and no single etiology is at the forefront. The proposed mechanisms of erectile dysfunction in diabetic patients includes elevated advanced glycation end-products, increased levels of oxygen free radicals, impaired nitric oxide synthesis, increased endothelin B receptor binding sites and up-regulated RhoA/Rho-kinase pathway, neuropathic damage and impaired cyclic guanosine monophosphate (cGMP)-dependent protein kinase-1. The treatment of DIED is multimodal. Treatment of the underlying hyperglycemia and comorbidities is of utmost importance to prevent or halt the progression of disease. Oral medications are considered as the first line therapy for management of DIED. If oral agents cannot be used or have insufficient efficacy despite appropriate dosing and education, second-line treatments should be addressed. When there is lack of efficacy or when there is dissatisfaction with other modalities, penile prostheses are often the best alternative for ED and are considered as the third line therapy for DIED. Future strategies in the evolution of the treatment of DIED are aimed at correcting or treating the underlying mechanisms of DIED.

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1. Introduction

Diabetes mellitus is categorized as a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. As a result, the amount of glucose in the blood increases while the cells are starved of energy (Kumar, Cotran, & Robbins, 2004). It is predicted that by 2030, India, China and the United States will have the largest number of people with diabetes (Wild, Roglic, Green, Sicree, & King, 2004).

Sustained higher levels of blood glucose cause damage to nerves and blood vessels, leading to complications such as heart disease and stroke, the leading causes of death among people with diabetes. Uncontrolled diabetes can eventually lead to other health problems as well, such as vision loss, nephropathy, neuropathy and sexual dysfunction. Uncontrolled high blood glucose level for long time may develop depression, foot or leg amputation and skin complications (Haslett et al., 2002).

Impotency in males, which is also referred as erectile dysfunction (ED), is defined as the inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual intercourse. Normal penile erection is a hemodynamic process that is dependent upon corporal smooth muscle relaxation mediated by parasympathetic neurotransmission, nitric oxide (NO), electrophysiologic events and possibly other regulatory factors (Arie et al., 2003).

An association between diabetes mellitus (DM) and the development of erectile dysfunction has been documented in
the literature since 1798 (McCulloch, Campbell, Wu, Prescott, & Clarke, 1980). Generally 25–75% of men with Type 2 diabetes complain of erectile dysfunction (Klein, Klein, Lee, Moss, & Cruickshanks, 1996). In numerous epidemiological studies the odds ratio of having erectile dysfunction if a man is diabetic is 1.9–4 times greater than a population without diabetes, making diabetes one of the greatest risk factors for erectile dysfunction (Lewis, 1996).

2. Significance of sexual health

Sexuality is an integral part of a human life and well-being. Sexuality in health and illness includes a wide spectrum of excitations and activities, which are a source of different drives, affects impulses like pleasure, anxiety, feelings of shame, disgust, etc., throughout the lifespan (Laumann, Paik, & Rosen, 1999). Proper sexual functioning is one of the most important components of quality of life and of maintaining a satisfying intimate relationship (Rosen et al., 2000). When sexual health encounters a problem and if not addressed well, it can lead to psychological trauma, frustration and may even heighten the already existing problem thus lowering the self-esteem. A healthy sexuality requires balance of physical, psychological and social factors and an imbalance in one or more of these factors can result in a sexual dysfunction (Kwan, Lindy, & Delphin, 2005).

3. Epidemiology of DIED

The increasing worldwide incidence of DM in adults constitutes a global public health burden (Fig. 1) (Hilary, Ronald, & William 1998). ED is a worldwide problem as its prevalence is projected to increase in all continents (Fig. 2) (Ayta, McKinlay, & Krane, 1999).

ED has been reported to occur in ≥50% of men with DM worldwide. It is usually present within 10 years of diagnosis of DM. The incidence of ED was reported to be higher in men with DM than for men without DM and up to 12% of men who present with ED were found to have previously undiagnosed DM (Johannes et al., 2000). ED occurs at a younger age in men with Type 1 DM than in the general population and the incidence of insulin resistance is three times higher in men with ED (Guay & Jacobson, 2007). In the Health Professionals Follow-Up Study cohort reported by Bacon et al. (2002) men with DM had an age-adjusted relative risk (RR) of 1.32 (95% crude incidence (CI), 1.3–1.4) for having ED compared with their non diabetic counterparts. Men with type 1 DM were at a significantly higher risk for ED (RR, 3.0; 95% CI, 1.5–5.9) compared with men with type 2 DM (RR, 1.3; 95% CI, 1.1–1.5). Furthermore, men with Type 2 DM had an increasingly greater risk of ED with increased duration since diagnosis, particularly for men whose DM was diagnosed >20 years previously.

The RR for ED in men with DM increases with coexisting cardiovascular disease, renal disease, diabetic foot and retinal disease (Fedele et al., 2000). In addition to ED, the presence of DM at baseline was significantly associated with all aspects of sexual dysfunction, including sexual drive, ejaculatory function and sexual satisfaction (Burke et al., 2007).

4. Pathophysiology of DIED

The pathophysiology of diabetic impotency is multifactorial and no single etiology is at the forefront. Following are the proposed mechanisms of ED in diabetic patients (Moore & Run, 2006).

4.1. Advanced glycation end-products (AGEs) and increased levels of oxygen free radicals

Hyperglycemia in diabetes will lead to the formation of AGEs. AGEs are the products of non-enzymatic reactions between glucose and lipids, proteins or nucleic acids (Cartledge, Eardley, & Morrison, 2001). AGEs form covalent bonds with vascular collagen, which leads to vascular thickening, decreased elasticity, endothelial dysfunction and atherosclerosis (Singh, Barden, Mori, & Beilin, 2001). AGE products had higher levels in corpus cavernosum of diabetic patients, suggesting a tissue-specific effect of the AGEs (Giuseppe, Ferdinando, Ciro, & Vincenzo, 2006). AGEs might contribute to diabetic ED by generating oxygen free radicals, which induce oxidative cell damage and quench NO, culminating in decreased cyclic guanosine monophosphate (cGMP) and impaired cavernosal smooth muscle relaxation. AGEs may have an effect at the molecular level on several different channels and receptors on the cavernosal smooth muscle cell, particularly on the potassium channels, which facilitate intracellular calcium release and subsequent cavernosal smooth muscle relaxation. Early damage to potassium channels may lead to the early onset of DIED (Cartledge et al., 2001; Costabile, 2003).

4.2. Impaired NO synthesis

NO is produced by the endothelium of the arteries of the penis and nitricergic neurons utilizing endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase, respectively. NO mediates relaxation of the corpus cavernosum by the formation of cGMP (Cellek et al., 1999). Superoxide radicals are present in higher amounts in cavernosal tissue and levels of NO synthase are decreased in men with DIED, suggesting another possible pathways leading to smooth muscle and cavernosal dysfunction (Christ, Gondrel, Melman, Gradwood, & Murray, 1995). It is also hypothesized that diabetes impairs the activity of guanylyl cyclase, thereby decreasing the production of cGMP. Furthermore, endothelial dysfunction rapidly renders the functional syncytium of the corpora cavernosa ineffective (Costabile, 2003). Thus, decreased NO and its effectors
molecule, cGMP, participate significantly in the development of DIED.

4.3. Increased endothelin and endothelin-B receptor binding sites

Endothelins (ETs) are a family of endogenous peptides having three isopeptides (Moore & Run, 2006), mainly secreted by endothelial cells, which exert a potent vasoconstrictor and pressor activity, acting through two classes of receptors named ETA and ETB (Giuseppe et al., 2006). There is evidence to suggest that ED in diabetics is linked to an imbalance toward increased penile vasoconstriction as the result of endothelin and its receptors and ultrastructural changes in the endothelium. ET-1 is a potent vasoconstrictor in the penis (Mills, Pollock, Lewis, Branam, & Wingard, 2001), and it has been shown to be elevated in the plasma of diabetic patients (Takahashi, Ghatel, Lam, O’Halloran, & Bloom, 1990). ETA receptors are located on smooth muscle and mediate vasoconstriction and cellular proliferation. ETB

Fig. 1. Diabetes: a global public health burden (Hilary et al., 1998).

Fig. 2. Worldwide projected increase in prevalence of erectile dysfunction by year 2025 (Aytta et al., 1999).
receptors are located predominantly on vascular endothelium, where they mediate vasodilation (Sullivan et al., 1997). ETB receptors have also been shown to mediate vasoconstriction in the coronary arteries of canines and the mammary arteries of humans (Clozel, Gray, Breu, Loffler, & Osterwalder, 1992). The ETB receptors have been shown to be up-regulated 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 ETB receptor and its ligand might cause the penile vasoconstriction (Sullivan et al., 1997).

4.4. Up-regulated RhoA/Rho-kinase pathway

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 (Park et al., 2002; Wang, Eto, Steers, Somlyo, & Somlyo, 2002). The activation of pathway suppresses eNOS, decreasing the production of NO (Ming et al., 2002). Rho-kinase is present in rat, rabbit and human cavernosal tissue, and it has been shown to be up-regulated in diabetic rats. It is proposed that the RhoA/Rho kinase pathway mediates ED through decreased production of NO in the penis (Bivalacqua et al., 2004; Rees et al., 2002).

4.5. Neuropathic damage

Neuropathic damage is another important mechanism that causes DIED (Costabile, 2003). Diabetes is notorious for its microvascular complications particularly autonomic neuropathy and peripheral neuropathy (Agarwal, Prakash, & Singh, 2003). Extensive literature points to early somatic and autonomic nerve dysfunction in diabetic patients documented by longer latencies in the evoked potentials of pudendal nerves and in abnormal bulb urethral and urethral reflexes (Vernet et al., 1995). This neuropathic pathway also appears to occur early in the mechanism of DIED. A central neuropathic mechanism may also contribute to the neuropathy associated with DIED (Costabile, 2003).

4.6. Impaired cGMP-dependent protein kinase-1 (PKG-1)

The 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 (Chang et al., 2004). Studies have illustrated that PKG-1 have impaired cavernosal smooth muscle relaxation in response to neuronal and endothelial NO (Hedlund et al., 2000). Further, in vitro studies have shown that both isoforms of PKG-1 protect cGMP from hydrolysis, albeit PKG-1α protected cGMP from hydrolysis more effectively than PKG-1β (Kotera, Grimes, Corbin, & Francis, 2003). In diabetic rabbit, corpus cavernosum, both isoforms of PKG-1 were significantly reduced. This proves the role of PKG1 in DIED (Chang et al., 2004).

5. The therapeutic approach and strategies for the management of DIED

Despite considerable progress, the treatment of erectile dysfunction is often difficult due to its multifactorial etiology. Consequently, a global approach, requiring not one but several treatment modalities is needed for management of ED, instead of an approach localized to the organ. Oral medications are considered as the first line therapy for the management of DIED (Gerald, 2002). If oral agents cannot be used or have insufficient efficacy despite appropriate dosing and education, second-line treatments should be addressed which include vacuum erection devices, transurethral suppositories and intracavernous injection therapy. When there is lack of efficacy or when there is dissatisfaction with other modalities, penile prostheses are often the best alternative for ED and is considered as the third line therapy for DIED (William, Anthony, & Tom, 2007).

5.1. General measures

The first step in the treatment of ED is to correct the modifiable risk factors for atherosclerotic vascular disease. Glycemic control should be optimized with oral anti-diabetic drugs or insulin while the blood pressure and lipid levels should be normalized with appropriate medications. Patient should be encouraged to quit smoking, to reduce their alcohol intake and to give up recreational drugs. Prescription drugs and over the-counter medications should be checked for possible contributors to ED. Effort should be made to avoid or to find substitutes for drugs with negative impact of sexual function (Atul & Anoop, 2008). Relationship counseling and psychiatric medications is useful to treat anxiety and depression (Hartman, 1998).

5.2. Medical therapy

5.2.1. Oral agents

5.2.1.1. Phosphodiesterase inhibitors. The peripherally acting oral phosphodiesterase type 5 currently considered first-line treatment by most physicians (Konstantinos & Dimitrios, 2009). PDE5 inhibitors have no direct relaxant effect on isolated human corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 causes increased levels of cGMP in the corpus cavernosum as the primary phosphodiesterase in cavernosal tissue is responsible for the degradation of cGMP (Wallis, Corbin, Francis, & Ellis, 1999). The cGMP is responsible for
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 (Beavo, 1995). Thus, by inhibiting PDE5, there is a prolonged level of cGMP and improved smooth muscle relaxation. Sildenafil, vardenafil and tadalfal are the drugs of this class which are used in the clinical practice. Sildenafil has been noted to improve erections and attempts at successful intercourse in patients with diabetic ED (Moore & Run, 2006). Common side-effects of drugs from this class include headache, flushing, dyspepsia, nasal congestion, abnormal vision and diarrhoea. Patients should take medicine 1–2 h before sexual activity. Most men with diabetes require sildenafil up titration to 100 mg for an effective response, but dose needs to be reduced in hepatic and renal impairment. Though reports of myocardial infarction and sudden cardiac death exist in men taking sildenafil for ED, evidence suggests that it is safe, effective and well tolerated in coronary aterial diseases. However, nitrates should be withdrawn before sildenafil initiation, since it may potentiate vasodilatation and hypotension (Agarwal et al., 2003).

5.2.1.2. Dopamine agonists. Apomorphine is a short-acting dopamine agonist known to cause erection (Heaton, Adams, & Morales, 1996). Sublingual apomorphine enhances central proerectile mechanisms by binding to dopamine receptors in the paraventricular nucleus of the hypotalamus. Apomorphine was found to be effective in patients with ED of various etiologies and levels of severity, albeit with substantially less efficacy than any of the PDE5 inhibitors (Heaton, 2001). The adverse events reported most frequently during clinical trials with sublingual apomorphine were nausea, headache and dizziness. The sublingual formulation of this drug permits rapid absorption and a rapid onset of action, with an average median time of 16–23 min after dosing to attain an erection with sexual stimulation (Heaton, 2001; Mulhall, Bukofzer, Edmonds, George, & the Apomorphine SL Study Group, 2001). Overall, sublingual apomorphine meets the criteria to be a first-line treatment for ED.

5.2.1.3. α-Adrenoreceptor antagonists. The stimulation of adrenoreceptors is considered the main mechanism of cavernous smooth muscle contraction, so antagonizing antierectile mechanism with alpha-adrenergic receptor antagonists is a potential treatment for ED. Yohimbe is recommended in a dose of 5–10 mg thrice daily. It is considered to have modest efficacy in ED with positive response rates in 34–43% cases. Side-effects such as anxiety and headache have been reported to be low and mild (Agarwal et al., 2003). Phentolamine is an α₁- and α₂-adrenergic receptor antagonist. Clinical trials have demonstrated that oral phentolamine may have a beneficial effect on erectile function (Goldstein, Carson, Rosen, & Islam, 2001).

5.2.2. Intracavernosal vasoactive injections

The most common injectable agents for the treatment of ED include papaverine, phentolamine and prostaglandin (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 (Savoca, Silvestre, & Belgrano, 2002). Phentolamine is a competitive antagonist of α₁- and α₂-adrenoreceptors. Antagonism of the α₁-receptors results in vasodilatation of the penile vasculature and antagonism of the pre-synaptic α₂-receptors is hypothesized to result in decreased intracrorporeal norepinephrine (Broderick, & Lue, 2002; Savoca et al., 2002). PGE₁ stimulates adenylyl cyclase increasing the level of cAMP, resulting in smooth muscle relaxation, vasodilation and inhibition of platelet aggregation (Broderick & Lue, 2002). Intracavernosal injections have been shown to be an effective long-term treatment modality for diabetic ED regardless of the type of diabetes (Moore, & Run 2006). The adverse effects include painful penile sensation, hematoma, penile fibrotic changes and hemosiderin deposits (Agarwal et al., 2003). The incidence of side effects like priapism and cavernosal fibrosis occur with a higher incidence in the papaverine and papaverine/phentolamine groups versus the PGE₁ and papaverine/phentolamine/PGE₁ groups (Moemen, Hamed, Kamel, Shamoul, & Ghanem, 2004; Porst, 2000). Intracavernosal injection therapy for ED is plagued 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 (Hatzimouratidis & Hatzichristou, 2005).

Other intracavernosal agents including the 3′P′ solution (12 mg papaverine, 9 µg PGE₁ and 1 mg phenolamine), vasoactive intestinal peptide and phenolamine combination, chlorpromazine, moxisylylate hydrochloride, linsidomine, calcitonin gene related peptide have been used individually with variable success rates. Combination therapy is preferred because of increased efficacy and more favorable adverse effect profile (Burns & Gingell, 1998; Nraga & Braga, 1996). If an erection lasts longer than 60 min or is painful, 30 mg of pseudoephedrine may be taken orally to ensure detumescence (Agarwal et al., 2003).

5.2.3. Intracatheral suppository

PGE₁ is also available as an intracatheral suppository. The proposed mechanism of action is that intracatheral alprostadi 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 (Moore & Run, 2006). It is less
invasive and easier to use than intracavernosal injection, but it may reduce sexual spontaneity. The efficacy of alprostadil was similar regardless of the etiology of ED; side-effects include penile pain, minor urethral bleeding, testicular pain and dizziness. Complications like priapism and penile fibrosis are less common. Female partners may complain of vaginal burning or itching and it is not recommended for use with pregnant partners. PGE1 is contraindicated in men with abnormal penile anatomy and with hyperviscosity syndromes (Padma-Nathan et al., 1997).

5.2.4. Vacuum constriction devices

A vacuum erection 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 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 in the corporal bodies of the penis. After penile engorgement, a tension ring is placed at the base of the penis to trap 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. 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 (Price et al., 1991; Sidi, Becher, Zhang, & Lewis, 1990). Disadvantages include lack of spontaneity, and in a minority, the partner found it an unacceptable method (Price et al., 1991).

5.2.5. Testosterone replacement therapy

Testosterone modulates the expression of NO synthase in corpus cavernosum and the production of NO and acts on the cavernosal arterioles enhancing penile rigidity. It influences genital sensitivity and the pleasurable enhancement of erectile activity. However, if it is the confirmed cause, treatment with testosterone supplementation is rewarding (Kew-Kim, 2006). Testosterone therapy is recommended only for individuals who have low serum testosterone levels/primary gonadal deficiency. Before using testosterone, men should undergo screening for Benign prostatic hyperplasia and prostate cancer, as androgen therapies can worsen these conditions. The adverse effects of testosterone therapy (e.g., weight gain, acne, exacerbation of hypertension, gynecomastia, edema) are numerous and common. However, very few diabetics in fact require it as a treatment for ED (Agarwal et al., 2003).

5.3. Surgical therapy

Penile implants are suitable for patients with ED when pharmacologic therapy fails or are contraindicated and/or patients do not tolerate vacuum erection devices. Penile implants are generally classified into two different types: non-inflatable (or malleable) and inflatable. The inflatable implant offers the patient the ability to achieve near normal erection and flaccidity (Moncada, Martinez-Salamanca, Allona, & Hernandez, 2004). Studies have documented a 2–10% incidence of penile prosthesis infection in diabetics, but there was no significant difference between diabetics and non-diabetics (Montague, Angermeier, & Lakin, 2001). In light of these findings between diabetics and risk of penile prosthesis infections, the practitioner must assess each patient on an individual basis until conclusive data is reached.

6. Future prospects in management of DIED

Based on the more extensive knowledge and understanding of physiological mechanisms regulating male erectile function, orally delivered drugs have been established as a logical and straightforward pharmacological approach for treating male DIED. Increased public awareness in this field will undoubtedly promote the identification of new compounds that might be effective in the treatment of such sexual disorder. Due to the unending charge to conceive a first-line treatment more advanced than the previous options and with superior efficacy and safety, research efforts will continue to offer a promising future for the therapy of DIED. Although the ideal drug for treatment of DIED should somehow involve the NO/cGMP cascade, upcoming strategies will also take into account compounds modulating signal transduction mediated by cyclic adenosine monophosphate, as well as combining agents to affect multiple peripheral intracellular targets (e.g., a drug that combines PDE5 inhibitory and NO-releasing properties). Future orally delivered selective drugs will be efficacious in terms of maximizing erectile function and exert limited systemic adverse events (Christian, Stefan, & Udo, 2005). The application of gene therapy for ED represents an exciting new field. Although preclinical studies have highlighted the application of local gene therapy as a viable treatment option for ED in diverse pathologic conditions including diabetes, ageing, hypercholesterolaemia and cavernous nerve injury, this therapeutic approach still requires more clinical studies in humans (Muammer, Patrick, Hunter, Wayne, & Trinity, 2006).

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7. Conclusion

Prevalence of ED in diabetic patients is increasing day by day. The pathophysiology of diabetes induced erectile dysfunction is multi factorial and no single etiology is at the forefront. However, in the past few years, our knowledge on the pathophysiology of ED and on male sexual problems
in general has expanded enormously. However, there are still many unanswered questions that need to be addressed and more efforts need to be made in order to improve drug design and therapy. Treatment ranging from medical management to surgical implantation of a penile prosthesis is the standard at this time. The therapy has to be individualized and with the prospect of newer drugs in the pipeline; management of ED in diabetics may become more and more simple and rewarding for both the physician and the patient. In addition, even though DIED is not a life-threatening disease, it is an important factor to be considered in the global assessment of quality of life.

References


