

Review

ERECTILE DYSFUNCTION IN DIABETES MELLITUS: NOVEL TREATMENTS

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ABSTRACT

Erectile dysfunction (ED) is a common accompaniment of diabetes mellitus in males; prevalence of impotence being 35-50%. ED may be due to psychogenic or organic causes. Treatment of ED is a challenge because of its multifactorial causation in diabetics. Achievement of euglycemia is the foremost problem to be addressed. Psychosexual counseling, medical therapy and surgery form the alternatives for management of ED in diabetes. Psychosexual counseling alone is not useful but benefits individual patients. Medical treatment includes oral agents, intracavernosal vasoactive injections, intraurethral suppository, vacuum constriction devices and testosterone replacement therapy. The availability of phosphodiesterase 5 inhibitors viz. sildenafil has revolutionized the management of ED in diabetics. Sildenafil is effective in patients with a wide range of concomitant ailments including CAD, peripheral vascular disease, hypertension, depression and on drugs viz. antidepressants, antipsychotics and antihypertensives, but not nitrates. Other oral agents include yohimbine, apomorphine, trazodone, yohimbine+arginine combination and newer phosphodiesterase 5 inhibitors, vardenafil and IC 351. Intracavernosal injections of papaverine, phentolamine and alprostadil (PGE₁) in combination or alone may be used if oral therapy fails or is contraindicated; however, it is more invasive. Alprostadil suppositories and vacuum constriction devices may also be used with good effect (success in 65-70% of cases). Surgery is indicated when medical management fails and includes venous or arterial bypass surgery and penile prosthetic implants.

KEY WORDS – Erectile dysfunction; Diabetes mellitus; Sildenafil; Impotence.

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability of the male to attain and maintain erection of penis sufficient to permit satisfactory sexual intercourse (1). ED is recognized as a common problem with overall incidence around 10% throughout all ages. This

disorder increases with age increasing from 5% at 40 years to >50% at 75 years age (2, 3). In diabetic men, prevalence of impotence lies between 35-50% (4).

ETIOLOGY

The etiology of ED is classified as:

1. Psychogenic ED
2. Organic ED
 - a. Endocrinological
 - b. Neurogenic
 - c. Arteriogenic
 - d. Cavernosal
 - e. Drug-induced

Psychological Causes: From 10-30% of impotent men belong to this group. However, what percentage of diabetics have this component is exactly not clear. Psychogenic stimuli can not only stimulate erection, but also completely block the process. Two possible mechanisms have been proposed – direct inhibition of the brain on spinal centers and excessive sympathetic outflow or increased peripheral catecholamine levels that decrease cavernous smooth muscle relaxation. Various causes are:

- Fear – of failure of sex, disease, pregnancy, etc.
- Hostility – towards the partner.
- Disgust – of sex, of female sexual organ.
- Shame – due to upbringing.
- Humiliation – due to unemployment or social failure.
- Psychiatric disorder – depression, psychosis

ED in diabetes may take any of the above forms, but invariably it is an accompaniment of diabetic complications. Sexual dysfunction is very common in diabetic men, as already discussed. This causes much distress and disappointment to the patient and his partner. Of all the complications of diabetes, sexual dysfunction is said to be the “Secret Complication”. ED is the commonest sexual dysfunction. ED usually develops over a period of months and years in diabetics. ED is not related to

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duration of diabetes (5). Moreover, since diabetes may remain latent for a variable period of time and may present with one of its complications, ED may be present at diagnosis of diabetes itself and specific interrogation needs to be done.

Arterial insufficiency is possibly the most frequent cause of ED. However, in diabetics, neuropathic factors rank above vascular factors.

Autonomic and Somatic Peripheral Neuropathy: As erection is a neurovascular event, any dysfunction or disease affecting the brain, spinal cord, cavernosal, pudendal nerves or their terminal branches can cause ED. Diabetes is notorious for its microvascular complications particularly autonomic neuropathy and peripheral neuropathy which may remain asymptomatic despite presence of other microvascular complications. Somatic and autonomic nerve dysfunction can be demonstrated in diabetic men who have longer latencies of somatosensory-evoked potentials of the pudendal nerves and of bulbocavernous and urethroanal reflexes (6). The long parasympathetic nerves to the pelvic organs are the most vulnerable of the autonomic nerves, which may explain why erectile failure is often the earliest and most common manifestation of diabetic autonomic neuropathy.

Extra penile arterial insufficiency can include disease of terminal aorta and hypogastric, internal pudendal and common penile arteries. Majority of such ED cases are due to atherosclerosis.

Arteriogenic: Since diabetics have accelerated atherosclerosis, arteriogenic causes may also result in ED in diabetics. Studies in animal models of diabetes, as well as in humans, have revealed penile arterial narrowing and arteriolar closure leading to "penile hypotension" and cavernous arterial insufficiency. A primarily vasculogenic etiology based on microvascular changes in smooth muscle integrity is thought to be the most likely end point of the pathophysiology of ED in the diabetic male patient (7).

Disturbance in Local Neuro-regulatory Mediators: Lower penile neuronal nitric oxide synthase (NOS) activity in genetically diabetes-prone rats and resistance to nitric oxide (NO) action at the receptor level or its increased catabolism has been found in streptozotocin-induced diabetic rats with impotence. Abnormalities in local levels of vasoactive intestinal peptide, prostaglandins, endothelins and other mediators have been reported in animal and human studies in causation of ED in diabetes.

Hormonal Alterations: These have also been implicated in diabetic men with organic impotence suggesting existence of primary gonadal dysfunction. However, this association is not direct and androgens do not benefit ED unless hypogonadism coexists.

Drugs: Many drugs have been implicated in the genesis of ED. Antihypertensive agents (beta-blockers, calcium channel blockers, methyl dopa, diuretics, clonidine, reserpine), psychotropics (major tranquilizers, anxiolytic agents, tricyclic antidepressants, MAO inhibitors, barbiturates), hypolipidemic agents, metoclopramide, cimetidine, tobacco, alcohol, isoniazid, nitrofurantoin are commonly used/abused in diabetics and have been shown to impair sexual function.

TREATMENT OF ERECTILE DYSFUNCTION IN DIABETES

Despite considerable progress, the treatment of erectile dysfunction is often difficult due to its multifactorial etiology and lack of existence of the three components of a satisfying sex life:

- Sufficient penile rigidity with no other associated sexual dysfunctions
- An adapted mental state
- A loving relationship with the partner.

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.

It is essential to improve glycemic control since it benefits ED in diabetic men. The therapeutic options include:

- Psychosexual therapy
- Medical treatment
- Surgical treatment.

Psychosexual Counseling alone is often not useful but may benefit individual patients. The results of psychosexual therapies of ED depend mainly on patient-related factors. Certain psychosexual factors appear to decrease the chance of improving ED by psychosexual therapy and are considered contraindication to such therapy. They are:

- Unrealistic expectation (of improvement in sexual desire, arousal, ejaculation, orgasm)
- Psychosis or major mood disorder
- Somatoform mental disorder

- Substance use disorder
- Crisis situation (divorce, grief, serious illness, major surgical procedure)
- Major interpersonal problems with sexual partners

Medical Treatment: This includes

- Oral agents
- Intracavernosal vasoactive injections
- Intraurethral suppository (MUSE)
- Vacuum constriction devices
- Testosterone replacement therapy

ORAL AGENTS:

Phosphodiesterase V (PDE5) inhibitors have revolutionized the medical management of ED with great success. Oral therapy permits discreet administration and is less invasive than some other treatment options including intracavernosal injection, transurethral delivery and prosthesis implantation.

Phosphodiesterase Type 5 Inhibitors

Sildenafil is a potent inhibitor of cGMP specific PDE5. It is effective in a broad range of patients with ED, including patients with CAD, peripheral vascular disease, hypertension, depression and on drugs viz. antidepressants, antipsychotics and antihypertensives (8). However, it has no direct relaxant effect on isolated human corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, an essential stage in the erectile process. It is rapidly absorbed after oral administration, with absolute bioavailability of >40%, has a predominant hepatic clearance, 80% excreted in feces and 13% in urine. Improved erections were reported in 83% nondiabetic and 59-63% of diabetic patients in one series (9) and safety and tolerability were established too (10). Common side-effects include headache, flushing, dyspepsia, nasal congestion, abnormal vision and diarrhoea. Patients should take medicine 1-2 hours before sexual activity. Most men with diabetes require 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 CAD. However, nitrates should be withdrawn before sildenafil initiation, since it may potentiate vasodilatation and hypotension.

Apomorphine

Apomorphine (11) is a short-acting dopamine agonist known to cause erection. Recent studies

have shown that more than 70% patients achieved successful intercourse at home, more than 50% of times specially when taken in the sublingual form.

Yohimbine

Yohimbine is an alpha-2 adrenergic blocker derived from bark of yohimbine tree. It has been used for many years as an aphrodisiac and as a treatment for erectile dysfunction. It 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.

Trazodone

The antidepressant trazodone was noted to occasionally induce priapism. There are reports of good erectogenic activity with trazodone, although no significant benefit was found in a placebo-controlled trial.

Several other compounds being researched include two new PDE5 inhibitors vardenafil (12) and IC351; and the combination of yohimbine and L-arginine are in phase 3 trials. Cloning of penile-inducible NOS heralds the potential use of gene therapy for ED. Early clinical and pre-clinical studies are investigating new PDE inhibitors, cAMP activators, alpha-adrenergic antagonists, dopamine agonists, melanocyte-stimulating hormone, potassium channel modulators, endothelin antagonists, and nitric acid donors (7).

INTRACAVERNOSAL INJECTIONS

It is used for patients where oral therapy fails or is contraindicated. Here vasoactive agents, injected into corpus cavernosum of penis, initiate the action of endogenous neurotransmitter and lead to changes in penile hemodynamics i.e. relaxation of sinusoidal smooth muscle, increase in arterial blood flow, and restriction of venous drainage eventually causing penile erection. The technique is considered to be very effective unless there are no severe arteriolar or veno-occlusive problems (13). The agent of choice earlier was papaverine (15-30 mg), sometimes given in combination with phentolamine (1mg/ml, dose range 0.2-1.0 ml). However, with availability of alprostadil (PGE₁, dose 5-20 microgram), it is the agent of choice because of its safety and efficacy. Patient satisfaction has been reported to be good to very good in about 90% of patients using alprostadil (14, 15). It is recommended to be initiated at dose of 2.5 µg and increased by 2.5 µg increments at

different visits. Higher maintenance dose up to 20 µg is required if ED is of vasculogenic etiology and 5 µg with neurological etiology.

No significant rise in systemic levels of alprostadil has been observed following intracavernosal injection and it is metabolized by the lungs with a half-life of about 1 minute. It is very safe and effective drug. Rate of priapism, the most serious side-effect of intracavernosal injection therapy, is reduced with PGE₁ and is reported to be about 1% compared to 2.3-16% with papaverine. Adverse effects include painful penile sensation, hematoma, penile fibrotic changes and hemosiderin deposits.

Other intracavernosal agents including the 3'P' solution (12mg papaverine, 9µg PGE₁ and 1mg phentolamine), VIP (vasoactive intestinal peptide) + phentolamine combination, chlorpromazine, moxisylyate hydrochloride, linsidomine, calcitonin gene related peptide have been used individually with variable success rates (16-18). Combination therapy is preferred because of increased efficacy and more favorable adverse effect profile.

If an erection lasts longer than 60 minutes or is painful, 30 mg of pseudoephedrine may be taken orally to ensure detumescence. Priapism not responding to oral therapy should be treated with intracavernosal alpha agonists.

INTRAURETHRAL SUPPOSITORY

PGE₁ is also available as an intraurethral suppository. It is less invasive and easier to use than intracavernosal injection, but it may reduce sexual spontaneity. It was devised as MUSE (Medicated Urethral System for Erection), non-injectable delivery system (19). Alprostadil urethral suppository available in doses of 125, 250, 500 and 1000 mcg are used intraurethrally. MUSE can be used twice daily and the response rates are as high as 65%. 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.

VACUUM-CONSTRICTION DEVICES (20)

These combine the twin effects of a negative pressure mechanism to induce an erection by increasing corporeal blood flow and an occlusive constriction ring around the base of penis to prolong erection by

decreasing corporeal venous drainage. These devices are usually effective in over 70% diabetic men with ED. It requires certain amount of mechanical dexterity and the complications are minimal Pain and lack of satisfactory ejaculation are the commonest problems. These are recommended for individuals who cannot tolerate or do not respond to oral medications and intracavernosal injections. Side-effects are few and include pain, petechiae, bruising at site of constricting rubber ring at the base of penis and discomfort at the time of ejaculation. Disadvantages include lack of spontaneity, and in a minority, the partner found it an unacceptable method.

TESTOSTERONE REPLACEMENT AND SUPPLEMENTATION

Reversible causes like hormonal deficiencies/excesses should be addressed. Testosterone is recommended only for individuals who have low serum testosterone levels/primary gonadal deficiency (21). However, very few diabetics in fact require it as a treatment for ED.

Surgical Treatment

In the past it was the only effective therapy for ED, but now is considered to be the last option. It is indicated if medical management fails or is contraindicated.

VENOUS AND ARTERIAL SURGERY

Venous or arterial bypass surgery is used when less invasive treatment for veno-occlusive or arterial diseases fails. However, it is less preferable to penile prosthesis in diabetics because of diffuse atherosclerosis and peripheral vascular disease invariably accompanying the diabetic state.

PENILE PROSTHESIS

Surgically implanted penile prosthesis is an acceptable alternative in patients unresponsive to or unwilling to use other forms of therapy. Although invasive, this approach uniformly results in return of patient's ability to engage in sexual activity. Improvements over the past decade have resulted in excellent patient and partner satisfaction with a low complication rate. Adverse effects include those related to anesthesia, local wound infections, and mechanical failure necessitating surgical failure. Different types of devices are listed below:

1. Semi-rigid rod
2. Mechanical rod
3. Malleable devices
4. Inflatable devices

- a. One component
- b. Two component
- c. Three component

The rod prosthesis is outdated because of the disadvantage of a more or less permanent erection due to the rigid rods which were positioned inside the corpora cavernosa. The malleable prosthesis consists of paired rods of silicon of appropriate size with a central woven stainless steel wire core. The internal design allows the prosthesis to be malleable so that when not in use the implant holds a bent down position to aid in concealment. The inflatable devices consist of three components – the inflatable cylinders two in number, placed in each corporeal body; the pump device and the reservoir which contains fluid used to inflate the cylinders. The reservoir capacity is either 65-100 ml depending on the cylinder size used. The components are connected to pump by silicon tubing. The pump device transfers the fluid from reservoir to the cylinder and from the cylinder to reservoir. A spring loaded resistor mechanism controls the duration of fluid transfer.

CONCLUSION

Erectile dysfunction in diabetics is common and requires special consideration not only because of the patient's concerns but also for its evaluation and management. Availability of effective, well-tolerated therapies (PDE5 inhibitors) which work on the final common pathway of ED has dramatically changed the clinical approach to this disorder in the past few years. In fact, pharmacotherapy is cost-effective and preferred over extensive diagnostic testing, more so when vascular causes are suspected to be the culprit. Currently, no single treatment is suitable or effective for all diabetic men with ED. The therapy has to be individualized for a particular person 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.

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