

Diabetes and Erectile Dysfunction

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Until recently, erectile dysfunction (ED) was one of the most neglected complications of diabetes. In the past, physicians and patients were led to believe that declining sexual function was an inevitable consequence of advancing age or was brought on by emotional problems. This misconception, combined with men's natural reluctance to discuss their sexual problems and physicians' inexperience and unease with sexual issues, resulted in failure to directly address this problem with the majority of patients experiencing it.

Luckily, awareness of ED as a significant and common complication of diabetes has increased in recent years, mainly because of increasing knowledge of male sexual function and the rapidly expanding armamentarium of novel treatments being developed for impotence. Studies of ED suggest that its prevalence in men with diabetes ranges from 35–75% versus 26% in general population. The onset of ED also occurs 10–15 years earlier in men with diabetes than it does in sex-matched counterparts without diabetes.

A sexually competent male must have a series of events occur and multiple mechanisms intact for normal erectile function. He must 1) have desire for his sexual partner (libido), 2) be able to divert blood from the iliac artery into the corpora cavernosae to achieve penile tumescence and rigidity (erection) adequate for penetration, 3) discharge sperm and prostatic/seminal fluid through his urethra (ejaculation), and 4) experience a sense of pleasure (orgasm). A man is considered to have ED if he cannot achieve or sustain an erection of sufficient rigidity for sexual intercourse. Most men, at one time or another during their life, experience periodic or isolated sexual failures. However, the term "impotent" is reserved for those men who experience

erectile failure during attempted intercourse more than 75% of the time.

Physiology

Normal male sexual function requires a complex interaction of vascular, neurological, hormonal, and psychological systems. The initial obligatory event is acquisition and maintenance of an erect penis, which is a vascular phenomenon. Normal erections require blood flow into the corpora cavernosae and corpus spongiosum. As the blood accelerates, the pressure within the intracavernosal space increases dramatically to choke off penile venous outflow. This combination of increased intracavernosal blood flow and reduced venous outflow allows a man to acquire and maintain a firm erection.

Nitric oxide also plays a significant role. High levels of nitric oxide act as local neurotransmitters and facilitate the relaxation of intracavernosal trabeculae, thereby maximizing blood flow and penile engorgement. Loss of erection, or detumescence, occurs when nitric oxide-induced vasodilation ceases.

Low intracavernosal nitric oxide synthase levels are found in people with diabetes, smokers, and men with testosterone deficiency. Interference with oxygen delivery or nitric oxide synthesis can prevent intracavernosal blood pressure from rising to a level sufficient to impede emissary vein outflow, leading to an inability to acquire or sustain rigid erection. Examples include decreased blood flow and inadequate intracavernosal oxygen levels when atherosclerosis involves the hypogastric artery or other feeder vessels and conditions, such as diabetes, that are associated with suboptimal nitric oxide synthase activity.

Erections also require neural input to redirect blood flow into the corpora cavernosae. Psychogenic erections sec-

ondary to sexual images or auditory stimuli relay sensual input to the spinal cord at T-11 to L-2. Neural impulses flow to the pelvic vascular bed, redirecting blood flow into the corpora cavernosae. Reflex erections secondary to tactile stimulus to the penis or genital area activate a reflex arc with sacral roots at S2 to S4. Nocturnal erections occur during rapid-eye-movement (REM) sleep and occur 3–4 times nightly. Depressed men rarely experience REM sleep and therefore do not have nocturnal or early-morning erections.

Etiology

The causes of ED are numerous but generally fall into two categories: organic or psychogenic. The organic causes can be subdivided into five categories: vascular, traumatic/postsurgical, neurological, endocrine-induced, and drug-induced. Examples of the psychogenic causes are depression, performance anxiety, and relationship problems. In people with diabetes, the main risk factors are neuropathy, vascular insufficiency, poor glycemic control, hypertension, low testosterone levels, and possibly a history of smoking.

Pathology of Diabetic ED

The natural history of ED in people with diabetes is normally gradual and does not occur overnight. Both vascular and neurological mechanisms are most commonly involved in people with diabetes. Atherosclerosis in the penile and pudendal arteries limits the blood flow into the corpus cavernosum. Because of the loss of compliance in the cavernous trabeculae, the venous flow is also lost. This loss of flow results in the inability of the corpora cavernosae to expand and compress the outflow vessels.

Autonomic neuropathy is a major contributor to the high incidence of ED in people with diabetes. Norepinephrine-

and acetylcholine-positive fibers in the corpus cavernosum have also been shown to be reduced in people with diabetes. This results in loss of the autonomic nerve-mediated muscle relaxation that is essential for erections.

Evaluation

The initial step in evaluating ED is a thorough sexual history and physical exam. The history can help in distinguishing between the primary and psychogenic causes. It is important to explore the onset, progression, and duration of the problem. If a man gives a history of "no sexual problems until one night," the problem is most likely related to performance anxiety, disaffection, or an emotional problem. Aside from these causes, only radical prostatectomy or other overt genital tract trauma causes a sudden loss of male sexual function.

Nonsustained erection with detumescence after penetration is most commonly caused by anxiety or the vascular steal syndrome. In the vascular steal syndrome, blood is diverted from the engorged corpora cavernosae to accommodate the oxygen requirements of the thrusting pelvis. Questions should be asked regarding the presence or absence of nocturnal or morning erections and the ability to masturbate. Complete loss of nocturnal erections and the ability to masturbate are signs of neurological or vascular disease. It is important to remember that sexual desire is not lost with ED—only the ability to act on those emotions.

A medical history focused on risk factors, such as cigarette smoking, hypertension, alcoholism, drug abuse, trauma, and endocrine problems including hypothyroidism, low testosterone levels, and hyperprolactinemia, is very important. Commonly used drugs that disrupt male sexual function are spironolactone (Aldactone), sympathetic blockers such as clonidine (Catapres), guanethidine (Islemin), methyl-dopa (Aldomet), thiazide diuretics, most antidepressants, ketoconazole

(Nizoral), cimetidine (Tagamet), alcohol, methadone, heroin, and cocaine. Finally, assessment of psychiatric history will help identify emotional issues such as interpersonal conflict, performance anxiety, depression, or anxiety.

The physical exam should focus on femoral and peripheral pulses, femoral bruits (vascular abnormalities), visual field defects (prolactinoma or pituitary mass), breast exam (hyperprolactinemia), penile strictures (Peyronie's disease), testicle atrophy (testosterone deficiency), and asymmetry or masses (hypogonadism). A rectal exam allows for assessment of both the prostate and sphincter tone, abnormalities that are associated with autonomic dysfunction. Sacral and perineal neurological exam will help in assessing autonomic function.

Investigation

Few simple laboratory tests can help identify obvious causes of organic ED. Initial labs should include HbA_{1c}, free testosterone, thyroid function tests, and prolactin levels. However, patients who do not respond to pharmacological therapy or who may be candidates for surgical treatment may require more in-depth testing, including nocturnal penile tumescence testing, duplex Doppler imaging, somatosensory evoked potentials, or pudendal artery angiography.

Treatment

Initially, preventive measures will help reduce the risk of developing ED. Improving glycemic control and hypertension, ceasing cigarette smoking, and reducing excessive alcohol intake have been shown to benefit patients with ED. Avoiding or substituting medications that may contribute to ED is also helpful.

Once ED has developed, oral agents are considered first-line therapy.

Sildenafil (Viagra) acts by blocking the catabolism of cGMP, resulting in an increase in nitric oxide. Fifty-six percent of diabetic men with ED expe-

rience improvement with sildenafil, compared to ~70% of nondiabetic men with ED.

Sildenafil should be taken 1–2 h before intercourse. It is important to tell patients that the drug's effectiveness requires sexual stimulation. One patient in our clinic recently complained that he had no effect from taking sildenafil. It was later discovered that he took the pill and then sat on his couch and read a book about how to grow tomatoes!

The initial dose for sildenafil is 50 mg, and the dose can be increased to 100 mg. (The pills can also be split in half with a pill cutter). Each pill costs \$8–10, and patients can easily shop for the best price on the Internet.

Side effects of sildenafil are similar to those from taking niacin or any vasodilator, namely, headaches, lightheadedness, dizziness, and flushing. Some individuals experience a bluish tinge of their cornea, which makes them feel as if they are wearing light blue-tinted sunglasses. This effect can last for several hours. Syncope and myocardial infarction, the most serious side effects, are seen in men who are also taking nitrates for coronary heart disease. Sildenafil also has adverse effects in people with hypertrophic cardiomyopathy because a decrease in preload and after load in the cardiac output can increase the outflow obstruction, culminating in an unstable hemodynamic state.

Sildenafil is strongly contraindicated in men who take nitrates. Other men for whom its use holds potential hazards include those:

- with active coronary ischemia (e.g., positive exercise tolerance test) who are not taking nitrates
- with congestive heart failure (CHF) and borderline low blood pressure or low volume status
- with a complicated multi-drug anti-hypertensive regimen
- who use drugs that prolong the half-life of sildenafil by blocking CYP3A4

Another oral treatment that has been used with very little success is yohimbine (Yocon, Yohimex). This is an alpha 2 adrenergic receptor blocker that increases cholinergic and decreases adrenergic tone. It stimulates the mid-brain and increases libido. Optimal results occur when used in men with psychogenic ED. Side effects include anxiety and insomnia.

For those patients who are not candidates for oral therapy, intracavernosal injections are an acceptable alternative. Injections with alprostadil (Caverject) and papaverine (Genabid) have been used to induce erection.

This form of therapy has a response rate of well over 70%. The sympathetic nervous system normally maintains the penis in a flaccid or non-erect state. All of the vasoactive drugs, when injected into the corpora cavernosae, inhibit or override sympathetic inhibition to encourage relaxation of the smooth muscle trabeculae. The rush of blood engorges the penile corpora cavernosae sinusoidal spaces and creates an erection.

Patients who use this therapy should be trained under the guidance of a urologist, and sterile technique must be used. The drugs must be injected into the shaft of the penis and into one of the penile erectile bodies (corpus cavernosum) 10–15 min before intercourse. Most patients do not complain of pain upon injection. Sexual stimulation is not required, and resulting erections may last for hours. Side effects include penile pain and priapism. The cost is about \$12–20 per injection.

Intraurethral alprostadil (Muse) provides a less invasive alternative to intrapenile injection. It is a pellet that is inserted 5–10 min before intercourse, and its effects last for 1 h. The response rate is ~50–60%. It can be

used twice daily but is not recommended for use with pregnant partners. Complications of priapism and penile fibrosis are less common than after alprostadil given by penile injection. The cost is ~\$18–24 per treatment.

Mechanical therapy is also effective and is especially well-accepted in men with stable partners. Vacuum-assisted erection devices are effective in creating erections in as much as 67% of cases. Vacuum pressure encourages increased arterial inflow, and occlusive tension rings discourage venous outflow from the penile corpus cavernosae. The penis placed inside the cylinder, a pump is used to produce a vacuum that pulls the blood into the penis. After the tension ring is slipped onto the base of the penis, the cylinder is removed. Erection lasts until the rings are removed. The one-time expense of this therapy is \$120–300.

Penile prosthesis is a viable option for men who cannot use sildenafil and who find the injections or vacuum erection therapy distasteful. A non-adjustable semi-rigid prosthesis is easy to insert and has no postoperative mechanical problems. The inflatable prosthesis has a pump that is put in the testicular sac for on-demand inflation and deflation. Future versions will have a remote control device similar to a garage-door opener.

The primary complication of the surgical implantation is postoperative infection, which occurs in about 8% of cases involving diabetes. This infection can be difficult to treat and may require the removal of the device, although this occurs <3% of the time. The infection can also cause penile erosion, reduced penile sensation, and auto-inflation. Glycemic control should be optimized several weeks before surgery. Once a patient has sur-

gery, none of the oral agents or vacuum devices will work because of the destroyed penile architecture.

Testosterone therapy with injections or patches should be tried in patients with documented low testosterone levels. Testosterone deficiency is a rare cause of impotence but should always be ruled out with a serum value.

Psychotherapy should be offered to the patients and their partners to address any interpersonal conflicts, because ED is a problem for couples—not just men.

Conclusion

ED is an under-recognized, under-discussed, and commonly untreated complication of diabetes. But it is also one of the most treatable diabetic complications. It is a “couples disorder,” affecting both the patient and his partner.

Knowledge of sexual dysfunction is rapidly expanding, and effective new treatments are now available, including oral medications, injectables drugs, vacuum devices, and inflatable prostheses. It is therefore important for both physicians and patients to be educated and aware of the causes and treatments of ED.

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