Diabetes and erectile dysfunction

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Erectile dysfunction is a common condition affecting men with diabetes. Thorough medical assessment is necessary to exclude secondary causes and classic risk factors should be managed concurrently.

Key points

- **Erectile dysfunction affects more than 50% of men with diabetes.**
- **Poor glycaemic control and longer duration of diabetes confer greater risk and severity of erectile dysfunction.**
- **Phosphodiesterase type 5 inhibitors are the first-line pharmacotherapies.**
- **Treatment failure may be higher in men with diabetes, depending on extent of microvascular and macrovascular complications.**

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Erectile dysfunction (ED), defined as an inability to achieve and maintain an erection of sufficient rigidity for satisfactory sexual intercourse, usually affects men over the age of 40 years. Other types of sexual dysfunction include premature ejaculation, delayed ejaculation and reduced sex drive (libido), however, this article will focus primarily on ED.

Prevalence

ED has an estimated prevalence of about 20% in the general population but the prevalence is higher in older men and in those with diabetes. The '45 and Up' study, which surveyed 108,477 men in New South Wales on self-reported ED, showed that the prevalence of moderate (usually present) or complete ED (always present) was 62.5% in men with diabetes, compared with 32.4% in men without diabetes. This gave an odds ratio of 2.39 (95% confidence interval [CI], 2.27 to 2.51; p<0.01) for men with diabetes after adjusting for age, comorbidities and sociodemographic characteristics.[1] A recent systematic review and meta-analysis of 145 studies estimated the prevalence of ED in men with diabetes at 52.5% with an odds ratio of 3.62 (95% CI, 2.53 to 5.16; p<0.0001) compared with healthy controls.[2] The same study reported the prevalence of ED to be 37.5% in men with type 1 diabetes and 66.3% in men with type 2 diabetes, but this was likely due to younger mean age in the type 1 diabetes population. A retrospective analysis of self-reported ED in the Health Professionals Follow-up Study cohort showed a higher risk of developing ED in men with type 1 diabetes than in men with type 2 diabetes, with a relative risk of 3.0 (95% CI, 1.5 to 9.5) and 1.3 (95% CI, 1.1 to 1.5), respectively, compared with men without diabetes after adjusting for age, comorbidities and lifestyle factors.[3]

Physiology of erections

During sexual arousal, parasympathetic nerves innervating the penis release acetylcholine, which stimulates endothelial cells that line the trabecular sinusoids within the penis. This results in the

release of nitric oxide from the endothelial cells. Nitric oxide is also released from nonadrenergic noncholinergic neurons. Nitric oxide activates guanylate cyclase, which increases the concentration of cyclic guanosine monophosphate (cGMP), resulting in the relaxation of trabecular smooth muscle. This relaxation of smooth muscle in the arterial walls and the sinusoids of the corpora cavernosa increases arterial blood flow and allows blood to pool in the sinusoids. This in turn causes compression of the draining veins against the rigid tunica albuginea and a reduction in venous outflow.[4] Phosphodiesterase type 5 (PDE5) breaks down cGMP, eventually resulting in detumescence (Figure).

Pathophysiological changes that occur in ageing men with diabetes

Certain changes occur in ageing men with diabetes that contribute to ED, including:

- reduced number of trabecular smooth muscle cells
- generation of reactive oxygen species, resulting in endothelial dysfunction
- reduced percentage of elastic fibres within the penis
- presence of advanced glycation end products
- development of peripheral and autonomic neuropathy
- development of macrovascular disease.

Common causes

Common causes of ED are listed in the Box. In men with diabetes, the cause is often multifactorial, with diabetes-related neuropathy and microangiopathy of the penile vasculature being significant pathology. However, it is important to consider other causes, as with the general population, when assessing the patient.

Assessment

A full sexual history should be taken in men with ED. This should include information about libido, sexual and social factors, the quality of erections, the existence of premature or delayed ejaculation, curvature of the penis, pain with intercourse or ejaculation, phimosis, and the presence or absence of morning as well as nocturnal erections. Researchers use the International Index of Erectile Function questionnaire, made up of 15 questions, which gives a more objective assessment of sexual function in four domains: erectile function, orgasmic function, sexual desire and intercourse satisfaction.[5]

A comprehensive medical history should be taken to identify additional causes that may contribute to ED and also to guide what treatments may be appropriate. The most important comorbidity to identify is cardiovascular disease and its risk factors, such as hypertension, dyslipidaemia, obstructive sleep apnoea and smoking. In men with severe cardiovascular disease, such as those with high-risk arrhythmias, unstable or

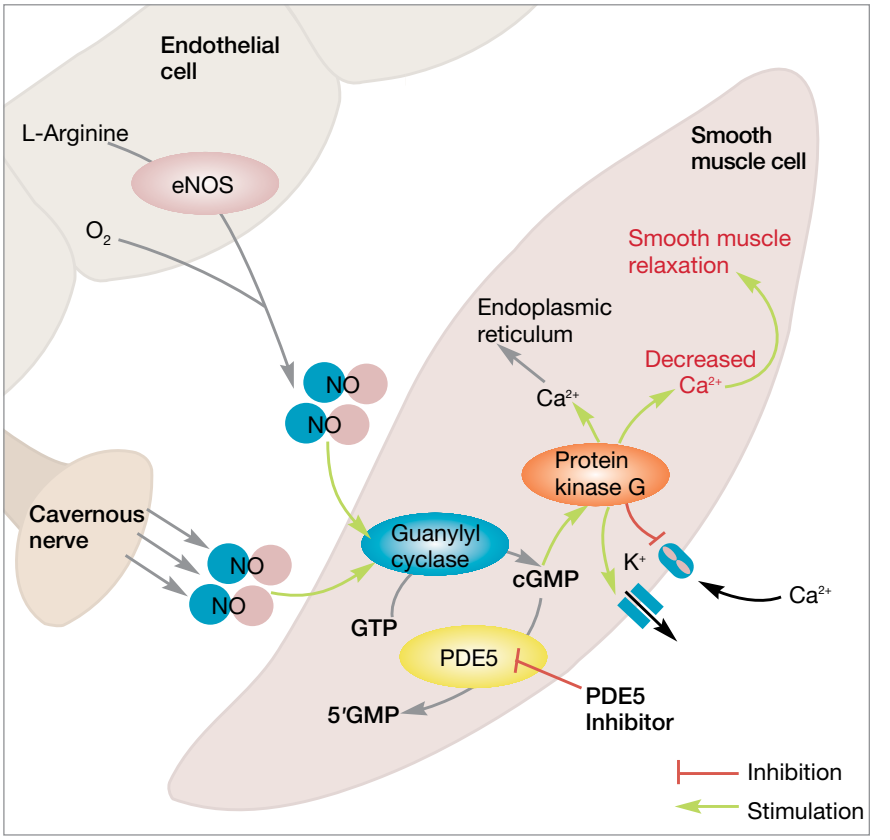

Figure. During sexual arousal, the release of nitric oxide (NO) activates the cyclic guanosine monophosphate (cGMP) pathway, resulting in relaxation of smooth muscle and increased arterial blood flow, which in turn results in penile erection. In men with erectile dysfunction, inhibition of phosphodiesterase type 5 (PDE5) isoenzyme results in increased cGMP levels and an augmented penile erection.

Common causes of erectile dysfunction

- **Psychogenic**
  - performance anxiety
  - relationship issues
  - stress and depression
- **Medications** (e.g. antidepressants, antihypertensives, beta blockers)
- **Neurogenic**
  - diabetic neuropathy
  - pelvic surgery/injury
  - neurodegenerative conditions (e.g. Parkinson's disease, multiple sclerosis)
  - spinal cord Injury
- **Vascular disease**
- **Hypogonadism**
- **Peyronie's disease**

refractory angina or myocardial infarction less than two weeks prior, sexual activity is contraindicated and appropriate counselling should be provided.

Assessment of the patient's glycaemic control is essential, with poor glycaemic control and longer duration of diabetes conferring higher risk for ED.[6] However, ED may also be the first symptom of diabetes and diagnostic tests should always be considered if a prior diagnosis of diabetes has not previously been made.

Other important risk factors for neuropathy causing ED include previous prostate cancer treatments, smoking and high alcohol consumption. Men should also be asked questions to identify hypogonadism, with symptoms often being nonspecific but may include low libido, loss of muscle bulk, general fatigue, loss of facial or body hair and development of gynaecomastia. Depression and other psychological conditions commonly cause or worsen ED. Conversely, ED may worsen depressive symptoms.

Some commonly prescribed medications that can worsen ED include antidepressants (especially selective serotonin reuptake inhibitors), spironolactone, thiazides, beta blockers and centrally-acting antihypertensives (such as clonidine or methyldopa). It is important to ascertain if a patient is taking any short- or long-acting nitrates as this is a contraindication for the use of PDE5 inhibitors as a potential treatment.

Physical examination should be performed to assess for signs of cardiac disease and clinical features of hypogonadism. Testicular examination is essential if hypogonadism is suspected, taking care to document the size and consistency of the testes. If the penis is uncircumcised, the presence or absence of phimosis should also be assessed. If Peyronie's disease is suspected, a fibrotic plaque can often be palpated along the length of the penis. Finally, in men with poorly controlled diabetes, balanitis may often be found.

Appropriate pathology tests should be ordered, including full blood count, renal function, liver function, and measurement of HbA_{1c}, total testosterone, sex hormone binding globulin, prolactin and luteinising hormone levels.

If Peyronie's disease is suspected, a penile ultrasound will confirm the presence of a fibrotic plaque. Nocturnal penile tumescence monitoring or invasive investigations are usually unnecessary.

Management

It is preferable to see the patient together with his partner to gain an understanding of their needs and expectations. They often have quite different expectations. It is equally important to explain the expected decline in erectile function and libido with ageing. In many cases only reassurance is necessary or possibly referral to a sex counsellor. If treatment is necessary most men with diabetes and ED can be helped substantially.

Optimising glycaemic control and cardiovascular risk factors

The treatment of ED in men with diabetes should start with review of their glycaemic control as poor glycaemic control will cause progression of microvascular damage and possibly worsen ED. Studies have shown a correlation between poor glycaemic control and severity of ED.[6] If the patient has neglected his diabetes management in the past, this may be a good opportunity to educate him on the importance of good glycaemic control to avoid the progression or development of other complications. It is also essential to optimise the patient's cardiovascular risk factors because ED is often an early symptom of atherosclerotic disease.

Lifestyle factors

Smoking, obesity and lack of exercise have been associated with ED in cross-sectional studies.[1] Additionally, exercise has been shown to improve ED, particularly in younger men.[7] Lifestyle advice on exercise, smoking cessation and weight loss is applicable to all patients with diabetes but the importance should be emphasised for men presenting with ED. Appropriate aids, such as nicotine replacement and referral to a dietitian or exercise physiologist, should be considered.

Psychological and sex counselling

It is common for men to have secondary psychological reactions to ED, with perceived loss of masculinity and low self-esteem, which can cause or worsen mood disturbances. Supportive counselling of the patient and partner should be provided by an expert psychologist or psychiatric referral if required.

In general, the younger a patient is at presentation, the more likely it is that the cause of the ED is psychogenic in nature. If this is the case, the most appropriate management is referral to a sex counsellor.

Pharmacotherapies

PDE5 inhibitors

PDE5 inhibitors are the first-line pharmacotherapy option for most men with ED. The mechanism of action is to inhibit the breakdown of cGMP (Figure). The PDE5 inhibitors sildenafil, tadalafil and vardenafil have been available in Australia for many years, with the main difference being their half-lives and side effects. They are very effective in mild-to-moderate ED but less effective in severe ED. The efficacy of PDE5 inhibitors for successful intercourse is reported to be between 60 and 70% in the general population, compared with 40 to 50% in men with diabetes.[8,9]

Patients must be counselled on the correct use of PDE5 inhibitors and that erection will only occur after sexual stimulation. Sildenafil and vardenafil should be taken about one hour before planned sexual activity. Tadalafil should be taken two hours before planned sexual activity, but due to the longer duration of action, its effect may last up to 24 hours.

Common side effects include headache, facial flushing, nasal congestion, dizziness, colour vision disturbance (sildenafil and vardenafil) and back pain (tadalafil). Short-acting nitrates (e.g. glyceryl trinitrate) should be avoided for 24 hours after taking sildenafil and vardenafil or for five days after taking tadalafil as they can cause significant hypotensive episodes. For patients taking long-acting nitrates, PDE5 inhibitors are contraindicated. Precaution is also needed in patients taking multiple

antihypertensives or those with significant heart failure.

As of January 2019, another PDE5 inhibitor, avanafil, became available in Australia. This drug has a faster onset of action (may be taken 15 to 30 minutes before planned sexual activity) with contraindications and side effects similar to the three other PDE5 inhibitors.

Intracavernosal prostaglandin E1 injections

Alprostadil is the only prostaglandin approved for intracavernosal injection in men with ED. Intraurethral alprostadil pellets are no longer available in Australia. Alprostadil works by causing smooth muscle relaxation and vasodilation, and can be considered when PDE5 inhibitors are contraindicated or have been ineffective.

Administration of alprostadil is limited by patient dexterity. It must be injected directly into the corpus cavernosum before intercourse and takes 5 to 20 minutes to take effect. The sites for injection are on the side of the penile shaft, avoiding the neurovascular bundle on the dorsum of the penis or any subcutaneous veins. It is important to draw back on the needle to ensure it has not entered a blood vessel, but it is normal for a small drop of blood to be visible, which indicates entry into the corpus cavernosum. Firm pressure should be applied for 30 to 60 seconds after the injection to prevent excessive bruising or bleeding. The most common side effects are local pain, haematoma and priapism. Cavernosal fibrosis has been reported with long-term use.

Penile rings and vacuum devices

In men who have nonsustained erections, a venous constriction ring is often effective and cheap. This can be used alone or in conjunction with a vacuum-assisted device, which works by creating a vacuum around the penis, pulling blood into the corpus cavernosum. The vacuum device is safe and inexpensive but the effect is temporary and results may vary. In both of the above methods, the ring cannot be left in place for longer than 30 minutes.

Surgical implants

Penile implants are only considered if all other therapies have failed and the patient wishes to pursue surgical management. This may be particularly relevant in men with diabetes who have autonomic neuropathy, advanced microvascular disease and longer duration of diabetes, as they are more likely to fail pharmacotherapies. There are two major types of penile prostheses, with the simpler form involving insertion of semi-rigid malleable rods into the shaft of the penis, which the patient positions into the erect position for intercourse. The other type of implant is the inflatable penile prosthesis, which involves insertion of balloons in the penile shaft connected to a fluid reservoir in the pelvis with a pump that resides in the scrotum. The patient can use the pump to inflate or deflate the balloons as needed for intercourse. The inflatable penile prostheses have high rates of satisfaction, reported to be between 70 and 90%, with low rates of mechanical failure.[10]

Conclusion

ED is a common condition affecting men with diabetes. It is important for clinicians to ask about ED as men will often not volunteer the information thereby denying themselves the opportunity for treatment. Thorough medical assessment is necessary to exclude secondary causes and classic risk factors should be managed concurrently. Available management strategies include sex counselling, pharmacotherapy, physical devices and, if more conservative measures have failed, surgical implants. **ET**

References

A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

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