

Erectile dysfunction in general medicine

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ABSTRACT – Erectile dysfunction (ED) affects millions of men worldwide with implications that go far beyond sexual activity. ED is now recognised as an early marker of cardiovascular disease, diabetes mellitus (DM) and depression. The risk factors that are associated with ED (sedentary lifestyle, obesity, smoking, hypercholesterolaemia and the metabolic syndrome) are very similar to those for cardiovascular disease (CVD). Arguably, the awareness of ED as a symptomatic entity in the post-Viagra™ age is on the rise. Nevertheless, ED is commonly missed when evaluating patients in the hospital setting, either because of lack of consideration or awareness, or through simple embarrassment (of both clinician and patient). This article provides an overview of the aetiology, assessment and importance of ED and hopes to promote its consideration in day-to-day clinical practice.

Introduction

Erectile dysfunction (ED) is a common medical problem that is frequently overlooked by clinicians. The seminal Massachusetts Male Ageing study revealed that in a healthy population of men in New England aged 40–70, 52% had ED (Fig 1).¹ What was especially interesting about this research was that multiple correlates were identified. These included diabetes, among other chronic diseases, as well as additional age-related modifiable phenomena such as cardiovascular risk factors.

Inquiry into symptoms of ED should be a standard part of the evaluation of adult males presenting to clinical practice. In the same way as a menstrual history can provide valuable information about the general health of young females, ED can be a sensitive marker of systemic disease, be it metabolic, cardiovascular, neurological or otherwise. It is also likely to be of considerable importance to individual patients (having a significant psycho-social impact) and might never have been asked about before. This is especially relevant in the post-Viagra™ age in which several different treatment modalities are now available.

Evaluation of the patient with ED

ED can emerge as part of a screen for something else entirely; for example, it is often reported when physicians enquire about the side effects of medications such as thiazides or β -blockers (ED

being a well-recognised adverse effect of these drugs) or during screens for complications of other conditions such as diabetes (a specific annual enquiry about ED has now become a recommendation of NICE). A careful, sensitively taken history is key to determining the underlying cause of ED (Table 1). Such a history also allows the physician to gauge the severity of the problem and potential routes for treatment. The sexual health inventory of men (SHIM) is a useful and simple guide that the patient can use to identify the severity of the ED and it also enables the monitoring of treatment progress.

Patients can find ED to be a very difficult subject and outright, initial declaration of their problem a huge barrier to diagnosis and treatment (and this might also depend on the gender of the doctor or the patient’s relationship with them).²

Factors that need to be covered include speed of onset (gradual development of symptoms usually indicates an organic cause, whereas sudden onset ED often has a psychological or traumatic cause), duration since onset, relation to the patient’s libido, whether the ED is partial or complete, the circumstances under which the ED is likely to occur, and whether the patient is still able to get spontaneous morning erections (this last issue also being a good marker of testosterone status). Physical examination should focus on the patient’s blood pressure, peripheral pulses, testicular size and volume, secondary sexual characteristics and any obvious anatomical defects of the penis.

Baseline investigations

Recording of cardiovascular risk factors is essential. Blood tests should include levels of gonadotrophins (luteinising hormone (LH) and follicle-stimulating hormone (FSH)), testosterone level between 9–11am (there is a marked diurnal variation in

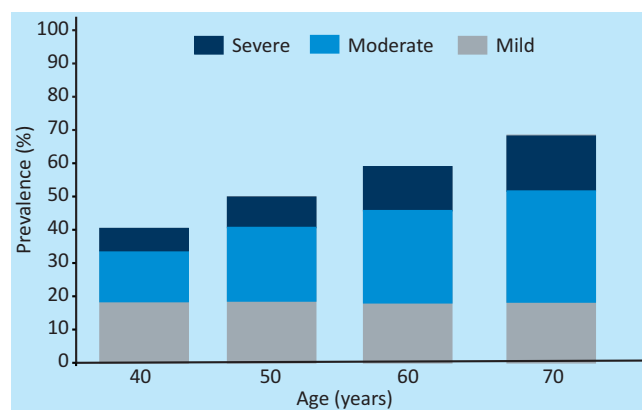


Fig 1. Prevalence of erectile dysfunction in men taking part in the Massachusetts male ageing study.¹

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testosterone levels), sex-hormone-binding globulin level, prolactin level, fasting lipid profile and thyroid function tests. In addition, it is important to check the full blood count (testosterone has a direct effect on bone marrow and red cell production), renal function, blood glucose, liver function test and prostate-specific antigen (PSA).³

Patients should be referred to specialists if there is any obvious abnormality, be it endocrine, neurological, cardiovascular or urological.

Diabetes mellitus

Type 2 diabetes is associated with lower levels of total and free testosterone and with a higher prevalence of hypogonadism (around 25–50%) in numerous studies. This diabetic population has higher prevalence of metabolic syndrome and obesity, which are strongly associated with hypogonadism and ED. Interestingly, testosterone concentrations are inversely related to body mass index (BMI).⁴ Nevertheless, a significant number of non-obese patients with diabetes have subnormal testosterone levels. Consequently, this group have health-related reductions in their quality of life and are at 2–3 times greater risk of cardiovascular disease regardless of age, smoking status and low-density-lipoprotein (LDL) levels.⁵ By contrast, patients with type 1 diabetes have normal testosterone levels and rarely develop hypogonadism.⁶

The mechanism of hypogonadism in type 2 diabetes mellitus is unclear. A possible explanation relates to the effects of insulin resistance as the prevalence is higher in obese patients with diabetes. It is believed that increased aromatase enzyme activity in adipose tissue leads to increased synthesis of oestrogen, which in turn suppresses the hypothalamic secretion of gonadotropin-releasing hormone (GnRH).⁴ The role of insulin resistance has been demonstrated by the selective deletion of the insulin receptor gene from neurons, resulting in both a state of systemic insulin resistance and a syndrome of hypogonadotrophic hypogonadism in mice.⁷ Also, studies have shown a negative effect of hyperglycaemia on both the hypothalamic secretion of GnRH and the secretion of testosterone by Leydig cells, with testosterone secretion improving glycaemic control.⁸

Clinical features

The majority of patients with hypogonadism have non-specific symptoms such as fatigue and weakness, and around 60% of them present with ED and/or loss of libido.³ These patients are consequently at increased risk of osteoporosis, anaemia and cardiovascular disease.⁵ Diagnosis is confirmed by demonstrating low total and free testosterone levels together with inappropriately low LH and FSH levels. Around 5% of patients with diabetes presenting with hypogonadism have primary hypogonadism.

Evidence for treatment with testosterone

Testosterone replacement in patients with hypogonadism remains controversial. A double-blind placebo controlled study using

Table 1. Causes of erectile dysfunction.

| | |
|-----------------------------|--|
| Medications | Thiazides, β -blockers (much debated), anti-depressants (serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs)) etc |
| Neurogenic disorders | Spinal cord and brain injuries, Parkinson's disease, Alzheimer's disease, multiple sclerosis and stroke |
| Cavernosal disorders | Peyronie's disease |
| Surgery | Previous bowel, bladder, prostate or rectal surgery or radiotherapy can damage the nerves and vasculature involved in developing an erection |
| Metabolic disease | Diabetes mellitus, hypopituitarism/secondary hypogonadism, hyperprolactinaemia or renal failure |
| Lifestyle | Smoking is a major cause of ED, as are obesity and lack of physical exercise |
| Ageing | ED is four times more common in men in their 60s relative to men in their 40s |
| Psychological causes | Anxiety, depression or stress |
| Vascular disease | Atherosclerosis, venous insufficiency |

ED = erectile dysfunction.

long-acting testosterone undecanoate and involving seven UK general practices showed small changes in glycated haemoglobin (HbA1c) (reduced from 7.61% to 7.52%) over 30 weeks but marked changes after a further 22 weeks (down from 8.3% to 7.3%). Mean weight loss was 2 kg with a 1.5 cm reduction in waist circumference.⁹ There was no significant increase in mean PSA and mean haematocrit was unchanged. Another meta-analysis showed significant reduction in fasting plasma glucose, HbA1c, fat mass and triglycerides, but no significant change in total and high-density lipoprotein cholesterol, blood pressure or BMI.¹⁰

The TIMES2 trial conducted using transdermal testosterone demonstrated a 15.2% reduction in insulin resistance (as measured by homeostasis model assessment of insulin resistance) and significant reduction in total and LDL cholesterol. There was significant increase in the International Index of Erectile Function score (IIEFs) mainly because of improvement in sexual desire and intercourse satisfaction scores.¹¹ Another UK study has shown that testosterone replacement reduced the incidence of myocardial infarction and diabetes-related complications, improved quality-adjusted life years and is a cost-effective therapy.¹²

Testosterone replacement is associated with polycythaemia and liver dysfunction, so long-term monitoring is required. Finally, as the prostate is an androgen-dependant organ, there are concerns that testosterone replacement might result in testosterone-induced prostate hypertrophy and cancer. Six-monthly review of testosterone and PSA is recommended, and where there are any doubts, a urologist should perform a digital rectal examination. Studies to date have not, however, confirmed any link between testosterone replacement and prostate cancer, as outlined in a recent review by Landau and colleagues.¹³

Table 2. Relative risks for men with ED when compared to those with no ED.¹⁷

| | Relative risk | 95% confidence interval | p value |
|-------------------------|---------------|-------------------------|---------|
| Overall relative risks | 1.48 | 1.25–1.74 | <0.001 |
| Coronary artery disease | 1.46 | 1.31–1.63 | <0.001 |
| Stroke | 1.35 | 1.19–1.54 | <0.001 |
| All-cause mortality | 1.19 | 1.05–1.34 | =0.005 |

ED = erectile dysfunction.

Table 3. Artery size and atherothrombosis. A level of atherothrombosis that is sufficient to cause significant restriction to flow in the penile arteries can be subclinical in larger vessels.

| Artery | Diameter (mm) | Clinical event |
|----------|---------------|-------------------------------------|
| Penile | 1–2 | ED |
| Coronary | 3–4 | Ischemic heart disease |
| Carotid | 5–7 | Transient ischemic attack or stroke |
| Femoral | 6–8 | Claudication |

ED = erectile dysfunction.

Hypogonadism is common in patients with type 2 diabetes, more so if ‘metabolic syndrome’ or obesity is present. The Endocrine Society recommends routine measurement of testosterone levels in patients with type 2 diabetes, but even diabetologists can be tardy in checking this.² Studies to date have demonstrated strong benefits resulting from testosterone replacement, but this treatment should be individualised and under specialist supervision until long-term studies fully establish its benefits and risks.

Significance of ED and cardiovascular risk

ED has the same risk factors as both coronary artery disease (CAD) and generalised vascular disease.¹⁴ These include hypertension, diabetes, hyperlipidaemia, obesity, lack of physical exercise, excess alcohol intake, poor diet and psychological stress, in particular depression. As mentioned earlier, ED is now recognised as a marker of increased cardiovascular disease (CVD) that is independent of conventional risk factors.¹⁵

A meta-analysis of prospective studies evaluated the association between ED and the risk of CVD and all-cause mortality, which had been previously recognised by consensus panels.^{16,17} Twelve studies involving 36,744 men with no known CVD were included. ED significantly increased the risk of CVD, CAD, stroke and all-cause mortality independently of potentially confounding conventional risk factors (Table 2). Of concern is the substantially increased 10-year risk of a cardiac event in younger men with ED (>7-fold aged 20–40 years, 50-fold aged 40–50 years), for whom a focus for risk reduction is clearly needed.^{18,19}

The artery size hypothesis has been used to explain how ED acts as a silent marker of vascular disease elsewhere in the body, and particularly as a marker of CAD. The lumen of the penile arteries is considerably smaller (1–2 mm) than those of the coronary (3–4 mm), carotid (5–7 mm) and femoral (6–8 mm) arteries.²⁰ The same level of plaque burden and/or endothelial dysfunction has a greater effect on blood flow through the penile arteries than through the coronary, carotid and femoral arteries because of their smaller size (Table 3). Therefore the clinical manifestation of penile atherosclerosis, that is ED, becomes evident before the consequences of coronary (eg CAD), carotid (eg transient ischaemic attack or stroke) and femoral (eg claudication) artery atherosclerosis. The lumen of the larger arteries become significantly obstructed (>50%) only when atherosclerosis intensifies, which explains why a lot of men who present with CVD have a history of preceding ED. Furthermore, because an acute coronary syndrome often arises as the result of the rupture of a subclinical plaque, the presence of ED can also be an early warning sign of an acute event or of sudden death.

In men with known CVD, in whom ED is common (prevalence 70%), ED substantially increases cardiovascular risks and is predictive of increased all-cause mortality and of the composite of cardiovascular death, myocardial infarction, stroke and admission for heart failure (hazard ratio 1.42).²¹

As ED and CVD frequently coexist, men with CVD should be asked about ED. Similarly, men with ED and no cardiac symptoms should be evaluated for cardiovascular risk. The time window from the onset of ED to a cardiovascular event including mortality in a man with no cardiac symptoms is two to five years, which allows time for risk-factor modification.^{18,19} ED should be considered a cardiovascular equivalent, and a man with ED and no cardiovascular symptoms should be considered to be a cardiovascular patient until proved otherwise. It logically follows that ED should be included in every cardiovascular risk calculator.

Lifestyle modification and aggressive management of risk factors

As ED shares modifiable risk factors with CVD, reductions in risk factors that are known to benefit CVD should in turn benefit ED. Furthermore, as ED is an independent predictor of cardiovascular events in men with no cardiac symptoms, it is now recognised to be a sentinel marker for CVD risk reduction. A recent systematic review and meta-analysis of lifestyle modification evaluated 740 men from six clinical trials, two of which included statin therapy.²² The authors concluded that an improvement in ED and sexual function results from lifestyle intervention and reduction of cardiovascular risk, and that ED gives a man the opportunity to identify cardiovascular risk factors and initiate their reduction. As physical inactivity and obesity are strongly associated with ED and CVD, they represent ideal treatment targets for improving both ED and the underlying vascular disease.

Exercise

Overall, the data suggest that increased physical activity is both a strategy to prevent the development of ED and a treatment strategy to improve erectile responses in those already suffering from ED. In a randomised controlled trial, Esposito *et al* performed a two-year lifestyle intervention that addressed physical activity and caloric restriction in 110 healthy obese men with ED.²³ The 55 men in the intervention arm attended monthly sessions aimed at improving exercise and diet in order to achieve a 10% weight reduction, whereas those in the control group received general information regarding exercise and diet. After the two years, men in the intervention group significantly increased their physical activity, reduced their caloric intake, improved the quality of their diet and accordingly improved their erectile function from baseline, as compared with the control group. Intervention led to the complete return of erectile function in over 30% of the participants.

Obesity

Importantly, the health risk associated with obesity appears to be highly dependent on the regional deposition of adipose tissue.²⁴ The association between anthropometric measures of abdominal obesity (eg waist circumference) and ED can be explained by excess accumulation of abdominal visceral tissue, which is an independent predictor of dyslipidaemia and insulin resistance, CVD, type 2 diabetes, inflammation and the metabolic syndrome.

Smoking

In the Health Professionals Study, smoking increased the risk of developing ED by 50%.²⁵ In the Massachusetts Male Aging Study, men who smoked at baseline increased their risk of developing moderate or total ED to 24%, compared with 14% of non-smokers ($p=0.01$).²⁶ When considering overall vascular health, advice and support to enable individuals to stop smoking are essential lifestyle interventions.

Alcohol

Excessive alcohol intake increases cardiovascular risk, but there is little evidence of increased ED risk other than the acute effect of binge drinking. Men with a very high alcohol intake are, however, unlikely to participate in studies of risk association and reduction, so the data are inconclusive at present.

Mood

Depressive disorders range from mild symptoms to major depression. Core symptoms of a depressive disorder are sadness or loss of interest or pleasure in usual activities for a period of at least two weeks, accompanied by at least five of the following: sleep difficulties, fatigue, low self-esteem, guilt, psychomotor agitation or retardation, and loss of appetite. Depressive symptoms may lead to loss of libido and reduced sexual function. Therefore, it is appropriate that patients who present with ED

Table 4. Effective use of PDE-5 inhibitors.

| | |
|-------------------------|--|
| Cautions in prescribing | Cardiovascular disease, left ventricular outflow tract obstruction, anatomical deformation of the penis, patients with a predisposition to priapism, eg those with sickle cell disease. |
| Drug interactions | Concomitant use with an α -blocker can increase the risk of postural hypotension. Protease inhibitors in HIV. |
| Contraindications | Use of nitrates, hypotensive patients, recent stroke, unstable angina and myocardial infarction. |
| Side effects | Gastrointestinal upset, headache, flushing, dizziness, myalgia, back pain, visual disturbances and nasal congestion. |
| Administration | It is advised that PDE-5 inhibitors should be taken on an empty stomach, 30 minutes to 1 hour before intercourse. They are also less effective in the context of smoking and alcohol. |
| Lack of efficacy | Patients have not waited long enough or too long after taking the medication. The dose might not be high enough. Patient might not have had enough sexual stimulation. Patients should take the tablets on up to 7–8 occasions before deciding that they have failed to be effective. |

PDE-5 = phosphodiesterase-5.

should be screened for depression and vice versa.^{27,28} This depressive symptom complex can also be caused by hypogonadism, and all men with ED should have their testosterone levels checked, as has previously been highlighted.

Offering treatment

For those with 'generalised' ED, the therapeutic pathway (other than targeting the underlying cause) provided in concert with lifestyle modification, is as follows:

- 1 Phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, tadalafil and vardenafil, are among the most widely used and effective drugs for the treatment of ED. They work by temporarily increasing the blood supply to the penis (Table 4).
- 2 Urethral alprostadil is a synthetic hormone that stimulates blood flow to the penis. A small pellet can be inserted into the urethra.
- 3 Alprostadil that is administered by a direct intracavernosal injection is successful in about 85% of men who do not respond to PDE-5 inhibitors.
- 4 Surgical intervention is usually recommended only if all other treatment methods have failed. It can also be used in the context of trauma or anatomical problems. Surgery might include penile implants or vascular intervention.
- 5 Psychological therapies are important as ED can be both the cause and a consequence of a variety of mental health

problems. Sex therapies such as sensate focus are available on the NHS.

Local treatment pathways tend to vary and it might be that many of the treatments listed above are co-ordinated by the urologists or a dedicated ED nurse. Vacuum-assist devices can be used at any stage. After using a vacuum pump, 9 out of 10 men are usually able to have sex, irrespective of the cause of the ED.²⁹

Conclusions

Erectile dysfunction is an extremely important problem, with implications far beyond sexual activity. ED can be both a herald marker and a consequence of several chronic disease states. Early recognition is important because of the opportunities relating to cardiovascular risk modification.

Ultimately, the problem for clinicians is one of awareness. The signs and symptoms of ED are under-reported and are not enquired about enough routinely, which means that we miss the chance to both intervene at an early stage and to make a difference to an individual's health- (and sex-)related quality of life. If we don't ask the question, we can't do anything about the problem.

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