Erectile dysfunction and diabesity: A clinical management perspective

Rajesh Rajendran, Michael Cummings

Erectile dysfunction (ED) is an extremely common complication of diabesity with an adverse effect on quality of life. It can also indicate underlying silent cardiovascular disease and hypogonadism. Apart from neurovascular factors, abnormalities in the chemical mediators of penile muscle relaxation have led to the development of oral phosphodiesterase-5 inhibitors that have revolutionised treatment of ED in men. There is mounting evidence that lifestyle interventions such as weight loss, smoking cessation and increase in physical activity are helpful in preserving erectile function in diabesity. It is important for all healthcare professionals involved in delivering diabetes care to ask about the sexual health of their patients and offer treatment or refer to appropriate specialists in the field.

The word "diabesity" was originally used by Ethan Sims in the 1970s in the context of studies of experimental human obesity. More recently the term has been used to describe the co-existence of type 2 diabetes and obesity (Haslam, 2012). Erectile dysfunction (ED) is one of the most under-diagnosed complications in men with diabetes. It is expected to affect more than 300 million men by the year 2025 (Rajendran and Cummings, 2012), with the diabesity pandemic being a major contributing factor. The prevalence of ED in men with diabetes averages about 35%, varying from 6–52%. This is far higher than the average of about 20% in men without diabetes (Rajendran and Cummings, 2012). The risk of ED is increased approximately 1.5- to three-fold in obese men (Chitaley et al, 2009) and three-fold with an HbA_{1c} level >65 mmol/mol (8.1%; Al-Hunayan et al, 2007).

Better understanding of the biochemical pathways underlying the mechanisms of ED has led to the development of a number of successful therapeutic options in recent years. In this article, we discuss the management of ED in the context of diabesity.

Pathophysiology

Changes within corpus cavernosum

There are several abnormalities in either the availability or effectiveness of several key chemical mediators involved in smooth muscle relaxation and constriction in the corpus cavernosum of men with diabetes. Both parasympathetic nerve and endothelium-dependent smooth muscle relaxation are affected in men with ED and diabetes (Cummings, 2004). Reduced nitric oxide (NO) synthase levels and increased superoxide radicals leads to oxidative stress and free radical damage of endothelium (Shin et al, 2011).

Other abnormalities demonstrated include: reduced acetylcholine-mediated muscle relaxation; reduced vasoactive intestinal polypeptide (smooth muscle relaxant) activity; reduced noradrenaline (smooth muscle contraction) levels (Cummings, 2004); increased endothelin-1 (smooth muscle contraction) levels (Francavilla et al, 1997); and accumulation of advanced glycation end products that result from non-enzymatic reactions between glucose and lipids, proteins or nucleic acids (Wen et al, 2002), apart from structural abnormalities such as fibrosis of the penile

Citation: Rajendran R, Cummings M (2013) Erectile dysfunction and diabesity: A clinical management perspective. *Diabesity in Practice* **2**: 15–22

Article points

1. Erectile dysfunction (ED) is one of the most under-diagnosed complications of diabesity.
2. Hypogonadism has become increasingly recognised in men with ED and diabesity with evidence of benefit in concurrent administration of phosphodiesterase-5 inhibitors and testosterone replacement therapy.
3. The onset of ED could be a potential screening tool for silent cardiovascular disease in men with diabesity.
4. Weight loss, increased physical activity and smoking cessation are important lifestyle modifications that may help in improving erectile function in men with ED and diabesity.
5. Phosphodiesterase-5 inhibitors remain the mainstay of therapy in ED.

Key words

-Erectile dysfunction
-Hypogonadism

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Page points

1. Diabetic neuropathy and microvascular blood supply are closely linked.
2. The link between obesity, diabetes, hypogonadism and erectile dysfunction has been better recognised in the last decade.
3. There is increasing evidence that sedentary lifestyle, smoking and alcohol consumption are associated with the development of erectile dysfunction.

arteries and corpus cavernosum and reduced amounts of cavernous nerve fibres of unmyelinated axons with collagen, factors that impair smooth muscle relaxation and vasodilatation (Cummings, 2004).

Neural and vascular factors

Diabetic neuropathy and microvascular blood supply are closely linked. Neuropathy, especially autonomic neuropathy, has been linked to the development of ED and the principal abnormality seems to be the parasympathetic nervous system, responsible for achieving tumescence (Cummings, 2004), with dysfunction of the penile nerves preceding neuropathy in the other peripheral nerves in some men with diabetes (Bleustein et al, 2002). There appears to be no impairment of the sympathetic nervous system.

The penis is a highly vascular organ and diabetes may be associated with diffuse atherosclerosis or isolated disease of the external iliac artery, both of which may contribute to the development of ED. Up to 95% of men with diabetes and ED show impaired penile blood flow (Cummings, 2004). It has been shown that significant ED is associated with diabetic retinopathy severity that is independent of age, duration of diabetes and cardiovascular risk factors (Henis et al, 2011), and that ED in men with diabetes is associated with proteinuria, which is a marker for diabetic nephropathy (Yamasaki et al, 2004). Other abnormalities in vascular function, in particular NO-mediated vasodilatation, have been described earlier.

Hormonal factors

Hypogonadism is defined as a clinical condition comprising both symptoms with or without signs and biochemical evidence of testosterone deficiency (Jones, 2007). It is now clear that penile erection and blood flow is associated with circulating testosterone levels and that testosterone controls several mechanisms that lead to erection and detumescence (Corona and Maggi, 2010). Testosterone also appears to mainly regulate the timing of the erectile process as a function of sexual desire (Corona and Maggi, 2010).

The link between obesity, diabetes, hypogonadism and ED has become better recognised in the last decade (Jones, 2007; Corona and Maggi, 2010; Wang et al, 2011) with several cross-sectional studies showing that the prevalence of biochemical and symptomatic hypogonadism in men with diabetes ranges from 33% to 42% (Corona and Maggi, 2010). This justifies the need for hypogonadism screening in this population.

Hypogonadism with low testosterone and normal gonadotrophins (mixed hypogonadism) are more commonly described in the context of diabesity, as visceral obesity and metabolic syndrome directly impact on testosterone levels and vice versa (Jones, 2007; Wang et al, 2011). A number of mechanisms have been suggested, including: low circulating levels of plasma sex hormone-binding globulin causing low total testosterone, which leads to increased insulin resistance; and increased aromatase activity resulting in increased conversion of testosterone to oestrogen in visceral adipose tissue thereby decreasing testosterone levels and insulin resistance in type 2 diabetes per se, leading to reduced insulin action in the hypothalamus (Jones, 2007; Corona and Maggi, 2010; Wang et al, 2011).

Other endocrine disorders such as hyperprolactinaemia, hypothyroidism, hyperthyroidism or growth hormone deficiency can be concurrently present in men with ED and diabesity, with thyroid abnormalities more commonly observed in diabetes, although there is no significant difference in the circulating levels of these hormones when compared with the general population (Cummings, 2004).

Other factors

There is evidence that sedentary lifestyle, smoking and alcohol consumption are linked to the occurrence of ED, with increased physical activity conferring some protection upon development of ED (Rajendran and Cummings, 2012).

A number of drugs that have been used to treat diabetes or its complications have been associated with the development of ED, although the aetiological process is unclear.

The prevalence of psychological or psychiatric disease can be up to 40% causing performance anxiety, although it is not possible to implicate this as the primary aetiological precipitant of ED, as generally organic disease predominates (Cummings, 2004). There are a number of other factors which have been described in men with ED and diabetes (see *Table 1*).

Table 1. Factors affecting erectile function in men with diabetes.

Factors	Comments
Changes within corpus cavernosum	Abnormalities in the biochemical mediators of smooth muscle relaxation and constriction and smooth muscle function
Drugs	Iatrogenic (used for treatment of diabetes and its complications)
Endocrine	Hypogonadism, hyperprolactinaemia, hypothyroidism, hyperthyroidism, growth hormone deficiency
Localised penile abnormalities	Traumatic injuries, Peyronie's disease, phimosis, balanitis, tumours etc.
Miscellaneous	Renal failure, dialysis, alcohol abuse, psychiatric disorders etc.
Neurological	Spinal cord lesions, autonomic neuropathy
Vascular	Atherosclerosis, chronic low grade inflammation, endothelial dysfunction, arterial insufficiency, venous leakage

"The emerging evidence shows that erectile dysfunction may be the early clinical manifestation of generalised vascular disease."

The risk of cardiovascular disease

The emerging evidence shows that ED may be the early clinical manifestation of generalised vascular disease and is an independent risk for cardiovascular events (Shin et al, 2011). ED precedes clinically evident coronary artery disease (CAD) and can predict future cardiovascular events, with the severity of ED correlating to the extent of CAD.

There are two hypotheses linking ED, cardiovascular disease (CVD) and diabetes (Araña Rosaínz Mde et al, 2011; Shin et al, 2011). One hypothesis implicates endothelial dysfunction and chronic inflammation that can be caused by various vascular insults including diabetes. The other theory is the artery size hypothesis, with the same plaque burden having greater effect on blood flow in penile arteries (due to smaller diameter) compared to coronary arteries. This would explain why ED manifests earlier than CVD. In summary, the onset of ED could be a potential screening tool for silent CAD in men with diabesity.

Clinical examination and investigations

Broadly, the assessment and treatment of ED is similar in men with or without diabesity, but there are some specific therapeutic approaches which are important in the context of diabesity. It is important to assess for any underlying microvascular or macrovascular complications, especially silent CAD, due to its well-described association with ED and diabetes. The second Princeton consensus guidelines (*Table 2*) are very useful in assessing the cardiovascular risk of a patient in relation to considering treatment for ED (Jackson et al, 2006). The international index of erectile function (IIEF), or its more recent abridged 5-item version, is a useful questionnaire tool that can be used as a guide to detect ED and monitor response to treatment (Rosen et al, 1999).

Box 1. Investigations to use in clinical practice.

Glycaemic control
- HbA_{1c}, fructosamine

Hormone axis
- Testosterone
- Follicle-stimulating hormone
- Luteinising hormone
- Prolactin
- Thyroid-stimulating hormone
- Free T4 and T3
- Growth hormone
- Insulin-like growth factor 1
- Magnetic resonance imaging of the pituitary gland

Vascular and neural factors
- Penile doppler studies
- Physiological tests of the autonomic nervous system
- Cavernosography and arteriography

Others
- Psychosexual assessment
- Responsiveness to a standard intra-cavernosal injection (papaverine test)
- Nocturnal penile rigidity studies
- Prostatic specific antigen

Table 2. The second Princeton consensus guidelines on cardiovascular risk stratification in patients with sexual dysfunction (Jackson et al, 2006).

Grading of risk	Cardiovascular status at presentation	Recommendation for the management of ED
Low risk	Controlled hypertension Asymptomatic and <3 major risk factors for CAD, excluding gender Mild valvular disease Mild stable angina Post MI (>6–8 weeks) or post successful re-vascularisation (3–4 weeks) CHF (NYHA class I)	Manage ED within primary care setting Review treatment options with patient and partner (where possible)
Intermediate risk	Recent MI (between 2–6 weeks) Asymptomatic and ≥3 risk factors for CAD, excluding gender CHF (NYHA Class II) Non-cardiac atherosclerotic sequelae (e.g. CVA) Moderate stable angina	Specialised evaluation recommended (for example exercise testing or echocardiography) Place patient in high or low group depending upon outcome of testing
High risk	Unstable or refractory angina Uncontrolled hypertension CHF (NYHA Class III, IV) Recent MI (within last 2 weeks) High-risk arrhythmias Obstructive hypertrophic cardiomyopathy Moderate/severe valvular disease	Refer for specialised cardiac evaluation and management Treatment for ED to be deferred until cardiac condition stabilised and/or specialist evaluation completed

CAD=coronary artery disease; CHF=congestive heart failure; CVA=cardiovascular accident; ED=erectile dysfunction; MI=myocardial infarction; NYHA=New York Heart Association.

Investigations available in clinical practice for men with ED and diabesity are shown in *Box 1*. In our own practice, we limit investigations to hormonal blood tests, although we acknowledge that the yield of unrecognised endocrine abnormalities (apart from hypogonadism) is low. Screening for hypogonadism is important as concurrent treatment with both testosterone replacement therapy and phosphodiesterase-5 (PDE5) inhibitors may be of benefit (Jones et al, 2007).

Pharmacotherapy

Lifestyle modification and glycaemic control

Weight loss, increased physical activity, stopping smoking and limiting alcohol consumption are important lifestyle changes that need to be reinforced in people with ED and diabesity. *Table 3* summarises the studies that suggest that weight loss may be beneficial in improving ED in diabesity (Dallal et al, 2008; Wing et al, 2010; Khoo et al, 2011). Psychosexual counselling (such as sensate focusing) is important in men with an overt psychological or psychiatric aetiology to their ED. While drug therapy improves glycaemic control when ED develops concomitantly with acute deterioration in glycaemic control, there is no evidence of enhanced erectile performance when glycaemic control is improved in patients with chronic hyperglycaemia and ED (Cummings, 2004). Also, in our experience despite drugs being associated with development of ED, restoration of potency is only successful in those patients when a clear temporal relationship between

Table 3. Summary of studies comparing weight loss and erectile dysfunction in obese men with diabetes.

Source	Type and length of study	Number of subjects analysed in the study	Primary measure of erectile function	BMI at baseline (kg/m²)	% Weight loss (kg)	Outcome
Dallal et al, 2008	Prospective study, follow-up ranged from 6 to 45 months (mean=19 months)	97 (only had 49 individuals with diabetes)	BSFI	51.4	34.2% **Intervention:** Roux-en-Y gastric bypass	The degree of improvement in sexual function after gastric bypass was directly related to the amount of weight loss
Wing et al, 2010	Randomised controlled trial, 12 months	306, including DSE group (*n*=153) and ILI group *n*=153)	IIEF	35.1 ± 5.2 (DSE group); 35.6 ± 5.5 (ILI group)	0.6% (DSE group); 9.9% (ILI group) **Intervention:** Diet and increased physical activity	Though weight loss is ineffective in improving erectile dysfunction over time, weight loss may maintain erectile function or prevent deterioration
Khoo et al, 2011	Randomised controlled trial, 52 weeks	31, including HP diet group (*n*=12) and LCD group (*n*=19)	IIEF-5 score	35.6 ± 4.8 (HP diet group); 35.1 ± 4.3 (LCD group)	8.2% (HP diet group); 8.5% (LCD group); **Intervention:** Diet	Sexual function was improved by rapid diet-induced weight loss

BSFI=brief male sexual inventory; DSE=diabetes support and education; HP=high protein; IIEF=International Index of Erectile Function; IIEF-5=five item version of the International Index of Erectile Function; ILI:=intensive lifestyle intervention; LCD= low-calorie diet, subjects were switched to high-protein diet at 8 weeks for weight maintenance.

the commencement of the drug (within 2 weeks) and the development of ED has been established and the drug withdrawn. This may not be always possible due to other therapeutic reasons.

Figure 1 is a simple algorithm that we suggest to guide physicians in treating ED and diabesity. For a summary of treatment options, see *Table 4*.

Testosterone replacement therapy in hypogonadal men

Testosterone replacement can be successful in hypogonadal men, with some recipients often noticing dramatic improvement within days of commencing treatment. This can be either intramuscular testosterone (given every 3 weeks with standard testosterone or every 3 months with longer-acting preparations) or topical testosterone in the form of gels or creams. The method is largely a lifestyle choice as topical therapy involves avoiding contact with water and other people for a short time after application whereas parenteral therapy can sometimes be quite painful.

Other routes such as buccal or subcutaneous implants are rarely used. Nearly 60% of men with ED who previously failed to respond to PDE5 inhibitors and are now diagnosed as hypogonadal respond to PDE5 inhibitors alongside testosterone replacement therapy (Jones, 2007; Corona and Maggi, 2010; Wang et al, 2011).

Oral agents

Oral PDE5 inhibitors have revolutionised the management of ED and sublingual apomorphine and oral yohimbine are now rarely used. PDE5 inhibitors facilitate erections through prolonging the availability of cyclic guanosine monophosphate that promotes smooth muscle relaxation within the corpus cavernosum. Currently there are four commercial forms of PDE5 inhibitors available: sildenafil, vardenafil, tadalafil and avanafil.

Though it is difficult to reliably interpret any clinical differences in effectiveness between these agents, tadalafil has the added advantage in that it can be administered daily without timing the PDE5

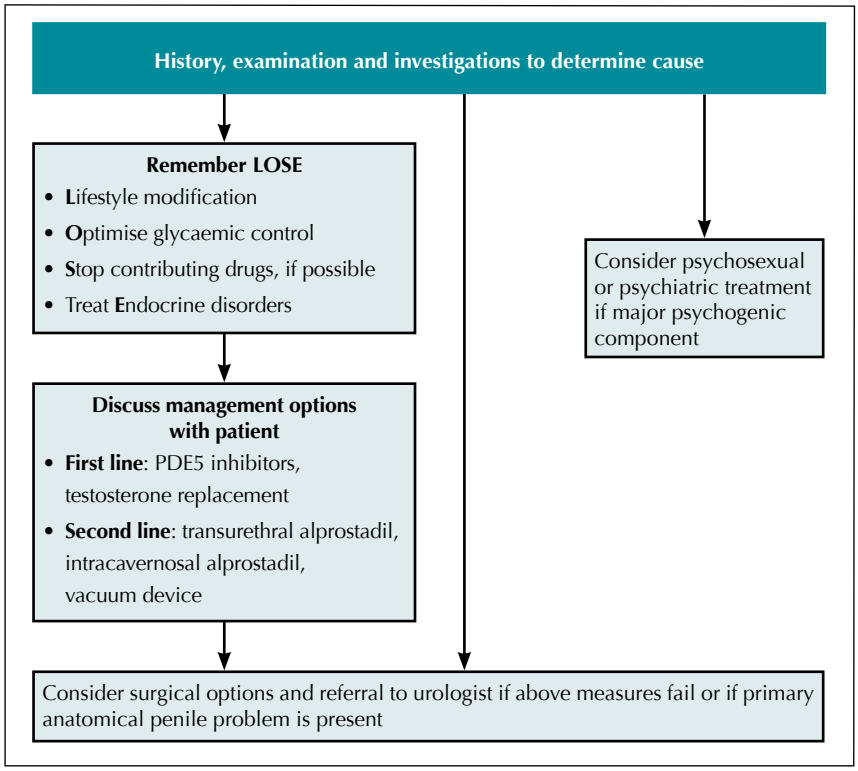

Figure 1. Simple algorithm for treatment of an obese man with diabetes presenting with erectile dysfunction.

inhibitor to sexual activity. In general, between three and four out of five patients will respond, a response rate that is slightly less than that of the general population with ED. They are cost-effective and generally well tolerated. Selected CAD patients with stable disease who are not on nitrate therapy can take PDE5 inhibitors. Though some studies have shown beneficial effects on endothelial dysfunction and fewer cardiovascular events (Phé and Rouprêt, 2012), more robust randomised controlled trials are needed to establish the long term cardio-protective effects of PDE5 inhibitors.

There are very few published studies assessing the use of over-the-counter herbal or Chinese traditional medicines such as panax ginseng, butea superba and yohimbine and even they are not considered robust. Many of these natural products contain either potent inhibitors of PDE5 (Chen, 2009) or pharmacological doses of PDE5 inhibitors such as sildenafil or tadalafil (Fleshner et al, 2005). This is clearly a concern when marketed freely because they have a potentially fatal interaction with nitrates.

Second- and third-line options

Intracavernosal injections with papaverine and phentolamine have been used to treat ED since the 1980s, but both drugs can cause priapism (erections lasting greater than 6 hours) and other side effects. As such, their use has been superseded by a licensed intracavernosal preparation of prostaglandin E1 (alprostadil) that can be self-administered directly into the corpus cavernosum. It is the most potent treatment available (approximately nine out of 10 injections in the general population resulted in successful erections) with a lower incidence of priapism and there is no significant difference in

Table 4. A summary of treatment options for obese men with diabetes and erectile dysfunction.

Treatment		Comments
First line	Oral therapy	Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil, avanafil)
	Testosterone replacement therapy (for proven hypogonadism only)	Topical or parenteral therapy
Second line	Intracavernosal therapy	More common: prostaglandin E1 (alprostadil) Less common: thymoxamine, papaverine, phentolamine
	Trans-urethral therapy	Alprostadil
	Vacuum devices	Manual or battery operated
Third line	Penile implants	Rarely used (after all other options exhausted)
Other	Surgery to correct any underlying defects	Venous leaks, traumatic injuries, Peyronie's disease, phimosis etc.
	Psychosexual therapies	Sensate focusing

response between men with and without diabetes. Other side effects include local pain and tingling, bruising, fibrosis, scarring and occasional infection.

The application of alprostadil in the form of a pellet into the urethra has been associated with a 65.9% success rate in achieving erections suitable for sexual intercourse in the general population, with similar success rates in the subgroup of men with diabetes. Side effects include penile pain, minor urethral trauma and dizziness, although priapism has not been reported.

Though vacuum devices provide a safe alternative strategy to pharmacological therapy, they require a moderate degree of manual dexterity and are usually only suitable for men in stable relationships with nearly one-third of men discontinuing it due to bruising, discomfort and ejaculatory failure.

Penile prostheses may be considered in men who have failed to respond to less invasive measures. Corrective surgery may be considered in men with primary penile abnormalities such as Peyronie's disease and venous ligation may be undertaken in men with established venous leaks (Cummings, 2004).

Future treatment options

Newer agents such as topical nitrates or combinations of aminophylline, isosorbide dinitrate and co-dergocrine, oral L-arginine, bremelanotide, and intracavernosal vasoactive intestinal polypeptide continue to be explored.

Though controversial, gene therapy and umbilical stem cell therapy may become available in the future for refractory cases (Bivalacqua et al, 2003; Cummings, 2004; Bahk et al, 2010).

Conclusion

In summary, effective intervention is now available for the vast majority of men with diabesity who present with ED. Lifestyle modification such as weight loss, increased physical activity and smoking cessation are beneficial in preserving erectile function.

Hypogonadism in men with ED and diabesity is now increasingly recognised and assessment should also include focus on silent CVD and this may influence treatment options. The advent of PDE5 inhibitors has revolutionised the management of ED but it important for healthcare professionals to adopt a more holistic approach to this under-diagnosed complication of diabesity. ■

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"Lifestyle modification such as weight loss, increased physical activity and smoking cessation are beneficial in preserving erectile function."

Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. Which ONE of the following is the most appropriate estimation of the PREVALENCE of erectile dysfunction (ED) in men with diabetes?
Select ONE option only.

A. 20%
B. 35%
C. 50%
D. 65%
E. 80%

2. Which ONE of the following physiological abnormalities has been demonstrated in the corpora cavernosa of men with diabetes and ED?
Select ONE option only.

A. Increased acetylcholine-mediated muscle relaxation
B. Increased NO synthase levels
C. Increased noradrenaline levels
D. Reduced endothelin-1 levels
E. Reduced vasoactive intestinal polypeptide activity

3. According to a 2004 paper, what was the percentage of men with diabetes and ED shown to have REDUCED penile blood flow?
Select ONE option only.

A. 25%
B. 33%
C. 50%
D. 66%
E. 95%

4. If a man with diabesity is diagnosed with hypogonadism, which is the MOST likely biochemical abnormality?
Select ONE option only.

	Gonadotrophins	Testosterone
A.	High	Low
B.	High	Normal
C.	Normal	High
D.	Normal	Low
E.	Low	High
F.	Low	Normal

5. Which SINGLE ONE of the following men with diabetes and ED is MOST LIKELY to notice an improvement in the potency of their erections?
Select ONE option only.

A. A 37-year-old who developed ED 6 months after starting propranolol and is now planning to stop taking it
B. A 47-year-old with obesity who intentionally lost weight upon the diagnosis of ED and significantly improved his chronic hyperglycaemia
C. A 57-year-old who developed ED within 2 weeks of starting bendroflumethiazide and did not renew his prescription
D. A 77-year-old who developed ED immediately after a cerebrovascular accident 3 months ago

6. A 53-year-old man with type 2 diabetes, hypogonadism and ED failed to respond to full doses of sildenafil. What APPROXIMATE percentage of men in this situation will respond to a combination of sildenafil and Testogel?
Select ONE option only.

A. <10%
B. 20%
C. 40%
D. 60%
E. 80%

7. What is the APPROXIMATE percentage of men with diabetes and ED who will have significantly improved erections with a phosphodiesterase-5 inhibitor?
Select ONE option only.

A. 10%
B. 25%
C. 33%
D. 50%
E. 75%

8. A 64-year-old man with type 2 diabetes, hypertension and ischaemic heart disease has recently developed ED. His erections are inadequate for penetrative sex. Which is the MOST appropriate medication to recommend for his ED?
Select ONE option only.

A. Alprostadil
B. Apomorphine
C. Ginseng
D. Phentolamine
E. Tadalafil

9. Which one of these treatments for ED (given by brand name) is the MOST POTENT?
Select ONE option only.

A. Caverject
B. Cialis
C. Levitra
D. MUSE
E. Viagra

10. The diagnosis of ED in a man with diabetes should be regarded as an independent risk factor for which ONE of the following?
Select ONE option only.

A. Benign prostatic hyperplasia
B. Colorectal cancer
C. Coronary artery disease
D. Hyperuricaemia
E. Spinal stenosis