Erectile dysfunction (ED) affects about 30 million men in the United States to some extent.\textsuperscript{1–3} It may indicate the presence of a serious underlying medical condition, such as cardiovascular disease (CVD), diabetes, or depression. It compromises multiple aspects of a patient’s life, including overall quality of life and interpersonal relationships.

ED is common among men with diabetes. Its incidence increases with advancing age, and it occurs at an earlier stage than age-matched counterparts without diabetes. The etiology of ED in the diabetic population is multifactorial. In order to ensure the best possible outcomes in managing this problem, clinicians need to be aware of the underlying pathophysiology.

Patients with diabetes respond to phosphodiesterase type 5 (PDE-5) inhibitors, but the response is lower than in those without diabetes. Coexistence of hypertension, CVD, and poor glycemic control worsens ED. A multidisciplinary approach should be considered to deal with the different comorbidities, including psychiatric, endocrine, cardiovascular, and urological issues.

**PREVALENCE OF ED IN DIABETES**

It is estimated that 35–75% of men with diabetes have ED. Compared to age-matched control subjects, men with diabetes develop ED ~5–10 years earlier.\textsuperscript{4} In a cross-sectional survey of 541 men with diabetes at a community-based clinic, the prevalence of ED increased progressively with age. The prevalence was 6% in the age group 20–24 years and 52% in the age group 55–59 years. After the age of 60 years, 55–95% of men with diabetes were affected by ED, compared to \textasciitilde{} 50% in an unselected population in the Massachusetts Aging Male Survey.\textsuperscript{5,6} In another cohort of patients having type 1 diabetes for at least 10 years, ED was reported in 1.1% of men in the age group 21–30 years, 55% of men in the age group 50–60 years, and 75% of men > 60 years of age.\textsuperscript{7}

ED in men with diabetes is correlated with hemoglobin A\textsubscript{1c} (A1C). The presence of peripheral neuropathy increases the risk of ED, possibly because of underlying autonomic neuropathy. Almost 100% of patients with diabetic neuropathy will have ED. Endothelial dysfunction is a major etiological factor that is common to diabetes, ED, and CVD.

Management of ED has been dramatically altered by the introduction of PDE-5 inhibitors. Data suggest that patients with diabetes do not respond to treatment as well as patients without diabetes.\textsuperscript{7–9} Alternative therapies may be needed to overcome this problem. This review focuses on the evaluation, management, and significance of ED in patients with diabetes.

**PATHOPHYSIOLOGY OF ED**

ED in men is multifactorial in origin. Diabetes is associated with accelerated large vessel atherosclerosis, microvascular arterial disease, autonomic neuropathy, dyslipidemia, concomitant hypertension, and prominent endothelial dysfunction. All of these conditions contribute to ED. It is the combination of impairments in nearly every step responsible for the production of penile erection (Table 1). Clinicians must take these etiological factors into consideration when treating ED in men with diabetes. In addition to the listed causes (Table 2), a comprehensive evaluation should include assessment of gonadal function, medications, and drug history, along with psychological and marital status.\textsuperscript{7}

**ENDOTHELIAL DYSFUNCTION**

The endothelium is vital to the maintenance of vascular health. It is a critical determinant of vascular tone and patency, reactivity, inflammation, vascular remodeling, and blood fluidity.\textsuperscript{7,10} Nitric oxide (NO) is the most potent vasodilator and is secreted by the endothelium. It is synthesized from L-arginine by the endothelial enzyme NO synthase (eNOS) (Figure 1). NO released in response to sexual stimulation relaxes penile vascular smooth muscle by increasing intracellular cyclic 3’, 5’-guanosine monophosphate (cGMP) concentration. Vasodilatation of erectile tissues allows the sinusoidal
Table 1. Pathophysiology and Factors Complicating Diabetic ED

- Increasing age and hyperglycemia leading to glycation of elastic fibers with failure of relaxation of the corpora cavernosa
- Peripheral vascular disease causing reduced arterial and arteriolar inflow
- Advanced glycation end products leading to increase in reactive oxidizing substances and reduced NO production
- Failed neural signal transmission to and from the spinal cord due to diabetic neuropathy and reduced production of neuronal NO synthase causing reduced levels of neuronal NO release to the cavernosal smooth muscle
- Endothelial dysfunction of the sinusoidal endothelial cells resulting in a decrease in NO release and impaired vasodilatation
- Hypogonadotrophic hypogonadism
- Multiple drug regimens
- Dyslipidemia

Table 2. Modifiable Risk Factors for ED and Their Management

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary lifestyle</td>
<td>Increase physical activity</td>
</tr>
<tr>
<td>Depression</td>
<td>Treatment of depression</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Improved control</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Abstinence from alcohol</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Quit smoking/use of patch</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Testosterone replacement</td>
</tr>
<tr>
<td>Overweight or obesity</td>
<td>Weight loss</td>
</tr>
<tr>
<td>(BMI &gt; 26.9 kg/m²)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Production and action of NO. GTP, guanosine triphosphate; 5 GMP, 5'-guanosine monophosphate; sol GC, soluble guanylate cyclase; O₂, oxygen. Cholinergic stimulation causes release of ACh. ACh activates eNOS to produce NO from L-arginine. NO in the smooth muscle cells activates solGC. This converts GTP to cGMP. cGMP causes Ca²⁺ efflux, which leads to relaxation of the smooth muscle. cGMP is degraded to 5 GMP via PDE-5, thus providing a therapeutic target to prolong the action of cGMP.

There is increasing evidence that ED correlates with the level of glycemic control. In animal experiments, elevated A1C significantly impairs endothelial NO-mediated corpus cavernosal relaxation in vitro. A retrospective analysis of a cohort of men with type 2 diabetes demonstrated that A1C was an independent predictor of erectile function score. An inverse relationship between severity of ED assessed by the International Index of Erectile Function (IIEF) score and A1C has also been demonstrated. The IIEF, a multidimensional scale for assessment of ED, provides a broad measure of sexual function (Table 3).

The ability to increase blood flow depends on an intact neurogenic vascular response. ED in men with diabetes is correlated with endothelial dysfunction. Since acetylcholine (ACh) is important in the production of NO, a decrease in the amount of ACh leads to decreased production of NO. Diabetic autonomic neuropathy leads to impaired endothelium-dependent and -independent vasodilatation even in the absence of clinical macrovascular dis-
Table 3. The IIEF

**International Index of Erectile Function**
Precede all questions listed below with the phrase, “Over the past 4 weeks, . . .” Use the scale below each question in determining response.

Q1. How often were you able to get an erection during sexual activity?
Q2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?

<table>
<thead>
<tr>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No sexual activity; 1 = Almost never/never; 2 = A few times (much less than half the time); 3 = Sometimes (about half the time); 4 = Most times (much more than half the time); 5 = Almost always/always</td>
</tr>
</tbody>
</table>

Q3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
Q4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

<table>
<thead>
<tr>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Did not attempt intercourse; 1 = Extremely difficult; 2 = Very difficult; 3 = Difficult; 4 = Slightly difficult; 5 = Not difficult</td>
</tr>
</tbody>
</table>

Q5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
Q6. How many times have you attempted sexual intercourse?

<table>
<thead>
<tr>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No attempts; 1 = One to two attempts; 2 = Three to four attempts; 3 = Five to six attempts; 4 = Seven to 10 attempts; 5 = More than 11 attempts</td>
</tr>
</tbody>
</table>

Q7. When you attempted sexual intercourse, how often was it satisfactory to you?
Q8. How much have you enjoyed sexual intercourse?

<table>
<thead>
<tr>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Did not attempt intercourse; 1 = Not enjoyable; 2 = Not very enjoyable; 3 = Fairly enjoyable; 4 = Highly enjoyable; 5 = Very highly enjoyable</td>
</tr>
</tbody>
</table>

Q9. When you had sexual stimulation or intercourse, how often did you ejaculate?
Q10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?

<table>
<thead>
<tr>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No sexual stimulation/intercourse; 1 = Almost never/never; 2 = A few times (much less than half the time); 3 = Sometimes (about half the time); 4 = Most times (much more than half the time); 5 = Almost always/always</td>
</tr>
</tbody>
</table>

Q11. How often have you felt sexual desire?

<table>
<thead>
<tr>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Almost never; 2 = A few times (much less than half the time); 3 = Sometimes (about half the time); 4 = Most times (much more than half the time); 5 = Almost always/always</td>
</tr>
</tbody>
</table>

Q12. How would you rate your level of sexual desire?
Q13. How satisfied have you been with your overall sex life?
Q14. How satisfied have you been with your sexual relationship with your partner?

<table>
<thead>
<tr>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very dissatisfied; 2 = Moderately dissatisfied; 3 = About equally satisfied and dissatisfied; 4 = Moderately satisfied; 5 = Very satisfied</td>
</tr>
</tbody>
</table>

Q15. How do you rate your confidence that you could get and keep an erection?

<table>
<thead>
<tr>
<th>Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very low; 2 = Low; 3 = Moderate; 4 = High; 5 = Very high</td>
</tr>
</tbody>
</table>

**SCORING**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Erectile function</th>
<th>Intercourse satisfaction</th>
<th>Orgasmic function</th>
<th>Sexual desire</th>
<th>Overall satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questions</td>
<td>1, 6, 9, 11, 13</td>
<td>2, 7, 10, 12, 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1–30)</td>
<td>(0–15)</td>
<td>(0–10)</td>
<td>(2–10)</td>
<td>(2–10)</td>
</tr>
</tbody>
</table>
ease. The presence of peripheral neuropathy also increases the risk of ED, possibly because of undiagnosed autonomic neuropathy; almost 100% of patients with diabetic autonomic neuropathy will have ED. The interaction between endothelial dysfunction and autonomic neuropathy results in an inability to increase blood flow under conditions of stress or increased demands, such as during an erection.

**SIGNIFICANCE OF ED IN PATIENTS WITH DIABETES**

Many of the risk factors of ED are the same as those for CVD, which in patients with diabetes may be asymptomatic (Table 2). ED may be the first warning sign of underlying cardiovascular problems.

Gazzaruso et al. evaluated the prevalence of ED in 133 diabetic men without apparent complications but with angiographically verified silent coronary artery disease (CAD) and in 127 diabetic men without myocardial ischemia at exercise electrocardiogram (ECG), 48-hour ambulatory ECG, and stress echocardiography. The prevalence of ED was significantly higher in patients with silent CAD compared to those without silent CAD (33.8 vs. 4.7%). Multiple logistic regression showed that apolipoprotein(a) polymorphism, smoking, microalbuminuria, HDL cholesterol, and LDL cholesterol were significantly associated with silent CAD. Among the various factors, ED appeared to be the most efficient predictor of silent CAD. Thus, there may be a strong and independent association between ED and silent CAD in apparently uncomplicated type 2 diabetic patients. ED may also be a potential marker to identify diabetic patients to screen for silent CAD.

Billups et al. examined the relationship between traditional and emerging risk factors for CVD and the severity of penile vascular disease in 137 men with ED and without clinical CAD. Plasma hs-C reactive protein levels correlated significantly with increasing severity of penile vascular disease as measured by penile Doppler.

ED may be an early sign or symptom of CVD. The same vascular/endothelial injuries that occur in the coronary arteries likely occur in the cavernosal arteries, the primary vessels supplying the penile erectile tissue.

**MANAGEMENT OF ED**

Management of ED includes a full clinical evaluation and a careful assessment of medications and other etiological factors in ED. Examination should include determination of the testes size and the secondary sexual characteristics for hypogonadism. Laboratory investigations should include levels of testosterone, prolactin, and ferritin, among others (Table 4).

Several therapeutic strategies including lifestyle changes have been shown to improve endothelial function in patients with type 2 diabetes. Epidemiological studies have identified sedentary lifestyle as a potential modifiable risk factor in men with ED and provide moderate support for the beneficial role of increasing exercise. Recent studies also have shown marked improvement in erectile function with exercise and weight loss in a group of obese men with moderate ED and no overt symptoms of CVD as compared to the control group.

It is important to consider the medication history, especially in men with

---

**Table 4. Evaluation and Management Strategies**

**Medication History:** It is extremely important to consider side effects and drug interactions

- **Antihypertensives:** especially
  - ♦ β-Blockers: consider ACE inhibitor/angiotensin receptor blocker/calcium channel blocker
  - ♦ Thiazide diuretics: consider switching to furosemide
- **Agents acting on the central nervous system:** tricyclic antidepressant drugs, selective serotonin reuptake inhibitors, phenothiazines, butyrophenones, atypical antidepressants: consider switching to trazodone
- **Agents affecting the endocrine system:** Antiandrogens, gonadotropin-releasing hormone agonists and antagonists, estrogens, cimetidine, metoclopramide, fibric acid derivatives, alcohol, marijuana

**Hormonal Status:**
- Leutinizing hormone, follicle-stimulating hormone, prolactin
- Testosterone level
- Ferritin (to evaluate for hemochromatosis)

**Autonomic Neuropathy:**
- ECG (R-R variability), heart rate variability
- Orthostatic blood pressure readings
- Tilt table testing

**Vascular Disease:**
- Doppler studies of penile blood flow
- Pharmacodynamic testing using vasoactive compounds
- Pudendal angiography and cavernosometry

**Psychosocial Assessment:**
- Combine with nocturnal penile tumescence test
- Marital counseling
diabetes who are often on multiple drugs to treat hypertension, dyslipidemia, depression, glaucoma, neuropathic pain, and diabetes itself. The major medications responsible for ED are antihypertensives, especially nonselective β-blockers, sympatholytics, and diuretics. The main problem in diabetes is that often these medications cannot be replaced; β-blocker therapy is essential in patients with coronary heart disease or heart failure. Equally important are treatments for patients who suffer from conditions such as pain and depression. These problems are real to patients and, if not adequately treated, are likely to exacerbate ED. Physicians should try and optimize therapy with agents that are less likely to cause ED (Table 4). ACE inhibitors, angiotensin II receptor blockers (ARBs), statins, and thiazolidinediones should theoretically improve erectile function as they either enhance NO levels or block production of oxygen radicals, which deplete NO and prevent vasodilatation.22–27

PDE-5 Inhibitors
The Food and Drug Administration approved three drugs of the PDE-5 category for clinical use in the treatment of ED. Sildenafil was the first drug in this class, followed by the newer agents tadalafil and vardenafil. These drugs are potent and selective inhibitors of cGMP-specific PDE-5. They prevent the breakdown of cGMP and prolong and improve smooth muscle relaxation. PDE-5 is the isoform of the enzyme highly expressed in cavernosal tissue. Hence, vasodilatation is greater in this tissue.

A meta-analysis of 11 randomized, double-blind, placebo-controlled trials of sildenafil citrate in patients with diabetes reported improved erections in 59% of those with type 1 diabetes and 63% of those with type 2 diabetes.8 Improvement was noted regardless of age, race, ED severity and duration, or presence of various comorbidities.28 Patients with diabetes experienced a decreased response rate as compared to those without diabetes (83%). There was a discontinuation rate from 5 to 17%, primarily due to insufficient clinical response.9

With tadalafil, 76% of men with diabetes taking the 20-mg dose had improved erections. Of the total number of patients in the group, 58% had erections satisfactory to complete intercourse. Comparatively, in nondiabetic men the rates were 81 and 75%, respectively.29 Use of vardenafil led to improved erections in 71–75% of non-diabetic men with 5-, 10-, and 20-mg doses. In men with diabetes, the response rates were comparatively lower at 57% with the 10-mg dose and 72% with the 20-mg dose.30 It is possible that this lower response rate in men with diabetes is related to their more severely impaired endothelial function.23

Taking into consideration the prevalence of CVD in patients with ED, concerns regarding the risk of sexual activity triggering acute cardiovascular events and potential risks of adverse or unanticipated drug interactions were addressed by the Princeton Consensus Panel. Patients were stratified into low-, intermediate-, or high-risk categories (Table 5).19 Exercise training after acute myocardial infarction (MI) improves cardiovascular efficiency and reduces myocardial oxygen consumption during regular activities, including sexual activity.17,31,32 Cardiac rehabilitation exercise programs are helpful in reducing coital symptoms and coital heart rates.17,19,33 Patients whose cardiac condition is uncertain and those with multiple risk factors require further testing or evaluation before resuming sexual activity.19 Patients at high risk should be stabilized by cardiological treatment before resumption of sexual activity is considered or treatment of sexual dysfunction is recommended.

The relative risk of a coitus-induced coronary event is not greater in patients with established CAD than in those without documented cardiac disease.19 Clinical studies of the PDE-5 inhibitors demonstrated no increase in MI or death rates in men compared to expected rates.19,33–35 Patients with known CAD or heart failure receiving PDE-5 inhibitors did not exhibit worsening ischemia, coronary vasoconstriction, or hemodynamics on exercise testing or cardiac catheterization.19,36–40 However, the use of nitrates is absolutely contraindicated in patients taking PDE-5 inhibitors for ED.39 α-Blockers are contraindicated with sildenafil and vardenafil. The PDE-5 inhibitors have a minimal effect on QTc interval.19,41 Vardenafil in one study was shown to increase the QTc interval by 6–9 milliseconds. It is not recommended in patients taking type IA antiarrhythmics, such as quinidine or procainamide, or type III antiarrhythmics, such as sotalol and amiodarone, or in patients with congenital prolonged QT syndrome.19 Statistically significant QTc interval changes have not been observed with either sildenafil or tadalafil.19

Intracavernosal Therapy
Several vasoactive substances can be used to stimulate the erectile process. These substances can be delivered directly into the corpora cavernosa by injection. Papaverine is a nonspecific PDE, and alprostadil is a prostaglandin E1 derivative. These two drugs, when given via the intracavernosomal route, relax the smooth muscle of the corpora cavernosa. Another agent in use is phentolamine. Phentolamine is a competitive inhibitor of α-adrenergic receptors, which reduces sympathetic tone. Some practitioners use a combination of these agents, although very few large clinical trials of these combinations have been carried out.

Alprostadil is a synthetic prostaglandin related to prostaglandin E1. It has α-blocking properties, is a vasodilator, and directly relaxes smooth muscle via a prostacyclin receptor. Use of alprostadil in men with diabetes and ED has been studied. The largest study included 577 men, of whom 69% completed the 6-month injection therapy study. Eighty-seven percent of the men
Intraurethral Prostaglandin Therapy
An intraurethral alprostadil suppository system was developed in an attempt to avoid the problems and issues related to injection therapy. Although it avoids the side effects of injection therapy, it may cause urethral pain in ~30% of the users. It has not been effective in those who have failed injection therapy. In a large study, 70% of men with diabetes were able to achieve an erection satisfactory for intercourse in 70% of their attempts. Only 2.4% of the men discontinued use because of pain.

Vacuum-Constriction Devices
Vacuum tumescence devices work irrespective of the underlying etiology of ED. Diabetic men with ED report a success rate of 75%. Most men find the technique acceptable, especially if they have tried and failed oral or injection therapy. Some individuals may find it cumbersome. It can also be added on to one of the other treatment modalities to enhance a partial response.

Surgery
With the availability of various newer treatment modalities, the use of penile prostheses has declined. However, there is an 86% success rate at 5 years, and 91% of erections are suitable for coitus. Diabetes, however, poses a risk for prosthesis-associated infection and can often necessitate the removal of the prosthesis and possible worsening of the primary problem. Rarely, severely compromised blood flow could lead to device failure. Revascularization might help some of these patients, but it is difficult to select patients with a predictable good outcome. Also, revascularization is relatively contraindicated in men with diabetes. In some patients, there could be venous incompetence, which can be improved by ligation of the deep dorsal vein and any incompetent circumflex veins.

The complexity of ED, the underlying endothelial dysfunction and neuropathy, and the extent of vascular disease in patients with diabetes leads to less successful outcomes for these surgical procedures. Surgery should be reserved for clear-cut cases of vascular or venous insufficiency in young patients with recent-onset diabetes.

α-Blockers
There are several over-the-counter herbal remedies but no adequate scientific data to support their efficacy or

---

Table 5. Risk Stratification for CVD and Management Recommendations

<table>
<thead>
<tr>
<th>GRADE OF RISK</th>
<th>CATEGORIES OF CVD</th>
<th>MANAGEMENT RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>• Asymptomatic, &lt;3 major risk factors for CAD</td>
<td>• Primary care management</td>
</tr>
<tr>
<td></td>
<td>• Controlled hypertension</td>
<td>• Consider all first-line therapies</td>
</tr>
<tr>
<td></td>
<td>• Mild, previously evaluated angina</td>
<td>• Reassess at regular intervals (6–12 months)</td>
</tr>
<tr>
<td></td>
<td>• Post-successful coronary revascularization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Uncomplicated past MI (&gt;6–8 weeks) with negative stress test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mild valvular disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Congestive heart failure (New York Heart Association Class I)</td>
<td></td>
</tr>
<tr>
<td>Intermediate or</td>
<td>• ≥3 major risk factors for CAD, excluding sex</td>
<td>• Specialized cardiovascular testing (e.g., exercise tolerance test, echocardiogram)</td>
</tr>
<tr>
<td>Indeterminate Risk</td>
<td>• Moderate, stable angina</td>
<td>• Restratification into high- or low-risk based on the results of cardiovascular assessment</td>
</tr>
<tr>
<td></td>
<td>• Recent MI or cardiovascular accident (&lt;6 weeks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Left ventricular dysfunction/congestive heart failure (New York Heart Association Class II)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Arrhythmia of unknown cause</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>• Unstable or refractory angina</td>
<td>• Priority referral for specialized cardiovascular management</td>
</tr>
<tr>
<td></td>
<td>• Uncontrolled hypertension</td>
<td>• Treatment for ED to be deferred until cardiac condition stabilized and dependent on specialist recommendations</td>
</tr>
<tr>
<td></td>
<td>• Congestive heart failure (New York Heart Association Class III, IV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recent MI (&lt;2 weeks), cardiovascular accident</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High-risk arrhythmias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypertrophic and other cardiomyopathies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Moderate/severe valvular disease</td>
<td></td>
</tr>
</tbody>
</table>
safety. Yohimbine and phentolamine are α-adrenergic blockers that have been shown to have modest efficacy in treating ED. However, they are not widely in use, especially in the United States. Side effects include palpitations and hypertension. In a recent study of 18 nonsmoker male subjects with ED, a 50% success rate (completion of intercourse) was reported in > 75% of the attempts. The patients who responded tended to have less severe ED. A meta-analysis of yohimbine use found it to be more effective than placebo (odds ratio 3.85, 95% confidence interval 6.67–2.22). Yohimbine has been advocated for more than a century as a treatment for ED. However, results of studies have been inconsistent, and adverse cardiovascular events have been observed in some studies.

Androgen Therapy

Hypogonadism is being increasingly recognized as a comorbid condition associated with type 2 diabetes, metabolic syndrome, and other chronic illnesses. Men who are obese and have type 2 diabetes are more prone to hypogonadotropic hypogonadism. This is attributed to elevated levels of estrone and estradiol produced by the aromatase enzyme in adipose tissue derived from adrenal (androstenedione) and testicular (testosterone) androgen. Aging is also associated with a progressive decline in androgens.

Workup of ED should always include a measured or calculated plasma free testosterone level. If this is low, a prolactin level should be checked to rule out a central problem. Screening serum testosterone levels of 105 consecutive patients with ED showed that 37 patients had previously unsuspected disorders of the hypothalamic-pituitary-gonadal axis. Twenty patients had hypogonadotropic hypogonadism, seven had hypergonadotropic hypogonadism, eight had hyperprolactinemia, and two had occult hyperthyroidism. Once the specific condition was defined and treated, 33 patients regained adequate erectile function.

Of note also is that serum testosterone concentration is inversely associated with carotid atherosclerosis in men with type 2 diabetes. Vascular cells contain sex steroid hormone receptors. Testosterone can exert its effect on the vascular wall, either directly or through aromatization to estrogen. It is uncertain if any of these etiologies contribute to ED. However, they must be considered and, if severe, treated with androgen replacement. There has been a poor yield of results when testosterone is used as monotherapy for treatment of ED, however. In a study of 78 obese men with type 2 diabetes, only 17% reported improved long-term sexual function when placed on testosterone enanthate.

The use of testosterone in men with normal testosterone levels is not advocated. Replacement therapy should be reserved for those who are androgen deficient, especially if they are contemplating the use of a PDE-5 inhibitor. This is because neural NO production is androgen dependent, and PDE-5 inhibitors require the presence of NO to be effective.

CONCLUSION

The etiology of ED is multifactorial. Workups of patients for ED must include a detailed medication history because medication regimens are quite often the culprit. Astute physicians must try to make appropriate therapeutic exchanges when possible. It is important to stress lifestyle changes in addition to pharmacological treatments. There are many therapeutic options for treating ED.

Given the prevalence of CVD in patients seeking medical attention for ED, the Princeton Consensus Conference emphasized the importance of risk factor evaluation and risk stratification of patients into low-, intermediate-, and high-risk groups for management of ED. Clinical trial data provide support for the overall cardiac safety of PDE-5 inhibitors in patients with ED, even though a majority of these patients have cardiovascular risk factors. A number of investigators have even proposed potential cardiovascular benefits of sexual activity and PDE-5 inhibitors.

Follow-up at regular intervals and reassessment of all patients receiving treatment for ED is highly recommended. Patients with ED should undergo evaluation of cardiovascular risk factors and assessment for subclinical CVD on a routine basis. Comprehensive evaluation and treatment of ED can lead to overall improved quality of life and well-being for patients.

ACKNOWLEDGMENTS

Diabetes research and education at Tulane University Health Sciences Center is supported in part by the John C. Cudd Memorial Fund, the Tullis–Tulane Alumni Chair in Diabetes, and the Susan Harling Robinson Fellowship in Diabetes Research.

REFERENCES

9. Guay AT, Bansal S, Heatley GJ: Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene...


*Tina K. Thethi, MD, is a fellow in Endocrinology, Metabolism, and Diabetes; Nana O. Asafu-Adjaye, MPH, is the clinical research coordinator for the ACCORD Trial; and Vivian A. Fonseca, MD, is the Tullis Tulane Alumni Chair in Diabetes and chief of the Section of Endocrinology and Metabolism at Tulane University Health Sciences Center in New Orleans, La.*