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Assessment of Cardiovascular Risk in Patients with Erectile Dysfunction

Focus on the Diabetic Patient

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Erectile dysfunction (ED) is commonly associated with risk factors for cardiovascular disease, including diabetes. The prevalence of ED in diabetic patients is high—about 75% of diabetic men 60 yr of age or older had ED in one study. Endothelial dysfunction, accelerated atherosclerosis, and diabetic neuropathy likely contribute to ED in diabetics. As silent ischemia is common in the diabetic patient, and diabetes is now often thought of as a coronary heart disease risk equivalent, diabetic men seeking therapy for ED may be considered candidates for exercise stress testing. Phosphodiesterase 5 (PDE5) inhibitors improve erectile function in diabetic men with ED; however, efficacy rates may be somewhat lower than in nondiabetic men. Studies to date have suggested that PDE5 inhibitors per se do not cause an increase in myocardial infarction rates in men being treated for ED.

Key Words: Diabetes; endothelial dysfunction; ischemia; sildenafil; tadalafil; vardenafil.

Introduction

It has been estimated that at least 30 million men in the United States have erectile dysfunction (ED). Studies over the last 15 yr have helped to clarify risk factors associated with ED. Major risk factors include aging; chronic diseases (such as heart disease, hypertension, diabetes, hyperlipidemia, peripheral vascular disease, and lower urinary tract symptoms); medications such as thiazide diuretics, β blockers, and selective serotonin reuptake inhibitors, lifestyle issues such as smoking, stress, alcohol, and drug abuse; and neurologic diseases such as stroke, multiple sclerosis, and spinal chord injury; and psychogenic causes such as depression, anxiety, and relationship difficulties *(1)*. There are associations between ED and other endocrine disorders such as hypothyroidism, hyperthyroidism, and hyperprolactinemia. Prostate disease and structural diseases such as Peyronie disease may contribute *(2)*.

In men over the age of 50, the most common cause of ED is based on vascular disease. Diseased blood vessels cannot deliver adequate blood for erection owing to endothelial dysfunction with the inability of the vasculature to dilate and/or the presence of structural narrowing owing to atherosclerotic plaques that impede blood flow *(2)*.

ED in Men with Diabetes

The prevalence of ED in diabetic patients is high *(1–5)*. In a study by Klein et al. *(5)*, about 75% of diabetic men 60 yr of age or older had ED. An increased duration of diabetes was associated with an increased incidence of ED *(6)*. Sometimes ED can be an early warning sign of the presence of diabetes *(7)*. Diabetes can induce ED by both vascular and neurogenic mechanisms. First, diabetes is known to induce endothelial dysfunction of the vasculature and accelerate atherosclerosis *(8)*. Diabetic patients have reduced brachial artery flow-mediated dilation, suggestive of endothelial dysfunction. Second, diabetic neuropathy contributes to ED, and in one study the physical finding of diabetic patients that most closely correlated with the development of ED was loss of vibratory sense, as a result of diabetic neuropathy *(5)*.

ED affects the quality of life in patients with type 2 diabetes mellitus. DeBerardis et al. *(9)* recently studied the prevalence of self-reported ED and its impact on quality of life. Of 1460 patients with diabetes who enrolled in the study, 58% reported occasional to frequent erectile problems. Quality-of-life scoring showed that in these patients ED related to poorer physical health, mental health, and sexual life. Diabetic patients with ED were more likely to exhibit depressive symptoms. Nevertheless, the proportion of clinicians who query their diabetic patients about sexual issues is low. Sixty-three percent of clinicians never queried their patients, 27% occasionally queried their patients, and only 10% always asked their patients about sexual issues.

Cardiac Issues in the Diabetic Patient with ED

The risk factors for endothelial dysfunction and atherosclerosis including hypertension, lipid abnormalities, smok-

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Table 1
Management Recommendations Based on Graded Cardiovascular Risk Assessment[a]

Grade of Risk	Categories of CVD	Management recommendations
Low	• Asymptomatic, <3 major risk factors for CAD • Controlled hypertension • Mild, stable angina • Post–successful coronary revascularization • Uncomplicated past MI (>6–8 wk) • Mild valvular disease • LVD/CHF (NYHA class I)	• Primary-care management • Consideration of all first-line therapies • Reassessment at regular intervals (6–12 mo)
Intermediate	• ≥3 major risk factors for CAD, excluding gender • Moderate, stable angina • Recent MI (>2, <6 wk) • LVD/CHF (NYHA class II) • Noncardiac sequellae of atherosclerotic disease (e.g., CVA, peripheral vascular disease)	• Specialized CV testing (e.g., ETT, Echo) • Restratification into high risk or low risk based on results of CV assessment
High	• Unstable or refractory angina • Uncontrolled hypertension • LVD/CHF (NYHA class III/IV) • Recent MI (<2 wk), CVA • High-risk arrhythmias • Hypertrophic obstructive and other cardiomyopathies • Moderate/severe valvular disease	• Priority referral for specialized CV management • Treatment for sexual dysfunction to be deferred until cardiac condition stabilized and dependent on specialist recommendations

[a]CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVA, stroke; CVD, cardiovascular disease; Echo, echocardiogram; ETT, exercise tolerance test; LVD, left ventricular dysfunction; MI, myocardial infarction; NYHA, New York Heart Association. (From ref. *14*.)

ing, diabetes, and obesity are also risk factors for ED. Diabetes is, of course, an important risk factor for both coronary artery disease (CAD) and ED *(1)*. This could pose certain unique issues for the physician dealing with diabetic patients with both ED and CAD. While the overall risk of a cardiac event during with sexual activity is low for the general population (<1% of all myocardial infarctions [MIs] are related to sexual activity; Muller et al. *[10]*), there is a lack of data on the incidence of sexually related cardiac events specific to diabetic patients, especially since a high percentage of MIs are silent in the diabetic population. Furthermore, there are few data regarding the incidence of sexually related cardiac events in diabetic patients with ED who are treated for ED, but in reports so far no untoward increase in cardiac events was noted *(11,12)*. Overall, MI and cardiac death rates in men treated with phosphodiesterase 5 (PDE5) inhibitors have been very low—which is an encouraging finding *(13)*. As part of clinical ED trials, about 18% of patients are diabetics, and thus far there has been no signal in these trials of PDE5 inhibitors suggesting an increase in the rate of adverse cardiovascular event in the diabetic cohort.

Complicating the issue of the cardiovascular safety of sexual activity in the diabetic patient is the observation that angina is often silent in the diabetic patient or not infrequently manifests as an atypical symptom. Although the Princeton guidelines *(14)* (Table 1, Fig. 1) describe reasonable approaches to the cardiovascular workup of the patient seeking therapy for ED, the question of the correct approach for the diabetic patient with CAD remains less certain. In that angina is often silent in these patients, one suggestion would be to consider the asymptomatic diabetic patient to be in the intermediate risk category, which would require additional cardiovascular diagnostic testing. For example, if a diabetic patient with ED came to the office seeking therapy for ED, one might consider an exercise stress test (electrocardiogram [ECG], thallium, or perhaps with echocardiography) before prescribing an agent that would allow the patient to achieve the 3–4 metabolic equivalents of the tasks (METS) associated with sexual activity (Table 2). The recent National Cholesterol Education Program (NCEP) has suggested that diabetes is a coronary heart disease risk equivalent in terms of managing lipids *(15)*. Studies have shown that the risk of having an MI in the diabetic patient with no known previous history of CAD is about the same as having an MI in the nondiabetic patient with known coronary heart disease *(15)*. Thus, one could make the argument that additional cardiovascular testing in the diabetic patient is warranted prior to prescribing therapy for ED. If

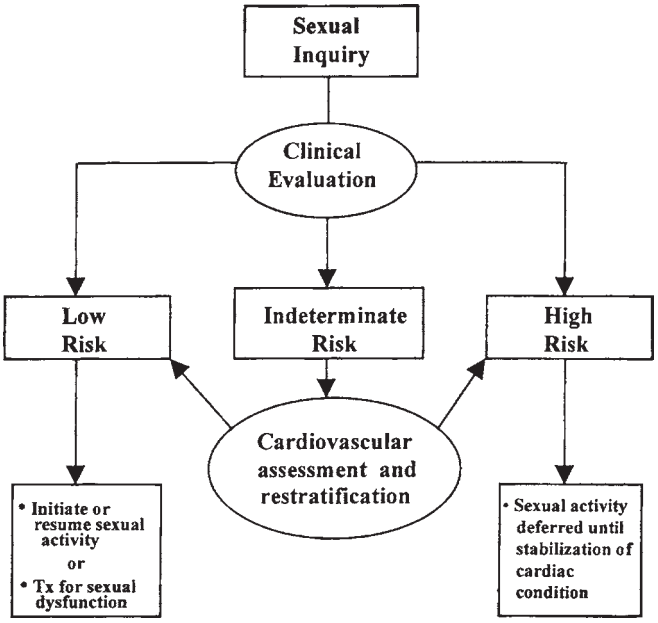

Fig. 1. Sexual activity and cardiac risk: a simplified algorithm. Tx, therapy. (From ref. *14*.)

a patient can achieve 3–4 METS, increase his heart rate to approx >120 bpm, and increase his systolic blood pressure (BP) to 150 or more without developing objective signs of ischemia, that patient is at low risk of developing ischemia during sexual activity *(16)*.

It is important to realize that exercise testing or pharmacologic stress testing will not absolutely guarantee that a patient will or will not have a cardiac event during sexual activity. Currently, there is no diagnostic test that is capable of doing this. Again, an exercise test will help guide the physician to determine whether the patient is at low or high risk. High-risk patients who develop ECG, echocardiography, or thallium evidence of ischemia with or without angina at low double product, or low METS, or who develop early hypotension with exercise stress testing should be considered for additional testing including diagnostic cardiac catheterization and revascularization, if warranted. Of course, modification of risk factors is warranted in all coronary patients. The concept that diabetics patients should be approached in a more aggressive fashion to rule out silent ischemia prior to prescription of therapy for ED is only an opinion and will require additional research. However, given the recent NCEP guidelines equating diabetes with a coronary risk equivalent, this concept may be worthy of exploration.

PDE5 Inhibition in the Diabetic Patient with ED

Overall rates of improvement in erection in diabetic men with ED who took the oral PDE inhibitor sildenafil have in most clinical studies ranged from ~50 to 65% *(12,17)*, with one study showing efficacy as high as 78% *(18)*. By comparison, in the general population of men with ED, efficacy rates have been somewhat higher at ~82% at the 100-mg dose. It should be noted that the general consensus among practitioners is that diabetic patients usually require the higher, 100-mg dose. There has been variability in the literature relating success of therapy with PDE5 inhibitors to HbgA1C levels. In a 12-wk efficacy evaluation utilizing the question "Has the treatment you have been taking improved your erections?" 61 and 76% of diabetic men with ED reported that the long-acting PDE5 inhibitor tadalafil improved their erections at the 10- and 20-mg dose, respectively *(19)*. In a general population of men with ED, efficacy rates were 67 and 81% at 10 and 20 mg of tadalafil. In diabetic men with ED, 58 and 49% receiving 10 and 20 mg of tadalafil, respectively, reported successful intercourse. Goldfischer et al. *(20)* reported that vardenafil significantly improved ED domain scores relative to placebo in diabetic men.

Thus, PDE5 inhibitors do work in a diabetic cohort of men with ED, although studies suggest that efficacy rates may be somewhat lower than in a general population of men with ED *(21)*. The autonomic neuropathy might be one potential reason for the lower rates of success in the population.

A recent study by Desouza et al. *(22)* suggested that PDE5 inhibitors may improve endothelial function in the diabetic patient. They studied brachial artery flow-mediated dilation in diabetic patients. A BP cuff was inflated around the brachial artery for 5 min. The cuff was then deflated and flow-mediated dilation of the brachial artery was measured by ultrasound. In diabetic patients receiving placebo, post-occlusion hyperemic brachial artery dilation was 9% (% increase) and was increased significantly to 14% ($p = 0.003$) with sildenafil. Sildenafil also was shown to enhance endothelial dysfunction in patients with heart failure *(23)*.

Table 2
METS for Various Activities[a]

Activity	METS
Walking 2 mph level	2
Walking 3 mph level	3
"Sexual activity" preorgasm	2–3
"Sexual activity" during orgasm	3–4
Cycling 10 mph level	6–7
Walking 4.2 mph, 16% grade (Bruce treadmill Stage 4)	13

[a]Adapted from ref. *31*.

Hemodynamics and Safety of PDE5 Inhibitors

PDE5 is found not only in the vasculature of the genitals but in the systemic arteries and veins throughout the body. Hence, PDE5 inhibitors such as sildenafil, tadalafil, and vardenafil are mild vasodilators and in clinical studies result

in small, usually nonclinically significant falls in BP. Nitrates are contraindicated with these agents. Studies with both sildenafil and tadalafil have shown a synergistic drop in BP when organic nitrates are administered with PDE5 inhibitors. This occurs because organic nitrates are nitric oxide (NO) donors. NO stimulates guanylate cyclase, which produces cyclic guanosine 5'-monophosphate (cGMP), the substance that ultimately causes smooth muscle cell relaxation and vasodilation. PDE5 inhibitors block PDE5, the enzyme that breaks down cGMP. Therefore, when both an NO donor and a PDE5 inhibitor are administered simultaneously, there is a buildup of cGMP, enhanced vasodilation, and hypotension in some patients *(16)*.

The PDE5 inhibitors are in general safe in patients with mild stable angina and chronic stable CAD. Studies in which sildenafil, vardenafil, or tadalafil were administered to coronary patients did not show an increase in ischemia, or shortening of exercise tolerance times or times to development of ischemia on exercise stress tests *(24–26)*.

Hermann et al. *(27)* showed that sildenafil given to men with severe CAD did not exacerbate ischemia (which might have occurred if this agent were to have caused a coronary artery steal phenomenon). Men with severe CAD were studied in the catheterization laboratory. Sildenafil at its maximum recommended dose of 100 mg resulted in no direct cardiovascular adverse events such as hypotension or chest pain in men with severe CAD. Sildenafil did not have any effect on coronary artery diameter or coronary flow velocity. Sildenafil did have a small positive effect on coronary blood flow reserve.

In patients with hypertension, the PDE5 inhibitors appear to be quite effective for treatment of ED. PDE5 inhibitors when administered to patients already taking many common antihypertensive medicines resulted in either no or small additive drops in BPs. Most studies did not show increases in cardiovascular adverse events when patients already taking antihypertensive medicines also took a PDE5 inhibitor *(28)*. One recent precaution was issued when a study suggested that some patients may develop orthostatic hypotension when doxazasin is administered simultaneously with sildenafil. It is now suggested that sildenafil >25 mg not be given within a 4 h window of an alpha blocker. Valdenafil is contraindicated with alpha blockers and tadalafil is contraindicated with alpha blockers except tamsulosin—because some patients do develop hypotension with these combinations.

Rates of MI and death in men with ED taking PDE5 inhibitors have been well within expected rates for age-matched populations. Placebo-controlled and open-label safety studies have come to this conclusion *(13)*. Even a recent Food and Drug Administration analysis of patients taking sildenafil concluded that there was no evidence of an increase in death in men taking sildenafil compared to expected rates *(29)*.

Conclusion

In summary, PDE5 inhibitors are in general a safe group of drugs in most cardiac patients and diabetic patients. However, they remain contraindicated in patients taking organic nitrates (such as nitoglycerin, isosorbide mononitrate, isosorbide dinitrate) and in some cases, alpha blockers. Furthermore, as described in the Princeton Guidelines, treatment of sexual dysfunction should be deferred in patients with unstable cardiac conditions. PDE5 inhibitors do work in diabetic patients *(21,30)*, although some studies show a lower efficacy rate than that observed in the general population of men with ED. PDE5 inhibitors appear to improve endothelial dysfunction. Because diabetic patients are prone to silent ischemia and because new NCEP guidelines associate diabetes with a coronary risk equivalent, the threshold for additional cardiac evaluation, such as stress testing, may be lower in this group, in my opinion. Therefore, the asymptomatic diabetic patient might be considered to be in the intermediate risk category of the Princeton guidelines, which would require additional diagnostic testing.

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