

Vascular Erectile Dysfunction in Chronic Renal Failure

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The prevalence of erectile dysfunction (ED) has increased dramatically worldwide in parallel with the aging of the population. In 1995, ED was estimated to be present in more than 150 million men. Considering population aging in Western countries, estimates predict that more than 300 million men will be affected by ED by the year 2025. ED is a common and often distressing side effect of renal failure. It is present in 30% of patients with chronic renal failure and in 50% of patients undergoing dialysis treatment. Uremic men of different ages report a high variety of sexual problems including sexual hormonal pattern alterations, reduced or loss of libido, infertility, and impotence, thereby influencing their well-being. The pathogenetic mechanisms include physiologic, psychologic, and organic causes. Since the release of sildenafil citrate, the relationship between ED and the presence of cardiovascular disease (CVD) has been evaluated in several studies. Many of the risk factors for ED are the same as those for cardiac disease. CVD and ED are closely interrelated disease processes. Indeed, ED can be considered a symptom of vascular endothelial damage. Therefore, it can be expected that impotence will appear along with CVD, and the presence of ED suggests the existence of CVD. An accurate evaluation of the sexual histories of all men who present to internists, cardiologists, and also nephrologists for early detection of ED may allow for early diagnosis and management of CVD. *Semin Nephrol* 26:42-45 © 2006 Elsevier Inc. All rights reserved.

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There are 2 words to describe sexual dysfunction that express 2 different concepts: impotence and erectile dysfunction (ED). Impotence is a general male sexual dysfunction that includes libidinal, orgasmic, and ejaculatory dysfunction. ED is the inability to attain and maintain an erection sufficient to allow satisfactory sexual intercourse and it is part of the general male sexual dysfunction termed *impotence*. Because penile erection is a neurovascular phenomenon, vascular disease, including hyperlipidemia, atherosclerosis, and diabetes mellitus can interfere with the vascular mechanism underlying normal erection.

For this reason, the most common risk factors related to impotence are diabetes, hypertension, and smoking. Moderately common risk factors include coronary artery diseases, peripheral vascular diseases, alcohol abuse, multiple medications, anxiety or depression, relationship problems, and hor-

monal abnormalities.¹ Impotence also can be accentuated by various pharmacologic agents including antihypertensive agents and antidepressants.

Hypertension and Antihypertensive Therapy

In the Massachusetts Male Aging Studies, ED was associated with 2 treated medical conditions: diabetes, and hypertension and heart disease. As many as 25% of ED cases may be attributable to medications taken to treat concomitant illnesses, especially arterial hypertension.²

Arterial hypertension is associated with structural and functional alterations of the vessel walls. Because the vascular endothelium plays a central role in vascular tone control, endothelial dysfunction also can cause certain types of ED. In particular, the endothelium plays a major role in modulating vascular tone by synthesizing and metabolizing various vasoactive substances including vasodilators (prostacyclin and [NO]) and vasoconstrictors (endothelin-1 and prostaglandin). Hypertension itself is the product of increased vascular

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resistance, which is under endothelial control. Because a continual basal release of NO from endothelial cells maintains vasodilatation, a lack of NO production and release could contribute to hypertension. Indeed, many experiments have shown that vessels release less NO in hypertensive animals compared with normotensive animals. Furthermore, decreased formation of NO may contribute to atherosclerosis, increased mitogenesis of fibroblasts, and thickening of the vessel walls.³ Moreover, new treatments for ED are able to maintain increased levels of NO necessary for vasodilatation and therefore an erection.

Physicians need to inquire about patient sexual function and discuss the possibility of ED caused by antihypertensive therapy. The association between hypertension and ED is well known, but the effects of the disease per se are difficult to distinguish from the effects caused by the antihypertensive drugs. In 1 study, Barksdale and Gardner⁴ showed a prevalence of ED in 24.8% of hypertensive patients undergoing treatment, but only in 17.1% of patients with nontreated hypertension and in 6.9% of controls. The most common antihypertensive drugs that may produce ED are diuretics (thiazides and spironolactone), alfa-methyldopa, clonidine, reserpine, β -blockers, and verapamil. Alfa-methyldopa and reserpine induce ED through an increase of prolactin levels. Most likely, the other antihypertensive drugs cause ED by decreasing blood pressure levels to less than the critical level necessary to maintain sufficient blood flow for a penile erection, especially if an atherosclerotic artery is present.

Cardiovascular Disease

Cardiovascular diseases can influence sexual performance through many mechanisms. ED is present in 45% of men after a myocardial infarction, but the same prevalence is present in men before cardiac accidents. Psychologic factors can play an important role in this type of ED because men can be afraid to have sexual intercourse with their partners.⁵

Patients with moderate angina, a recent myocardial infarction (<6 wk), left ventricular dysfunction and/or class II congestive heart failure, and nonsustained low-risk arrhythmia should receive further cardiologic evaluation before they resume sexual activity. Patients in the high-risk category include those with unstable or refractory angina, uncontrolled hypertension, congestive heart failure (class III or IV), very recent myocardial infarction (<2 wk), high-risk arrhythmia, obstructive cardiomyopathies, and moderate-to-severe valvular disease. These patients should be stabilized by specific treatment for their cardiac condition before resuming sexual activity or being treated for sexual dysfunction. After that they safely can be encouraged to initiate or resume sexual activity or to receive treatment for sexual dysfunction. An important exception is the use of sildenafil in patients taking nitrates in any form.⁶

Sasayama et al⁷ observed that up to 81% of 6,112 Japanese male patients from 447 outpatient clinics who underwent medical examination by a general practitioner on an outpatient basis had some degree of ED, ranging from mild to severe. ED was noted to be predominant among patients

affected by cardiovascular disease (CVD) or diabetes mellitus, and the presence of CVD increased the risk for ED.

ED, together with depression and cardiovascular disease, may seem to be independent medical problems at a superficial level, managed by 3 separate and unrelated health care disciplines. It has been reported that all 3 medical conditions share many of the same risk factors and causative associations and may be best modeled in a 3-way, holistic, mutually reinforcing relationship. Moreover, patients with sexual dysfunction have a likely comorbidity of CVD and depression, and the potential increased risk for cardiac morbidity and mortality.⁸

Feldman et al² investigated, in the Massachusetts Male Aging Study, a random-sample cohort study, the relationship between baseline risk factors for coronary heart disease and subsequent ED on the premise that subclinical arterial insufficiency might be manifested as ED.

These investigators showed that ED and coronary heart disease share some behaviorally modifiable determinants in men who, similar to their sample, are free of manifest ED or predisposing illness. Open questions include whether modification of coronary risk factors can prevent ED and whether ED may serve as a sentinel event for coronary disease.²

Management of ED

Until recently, the management of sexual dysfunction had been the domain of urologists, nephrologists, gynecologists, and mental health specialists. The field of sexual health medicine recently has broadened to encompass multiple medical specialties, particularly primary care and cardiology. This evolution largely is owing to the increased number of patients who have been brought into treatment by the availability of an oral agent for ED: sildenafil citrate. The introduction of sildenafil in the therapy of impotent patients has changed the treatment approach completely in the evaluation of these patients.

There has been considerable media attention surrounding the commercialization of sildenafil. The advice of cardiologists often is solicited before its prescription because of its potential side effects; the cardiovascular stress caused by sexual activity generally is modest, both in normal patients and coronary patients with, however, important individual variations, the legitimate nature of the intercourse seeming to be one of the principal factors. Recent coronary events, poorly controlled hypertension, and uncompensated cardiac failure are the main contraindications; the prescription should be based on the results of maximal exercise stress testing in patients at risk.

New phosphodiesterase (PDE5) inhibitors such as vardenafil should be tried first as therapy for sildenafil nonresponders before exploring any combination therapy options. The dopamine agonist apomorphine acts on the central control of penile erection to allow a sublingual preparation to produce a prompt response. It is not contraindicated in patients on nitrate medication for coronary artery disease or in patients with depression or on antidepressants.⁹

Tadalafil, an inhibitor of phosphodiesterase type 5, has been shown to be effective up to 36 hours after dosing and

was effective regardless of disease severity and causes, and in patients of all ages. The most frequent adverse events were headache, dyspepsia, back pain, and myalgia.¹⁰

Another available treatment is alprostadil, administered either by intracavernosal injection or by the medicated urethra system for erection. When intracavernosal alprostadil monotherapy injection fails, the addition of papaverine or phentolamine may be effective. Vacuum constriction devices also have been used with variable success. Penile prosthesis implantation and revascularization surgery are recommended in patients refractory to more conventional therapies. Testosterone replacement can be effective in restoring normal erectile function in men who are hypogonadal.

ED also is present after cerebrovascular strokes in 85% of reported cases. Other studies reported an increase of sexual performance after 6 to 8 weeks.¹¹

Sexual dysfunction is a common problem in diabetic patients; however, diabetes need not be the cause. Diabetic men with hypertension have an increased sensitivity to the side effect of sexual dysfunction, which occurs from the use of centrally acting antihypertensive agents. With the use of prazosin, an α 1-adrenergic blocking agent, this cause of sexual dysfunction can be eliminated.¹²

Tobacco produces blockage in peripheral circulation, correlating directly with the number of pack-years of smoking. Smokers are reported to have a higher prevalence of complete impotence than nonsmokers in the following situations: treated hypertension (20% versus 8.5%), treated heart disease (56% versus 14%), cardiac drug therapy (41% versus 14%), and vasodilator therapy (52% versus 21%). Smoking produces atherosclerosis of the pudendal artery, thus decreasing blood flow through the corporeal artery and reducing the vascular flow required for tumescence.

Alcohol may cause damage to the penile nerve conduction and testicular atrophy through cirrhosis with high estrogen levels and severe generalized neuropathy. Short-term alcohol consumption can induce ED through its central sedative effects.

Chronic Renal Failure

Sexual dysfunction is a common feature of patients with chronic renal failure. It has been related to several disturbances common in uremic patients. In females, for example, a delay in sexual development, amenorrhea, metrorragia, and reduction of libido frequently are observed, and conception is rare (spontaneous abortion is a common eventuality). In males we find a delay in sexual development, reduction in sexual drive, reduced frequency of sexual intercourse, partial or total impotence, decreased nocturnal penile tumescence, ginecomastia, testicular atrophy, oligospermia, or azospermia. In addition, among kidney transplant patients it is possible to find an increased frequency of these disturbances. The pathogenesis of these disturbances has been attributed to several factors, but to none of them conclusively. It has been linked to depression, zinc deficiency, autonomic dysfunction, dysfunction of the muscles of the cavernous bodies, and to alterations of the hypothalamus-pituitary-gonad axis hor-

mones, secondary hyperparathyroidism, and antihypertensive therapy such as β -blockers, thiazide diuretics, clonidine, and so forth. However, for none of these factors are rigorous scientific evidence available that are applicable to the majority of patients. In fact, if we apply the *ex adjuvantibus* criteria, testosterone therapy provides inconsistent results and bromocryptine is effective in a small number of patients. In addition, it also is possible that various factors play a role simultaneously, at least in some patients. Of course, a better knowledge of the mechanisms of action underlying sexual dysfunction would be of paramount importance for the adoption of effective therapeutic strategies to prevent or resolve the sexual dysfunction typical of these patients such as peripheral neuropathy, autonomic nervous system insufficiency, peripheral vascular disease, drug toxicity, and psychologic problems.¹³

In the uremic population more than 50% of patients showed symptoms that include erectile dysfunction, decreased libido, and marked decrease in the frequency of intercourse.¹⁴ With the start of dialysis some of these symptoms may improve without being normalized. Indeed, in our dialysis population the prevalence of impotence was 85% as assessed by a questionnaire, the international index of erectile function, proposed by Rosen et al.¹⁵ On the contrary, in the transplant population a well-functioning kidney can restore sexual activity, even if some of the symptoms relative to reproductive function may remain impaired, particularly reduced libido and ED.³

Among the various factors playing a role in the pathogenesis of sexual dysfunction in uremia we have generalized atherosclerosis. These patients prematurely suffer from atherosclerosis (to the point that it generally is recognized that an epidemic of cardiovascular accidents is present in this population), which is also the major culprit of the excess mortality. Traditional risk factors, or those typical of uremia, cannot explain this increased mortality. It is obvious that the internal iliac artery, the pelvic artery, or the pudendal artery can be the target of an atherosclerotic process, with consequent sexual dysfunction.¹³

In uremic patients on chronic dialysis, vascular damage frequently is observed and it is probable that disturbances in fibrinolytic activity and endothelial dysfunction may play an important role in peripheral vascular damage, of which ED represents a pathologic consequence.

Recent studies have shown that hyperhomocysteinemia is an important independent predictor of mortality and of cardiovascular events in hemodialysis patients.¹⁶ Hyperhomocysteinemia is present with a high prevalence in the uremic population. Indeed, this prevalence is estimated to be 60% and 90% in patients under conservative therapy and in those on hemodialysis, respectively. High levels of homocysteinemia also are seen in transplant patients. Because it has been shown that hyperhomocysteinemia has a proatherogenic effect on the endothelium, it is possible that it may represent another risk factor for sexual dysfunction in uremia and in kidney transplantation.

The identification of NO as the primary neurotransmitter of penile erection is well established and led to the develop-

ment of oral agents for the treatment of ED. Some studies reported that insulin growth factor-1 (IGF-1) may contribute to the regulation of vascular tone mediated by NO.¹⁷ In chronic renal failure, alterations in the expression of NO synthase with concomitant changes in IGF-1 have been shown. Because IGF-1 can dilate vascular beds selectively, leading to a decrease in regional blood flow, and its action is mediated by NO, it is clear that circulating inhibitor factors that depress the activity of NO synthase may decrease IGF-1 gene expression in penile tissue at the same time, thus leading to disturbances in sexual function.¹⁸

In conclusion, *ED* is a more appropriate term than *impotence* to describe the inability to sustain a satisfactory sexual performance. It increases progressively with age, but it is not an inevitable consequence of aging. It may be secondary to hypertension or to medications taken for treat hypertension. Although discontinuation of all antihypertensive agents generally is not an alternative, dosage reduction may be effective. Step-down therapy is recommended after 1 year of effective blood pressure control. For patients with adequate blood pressure control and complaints of ED, a dosage reduction in combination with appropriate lifestyle modifications can be effective.

Current therapies for ED and other sexual dysfunction are safe and effective in the large majority of patients with or without CVD, although the contraindications for sildenafil in patients taking nitrates always should be observed.

Contrary to current public and professional opinion, many patients can be managed successfully with appropriate selected therapy. In particular, we propose an algorithm according to the new insights in impotence treatment in the uremic population.¹⁹

Physicians need to be aware of the high incidence of ED among patients with CVD because ED represents a symptom originating from vascular endothelial damage. The risk becomes more pronounced with increasing age, indicating the need for cardiologists and internists to monitor ED patients who may not necessarily present with cardiovascular symptoms.

Although patients may be reticent to discuss problems of a sexual nature with a physician, health care professionals should realize that ED potentially can be present and should be willing to address the disorders with their patients. The education of patients and partners, and information on many aspects of ED are essential to the improvement of diagnosis and treatment.

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