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Treating Erectile Dysfunction in Renal Transplant Recipients

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Contents

Abstract

Erectile dysfunction is common in male kidney transplant recipients. Interference with the physiology of erections can be attributed to recipient co-morbidities, the renal transplant operation, medication adverse effects, relationship problems and changes in mental health. A treatment-oriented evaluation of erectile dysfunction allows the development of treatment plans that are patient-specific. Hypogonadal men whose hormone parameters do not improve after renal transplantation may respond to testosterone replacement therapy. Use of recommended doses of the phosphodiesterase-5 inhibitor sildenafil does not significantly modify trough concentrations of the calcineurin inhibitors ciclosporin and tacrolimus or result in impaired renal allograft function. Tacrolimus has been shown to increase the peak concentration and prolong the elimination half-life of sildenafil in kidney transplant recipients. Daily administration of sildenafil has resulted in decreased blood pressure in kidney transplant recipients with treated hypertension and tacrolimus immunosuppression. Intracavernosal injections of alprostadil, with or without papaverine and phentolamine, are effective treatments for erectile dysfunction after renal transplantation and have not resulted in alterations of ciclosporin concentrations or in deterioration of renal function. Penile prostheses can be successfully implanted after pelvic organ transplantation without significant risk of infection.

Erectile dysfunction (ED), the inability to achieve and maintain an erection adequate to perform sexual intercourse, is highly prevalent in men with renal failure, even after renal transplantation. Validated, self-administered questionnaires, such as the International Index of Erectile Function (IIEF), which scores the domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction, have found the prevalence of ED to be 55% of male kidney transplant recipients.[1] This figure falls between the estimates of 53% and 78% in other reports,[2-4] and is similar to the 52% reported in the Massachusetts Male Aging Study for men between the ages of 40 and 69 years who had not undergone renal transplantation.[5]

The aim of this article is to review the treatment of ED in renal transplant recipients. Most of the article is based on literature reviews and is written for the practising general clinician. In areas of uncertainty, professional judgement was applied.

1. Physiology of Erections

The physiology of erections has been well described.[6,7] A penile erection is a neurovascular event that requires a normal CNS, normal hypothalamic-pituitary-testicular hormone axis, normal autonomic and somatic innervation of the penis, adequate penile blood flow and normal corpora cavernosa.

Tactile, visual, auditory and olfactory sensory input, fantasy and testosterone are responsible for initiation and facilitation of neuroimpulses from the brain to the spinal cord. Thoracolumbar sympathetic nerves emerge from the T_{11} to L_2 segments of the spinal cord and provide fibres to the hypogastric nerves and then to the cavernous nerves. Parasympathetic nerves emerge from the S_2 to S_4 segments of the spinal cord and pass in the pelvic nerve into the pelvic plexus and then into the cavernous nerves. The cavernous nerves provide parasympathetic, sympathetic and nonadrenergic, noncholinergic fibres that accompany the arteries that feed the corpora cavernosa. Arterial blood flow to the paired corpora cavernosa is from the right and the left cavernosal arteries, which are terminal branches of the internal iliac artery system. The internal iliac artery is commonly used to revascularise a kidney transplant. Although the cavernosal arteries usually originate from the ipsilateral penile arteries, they can also arise from accessory pudendal arteries. Multiple, small helicine arteries branch off each cavernosal artery and open into the lacunar spaces. These spaces are lined with endothelium and surrounded by smooth muscle cells.

Relaxation of vascular smooth muscles within the corpora cavernosa and increased blood flow to the lacunar spaces leads to penile erection. Expansion of the lacunar spaces against the tunica albuginea, which surrounds the corpora cavernosa, causes compression of subtunical venules, restricts blood outflow, and leads to an increase in intracavernosal pressure. The relaxation of smooth muscle that surrounds the lacunar spaces is controlled locally by acetylcholine from cholinergic nerves and nitric oxide from nonadrenergic, noncholinergic nerves and endothelial cells. Endothelial cells release nitric oxide in response to acetylcholine, bradykinin and sheer stress. Nitric oxide diffuses into smooth muscle cells, where it activates soluble guanylyl cyclase. This converts cyclic guanosine triphosphate to cyclic guanosine monophosphate (cGMP). cGMP activates protein kinase G. This causes a cascade of intracellular events that results in the opening of potassium channels, hyperpolarisation of the cell membrane, sequestration of intracellular calcium by the endoplasmic reticulum, and blocking of calcium influx by the inhibition of calcium channels. The consequence is a drop in cytosolic calcium concentration and relaxation of the vascular smooth muscles. During the return to the flaccid state, cGMP is hydrolysed to GMP by phosphodiesterase (PDE)-5. PDE-5 inhibitors such as sildenafil, vardenafil and

tadalafil prevent the break-down of cGMP and prolong smooth muscle relaxation. This is why they are effective in the treatment of ED.

Alprostadil (prostaglandin E_1) stimulates adenylyl cyclase and the conversion of cyclic adenosine triphosphate (cATP) to cyclic adenosine monophosphate (cAMP) which, like cGMP, is a second signal that activates protein kinases to mediate vacular smooth muscle relaxation and cause penile tumescence. Breakdown of cAMP by PDE-2, -3 and -4 contributes to penile flaccidity. Papaverine is a nonspecific PDE inhibitor that increases both cGMP and cAMP levels, and this is its mechanism of action in the treatment of ED.

Penile flaccidity and detumescence are the result of vascular smooth muscle contraction evoked by adrenergic neurotransmission and the release of noradrenaline, which causes contraction of corporal smooth muscle via α_1-adrenoceptors and endothelium-derived contracting factors such as endothelin I, angiotensin II and thromboxane A_2. This is mediated, in part, by the RhoA/Rho-kinase pathway. This is the cause of psychogenic ED or the 'fear-of-failure' syndrome.

Drugs or diseases that interfere with facilitative cerebral impulses, cavernosal blood supply, autonomic and somatic neurotransmission, or that impair the mechanisms that relax vascular smooth muscle, can result in ED after renal transplantation.

2. Evaluation

The goal of an ED evaluation in a kidney transplant recipient is to arrive at a probable diagnosis and a treatment plan without unnecessary expense (figure 1). Potential causes of ED in renal transplant recipients are listed in table I.[8]

Prior to the clinic appointment, completion of a sexual function questionnaire, such as the validated IIEF, Arizona Sexual Experience Scale (ASEX), Brief Sexual Function Inventory (BSFI), or Sexual Health Inventory for Men (SHIM), together with

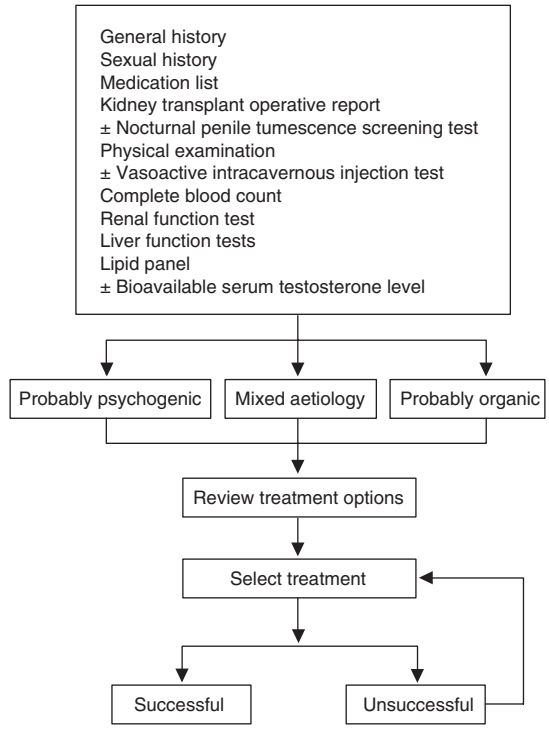

Fig. 1. Algorithm for the diagnosis and treatment of erectile dysfunction in renal transplant recipients (reproduced from Barry,[8] with permission from Lippincott, Williams & Wilkins).

three nights of a screening test for nocturnal penile tumescence, will provide the clinician with valuable information and encourage the patient to focus his thoughts on his symptoms of sexual dysfunction and his relationship with his sexual partner. It is important to determine the following:

- whether or not the sexual dysfunction is situational, an indication of psychogenic impotence;
- the quality of erections;
- any change in libido since the time of transplantation;
- the presence or absence of orgasm and ejaculation;
- the presence of associated co-morbidities such diabetes mellitus, hypertension, arteriosclerosis,

Table I. Potential causes of erectile dysfunction following renal transplantation (reproduced from Barry,[8] with permission from Lippincott, Williams & Wilkins)

Anatomical location	Cause	Mechanism
Central	Clonidine	α_2-Adrenoceptor agonist → ↓ libido
	Propranolol	β-Adrenoceptor antagonist → ↓ libido
	Cimetidine	↑ Prolactin → ↓ testosterone
	Corticosteroids	↓ LH → ↓ testosterone
	Anxiety	↑ Noradrenaline → contraction of corporal smooth muscle
Autonomic and peripheral nerves	Diabetes mellitus, uraemia	↓ Genital sensation ↓ NOS nerves
Testes	Hypogonadism	↓ Libido
Cavernosal blood supply		
internal iliac arterial tree	Renal artery anastomosis	↓ Penile blood flow
accelerated arteriosclerosis	Prednisone, ciclosporin, propranolol, diabetes	↑ LDL-C → ↓ penile blood flow
	Antihypertensives	↓ Penile blood pressure and blood flow
	Diuretics	↓ Blood volume and penile blood flow
Cavernosal smooth muscle	Diabetes, ↑ LDL-C, ciclosporin, tacrolimus	Impair NO-mediated smooth muscle relaxation

LDL-C = low-density lipoprotein-cholesterol; **LH** = luteinising hormone; **NO(S)** = nitric oxide (synthase); ↓ indicates decreased; ↑ indicates increased; → indicates leads to.

obesity, dyslipidaemia, nicotine use and excessive alcohol consumption;

- the sexual partner's attitude to treatment;
- medications that may interfere with sexual performance;
- prior treatments.

The operative report is also of value in kidney transplant recipients because renal revascularisation with the internal iliac artery has been shown in a prospective study to result in decreased blood flow to the cavernous arteries of the penis and not to cause ED, provided that the contralateral internal iliac artery was not compromised.[9] The operative report becomes especially important when both internal iliac arteries have been used to revascularise sequential renal transplants.[10] Testicular atrophy may be present if exposure of the iliac fossa for the renal transplant procedure has included ligation and division of the spermatic cord.

The assumption of nocturnal penile tumescence testing is that men with organic impotence have impaired nocturnal erections that correspond to their awake performance, whereas men with psychogenic impotence have normal nocturnal erections.[11] The exception is that depressed men will sometimes have depressed nocturnal penile tumescence that improves after resolution of the depression.[12] Formal sleep laboratory evaluation is usually reserved for clinical investigation or for cases that may lead to litigation. Nocturnal penile tumescence screening tests can be performed simply with stamps.[13] In a reliable patient, three consecutive nights without breakage of a stamp ring suggests organic impotence. A disadvantage of this screening test is that it does not indicate the duration or number of erections, and some investigators have found it to be unreliable. Home and sleep laboratory testing is available with a mercury strain-gauge recorder that can measure not only the frequency and duration of nocturnal erections, but also the rigidity.

Absent or reduced pedal pulses with absent toe hairs and presence of abdominal or femoral bruits indicate vascular disease. The presence of an anal reflex indicates that the somatic sacral reflex arc is intact. Normal genital sensation is important to document. Decreased libido, decreased semen volume in the absence of α-adrenoceptor antagonist therapy, and incomplete development of secondary sex char-

acteristics or atrophic testes are indications for obtaining a morning bioavailable serum testosterone level. Measuring serum prolactin and luteinising hormone (LH) levels is indicated when the patient has a low bioavailable serum testosterone level on a repeat determination, gynaecomastia or galactorrhoea.[14] Pituitary imaging, usually with magnetic resonance imaging with and without contrast, is indicated to detect a pituitary tumour when the serum prolactin level is more than two times normal, or the serum testosterone level is low and associated with a low or low-normal LH level.[14,15] Men treated with sirolimus have been shown to have low serum testosterone levels and higher LH and follicle-stimulating hormone (FSH) levels and no difference in serum prolactin levels when compared with control subjects,[16] whereas men treated with the calcineurin inhibitors ciclosporin or tacrolimus have been shown to have normal sex hormone levels.[17]

Preliminary laboratory data, including plasma lipid and glucose determinations, are usually available for all kidney transplant recipients. Elevated plasma low-density lipoprotein (LDL)-cholesterol has been shown to impair vascular smooth muscle relaxation.[7] The intracavernous injection test, with or without sexual stimulation, can be performed with alprostadil 20μg. Lower doses are recommended if spinal cord injury is suspected as the primary aetiology of ED because an exaggerated response in the form of priapism can occur in this clinical setting. If the response is inadequate with the initial dose, and pain has not been significant, the dose can be doubled. The goal is simply to provide an erection adequate for intercourse. Inadequate tumescence in the office setting can be due to anxiety and high circulating noradrenaline levels, arteriosclerotic vascular disease, disorders of the corporal smooth muscle or failure to trap blood within the corpora cavernosa. This last phenomenon is often referred to as 'venogenic impotence'. The value of the vasoactive penile injection test is that if the patient develops an adequate erection with or without sexual stimulation, a vasoactive injection programme or an aloprostadil urethral suppository programme is a reasonable home treatment option.

Doppler flow studies of the cavernous arteries and vasoactive pudendal arteriography are unnecessary in the treatment-oriented evaluation of a transplant recipient with ED unless an isolated lesion that can be treated by transluminal angioplasty or bypass is suspected in a young man with otherwise normal vasculature.[18] If the patient is not a candidate for penile venous surgery with its attendant poor long-term results, dynamic cavernosometry and cavernosography are unnecessary. Penile latency nerve testing and biothesiometry can be carried out to confirm neuropathy; however, this information is usually available from the history and physical examination

3. Treatment

The goals of therapy for kidney transplant recipients with ED are (i) sexual function satisfactory to the patient; (ii) no interference with current or future function of a kidney transplant; (iii) no significant drug interactions; and (iv) minimal risk of infection from a treatment choice (table II).

When a renal transplant recipient with ED has a clinic visit with his primary care physician, nephrologist or transplant surgeon, a brief history is usually taken, the patient's medication list is reviewed, and the offer of a trial of a PDE-5 inhibitor is made. If the patient prefers other treatment options or the 5-PDE inhibitor trial fails, referral is made to a specialist. A 'process of care model' is commonly practised utilising three lines of therapy.

3.1 First-Line Therapy

First-line therapy of ED is noninvasive. Examples are psychotherapy and counselling, lifestyle or medication changes, hormone replacement therapy,

Table II. Treatment options for renal transplant recipients with erectile dysfunction[a]

Treatment	Example	Risks
Lifestyle changes	Counselling, alternative sexual techniques, stop alcohol use, stop tobacco use, weight reduction, exercise	Problems with sexual partner
Medication changes	Modify antihypertensive treatment	Compromised blood pressure control
Medication addition	Hormone replacement therapy Phosphodesterase-5 inhibitor therapy Low-density lipoprotein-cholesterol control	Prostate growth Hypotension, headaches Myopathy
Block venous overflow	Rubber band at penis base Vacuum erection device	Bruises Bruises
Intracavernous injection	Alprostadil (prostaglandin E_1) Papaverine	Penile pain, priapism Penile fibrosis, priapism
Vascular procedures	Venous ligation Revascularisation	Poor results Surgical complications, including infection
Penile prostheses	Inflatable without intra-abdominal reservoir	Surgical complications, including infection

a None of the above treatments has been shown to significantly interfere with the pharmacokinetics of immunosuppressants. Calcineurin inhibitors may increase levels of HMG-CoA reductase inhibitors (statins) such as lovastatin, and of phosphodiesterase-5 inhibitors such as sildenafil.

vacuum erection systems, penile constriction devices and oral medication.

Psychotherapy and counselling can often be replaced with good advice from a non-judgemental, kind physician. Sexual techniques other than intercourse can be described for the patient. Discontinuance of alcohol and tobacco may result in restoration of acceptable sexual function.

If the ED is thought to be caused by centrally acting antihypertensives such as clonidine or propanolol, these medications can sometimes be changed to ACE inhibitors, calcium channel antagonists, angiotensin II type 1 (AT_1) receptor antagonists or α_1-adrenoceptor antagonists. These antihypertensive drugs have the reputation of being less disruptive to erectile function compared with β-adrenoceptor antagonists, centrally acting sympatholytic agents and diuretics.[19]

Several medications such as amitriptyline, amphetamines, methyldopa, levodopa, opioids and histamine H_2 receptor antagonists can cause hyperprolactinaemia and reduce bioavailable testosterone. Corticosteroid reduction or withdrawal can result in increased libido from increased LH and testosterone levels. Primary hypogonadism can be treated with testosterone replacement therapy, usually by injections of long-acting testosterone preparations, dermal patches or topical gels.[14] Improved cavernous smooth muscle relaxation can result from reducing LDL cholesterol levels.

A vacuum erection device is a reasonable treatment option for immunosuppressed men with ED. It is noninvasive and does not require medication changes. Sometimes, a simple rubber band at the base of the penis will trap enough blood to provide adequate tumescence for coitus. Oral PDE-5 inhibition is the most common medical treatment for ED. This requires sexual stimulation to be effective. Sildenafil has been shown to be effective in renal transplant recipients in a number of studies, including one randomised, placebo-controlled, crossover trial in which 81% of the sildenafil-treated patients showed improvement in IIEF scores compared with 19% of the placebo group ($p < 0.05$).[20] Other studies have shown improvements in sexual function in sildenafil-treated renal transplant patients ranging between 60% and 82%.[21-24]

Sildenafil, ciclosporin and tacrolimus are metabolised principally by the cytochrome P450 (CYP) system, specifically CYP3A4, and potent inhibitors of this system, such as ketoconazole, itraconazole and erythromycin, can cause increased

plasma concentrations of all three. The following are also associated with increased plasma sildenafil concentrations: age >65 years, reduced liver function, and reduced renal function. Administration of sildenafil to kidney transplant recipients did not increase area under the concentration-time curve (AUC) or maximum ciclosporin concentrations,[20] nor did it significantly modify trough ciclosporin concentrations.[23,24] In ten renal transplant recipients who took tacrolimus and sildenafil 50 mg/day, there were no significant effects of sildenafil on tacrolimus pharmacokinetics; however, peak concentrations, AUC and elimination half-lives were increased for sildenafil and its active metabolite, UK103,320.[25] Significant decreases in blood pressure were observed. None of the sildenafil studies with concomitant calcineurin inhibitor administration have shown deterioration of kidney transplant function, and one study showed improved glomerular filtration rates in kidney transplant recipients, perhaps because treatment caused afferent arteriolar relaxation.[26]

In view of these findings, it is reasonable to initiate sildenafil treatment for ED in kidney transplant recipients at a low dose (25mg) and to monitor blood pressure changes while seeking an effective dose. The drug is given 0.5–4 hours before sexual stimulation. The most common adverse effects of sildenafil are transient headache, facial flushing, nasal stuffiness, epigastric pain and blue-green colour vision changes. Sildenafil is contraindicated in patients receiving nitrate therapy because of severe hypotension that results from that drug combination. Other PDE-5 inhibitors, such as vardenafil and tadalafil, are readily available, and there is at least one report of the efficacy and safety of vardenafil treatment of ED in male renal transplant recipients.[27]

3.2 Second-Line Therapy

Examples of second-line therapy are penile injections and urethral suppositories. Intracavernous injection therapy with alprostadil as a single agent or in combination with papaverine and phentolamine has been successfully used in immunosuppressed transplant recipients.[3,28,29] Sexual stimulation is not necessary for this treatment to be effective. There have been no reports of renal impairment or calcineurin inhibitor level changes attributed to this therapy. If the problem is the 'fear-of-failure' syndrome, simply having the preparation available may be adequate to restore confidence and erections. Penile pain is common after alprostadil injection into the penis, priapism and penile fibrosis are more common with papaverine than with alprostadil, and liver function abnormalities have occurred with papaverine injections.[30,31] Alprostadil can be delivered by urethral suppository, with the required dosage being about 25 times that necessary to provide erections with alprostadil penile injection.[32]

3.3 Third-Line Therapy

Penis revascularisation and penile prosthesis surgery are considered to be third-line therapies for ED. Percutaneous angiodilation is a possible therapy if an arteriosclerotic lesion is localised to the common or internal iliac artery. Surgical revascularisation and venous ligation procedures are rarely indicated in kidney transplant recipients because the vascular disease is usually diffuse, and the long-term results are less than those achieved with less invasive treatments.

Penile prosthesis surgery has been reported to be successful in transplant recipients.[3,33] The prostheses with the lowest probability of device malfunction are those without an intra-abdominal reservoir.[33] When penile prosthesis implantation is being considered, a protocol reasonable for selection of this therapy includes the following:

- stable graft function for at least 6 months;
- low doses of maintenance immunosuppressants;
- low probability of device malfunction;
- no intra-abdominal components to avoid confusion of the reservoir with the bladder in the event of subsequent kidney transplantation;
- minimum tissue dissection;
- no skin or urinary tract infections;
- use of prophylactic antibacterials (parenteral, intraurethral and topical);
- treatment with post-operative broad spectrum oral antibacterials for 1–2 weeks.

The distal urethra is colonised with bacteria, and urethral instillation of neomycin-polymyxin B solution at the time of the surgical skin preparation will reduce contamination of the operative site when the urethral catheter is placed. A combination of vancomycin and an aminoglycoside at dosages appropriate for the patient's renal function will cover *Staphylococcus epidermidis* and the coliforms, the organisms commonly associated with penile prosthesis infections. Use of stress corticosteroid protocols for elective surgery is controversial.

4. Conclusion

The success of renal transplantation has resulted in a focus on quality-of-life issues. One of the quality-of-life issues is ED. The physiology of ED and a treatment-oriented approach to evaluation have been presented in this review. Treatment options were reviewed in order of risk to the patient and to the kidney graft. Erectile dysfunction in kidney transplant recipients can be effectively treated by a variety of progressively invasive therapies without compromising kidney tranplant function. A promising area of research for future first-line therapy is deactivation of the RhoA/Rho-kinase contractile pathway in the vascular smooth muscle of the penis.[7]

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