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Erectile Dysfunction in the Transplant Recipient

Erdal Erturk and Robert S. Davis

Renal, hepatic, pancreatic and cardiac failure requiring transplantation often involve factors which may cause erectile dysfunction (ED). Additionally, transplant surgery may cause ED from injury to the arterial blood supply of the penis. Common cofactors for both ED and renal and cardiac failure include hypertension, diabetes mellitus, and hyperlipidemia. Renal and hepatic failure may result in multiple metabolic abnormalities including hyperprolactinemia and hypogonadism contributing to ED. Although a well-functioning transplant may correct many of the metabolic abnormalities, residual vascular and neurologic disease may persist contributing to ED as may some of the medications the patient employs. There are also many psychological stress factors associated with end stage organ disease and chronic illness, which can alone cause functional ED or exacerbate ED from underlying medical factors contributing to both organ failure and ED. Since patients with end stage organ failure experience major medical and psychological stress factors, it is not surprising that ED remains a significant problem after transplantation with a negative impact on their quality of life.

ERECTILE DYSFUNCTION:

A common condition affecting more than 30 million men in the United States.

Introduction

Erectile dysfunction (ED) is a relatively common condition that affects more than thirty million men in the United States and is increasingly more common as men age.¹ Those patients who suffer from end stage renal disease (ESRD)² and functioning renal transplants have increased incidence of ED compared to the general population.^{3,4} Common cofactors for renal disease and ED include hypertension, diabetes mellitus and hyperlipidemia. Liver and cardiac transplant recipients experience ED less frequently than renal transplant patients, and the incidence of ED in lung transplant patients is unknown. With improved immunosuppression and rejection management, transplant patients are living longer and may manifest other signs of vascular disease including ED. With common public awareness of ED and well-advertised and published treatment options, patients are not living in silence with ED but rather are seeking treatment. Those physicians managing patients with solid organ transplants, and especially concurrent ESRD, should be aware of assessment and treatment options for them.

Etiology

The prevalence of ED in the transplant population is not well known. However, studies of patients with ESRD reveals a range between 38%-80%.⁵ Similar estimates exist for those with end-stage liver disease, especially from alcoholic cirrhosis and hemochromatosis. Not only is their sexual dysfunction more common, but its severity is more advanced with significant numbers of them lacking any sexual activity.⁶ Furthermore, the onset of ED in this group of patients may occur at a much younger age. The etiology of ED in the transplant recipients is generally multifactorial.⁷ Most of the comorbidities associated with their illness will lead to organic ED. Drug side effects and psychological factors may further exacerbate the ED. Thus, the patient's complaint can vary between total impotence to altered sensory and ejaculatory problems.

There are reports indicating that following successful renal transplantation erectile function can significantly improve.⁸ This can be attributed to a sense of well being contributed by correction of their anemia and increased levels of testosterone. There are also significant psychological changes including lack of dialysis, lack of dialysis disequilibrium syndrome,

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and less focus on chronic illness. Similar studies are not available for liver and heart transplant recipients.

In renal and pancreas transplant recipients, ED may be related to the transplant surgical procedure. Renal transplant surgery may damage the penile blood supply, which is the pudendal artery, a branch of the internal iliac artery. If the transplant renal artery is anastomosed end-to-end to the internal iliac artery, there is approximately 10% risk of vascular impotence.⁹ However, if a second renal allograft is performed on the contralateral side in a similar fashion the incidence is significantly increased to 65%.¹⁰ This would suggest that the transplant renal artery should be anastomosed using the external iliac artery in an end-to-side fashion to avoid injury to the pudendal penile blood supply. Patients with ESRD may also develop vascular calcifications and obstruction to arterial blood flow of the penis.¹¹ Duplex doppler ultrasound testing employing injectable prostaglandin E1 into the corpora cavernosa can evaluate the circulatory status of the penis.¹² When arterial insufficiency has occurred, a low peak systolic velocity and poor arterial dilatation after the drug will be observed. Unfortunately, arterial bypass operations to improve penile circulation do not work well in the face of generalized atherosclerosis often resulting in thrombosis of the donor artery (inferior epigastric).^{13,14} If an adequate erection is achieved by the injection, future penile injection therapy remains a treatment option.

Diabetes mellitus, hyperlipidemia and hypertension may all contribute to damage to the erectile tissue with increased fibrosis and loss of muscle cells. This change in the erectile tissue may cause venous insufficiency.¹⁵ This may be suggested by duplex doppler penile ultrasound testing where sustained diastolic flow persists despite maximal vasodilatation with injectable drug prostaglandin E-1 (PGE-1).¹⁶ More definitive demonstration of penile venous incompetence may be achieved with dynamic cavernosometry and cavernosography, again using maximal vasodilatation with high doses of injectable PGE-1.¹⁷ Successful recovery of erectile function following penile vein ligation surgery has been reported though surgery in general fails and is very selectively employed.^{18,19} Demonstration of veno-occlusive dysfunction may lead to trials of venous penile compression with or without a vacuum pump.

Hypertension is a very common condition in the renal and pancreas transplant recipient. Hypertension is known to enhance the development of occlusive small vessel disease, which in turn can lead to vasculogenic impotence.^{20,21} Anti-hypertensive agents, by lowering blood pressure, may diminish penile perfusion and cause ED, or due to their pharmacological effect as over expression of alpha sympathetic activity by beta blockers can either lead directly to erectile dysfunction.²² When appropriate, renal transplant patients are best treated with selective alpha-1 blockers. Otherwise, calcium channel blockers, angiotensin converting enzyme inhibitors, should be prescribed. However, in practice due to severity of their hypertension it is not uncommon to see multiple drug regimens prescribed. Cardiac transplant recipients usually require significant afterload reduction to maintain the failing heart. ACE inhibitors and peripheral vasodilators are the mainstay of therapy.

Diabetes mellitus is a leading cause of renal failure and subsequent transplantation. Diabetes mellitus can develop de novo following solid organ transplantation as a side effect of steroid or tacrolimus use. The impact of diabetes mellitus on erectile function is well-documented.^{23,24} Diabetes mellitus not only affects the vascular system, it also causes peripheral neuropathy and contributes to changes in the erectile tissue promoting development of ED.^{25,26} Compounding the organic basis of ED, diabetics, especially juvenile diabetics, often have psychological factors such as depression and anxiety which increases their performance impairment.²⁷

Testosterone also plays a significant role in libido and potency. Decreased testosterone levels have been reported in patients with liver failure, especially hemochromatosis or Laennec's cirrhosis. Testosterone in uremic patients is generally depressed either by decreased production or by increased clearance. Although this is not completely understood, it is believed to be a direct toxic effect of uremia on the testis. Furthermore there is evidence of irreversible damage to the testis, which theoretically can affect the renal transplant patients.²⁸ Hyperprolactinemia, on the other hand, is a common finding in the ESRD patients and the incidence reaches well over 50%.²⁹ This will generally depress serum testosterone levels, thus leading to loss of libido and ED. This is generally reversed following transplantation.³⁰ However, in situations with low testosterone levels hyperprolactinemia should be investigated.

PROSTAGLANDIN E1:

When applied directly into corpus cavernosa can lead to adequate erectile function.

Diagnosis and Evaluation

The most valuable tool for assessment of ED is a thorough history including a sexual history. The nature of the complaint, its onset, the relationship to major changes in management of the patient's organ failure, or new drugs should be sought. An awareness of relationship changes brought on by new medical needs, job changes, and role changes should be sought. The consistency of the problem, the status of nocturnal and morning erections and performance status with masturbation which avoids performance anxiety should be documented. Standardized questions³¹ may be employed as in the International Index of Erectile Function (IIEF)³² or the Brief Sexual Function Inventory (BSFI).³³ Looking for secondary factors contributing to ED includes a history of drugs used, documentation of recreational drug use, and inquiry regarding alcohol use and cigarette smoking.³⁴ Other signs of peripheral vascular disease such as angina, leg claudication, and other mechanisms of diminished penile blood flow (perineal trauma from straddle of bike injuries) should be sought.³⁵ Any history of a neurologic process, which may involve penile innervation such as multiple sclerosis, herniated disk, or peripheral neuropathy, should be questioned. Throughout the questioning, keeping an open ear to stress factors created by the chronic illness may lead to better insight into contributory functional issues from loss of body image, loss of independence, loss of job and role changes resultant from the limitations on the individual by his illness.

A detailed physical examination should be performed. This should focus on endocrine, peripheral vascular and neurological systems. A detailed genitourinary examination is essential with special focus on the phallus for penile sensation, Peyronie's plaque and congenital anomalies, such as hypospadias and chordae. Secondary sex characteristics and gynecomastia should be noted. Particular attention should be made for testicular size, tenderness and sensitivity. Careful inspection for sacral nerve function including the presence of perianal sensation, rectal sphincter tone and the reflex sphincter activity (anal wink or bulbocavernosus reflex) should be assessed. Peripheral muscle strength and reflexes are noted but sophisticated neurologic testing is normally not needed. Unfortunately, there is no objective test of the integrity of the penile neurologic innervation, though some believe the waveform analysis of penile electrical activity may be a future objective method for this assessment.³⁶

Laboratory evaluation of the renal transplantation with ED is focused on the conditions that may be contributory and are commonly observed. Assessment of renal function, liver function and a lipid profile has usually been done and recent values need be confirmed but usually not repeated. Relevant tests, which may be lacking include an endocrine assessment, including serum testosterone and prolactin levels. When abnormal, further clarification of the endocrine status with free and total testosterone, LH and FSH assessments are performed. When the prolactin is very high, a pituitary adenoma may be sought with cranial MRI imaging.

Dynamic studies to assess the status of the penile arteries can be performed with color doppler ultrasound and intracavernosal injections of vaso-active drugs such as prostaglandin E-1 (PGE-1) or trimix (papaverine+phentolamine+prostaglandin E-1).¹⁶ With these studies, useful information can be obtained regarding the blood flow in the cavernosal and dorsal penile arteries. Assessment of the venous drainage system and their competency can be established by the duplex doppler study with venous leak being suggested by sustained diastolic blood flow despite maximal vasodilatation with high dose penile injection. Normal venous closure is confirmed by achievement of a rigid erection and cessation of diastolic flow. When corrective venous surgery is being contemplated, more formal cavernosometry and cavernosography, again using high doses of penile vaso-active agent(s), should be employed.³⁷ An office injection of PGE-1 can give non-quantitative but clinically useful information regarding the patient's response to direct drug stimulation which may lead to clinical injection trial as therapy without the cost or inconvenience of formal vascular testing.

Another crucial aspect of ED in transplant recipients is to differentiate for treatment purposes between organic vs. psychogenic dysfunction, understanding that such chronic disease processes may involve significant elements of both.³⁸ Patients with chronic illness may suffer a host of psychological stress factors including loss of job, loss of independence, loss of body image and sexual ability, and possibly loss of partner. To find these needs, we must inquire with our patient's permission (usually welcomed and granted) regarding them and not just focus on the objective medical needs. When psychological factors are clearly significant, early referral of these patients to someone with sexual and couple counseling can

DOPPLER ULTRASOUND:

A valuable tool for evaluating erectile dysfunction.

have significant impact on the successful outcome of any treatment modality employed. Furthermore underlying significant psychiatric disorders, such as depression, may be identified and treated. Nocturnal penile tumescence (NPT) is a non-invasive study of erectile function. During rapid eye movement sleep normal males have several erections.³⁹ It has been suggested that psychogenic factors should not affect erectile function during REM sleep, therefore, this can be an important test for differential diagnosis.⁴⁰ These tests can be performed at home with erection snap gauge devices for screening, or with more detailed electric gauge monitoring for both nocturnal erections and penile rigidity as the Rigiscan.⁴¹ As psychogenic factors are a real concern in this group of patients, documentation by Rigiscan of definitely impaired nocturnal erections is strongly recommended prior to any irreversible therapy such as penile prosthesis insertion.

SILDENAFIL:

An effective oral agent for the treatment of erectile dysfunction.

Treatment

Psychological factors that can adversely affect sexual dysfunction in transplant patients should be identified. Physician acceptance and interest in these problems will greatly improve their definition and resolution by the patient. Those with severe problems or development of depression and anxiety should be identified and appropriate counseling should be obtained. The partners of these patients at some point should participate in these sessions.

When hormonal abnormalities are identified specific treatment can be very successful. Testosterone replacement therapy can result in improved libido and general well-being.⁴² Thus, it also can have significant positive impact on patients' depressed state. As testosterone will promote the growth of prostate cancer, documentation of a normal prostate specific antigen (PSA) value and rectal findings should be done prior to supplementing testosterone. Testosterone can be replaced by oral, parental and topical methods. Testosterone injection is usually considered the most reliable form of delivery but requires frequent biweekly visits. Topical androgen replacement applied daily as patches or a gel have recently gained significant popularity and provide a much more stable serum value of hormone replacement.⁴³ Hyperprolactinemia, if present after renal transplantation, can be effectively treated with bromocriptine or Lisuride. Once the prolactin levels return to normal, serum testosterone levels should appropriately rise.⁴⁴ Chronic anemia

has been noted to affect general well-being of the hemodialysis patients and may contribute to ED. Erythropoietin can reverse this process by increasing patients' hematocrit, but is an expensive therapy which is usually not needed after successful transplantation.

Sildenafil (Viagra, Pfizer) has been introduced as the most effective oral agent in the treatment of ED.⁴⁵ This drug inhibits phosphodiesterase enzyme (PDE5) that is relatively specific to the penile corporal smooth muscle. Sildenafil enhances nitric oxide-mediated penile vasodilatation and increases penile blood flow magnifying the normal vascular response to sexual arousal.⁴⁶ It is helpful in achieving and maintaining erections. This medication has been used widely in renal transplant patients with few side effects. A major contraindication of Sildenafil is its potential synergistic affect with nitrates in patients with significant coronary artery disease. This drug, along with nitrates, can lead to significant reduction in systemic blood pressure with resultant reduction in cardiac or brain perfusion.⁴⁷ As the duration of action of Sildenafil is long, it cannot be used even if the patient only carries but "does not use" the nitroglycerin. Thus, especially for the cardiac transplant recipients, Sildenafil therapy may not be an option. Unfortunately, other effective oral agents have not yet achieved FDA approval but will likely become future options.

Other injectable vaso-active agents have also been successfully employed in the treatment of renal transplant patients.⁴⁸ Prostaglandin E-1 5-20 µg, papavarine hydrochloride and phentolamine, when directly injected into the corpora cavernosa, can lead to increased blood flow and satisfactory erections. These medications alone or in combination (trimix) can be self-administered. Patients, however, need to undergo education in administration and dose selection to avoid priapism and permanent penile damage from the poor penile circulation that occurs during priapism.⁴⁹ There have been no deleterious effects on serum creatinine or serum cyclosporine levels with this form of treatment. With proper education and counseling, intracorporeal injection therapy can be successful in up to 90% of patients, though many patients drop out of treatment due to its invasive nature.⁵⁰ Prostaglandin E-1 can also be delivered intraurethral as a suppository. This drug (MUSE, Vivus) has been associated with relative success and can be used in the renal transplant patients.⁵¹ However, much higher doses (typically

1000 µg PGE-1) are required and many patients experience pain or hypotension as the drug is less effectively localized and administered to the penis.⁵²

Vacuum constriction devices has also gained significant popularity. They are commonly used in patients who are very motivated and reluctant to employ penile injection. Although cumbersome, proper usage can lead to success. They work mainly by applying negative pressure to the corporal body thus increasing local blood flow.⁵³ Several different types and brands are available in the market. Patients who partially respond to Sildenafil or MUSE urethral suppositories may obtain a satisfactory result with the addition of the vacuum device, possibly using a weaker constriction band than when using the vacuum device alone.

Surgical correction of ED with vascular reconstruction has limited application.⁵⁴ Bypass surgery and percutaneous angioplasty of the iliac blood vessels have reported success. Revascularization has had limited success due to thrombosis of the donor artery when there is generalized peripheral vascular disease, which is the usual case in patients with renal or cardiac failure and has done much better when the recipient vessels are normal as in traumatic arterial injury.⁵⁵ While creation of an arteriovenous fistula has been tried to maintain patency, this adds new problems of penile venous hypertension.⁵⁶ Correction of venous leak, when present, may also be tried prior to resorting to the irreversible surgery of a penile implant.¹⁸ While penile revascularization has limited applicability, penile prosthesis insertion has been performed in the renal transplant recipient with good results.⁵⁷ As prosthesis insertion is an irreversible process, it should only be selected after all the conservative treatment alternatives have been exhausted or rejected by the patient. Though complications of infection or device malfunction can occur, patient satisfaction with prosthesis exceeds that of all other options of ED management.^{57,58} These patients should be carefully selected and the organic nature of their ED confirmed by NPT testing. Confirmation of thorough counseling regarding the risks and expectations from their prosthetic surgery must be documented.

Fortunately, many renal, liver, pancreas and cardiac-failure patients with ED will have resolution of their problem with a successful transplant. They may, however, have significant underlying vascular or neurologic impairment contributing to future

development of ED. Those who fail to have return of sexual function or those who subsequently develop it are candidates for management of their problem. The future will hold more pharmacological choices and possible combination drug therapies. Physicians providing their care must ask and show interest in the patient's sexual health, as well as his renal, hepatic or cardiac well being. Successful treatment by transplantation not only prolongs life, it makes life better. When transplantation alone does not correct sexual dysfunction, additional therapy can greatly improve his sexual performance and quality of life.

Diagnosis and Treatment: Flow Sheet

From initial history, questionnaire, physical exam, snap gauge test and serum testosterone, patients can be categorized as having primarily organic, mixed or psychogenic ED.

All except those on nitrates or with severe cardiac impairment are given a trial of Sildenafil on the initial visit. Those responding to Sildenafil are maintained on it. Counseling is added to those with a psychogenic component, and altering medical parameters such as changes to hypertension medications or androgen supplementation where needed in those with primarily organic ED.

1. Those with primarily psychogenic ED or severe depression merit psychiatric consultation and added therapy often in the form of antidepressants.

Those unable to take Sildenafil or those not responding to it merit additional testing which may consist of an office trial injection of 10 µg PGE1. In addition to office injection and assessment, objective vascular testing with duplex doppler ultrasound further objectively defines the adequacy of arterial penile inflow and provides some knowledge of venous competency. Those responding well to trial injection may proceed to injection therapy, though some patients will decline this option.

2. Those unwilling to try injection therapy may try MUSE urethral suppositories. Those failing this may reconsider injection therapy.
3. Those failing MUSE or not accepting of injection therapy may consider the vacuum device. This device, though cumbersome, may help those who have some but inadequate response to MUSE or Sildenafil allowing an

PENILE PROSTHESIS SURGERY:

A viable option if all conservative treatment modalities fail.

adequate and functional erection with the combined therapy often using less painful and constricting rubber bands than when vacuum is used alone.

4. When none of the above prove useful or acceptable, consider surgery. Penile revascularization is rarely indicated as renal, pancreas and cardiac organ failure is usually associated with diffuse peripheral vascular disease. Surgical correction of venous leak may be considered when venous leak is documented and the patient not accepting of prosthesis.
5. Penile prosthesis insertion should be the last option due to its irreversible nature. Document organic ED as with NPT and document counseling regarding risks and functional expectations. Prosthesis is useful when concomitant Peyronie's disease also exists. Prosthesis is now much more reliable than in the past and is often done as an ambulatory surgical procedure. While uncomfortable for the first six weeks after insertion, long-term satisfaction is very high as they reliably provide an erection whenever desired for as long as desired.

PEYRONIE'S DISEASE:

A non-specific fibrosis of the corpora cavernosa of the penis which can lead to erectile dysfunction.

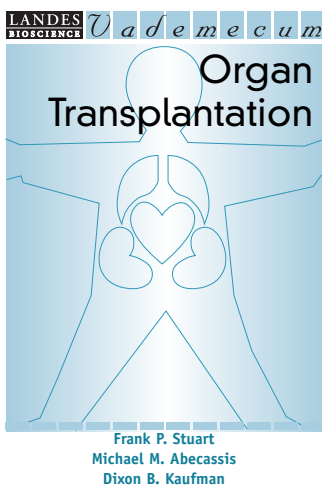
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