

Review

Sexual and reproductive function in end-stage renal disease and effect of kidney transplantation

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Abstract

Advanced chronic kidney disease is associated with impaired spermatogenesis and testicular damage. Semen analysis typically shows a decreased volume of ejaculate, oligo- or complete azoospermia, and a low percentage of motile sperm. Erectile dysfunction (ED) is also common in patients with chronic renal failure (CRF) and is observed in excess of 50% of these patients. There have been ongoing improvements in survival and quality of life after renal transplantation. One of the most impressive aspects of successful renal transplantation in the young people is the ability of the male patient to father a child. In this article we first review pathophysiology of reproductive failure in end-stage renal disease (ESRD), then ED in ESRD and its management are discussed, finally sexual function in renal transplant patients and management of ED in these patients are reviewed. (*Asian J Androl* 2008 May; 10: 441–446)

Keywords: end-stage renal disease; erectile dysfunction; reproduction; kidney transplantation

1 Introduction

For many male patients with renal failure, impotence and loss of libido and infertility are frequent occurrences. These problems might improve but rarely normalize with the institution of maintenance dialysis, commonly resulting in a decreased quality of life [1–3]. By comparison, a well-functioning renal transplant is much more likely to restore sexual activity; however, some features of re-

productive function might remain impaired.

The uremic milieu plays an important role in the genesis of sexual dysfunction in end-stage renal disease (ESRD). Psychologic and physical stresses that might contribute to disturbances in sexual function are also commonly present in patients with chronic renal failure [3, 4]. In the present article we first review pathophysiology of reproductive failure in ESRD, then erectile dysfunction (ED) in ESRD and its management are discussed. Finally, sexual function in renal transplant patients and management of ED in these patients are reviewed.

2 Pathophysiology of reproductive failure in ESRD

Advanced chronic kidney disease is associated with impaired spermatogenesis and testicular damage [3–5]. Semen analysis typically shows a decreased volume of

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ejaculate, oligozoospermia or complete azoospermia, and a low percentage of motile sperm. Testicular histology shows reduced spermatogenic activity varying from decreased numbers of mature spermatocytes to complete aplasia of germinal elements.

The factors responsible for testicular damage in uremia are not well understood. It is possible that plasticizers in dialysis tubing, such as phthalate, might play a role in patients undergoing maintenance hemodialysis.

Uremia also impairs gonadal steroidogenesis. The serum total and free testosterone concentrations are typically reduced, although the binding capacity and concentration of sex hormone-binding globulin are normal [5]. The serum concentration of luteinizing hormone (LH) is elevated in uremic men; this is a result of diminished testosterone feedback.

Follicle stimulating hormone (FSH) secretion is also elevated, although to a more variable degree [3]. Elevated FSH levels are probably the result of decreased testosterone and inhibin, a Sertoli cell product. The plasma FSH concentration tends to be highest in those uremic patients with the most severe damage to seminiferous tubules and presumably the lowest levels of inhibin. It has been suggested that increased FSH levels indicate a poor prognosis for recovery of spermatogenic function after renal transplantation [3]. The basal levels of serum prolactin are elevated in the majority of uremic patients, and the response to thyrotropin-releasing hormone is reduced and delayed [6]. The mechanisms for the hyperprolactinemia in chronic renal failure are not well defined. An increased autonomous production rate of prolactin is a major mechanism for the hyperprolactinemia but a decreased metabolic clearance rate might also play a role.

3 ED in ESRD

ED is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse [7]. ED might result from psychological, neurologic, hormonal, arterial or cavernosal impairment or the combination of these factors. ED is observed in more than 50% of patients with chronic renal failure (CRF) [8]. Several factors appear to participate in the genesis of impotence in CRF patients. These include abnormalities in the neurohormonal control system of the hypothalamic-pituitary-gonadal axis, secondary hyperparathyroidism and dysfunction of the corporal smooth muscle of the penis, or in the penis's response

to relaxing stimuli and/or derangements in the arterial supply or the venous drainage of the penis [9].

Patients with a history of normal erectile function prior to onset of renal disease might have a secondary cause, such as neuropathy or peripheral vascular disease. The presence of a neurogenic bladder suggests an underlying neuropathy, while findings of peripheral vascular disease point toward inadequate penile blood flow. The lack of secondary sexual characteristics combined with small soft testicles suggests hypogonadism. The ingestion of a number of medications, such as beta blockers and tricyclic antidepressants, might cause ED.

For patients without obvious causes of impotence after an initial evaluation, consideration should be given to psychological difficulties, such as stress or depression. The occurrence of nocturnal penile tumescence (NPT) among a large population of uremic patients is significantly lower than that in the normal population [10]. The administration of a nocturnal penile tumescence test might help to distinguish between an organic and a psychological disorder; the absence of an erection during sleep suggests underlying organic dysfunction. A positive test, however, does not exclude a physical cause [10].

4 Management of ED in ESRD

The first step in the treatment of uremic men with sexual dysfunction is increasing the delivered dose of dialysis, discontinuing medications with side effects of impotence and correcting the anemia of chronic renal disease. As an example, the administration of recombinant human erythropoietin to raise the hematocrit to between 33% and 36% might enhance sexual function [11]. The treatment of CRF patients with erythropoietin is associated with a decreased in serum prolactin levels and improvement in sexual dysfunction [12]. Correction of hyperprolactinemia by bromocriptin is also associated with an improvement in sexual dysfunction. Cabergoline, which causes nausea much less often than does bromocriptine and is at least as effective in treating hyperprolactinemia, should be tried first [13].

Sildenafil has been effectively used in the treatment of ED in both hemodialysis and peritoneal dialysis patients and is often used for psychologic, vascular, or neurogenic causes [14–17]. Sildenafil is a selective inhibitor of phosphodiesterase type 5 (PDE5), which inactivates cyclic guanosine monophosphate (GMP). Since its release in March 1998, it has become the drug of

choice for most men with ED. When sexual stimulation releases nitric oxide (NO) into the penile smooth muscle, inhibition of PDE5 by sildenafil causes a marked elevation of cyclic GMP concentrations in the glans penis, corpus cavernosum and corpus spongiosum, resulting in increased smooth-muscle relaxation and better erection. Sildenafil has no effect on the penis in the absence of sexual stimulation, when the concentrations of NO and cyclic GMP are low [18]. Sildenafil has little effect on libido. Among more than 3 700 men with average 6 months of exposure to sildenafil, most adverse events were mild to moderate and self-limited in duration [19]. Among men taking 25–100 mg of sildenafil, 16% reported headache, 10% flushing, 7% dyspepsia, 4% nasal congestion and 3% abnormal vision (described as a mild and transient color tinge or increased sensitivity to light). These rates were twice as high among men taking 100 mg of sildenafil as among men who were taking lower doses. The visual effect is probably related to inhibition of phosphodiesterase type 6 in the retina. No chronic visual impairment has been reported, and the incidence of visual side effects was similar in diabetic and nondiabetic men [20]. Nevertheless, because of the short duration of the clinical trials and the difficulty in detecting subtle retinal changes, the long-term safety of sildenafil treatment is still unknown. In men with retinal diseases, an ophthalmologic consultation might be warranted before sildenafil treatment is initiated. Adverse cardiovascular events (nasal congestion, headache and flushing) are mild and transient in the majority of men. The rate of serious cardiovascular events (angina and coronary-artery disorder) is low. Sildenafil is absorbed well during fasting, and the plasma concentrations are maximal within 30–120 min (mean, 60 min). It is eliminated predominantly by hepatic metabolism, and the terminal half-life is approximately 4 h. The recommended starting dose is 50 mg taken 1 hour before sexual activity. The maximal recommended frequency is once per day. On the basis of effectiveness and side effects, the dose may be increased to 100 mg or decreased to 25 mg [18]. Concurrent use of sildenafil and nitrates in any form, regularly or intermittently, is contraindicated. The administration of testosterone to uremic men usually fails to restore libido or potency, despite normalized serum testosterone.

A vacuum tumescence device might be effective in restoring potency in uremic impotent males unresponsive to medical therapy. Administration of zinc is also a reasonable therapeutic option in uremic men.

5 Reproductive function in renal transplant patients

Kidney transplantation is the best and most effective option that can be offered to patients with severe renal damage to restore their health and to offer possibility of recovering their sexual and reproductive functions.

Fertility as assessed by sperm count improves in half of transplant patients. The sex hormone profile tends to normalize [21].

The factors that might cause certain difficulties for the recovery of sexual and reproductive functions in this type of patient include prolonged use of peritoneal dialysis, high FSH serum levels before the transplant, and a deficient function of the graft [22].

A certain improvement has been reported as to semen quality in the three main parameters (number, morphology and motility of the spermatozoa) in patients after kidney transplantation [22].

Generally, immunosuppressive drugs commonly used in patients with kidney transplants have not been associated with adverse effects on patient spermatogenesis or with teratogenic effects on their offspring [23]. Nevertheless, several studies conducted to evaluate the effects of immunosuppressive regimens suggest that some of these agents are potentially gonadotoxic because they affect testicular function and decrease fertility. Cyclosporine (CSA) is an important therapeutic agent and a common component in multiple immunosuppressive regimens used in recipients of kidney transplants [23, 24]. Some studies imply that CSA is a potentially gonadotoxic drug: it has produced adverse effects on reproductive capability in experimental models as well as in humans. In certain animal species, such as the Sprague-Dawley strain rats, Seethalakshmi *et al.* [25] showed that the administration of CSA induces a deficient intratesticular synthesis of androgens and a reduction in spermatogenesis, although this reduction was reversible after exogenous gonadotrophins were administered. It has also been possible to observe the adverse effect of CSA by means of testicular biopsies performed in dogs [26] and rats [27] treated with CSA for short periods, where marked abnormalities in spermatogenesis have been seen. CSA might impair testosterone biosynthesis through direct damage to leydig cells and germinal cells, and a direct impairment of the hypothalamic-pituitary-gonadal axis has been suggested.

Computer-aided sperm analysis in infertile renal transplant recipients showed that both sperm concentration

and straight line velocity (VSL) were inversely correlated to the cyclosporine whole blood trough levels. Stabilization of the cyclosporine whole blood by leveling within the target therapeutic level could improve the fertility potential in kidney transplant recipients. Duration of hemodialysis before transplantation is also important in this regard. The time spent on hemodialysis is inversely correlated with the percentage of motile spermatozoa and the amplitude of lateral head displacement [28].

Azathioprine (AZA), another drug that is frequently combined with CSA, is considered to be genotoxic [29]. However, very few studies have analyzed the effects of AZA on the reproductive function of humans. Several studies suggest that prednisone might not be involved in sperm cell damage [29].

Kaczmarek *et al.* [30] found that heart transplant recipients treated with sirolimus had significantly lower free testosterone levels and significant higher levels of gonadotropic hormones, LH and FSH compared with a calcineurin inhibitor-based immunosuppression group.

There is no increased incidence of neonatal malformations in pregnancies fathered by transplant recipients [21]. However, there is some concern about infertility associated with Ganciclovir, which is used for treatment of cytomegalovirus infection in transplant patients [31].

6 Sexual function in renal transplant patients

Renal transplant recipients have all suffered from uremia. They have frequently spent a significant amount of time on dialysis and often have other comorbidities, including hypertension and diabetes. Although a successful transplant might improve erectile function and return libido, in many cases some degree of sexual dysfunction might persist.

Hypertension is common among transplant patients; CSA can exacerbate preexisting high blood pressure and also induce hypertension in patients who had normal blood pressure prior to the kidney transplant.

Antihypertensive medications have negative effects on male sexual functions, including effects on libido and erection [32]. Medications are implicated in ED include beta blockers (propranolol and labetalol), alpha blockers (prazosin), sympatholytics (clonidine), vasodilators (hydralazine) and diuretics (thiazides and spironolactone).

Other drugs that might also play a role in ED in transplant patients are: HMG-CoA reductase inhibitors (lovastatin and simvastatin), antidepressants (serotonin

reuptake inhibitors, tricyclics and monoamine oxidase inhibitors) and H2 antagonists (cimetidine, ranitidine and famotidine).

Ketoconazole, which is used in some transplant centers to increase cyclosporine levels and reduce the costs of calcineurin inhibitors, can cause ED because of its antiandrogenic action.

Additional factors such as smoking and alcohol intake might account for failure of male sexual function to improve after transplantation.

Cigarette smoking might induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle [33]. Alcohol in small amounts improves erection and increases libido because of its vasodilatory effect and the suppression of anxiety; however, large amounts can cause central sedation, decreased libido and transient ED. Chronic alcoholism might cause hypogonadism and polyneuropathy, which can affect penile nerve function [34].

Autonomic neuropathy can impair erectile function, and interruption of both hypogastric arteries can occasionally impair vascular supply.

7 Management of ED in renal transplant patients

Male patients should be asked about their sexual function and referred for urologic evaluation when necessary. Historically, androgens were touted as enhancing male sexual function. Today, more effective treatments are available, and testosterone therapy should be discouraged in men in whom ED is not associated with hypogonadism [18]. There is no specific contraindication to use sildenafil in transplant patients so long as standard precautions are taken regarding concomitant coronary artery disease. Sexual activity was thought to be a likely contributor to myocardial infarction in only 0.9% of 858 men in one study [35]. Therefore, the absolute increase in risk caused by sexual activity is low (1 chance in one million for a healthy man). According to data from the National Center for Health Statistics and the Framingham Heart Study, the rate of death from myocardial infarction or stroke for men in the age range in which ED is common is approximately 170 per one million men per week. Therefore, it appears that sildenafil therapy is safe for most men. Nevertheless, given that most of the men who died had underlying cardiovascular disease, cardiovascular status should be carefully assessed before treatment. The combination of nitrates and sildenafil has

resulted in severe hypotension and 16 deaths in the USA. Therefore, nitrate therapy is an absolute contraindication to sildenafil therapy [18].

Transurethral administration of alprostadil (synthetic form of prostaglandin E1) or intracavernous injection resulting in an erection sufficient for intercourse has been used successfully. The most effective intracavernous therapy used is a three-drug mixture containing papaverine, phentolamine and alprostadil (Trimix, Wedgewood Pharmacy, Swedesboro, NJ, USA). The usual dose of trimix solution ranges from 0.1 mL to 0.5 mL. The rate of response to this solution is as high as 90% [36].

The majority of men with functioning kidneys can look forward to a return of sexual activity comparable to pre-illness level. However, sexual impairment might persist in some patients after transplantation, emphasizing the need for further evaluation in this group of patients.

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