**Invited Comment**

**End-stage renal disease and erectile dysfunction. Is there any hope?**

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**Introduction**

A common problem that remains difficult to diagnose and treat in patients with chronic renal failure (CRF) is sexual dysfunction. Prevalence estimates of sexual dysfunction range from 9% in predialysis to 70% in dialysis patients of either sex [1,2]. The presence of erectile dysfunction ranges between 21 and 43% among dialysis and transplant patients and this prevalence has remained the same since the 1970s [3]. The causes of erectile dysfunction are frequently combinations of both organic and psychological factors. We review the pathogenesis, investigations, and treatment currently available for erectile dysfunction.

**Pathophysiology of erectile dysfunction**

Numerous sexual stimuli are processed by the brain and transmitted to the penis by parasympathetic impulses that pass through the nervi erigentes to the penis. This results in vasodilatation of the arteries, relaxation of the smooth layer, and compression of the veins against the rigid tunica albuginea, thus allowing blood to build up under high pressure in the erectile tissue of the penis. The vascular muscle in the spongy area becomes engorged with blood resulting in ballooning of the erectile tissue to such an extent that the penis becomes hard and elongated.

Erectile dysfunction is often the result of multisystem disease processes involving the hypothalamic–pituitary–gonadal axis, vascular supply, and penile tissue damage from either infections or trauma. Psychological factors such as fatigue, stress, and depression may result from chronic illness and contribute further to the patient’s loss of erection.

End-stage renal disease (ESRD) causes imbalance in the hypothalamic–pituitary–gonadal axis in man, and the pulsatile mode of gonadotrophin-releasing hormone (GnRH) release is critical for sustained physiological function of gonadotrophin cells and is a pre-requisite for reproductive capability [4]. In the pathophysiological state of uraemia with associated inadequate nutrient intake, stress, and systemic illness, the pulsatile release of gonadotrophic hormones is dramatically impaired and can bring about hypogonadism by suppression of GnRH pulse generator output. There is reduction in plasma testosterone and an increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. The decrease in testosterone is attributed to a variety of mechanisms including an elevated testosterone elimination profile, impaired Leydig cell production, and a reduction in the response to human chorionic gonadotrophin stimulation [5–8]. The low testosterone levels stimulates LH secretion and plasma LH levels are further increased by the impairment in degradation in patients with ESRD. FSH levels are increased due to atrophy of the Sertoli cells which are normally responsible for its suppression by the secretion of the peptide inhibin [7–9].

Hyperprolactinaemia has been reported in 25–57% of male ESRD patients and has been implicated in impotence, hypogonadism, and reduced desire. Hyperprolactinaemia interferes with gonadal responses to gonadotrophins, resulting in a reduction in sexual steroid secretions. Interestingly, it is not clear from the literature what the sexual effects of hyperprolactinaemia are and the underlying mechanism remains obscure [10].

Erectile dysfunction may be the earliest feature of diabetic autonomic neuropathy; however, uraemic men without diabetes can also present with this complaint. Tissue obtained from diabetic men with impotence exhibits a functional impairment in the neurogenic and endothelium-mediated mechanisms that allow relaxation of the smooth muscle of the corpus cavernosum [11]. Precautious (premature) arteriosclerosis, including pelvic arteries and alteration of these relaxation mechanisms, may explain the unusually high prevalence of impotence among men with diabetes mellitus, but it is not clear to what extent neurogenic factors may contribute to their sexual impairment. Studies evaluating the responses obtained by frequency of
intercourse questionnaire and nocturnal penile tumourance (NPT) have found abnormal Valsalva ratios that correlate to significant abnormalities in NPT and decrease in intercourse frequency [12].

ESRD results in an acceleration of atherosclerosis and may lead to vascular erectile dysfunction by occluding large vessels and their arterial tributaries [13]. Large proportions of patients with ESRD (78%) were found to have significant cavernosal artery occlusive disease, resulting in erectile dysfunction [14]. Other arterial risk factors such as hypertension, hyperlipidaemia, and smoking, on their own seem to be less important factors in causing penile atherosclerosis [15]. Several drugs are implicated (diuretics, beta-blockers) but substitution with other agents frequently does not result in any improvement in sexual dysfunction. Altered erythropoietin synthesis in ESRD leads to anaemia with low oxygen delivery to the corpora cavernosa. This has been shown to decrease nitric oxide synthesis and increase endothelial-derived contractile factors, resulting in increased smooth-muscle tone and inhibiting erection [16,17]. Finally, urinary metabolites that are nitric oxide synthase inhibitors are found in high concentrations in ESRD patients, and contribute further to erectile dysfunction.

Patients with ESRD suffer from chronic fatigue, anxiety and a decline in self-esteem; not surprisingly these factors result in lack of sexual interest. Bancroft [10] has probably comes closest in explaining the sexual response cycle, which depends on emotional, cognitive, and genital components, and failure in any of these areas may lead to sexual difficulties.

Assessment of sexual dysfunction

The problem of sexual dysfunction should ideally be managed in a dedicated clinic. Precise investigations will depend on history and examination findings. There have been recent developments such as waking erectile assessment that objectively assess psychophysiological criteria for evaluation of erectile dysfunction [18].

Management

Treatment must start with determining and treating the underlying causes. Honest evaluation of alcohol, tobacco, and recreational drugs is essential. Assessment of emotional life, i.e. how well the patient gets along with his partner is vital. He may benefit from a referral to a psychotherapist, or the couple may be advised to seek marriage guidance. For men in whom vascular problem appears to predominate: Doppler studies, pharmacocavernosometry, pharmacocavernosography, dynamic infusion studies, and colour Doppler response studies may be helpful. Once erectile dysfunction is diagnosed and psychosexual component is ruled out a review of the drugs, haemoglobin levels and dialysis adequacy should be corrected. They should have hormonal studies, including testosterone, LH, FSH, and prolactin. Correction of these hormones may not necessarily restore libido. The use of testosterone injections have shown only a small and variable response in erectile function [19,20]. Using clomiphene in uraemic males may correct the androgen deficiency and increase the sense of well-being, libido, and potency, similarly to testosterone administration; however, its long-term use in uraemia is inconclusive [21]. In patients with increased prolactin levels, both drug-induced hyperprolactinaemia and pituitary adenomas should be excluded. Drugs that induce hyperprolactinaemia include dopamine receptor antagonists such as phenothiazine, chlorpromazine, promazine, haloperidol, metoclopramide, and CNS dopamine depleting agents such as methyldopa and reserpine, and also oestrogen in high doses. Dopamine receptor agonists such as bromocriptine and lisuride hydrochloride can be used. To treat erectile dysfunction, bromocriptine in doses of 2.5–5 mg has been shown to improve libido and potency; the mechanism, however, remains unclear and it is possible that bromocriptine may influence potency directly as a result of its dopaminergic properties [22].

Lisuride hydrochloride has a similar effect but with few reported side-effects [23]. If there is no benefit from supplementation with these agents, further treatment options should be discussed with the patient. An algorithm of management is given in Figure 1. Several categories of treatment are available.

Oral

Sildenafil (Viagra)

The first of possibly many phosphodiesterase 5-inhibitors was launched in the USA in 1998. It produces an erection in approximately 60–80% of patients with erectile dysfunction approximately an hour after taking the drug. Sildenafil acts by inhibiting the conversion of active cGMP to inactive non-cyclic GMP. Active cGMP relaxes the arteriolar smooth muscles, causing vasodilatation in the corpora cavernosa and so initiating and maintaining erection. Sildenafil is metabolized by cytochrome P450 and is excreted as active and inactive metabolite in the faeces. In the original study of its efficacy and safety, patients with renal failure were excluded [24]. The rates of myocardial infarction and other serious cardiovascular events were not significantly greater than in those subjects on placebo. However, since its launch in the USA the food and drug administration (FDA) have received 69 reports of deaths in patients whilst on Sildenafil. No cases of priapism were reported in any of the 28 trials but at least six cases were reported to the FDA and there may be a real danger of penile muscle damage and fibrosis [25]. Use of Sildenafil in dialysis patients has shown significant improvement in erectile dysfunction in two small studies [26,27]. The major side-effect reported was headache although with
Oral phentolamine, a short-acting alpha-blocker, is not yet licensed for use in erectile impotence. Sublingual apomorphine, a potent stimulator of D1 and D2 receptors, is also not licensed. Phosphodiesterase 5-inhibitor in the form of nasal spray is soon to be marketed. Minoxidil (topical to the glans penis) in one trial was found to increase both diameter and rigidity of the penis [32]. Condoms are recommended if minoxidil cream is used, to protect the partner. This again has not been studied in CRF patients.

**Intraurethral**

**Alprostadil (prostaglandin E1)**

This provides transurethral delivery of prostaglandin to the corpus cavernosum. The medication is put in an applicator that is inserted in the urethra. Depressing the button on the applicator releases the medicated pellet. It is sold under the brand name of MUSE (Medicated Urethral System for Erection). In a large study of 1511 men with organic erectile dysfunction, the success rate was about 70% [33]. Penile pain was reported in 35.7% of the men and caused 2.4% of them to discontinue the study.

**Intracavernosal**

**Alprostadil (prostaglandin E1)**

Alprostadil is injected into the shaft of the penis (Caverject). It causes smooth-muscle relaxation, vasodilatation, and inhibition of platelet aggregation. Patient and partner satisfaction is reported as 80–85%. Side-effects are mainly local and include pain (17%), haematoma or ecchymosis (1.5%) and priapism (1.3%). Patients with ESRD have a coagulopathy, which is greater in those on haemodialysis; therefore intracavernosal injections should be used with caution.

**Vacuum devices**

Vacuum constriction devices and constriction bands have been used for many years and have been reported as effective in patients with erectile dysfunction. A cylinder is placed over the penis and the air is withdrawn, creating a negative pressure, which is filled by an increase in blood flow into the penis, resulting in an erection. A tension ring is then placed on the base on the erect penis to maintain rigidity. This can be left in place for up to 30 min. This is effective with success rates of up to 90%. Side-effects include local pain, numbness of the penis, a cold, dusky penis, and local irritation.

**Penile prostheses**

These procedures should await renal transplantation, since many of the men may improve their sexual function after transplantation. Testosterone levels return to normal range within 2–3 months and this parallels LH, FSH, and prolactin normalization [34].
It is important to remember that, post-transplant, 87% of men will continue to have erectile dysfunction despite normalization of hormonal laboratory values and improved physiology [35,36].

Conclusion

Despite improvement in the delivery of renal support, sexual dysfunction in ESRD remains largely difficult to diagnose and treat. There are now many new assessment techniques and treatments. There are encouraging reports in the use of phosphodiesterase 5-inhibitors but their use is limited and larger studies are required for safe use in patients with ESRD. A greater awareness of this common problem should be encouraged so that patients and their partners do not feel embarrassed about broaching this subject with their physicians. The diagnosis will require ruling out any underlying psychological problem and referring patients to dedicated clinics. Although renal transplant may effectively reverse many of the hormonal and psychological changes of chronic renal failure, many patients will remain on a transplant waiting list for a considerable length of time. Patients who develop significant vascular disease may still remain impotent even after a successful transplant.

References