Introduction

Erectile dysfunction (ED), defined as an inability to obtain or maintain an erection adequate for satisfactory sexual function, is present in up to 50–80% of patients with chronic kidney disease (CKD) (1). The etiology of ED in this population is multifactorial, with abnormalities in the hypothalamic-pituitary-gonadal axis, the endothelial paracrine signaling system, calcium and vitamin D homeostasis, along with several other factors. Efficacy of treatment of ED in the CKD population is comparable to non-CKD patients across multiple modalities, including PDE5 inhibitors, vacuum erectile devices, intracavernosal injections and penile prostheses. Renal transplant improves the contributing comorbid conditions that lead to ED in CKD patients; thus rates of ED are improved post-transplant. It is important to note that there is a small percentage of patients with persistent ED after renal transplantation.

Definitions

CKD, a deterioration of kidney function due to multiple etiologies, is classified in stages based on patients’ glomerular filtration rate (GFR), which measures the filtering capability of the kidneys. End stage renal disease (ESRD) is defined as CKD stage 6, requiring renal replacement therapy such as hemodialysis.

Pathophysiology of ED in CKD

It is important to note that the majority of studies in this area focus on patients either on dialysis or after receiving a renal transplant; limited data exists on pre-dialysis CKD patients with ED (2).

Hormonal abnormalities

Several hormonal abnormalities have been consistently noted in CKD patients. Total and free testosterone levels tend to be reduced, with a normal binding capacity and concentration of sex hormone binding globulin (SHBG). In acute renal failure these disturbances are reversible with return of renal function; in chronic renal failure, the
Hypogonadal changes seem to persist (5). The cause of hypogonadism in this population is likely poor response of Leydig cells to stimulation, as serum luteinizing hormone (LH) levels are elevated in CKD patients and administration of HCG, with its LH-like actions, shows a minimal response in serum testosterone levels (6). In vitro studies also suggest uremic serum may contain an LH receptor antagonist, which is inversely proportional to GFR and is virtually eliminated by renal transplant (7). Follicle stimulating hormone (FSH) levels are also increased in men with CKD, thought to be secondary to decreased negative feedback from inhibin due to Sertoli cell damage from the uremic state (7). Hyperprolactinemia, though rare in the general population, is common in men with CKD, likely due to increased production as the kidneys play little role in its catabolism and excretion (8). This elevation in prolactin can lead to the suppression of the normal pulsatile release of gonadotropin-releasing hormone (GnRH) (9). Hyperprolactinemia can cause ED both via directly decreasing GnRH secretion, and thus ultimately testosterone, and by increasing the synthesis, turnover, and release of hypothalamic dopamine (10,11). Secondary hyperparathyroidism and depletion of zinc reserves have been postulated as alternative causes of hyperprolactinemia in the CKD population (12,13). These hormonal abnormalities in combination lead to the hypergonadotropic hypogonadal state of the CKD patient.

It is unclear whether uremic metabolites damage the Leydig and Sertoli cells of the testes more than they do hypothalamic and pituitary function, or if degradation of these metabolites occurs at a faster rate in the hypothalamus and pituitary than the testes. Both situations result in hypergonadotropic hypogonadism. Alternatively, as LH and prolactin are polypeptide hormones, their renal clearance may be decreased to a greater degree with impaired GFR than that of testosterone, which is a lipid-based hormone (14). This would lead to increased LH and prolactin levels while simultaneously lowering testosterone levels, due to increased clearance, thus again resulting in hypergonadotropic hypogonadism.

The male hormonal milieu has been shown to play a critical role in ED. Low testosterone and high prolactin both lead to decreased libido. Several older studies have shown elevated prolactin levels are correlated with decreased libido (15,16). It is important to note that hyperprolactinemia also leads to low testosterone through negative feedback in the hypothalamic—pituitary—gonadal axis, thus leading to potential confounding. Additionally, testosterone is critical for maintaining normal physiology of the penis, with low testosterone causing replacement of cavernosal smooth muscle with collagen fibers, potentially leading to corporal veno-occlusive dysfunction and fibrosis (17). On the molecular level, nitrinergic activity, responsible for vasodilation, and PDE5 (phosphodiesterase-5), the enzyme responsible for cGMP degradation, are both influenced by testosterone (18,19). The relationship between serum testosterone has been demonstrated in several studies. A 2006 cohort study of 434 men demonstrated that ED, although likely also due to a combination of factors such as metabolic syndrome, smoking, and depression, has serum testosterone less than 231 ng/dL as an independent risk factor (20). An inverse relationship between probability of questionnaire self-reported symptoms and testosterone levels was demonstrated in an age stratified, random sampling of 3,200 men in the European Male Aging Study. Patients were more likely to report ED at the threshold T level of 245 ng/dL (21).

Furthermore, there is evidence that testosterone therapy improves erectile function in men with testosterone deficiency. A 2016 prospective observational longitudinal study of 261 hypogonadal men on intramuscular testosterone therapy showed a 71% improvement in Index of Erectile Function (IIEF) scores within the first 3 months, with an additional 65% improvement by the end of the mean 4.25 years of treatment. The change in mean IIEF score over the duration of the study, baseline 7.8 to 21.96, indicated that many patients improved from being categorized as having severe ED to no ED (22). Data from the recent double-blinded, placebo-controlled Testosterone Trials study supported this assertion, though to a lesser extent. In a randomized group of 790 hypogonadal men (baseline T less than 275 ng/dL) aged 65 or older receiving either testosterone gel or placebo for one year, the testosterone treated group saw a 2.64 points improvement in their IIEF erectile function domain, downstaging many patients from severe ED to moderate ED (23). It is important to note that this study has received criticism for its industry funding, reliance on questionnaire responses, and lack of reporting of degree of serum testosterone level improvement. A 2017 meta-analysis of 14 randomized controlled studies, including 2,298 men, suggested that testosterone therapy improved the IIEF erectile function domain score by 2.31 when compared to placebo. The effects of therapy on erectile function were more pronounced in patients with a lower baseline testosterone (less than 231 ng/dL vs. less than 345 ng/dL) and less effective in men with comorbidities such as diabetes.
mellitus or obesity (24).

**Cardiovascular and endothelial dysfunction**

It is well established that CKD increases patients’ risk for cardiovascular disease (CVD) (25). Endothelial dysfunction, which is noted early in CVD, is also a critical component of ED, as nitric oxide (NO) production is decreased in poorly functioning endothelial cells. Endothelial dysfunction, similar to that seen in CVD, has been reported in CKD—thus it is unsurprising that CKD patients also frequently report ED (26). Furthermore, CKD patients often suffer from comorbid metabolic conditions, such as diabetes, hypertension, and dyslipidemia, each of which are risk factors for ED (27-31). Thus CKD contributes to ED both indirectly, via associated metabolic conditions, and directly, via impact on endothelial function.

**Nervous system abnormalities**

Autonomic neuropathy, which occurs both secondary to diabetes and independently in CKD patients, has been postulated as a potential cause for ED. One early study compared nocturnal penile tumescence rates and blood pressure responses to Valsalva maneuver, as a proxy for autonomic nervous system function, in both uremic and non-uremic patients. Uremic patients were found to have both lower nocturnal penile tumescence rates and abnormal Valsalva responses (32). This suggests that uremia itself may lead to autonomic dysfunction and thus ED. Diabetes, in addition to potentially causing CKD, has been shown to cause peripheral neuropathy. Diabetic patients with decreased vibratory perception thresholds, a measure of peripheral nerve function, have been found to have higher rates of ED (33).

**Anemia and erythropoietin deficiency**

Erythropoietin (EPO) is a cytokine secreted by the interstitial cells in the peritubular capillary bed of the kidney cortex in response to hypoxia and is responsible primarily for upregulating red blood cell production in the bone marrow. CKD patients do not have an appropriate increase in EPO secretion in times of hypoxia, and thus often experience a chronic anemic state. EPO is commonly used to treat anemia in CKD patients; and several studies report that use of EPO in CKD patients on dialysis improved erectile function (34-36). The mechanism by which EPO administration improves ED is not entirely clear, though several theories have been postulated. EPO has been shown to normalize elevated prolactin levels in early studies, though later studies did not confirm this finding (37-40). EPO was also shown to increase serum testosterone in some studies, but was inconclusive in others (34,35,38-41). An early study using 4 weeks of recombinant EPO therapy demonstrated a decrease in serum prolactin from 39.5±10.5 to 10.3±1.0 ng/mL in male dialysis patients, while serum testosterone levels remained unchanged (34). Another small cohort of dialysis patients on EPO demonstrated a mild increase in anterior pituitary function, and thus downstream circulating testosterone, after receiving EPO treatment (38). It is possible that EPO has a more direct impact on erectile function, as demonstrated by increased regeneration of the injured cavernous nerve after EPO administration in a rat model (42). EPO has also been shown to have anti-apoptotic effects, thus protecting the cavernous nerve against ischemic injury (43,44). The natural receptor for EPO is expressed on vascular endothelial cells; when EPO binds to this receptor, it stimulates their proliferation and migration. Additionally, EPO binding mobilizes endothelial progenitor cells from the bone marrow, which differentiate into vascular endothelial cells. These progenitor cells have been shown to migrate to the capillaries and small arteries of ischemic tissues in vivo, thus stimulating angiogenesis (45). It has been reported that ED patients have low numbers of circulating endothelial progenitor cells; thus treatment with EPO may restore this imbalance and improve erectile function via increased angiogenesis (46-48). It appears that EPO plays a multifactorial role in improving erectile function in CKD patients through its neuroprotective, anti-apoptotic and angiogenic properties.

**Vitamin D deficiency and secondary hyperparathyroidism**

Vitamin D, in its inactive precursor form, is obtained either via diet or through skin synthesis. It then undergoes two hydroxylation steps to become active, first in the liver and then primarily the kidney, with additional secondary hydroxylation sites having been described recently (49-51). With a decrease in the second hydroxylation step, CKD patients typically have severe hypovitaminosis D. Although there is a lack of conclusive evidence, it has been reported that treatment with 1,25 (OH) D3 decreased serum PTH concentrations and improved erectile function in patients on dialysis (52). PTH administration has also been shown to increase serum prolactin levels, thereby potentially implicating secondary hyperparathyroidism as an etiologic
factor for ED in CKD patients (12).

**Zinc deficiency**

Zinc deficiency has recently been demonstrated in a subset of CKD patients, and may explain EPO resistant anemia in this population (53). CKD patients, particularly those on hemodialysis, suffer from zinc depletion via direct removal during hemodialysis and decreased GI absorption, and demonstrate an increased reticulocyte count and improved erythropoietin response after correcting low serum zinc levels. The mechanism behind this is not entirely clear but may be related to zinc-finger regions of transcription proteins regulating hematopoietic progenitor cell development (53,54). Oral zinc supplementation in this population has also been shown to increase serum testosterone levels and improve erectile function (55,56). However, at least one independent study showed no reversal of ED with zinc supplementation in this population (57).

**Psychosocial factors**

There is increasing evidence that psychosocial factors, such as depression, anxiety, and health-related quality of life impact the pathophysiology of chronic disease. In CKD, depression in particular has been studied in depth, with dialysis patients having an increased risk of depressed and consequent risk of mortality as well as poor health-related quality of life (58). Up to 30% of CKD patients meet the criteria for clinical depression (59-61). Depression has been shown to be an independent risk factor for ED in several studies, thus increasing the ED risk in the CKD population (62,63).

**Medication effects**

CKD patients are often prescribed multiple medications, many of which are known to contribute to ED. Antihypertensive drugs, particularly thiazide diuretics, aldosterone receptor blockers, and beta-adrenergic receptor blockers have been implicated in ED in CKD patients (64). Additionally, cimetidine, tricyclic antidepressants, and metoclopramide may exacerbate ED symptoms in these patients (65-68).

**Treatment of ED in CKD patients**

**PDE5 inhibitors**

For erections to occur in human males, sexual arousal must stimulate neural pathways to release NO from nerves and endothelial cells within the penis. NO then penetrates through the membranes of smooth muscle cells, binds to guanylyl cyclase and results in formation of 3’-5’-cyclic guanosine monophosphate (cGMP). Cyclic GMP then binds with and activates cGMP dependent protein kinase, which phosphorylates several proteins and acts as the intracellular trigger for erection. These phosphorylated proteins lead to an influx of calcium, relaxation of arterial and trabecular smooth muscle, influx of blood into the penis and consequent venous compression, ultimately leading to tumescence (69).

PDE5 is an enzyme that degrades cGMP back to its inactive form; thus PDE5 inhibitors prolong the duration of active cGMP and improve erections. Multiple studies have demonstrated the efficacy of PDE5 inhibitors in the CKD and dialysis population with success rates comparable to non-CKD patients (70-74). The side effect profile is similar to the non-CKD patient population, with headache, flushing, and GI upset reported as the most common adverse effects (75). As PDE5 inhibitors may have a protective effect against renal injury, renal protective dose adjustment is not usually required in the CKD population (76-78). However, some authors have noted an increase in transient hypotension after administering 50 mg of sildenafil, particularly on those days that patients receive hemodialysis and may already be hypotensive compared to baseline. It has been suggested that PDE5 inhibitors should only be used on non-dialysis days and that a smaller starting dose (25 mg of sildenafil) be used (79). Data on the use of more selective drugs, such as vardenafil and tadalafil (both more selective for PDE5 compared to other PDEs), is still lacking in the CKD population.

**Testosterone replacement therapy**

Testosterone simultaneously upregulates the activity of neuronal nitric oxide synthase (nNOS) and PDE5, thus increasing NO levels and increasing the degradation of cGMP (80,81). These two antagonistic effects may effectively cancel each other out, explaining why administration of testosterone to CKD patients usually fails to restore libido and erections, despite an increase in serum testosterone (82,83). While combination therapy with testosterone and PDE5 inhibitors has been shown to be effective in hypogonadal men who do not respond to PDE5 inhibitors alone, the data is mixed in the CKD population (84-88). In particular, a recent randomized, double
blind, placebo-controlled trial failed to show significant improvement of erectile function with the addition of testosterone to sildenafil in the CKD population (89). Thus the role of testosterone supplementation for the purpose of improving erections in the CKD population remains controversial at best.

Other ED treatments

Further ED treatments include vacuum erectile devices, intracavernosal injections, urethral suppositories, and prosthesis implantation. A single study evaluated effectiveness of vacuum therapy in dialysis patients, with 73.1% of patients achieving erection with the vacuum device. Of note, all hypogonadal men in this cohort first received testosterone therapy via implantation of depo-testosterone (82). Intracavernosal injections may be performed with a variety of medications in combination or alone, including prostaglandin E1, papaverine, and phentolamine. While the success rate in the general population is 80-85%, they must be used with caution in the CKD population, particularly with ESRD, due to a greater degree of coagulopathy leading to potential bleeding complications at the needle injection site (90). Alprostadil suppositories have not been studied in the CKD population. Penile prostheses, often used after failure of first and second line therapies, can safely be performed in CKD patients without an increased risk of infection (91). Given that erectile function improves for many men post renal transplantation, it is recommended that penile prosthesis placement wait until after transplantation. One potentially challenging step during penile prosthesis placement post-transplant is selecting a location for the reservoir. The authors favor placing the reservoir on the contralateral side of the transplant as a first choice. If the patient has had a hernia repair with mesh or another kidney transplant on that side, the authors propose a small, open midline fascial incision or an ectopic submuscular reservoir placement. We have begun favoring ectopic placement in this situation due to several studies showing good outcomes with this technique (92,93).

Role of renal transplant on ED

While dialysis itself has not been shown to improve sexual function, several studies report improvement of erectile parameters after renal transplantation (94-97). The IIEF scores of thirty ESRD patients collected before, 3 months after, and 6 months after renal transplantation showed a significant improvement in 40% of recipients (97). In another more recent longitudinal study of CKD patients receiving a spectrum of treatment, from peritoneal and hemodialysis to renal transplant, renal transplant patients showed a statistically significant increase in IIEF score (95). Renal transplantation has also proven to improve sperm motility without changing morphology or sperm count. Additionally, post transplantation serum levels of testosterone significantly increase, while LH, FSH and prolactin significantly decrease (98,99). In addition to the normalization of hormonal and metabolic functions post-transplant, there is a significant improvement of psychosocial parameters in transplant recipients, which likely impacts sexual function as well (100). It is important to note that there is a notable population of post-transplant patients with persistent ED, likely due to the fact that transplant alone cannot eliminate all comorbidities affecting both renal and erectile function (101,102).

Conclusions

ED is an important sequelae of CKD that is often overlooked by providers. The metabolic, homeostatic, hormonal, cardiovascular and neurologic physiology of CKD can all lead to ED (Figure 1). Though its’ etiology is multifactorial, treatment for ED in CKD patients achieves success rates comparable to those in a non-CKD population. Renal transplant does not worsen, and indeed may often improve, ED, though ED that persists after transplantation is likely due to multiple preexisting comorbidities.
Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Fiuk JV, Tadros NN. Erectile dysfunction in renal failure and transplant patients. Transl Androl Urol 2018. doi: 10.21037/tau.2018.09.04