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MINIREVIEWS

Erectile dysfunction in chronic kidney disease: From pathophysiology to management

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Abstract

Chronic kidney disease (CKD) is encountered in millions of people worldwide, with continuously rising incidence during the past decades, affecting their quality of life despite the increase of life expectancy in these patients. Disturbance of sexual function is common among men with CKD, as both conditions share common pathophysiological causes, such as vascular or hormonal abnormalities and are both affected by similar coexisting comorbid conditions such as cardiovascular disease, hypertension and diabetes mellitus. The estimated prevalence of erectile dysfunction reaches 70% in end stage renal disease patients. Nevertheless, sexual dysfunction remains under-recognized and under-treated in a high proportion of these patients, a fact which should raise awareness among clinicians. A multifactorial approach in management and treatment is undoubtedly required in order to improve patients' quality of life and cardiovascular outcomes.

Key words: Chronic kidney disease; Erectile dysfunction; Management; Quality of life; Hypertension; Diabetes mellitus; Phosphodiesterase-5 inhibitors

Core tip: Erectile dysfunction is highly prevalent among patients with chronic kidney disease in rates that reach even 70%, especially in those suffering from end stage renal disease. The rates of patients suffering from sexual dysfunction tend to be higher when additional risk factors, such as coronary artery disease, diabetes mellitus, hypertension or prescription of antihypertensive drugs, coexist. Integrated management of these patients through lifestyle measures, hormonal replacement, and use of drugs such as phosphodiesterase-5 inhibitors, is essential in order to improve sexual function among these patients, thereby maintaining a satisfactory quality of life.

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INTRODUCTION

Sexual dysfunction is highly prevalent in patients with chronic kidney disease (CKD) especially those receiving dialysis. Almost 70% of men with CKD report erectile dysfunction (ED) and these estimates are higher than in the general population[1]. The cause is generally multifactorial with psychological, neurological, endocrinological, vascular and iatrogenic factors acting in concert to increase the likelihood of ED[2]. A number of recent studies suggest an association between endothelial dysfunction and ED[3].

This review aims to analyze the pathophysiology of ED in patients with CKD, to present its prevalence rates in various stages of CKD, to highlight comorbid conditions and common risk factors, which both diseases share and, eventually, to discuss possible therapeutic options, which might improve sexual function of CKD patients.

We performed a systemic search of the literature using the PubMed, OVID, EMBASE and Cochrane Central Register databases from their inception to July 2014. The studies addressing the association between ED and CKD were identified by using the following terms in various combinations: CKD, erectile dysfunction, impotence, renal failure, end stage renal disease, kidney transplantation, phosphodiesterase (PDE)-5 inhibitors. In addition, we reviewed the reference lists of the identified original papers, the studies citing identified papers and review papers relevant to this topic.

Data were extracted by four independent members of our team (Papadopoulou E, Varouktsi A, Lazaridis A, Boutari C) and were discussed with the senior author of our paper (Doumas M). The following criteria were required for a study to be included in our review: observational studies with at least 20 participants, detailed description of a proper estimation of renal function and erectile function.

PATHOPHYSIOLOGY

Erectile dysfunction is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse[4]. The erectile process is a complex neurovascular event. In response to sexual stimulation, cavernous nerve terminals and endothelial cells release nitric oxide (NO) which is believed to be the main vasoactive mediator of penile erection. NO promotes penile vasodilation and blood flow, by activating soluble guanyl cyclase to produce 3, 5-cyclic guanosine monophosphate resulting in an enzymatic cascade that reduces intracellular calcium and induces relaxation of cavernosal smooth muscle[5].

Appropriate hormonal environment permits a successful erection with testosterone playing a primary role[6]. Disturbances in neurovascular control, abnormal hormone levels or psychological factors are responsible for the vast majority of ED that is broadly classified as psychogenic (generalized, situational), organic (vasculogenic, neurogenic, anatomic, endocrinologic) or mixed[7].

Psychological factors include primary lack of sexual arousal, chronic disorder of sexual intimacy, depression and performance anxiety. Physiological factors are a more common aetiology and neurological disorders such as Parkinson's disease, stroke, tumour, multiple sclerosis and spinal cord injury are noted to be associated with ED. In addition hormonal disorders such as hypogonadism, hyperprolactinemia and both hyperthyroid and hypothyroid states are known to result in ED. Arterial insufficiency associated with diabetes, hypertension, dyslipidemia, cigarette smoking, blunt perineal or pelvic trauma and pelvic irradiation, tend to be the most common cause of ED[8].

In men with chronic renal disease a combination of testicular failure and secondary disturbances in the pituitary-gonadal axis can be detected in the early stages of CKD and progressively worsen as the renal disease progresses[9]. Some authors have reported that successful kidney transplantation may improve sexual function with reference to the previous situation of haemodialysis[10]. Impaired spermatogenesis and testicular damage with decreased volume of ejaculate, either low or complete azoospermia, low percentage of motility and infertility were reported[11].

Histological changes in the testes revealed decreased spermatogenic activity especially in the later stages of spermatogenesis which are hormonally dependent[12]. Testicular biopsy is often performed to demonstrate reduced spermatogenesis[13]. Leydig and Sertoli cells show absence of hypertrophy or hyperplasia and the reduced levels of total and free testosterone presented in CKD, suggest a Leydig cell dysfunction[14].

Hypogonadism (low testosterone) defined as total testosterone below 300 ng/mL is a prevalent condition in men with CKD especially in those undergoing dialysis and can contribute to decreased libido, ED, oligospermia infertility and anaemia[15]. On the other hand total plasma estrogen concentration is often elevated. The plasma concentration of the pituitary gonadotropin luteinizing hormone (LH) is elevated probably as a result of the decreased release of testosterone from the Leydig cells and the consequent loss of normal negative feedback. In addition the metabolic clearance rate of LH is reduced and it is not corrected by dialysis[16].

In uremic subjects disturbances in LH secretion has been observed but it is not known whether this is the result of a change in GnRH release from the hypothalamus or a change in the responsiveness of the pituitary. However kidney transplantation seems to restore the secretory pattern of LH. Follicle-stimulating hormone (FSH) secretion is also elevated in men with CKD. A peptide

called inhibin produced by the Sertoli cells has a negative feedback on the release of FSH. Uremic patients with severe damage in seminiferous tubules and Sertoli cells tend to have higher plasma FSH concentrations as less inhibin is secreted[9].

Prolactin levels also appear substantially elevated in men with CKD, with a prevalence of hyperprolactinemia from 30%-65%, as a consequence of both reduced renal clearance and increased production. Again these abnormalities seem to resolve after kidney transplantation. Evidence indicates that hyperprolactinemia is associated with infertility, loss of libido, testosterone deficiency and increased risk of cardiovascular events and mortality in CKD. Bromocriptine treatment reduces prolactin levels with no significant side effects[14].

According to the "artery size hypothesis" atherosclerosis is more likely to develop first in the smaller arteries than in the larger ones. Since penile arteries are significantly smaller (1-2 mm diameter) than coronary arteries (3-4 mm), symptoms of ED occur several years before coronary artery disease (CAD) symptoms. ED is also found to be a stronger predictor of CAD than any of the traditional risk factors such as family history, hypertension, dyslipidemia and can be considered as a marker of ischemic heart disease in both CKD and non CKD patients[17,18].

NO is the primary neurotransmitter of penile erection. In chronic renal failure NO bioavailability is reduced. The expression of NO-synthase (NOS) has been shown to be alterned thus leading to a disturbance in sexual function[12]. Possible causes of NO deficiency are substrate limitation (L-arginine), as a result of disturbances in the renal biosynthesis of this amino acid and increased levels of circulating endogenous inhibitors of NOS especially asymmetric dimethylarginine (ADMA). Elevated levels of ADMA has emerged as an independent risk factor in end stage renal disease and reducing ADMA concentration might be a therapeutic goal[19].

Uremic polyneuropathy is an important contributor of ED. Patients undergoing haemodialysis are reported to have an abnormal response to Valsalva manoeuvre, impaired nocturnal penile tumescence and bulbocavernous reflex as evidence of autonomic and peripheral neuropathy, all correlated to sexual dysfunction[20].

CKD is associated with higher anxiety, higher distress, high depression and especially dialysis patients report interpersonal difficulties, lower employment, reduced social activity and low quality of life (QoL)[21]. Changes in body shape and image (catheter, fistula) also contribute to lack of desire and sexual dysfunction. The presence of higher depressive symptoms which are highly prevalent in patients undergoing haemodialysis are independently associated with sexual dysfunction and probably common factors are responsible for both[22].

Treatment of hypertension has also been associated with sexual dysfunction. B-blockers could cause ED by decreasing testosterone levels and potentiating α1-adrenergic activity in the penis. Patients taking thiazide diuretics report difficulty in gaining and maintaining an erection and difficulty with ejaculation. Spironolactone can cause gynecomastia, decreased libido and ED while drugs such as calcium antagonists, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, are associated with lower incidence of these side effects. Other drugs commonly involved in the development of ED are cimetidine, tricyclic antidepressants and metoclopramide[9,23,24].

Available data point towards a detrimental effect of CKD on spermatogenesis[9]. Moreover, zinc deficiency caused by reduced dietary intake, malabsorption and possible loss during haemodialysis, has been implicated in the pathophysiology of reduced sperm motility in CKD patients[9,23,25].

PREVALENCE

Sexual dysfunction is a common feature in patients with CKD despite the fact that is often underestimated by clinicians. Existing comorbidities such as diabetes mellitus, hypertension, atherosclerosis, and certain medications (medications *e.g.,* antidepressants diuretics, beta-blockers and other antihypertensive drugs) as well as pathophysiological conditions such as peripheral vascular disease, peripheral neuropathy and uremia are associated with a decrease in erectile function of male patients[26].

Since 1997, Rosen *et al*[27] have developed the International Index of Erectile Dysfunction (IIEF), a questionnaire which includes all aspects of male sexual functions (erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) and can evaluate as objectively as possible sexual function in male patients. Variable prevalence rates have been reported, mainly due to the study populations' diversity and the variety of sexual dysfunction assessment instruments. Bellinghieri *et al*[11] reported a direct correlation between IIEF and GFR, an inverse correlation between testosterone and cholesterol and an increased number of diabetic patients with ED in stage 3 of chronic renal failure.

The prevalence of erectile dysfunction is strongly age-dependent. The prevalence rises sharply with age. In particular, in the Massachusetts Male Aging Study (MMAS), erectile dysfunction is found in 8% in patients aged in their 40 s and rises up to 80% in patients over 70 years of age[28]. Messina *et al*[29] reported that men under 50 years old with CKD have a higher prevalence of ED than men over age 50 years, while in the MMAS the level of impotence and the prevalence of erectile dysfunction was positively associated with the subjects' age[30].

During the last decades the prevalence of end stage renal disease has significantly increased worldwide and due to the progress in renal replacement therapy. People with end stage renal disease (ESRD) appear to have a reduction in the QoL, which is associated with several factors such as age, therapy complications, psychological factors, and co-existing diseases[31]. Mesquita *et al*[32] reported that the prevalence of ED

was 76.5%, with 72.3% in stage 3 CKD, 81.5% in stage 4 and 87.5% in stage 5 CKD.

A study of 174 male HD patients (controls: 1133 healthy males) revealed that the prevalence of ED in men older than 40 years was higher than 80%, significantly higher than that described in control groups of the same age[33]. Espinoza *et al*[34] reported an ED prevalence of 48.9% in kidney transplant recipients in a study conducted among men with kidney transplantations. Rosas *et al*[26] reported that the prevalence of ED was 82% for all HD patients in a cross sectional study of 302 subjects treated with haemodialysis. ED was present in 90% of older HD patients (> 50 years) whereas its prevalence in younger subjects (< 50 years) was 63%[26].

A large systematic review and meta-analysis of observational studies (50 studies, 8343 patients) reported that the prevalence of any level of erectile dysfunction is approximately 70% (21 studies, 4389 patients) with no difference in prevalence rates among hemodialysis and peritoneal dialysis patients. However, in kidney transplant recipients the prevalence was lower (59% *vs* 75%)[35].

EFFECT OF COMORBIDITIES

Erectile and kidney dysfunction share common risk factors and are associated with diseases involving endothelial impairment such as diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, smoking and obesity[32].

Cigarette smoking is an established modifiable risk factor of arteriosclerosis. As a result of the MMAS, Feldman *et al*[28] reported that current smokers presented an adjusted odds ratio of 1.97 for incident ED compared to non-smokers (P = 0.03). Other studies also report a higher prevalence of ED in the groups of smokers compared to non-smokers and a higher percentage of smoking in men with severe/complete ED but these results did not appear to be significant in multivariate analysis[36].

As far as obesity is concerned, the nine-year follow-up prospective study from the MMAS revealed that it had an independent effect on ED, as a BMI $\geqslant$ 28 kg/m^2 predicted incident ED (OR: 1.96, P = 0.01). Similar results were observed in the Rancho-Bernando Study, where the age-adjusted BMI appeared to be significantly higher in men with severe ED or men who were sexually inactive (P < 0.05)[28,37].

Dyslipidemia is associated with an increased risk of erectile dysfunction due to its effect on endothelium and smooth muscle cells of the corpus cavernosum. The prospective study of MMAS failed to indicate a link between serum lipids and prediction of ED[28]. On the other hand, in the Rancho-Bernando Study elevated serum cholesterol levels and triglyceride levels were associated with more severe ED, as men without ED had lower cholesterol levels compared to men with moderate ED (P < 0.05), and men with no sexual activity or severe/complete ED had higher triglyceride levels than men without ED (P < 0.05)[37]. In a prospective study among 2869 men, Ponholzer *et al*[38] reported that hyperlipidemia was independently and significantly correlated to the presence of erectile dysfunction with an OR of 2.29 (P = 0.04). Hyperlipidemia is common among men with ED at rates that may reach 40%[39]. There have been reports that lipid-lowering therapy and use of statins may have a negative impact on erectile function; nevertheless statins are not generally accepted as a cause of ED and through their pleiotropic effects, statins may increase vascular NO activity and improve endothelial function[40].

Diabetes mellitus is considered to be a risk factor for ED due to vasculopathy and autonomic neuropathy and, additionally, one of the most frequent causes of CKD. Several studies have shown that it is highly prevalent and independently associated with erectile dysfunction in general population. Giuliano *et al*[41] reported a prevalence of ED of 71% among patients with DM and noted a trend of association between decreased mean IIEF-5 score and an increased duration of type 1-diabetes, lack of glycemic control and existence of complications. In a study of arterial risk factors (diabetes, hypertension, hyperlipidemia and smoking) among 440 impotent men, diabetes was the only risk factor that in isolation significantly reduced the penile blood-pressure index[42]. In another large prospective study including 2869 men diabetes was associated with a three times higher risk for ED[38]. Diabetic nephropathy is one of the most common causes of CKD and highly prevalent among end stage renal disease patients. Diabetes mellitus is significantly associated and considered to be an independent risk factor for erectile dysfunction in these patients[29,33,43]. No association between ED and cause of CKD has been proven. Nevertheless, in a study including 119 men with CRF in hemodialysis program, the highest prevalence of ED was among men whose kidney disease was due to diabetes[36]. Rosas *et al*[26] found that men with diabetes had twice the odds of suffering from erectile dysfunction compared to non-diabetic men in a cohort study among 302 subjects in hemodialysis, whereas Mesquita *et al*[32] reported that among 81 patients with CKD, diabetic patients were 4 times more likely to have impaired erectile function compared to non-diabetic subjects (P = 0.048).

In the general population, hypertension is considered to be a risk factor for erectile dysfunction due to its contribution in the atherosclerotic process and the endothelial dysfunction in penile vessels. In a multicenter prospective study conducted in Spain among 2130 men with primary hypertension, erectile dysfunction was reported in 45.8% of them[44]. In a smaller study, which included 634 Greek patients with essential hypertension, erectile dysfunction was prevalent in 35.2% of them compared to a rate of 14.1% found in the normotensives subjects (P < 0.01) and was associated with the severity of hypertension[23]. Despite the fact that a

strong association between hypertension and the emerge of erectile dysfunction has been well established in several other studies[38,41,45], data occasionally remain uncertain if hypertension is an independent risk factor for[28,42]. Although the frequency of hypertension is high among patients with CKD in rates reaching even 70%-95%, its association with sexual dysfunction among these patients is not always statistically significant[29,32,36,43]. Erectile dysfunction observed in hypertensive patients may be associated with the disease itself or it may be caused by the antihypertensive therapy being administered to these patients. In CKD patients, the drug therapy prescribed is often multifactorial including many types of old-antihypertensive drugs such as central acting antihypertensive drugs, diuretics (*e.g.,* thiazide diuretics and spironolactone), and beta-blockers, especially nonselective ones, which have shown a major influence on erectile function. New-generation agents, which include calcium-channel blockers, nebivolol and renin-angiotensin system inhibitors seem to have less deteriorating effects in sexual activity[6,46]. Indeed, Giuliano *et al*[41] reported greater IIEF-5 scores in patients receiving ACE inhibitors or angiotensin II receptor blockers compared to other antihypertensive treatment, while Rosas *et al*[26] revealed a significant association between ACE inhibitors and a decreased prevalence of erectile dysfunction in hemodialysis patients (OR: 0.42). As far as CKD patients are concerned, other widely used drugs, which are traditionally associated with increased rates of erectile dysfunction such as antidepressants, H_2 antagonists and benzodiazepines, should be taken into account as their use may impair sexual function[46].

Atherosclerosis and vascular calcification are very common in the CKD population, thus contributing to higher rates of cardiovascular disease and mortality among these patients. These findings tend to be present even among young adults undergoing hemodialysis compared to healthy subjects of the same age[47]. In the uremic subjects with ESRD, cardiovascular disease (CVD) is responsible for 40%-50% of all deaths and CVD mortality rates in those patients are approximately 15 times higher than the general population[21]. In addition to typical cardiovascular disease risk factors, end stage renal disease patients have impaired calcium and phosphorus homeostasis, deficiency of calcification inhibitors and receive high doses of vitamin D treatment, factors which have shown to promote the vascular calcification process[48]. In the general population, it has been reported that erectile dysfunction is associated with silent coronary disease as patients experiencing sexual dysfunction symptoms tend to have higher coronary artery calcification scores even in the absence of angina symptoms[49,50], a finding which is additionally observed among hemodialysis patients with severe ED, who also tend to present greater coronary artery calcium scores[3]. In a retrospective cohort study of 12825 ED patients, it was reported that there was a two-fold increase in the risk of acute myocardial infarction among men with ED[51]. Due to the apparent link between erectile dysfunction and other vascular abnormalities, CKD patients suffering from erectile dysfunction are in high risk of CVD. Therefore, clinicians should perform a careful evaluation in order to assess coexisting comorbid conditions and modify possible risk factors.

Cardiovascular risk and its association with sexual activity should be evaluated in all men with indications or confirmed cardiovascular disease. According to the Second Princeton Consensus Conference algorithm, patients are classified as low, intermediate or high cardiac risk depending on their sexual activity and their management depends on which category they are integrated. Although the Princeton-Ⅱ algorithm is based on acknowledged cardiovascular risk factors such as hypertension, diabetes mellitus or history of myocardial infarction or angina symptoms, CKD is not included as a condition increasing the cardiovascular risk in men with erectile dysfunction. Considering the increased risk of cardiovascular disease among patients suffering from renal failure and sexual dysfunction, it becomes obvious that these patients should be likewise evaluated and managed[52].

MANAGEMENT OF ED

The improvement of sexual function in CKD patients through a multifactorial approach is associated with an increase in patients' QoL and improved cardiovascular outcomes.

Lifestyle and general measures

Treatment of erectile dysfunction should start with an assessment of general status, evaluation of possible covariates and adoption of lifestyle measures, such as quit smoking, decrease of alcohol consumption and regular physical activity. As far as dialysis patients are concerned, clinicians should focus on optimization of dialysis delivery and adequate nutritional intake of these patients. The medication profile of each patient should be reviewed, considering that many drugs such as diuretics, beta-blockers, antidepressants, and H_2-antagonists are related to erectile dysfunction. Moreover, drugs inducing hyperprolactinaemia such as metoclopramide, haloperidol, phenothiazine, chlorpromazine, and methyldopa should be taken into account[53].

"Curable" causes of erectile dysfunction

Psychogenic ED: Psychotherapy and psychoeducational interventions such as rational, emotive therapy, sex group therapy and sexual counseling should be recommended when depression and other psychogenic causes of erectile dysfunction are suspected or in cases, in which it is indicated[53].

Hormonal-endocrine approach: Therapy with recombinant human Erythropoietin (rHuEPO) has shown to improve many aspects of functional health, such as exercise tolerance, sexual function, and QoL

of patients with CKD[54]. This improvement is likely to be associated with the correction of anemia, induced by the introduction of rHuEPO. In addition, some studies have shown that rHuEPO therapy is associated with alterations on endocrine function, affecting the pituitary-gonadal feedback mechanism. There is evidence supporting that it is associated with reduced prolactin, FSH and LH levels and increased plasma testosterone levels[55,56], although some small studies support that the prolactin levels suppression remains controversial among rHuEPO recipients[57]. Testosterone deficiency is a recognizable contributing factor in the development of anemia in CKD patients. Testosterone replacement therapy may increase blood count, QOL and sexual function[56].

Testosterone replacement therapy has been associated with multiple benefits in men with late onset hypogonadism. However, its effectiveness in men with CKD remains controversial considering that the improvement noted in libido, sexual desire, mood and energy is more profound than in erectile dysfunction individually[58]. Testosterone treatment may be also beneficial in increasing muscle mass and strength and in enhancing erythropoiesis[56]. Derivatives of testosterone can be delivered as injectable, oral, buccal, transdermal and subdermal preparations. Potential side effects such as cardiovascular adverse events, prostate cancer or exacerbation of sleep apnea should be identified and carefully assessed by clinicians[56].

An additional potential therapeutic option affecting endocrine disorders in CKD patients is dopaminergic agonists such as bromocryptine, which normalize prolactin levels, elevate plasma testosterone levels and improve libido and potency[59]. It has been reported that oral zinc supplements improve testosterone levels but its effect on sexual function remains conflicting. Subsidiary administration of oral vitamin E has shown that it may decrease prolactin and plasma testosterone levels[56].

First line therapy-oral pharmacotherapy

Since their introduction in 1998, phosphodiesterase-5 inhibitors are considered first-line agents for erectile dysfunction treatment in the general population. Sildenafil which is the agent most widely used is metabolized mainly in the liver and excreted approximately 80% in the feces and 13% in the urine; therefore, its pharmacokinetics are not significantly different in mild to moderate renal disease compared to healthy men, although its bioavailability may be increased in patients with creatinine clearance < 30 mL/min[60]. In several RCTs for treatment of sexual dysfunction in patients with CKD, treatment with sildenafil and vardenafil is associated with improvement in the overall score of IIEF-5, an increase of the score of all individual IIEF-5 tool domains (erection frequency, erection quality, penetration ability, maintenance frequency of penetration, maintenance of erection after penetration and erection confidence) compared to placebo and an increase of the overall satisfaction score of the IIEF-15 sexual assessment tool. For the use of other agents such as tadalafil or mirodenafil in CKD patients data is limited[61]. Sildenafil citrate is also considered an important first-line therapeutic option among kidney transplant recipients with sexual dysfunction as it has no effect on renal function or immunosuppressive drug levels[62]. The frequency of adverse events in CKD patients is similar to the general population, with headaches, flushing, dyspepsia, myalgia, and back pain, nasal congestion being most commonly reported, while more serious adverse events such nonarteritic anterior ischemic optic neuropathy or cardiovascular events are extremely rare. Due to the possible emerge of hypotension these agents are contraindicated in patients receiving nitrates. In addition, PDE-5 inhibitors should not be administered with PDE-3 inhibitors, such as cilostazol which is used for the management of peripheral artery disease.

Other therapeutic options beyond PDE-5 inhibitors

Vacuum constriction devices are an alternative therapeutic option. They provide negative pressure to the penis, resulting in increased blood flow and thus, causing erection. However, the satisfaction rates among patients remain variable.

Intraurethral or intracavernosal delivery of alprostadil (prostaglandin E_1) individually or in combination with other drugs such as papaverine or phentolamine can be used as a second-line therapy in case of non-response to oral drugs. A penile prosthesis is another therapeutic option in case of previous therapeutic failure and is preferred by some patients as it provides more permanent results. Nevertheless, it is recommended to be delayed after renal transplantation, as a percentage of ESRD patients may improve their sexual function afterwards[53].

Erectile dysfunction in post-transplant patients

Kidney transplantation is considered to be the most effective therapeutic option for patients suffering from CKD. The majority of kidney transplantations are carried out in middle age, where sexual function and fertility remain important[62]. Several studies suggest that erectile dysfunction remains highly prevalent, reaching 50% after kidney transplantation[34,63]. Sexual function post-operatively may be limited by graft malfunction, preexisting comorbid conditions of diabetes mellitus, hypertension, smoking and dyslipidemia, duration of dialysis before transplantation, effects of immunosuppressive or hypertension therapy and is associated with the original cause of kidney insufficiency[10,64]. The influence of haemodialysis duration before kidney transplantation observed by Rebollo *et al*[10] may be owing to the longer duration of peripheral vascular disease, and thus, prolonged vascular damage and hormonal changes in dialysis patients. With regard to immunosuppressive treatment, Malavaud *et al*[63] reported no statistically significant

association between cyclosporine therapy and erectile dysfunction, while the study of Rebollo *et al*[10] showed no association between ED and use of tacrolimus as immunosuppressant. The combination of cyclosporine and prednisone may have a more beneficial effect than azathioprine in gonadal function after kidney transplantation[65]. Renal transplantation usually results in normalization of hormonal profiles of kidney transplant recipients, reducing high levels of prolactin and LH and elevating plasma testosterone[65-68]. Despite these alterations, recovery of sexual function is not present in all patients, as erectile dysfunction may be affected by various factors and thus, can be highly prevalent in patients with renal insufficiency even after kidney transplantation.

CONCLUSION

Sexual dysfunction and chronic renal failure share common pathophysiological pathways and are affected by similar comorbid conditions. Erectile dysfunction tends to be more frequent in patients with CKD. Its incidence is strongly associated with age and stage of renal failure. Despite the advances in therapeutic options, especially the emerge of PDE-5 inhibitors, and the potential relief they may offer, erectile dysfunction still remains highly prevalent and further studies are needed.

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