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REVIEW

Chronic kidney disease and erectile dysfunction

Etsu Suzuki, Hiroaki Nishimatsu, Shigeyoshi Oba, Masao Takahashi, Yukio Homma

Etsu Suzuki, Institute of Medical Science, St. Marianna University School of Medicine, Miyamae-ku, Kawasaki 216-8512, Japan
Hiroaki Nishimatsu, Yukio Homma, The Department of Urology, Faculty of Medicine, University of Tokyo, Bunkyo-ku, Tokyo 113-8655, Japan
Shigeyoshi Oba, Masao Takahashi, The Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Bunkyo-ku, Tokyo 113-8655, Japan
Author contributions: All the authors solely contributed to this paper.
Correspondence to: Etsu Suzuki, MD, PhD, Institute of Medical Science, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8512, Japan. esuzuki-tky@umin.ac.jp
Telephone: +81-44-9778361 Fax: +81-44-977-8361
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Abstract

Erectile dysfunction (ED) is a common condition among male chronic kidney disease (CKD) patients. Its prevalence is estimated to be approximately 80% among these patients. It has been well established that the production of nitric oxide from the cavernous nerve and vascular endothelium and the subsequent production of cyclic GMP are critically important in initiating and maintaining erection. Factors affecting these pathways can induce ED. The etiology of ED in CKD patients is multifactorial. Factors including abnormalities in gonadal-pituitary system, disturbance in autonomic nervous system, endothelial dysfunction, anemia (and erythropoietin deficiency), secondary hyperparathyroidism, drugs, zinc deficiency, and psychological problems are implicated in the occurrence of ED. An improvement of general conditions is the first step of treatment. Sufficient dialysis and adequate nutritional intake are necessary. In addition, control of anemia and secondary hyperparathyroidism is required. Changes of drugs that potentially affect erectile function may be necessary. Further, zinc supplementation may be necessary when zinc deficiency is suspected. Phosphodiesterase type 5 inhibitors (PDE5Is) are commonly used for treating ED in CKD patients, and their efficacy was confirmed by many studies. Testosterone replacement therapy in addition to PDE5Is may be useful, particularly for CKD patients with hypogonadism. Renal transplantation may restore erectile function. ED is an early marker of cardiovascular disease (CVD), which it frequently precedes; therefore, it is crucial to examine the presence of ED in CKD patients not only for the improvement of the quality of life but also for the prevention of CVD attack.

Key words: Erectile dysfunction; Chronic kidney disease; Nitric oxide; Phosphodiesterase type 5; Testosterone

Core tip: Erectile dysfunction (ED) is a common condition in chronic kidney disease (CKD) patients. The etiology is multifactorial. Phosphodiesterase type 5 inhibitors are commonly used for the initial treatment. ED has gained attention as an early marker for cardiovascular disease (CVD), which it frequently precedes. Therefore, it is pivotal to examine the presence of ED in CKD patients not only for the improvement of quality of life but also for the prevention of CVD attack. The pathophysiology of erection, which most nephrologists are not familiar with, is also discussed.

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INTRODUCTION

Erectile dysfunction (ED) is defined as an inability to

attain and/or maintain penile erection sufficient for satisfactory sexual performance. It is now a common condition and approximately 150 million males worldwide are estimated to suffer from ED[1]. The prevalence of ED in 2025 is projected to be approximately 300 million worldwide[2]. It is well known that age, metabolic disorders (hypertension, diabetes, and hyperlipidemia), and smoking are major risk factors for ED. Recently, chronic kidney disease (CKD) has also gained attention as a risk factor for ED. Although CKD causes sexual dysfunction in both genders, this review article focuses on the role of CKD in the development of ED. We discuss the etiology and treatment of ED in CKD patients.

PREVALENCE OF ED IN CKD PATIENTS

The prevalence of ED in the United States male population aged > 50 years (Participants: 31,742 men, age 53-90 years) was reported to be 33%[3], whereas that in the Turkish male population aged > 40 years (Participants: 2158 men) was 69.2%[4]. However, the prevalence was 36% when mild ED cases were excluded. Navaneethan *et al*[5] reported in their meta-analysis study that the prevalence of ED in CKD patients was 70% on average. Furthermore, Mesquita *et al*[6] reported that the prevalence of ED in CKD outpatients with stages 3, 4, and 5 was 72.3%, 81.5%, and 85.7%, respectively. Nassir reported that the prevalence of ED in patients just entering dialysis programs was 82.7%[7]. Thus, it is observed that ED frequently occurs in CKD patients.

BLOOD SUPPLY TO THE PENIS

The blood supply to the penis originates predominantly from the internal pudendal artery, which branches into the penile artery. The penile artery then branches into the cavernous arteries. The cavernous artery enters the cavernous body and subsequently divides into many branches called the helicine arteries, which open into the cavernous sinuses. Blood in the cavernous sinuses is drained by the subtunical veins that form the venous plexuses just beneath the tunica albuginea and then returns to the circulation *via* 3 sets of veins; the superficial, intermediate and deep veins.

PATHOPHYSIOLOGY OF PENILE ERECTION

Penile erection and detumescence are regulated by relaxation and contraction, respectively, of the smooth muscle located in the arteries and the cavernous body. In the flaccid state, the sympathetic nervous system is dominant, and the arterial and corporal smooth muscle is tonically contracted. As a result, only a minimal amount of blood flows through the cavernous artery into the cavernous body. After sexual stimulation, parasympathetic activity causes a decrease in the peripheral resistance due to vasodilatation, and the blood flow through the cavernous and helicine arteries increases. The intracavernous pressure increases without any increase in the systemic pressure. In the full erectile state, increased blood volume in the cavernous body and the following compression of the subtunical drainage veins against the rigid tunica albuginea lead to a reduction in the venous outflow (referred to as the veno-occlusive mechanism), and therefore, high intracavernous pressure is maintained. However, when the corporal smooth muscle is unable to relax sufficiently and/or the corporal tissue loses its normal compliance, the increased intracavernous pressure during erection cannot adequately compress the subtunical veins, resulting in the leakage of blood out of the cavernous body during erection. This is a major cause of ED and is referred to as the corporal veno-occlusive dysfunction (CVOD). CVOD occurs when the smooth muscle content decreases and/or when the collagen content increases in the cavernous body[8]. Therefore, the ratio of the smooth muscle content to the collagen content in the cavernous body decreases in CVOD.

REGULATION OF PENILE SMOOTH MUSCLE CONTRACTION

Detumescence of the penis is predominantly mediated by adrenergic nerve terminals whose neurotransmitter, norepinephrine, activates adrenergic receptors on the penile smooth muscle. The contraction of penile arteries and trabecular smooth muscle is largely mediated by α-1 adrenergic receptors[9,10]. Other vasoconstrictors including endothelin-1, prostaglandin F2α, thromboxane A2 and angiotensin II are also implicated in the contraction of smooth muscle in the penis[11-13].

REGULATION OF PENILE SMOOTH MUSCLE RELAXATION

Dilatation of the cavernous artery and helicine arteries is the first event in the development of an erection. The blood flow and pressure increase in the cavernous sinuses, and subsequently, smooth muscles surrounding the trabeculae relax, resulting in further expansion and accumulation of blood in the cavernous body. It is now well established that nitric oxide (NO) plays a pivotal role in the initiation and maintenance of erection. NO acts through the stimulation of the soluble guanylate cyclase, which mediates the subsequent formation of cyclic-GMP (cGMP). cGMP activates protein kinase G (PKG), and PKG is implicated in the relaxation of smooth muscle. cGMP is inactivated by phosphodiesterase type 5 (PDE5), which is predominantly located in the cavernous smooth muscle and is the target of PDE5 inhibitors (PDE5Is) such as sildenafil and vardenafil. NO synthase (NOS) uses the amino acid L-arginine and molecular oxygen to produce NO. Three distinct isoforms of NOS have been identified. Two constitutive forms, neuronal NOS (nNOS) and endothelial NOS (eNOS), are present in the

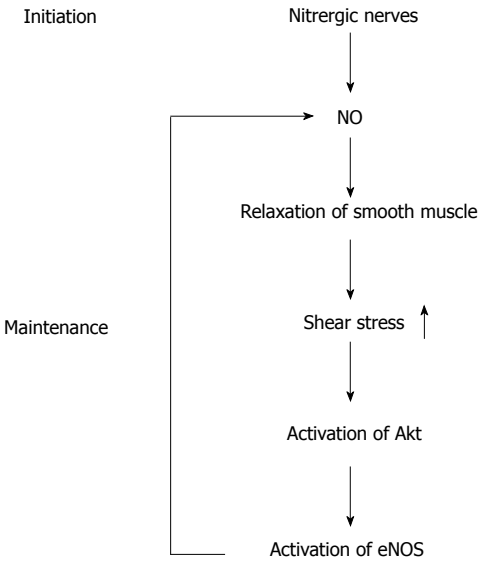

Figure 1 Nitric oxide is critically implicated in the initiation and maintenance of penile erection. NO: Nitric oxide; eNOS: Endothelial nitric oxide synthase.

nervous system and vascular endothelial cells, respectively. A third isoform, inducible NOS (iNOS) is expressed in a variety of cells in response to inflammatory mediators and bacterial products. The isoforms nNOS and eNOS are expressed in the autonomic nerves and endothelium of the penis, respectively[14-17]. Under physiological conditions, iNOS is not expressed in the penis. Postganglionic parasympathetic nerves, which express nNOS and release NO as a cotransmitter with acetylcholine, are now termed nitrergic nerves[17,18]. The stimulation of the cavernous nerve activates nitrergic nerve fibers and elicits NO release at the nerve terminals, which causes relaxation of penile smooth muscle. The functional role of NO released from the nitrergic nerve termini during the relaxation of penile smooth muscle has been demonstrated in many studies in which penile erection induced by stimulation of the cavernous nerves or the spinal cord can be inhibited by NOS inhibitors[14,19-21]. The role of eNOS in erection has also been studied. One possibility was that acetylcholine released from postganglionic cholinergic nerves evoked the release of NO from the endothelium to induce endothelium-dependent relaxation of the penile smooth muscle. However, atropine, a competitive inhibitor of the muscarinic effect of acetylcholine, did not inhibit cavernous nerve-induced penile erection[14]. Furthermore, neurogenic relaxation of the cavernous body does not require a functional endothelium[22,23], suggesting that acetylcholine-induced endothelium-dependent relaxation of the smooth muscle is not required for cavernous nerve-induced penile erection. A second possibility was the activation of eNOS by shear stress. During erection, an increased blood flow on the luminal surface of the penile artery and cavernous sinuses can cause shear stress, which may lead to the activation of protein kinase Akt (also known as Protein kinase B) and subsequent phosphorylation and activation of eNOS, facilitating NO release from the endothelium. Hurt *et al*[24] demonstrated that both electrical stimulation of the cavernous nerve and direct intracavernosal injection of a vasorelaxant drug, papaverine, caused a rapid increase in the phosphorylation and activation of Akt and eNOS. The authors also showed that penile erection elicited by papaverine is significantly reduced in eNOS gene knockout mice. They proposed a model in which the rapid, brief activation of nNOS initiates the erectile response, whereas Akt-dependent phosphorylation and activation of eNOS are necessary for sustained NO production and maximal erection (Figure 1).

POSSIBLE CAUSES OF ED IN CKD PATIENTS

Most studies in this field have been performed using dialysis patients and renal transplant recipients. Little data exist on the etiology and treatment of ED in CKD patients before entering a dialysis program.

Hormonal abnormalities

Chronic renal failure (CRF) is associated with impaired spermatogenesis, and it often results in infertility[25]. In addition, testes develop endocrine dysfunction. Total and free testosterone levels are typically reduced, although the binding capacity and concentration of sex hormone-binding globulin are normal[26-28]. Serum luteinizing hormone (LH) level increases in CRF patients, and testosterone secretion in response to acute administration of human chorionic gonadotropin (HCG), a compound with LH-like actions, shows a blunted response, suggesting that the testosterone-producing Leydig cells have low responsiveness to LH and that this is the primary cause of low testosterone levels in CRF[29]. Interestingly, a factor capable of blocking the LH receptor *in vitro* has been identified in uremic serum, providing an explanation for the blunted response of Leydig cells to infusion of HCG. This blocking activity is inversely correlated with GFR and almost disappears after renal transplantation[30]. In addition, follicle-stimulating hormone (FSH) secretion increases in men with CRF. FSH release from the pituitary gland is negatively regulated by inhibin, a peptide product of Sertoli cells that are located in the convoluted seminiferous tubules. FSH concentration appears to increase in uremic patients because of the damage to seminiferous tubules, resulting in the suppression of inhibit production[31].

Testosterone is required not only for libido but also for the maintenance of the normal morphology and function of the penis. Testosterone deficiency leads to the loss of smooth muscle in the cavernous body and its replacement with collagen fibers[32,33]. This may result in CVOD. It has also been demonstrated that the activity of nNOS and PDE5 are positively regulated by testosterone[32].

Elevated plasma prolactin levels are commonly found in CRF[34]. Increased production is the main cause because the kidney plays little, if any, role in its catabolism. Secondary hyperparathyroidism may be implicated in the increased prolactin secretion in CRF because an infusion

of parathyroid hormone (PTH) in healthy men enhances prolactin release[35]. Depletion of zinc reserves may also play a role in uremic hyperprolactinemia[36]. Hyperprolactinemia induces the loss of libido and low serum testosterone levels[37], which may cause ED.

Endothelial dysfunction

It is now well known that CKD is a risk factor for cardiovascular disease (CVD)[38,39]. Endothelial dysfunction is an early marker of CVD, and has also been reported to occur in CKD patients[40-42]. In addition, endothelial dysfunction is a cause of ED, because NO production from the endothelium decreases in this state. Therefore, it is not surprising that ED frequently occurs in CKD patients. Furthermore, CKD patients often suffer from metabolic diseases such as hypertension, hyperlipidemia, and diabetes. Diabetes is a major cause of CKD. These metabolic diseases also cause endothelial dysfunction and are risk factors for ED. Therefore, in addition to the concomitant metabolic diseases, CKD *per se* appears, at least in some part, to cause ED via the induction of endothelial dysfunction.

Disturbance in the autonomic nervous system

Autonomic neuropathy occurs in end-stage renal disease and can be a cause of ED[43,44]. It is well known that autonomic neuropathy is a common complication of diabetes, and it can be a cause of ED in CKD patients.

Anemia and erythropoietin deficiency

Erythropoietin (Epo) has been widely used to treat anemia in uremic patients. Several reports have demonstrated that treatment with Epo improved erectile function in dialysis patients[45-47], suggesting that anemia and/or Epo deficiency are implicated in ED. The mechanism by which Epo restores erectile function remains unclear. Epo normalized the increased serum prolactin level in early studies[45,48], but this finding was not confirmed by other studies[49-51]. Moreover, Epo increased serum testosterone levels in some studies[51,52]; however, this finding was again not confirmed by other studies[45,46,49,50]. Allaf *et al*[53] examined the effects of Epo on the recovery of erectile function in a rat model of cavernous nerve injury and found that Epo restored erectile function. They also found that Epo stimulated axonal regeneration of the injured cavernous nerve. Therefore, Epo may stimulate the regeneration of the cavernous nerve. Epo reportedly has protective effects against ischemic damages *via* its anti-apoptotic activity[54-59]. Therefore, Epo may protect the cavernous body against injuries *via* its anti-apoptotic activity. Furthermore, the receptor for Epo is expressed on vascular endothelial cells (VECs) and Epo stimulates the proliferation and migration of VECs[60,61]. Epo is also capable of mobilizing endothelial progenitor cells (EPCs) from the bone marrow[62,63]. EPCs were originally isolated from human peripheral blood[64]. EPCs are progenitor cells whose differentiation potential is restricted to VECs. They were incorporated in the capillaries and small arteries of ischemic tissues *in vivo* and expressed markers for VECs such as CD31 when introduced into the circulation using a hindlimb ischemia model[64], suggesting their involvement in the stimulation of angiogenesis. Several studies have reported that the number of circulating EPCs decreased in ED patients[65-67]. These data suggest that Epo may restore erectile function *via* its proangiogenic activity. In summary, Epo has nerve-protective, anti-apoptotic, and proangiogenic activities, at least in animal models, and these activities may be implicated in Epo-induced restoration of erectile function. It is likely that Epo restores erectile function via interaction with its receptors on cells such as nerves and VECs rather than on red blood cells with a resultant improvement in anemia.

Vitamin D deficiency and secondary hyperparathyroidism

Although no conclusive data have been published, Massry *et al*[68] reported that a decline in serum PTH concentration by treatment with 1,25(OH)$_2$ vitamin D$_3$ correlated with the recovery of erectile function in dialysis patients. It was also reported that PTH administration increased serum prolactin concentration[35]. Therefore, it is possible that secondary hyperparathyroidism is implicated in erectile dysfunction in dialysis patients.

Drugs

Many drugs used for CKD patients potentially cause ED. Common examples are anti-hypertensive drugs including diuretics, agonists for α-2 adrenergic receptors, and beta-blockers. Other examples are cimetidine, tricyclic antidepressants, and metoclopramide.

Depression

The prevalence of depression among dialysis patients has been estimated to be 20%-30%[69-71]. Several studies demonstrated that depression is an independent risk factor for ED[72,73].

Zinc deficiency

Several reports demonstrated that oral zinc supplementation restored erectile function, which was associated with an increase in serum testosterone concentration[74,75]; however, some negative effects of zinc supplementation on erectile function were also reported[76]. Possible causes of ED in CKD patients are summarized in Table 1.

ED AS AN EARLY MARKER FOR CVD

Because of the high prevalence of ED among CVD patients, ED was traditionally regarded as a secondary complication of CVD. Recently, ED has gained attention as an early marker of CVD, because ED often precedes the occurrence of CVD. The Prostate Cancer Prevention Trial was a prospective, randomized, and placebo-controlled trial to assess whether finasteride decreased the prevalence of prostate cancer[77]. Finasteride is an

Table 1 Possible causes of erectile dysfunction in chronic kidney disease patients

Abnormalities in the gonadal and pituitary systems
Testosterone↓
LH↑, FSH↑
Prolactin↑
Endothelial dysfunction
Hypertension, diabetes, hyperlipidemia
Autonomic neuropathy
Anemia (Erythropoietin↓)
Secondary hyperparathyroidism
Drugs
Diuretics
Agonists for α-2 adrenergic receptors and β-blockers
Cimetidine
Tricyclic antidepressants
Depression
Zinc deficiency

LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

inhibitor of 5α-reductase, and inhibits the conversion of testosterone to dihydrotestosterone, which is the primary androgen in the prostate. Participants were regularly monitored for overall health, including cardiovascular events and sexual function. Data from 9457 men randomized to the placebo group in this trial were analyzed to assess the hypothesis that ED is an early marker of patients with occult CVD[78]. At entry to the study, 8063 (85%) men had no CVD; of these men, 3816 (47%) patients reported some level of ED. Among the 4247 men without ED at study entry, 2420 men (57%) reported an incident ED after 5 years, and this incidence increased to 65% at 7 years. Incidents of ED were significantly associated with subsequent angina, myocardial infarction, or stroke; hazard ratio after adjustment was 1.25. Several other studies also confirmed this finding that ED often precedes the onset of CVD[79-81]. Furthermore, ED has been recognized as an early marker for silent coronary artery disease (CAD). Gazzaruso *et al*[82] examined the prevalence of ED in 133 uncomplicated type 2 diabetic men with angiographically verified silent CAD and in 127 diabetic men without myocardial ischemia[82]. The groups were comparable for age and diabetes duration. The prevalence of ED was significantly higher in patients with silent CAD than in those without silent CAD (33.8% *vs* 4.7%, $P = 0.000$). Significant risk factors for silent CAD were identified using multiple logistic regression analysis. These risk factors included ED, apolipoprotein (a) polymorphism, smoking, microalbuminuria, HDL, and LDL. Interestingly, among these risk factors, ED was the strongest predictor of silent CAD (odds ratio 14.8). García-Malpartida *et al*[83] also examined the association between ED and silent myocardial ischemia (SMI) in 154 type 2 diabetic patients without a clinical evidence of CVD and demonstrated that ED was significantly associated with SMI (18.1% in patients with ED *vs* 4.1% in patients without ED, $P = 0.018$). Therefore, ED should be examined carefully in CKD patients not only for the improvement of their quality of life but also for the prevention of CVD.

TREATMENT

Sufficient dialysis and adequate nutritional intake are necessary to improve the general condition of uremic patients. In addition, control of anemia using Epo and control of secondary hyperparathyroidism using phosphate binders, an active form of vitamin D and/or cinacalcet hydrochloride are required. Zinc supplementation may be necessary when zinc deficiency is suspected. If a psychological problem is suspected, psychotherapy and/or antidepressant medications may be necessary.

PDE5Is

PDE5Is are inhibitors of PDE5 and suppress the degradation of cGMP, thereby stimulating the relaxation of smooth muscle in the cavernous body. Many studies have demonstrated the efficacy of PDE5Is for the treatment of ED in dialysis patients and in renal transplant recipients[84-90]. Although headache, flushing, and dyspepsia are the most common adverse effects[91], PDE5Is were well tolerated among dialysis patients in these studies. Among PDE5Is, sildenafil without dose adjustment has been used to treat ED in dialysis patients in several studies. However, it may be safer to start with half the dose (25 mg) and subsequently increase it up to 100 mg, depending on the patients' responses. Special care should be taken when PDE5Is are administered to patients with cardiovascular or hepatic diseases.

Testosterone replacement therapy

Although testosterone replacement therapy is generally effective for patients with low circulating levels of testosterone when causes of ED are other than CKD, the administration of testosterone to uremic men usually fails to restore libido or potency, despite increased testosterone levels[92,93]. However, one pilot study demonstrated that treatment with testosterone gel improved erectile function in hypogonadal hemodialysis patients[94]. Testosterone stimulates an increase in NO production and degradation of cGMP, because it reportedly increases the activities of nNOS and PDE5 simultaneously[32,95,96]. Thus, the stimulatory effect of testosterone on NO production may be negated by its stimulatory effect on PDE5 activity. In this regard, combination therapy of testosterone and PDE5Is may be more effective than treatment with either testosterone or PDE5Is alone. Indeed, several reports demonstrated the efficacy of combination therapy on erectile function in hypogonadal men who did not respond to PDE5Is[97-100]. The efficacy of the combination therapy was also reported in dialysis patients and renal transplant recipients[101]. However, a recent randomized, double-blind, placebo-controlled trial did not show a significant effect of the addition of testosterone to sildenafil therapy on erectile function[102]. Therefore, the efficacy of the combination therapy is still controversial.

Other treatments for ED

Other options for the treatment of ED include injecting prostaglandin E1 into the shaft of the penis, vacuum constriction devices and constriction bands, and penile prostheses. These treatments are beyond the scope of this review, and have not been discussed in detail.

EFFECT OF RENAL TRANSPLANTATION ON ERECTILE FUNCTION

It is well recognized that dialysis therapy does not improve sexual function[103,104]. Several reports demonstrated the improvement of erectile function after renal transplantation[104-106]. Nassir performed a prospective study in which the erectile function of 52 patients undergoing dialysis therapy was analyzed before and after renal transplantation[104]. No improvement of erectile function was observed in patients during dialysis therapy, whereas renal transplantation significantly improved erectile function. Akbari *et al*[107] examined the effect of renal transplantation on sperm quality and sex hormone levels. The authors found that sperm motility significantly improved, although morphology and sperm count did not change significantly. They also found that the level of testosterone significantly increased, whereas levels of FSH, LH and prolactin significantly decreased after renal transplantation. Furthermore, erectile function was compared between patients on dialysis therapy and renal transplant recipients in several studies, and erectile function was reportedly better in renal transplant recipients[108-110]. However, ED is still common in renal transplant recipients (approximately 50%)[111,112], and the prevention of the occurrence of CVD seems necessary in these patients to maintain erectile function[113,114].

STUDY LIMITATIONS

Most studies on this topic collect information from patients on dialysis therapy and renal transplant recipients. Little reliable data exist with regard to the prevalence, etiology, and treatment of ED in CKD patients before starting dialysis therapy. Future studies are required to elucidate these points.

CONCLUSION

ED is a very common disease in CKD patients, and it is a multifactorial disease whose causes include hormonal, metabolic, nutritional, and psychological factors. PDE5Is are commonly used during treatment. Testosterone replacement therapy together with PDE5Is may be useful, particularly for CKD patients with hypogonadism. Renal transplantation may restore erectile function, particularly for young patients. ED is an early marker for CVD and it precedes the occurrence of CVD; therefore, ED should be examined carefully in CKD patients to avoid occurrence of CVD.

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