Sexual Dysfunction in Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- Physiology of erectile function is dependent on a balanced vascular, neurologic, hormonal, and psychological system.
- Prevalence of erectile dysfunction (ED) in the Western industrialized countries amounts to 20–30 % in the general male population and probably higher, about 75 % in patients at high risk for cardiovascular disease.
- Sexual dysfunction (SD) in patients with CKD should be thought as a multifactorial problem that is caused by a variety of physiological and psychological factors, as well as by comorbid conditions. For example, diabetes and vascular disease (commonly encountered in patients with CKD) can impair the ability of male patients to achieve an erection and of female patients to become sexually aroused.
- Drugs that sustain cyclic-GMP-mediated smooth muscle relaxation in the corpus cavernosum, such as sildenafil, vardenafil, and tadalafil, can improve erectile function in male patients.

Sexual dysfunction (SD) is a common problem in people with chronic kidney disease (CKD). SD in these patients should be considered as a multifactorial problem, caused by a variety of physiological and psychological factors, as well as by comorbid conditions [1]. Male patients with CKD suffer from reduced libido, erectile dysfunction (ED), and difficulty reaching the orgasm. In females with CKD, dyspareunia, amenorrhea, reduction of libido, and a delay in sexual development are frequently observed (Table 24.1) [1]. Approximately 50 % of male predialysis CKD patients and 80 % of male dialysis patients have ED [2]. These patients have diffuse atherosclerotic disease of the penile arteries and hypoxic changes of the contractile and structural components of the erectile tissue. In 1972, the first epidemiological survey of sexual function in patients with CKD was conducted. Since then, multiple studies confirmed that SD in CKD patients is highly prevalent. Although it is a major factor that impacts quality of life in end-stage renal disease (ESRD), SD in dialysis patients receives very limited attention from the patients' attending medical team. Despite its importance, only 25 % of patients discuss about SD with their physicians [2–4].

24.1 Male Sexual Dysfunction

Erection is a neurovascular event. Under sexual stimulation, vasodilation and relaxation of trabecular smooth muscle allows blood flow into the cavernosal sinusoids and increase the intracavernosal

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Table 24.1 Clinical manifestations of SD in CKD patients

Women	Men
Premature menopause	Erectile dysfunction
Decreased libido	Decreased libido
Sexual aversion disorder	Oligospermia
Hypoactive sexual desire	Decrease in muscle mass
Endocrine abnormality: decrease in estrogen production, vaginal dryness, dyspareunia	Azoospermia, infertility
Irregular menstrual cycles, anovulatory cycles, infertility Depression, anxiety	Depression, anxiety

pressure (ICP) [1, 5]. Erection is maintained by the compression of subtunical venules against tunica albuginea. Relaxation of the smooth muscle of the corpus cavernosum is the crucial physiological event in penile erections. Nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway had been acknowledged as a classic pathway in mediating relaxation of corpus cavernosum smooth muscle. Cavernous nerve activation induces the release of NO from the nerve terminals in the corpus cavernosum. Additionally, NO is released from the endothelium in response to shear stress. NO is synthesized by neuronal nitric oxide synthase (nNOS) in the corpus cavernosum nerve terminals and by endothelial oxide synthase (eNOS) in endothelium, which utilizes L-arginine and oxygen as substrate to produce NO. Subsequently, NO activates soluble guanylate cyclase (GC) and increases cGMP levels in smooth muscle cells. The increase in blood flow required for erection is comparable to that required by the heart for vigorous exercise [5, 6].

ED is the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual intercourse [6, 7]. ED can mask as yet undiagnosed comorbid conditions such as cardiovascular disease and diabetes. Irrespective of the etiology, ED will almost be accompanied by psychological symptoms if the man is "bothered" by his condition (performance anxiety). Risk factors for ED can be grouped into those that have an effect upon the vasculature, those in which the mode of action is nonvascular in nature, and age. Causes of vasculogenic ED include diabetes, dyslipidemia, and hypertension, while causes of nonvascular ED include surgery for prostate cancer and diseases of the central nervous system (CNS).

Aging is one of the most important and well-defined risk factors for ED and mediates its effect through both vascular and nonvascular modes. The increasing incidence of atherosclerosis with age is matched by the negative impact of age on sexual desire and libido. These categories are, therefore, not mutually exclusive; indeed, there is a high degree of overlap.

It is well documented that hormonal alterations characterized by prolactin, gonadotropins, and gonadal hormone change are present in men and women [5].

In male CKD patients, there are abnormalities in testicular structure and function. Common histological findings show damage to the testes in the seminiferous tubules, interstitial fibrosis, calcifications, thickening of the basement membrane, and stopped germinal maturation but also decreased volume of ejaculate, low or complete azoospermia, and low percentages of motility and infertility [1]. High levels of prolactin hormone in CKD are responsible for reduced libido. Modification of androgen synthesis and metabolism begin to appear early in the course of CKD. Reduction of testosterone level is correlated to Leydig cell dysfunction. Today there is a new field of interest, represented by molecular mechanism of testosterone and its role in the pathogenesis of cardiovascular diseases. Recent studies have been carried out in order to correlate the blood levels of testosterone in patients with ED with different degrees of CKD (stages I–IV) [5]. Autonomic nervous system alterations are a frequent cause of SD in CKD; the integrity of this system can decrease sensation and arousal stimuli during sexual activity. Anemia, a common complication of CKD, has been linked with a reduction of libido and ED [6, 7]. The decrease of oxygen that accompanies reduction of hemoglobin levels has been associated with a decrease of NO synthesis and an increase in endothelium-derived contracting factor, which results in inhibition of erectile capacity. Recombinant human EPO therapy has been shown to improve erectile function and sexual performance in some, but not all, patients with CKD [8].

24.2 Female Sexual Dysfunction

In women, with CKD, decrease of libido, amenorrhea, and irregular menstrual and anovulatory cycles are caused by elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Midcycle LH surge cannot be mitigated with endogenous administration of estrogen, confirming a central hypothalamic derangement. Clinical manifestations of SD in women include premature menopause, skin wrinkling, urinary incontinence, hot flushes, sleep and cognitive disorders, and cardiovascular disease. The reduction of libido is frequently observed, while pregnancy is rare (spontaneous abortion is a common eventuality). Few studies carefully examined ovarian function in women with CKD; this lack of data reflects probably the complexity of studying the reproductive system in women [5].

The high prevalence of SD in patients with ESRD emphasizes the need to investigate the impact of SD at all stages of CKD [9, 10].

Psychosocial factors can have a substantial effect on the sexual function in patients with CKD. It has been noted in several studies that 20–30 % of patients with CKD suffer from clinical depression. Studies have also shown an association between SD and a variety of other quality-of-life parameters, such as mental and physical components of the 36-item short-form (SF-36) health survey, and depression scores [5].

24.3 Diagnosis and Evaluation of Sexual Dysfunction

The first step in the evaluation of SD in patients with CKD is to obtain a detailed sexual history about the sexual desire, arousal and orgasmic capabilities, fertility, and ED in men. Changes in the frequency of intercourse need to be determined. Often the patients are very reluctant to tell such concerns. The physicians should determine the time of the onset of these problems in relation to the stage of CKD. In addition, the medical history should focus on the patient's past and present medical illness, i.e., chronic/medical illness, such as diabetes; anemia; neurological illness or lumbosacral disk disease; endocrinological disease, like hypogonadism, hyperprolactinemia, and thyroid disorders; and atherosclerotic vascular risk, such as diabetes, hypercholesterolemia, hypertension, hyperhomocysteinemia, smoking habits, or family history. Current drug therapy should also be reviewed in detail. Drugs such as cimetidine, tricyclic antidepressant, phenothiazines, and metoclopramide are often implicated in ED.

Finally, it is important to investigate patients for presence of psychosocial problems (depression, psychiatric illness) and current stress factor (loss of job or home and so on).

24.3.1 In Men

The physical examination is important for assessment of the male patient's sexual function. These assessments should include vascular disease, autonomic disease, autonomic dysfunction, and hypogonadism [1, 5]. The lack of secondary sexual characteristics and the presence of small and soft testicles suggest hypogonadism. The test of nocturnal penile tumescence (NPT) may be used to discriminate organic and psychological causes of impotence. A patient with normal nocturnal erections during rapid eye movement (REM) sleep may benefit from psychological testing and evaluation [11]. Consideration should be given to laboratory assessment of hormone levels (testosterone, estrogen, FSH, LH, TSH, PTH, prolactin levels) and zinc levels, on the basis of the specific complaints of each patient. The test that discriminates between a neurogenic and a vascular cause of impotence includes Doppler studies to measure penile blood flow, measurement of penile blood pressure, and penile pulse palpation. The NIH Consensus Panel on ED outlined several goals for basic and clinical research on ED. One of these goals was to create a staging system for the quantitative and qualitative classification of ED. Such a system would assist research and patient management by (1) quantifying the specific type of patient population to include in a clinical trial, (2) determining and comparing responder rates associated with different treatments, (3) improving clinical decision-making and patient care, (4) fostering educational initiatives, and (5) supporting

claims for reimbursement. The EF domain of the International Index of Erectile Function (IIEF) was considered for such purpose. This subscale in particular showed a high degree of reliability, as well as excellent sensitivity and specificity to treatment effects in validation studies [8]. The IIEF was developed in conjunction with the clinical trial program for sildenafil, and since that period, it has been adopted as the "gold standard" measure for efficacy assessment in clinical trials of ED. Total scores of 22–25 suggest a normal EF, while lower scores indicate ED (mild ED, 17–21; mild to moderate ED, 12–16; moderate ED, 8–11; and severe ED, less than 8 points). The Arizona Sexual Experiences Scale (ASEX) is a five-item rating scale, which quantifies sexual drive, arousal, vaginal lubrication or penile erection, ability to reach orgasm, and satisfaction from orgasm. Possible total scores range from 5 to 30, with the higher scores indicating more SD. Its reliability has been positively assessed for use in dialyzed patients [8]. The Mell–Krat scale is commonly used in Poland and Czech Republic as a validated tool helpful in a complex assessment of sexual function and quality of sexual life. The version for males includes 13 and that for females includes 20 questions with answers scoring from 0 to 4. The higher the score, the better the sexual function. Optimal results for men are 38 points or higher, for women 55 points or higher. Beck Depression Inventory (BDI) is one of the most widely used instruments for measuring the severity of depression. It is composed of 21 questions scored from 0 to 3, each evaluating a specific symptom commonly existing in people with depression. Total scores of 10 or higher indicate depression (10–18 for mild, 19–29 for moderate, and more than 30 points for severe depression).

24.3.2 In Women

Assessing sexual function in women perhaps is more difficult than in men, which may be one explanation for the lack of studies of SD in women with CKD [1–5]. The domains of sexual function in women include desire, arousal, pain, and satisfaction. These can be assessed using the 9-item FSFI. There are several validated screening tools that focus on hypoactive sexual desire disorder (HSDD), which is the most common sexual concern of women of all ages. These screening tools will vary in their usefulness depending upon your clinical specialty and the patient population you serve (Box 24.1). Menstrual abnormalities are common in CKD and many women are anovulatory. The hormonal alterations that lead to premature menopause in women with CKD likely contribute to SD and are, at least, partially responsible for higher reported prevalence of sexual dysfunction in women with CKD compared with general population. The ovarian failure in women with CKD can be associated with abnormalities in the hypothalamic–pituitary–ovarian axis [9, 11].

Box 24.1. Screening Tools for Female SD

- Decreased Sexual Desire Screener (DSDS): 5 questions, self-administered; assesses for generalized acquired HSDD [12].
- Female Sexual Function Index (FSFI): 19 questions, self-administered; assesses all of the dimensions of female sexual function including sexual satisfaction [13].
- Sexual Interest and Desire Inventory – Female (SIDI-F): 13 items, clinician administered; assesses severity of female HSDD [14].
- Brief Hypoactive Sexual Desire Disorder Screener: 4 questions, self-administered HSDD in postmenopausal women [15].
- Brief Profile of Female Sexual Function (B-PFSF): 7 questions, self-administered HSDD in postmenopausal women [16].
- Female Sexual Distress Scale – Revised (FSDS-R): 13 questions, self-administered; assesses distress associated with female SD [17].

24.4 Management of Sexual Dysfunction in Men and Women

24.4.1 In Men

In the general population, drugs that sustain cyclic-GMP-mediated smooth muscle relaxation in the corpus cavernosum, such as sildenafil, vardenafil, and tadalafil, can improve ED in male patients.

The introduction of sildenafil has completely changed the approach to evaluating the subjects with SD, because this drug is considered an effective well-tolerated treatment for men with ED (Table 24.2). It is important to avoid the use of sildenafil in selected conditions (Box 24.2). In the past, we proposed an algorithm in CKD patients that gave the opportunity to explore the previously mentioned factors using some instrumental interventions, such as the NPT test, penile echo color Doppler, nervous conduction velocity, or cavernous body biopsy, addressed to prescribe needed surgical or medical interventions [6, 7]. The complexity of the proposed algorithm requires many diagnostic procedures and much time and economic resources to localize the pathological lesions responsible for the ED. Because of the new oral drug sildenafil, we proposed in the past an algorithm to test the possibility of obtaining an erection and classify patients as responders or nonresponders to the sildenafil test (Fig. 24.1). In nonresponders, it is necessary to explore other factors (hormonal, psychological, neurological, vascular, cavernous body alteration, or particular drugs) involved in inducing or maintaining the ED [7] (Box 24.3).

Testosterone therapy is indicated in adult men with diagnosis of hypogonadism. Clomiphene citrate has also been used to increase testosterone levels, with improvement in sexual function. Oral testosterone and testosterone derivatives are not used because of their lack of efficacy and adverse

Table 24.2 Common adverse effects of medical treatment of SD

Sildenafil	Testosterone
Headache	Decrease in high-density lipoprotein, fibrinogen, lipoprotein (a)
Nasal congestion	Increase prostate volume, prostate cancer, exacerbating symptoms of benign prostate hypertrophy
Gastric reflux	Alterations in liver function
Muscle/back pain	Polycythemia
Flushed face	Exacerbation of sleep apnea

Box 24.2. Precautions to the Use of PDE5 Inhibitors

- Nitrates and PDE5 inhibitors must not be used together.
- Amyl nitrate should not be used together with sildenafil.
- Any treatment for ED is contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors.

Box 24.3. What the Guidelines Say You Should Do: Workup on ED [18]

- Sexual history and physical examination are needed in the initial assessment of ED to identify underlying medical conditions associated with ED.
- Clinical use of a validated questionnaire related to ED may help assess all sexual function domains.
- Routine laboratory tests, including glucose–lipid profile and total testosterone, are required to identify and treat any reversible risk factors and modifiable lifestyle factors.
- Specific diagnostic tests are indicated by only a few conditions: nocturnal penile tumescence and rigidity testing using RigiScan, intracavernous vasoactive drug injection, duplex ultrasound of the cavernous arteries, dynamic infusion cavernosus arteries, dynamic infusion cavernosometry, and cavernosography.

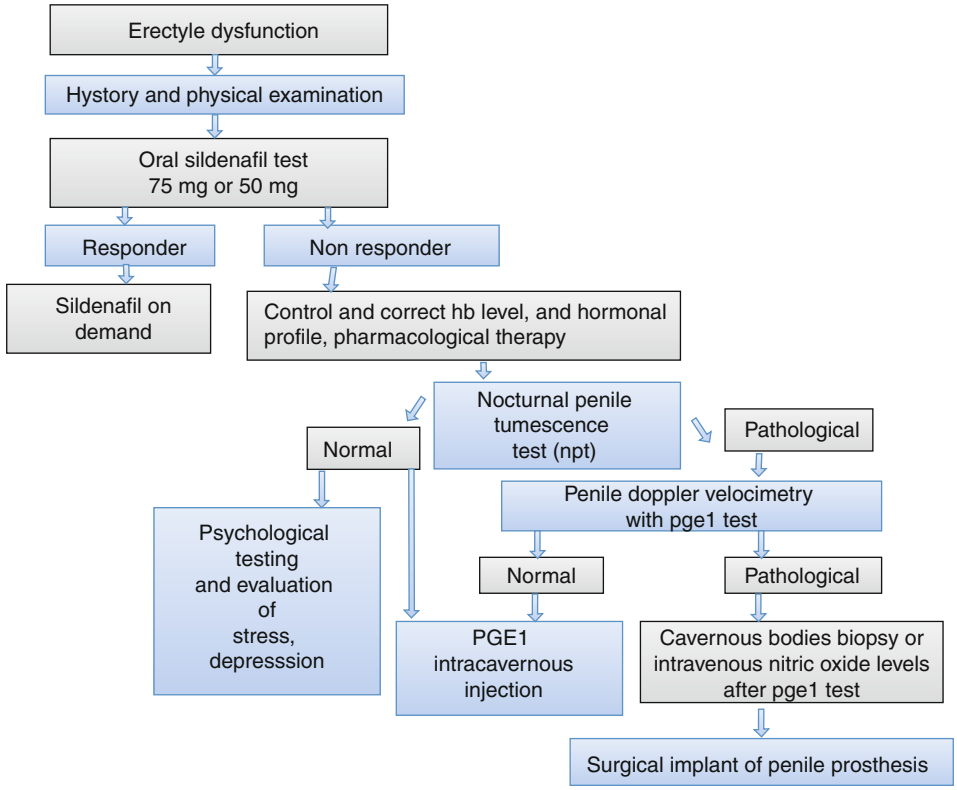

Fig. 24.1 Diagnostic and therapeutic algorithm for the evaluation of ED in CKD patient

Box 24.4. What the Guidelines Say You Should Do: Treatment of ED [18]

- Lifestyle changes and risk factor modification must precede or accompany ED treatment.
- The American College of Physicians recommends that clinicians initiate therapy with a PDE-5 inhibitor in men who seek treatment for ED and who do not have a contraindication to PDE-5 inhibitor use.
- Clinicians must base the choice of a specific PDE-5 inhibitor on the individual preferences of men with ED, including ease of use, cost of medication, and adverse effects profile.
- The evidence is insufficient to compare the efficacy and adverse effects of different PDE-5 inhibitors for the treatment of ED because only few head-to-head trials are available.
- Pro-erectile treatments must be given at the earliest opportunity after radical prostatectomy.
- Testosterone replacement restores efficacy in hypogonadic nonresponders to PDE5-Is.
- Apomorphine can be used in mild to moderate ED, psychogenic ED, or in patients with contraindications to PDE5-Is.
- A vacuum constriction device can be used in patients with stable relationship.
- Intracavernous injection is second-line therapy.
- Penile implant is third-line therapy.

effects on liver function and lipid profile and thus are used as parenteral and transdermal preparation (Boxes 24.4 and 24.5). Studies on the use of testosterone in patients with CKD are few, and several studies suggest that ED in the CKD does not improve with testosterone (Table 24.2 Boxes 24.4 and 24.5) [11, 19–22].

24.4.2 In Women

Few studies address decreased libido and sexual function in women with CKD. Quality-of-life surveys suggest that discussion of sexual function and other reproductive issues are a key component of psychosocial assessment and that education on sexual function in the setting of CKD is widely needed (Box 24.5). Pharmacologic therapy with estrogen/progesterone and androgens along with correction of anemia, ensuring adequate dialysis delivery, and treatment of underlying depression is important [1, 4]. Changes in lifestyle such as smoking cessation, strength training, and aerobic exercises may decrease depression, enhance body image, and have positive impacts on sexuality. Women with CKD who suffer from chronic anovulation and lack of progesterone secretion may be treated with oral progesterone at the end of each menstrual cycle to restore menstrual cycles. It is not clear whether unopposed estrogen stimulation of the endometrium (due to anovulatory cycles) predisposes women with CKD to endometrial hyperplasia or endometrial cancer. Routine gynecologic follow-up is recommended in these cases, and some women may also benefit from the use of a progestational agent several times a year to mitigate the effects of estrogen on the endometrium (Boxes 24.5 and 24.6) [24, 25].

Box 24.5. Relevant Guidelines on Sexual Dysfunction

1. European Association of Urology for diagnostic workup and treatment of ED in general population [18]
2. Hormonal testing and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians [23]
3. Practice guidelines on sexual dysfunction in women from American College of Obstetricians and Gynecologists (ACOG) [24]
4. British Society for Sexual Medicine (BSSM). Guidelines on the management of sexual problem in women: the role of androgens [25]

Box 24.6. What the Guidelines Say You Should Do: Treatment of SD in Women and the Opportunity for Psychosexual and/or Couples Counseling [24, 25]

- The generalized use of testosterone by women has been advised against, because of inadequate indications and lack of long-term data. However, postmenopausal women who are distressed by their decreased sexual desire and who have other identifiable cause may be candidates for testosterone therapy. Androgens may also be used by those women who are hypogonadal as a result of pituitary problems in premenopause.
- Although there is no consistent correlation between sexual functioning and levels of androgens (free and total testosterone, androstenedione, dehydroepiandrosterone, and SHBG) across wide age range, in some women androgen therapy can improve sexual desire.
- Transdermal patches and topical gel or creams are preferred over oral products because of first-pass hepatic effects documented with oral formulation.
- The major side effects of androgens are hirsutism and acne. No safety with regard to testosterone implants. There is no indication for increased frequency of breast cancer.

Low estradiol levels in amenorrhoeic women on dialysis leads to vaginal atrophy and dyspareunia. Topical estrogen cream and vaginal lubricants may be helpful in this situation. Women with CKD who do have menstrual cycles should be encouraged to use contraception; because of poor pregnancy outcomes, restoring fertility is not an advisable therapeutic goal. HSDD is the most common sexual problem reported by women with CKD. Testosterone replacement therapy to treat HSDD has been effective in some women without CKD. However, long-term safety data on the use of androgens in women with CKD and ESRD are very limited [21, 22, 26].

Before You Finish: Practice Pearls for the Clinician

- A detailed history of menstrual patterns should be obtained for women and history of ED obtained for men.
- Consideration should be given to laboratory dosage of hormone levels (testosterone, estrogen, FSH, LH, thyroid-stimulating hormone, PTH, and prolactin level).
- For male and female patients, it is important to address the psychosocial factors that might contribute to SD.
- As first-line therapy, phosphodiesterase inhibitors are recommended for their effectiveness, ease of use, and good side-effect profile.
- Sildenafil, vardenafil, and tadalafil equally seem to be effective; tadalafil is preferable for a longer duration of action.
- As a second-line therapy, recommended drugs are injectable intrauretral/intracavernous, such as alprostadil, according to the preferences of the patient.
- As third-line therapy, surgical implantation of penile prosthesis is reserved for patients who cannot use or which have not responded to the first- and second-line therapies.
- Androgen replacement therapy may be indicated only in cases of documented hypogonadism.

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