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Erectile dysfunction and reproductive disorders in patients with chronic kidney disease

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Abstract

Introduction. *Erectile dysfunction (ED) and associated reproductive disorders (RD) are a significant medical and social problem, especially in patients with chronic kidney disease (CKD). In this category of patients, the frequency of erectile and reproductive disorders is significantly higher than in the general population, which negatively affects their quality of life and psychoemotional state.*

Objective. *The purpose of this review is to systematize current data on the prevalence, pathogenetic mechanisms and consequences of ED in patients with CKD and in kidney transplant recipients, as well as to analyze the effect of kidney transplantation (KT) on the restoration of sexual and reproductive function.*

Material and methods. *The review includes homeland and foreign studies mostly published in the recent 5 years, which have devoted to the*

assessment of erectile function in patients with CKD and after KT. Particular attention is paid to the use of standardized assessment methods, such as the International Index of Erectile Function (IIEF-5), as well as the analysis of data on hormonal background, psychoemotional and social aspects.

Conclusion. *ED is a common complication of CKD caused by vascular, hormonal and psychoemotional factors. Effective treatment requires an interdisciplinary approach taking into account the somatic and psychological state of the patient. KT improves sexual function, but in some patients ED persists due to immunosuppression and concomitant diseases. Further research is needed to optimize diagnostics, therapy and improve the quality of life of such patients.*

Keywords: chronic kidney disease, erectile dysfunction, hemodialysis, kidney transplantation

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CKD, chronic kidney disease
ED, erectile dysfunction
EF, erectile function
HD, hemodialysis
IIEF, International Index of Erectile Function
KT, kidney transplant
KTR, kidney transplant recipient
mTOR, mammalian Target of Rapamycin
PAIRS, Psychological and Interpersonal Relationships Scale
RD, reproductive disorder
RRT, renal replacement therapy
SWE, shear wave elastography

Introduction

Erectile dysfunction (ED) and associated reproductive disorders (RDs) represent a significant medical and social problem, negatively affecting the quality of life for millions of people. This problem is especially relevant in patients with chronic kidney disease (CKD), in whom the ED prevalence is significantly higher than in the general population. In recent decades, the mechanisms of ED and RD development in patients with CKD, and in kidney transplant recipients (KTRs), have been actively studied. This problem is vital due to both the physical consequences of ED, and also its impact on the psychoemotional status of patients, which lead to social isolation and deterioration in the overall quality of life [1–6].

Epidemiological and etiopathogenetic aspects of erectile dysfunction in patients with chronic kidney disease

According to literature, the ED prevalence among sexually active men varies from 11.3% to 64%. By 2025, 322 million people are expected to have ED of varying severity [3]. However, a data comparison is difficult due to differences in diagnostic criteria and geographical peculiarities of studies [4, 7].

ED is one of RD manifestations representing a serious medical and social problem, and, according to A. Agarwal et al., the male infertility prevalence varies from 2.5% to 12%, but the exact regional data and causes of its incidence remain poorly understood [5].

ED occurs at early stages of CKD, even before the need for dialysis therapy, and worsens as the disease progresses. According to some studies, the ED incidence in patients with stage 5 CKD exceeds 80%, including the patients on hemodialysis (77%–84%) and peritoneal

dialysis (up to 84%), as well as in kidney transplant recipients (KTRs), among whom this figure reaches 64% [6, 8, 9].

The main causes of ED in patients with CKD are the autonomic innervation disorders, endothelial dysfunction, hormonal abnormalities (hyperparathyroidism, hyperprolactinemia, hypotestosteronemia), and side effects of drug therapy [6, 9].

In the study by N. Tekkarismaz et al., in patients on dialysis, sexual dysfunction was more common in those on peritoneal dialysis compared to those on hemodialysis (HD), which could be explained by a greater metabolic load and changes in the hormonal profile [10]. In the study by A.A. Kamalov et al., the urgency of maintaining or improving EF was noted by 77.2% of patients receiving renal replacement therapy (RRT) using the program HD method, 92.3% of patients receiving RRT using peritoneal dialysis, and 77.1% of patients after kidney transplantation [11].

Among KTRs, the key risk factors for ED development are age, type II diabetes mellitus, hypertension, dyslipidemia, smoking, repeated transplants, and the type of immunosuppressive therapy [4]. It has been established that calcineurin inhibitors (cyclosporine, tacrolimus), mammalian target of rapamycin (mTOR) inhibitors, corticosteroids, and antihypertensive drugs (alpha-blockers, beta-blockers, diuretics) can negatively affect sexual function after transplantation [9].

ED in CKD is associated with impaired vascular tone and endothelial function [12]. Normally, erection is a complex neurovascular process involving the release of nitric oxide, activation of cyclic guanosine monophosphate, and relaxation of the smooth muscles of the corpora cavernosa. In CKD, this process is impaired due to increased oxidative stress, inflammation, and vascular changes [13].

In experimental models, it has been proven that arterial hypertension leads to decreased endothelium sensitivity to acetylcholine, which worsens the vasodilation of penile vessels. [14].

Although successful kidney transplantation (KT) improves many aspects of reproductive health, the incidence of ED among KT patients remains high. While some patients experience an improvement in sexual function, others experience persistent or worsening ED. This may be due to a residual endothelial dysfunction, vascular disorders, and immunosuppressive therapy effects [6].

Some studies show that younger patients experience improved sexual function after KT, while in patients over 45 years of age the dysfunction progresses [15]. Risk factors such as depression, hypotestosteronemia, low hemoglobin levels, and a long period of previous dialysis also play a significant role [16].

Given a high prevalence of ED among CKD patients and KTRs, special attention should be paid to the comprehensive management of patients, including monitoring by nephrologists, urologists, and transplantologists. Researchers emphasize the need for early counseling of patients about possible sexual dysfunctions and their correction after transplantation [17].

In addition, compliance with the treatment regimen plays an important role [18]. Studies show that stress and poor compliance with immunosuppressive medication may cause worsening the KTR condition. Poor adherence to physician recommendations, alcohol consumption, smoking, poor diet, and sedentary lifestyle are also associated with worse sexual health outcomes [19].

Psychoemotional state as a risk factor for the erectile dysfunction progression in patients with chronic kidney disease

ED in CKD patients is not only a consequence of vascular, hormonal and neurogenic disorders, but is also closely associated with psychoemotional factors. Depression, anxiety disorders and psychological distress have a significant impact on sexual function, aggravating existing disorders and reducing the quality of patient life [20].

This problem is especially pronounced in patients undergoing dialysis. The impact of psychoemotional factors on ED in this category of patients may be explained by several mechanisms. First, depression and anxiety disorders contribute to the activation of the sympathetic nervous system, which leads to vasoconstriction and decreased blood flow in the cavernous bodies of the penis. Second, psychological stress worsens the endothelial function and reduces the release of nitric oxide, a key mediator of the erection. Third, anxiety disorders can provoke psychogenic ED, aggravating organic changes [16].

There is a clear relationship between the depression level and the EF impairment severity. Studies have shown show that patients with severe depressive symptoms are more likely to suffer from severe forms of ED, and the treatment of depression can partially improve the sexual function [21]. However, the very fact of having ED is also a risk factor for developing depression, creating a two-way relationship in which the deterioration of one condition provokes an exacerbation of the other [6].

The situation is aggravated after KT. Despite the fact that kidney transplantation in many cases leads to an improvement in general well-being and a decrease in the severity of uremic symptoms, a significant proportion of patients continue to experience anxiety disorders. This may be associated with changes in hormonal levels, long-term use of immunosuppressive drugs, and worries about possible transplant rejection [6].

The impact of COVID-19 on the psycho-emotional state of patients with CKD cannot be ignored, either. Long-term isolation, increased stress levels, and decreased availability of medical care have resulted in an increase in cases of anxiety and depressive disorders, which in turn has affected the ED prevalence in this category of patients [22].

To assess the impact of psychological factors on sexual function, the Psychological and Interpersonal Relationships Scale (PAIRS) was developed. This tool allows for an objective assessment of the impacts of emotional and social distress associated with ED, as well as the efficacy of psychotherapeutic and pharmacological treatments. Validation studies have shown high reliability and reproducibility of the PAIRS, making it a useful tool in clinical practice [23].

Up-to-date aspects and criteria for the diagnosis of erectile dysfunction and reproductive disorders

ED and RD in patients with CKD and after KT remain relevant areas of research, especially given their impact on the quality of life and general condition of patients. In recent years, many papers have been published on diagnostic methods that allow identifying and differentiating the causes of sexual dysfunction.

One of the most common tools to diagnose ED is the International Index of Erectile Function (IIEF-5). A. Salonia et al. have noted that this questionnaire remains the gold standard for diagnosing ED, as it covers key aspects of the sexual function, including erectile ability, orgasmic function, sexual desire, and satisfaction with sexual life [24]. However, K.I. Neijenhuijs et al. have indicated that IIEF-5 scores may vary depending on the patient's psychological state, and patients with psychogenic ED demonstrate higher scores compared to patients with organic ED causes [25].

Other investigators have explored additional questionnaires that can complement the data obtained with the IIEF-5. For example, S.S. Jabali et al. investigated the use of the J.C. Cappelleri Scale to differentiate the severity of ED, but their results showed that the sensitivity of this tool in patients with CKD remains insufficient [26]. In turn, the Male Copulative Function Scale and the GAD-7 Anxiety Disorders Scale were used in the studies of Z. Tang et al., who confirmed their usefulness in identifying psychogenic factors of ED in patients with CKD [27].

In addition to questionnaire methods, laboratory parameters that may be associated with the ED development in CKD patients have been actively studied. Q. Wang et al. have noted that decreased testosterone levels and hyperprolactinemia in CKD patients are among the key risk factors for the ED development [28]. The study by D.K. Zhang et al. confirmed that dyslipidemia and impaired glucose metabolism also played an important role in the development of vascular disorders contributing to ED [29].

To assess vascular changes in ED, instrumental methods are actively used, including pharmaco-Dopplerography and shear wave elastography (SWE). D.K. Zhang et al. studied the potential of shear wave elastography in differentiating vasculogenic and non-vasculogenic ED. Their data have shown that the SWE method has high sensitivity and specificity in detecting fibrotic changes in the corpora cavernosa in patients with CKD and after KT [29].

Morphological studies of penile and testicular tissues are also of interest in the diagnosis of ED in stage 5 CKD patients. A. Perri et al. analyzed biopsies of the cavernous bodies and revealed pronounced fibrous changes that retained even after successful KT, which may explain the persistent ED in this category of patients [30]. In turn, S.D. Lundy et al. studied histological alterations in the testicles of patients before and after

kidney transplantation and showed that despite getting rid of uremia, most patients retained signs of delayed spermatogenesis and morphological changes in Sertoli cells [31].

The effect of renal replacement therapy type, dialysis length and immunosuppression regimen on reproductive disorders and erectile dysfunction

The impact of dialysis duration on sexual function remains a subject of scientific debate. Several studies have been published in recent years examining this aspect, but their results have often been contradictory.

According to J. Chou et al., increasing the "dialysis length" can contribute to the progression of organic changes in cavernous tissue, leading to persisting ED forms [21]. Similar results were obtained by M. Antonucci et al., who noted that ED was observed more often in patients on long-term HD compared to KTRs [32]. At the same time, the study by H.M. El Hennawy et al. showed that the pretransplant dialysis length did not have a significant effect on the improvement of sexual function after KT [33].

Hormonal changes are also thought to play an important role in the ED development in dialysis patients. However, A.F. Ahmed et al. did not find a statistically significant relationship between dialysis length, testosterone levels and EF in patients with ESRD, suggesting that other mechanisms, such as endothelial dysfunction and vascular impairment may have a more significant impact [34].

In addition, the question of the impact of dialysis type remains open. Some studies have indicated that peritoneal dialysis is more favorable for maintaining testosterone levels than HD, but these data require further confirm [35].

Another important aspect is the impact of immunosuppressive therapy after KT on reproductive function. S.D. Lundy et al. have noted that calcineurin inhibitors and mTOR inhibitors used in KTRs may negatively affect spermatogenesis, reducing sperm motility and worsening fertility rates [31]. However, a number of studies have confirmed that after KT, patients experience a partial recovery of spermatogenesis, which is associated with an improvement in the general condition and a decrease in the uremic load.

Erectile dysfunction and reproductive disorders after kidney transplantation

In recent years, studies have been published assessing the ED incidence in KTRs, the pathophysiological mechanisms of these disorders, and the impact of various factors on sexual health after KT.

According to L. Dell'Atti et al., the ED after KT occurs in 20–50% of patients, but the sexual dysfunction includes not only the erectile dysfunction, but also a decreased libido, the frequency of sexual intercourse, and satisfaction with sexual life [36]. A. Perri et al. showed in their study that ED in KTRs was multifactorial by nature, and its long-term persistence was associated with the presence of concomitant diseases, surgical intervention, drug therapy side effects, and psychological changes associated with chronic diseases [30].

Despite the overall positive effect of KT, the sexual function is recovered only in a number of patients. L. Spirito et al. assessed EF and ejaculatory function at 6 and 12 months after KT and found that the quality of men's sexual health was significantly reduced, in particular, a significant decrease in the mean IIEF-5 score was found at 6 months ($p<0.001$), remaining unchanged at 12 months after KT ($p=0.228$), and this parameter correlated with ejaculation disorders [37].

The opposite result was obtained in the study by N.A. Deebel et al., who associated an improvement in sexual function with significant improvements in total and free testosterone levels after KT [38].

The study by S.D. Lundy et al. confirmed that the normalization of reproductive hormone parameters after KT improved the sperm quality, including the sperm concentration, motility, and morphology [31]. However, the use of immunosuppressive drugs, especially calcineurin inhibitors, and mTOR inhibitors, may negatively affect spermatogenesis and reproductive parameters.

The study by H.M. El Hennawy et al. showed that in stage 5 CKD patients receiving dialysis therapy, the sexual function worsens, but after KT, positive dynamics are noted. In a single-center study with a crossover design, the authors used the IIEF-5 to assess ED one month before and one year after KT and found that the sexual function scale assessments in KTRs were significantly better compared to the patients on dialysis [33].

However, some studies have note confirmed a clear improvement in reproductive parameters after KT. In a meta-analysis that included 28 cohort studies, A. Miron et al., noted an increase in EF by a mean of 13% after KT, but ED persisted in 46% of patients [9]. I.A. Rahman et al. also reported that despite the normalization of hormonal levels after KT, some patients still had symptoms of hypogonadism and impaired spermatogenesis [39].

The use of immunosuppression after KT, especially calcineurin inhibitors, is associated with negative effects on sexual function. Study by S.S. Jabali et al. confirmed that testosterone levels in KTRs might decrease in relation to the immunosuppressive therapy regimen; and the patients receiving mTOR inhibitors reported a decreased libido and EF worsening [26]. Meanwhile, a number of studies have shown that dosage

adjustments and changes in immunosuppressive drugs can mitigate these effects.

The impact of KT surgical technique on the ED development has been also discussed. WE Matheus et al. studied the relationship between the vascular anastomosis type (end-to-end with the internal iliac artery or end-to-side with the external iliac artery) and EF. The authors did not find significant differences between these types of vascular anastomoses, but emphasized the need for further studies to clarify the risk of renal artery stenosis, which may affect EF [40].

A.R. Zagitov et al. studied the relationship between the choice of vascular anastomosis option in KT and the risk of ED developing. The authors noted that anastomosis of the graft renal artery with the internal iliac artery was often associated with more pronounced EF disorders [41].

Conclusion

The erectile dysfunction is a common complication of chronic kidney disease caused by vascular, hormonal and psychoemotional factors. An effective treatment requires an interdisciplinary approach taking into account the somatic and psychological state of the patient. Kidney transplantation improves the sexual function, but in some patients an erectile dysfunction persists due to immunosuppression and concomitant diseases. Further studies are needed to optimize diagnosis and therapy, and improve the quality of life for such patients.

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